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## Lung Mechanotransduction, the minuet of Biophysics (Part 2)

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**Abstract**

The dynamic processes associated with lung pathophysiology have always been explored from a traditionalist perspective. This review conceptualizes an amalgam of biological and biophysical concepts that aim to optimize the understanding of the pathophysiology associated with lung injury from a broader, more complex, and at the same time more complete perspective using arguments from the exact sciences. We hypothesize that the Anti-Zener model could be a more accurate potential explanatory model to support mechanotransduction.

The Anti-Zener model represents a more accurate and structured tool to describe the viscoelastic behavior of lung tissue, overcoming the limitations of classical models such as Young's modules This approach allows a better understanding of pathophysiological processes in the respiratory system, which could optimize treatments for lung diseases such as ARDS and asthma. The integration of exact sciences in the study of lung viscoelasticity opens new possibilities for improving medical care and the design of biomedical materials.

**Keywords:** Mechanotransduction, Young´s modulus, Zener model, Stress, Strain

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**Viscoelastic behavior and thermodynamics**

When an elastic solid is subjected to deformation, according to Hooke's Law the stress is always proportional to the strain and independent of the strain-rate. On the other hand, according to Newton's Law for a viscous liquid, the stress is proportional to the strain-rate but independent of the strain itself. Viscoelastic materials present an intermediate behavior between an elastic solid and a viscous fluid, exhibiting combined similar to both solids and liquids. [72] An example of this type of behavior is the so-called Weissenberg effect. [73]

When a Newtonian fluid is subjected to rotational stress, inertial forces push the fluid away from the experimental set rod. However, when a non-Newtonian (viscoelastic) fluid is subjected to the same experiment, the rotational stress will be distributed along the normal axis, generating an upward flow on the stick.

There are several modules used to experimentally evaluate the viscoelastic behavior of materials: Small Oscillatory Amplitude Shear (SAOS) and Long Amplitude Shear (LAOS).

These in turn could be classified as linear and nonlinear models. In SAOS models, a sinusoidal strain is imposed, and the resulting stress is measured.
The strain would be: $\gamma = \gamma_0 \operatorname{sen}(\omega t)$, the strain rate would be: $\gamma = \gamma_0 \cos(\omega t)$, and the resulting stress would be:

$$G'\gamma + \frac{G''}{\omega}\gamma$$

where G' and G" are the storage and loss modulus of viscoelastic materials. The storage modulus measures just the stored energy and represents the elastic portion, while the loss modulus measures the dissipated energy and represents the viscous portion.

In simple linear models, the solid-like behavior is described by Hook's Law and represented by an analogous mechanical spring:

$$T = G\gamma$$

where $T$ is the stress, G is the elastic modulus of the material, $\gamma$ is the strain.

On the other hand, the liquid-like behavior is described by Newton's Law and represented by an analogous mechanical dashpot:

$$T = \eta\gamma^*$$

Where $T$ is the stress, $\eta$ is the viscous modulus of the material, $\gamma^*$ is the strain rate.

Now, linear models could be used in combination (spring and dashpot) to complex the storage moduli to obtain viscoelastic behavior. The Kelvin-Voight model is represented by the following constitutive equation:

$$\eta\gamma + G\gamma = \sigma$$

**Non-linear constitutive models**

Just as there are several basic and combined models for the linear category, there are also some for the nonlinear constitutive models. However, one of the most relevant is the Giesekus model. [74] This model is based on the concept of anisotropy between the material components and is represented by Hooke's rod immersed in a Newtonian solvent. Its constitutive equation is:

$$\lambda T_{(1)} + T + \frac{\alpha_g \lambda}{\eta_p} T * T = 2\eta_p D$$

where $\alpha_g$ is a mobility parameter, $\lambda$ is the fluid relaxation time, and $\eta_p = \eta_0 - \eta_s$ is the polymer viscosity, with $\eta_0$ being the initial shear viscosity. The strain-rate would be $2D = (\nabla v)^T + (\nabla v)$.

Finally, within the LAOS models, the mathematical structure of the nonlinear response to stress is fairly well captured by the model of Lissajous curves. [73] The elastic Lissajous curves show the plot of oscillatory stress versus input strain, while the viscous curves show the stress versus strain-rate. That is, for an elastic solid, the Lissajous curves are represented by straight lines and the viscous curves by circles. On the other hand, for generic viscoelastic fluids, the Lissajous curves are elliptic.

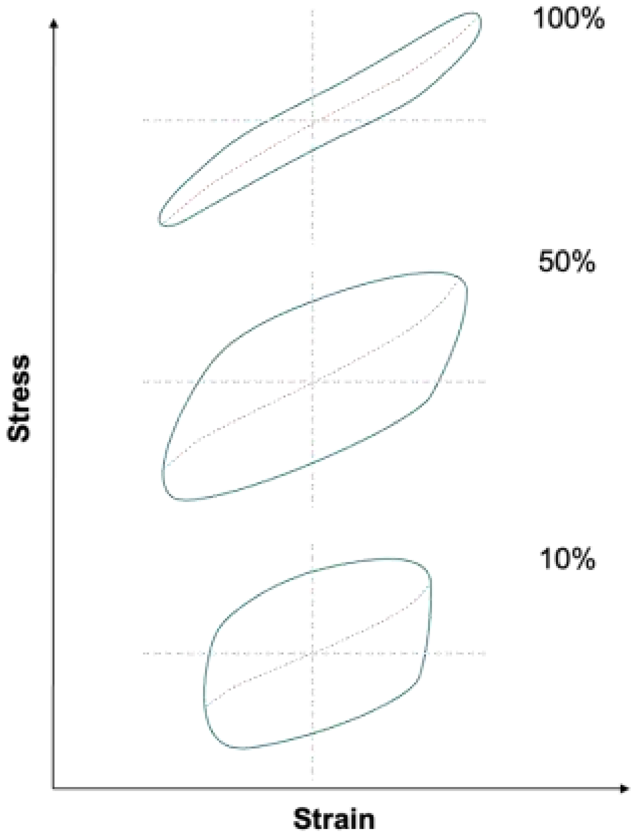


Figure 3 Lissajous curves for the viscoelastic model

**Zener Model**

Taking into account that all materials that are subjected to cyclic loads release energy, polymers are those materials that present a high dissipation rate. [75] Damping is defined as the conversion of mechanical energy into thermal energy. [76]

It is now clear that a simple configuration could make it easier to understand the dynamic behavior of objects, although not their real underlying complexity. In this sense, classical models such as Young's or Kelvin-Voigt, whose parallel configuration generates reliable results, are not adequate to represent the viscoelastic behavior of certain materials. The most basic configuration of the Zener model

comprises an elastic component and a dashpot in series, which in turn is in parallel with another elastic element. For greater accuracy of analysis, a larger number of elements can be added (composite Zener model), although this would also increase the complexity of the interpretative analysis.

The Zener model is also known as the relaxation oscillator, [77] due to the following viscoelastic properties:

- If the stress remains constant, the strain increases with time.
- If the strain remains constant, the stress decreases with time.
- The effective elasticity depends on the rate of load application.
- When cyclic loads are applied, there is dissipation of mechanical energy (hysteresis).

These properties are generally affected by temperature, frequency, dynamic deformation range, static preload, aging of the material, always depending on the damping mechanism, and it is mechanical relaxation that is the principle of damping. Fundamentally, both elasticity and loss factor are highly dependent on frequency. Since it is a complex elasticity because of two elastic elements in parallel, and because the elastic element (Nk) and the dashpot(c) are in series, mathematically it is described:

$$k_{eff} = \frac{k + \mathrm{j}k\ (\mathrm{N}+1)\left(\frac{\omega c}{Nk}\right)}{1 + \mathrm{j}\ \left(\frac{\omega c}{Nk}\right)}$$

While the dynamic elasticity is given by:

$$k_d = \frac{k + k\ (\mathrm{N}+1)\left(\frac{\omega c}{Nk}\right)^2}{1 + \mathrm{j}\ \left(\frac{\omega c}{Nk}\right)^2}$$

And its loss factor would be:

$$\eta = \frac{\omega c}{k + k\ (N+1)\ \left(\frac{\omega c}{Nk}\right)^2}$$

At low frequencies, the Zener model is reduced to a system explained only by the elastic element.

However, under the logic of the Zener model and from the perspective of the relationship between the mass force, the spring force and the dashpot force (MKC model), it can be represented as follows:

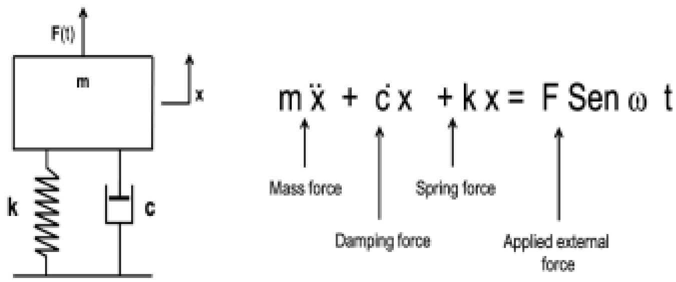


Figure 4: Zener model: representation of the component forces

This model assumes that the springs are linear and metallic (Hooke's Law), that the dashpot is linear and that it is conditioned to an initial stimulus. Then, when the mass (m) is subjected to a force (stress) that generates a certain displacement (strain), its equilibrium point is affected.

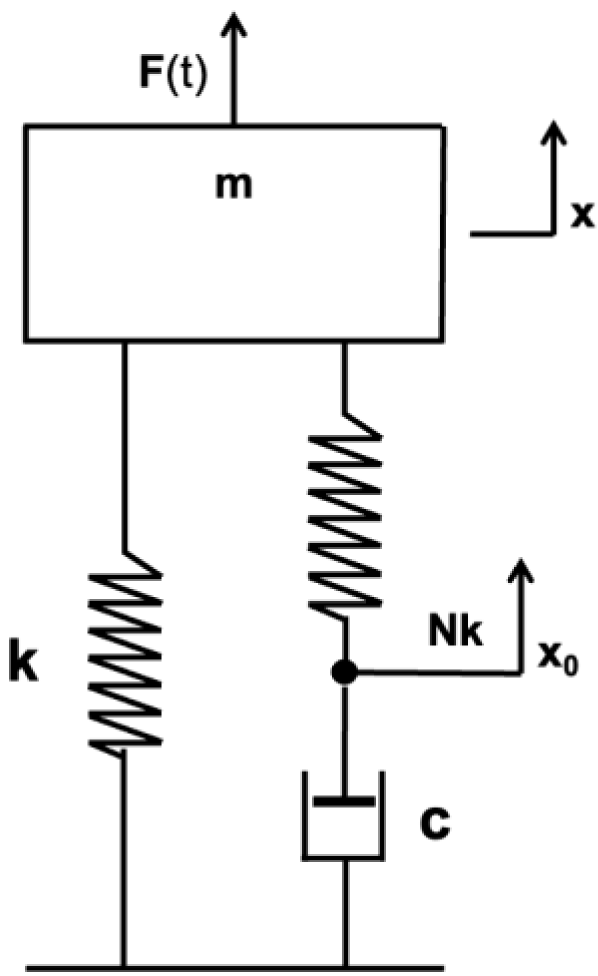


Figure 5: Strain displacement according to the Zener model

This has been described by means of algebraically modified equations:

$$m\ddot{x} + \frac{Nkm}{c}\,\ddot{x} + k\,(N+1)\dot{x} + \frac{Nk^2}{c}\,x = 0$$

So, the standard Zener model is nothing more than the Maxwell model with an additional spring in parallel.

The Maxwell model does not describe the deformation or the post-event (deformation) recovery capability. On the other hand, the Kelvin-Voigt model does not describe the relaxation stress, while the Zener model is able to predict both phenomena and provides information on the behavior at high frequencies.

However, when using representative fractional models, the dynamic parameters of most viscoelastic materials are adequately represented, and their plausibility will be a function of temperature, frequency and amplitude of the vibrating force (stress). This is why the correct identification of the rheological properties of a given viscoelastic material takes on a superlative value when trying to optimize the measurability of such behavior. [78] Therefore, the main advantage of using fractional models is based on the use of a relatively small number of parameters that can accurately describe the dynamic behavior of the dashpot component at different temperatures and frequencies, facilitating its applicability at the experimental level. As already mentioned, the storage and loss modules have the same functions in the appropriate frequency ranges, but for different temperatures. Therefore, the function determined at temperature T, after modifying the frequency range as the shift factor, will be valid for the reference temperature T0. This can be represented by the master curves, shifting the data obtained at different temperatures along the logarithmic scale of frequencies. [79] In most cases, such displacement is not only horizontal but also vertical. In this way, rheological parameter functions (master curve) can be obtained over a wide range of frequencies, although they are difficult or even impossible to obtain at the experimental level. However, the Williams-Landel-Ferry (WLF) formula [79] is the most popular method for determining the horizontal displacement factor, whose calculation is based on the method of least squares. [80]

### Hysteresis loop

To achieve this representation, a sinusoidal stress σ (t) is applied to the viscoelastic material and the strain ε (t) is measured. For any viscoelastic material, the response is a function that will depends on the excitation frequency λ, and it that the response is delayed relative to the excitation pulse by the phase angle δ:

$$\varepsilon(t) = \varepsilon_0 \,\mathrm{sen}(\lambda t) \qquad \text{(a)}$$

$$\sigma(t) = \sigma_0 \,\mathrm{sen}(\lambda t + \delta)$$

where $\varepsilon_0$ and $\sigma_0$ are the strain and stress amplitudes, respectively. The stress formula, after some transformation, [81] can be expressed as:

$$\sigma(t) = \varepsilon_0 [E'(\lambda)\ \mathrm{sen}(\lambda t) + E''(\lambda)\cos(\lambda t)] \qquad \text{(b)}$$

where $E'(\lambda) = \sigma_0/\varepsilon_0 \cos(\delta)$ corresponds to the storage modulus, $E''(\lambda) = \sigma_0/\varepsilon_0\ \mathrm{sen}(\delta)$ is the modulus loss, and the radius between them is called the loss factor:

$$\eta = E''/E' = \tan(\delta) \qquad \text{(c)}$$

After determining the functions of $\mathrm{sen}(\lambda t)$ and $\cos(\lambda t)$ respectively from equations (a) and (b), and using the relation: $\mathrm{sen}^2(\lambda t) + \cos^2(\lambda t) = 1$, the loop function is obtained:

$$\left(\frac{\sigma(t) - E'(\lambda)\varepsilon(t)}{E''(\lambda)\varepsilon_0}\right)^2 + \left(\frac{\varepsilon(t)}{\varepsilon_0}\right)^2 = 1 \qquad \text{(d)}$$

From equation (d), the relationship between stress and strain is obtained and plotted by the following loop:

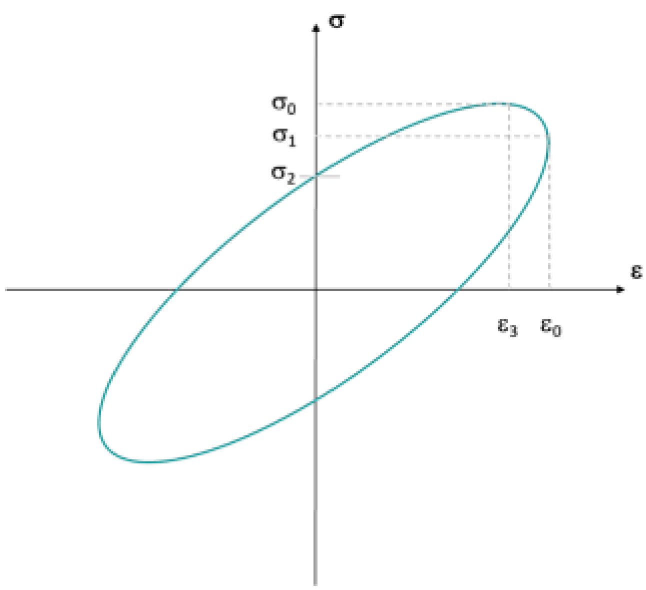


Figure 6: Stress-strain curve: example of hysteresis loop for viscoelastic materials

$\sigma_2$ denotes the stress value, which corresponds to zero strain.

The physical equation of the Zener model for viscoelastic materials can be represented as: [82]

$$\sigma(t) + \tau\sigma(t) = E_0\,\varepsilon(t) + \tau E_\infty \varepsilon(t) \qquad \text{(e)}$$

Where, $E_0$ is considered as the relaxation of the rigid modulus, $E_\infty = E_0 + E_1$ as the non-relaxed rigid modulus, and $\tau = c_1 / E_1$ is the relaxation time of the material.

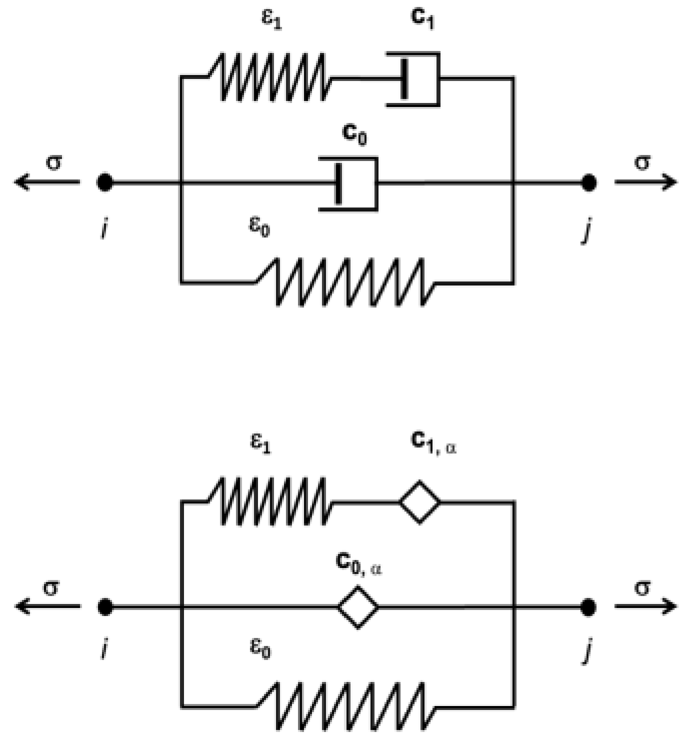


Figure 7: Complexed model for viscoelastic materials: (a) classical, (b) fractional

**Influence of temperature**

The integration of temperature and its influence on the dynamic behavior of viscoelastic materials is based on the principle of temperature-frequency superposition. [83] For a thermoreological material, the complex value of a modulus ($E^*$) is determined by the selected frequency ($\lambda$) and temperature (T) and is equal to the value of the modulus for a suitable frequency at a reference temperature ($\lambda_0$, $T_0$). This frequency value at the reference temperature can be obtained by using the displacement factor $\alpha_T$ (i.e., $\lambda 0 = \alpha_T \lambda$ ):

$$E^*(\lambda, T) = E^*(\lambda_0, T_0) = E^*(\alpha_T, \lambda, T_0) \qquad \text{(f)}$$

The shift in the frequency domain of the data obtained for different temperatures makes it possible to create a functional relationship for a complex modulus (master curve) for a wide range of frequencies. The horizontal displacement factor □T is usually determined empirically. This fractional Zener model has been experimentally tested showing effective descriptions of the viscoelastic behavior of materials over a wide range of frequency ranges and at controlled temperatures. [84]

**Clinical plausibility**

A major advance in this context, is the application of intravascular viscoelastic prostheses (aorta, carotid artery) [85] that could absorb pulsatile energy and smooth the arterial impulse, [86] preventing brain damage. [87] When the tubing material is elastic, the effect of friction is negligible. In this context, many viscoelastic materials have been used for this purpose, in which different explanatory models have been applied. The Kelvin-Voigt or Maxwell models are not able to represent the viscoelastic behavior of materials exhibiting permanent deformation, whereas the Zener model can predict the repetitive viscoelastic behavior [88] of the materials used and fit the mechanical properties of vascular prostheses, [89] studied according to their wave attenuation. Other non-linear and non-isotropic models are not suitable for medical use.

When applying the model as a function of space, an important conclusion from the authors ‘work is that in the Zener model, the time constant is only valid for the steepest part of the pulse. Because the Maxwell model did not adequately fit the requirements, the authors adjusted the cyclic stress-strain relation and the cyclic stress-time relationship. They concluded that for the silicone prosthesis, this model showed significant energy absorption [87] and thus demonstrated that it can be used as a predictor of pulse attenuation in medical materials. Despite the model´s promise, experimental studies have not considered viscous interaction with blood or the stress generated at bifurcations or curvatures. The characterization of fractional viscoelastic models is based on classical models to which a spring-pot (fractional element) is added, and whose derivative is of non-integer order and is therefore lies between 0 and 1. [90]

Soft tissues exhibit a very interesting elastic characteristic which consists in the ability to store energy when subjected to low load stress, but at the same time can return all this energy when the load has ceased. A viscous fluid continuously dissipates mechanical energy in the form of heat. However, viscoelastic fluids are able to store and dissipate mechanical energy simultaneously when subjected to stress. That is, mechanical stress is related to deformation, but its rate of change in terms of temporality is also involved. The application of mathematically modeled fractional derivatives [91] by means of viscoelastic models are currently the explanatory boom in the characterization of mechanical effects in different tissues. [92] The determination of the fractional order is performed by means of an algorithm based on the Levenberg-Marquardt numerical method for curve fitting by least squares in nonlinear models, approximating the relaxation function to the stress. [93] Then, the Zener model can determine the nonlinear deformation in relation to the applied stress (viscous fluid behavior), while at the cessation of the applied stress it is able to determine the viscoelastic behavior that tends to relaxation. Palomares et al [94] used the Zener model to analyze the response of the system to pulse variations at the arterial level, even when the flow change is associated with the use of invasive mechanical ventilation. The authors conclude that the fractional derivative that best fits the model resembles the work of Magin [92] and Nagehan [95] on soft tissues, highlighting the great adaptability of the Zener model to explain this viscoelastic behavior. Lung parenchyma is highly viscoelastic, and many pathologies such as ARDS or asthma significantly modify this characteristic. [96]

**Anti-Zener model: a new proposal**

The viscoelastic properties of lung tissue were first described in 1939, [97] while hysteresis related to lung relaxation stress was described in 1961. [98] Nowadays, sophisticated studies have used fractional viscoelasticity to model the mechanical behavior of lung tissue, raising hypotheses with a molecular basis. [99] The mechanical analogy of springs and dashpots used to represent viscoelastic properties has been reduced to the use of estimates based on least-squares computational fits and in other cases to temporal spectral response models. The latter has traditionally been represented by Young's modulus for prediction. However, as already mentioned, this classical explanatory model exhibits limitations mainly linked to its inability to predict dynamic behavior on multiple time scales, mainly in biological tissues. One way to overcome this limitation of Young's module is to make use of more complex and multiparametric models. Recently, some models based on fractional designs of the derivative order have been successfully applied to measure viscoelastic behavior in biological tissues. [100],[101] In these models, both temporal relaxation and frequency response are the main rheological characteristics associated with the viscoelastic properties of the tissues. Dai et al [102] in an experimental study using ex vivo pig lungs (applying a transpulmonary pressure of 20 $cmH_2O$), argue that the relaxation stress is finite and would asymptotically reach a non-zero stationary value, [99,103] so those models with stress equal to 0 (t=0) or those with zero stress for long periods of time should always be excluded. An interesting finding of this study (LD320-5 sensor, Omega Engineering, Stamford, CT; Labview) is that when considering Voigt's model, they observed a stress t=0, and when considering Maxwell's model, they observed a stress that exponentially trended to 0. However, when they analyzed the tissues with the Zener and anti-Zener models(104), they noticed that by incorporating a spring (a three-parameter integral order model), they managed to prevent the stress coming from the tendency to zero. They finally concluded that, regarding the intrinsic power related to the rate of decrease in the relaxation process of biological tissues, the range corresponding of relaxation stress on a macroscopic scale might not depend on Young's modulus.

With the above, it is likely that the Zener model, or better yet the anti-Zener model, is the one that best correlates dynamically with the viscoelastic properties of lung tissue. The system of deformation per unit stress, called J (compliance), is given by the following equation: [105]

$$J(t) = \underbrace{\frac{1}{G_0}}_{\text{Elastic}} + \underbrace{\frac{1}{G_1}\left[1 - \exp\left(\frac{-tG_1}{\eta_1}\right)\right]}_{\text{Viscoelastic behavior}} + \underbrace{\frac{t}{\eta_0}}_{\text{Viscous flow}}$$

where J(t) is the compliance of the whole system at any time during the deformation phase (t), G0 is the unit elastic component corresponding to the Maxwell model, G1 corresponds to the Kelvin-Voigt model which contributes to the delayed elastic zones that make up the total compliance, η0 is the damping element of the Maxwell model, representing the residual viscosity, and η1 corresponds to the damping component related of the Kelvin-Voigt model, which represents the internal viscosity.

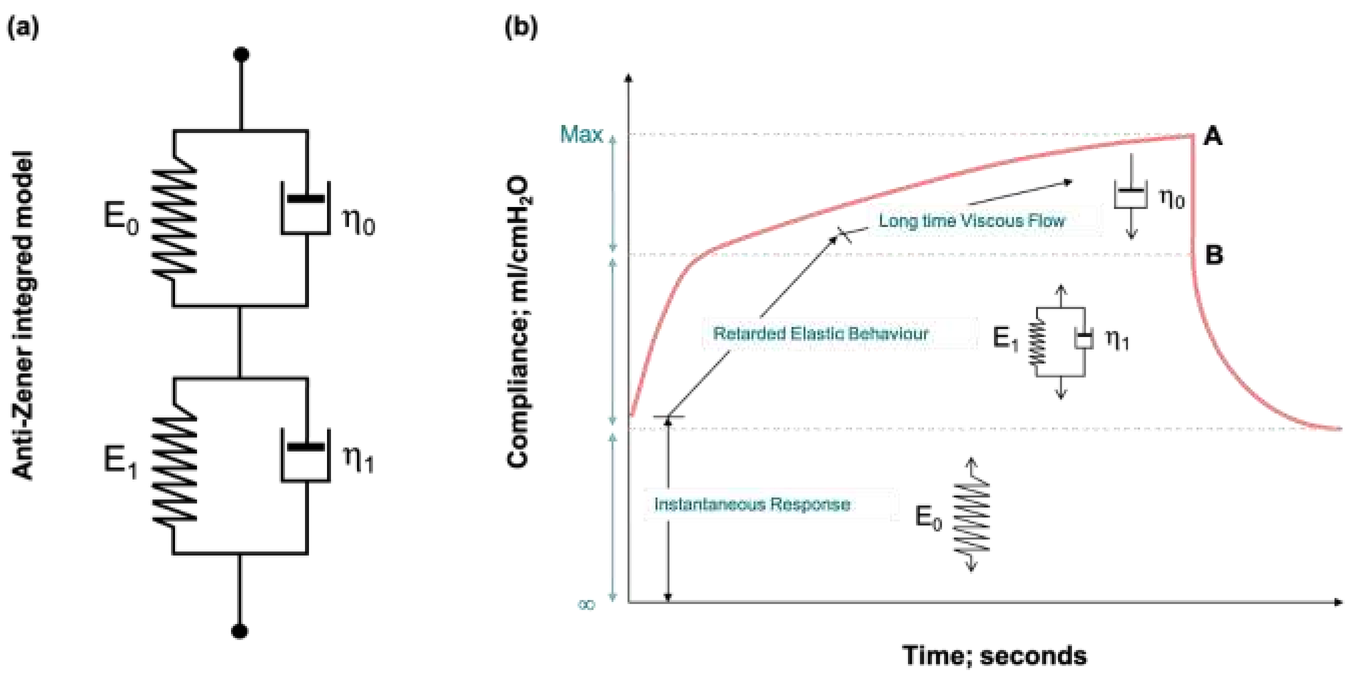


Figure 8: Proposed model to obtain a better understanding of lung viscoelastic behavior. (a) Anti-Zener model, and (b) compliance [J] versus time in a creep and recovery test.

In the classical theory of elasticity, according to Hooke's Law, the deformation achieved is directly proportional to the applied stress. On the other hand, according to hydrodynamic theory and according to Newton's Law, the applied stress is directly proportional to the strain rate but independent of the deformation itself.

In this case, the elastic modulus is associated with the energy stored in the material, while the viscous modulus is associated with the energy dissipated by the material. Furthermore, many elastic solids break the linear relationship determined by Hooke's Law beyond a certain strain value. The same concept applies to viscous fluids, which also break the linear relationship defined by Newton's Law beyond a certain value of strain rate. However, for viscoelastic materials, the behavior is similar. For very low strains or strains close to equilibrium, there is a linear stress-strain relationship (linear viscoelasticity). If these deformations increase, the relationship is no longer linear, and a state of non-linear viscoelasticity is reached. A relevant parameter used in rheology to classify materials according to their viscous,

elastic or viscoelastic behavior is the Deborah number, defined as the fraction between τ (characteristic relaxation time for a given material) and t (characteristic time of the deformation process to which a given material is subjected). Thus, the relaxation time is infinite for a Hookean solid, while the relaxation time is zero for a Newtonian fluid.
To explore linear viscoelasticity, it is necessary to define its characteristics:

1. Stress relaxation: applying a strain rate in simple shear to a given material, maintaining that strain and exploring its variability with respect to time.

2. Creep: maintain the stress constant and evaluate the variation of the deformation in relation to time. From this characteristic, the compliance or resilience function (J) is obtained.

Then:

$$J(t) = \frac{\gamma(t)}{\sigma}$$

However, purely viscous fluids express:

$$J(t) ) t/\eta$$

where η represents the viscosity.

In any case, viscoelastic materials exhibit a quadratic behavior at short times, and linear behavior at longer times.

3. Elastic recovery: apply a constant stress, analyze the deformation produced and then remove the stress to analyze the recovery as a function of time. In viscoelastic materials the recovery is partial.

4. Dynamic or oscillatory experiments: characterize the viscoelastic properties of materials. The applied strain varies sinusoidally with time, whereas the constant stress varies at the same frequency but is out of phase with the strain.

Thus, the storage modulus will be expressed by the quotient between the stress to generate the deformation and the deformation itself. On the other hand, the loss modulus is the ratio of the stress that is out of phase (π/2) with the deformation to the deformation itself.

So, the lag between the stress and the strain:

$$\text{tg}\ \delta = \frac{G''}{G'}$$

Which represents the ratio of dissipated to stored energy. For a viscoelastic material, δ will have values between 0 and 90°. Then:

$$\frac{\gamma *}{\sigma *} = G * = G' + iG''$$

Where G* is the dynamic modulus, which is the vector obtained from the sum of the elastic (G') and viscous (G") moduli.

The relaxation modulus E(t) is a characteristic of viscoelastic materials and is used to describe the relaxation stress of materials as a function of time (t). Thermal transitions of viscoelastic materials can be described in terms of free volume changes or relaxation time. [106] The Rouse model simulates the diffusion of a single polymer chain by Brownian motion in a system composed of beads and harmonic springs based on molecular dynamics theory, [107] while the Kremer-Grest model uses hundreds of chains and beads. [108] Likewise, the well-known tube model defines entangled polymer chains confined in tubes with permanent topological interactions and move along the tubes. [109] The tensile relaxation of the chain is calculated as the fraction of the tube that has not been emptied, where the relaxation time is related to the molecular mass of the cube. [110] The arm retraction model [111] describes entangled monomers as retracted by arms and was validated for the rheology of entangled polymer liquids.

For viscoelastic materials, the effect of temperature can be converted to relaxation time by the temperature-time superposition rule. Since the temperature and strain rate are constant over a short loading time period, it may be reasonable to consider Poisson's ratio as constant to simplify the numerical application. [112]

## Final message

The vortex in the evolution of current evidence forces to broaden the traditional horizons for a greater and better understanding of the pathophysiological concepts associated with the different processes of the respiratory system. The application of the exact sciences in the basis of the viscoelastic behavior of lung tissue allows optimizing the therapeutic approach to the different respiratory pathologies. The classical Young's modulus exhibits limitations linked to the inability to predict dynamic behavior on multiple time scales in biological tissues. One way to overcome this limitation is through more complex, multiparametric models. Therefore, the Anti Zener model could provide a more structured, realistic and accurate framework for describing the energy transfer process.

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