Constitutive Equation of Lung Tissue Elasticity

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A constitutive equation for the lung tissue elasticity is formulated under the hypotheses of a simplified alveolar geometry and a pseudo-strain-energy function for the interalveolar septa. The resulting equation contains four material constants. The theoretical result has been tested against published data on uniaxial and triaxial loadings, and is tested critically here with respect to new experimental results on biaxial loading. Comparison between theory and experiments shows that a general agreement is obtained in an approximate sense. The model fits our biaxial experimental data with most correlation coefficients above 0.995. Some details not predicted by the theory are discussed. Since the theory is derived for triaxial loading and the biaxial test is a severe one, the formula should be applicable to the triaxial case at least to the same degree of approximation. The form of the theoretical formula is convenient to use in analytic studies of lung mechanics. Additional key words: mechanical behavior of the lung; stress-strain relationship; strain energy; alveolus model; distortion; interdependence; pressure volume curves.

Introduction

The blood flow and ventilation in the lung is influenced by the stress and strain in the lung. In view of the very complex structure of the lung, a great simplification can be obtained if we consider the *macroscopic* stress and strain, defined on volumes much larger than the individual alveolus, separately from the *microscopic* details of stress and strain in the alveoli. For human lung the macroscopic results apply only for volumes where the linear dimensions are several millimeters or larger. The macroscopic approach *does not* determine microscopic stress distributions which may be important, for example, in understanding the behavior of alveolar ducts. The relationship between the macroscopic stress and strain is called the constitutive equation. The macroscopic stress is composed of two parts: one part is due to the elastic tissue in the interalveolar septa, the other is due to the interfacial tension between air and lung tissue. Correspondingly the constitutive equation can be separated into two parts, one for the elasticity and another for the surface tension. The present paper is concerned with the former.

In an earlier paper [6], a theoretical relationship between the macroscopic stress and strain is derived. To test the hypotheses on which the theory is based, the results can be compared with experiments. Limiting to the case in which the surface tension is eliminated, we have shown before [6] that the qualitative results of uniaxial tests of Fukaya, et al. [2] and Radford [13], and the triaxial tests of Hoppin, et al. [9] correlate well with our theory. A more critical test, however, is desired. We choose the severe test of biaxial loading. The philosophy of our approach and the results of the experiments are described in [20]. The comparison with theory is given in the forthcoming. It is shown that the agreement is satisfactory in an approximate sense. Thus the theory can be used with some confidence. In particular, we can use it to analyze the behavior of an intact lung with realizable boundary conditions, and use the experimental results to determine the material constants of the lung tissue in the intact state, including the surface tension effects. The greatly simplified theory, however, cannot be expected to account for the complex behavior of the lung in every detail. The areas of disagreement are discussed in detail.

Since the present article is concerned with the elastic stress only, a derivation simpler than that in reference [6] is possible. This is presented in the forthcoming in order to show our hypothesis more clearly.

Formulation of the Constitutive Equation

It is well known that if the energy state of a material is determined uniquely by its strain state, then the stress-strain relationship can be derived from a strain energy function. Since the lung shows hysteresis, relaxation, and creep, a strain energy function cannot exist in the strict sense. Fung [3, 4] has argued for the existence of a pseudo strain energy function for living soft tissues. The basic argument is the relative insensitivity of hysteresis of these tissues to strain rate. In a cyclic process the stress-strain curves in loading and unloading are individually virtually independent of the strain rate, and the stress-strain relationships are formally derivable from two pseudo-strain energy functions: one for loading (inflation of the lung) and another for unloading (deflation). The experimental results presented in reference [20] show that the lung parenchyma falls into this category, and the existence of a pseudo-strain energy

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function can be assured. The use of the pseudo-strain energy function greatly simplifies data reduction and further analysis of the lung by the method of finite elements.

To derive the pseudo-strain energy function of the lung tissue, we need information about the elasticity of the interalveolar septa, and a model of the way these septa are put together to form the lung parenchyma. A simple mathematical model is the cubic alveoli of Fung [6]. In this model, as is shown in Fig. 1, the interalveolar septa are arranged in rectangular arrays. In the resting state (unstressed saline-filled lung, with surface tension eliminated) each alveolus is a cube of edge length Δ. Under stress the alveoli are deformed into rectangular parallelopipes with edge lengths $\lambda_x\Delta$, $\lambda_y\Delta$, $\lambda_z\Delta$. The directions of the edges of the rectangular parallelopiped are called the *principal directions of stretch*, and a set of rectangular cartesian coordinates x, y, z is used to indicate these directions. The λ's are called the *principal stretch ratios*. By means of this simple model a stress-strain relationship can be derived for the lung tissue.

We now introduce two major hypotheses: 1 The elasticity of the interalveolar septa can be described by the pseudo-strain energy function given by equation (1) *infra*. 2 The constitutive equation of the real lung is of the same form as that of the mathematical cubic alveoli. We seek to justify these hypotheses experimentally.

According to the first assumption, we assume that the interalveolar septa also have a pseudo-strain energy function, and that that function has the form assumed by Fung [6] and Tong and Fung [16]. It is assumed that each alveolar wall is thin and behaves as a membrane. Consider first those membranes perpendicular to the z-axis, i.e., parallel to the x-y plane. These are labeled "1" in Fig. 1. For these membranes the following pseudo-strain energy function is assumed:

$$M_o W^{(1)} = (C'/2) \exp (a_1 E_x^2 + a_2 E_y^2 + 2a_4 E_x E_y) \qquad (1)$$

where M_o is the mass of the interalveolar septa per unit area of the membrane in the resting (unstressed) state, $W^{(1)}$ is the strain energy per unit mass of the interalveolar septa, E_x, E_y are the strains in the x and y directions as defined by Green, and C', a_1, a_2, a_4 are material constants. Green's strains are related to the stretch ratios λ_x and λ_y as follows:

$$E_x = (\lambda_x^2 - 1)/2, \qquad E_y = (\lambda_y^2 - 1)/2 \qquad (2)$$

Because the chosen coordinate axes are aligned along the principal directions of stretch of the membranes, the macroscopic stretch ratios of the lung tissue and the alveolar stretch ratios are indentical and need not be differentiated.

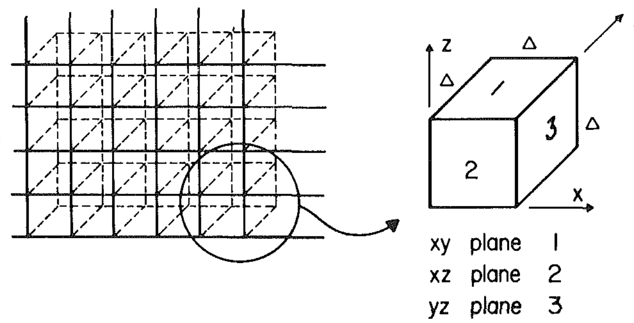

Fig. 1 Geometric model of alveoli; the principal directions of stretch are *x*, *y*, and *z*

Stress Resultants in the Interalveolar Septa. The stress resultants (force/unit length) in these interalveolar septa, denoted by $F_x^{(1)}$ and $F_y^{(1)}$, are related to the strain energy function by

$$F_x^{(1)} = \frac{\partial}{\partial \lambda_x} [M_o W^{(1)}]; \qquad F_y^{(1)} = \frac{\partial}{\partial \lambda_y} [M_o W^{(1)}] \qquad (3)$$

It should be noted that these are forces per unit *undeformed* length, and hence, are defined in the Lagrangian sense. Noting that on account of equation (2), we have $\partial/\partial\lambda_x = \lambda_x \partial/\partial E_x$; $\partial/\partial\lambda_y = \lambda_y \partial/\partial E_y$; hence,

$$F_x^{(1)} = C' \lambda_x (a_1 E_x + a_4 E_y) \exp (a_1 E_x^2 + a_2 E_y^2 + 2a_4 E_x E_y) \quad (4)$$

This equation shows that *the constant C' determines the overall stress level, whereas a_1 and a_2 determine the rate of change of stress with increasing stretch, and a_4 determines the coupling between two perpendicular directions.*

For interalveolar septa parallel to the x-z plane (labeled "2"), the strain energy function $W^{(2)}$ is given by replacing the subscript y by z in equation (1), and interpreting E_z as $(\lambda_z^2 - 1)/2$. In doing so, we are assuming all interalveolar septa to be equivalent, so that the stretching in the x direction will cause the same distortion in the z direction in membrane "2" as it does in the y direction in membrane "1." A similar expression gives the strain energy function for those septa parallel to the y-z plane (labeled "3").

These functions yield the membrane stress resultants $F_x^{(1)}$, $F_y^{(1)}$; $F_x^{(2)}$, $F_z^{(2)}$, $F_y^{(3)}$, $F_z^{(3)}$. All F's have the same form as in equation (4); they can be obtained as follows:

Nomenclature

- a_1, a_2, a_4 = material constants for the interalveolar septa, see equation (1)
- A_{ox}, A_{oy} = reference areas in x and y directions, respectively, for frozen specimens
- C', C = material constants in the strain-energy function and the constitutive equation, respectively; $C = C'/\Delta$
- E_x, E_y, E_z = Green's strains in x, y, z directions, respectively; $E_x = (\lambda_x^2 - 1)/2$, etc.
- $F_x^{(1)}, F_y^{(1)}$ = forces in x and y directions, respectively, per unit undeformed length, in alveolar membranes parallel to the x-y plane
- $F_x^{(2)}, F_z^{(2)}$ = forces in x and z directions, respectively, per unit undeformed length, in alveolar membranes parallel to the x-z plane
- $F_y^{(3)}, F_z^{(3)}$ = forces in y and z directions, respectively, per unit undeformed length, in alveolar membranes parallel to the y-z plane
- M_o = mass of interalveolar septa per unit area of the membrane in the resting (unstressed) state
- T_x, T_y, T_z = Lagrangian stresses in the x, y, z directions, respectively, calculated from the mathematical model
- V_o = initial volume
- $W^{(1)}, W^{(2)}, W^{(3)}$ = pseudo-strain energy per unit mass for membranes in x-y, x-z, and y-z planes, respectively
- x, y, z = directions of constant velocity stretch, lateral servo, and thickness, respectively
- Δ = alveolar spacing in resting state
- $\lambda_x, \lambda_y, \lambda_z$ = stretch ratios in x, y, z directions, respectively
- σ_x, σ_y = Lagrangian stress, F_x/A_{ox}, F_y/A_{oy}, respectively, measured in the triaxial experiments
- $\rho_o W$ = pseudo-strain energy per unit volume of lung tissue
- α, β = material constants defined in equation (7)
- I_1, I_2 = strain invariants defined in equation (8)

To obtain $F_y^{(1)}$, change subscript 1 to 2, x to y, y to x, in equation (4).

To obtain $F_x^{(2)}$, $F_z^{(2)}$, change subscript y to z in $F_x^{(1)}$, $F_y^{(1)}$, respectively.

To obtain $F_y^{(3)}$, $F_z^{(3)}$, change subscript x to z in $F_y^{(1)}$, $F_x^{(1)}$, respectively.

Macroscopic Stress-Strain Relationship of the Lung Tissue. Now we are ready to analyze the lung parenchyma as a structure. The force per unit area acting on any section perpendicular to the x-axis will be denoted by T_x. If the area used in the defintion is the area of the parenchyma in the resting (unstressed) state, then T_x is called *stress defined in the sense* of Lagrange which is the one used in the forthcoming.

The force acting on a unit undeformed area of parenchyma must be the resultant of the forces in the interalveolar septa. If the distance between membranes is Δ when the membranes are at rest, then there are $1/\Delta$ membranes per unit length. Thus in a unit area perpendicular to the x-axis there are $1/\Delta$ membranes parallel to the x-y plane, in which the stress resultant is $F_x^{(1)}$, and there are $1/\Delta$ membranes parallel to the x-z plane, in which the stress resultant is $F_x^{(2)}$. Summing up all the contributions, we obtain

$$\begin{aligned} T_x &= [F_x^{(1)} + F_x^{(2)}]/\Delta \\ &= C\lambda_x(a_1E_x + a_4E_y) \exp (a_1E_x^2 + a_2E_y^2 + 2a_4E_xE_y) \\ &+ C\lambda_x(a_1E_x + a_4E_z) \exp (a_1E_x^2 + a_2E_z^2 + 2a_4E_xE_z) \end{aligned} \quad (5)$$

where $C = C'/\Delta$. T_y and T_z can be formed by appropriate substitutions. This is the desired three-dimensional result.

Equation (5) can be derived by differentiating a pseudo strain energy function $\rho_o W$ with respect to λ_x:

$$\rho_o W = \frac{1}{2} C \exp [a_1E_x^2 + a_2E_y^2 + 2a_4E_xE_y] \quad (6)$$

$$+ \text{ symmetrical terms by permutation}$$

in which ρ_o is the density of the lung in the reference state, W is the pseudo-strain energy per unit mass, and the "symmetrical terms by permutation" means the sum of all terms obtained by cyclic permutation of the subscripts, x, y, of E by y, z, and x. T_y and T_z can be obtained by differentiating $\rho_o W$ with respect to λ_y and λ_z, respectively.

Question of Compressive Strain and Buckling. Interalveolar septa are thin elastic membranes. All thin membranes buckle under edge compression when the compressive stress exceeds a critical value. Because we know virtually nothing about how the interalveolar septa behave under compressive stress or strain, two alternatives were proposed in reference [6]:

(*a*) We assume that the septa can carry compressive stress and strain without buckling and that the constitutive equation, equation (1), applies equally well to compression as to tension.

(*b*) We assume that the septa are so thin and the elastic modulus so low at the resting state that they buckle essentially at zero compressive load.

Under the first alternative equations (4) and (5) are valid for both tension and compression. Under the second alternative the membrane stresses must be set to zero when the strain in the membrane becomes compressive. In other words, in equations (4) and (5), E_x, E_y, or E_z is set to zero whenever λ_x, λ_y, or λ_z becomes less than one, respectively.

Recent experiments by Vawter [18] on dog's lung in the neighborhood of the resting state indicate that the interalveolar septa can sustain a small compressive load, because a lung compressed to a size slightly smaller than the resting state can slowly return to the resting state (asymptotically in 10 or 15 min). The amount of compression that can be carried must depend on the length-to-thickness ratio of the interalveolar septa, which is species dependent. For those animals with relatively thick interalveolar septa, buckling stress would be finite, and use of alternative 1 would be reasonable.

Specialization to Biaxial or Uniaxial Loading. In biaxial loading experiments in the x-y plane T_x and T_y are varied while T_z remains zero. In uniaxial loading in the x direction T_x is varied while $T_y = T_z = 0$. The general three-dimensional stress-strain relationship equation (5) can be easily specialized into these cases. The reduction depends on which of the two alternatives with regard to the compressive strain is used. Under the first alternative, one must set $T_z = 0$, solve the resulting equation for λ_z (or E_z), and substitute the solution back into the expressions for T_z and T_y to obtain finally formulas for T_x and T_y as functions of λ_x, λ_y only. Under the second alternative, with assumed zero buckling load, it is necessary only to delete terms involving E_z in $\rho_o W$, T_x and T_y, because in biaxial stretching E_z is negative and the strain energy associated with this state will be negligibly small. Since the second alternative is much simpler, and is believed to be closer to the truth, it is adopted herein.

Note that when the general three-dimensional stress-strain relationship (equation (5)) is specialized into the biaxial loading case *under the second alternative* (*zero buckling load*), *the physical meaning of the material constants* C, a_1, a_2 *and* a_4 *remains the same in the biaxial case as in the triaxial case.* This is certainly a great advantage. a_1, a_2, a_4 are the exponential constants for the interalveolar septa. C is the elastic constant of the septa divided by the alveolar spacing.

The Question of Isotropy Isotropy of the membrane is not assumed in the foregoing formulation although the cubic structure is assumed uniform. Anisotropy of the tissue is revealed by the difference in the constants a_1, a_2. If a_1 and a_2 were set as equal, then the stress-strain relationship for a membrane becomes isotropic. The real lung tissue is probably anisotropic. It is shown later in Table 1 that the correlation between the mathematical expression and the experimental data is better if the tissue is treated as anisotropic (compare numbers in column 7 of Table 1 with those in column 12). It can not be determined using this simplified model whether apparent anisotropy is due to alveolar anisotropy or to geometrical nonuniformity from point to point.

In actual application of the stress-strain relationship to pulmonary mechanics, it is, however, very inconvenient to use anisotropic law becasue we have little information on the anisotropy of the lung. A great simplification can be obtained if the lung tissue can be assumed to be isotropic in the initial, relaxed, and unstressed state. If initial isotropy is assumed, however, we can remove easily the cubic structure hypothesis which was used to derive equations (5) and (6). We consider a large ensemble of alveoli, and assume that the ensemble average is a sphere in the initial state. A tissue subjected to a macroscopic strain would distort the ensemble average alveolus into an ellipsoid. From the same membrane property (equation (1), with $a_1 = a_2$), we can derive the formula

$$\rho_o W = \frac{1}{2} C \exp \{\alpha I_1^2 + \beta I_2\}, \quad (7)$$

where I_1, I_2 are the strain invariants:

$$\begin{aligned} I_1 &= E_{xx} + E_{yy} + E_{zz} \\ I_2 &= E_{xx}E_{yy} + E_{yy}E_{zz} + E_{zz}E_{xx} - E_{xy}^2 - E_{yz}^2 - E_{zx}^2. \end{aligned} \quad (8)$$

and C, α, β are constants. The details are given in reference [7]. Numerically, equations (6) and (7) give essentially similar results. In the present paper, the comparison between theory and experiment is based on equation (6).

Determination of the material Constants C, a_1, a_2, and a_4. The constants were determined by minimizing the least-squares errors between observed and calculated stresses. T_x and T_y errors

Table 1 **Best-fit material constants of dog's lung tissue elasticity in loading process (stretching), without surface tension—normal saline bath 20°C, pH 6.7**

Sp. No.	F_y Newtons	A. Tissue Considered Anisotropic C (Pascals)	a_1	a_2	a_4	Correlation Based on T_x & T_y	B. Tissue Considered Isotropic C (Pascals)	$a_1 = a_2$	a_4	Correlation Based on T_x	Correlation Based on T_x & T_y
4081	0	74	2.84	*	*	.995	74.0	2.840	*	.995	*
	0.1	147	1.44	4.67	0.522	.996	88.0	1.705	5.049	.997	.932
	0.2	225	1.27	3.71	0.569	.995	141.3	1.512	1.688	.996	.934
	0.5	1210	0.481	0.860	0.177	.972	571.3	0.732	0.427	.992	.766
4181	0	58.4	3.51	*	*	.998	58.4	3.514	*	.998	*
	0.1	86.7	2.18	4.71	0.920	.997	50.2	2.587	4.063	.999	.973
	0.2	100	2.12	3.89	0.976	.996	122.5	1.962	0.879	.997	.976
	0.5	289	1.33	2.28	0.427	.966	313.2	1.259	0.613	.998	.863
5191	0	56.4	2.954	*	*	.997	56.4	2.954	*	.997	*
	0.1	420	0.807	1.95	0.641	.995	120.5	1.397	4.084	.999	.935
	0.2	802	0.524	1.37	0.477	.999	199.9	1.093	1.978	.998	.898
	0.5	741	0.762	2.60	1.02	.989	909.4	0.688	0.785	.999	.769
6021	0	160.7	3.75	*	*	.999	160.7	3.749	*	.999	*
	0.1	274	1.46	4.42	0.613	.994	233.8	1.560	4.486	.998	.982
	0.2	565	0.945	2.43	0.788	.995	582.9	0.917	0.985	.999	.974
	0.5	938	0.697	1.94	0.673	.990	611.6	0.941	0.769	.996	.782

* a_2 and a_4 cannot be determined from uniaxial loading experiments.

were simultaneously minimized when the material was assumed anisotropic. If isotropy was assumed, so that $a_1 = a_2$, the constants were determined by minimizing the sum of the squares of the difference between observed and calculated values of T_x alone. The minimization procedure was an iterative method based on the method of steepest descent. A standard software routine GAUSSHAUS, available on the UCSD Burroughs 6700, was used for minimization.

Note that under the hypothesis that all the interalveolar septa have the same constitutive equation, a set of four constants (C, a_1, a_2, a_4) is sufficient to describe the lung. Biaxial tests can yield all the four material constants; uniaxial tests cannot. Hence it is insufficient to do only uniaxial tests if one's objective is to identify the constitutive equation. However, the preparation of the test specimens in biaxial tests inevitably introduces considerable trauma to the tissue. For that reason we advocate the use of intact lung for the determination of the constants C, a_1, a_2, and a_4. Biaxial tests are used only to the extent of validating equations (5) and (6).

Results

Curve fittings were made for five specimens, each at four lateral loading conditions, with ascending and descending limbs fitted separately. Two specimens (5191 and 6021) were each fitted at two different pH values. Specimen 6231 was fitted at

Table 2 Best-fit material constants of dog's lung tissue elasticity in unloading process (releasing), without surface tension—normal saline bath, 20°C, pH 6.7

Sp. No.	F_y Newtons	A. Tissue Considered Anisotropic C Pascals	a_1	a_2	a_4	Correlation Based on T_x & T_y	B. Tissue Considered Isotropic C Pascals	$a_1 = a_2$	a_4	Correlation Based on T_x	Correlation Based on T_x & T_y
4081	.0	13.0	4.481	*	*	.989	13.0	4.48	*	.989	*
	0.10	45.7	1.95	10.5	0.651	.992	20.5	2.44	10.97	.993	.977
	0.20	80.7	1.79	8.0	1.09	.992	46.7	2.09	5.04	.991	.895
	0.50	35.7	1.99	5.88	0.755	.993	166.2	1.25	0.479	.991	.552
4181	0	23.9	4.14	*	*	.998	23.9	4.14	*	.998	*
	0.10	29.5	2.89	11.3	1.15	.987	14.7	3.46	10.03	.996	.983
	0.20	13.3	3.63	11.5	2.30	.993	10.8	3.82	4.30	.997	.921
	0.50	40.7	2.56	6.07	0.533	.990	78.0	2.01	1.14	.996	.725
5191	0.0	14.7	4.12	*	*	.993	14.7	4.12	*	.993	*
	0.10	67.0	1.70	8.56	1.02	.984	47.3	1.83	6.19	.998	.967
	0.20	63.7	1.55	9.65	1.18	.993	50.0	1.66	3.25	.993	.928
	0.50	109	1.72	10.7	2.41	.981	121.2	1.57	3.61	.999	.632
6021	0.0	47.9	5.49	*	*	.994	47.9	5.49	*	.994	*
	0.10	66.6	2.34	25.0	0.807	.989	60.2	2.41	10.25	.992	.989
	0.20	143	1.67	8.73	1.29	.984	143.6	1.60	2.71	.997	.944
	0.50	153	1.63	6.61	1.51	.985	266.7	1.37	0.455	.994	.575

* a_2 and a_4 cannot be determined from uniaxial loading experiments.

20°C and also 37°C. In order to minimize computer time usage, curves were fitted using only every tenth data point, which proved sufficient to obtain reliable parameter values. In all figures given in the forthcoming, every fourth data point is plotted. The experimental data used for the curve fitting are tabulated in reference [17], which also contains many more plotted curves.

The best-fit physiological material constants determined for specimens in a normal saline bath at 20°C are listed in Tables 1 and 2 for several values of lateral loading, and under both isotropic and anisotropic assumptions. Table 1 is for stretching—increasing load in the x direction. Table 2 is for releasing—decreasing load. The correlation coefficients, or the coefficients of determination, are defined as the correlation of the pairs of numbers representing the experimental data and their theoretic predictions. They are listed in the last columns in Tables 1 and 2. Under the anisotropy hypothesis the full set of experimental data are used to compute the correlation coefficients. Under the isotropy hypothesis two correlation coefficients are presented: one calculated from T_x data alone, the other for both T_x and T_y data. These correlations coefficients show that the fit between the observed data and the theoretical formula is quite good for each loading condition. The fit is better if isotropy is not assumed.

In Tables 3 and 4 the mean values of the material constants for each specimen in different temperatures and pH values are shown.

As the lateral load increases the calculated values for a_1 and a_2 decrease while C increases. There is no consistent trend in the variation of the coupling term a_4. Values of a_1 and a_2 are higher for unloading curves while C is lower, as is expected from the shape of hysteresis curves (reference [20]).

Since each loading condition yields a different set of constants it is of interest to assess the ability of the constants calculated from one loading condition to fit the experimental data generated by a different loading condition. Figs. 2–5 show the assessment for Specimen 4181. In each figure one set of experimental data

Table 3 Mean values of lung elasticity material constants in loading process

(A) LUNG TISSUE CONSIDERED ANISOTROPIC

Specimen No.	T°C	pH	C ± S.D. (Pascals)	a_1 ± S.D.	a_2 ± S.D.	a_4 ± S.D.
4081	20	6.7	414 ± 534	1.51 ± 0.98	3.08 ± 1.98	0.42 ± 0.21
4181	20	6.7	134 ± 105	2.29 ± 0.90	3.63 ± 1.24	0.77 ± 0.30
5191	20	6.7	505 ± 343	1.26 ± 1.13	1.97 ± 0.61	0.71 ± 0.28
5191	20	8.1	324 ± 217	1.22 ± 0.37	3.22 ± 1.43	0.76 ± 0.88
6021	20	7.3	484 ± 347	1.71 ± 1.39	2.93 ± 1.31	0.69 ± 0.09
6021	20	8.3	387 ± 104	1.62 ± 1.01	3.28 ± 0.20	0.73 ± 0.12
6231	37	6.7	192 ± 177	0.83 ± 0.56	2.60 ± 1.45	0.28 ± 0.14
Mean (20°C, pH 6.7 Normal Saline bath)			3.51 ± 1.88	1.69 ± 0.39	2.77 ± 0.67	0.62 ± 0.24

(B) LUNG TISSUE CONSIDERED ISOTROPIC

Specimen No.	T°C	pH	C ± S.D. (Pascals)	$a_1 = a_2$ ± S.D.	a_4 ± S.D.
4081	20	6.7	219 ± 237	1.70 ± 0.87	2.39 ± 2.39
4181	20	6.7	136 ± 122	2.33 ± 0.96	1.85 ± 1.92
5191	20	6.7	322 ± 396	1.53 ± 0.99	2.28 ± 1.67
6021	20	7.3	397 ± 233	1.79 ± 1.34	2.08 ± 2.09

Table 4 Mean values of lung elasticity material constants in unloading process

(A) LUNG TISSUE CONSIDERED ANISOTROPIC

Specimen No.	T°C	pH	C ± S.D. (Pascals)	a_1 ± S.D.	a_2 ± S.D.	a_4 ± S.D.
4081	20	6.7	44 ± 28	2.55 ± 1.29	8.13 ± 2.31	0.83 ± 0.23
4181	20	6.7	27 ± 11	3.31 ± 0.71	9.62 ± 3.08	1.33 ± 0.90
5191	20	6.7	64 ± 39	2.27 ± 1.23	9.64 ± 1.07	1.54 ± 0.76
5191	20	8.1	52 ± 39	1.97 ± 0.32	13.60 ± 7.02	1.36 ± 0.47
6021	20	7.3	103 ± 53	2.78 ± 1.83	13.40 ±10.00	1.20 ± 0.36
6021	20	8.3	135 ± 102	3.03 ± 2.79	8.11 ± 2.66	1.02 ± 0.27
6231	37	6.7	14 ± 15	2.21 ± 0.61	7.24 ± 3.20	0.69 ± 0.47
Mean (at 20°C, pH 6.7 Normal Saline bath)			0.45 ± 0.26	2.71 ± 0.50	9.13 ± 2.15	1.23 ± 0.26

(B) LUNG TISSUE CONSIDERED ISOTROPIC

Specimen No.	T°C	pH	C S.D. (Pascals)	$a_1 = a_2$ ± S.D.	a_4 ± S.D.
4081	20	6.7	61.6 ± 71.2	2.57 ± 1.37	5.50 ± 5.26
4181	20	6.7	31.9 ± 31.3	3.36 ± 0.94	5.16 ± 4.51
5191	20	6.7	58.3 ± 44.9	2.30 ± 1.22	4.35 ± 1.60
6021	20	7.3	129.6 ± 100.8	2.72 ± 1.90	4.47 ± 5.13

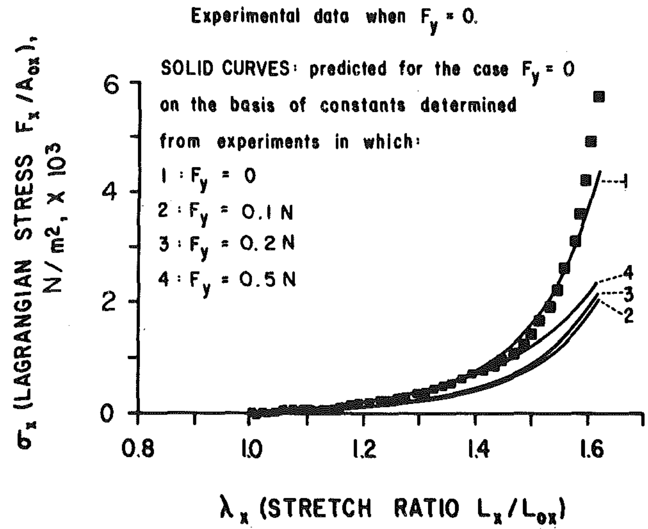

Fig. 2 Comparison of the predicted stress-strain curves for uniaxial loading with experimental data (shown in discrete square) of the uniaxial case. Stresses are predicted with four different sets of material constants. The constants are determined from the labeled experimental runs. Note that only curve 1, for which the material constants were determined from a uniaxial test, predict the behavior adequately.

for a specific loading condition are plotted by discrete points; and four theoretical curves using four different sets of constants are shown for comparison. The theoretical curves are derived from material constants (C, a_1, a_2, a_4) which are determined from four different experiments; one uniaxial and three biaxial tests with the lateral loads indicated in the figures. In the uniaxial case we assumed $a_2 = a_1$ and $a_4 = 0$. It is seen from Fig. 2 that only the curve 1, for which the material constants derived from a uniaxial experiment are used, fit the experimental data well. Curves 2, 3, and 4 in Fig. 2, derived with constants obtained from biaxial tests, do not fit the uniaxial data. Figs. 3, 4 and 5 show that the constants derived from different sets of biaxial tests can be used to predict another biaxial loading case quite well, but the constants derived from a uniaxial test are inadequate to predict the outcome of a biaxial experiment.

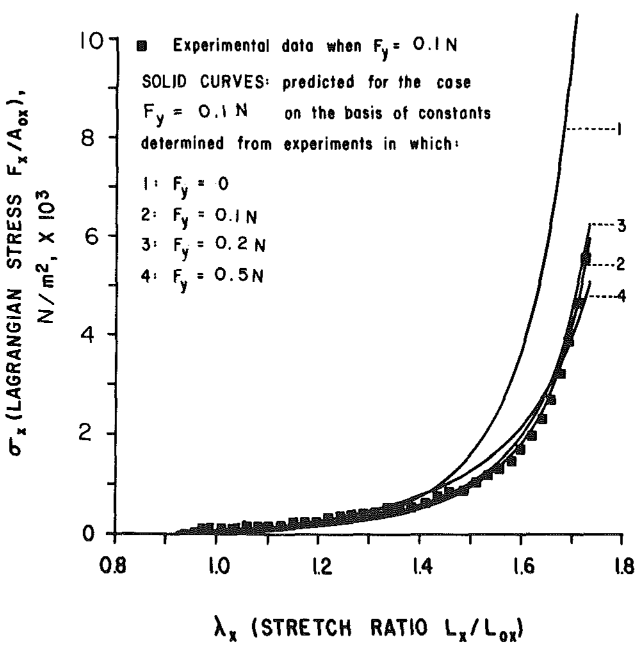

Fig. 3 This prediction uses the same four sets of constants as does Fig. 2 but now attempts to predict the response for a biaxial loading experiment with a lateral load of 0.1 N. Note that curves 2, 3, 4 fit well; but curve 1, which is calculated with constants derived from the uniaxial test, does not fit well.

Discussion

The theoretical formula for stress-strain relationship, derived from a very simple model, is able to fit the observed data very well for each given set of loading conditions. If isotropy is not assumed, the correlation coefficients of the experimental data with the theoretical predictions are generally greater than 0.990 and the majority of coefficients are above 0.995. With the imposition of isotropy hypothesis the correlation is not so good. Values of a_2 and a_4 are indeterminate under uniaxial loading since

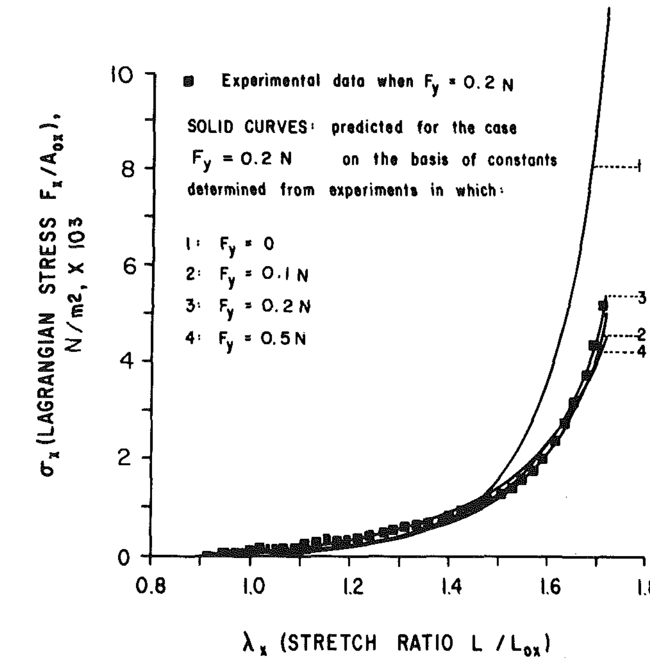

Fig. 4 Comparison of the predicted curves for the case of a biaxial loading with a lateral load of 0.2 N with experimental data of that case (discrete squares). Note that curves 2, 3, 4 fit well; but the one curve calculated with the constants derived from the uniaxial test does not fit well.

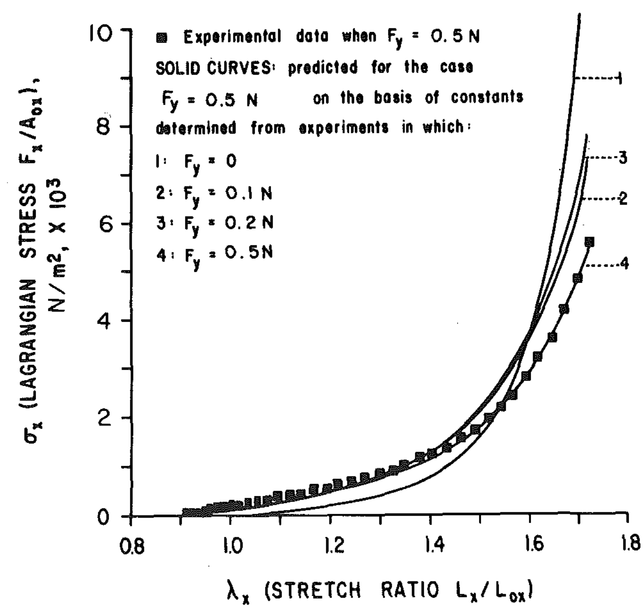

Fig. 5 A comparison similar to Fig. 4 for the biaxial loading case with a lateral load of 0.5 N

the least squares equations determining them are identically zero.

Values of a_2 are consistently larger than a_1 which might be a computational artifact. The parameters that affect the determination of a_2 most strongly are σ_y and λ_y. In the experiments analyzed σ_y was always greater than 400 Pa and information about behavior at low stresses was not obtained. Biasing the curve fitting to higher stresses overestimates the values of the constants in the exponential function. This is also seen in the initial guesses for a_1 which only utilizes peak stretch. Initial guesses for a_1 are usually 50 to 150 percent higher than the final calculated values. For this reason the reliability of a_2 is doubted.

The correlation coefficients for T_x data remain high under the assumption of isotropy because the constants C, $a_1 = a_2$, a_4 are determined from these data; but the correlation coefficients for T_y data is poor under the isotropy hypothesis. We believe that the lung tissue is anisotropic, but can be treated as isotropic without too much error. A much more extensive study is required in the future, however, in order to identify the degree of anisotropy in relation to the location and orientation in the lung for different animals.

The existence of a stress-free state that can be used as a reference state has been further demonstrated by Vawter [18]. In the neighborhood of the reference state the stresses and strains are all small, deviations between theory and experiment in this neighborhood will not cause large deterioration in the correlation coefficient. Hence the comparison between theory and experiment is biased toward the higher stress side. If deviations were express d in terms of percentages (instead of absolute values), then there is probably a loss of percentage accuracy in the neighborhood of the reference state.

Remaining Difficulties

The greatly simplified theory may be fortunate enough to represent the major features of the lung elasticity, but it cannot be expected to account for the extremely complex and nonlinear behavior of the real lung in every detail. For this reason we are certain that the theory will be refined in the future to better represent the lung behavior. At the present let us point out the areas where the theory and experiment do not agree.

The most perplexing feature revealed in the foregoing is the uniaxial test results. The uniaxial test seems to set itself apart from the general biaxial tests, although it is a special case of the latter. The reason for this could be related to the compressive strain in the lateral direction which occurs in uniaxial tests. The association of this compressive strain with the phenomenon of "cross over" is discussed at length in reference [20]. Our hypothesis of zero buckling stress for the interalveolar septa in compression is probably the culprit. We do not fully understand the uniaxial tests.

The difficulty with the uniaxial tests in the family of biaxial cases indicates that the biaxial test of our triaxial formula is one of special severity. The general agreement of the biaxial results with the three-dimensional theory gives us confidence in the validity of the latter at least to the same degree of approximation.

The other difficulty is the change in the values of material parameters with lateral load. This is not surprising when one considers the simplicity of the mathematical model. The cubic geometric model does not allow for geometric reorientation of the alveoli and the resultant redistribution of loads within the structure. A model of alveolar geometry in which the membranes are not aligned in the principal directions of stretch is necessary to allow membrane directional orientation changes as the lung is stretched.

Another reason for the variation of material constants with test conditions is believed related to the need for "preconditioning." All authors on biorheology, including Fukaya, et al. [2], Hoppin, et al. [9] recognize the need for preconditioning to get repeatable data. We believe that the reason is that biological tissues are *not* elastic. They do not have a unique, unchanging structure. They can be preconditioned into a homeostatic condition under cyclic loading; but each homeostatic condition corresponds to a different material. In this sense the word "pseudo-elastic," which was introduced by Fung [3, 4] to indicate that the tissue is viscoelastic but strain-rate insensitive, refers only to a given homeostatic condition and not to the changing conditions. A full analysis of changing homeostasis requires a much more extensive study and is not the objective of the present paper.

The existence of two pseudo strain energy functions, one for loading and another for unloading, is assured only for a given cyclic loading of a preconditioned specimen. Alteration of the loading cycle leads to a new state which must again be preconditioned. In particular, the strain energy function for the release curve cannot be independently determined, but depends on the maximum stretch attained in the stretching phase. Changing the peak stretch (λ_x) will certainly alter the constants for the descending limb and possibly those of the ascending limb as well.

The material constants tabulated and used in Figs. 2–5 are strictly applicable only for the cyclic loading paths for which they are computed. However, the ability of the model to predict adequately the behavior at a variety of lateral loading conditions suggests the possibility to use mean values of the constants to predict the lung behavior. Here again, however, we would like to stress the desirability to determine the material constants from the intact lung to avoid the trauma to the tissue associated with the preparation of the biaxial test specimens. An attempt in this direction is given in [21].

Comparison With Other Works

Of the more recent publications on lung elasticity, the paper by Mead, et al. [12] is the most influential. As far as the stress-strain relationship is concerned, they modeled the lung as a network of springs but stopped short of a mathematical formulation of the constitutive equation. The mathematical formulation was carried out shortly afterwards by Wilson [23] for a two-dimensional network of springs. Wilson's analysis is linearized, and is valid only for a small perturbation of an equilibrium configuration. A further extension was made by Lambert and Wilson [10], in which the lung tissue is pictured as a number of interconnected, randomly oriented, plane, elastic membranes; but again linearized for small incremental variations of stresses and strains about a state of uniform inflation. The incremental stresses and strains obey Hooke's law, for which the concepts of Young's modulus and Poisson's ratio apply, but these constants vary with the state of equilibrium on which the perturbations are imposed. In particular, unless the state of equilibrium is isotropic (as in a uniform inflation of a lung with material isotropy) the incremental law is anisotropic. Only the isotropic case is evaluated by Lambert and Wilson [10].

Another perturbation analysis was one by Frankus and Lee [1]. This time the lung structure was modeled by an assemblage of dodecahedrons, and a numerical finite element method was used.

The methods used by these authors are quite different from that of Fung [5, 7] who starts with the histological geometry of the alveoli and derives certain integrals which represents the macroscopic stresses. He then derives a statistical relationship between the macroscopic strains and the strains in the individual intervalveolar septa by means of a mathematical concept of a statistical *mean alveolus*. Linearization is quite unnecessary in Fung's approach. Two examples are given in [5]: In one an initial spherical mean alveolus is deformed into an ellipsoid, in another a cubic mean alveolus is deformed into a rectangular parallelopiped. Analytical results are obtained for both cases; the analysis being simpler than that of [1, 10, 23]. The cubic case is by far the simplest. It was then discovered that the final constitutive equation does not change very much with the shape of the mean alveolus. Hence in his later paper [6], the cubic mean alveolus was adopted as a major hypothesis. It is to the testing of the results of [6] that the present paper is addressed.

In all these studies it is necessary to know the stress-strain relation of the interalveolar septa. Setnikar [14] has proposed a formula for the Young's modulus of the interalveolar septa in the form

$$E = \frac{1}{K} \cdot \frac{l - l_o}{l_{mx} - l} \quad (9)$$

where l_o, l_{mx}, and k are constants, and l is the length of the tissue. West and Matthews [22] and Vawter, et al. [19] used a Hooke's law with a Young's modulus which is a modification of Setnikar's law, and a constant Poisson's ratio, to represent an incremental law for the lung parenchyma. Wilson [23], Lambert and Wilson [10], Frankus and Lee [1] used the test results of Fukaya, et al. [2] in their analysis. Fung [5, 6] used an exponential constitutive equation which is in common with other soft tissues such as the skin and the mesentery [4, 16]. See equation (1). Its adoptability is the second major hypothesis of the present paper.

Triaxial experiments were made by Hoppin, et al. [9]. Their results were analyzed by Lee and Frankus [11] who expressed the strain-energy function as a polynomial of 8th degree in stretch ratios. Isotropy was assumed so that the strain components in the polynomial were grouped into strain invariants. Although their approach is certainly valid, the present approach appears easier to interpret based on the following comparisons:

(*a*) The variation of the coefficients of the polynomial (which are material constants of the lung) is not easy to understand. These coefficients cannot be related to the properties of the interalveolar septa and the alveolar size in a simple manner.

(*b*) The expression is strictly isotropic. It is not clear how can the expression be generalized to represent an anisotropic material.

(*c*) It is not clear how can the polynomial be specialized to represent the mechanical behavior of the lung tissue in biaxial tension, with the stress in the third dimension zero. Hence we do not know how to evaluate their polynomial against the experimental data presented in the foregoing.

Concluding Remarks

The theoretical constitutive equation derived in [6] is shown to be valid in an approximate sense under the severe test of biaxial loading. The constitutive equation can then be used for the analysis of pulmonary physiology. We believe, however, that the material constants of the tissue (C, a_1, a_2, a_1) should be redetermined by intact lung experiments. To do this, we must first predict the results of possible intact lung experiments in terms of the constitutive equation. The constants can then be determined by comparing the prediction with the experimental data. In this process the assumed form of the constitutive equation is very important. The objective of the present paper is to validate this form by means of in-vitro experiments.

In experimenting with the intact lung, the effect of surface tension must be considered. A constitutive equation with respect to surface tension is derived in reference [7].

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