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Modeling the lung: Fractional viscoelastic models – Part 3

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Abstract

Lung viscoelasticity is governed by the intricate interplay of alveolar-interstitial architecture, including the elastin-collagen network, alveolar microgeometry, and surfactant dynamics. Traditional integer-order mechanical models have provided foundational frameworks for describing lung tissue mechanics but are limited by their inability to capture the empirically observed power-law responses and the broad distribution of relaxation times inherent to heterogeneous biological tissues, particularly in pathological states like acute respiratory distress syndrome (ARDS). Fractional viscoelastic models, grounded in fractional calculus, overcome these limitations by employing non-integer order derivatives and the spring-pot element, enabling a parsimonious and robust description of viscoelastic phenomena such as stress relaxation, creep, and hysteresis across wide temporal and spectral domains. These models encapsulate the memory effect and fractal architecture of lung parenchyma, offering a unified and physically interpretable parameterization of viscoelasticity. Composite fractional models demonstrate superior accuracy in fitting experimental data and predicting the dynamic response of the respiratory system. Their clinical application holds promise for optimizing protective ventilation strategies, individualizing PEEP titration, and reducing ventilator-induced lung injury (VILI) by enabling real-time assessment of tissue mechanics. The adoption of fractional viscoelastic models represents a paradigm shift in respiratory biomechanics, providing advanced tools for both research and clinical practice.

Keywords: fractional calculus, lung viscoelasticity, spring-pot, power-law, ARDS, respiratory mechanics.

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Introduction

Lung viscoelasticity arises from the complex interplay within the alveolar-interstitial architecture, encompassing the elastin-collagen network, alveolar microgeometry, and surfactant dynamics. In critical care settings, these intrinsic properties manifest as time- and frequency-dependent phenomena, including stress relaxation following inspiratory pauses, progressive deformation (creep) under sustained pressure, and hysteresis observed in pressure-volume loops. Accurate characterization and modeling of these behaviors are essential for advancing the interpretation of respiratory mechanics, optimizing protective ventilation strategies, and individualizing positive end-expiratory pressure (PEEP) in pathologies such as acute respiratory distress syndrome (ARDS). While classical integer-order mechanical models, such as Kelvin-Voigt, Maxwell, and Burgers, have provided foundational frameworks, the empirically observed power-law responses in lung tissue necessitate the adoption of fractional-order models and the spring-pot element. These advanced models offer a parsimonious and robust description of viscoelastic responses across broad temporal and spectral domains. [1]

Fractional models describe viscoelastic materials using non-integer order constitutive equations. In the lung, these models parsimoniously capture the empirical fact that stress relaxation and tissue impedance follow power (not exponential) laws across time and frequency scales, a key phenomenon in heterogeneous parenchyma. [2]

These models allow a more accurate representation of energy dissipation, often characterized by a damping factor, and the accumulation of elastic energy, expressed as elastance, which are frequency dependent. These models, for example, can describe how the coefficient α modulates the influence of fractional inductance on airway resistance in the frequency domain, and how the coefficient β influences the resistance and reactance of fractional compliance. [3]

Methods

A concise yet comprehensive literature review was conducted using online databases, employing search terms such as "rheology", "lung viscoelasticity", "fractional models", “fractional calculus” and “power law”. The authors critically selected the publications deemed most relevant to the subject matter.

Objectives

- To critically evaluate the limitations of classical integer-order mechanical models in capturing the complex viscoelastic behavior of lung tissue, particularly in pathological states such as ARDS.

- To introduce the theoretical framework of fractional calculus and its application to modeling lung viscoelasticity, highlighting the advantages of fractional-order models and the spring-pot element.

- To synthesize current evidence supporting the use of fractional viscoelastic models for accurately describing stress relaxation, creep, and hysteresis phenomena in the respiratory system.

- To discuss the clinical implications of advanced viscoelastic modeling for the interpretation of respiratory mechanics and the optimization of protective ventilation strategies, including individualized PEEP titration in ARDS.

Review

Integer order models represent the first systematic approach to mathematically describe the viscoelastic behavior of lung tissue, using combinations of ideal mechanical elements: springs (elastic behavior) and dashpots (viscous behavior). [4] The intrinsic limitations of integer-order models, which are constrained to representing only a discrete set of relaxation times, make them inadequate for accurately capturing the complex viscoelastic behavior of the heterogeneous lung in ARDS. Injured biological tissues exhibit a continuous and broad distribution of relaxation times, reflecting their multiscale and heterogeneous architecture. Fractional calculus (FC) provides a robust mathematical framework that overcomes these limitations by enabling the modeling of continuous relaxation spectra inherent to pathological lung tissue. [5]

Fractional models represent a paradigm shift in the mathematical description of lung viscoelasticity by incorporating fractional (non-integer) derivatives into the constitutive equations. This approach arises from FC, a branch of mathematics that generalizes the notion of differentiation and integration to arbitrary orders. [6] These models are able to capture more accurately the complex temporal and spectral response of biological materials, including lung tissue. [7]

This capacity arises from its ability to represent broad distributions of time scales, which is intrinsic to the hierarchical and heterogeneous nature of soft biomaterials. [8] Therefore, fractional models are more compact and require fewer parameters to characterize viscoelastic materials that exhibit power-law behavior. [7] This efficiency in parameterization arises from the ability of fractional

derivatives to model the loss modulus with a frequency dependence that follows a power-law relationship, in contrast to the linear frequency dependence characteristic of integer-order models. [9] This formulation enables a more precise characterization of complex phenomena such as stress relaxation and creep, without necessitating the use of numerous elements in series or parallel. As a result, it simplifies parameter identification and enhances the physical interpretability of the results. [7] Furthermore, the application of fractional order models has been shown to improve the understanding of various biomedical areas, from the properties of arterial walls to the mechanics of erythrocyte membranes and cerebral blood flow. [3]

Unlike integer derivatives, which are local operators that only consider information from their immediate surroundings, fractional operators are non-local, incorporating information about the past behavior of the function in a manner similar to integral equations. [10] This intrinsic characteristic of fractional operators allows for a more accurate modeling of the "memory effect" of viscoelastic materials, where the current response of the material depends on its entire deformation history, a fundamental property in biomaterials such as lung tissue. [11]

1. Concept of fractional calculus (FC)

FC is an extension of traditional mathematics that introduces differential and integral operators of arbitrary order (α), where α can be a non-integer value (fractional, $0 < \alpha < 1$). [5] This mathematical generalization is particularly relevant to lung biomechanics, where viscoelastic responses do not perfectly fit classical integer-order models due to the microstructural complexity of the tissue. [7]

A fractional derivative is distinguished from its classical counterpart by its non-local nature; rather than depending solely on the instantaneous behavior of a function, it integrates the entire historical trajectory of that function. This property, often described as “mathematical memory,” means that while the classical derivative (d/dt) captures only the immediate rate of change, the fractional derivative ($d\alpha/dt\alpha$) accumulates information from the entire past evolution of the system. [12]

The underlying physical rationale for employing fractional derivatives in biological systems lies in their capacity to model the intrinsic heterogeneity of complex media, such as biological tissues. Many biological structures, including the bronchial and vascular networks, exhibit fractal or self-similar characteristics. Lung injury disrupts homogeneity of the tissue’s multiscale architecture. Consequently, the fractional exponent (α) is not merely a mathematical fitting parameter but may serve as a quantitative descriptor of the deviation of the lung’s fractal geometric structure from an idealized state. [13]

2. The spring-pot element

In fractional viscoelastic modeling, the traditional concepts of the spring and dashpot are unified within the spring-pot element (also known as the Scott-Blair element) (Figure 1), a fractional-order rheological component that enables a continuous interpolation between ideal elastic (spring-like) and viscous (dashpot-like) behaviors. This element provides a versatile framework for capturing the complex, intermediate viscoelastic properties observed in biological tissues. [14]

The relationship between stress (σ) and strain (ϵ) is defined by a fractional derivative of order α. This fractional order α is the key parameter in the constitutive equation of the fractional viscoelasticity model, specifically the spring-pot. [6]

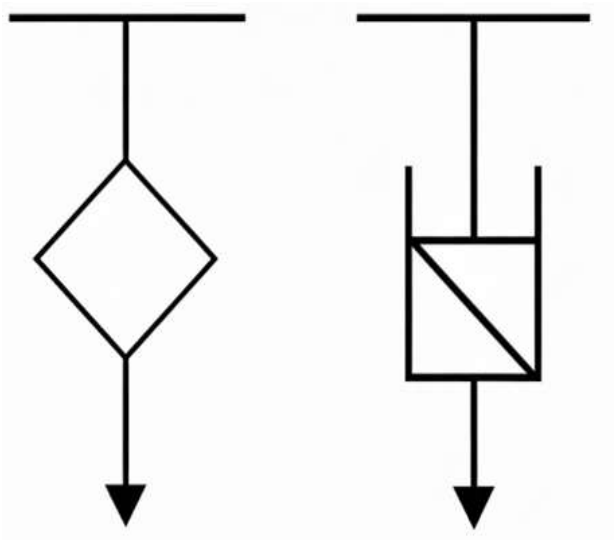

Figure 1: Representations of the spring-pot element (α).

This intermediate element is key to representing anomalous viscoelastic behavior. [5]

- If the differential order $\alpha = 0$, the spring-pot degenerates into a pure spring (Hooke's elasticity).
- If $\alpha = 1$, it degenerates into a pure dashpot (Newtonian viscosity).
- If $0 < \alpha < 1$, the element behaves as a genuine viscoelastic material, where energy storage and dissipation occur simultaneously. It exhibits power-law behavior. [6]

In ARDS, intermediate values $0 < \alpha < 1$ are typically observed, reflecting the presence of abnormal viscoelastic properties in lung tissue. [15]

This element is ideal for modeling the extracellular matrix of the lung, as it represents the continuous transition between the elastic stiffness of the fibers and the viscosity of the parenchymal tissue, allowing the capture of the organ's complex dynamics. [5] In the real lung, α typically ranges between 0.1 and 0.5, indicating a predominantly elastic behavior with a viscous component. [6]

The FC model allows the description of anomalous viscoelasticity with a single parameter (α) of the spring-pot element, unifying elastic stiffness and viscous dissipation. This parameter (α) becomes a direct metric of the system's deviation from an ideal solid or fluid, and therefore a potential indicator of the underlying heterogeneity of lung tissue, which is impossible to capture with integer-order models. [16]

3. Multiple relaxation phenomena and distribution of relaxation times (DRT).

The interplay among these concepts constitutes the fundamental rationale for transitioning from integer-order models to the adoption of FC, which offers superior accuracy and descriptive power in the modeling of biological tissues. [5]

In materials science, stress relaxation is the gradual decrease in internal stress that occurs when a material is subjected to constant strain over a prolonged period. This stress decrease reflects the dissipation of energy by the viscous component of the material. [17]

When an inspiratory pause is performed (constant volume), the alveolar plateau pressure drops. This initial, rapid drop is attributed to pressure redistribution in the airway and ventilator circuit, but the slower, sustained drop reflects the intrinsic relaxation of lung tissue (parenchyma and connective tissue) and the recruitment of slow alveolar units. [18]

The DRT is not a discrete set of values, but rather a continuous function that characterizes the probability or magnitude of all possible relaxation times (τ) contributing to the macroscopic viscoelastic response of biological tissue. [17]

A healthy lung has a narrow and rapid relaxation time (RRT). A lung with ARDS has a wide and extended RRT, reflecting the coexistence of healthy alveolar units (rapid relaxation), edematous or fibrous units (very slow relaxation), and the interface between them (sources of shear stress). [18]

While advanced integer-order models, such as the Generalized Maxwell, can only handle discrete multiple relaxation phenomena, ARDS requires a model that captures the continuous DRT, a role that only FC can fulfill with rheological accuracy. [18]

4. Power law

The lung parenchyma and bronchial tree possess a fractal structure. This means they exhibit self-similarity across multiple hierarchical levels and scales (from the main bronchus to the alveoli). [19] This complex hierarchical architecture implies that tissue deformation does not occur on a single timescale, but rather involves a wide and continuous distribution of mechanical relaxation timescales. [6,8]

Traditional whole-order viscoelastic models (composed of simple springs and dashpots) only predict exponential stress relaxation (governed by one- or a few-time constants τ). However, measurements of stress relaxation in the lung demonstrate that the pattern is not exponential but rather follows a power-law function. [6]

The power law mathematically describes this complex dynamic. It postulates that stress in the tissue decays over time (t) according to a power function, rather than an exponential function. The relationship is typically expressed as:
$(\text{Stress} \propto t^{-\beta})$. Where:
- Stress(t) (or transpulmonary pressure) is the tension in the relaxing tissue over time.
- t is the time elapsed since the cessation of flow.
- β (the power law exponent) is a key parameter, typically with values between 0 and 1.

Experimental measurements in pig lungs show that stress relaxation is not exponential. An exponential decay predicts that the tissue is "forgotten" quickly; a power law indicates that it has "long-range memory". [6]

The power law exponent β is the parameter that describes the stress relaxation response or impedance dependence that is observed or experimentally measured in lung tissue. In many of the fractional viscoelasticity (time domain) models used to describe the lung stress relaxation response, there is an equivalence or direct relationship between the order of the fractional operator α and the power law exponent β. [8] Fractional derivatives naturally generate power law behavior. [12]

5. Fractional models of respiratory mechanics

Modeling based on fractional calculus (FC) enables the development of hybrid models that have demonstrated superior accuracy in fitting experimental data on ventilatory mechanics across various modes, compared to traditional integer-order linear models. [13]

The conceptual failure of integer-order models (including the Generalized Maxwell model) lies in their need to postulate discrete relaxation times. In contrast, the lung in ARDS, given its zonal complexity (collapse, edema, aerated zones), exhibits a broad and continuous DRT, as we explain previously. Fractional models solve this problem by not requiring multiple discrete combinations of springs and dashpots. Instead, the fractional exponent (α) encapsulates the heterogeneity and multiscale complexity of damaged lung tissue. This means that α provides a unified metric that describes the dynamic response of the lung as a whole. [13]

Fractional differentiation offers a powerful tool for describing systems with heritable properties and a posteriori effects, which is crucial for understanding the dynamics of biological phenomena and diseases. [20]

The capacity of fractional models for the characterization of human tissues suggests that, if α can be estimated dynamically and in real time during ventilation, it could become a rheological biomarker of the severity of diffuse alveolar damage observed in ARDS and, potentially, a predictor of the alveolar recruitment response. [13]

A. Basic two-element fractional viscoelastic models

The introduction of the spring-pot allows the construction of fractional extensions of the basic classical models, overcoming their main rheological deficiencies.

a. Fractional Maxwell model (FMM).

It is obtained by replacing the Newtonian dashpot of the classical model with a fractional-order spring-pot, maintaining the configuration in series with the elastic spring [14] (Figure 2).

The classical Maxwell model fails because it predicts that, at constant stress, viscous strain grows indefinitely in a linear fashion. By using a spring-pot (with order $\alpha < 1$), the FMM inherently introduces the concept of viscosity memory or intermediate viscosity. The material no longer exhibits purely Newtonian flow in the long term, and the creep rate is gradually damped, providing greater versatility in simulating the behavior of complex materials. This allows the model to capture the behavior of weak viscoelastic solids, which classical models, better suited to viscoelastic liquids, are unable to represent adequately. [14]

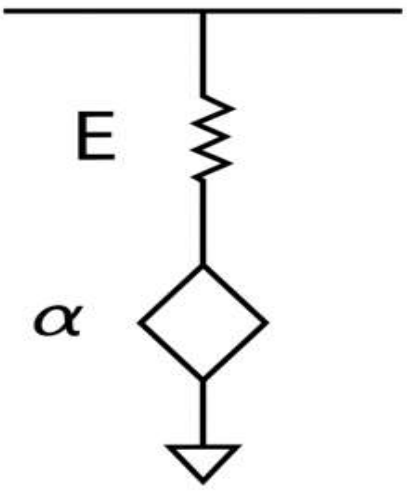

Figure 2: Fractional Maxwell model. A spring (E) and a spring-pot (α) in series.

b. Fractional Kelvin-Voigt model (FKVM)

It is constructed in an analogous manner, replacing the classic dashpot with a spring-pot and keeping the spring and fractional element in parallel [14] (Figure 3).

This model retains the strength of its classical counterpart in modeling delayed creep, but with superior accuracy. It thoroughly describes the exponential increase of strain over time and the corresponding diminishing exponential recovery, providing a more accurate representation of the material's actual behavior. However, the FKVM inherits the main structural limitation of the parallel configuration: it does not predict instantaneous elastic deformation when stress is applied, nor stress relaxation. [14]

The series configuration (Maxwell) is necessary to guarantee a non-zero initial strain, while the parallel configuration (Kelvin-Voigt) is necessary to guarantee a finite strain limit. This need drives the creation of more advanced composite models.

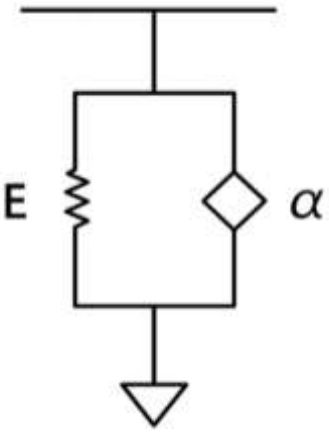

Figure 3: Fractional Kelvin-Voigt model. A spring (E) and a spring-pot (α) in parallel.

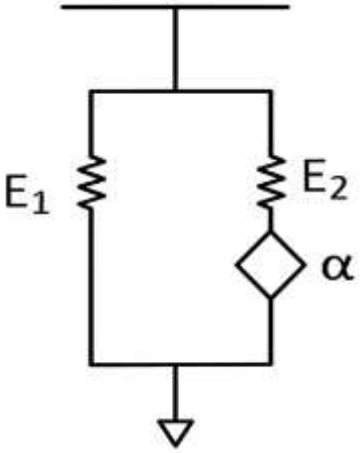

Figure 4b: FSLS. Maxwell representation.

B. Composite fractional models

To overcome the limitations of two-element models and provide a complete description of viscoelastic dynamics, the combination of basic fractional models is required, resulting in high-fidelity configurations that fit power-law phenomena.

a. Fractional Zener model or fractional standard linear solid (FSLS) model

It is the simplest composite model that integrates immediate, delayed, and equilibrium responses. In its fractional formulation, it generally consists of an ideal spring in series with a FKVM, or a spring in parallel with a FMM (Figure 4a and 4b). The classic Zener model uses a 3-element arrangement. [21]

The key analytical advantage of FSLS is its ability to capture all three phases of the viscoelastic response in stress relaxation, including the instantaneous elastic response and the delayed relaxation that leads to a long-term equilibrium value. [21]

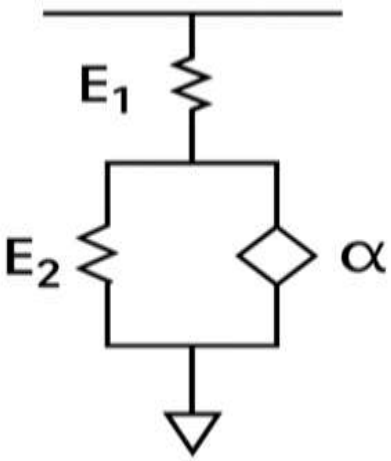

Figure 4a: FSLS. Kelvin representation.

b. Fractional Burger model (FBM)

It is the most advanced extension in the context of classical four-element rheological models. This configuration is achieved by placing a FMM in series with a FKVM. [22]

The FBM serves as the de facto standard for describing complete creep behavior, encompassing both primary creep (delayed deformation, associated with the fractional Kelvin-Voigt model component) and secondary creep (prolonged or terminal flow, associated with the fractional Maxwell model component). Additionally, it characterizes the full recovery cycle, including instantaneous elastic recovery upon load removal, followed by delayed viscous recovery over time. [22]

The exceptional fidelity of these composite models is attributable to the inherent capacity of fractional computation to introduce power-law responses into the transient dynamics of materials. Whereas integer-order models can only approximate the relaxation spectrum by superimposing multiple discrete exponential components, fractional models enable the simulation of a continuous relaxation spectrum. This power-law fitting is essential for accurately representing the behavior of polymers and biological tissues, including the impedance of the respiratory system, which exhibits pronounced power-law characteristics. The fractional Burger model (FBM) facilitates the superposition of these dynamics, establishing it as a superior tool for viscoelastic modeling. [23]

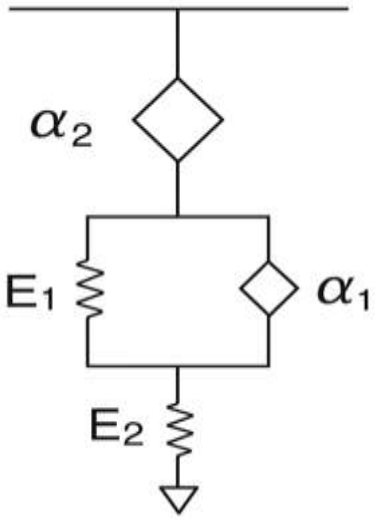

Figure 5: Fractional Burger model.

c. Fractional anti-Zener model

It is one of the most promising models for accurately describing the viscoelastic behavior of lung tissue, overcoming certain structural limitations of the Maxwell and the Kelvin-Voigt models. [24]

This model consists of a Scott-Blair dashpot, connected in parallel with a fractional Maxwell model [25] (Figure 6). This "fractionalization" allows it to describe relaxation with even greater precision, using the parameter α to fine-tune the rate and manner in which this residual stress relaxation occurs. [24]

The FSLS describes primarily elastic tissues with viscosity. However, there is a different pathophysiological scenario: the deeply damaged lung (ARDS), where viscous fluence dominates over elasticity; in this case, the anti-Zener model is more useful. [26]

This model is particularly important because:

- It produces linear creep (constant progressive deformation under stress) like fluids.
- It maintains a fractional elastic component.
- It is particularly advantageous for modeling the pathological progression of ARDS, wherein the lung parenchyma exhibits a gradual yielding behavior, reflecting the complex viscoelastic alterations characteristic of this condition. [26]

Ventilator-induced lung injury (VILI) operates through biomechanical mechanisms: volutrauma (overdistension), atelectrauma (repetitive opening and closing of the ventilator), and ergotrauma (inefficient energy dissipation). The fractional anti-Zener model allows for the quantification of energy dissipated at the tissue level during each respiratory cycle. [27]

This model represents a significant step toward realistic modeling of pulmonary viscoelastic behavior. Its ability to predict power-law stress relaxation, incorporate multiscale memory effects, and maintain thermodynamic compliance positions it as a superior tool for:

- Optimizing personalized ventilator parameters, reducing VILI.
- Early diagnosis of pulmonary pathology (ARDS, fibrosis, asthma) through changes in α.
- Designing adaptive ventilatory modalities that respect individual viscoelasticity.
- Molecular understanding of mechanotransduction: the model's mechanics accurately predict how mechanical forces are transformed into cellular signaling. [24,27]

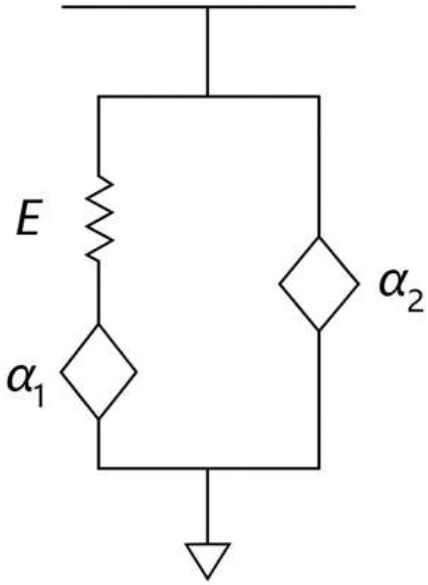

Figure 6: Fractional anti Zener mode

Table 1: Comparative summary of fractional viscoelastic models for lung tissue mechanics.

Model name	Configuration	Key features	Advantages	Limitations	Typical applications
Fractional Maxwell Model	Spring and spring-pot (fractional dashpot) in series	Captures power-law stress relaxation; fractional order α between 0 and 1	Accurate for long-term viscoelastic behavior; fewer parameters	Complex parameter estimation; limited physical interpretation	Modeling lung tissue viscoelasticity; polymer rheology
Fractional Kelvin-Voigt Model	Spring and spring-pot in parallel	Describes delayed creep; fractional order enhances flexibility	Good for short-term creep; simple structure	Less accurate for stress relaxation; parameter coupling	Soft tissue mechanics; damping analysis
Fractional Zener Model	Combination of spring, spring-pot, and dashpot (series/parallel)	Captures both creep and relaxation; intermediate complexity	Versatile; fits wide range of viscoelastic responses	Higher computational cost; parameter identifiability issues	Biomechanics; composite material modeling
Fractional Burger Model	Fractional Maxwell in series with Fractional Kelvin-Voigt	Describes complete creep and recovery cycles; power-law fitting	Superior fidelity for biological tissues; continuous relaxation spectrum	Most complex; requires advanced parameter estimation	Full viscoelastic characterization; respiratory system
Fractional Anti-Zener Model	Scott-Blair dashpot in parallel with Fractional Maxwell	Models linear creep and fractional elasticity; ideal for pathological lungs	Quantifies energy dissipation; predicts power-law relaxation; memory effect	Advanced; best for severe pathology; less used in healthy tissue	ARDS, fibrosis, asthma; ventilator-induced injury

Conclusions

Fractional viscoelastic models represent a significant advancement in the mathematical characterization of lung tissue mechanics. By leveraging the principles of fractional calculus, these models overcome the intrinsic limitations of classical integer-order frameworks, providing a more accurate and parsimonious description of the complex, power-law behaviors observed in healthy and pathological lungs. The introduction of the spring-pot element enables a continuous interpolation between elastic and viscous responses, capturing the broad distribution of relaxation times inherent to heterogeneous biological tissues such as those affected by ARDS.

The capacity of fractional models to encapsulate the memory effect and fractal architecture of lung parenchyma allows for a unified and physically interpretable parameterization of viscoelasticity. This not only enhances the fidelity of stress relaxation, creep, and hysteresis modeling but also facilitates the identification of rheological biomarkers, such as the fractional exponent α, which may serve as indicators of disease severity and tissue heterogeneity.

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