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THE ROLE OF COLLAGEN IN DETERMINING ULTRASONIC PROPAGATION PROPERTIES IN TISSUE

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The processes responsible for affecting the propagation of an ultrasonic wave as it passes through biological tissue are poorly understood. In large part, the research into this area is at a correlation level as contrasted to a modelling level. In other words, contemporary research is studying the relationships between ultrasonic properties of tissue and other tissue properties in order to elucidate trends. With very few important exceptions, minute information has prevented any successful modelling.

This paper represents a comparison of the ultrasonic attenuation and velocity properties of tissue to the tissue properties of water, protein and, specifically, collagen contents. Table I lists the ultrasonic attenuation, velocity and water percentage in approximate order of increasing ultrasonic attenuation at I MHz for the indicated biological materials and tissues. Table II lists the total protein and collagen percentages of the materials detailed in Table I. In those cases where blanks exist, either the information was not available or not found. The following discussion is intended to provide additional details which could not necessarily be quantified and placed in the tables.

The ultrasonic attenuation includes not only the absorption of the ultrasonic signal which is degraded to heat but also all other mechanisms by which the energy is extracted from the propagating wave or redirected by virtue of the inhomogeneous nature of the materials. The ultrasonic velocity, and the characteristic acoustic impedance which can be determined with density information, embcdy within them both the inertial and restoring parameters of the particular material. Thus knowledge of the ultrasonic velocity and loss terms may, in some sense, provide a basis for developing "tissue signatures" for various tissues.

Tendon

Ultrasonic	Attenuation, Velocity and Water Content for Various Tissues

TABLE I

	Attenuation		
Tissue	At 1 MHz (cm ⁻¹)	Velocity (m/s)	% Water
Water (20 ⁰)	0.0003 ^a	1483 ^b	100
Amniotic Fluid	0.0008 ^c	1510 ^c	97 ^c
Aqueous Humor		1497 ^d	99 ^{e f}
Vitreous Humor		1516 ^d	99-99.9 ^{ef}
CSF		1499-1515 ⁹	99 ^e
Plasma	0.01 ^h	1571 ⁱ	90-95 ^e j
Testis	0.019 ^k	• .	841
Blood	0.02 ^h	1571 ⁱ	74-83 ^{ej}
Milk	0.04 ^{mn}	1485 ⁿ	87 ^e
Fat	0.04-0.09 ^{iopq}	1410-1479 ^{io}	10-19 ^{jrs}
Spleen	0.06 ^p	1520-1591	76-80 ^{rs}
Liver	0.07-0.13 ^{ipt}	1550-1607 ⁱ	68-78 ¹ rs
Kidney	0.09-0.13	1558-1568 ⁱ	76-83 ^{1rs}
Brain	0.09-0.13	1510-1565 ⁱ	75-79 ^{lrs}
Spinal Cord	0.09-0.12 ^{iu}	, , , , , ,	64-80 ^{e1}
Striated Muscle	0.18-0.25 ⁱ	1568-1603	66-80 ¹ jrv
Against Grain	0.08-0.120	1592-1603 ⁰	00 00
With Grain	0.16°	1576-1587 ⁰	
Heart	0.25-0.38 ^{iw}	, , , , , , , , , , , , , , , , , , , ,	77-78 ^r
Tongue	,		62-68 ^r
Against Grain	0.58 ^w	1575 [×]	,
With Grain	0.28 ^w	1585 [×]	
Lens		1616 ^d	63-69 ^{fy}
Articular Capsule	0.38 ^{0q}		0) 0 ₃
Integument	0.40°	1498 ⁰	60-72 ^{jz}

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a) Pinkerton (

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z) Chvapil (10)

aa) Robb-Smith

Cartilage	0.58 ^{oq}	1665°	23-34 ^z 70 ^{aa} 63 ^z
Tendon Against Grain With Grain	0.54 ^{0q} 0.58 ^{0q}	1750 [°]	

- a) Pinkerton (1949)
- b) Greenspan and Tschiegg (1957)
- c) Zana and Lang (1974)
- d) Begui (1954)
- e) Altman and Dittmer (1961)
- f) van Heyningen (1962) g) van Venrooij (1971)
- h) Carstensen et al. (1953)
- i) Goldman and Hueter (1956)
- j) Wolf (1976)
- k) Brady et al. (1976)
- 1) Neufeld (1937)
- m) Hueter (1958)
- n) Maynard and Goss (1976)
- o) Dussik and Fritch (1955, 1956)
- p) Chivers and Hill (1975)
- q) Dussik et al. (1958)
- r) Watt and Merrill (1963)
- s) Ruch and Patton (1966)
- t) Pauly and Schwan (1971)
- u) Dunn and Brady (1974)
- v) Giese (1962)
- w) Hueter (1948)
- x) Ludwig (1950)
- y) Davson (1972)
- z) Chvapil (1967)
- aa) Robb-Smith (1954)

TABLE II

Total Protein and Collagen Content for Various Tissues
(Parentheses indicate a calculated value)

% Total Protein % Collagen								
Tissue	Wet	Dry	% Coll Wet					
			wet	Dry				
Amniotic Fluid	0.27 ^a	(9)						
Aqueous Humor	0.005-1 ^{bc}	(0.5-100)						
Vitreous Humor	0.02-0.25 ^{bcd}	(2-100)	0.014-0.067 ^{de}	(1.4-67)				
CSF	0.03 ^b	(3)		\(\)				
Plasma	7 ^f	100 f						
Testis	(12)	72 ⁹	Trace					
Milk	3-4 ^b	(23-31)						
Fat	5-7 ⁱ	(6-9)	yesj					
Spleen	17-18 ⁱ	(71-90)	(0.5-1.2)	2.4-4.8 ^k				
Liver	20-21 i	(66-95)	(0.1-1.3)	0.6-3.9 ^k				
Kidney	15-17 ⁱ	(63-100)	0.5-1.5 ^k	1.8-5.3 ^k				
Brain	10 ⁱ	(40-48)	(0.04-0.3)	0.2-1.2 ^k				
Striated Muscle	20-21 i	(59-100)	(0.7-1.2)	3.5 ^k				
Heart	17	(74-77)	(0.4-1.6)	2-7 ^k				
Tongue	14-17 ⁱ	(37-53)						
Lens	30-36 ^{cd} ·	(81-100)						
Integrment			7-30 ^k	60-80 ^{ek1}				
Cartilage	(49-63)	74-81 ^k	10-20 ^e	46-62 ^k 80 ^m				
Tendon	35 ^k	(95)	32 ^k	51-95 ^{k1}				

- a) Zana and Lung (1974)
- b) Altman and Dittman (1961)
- c) van Heyningen (1962)
- d) Davson (1972)
- e) Mathews (1975)
- f) Wolf (1976)
- g) Wolf and Leathem (1955)
- h) Bloom and Fawcett (1968)
- i) Watt and Merrill (1963)
- j) Bradley (1972)
- k) Chvapil (1967)
- 1) Crisp (1972)
- m) Robb-Smith (1954)

There are princ organisms. These ar nous system in anima animals. The basis molecular level. The linear polysaccharic collagen in the cell vides an alternative (Mathews, 1975).

Animal tissues gories, viz., epithe (Giese, 1962). Epit cover the surfaces coellular basal membroedded in a matrix. such as the lining coesophagus, kidney tu of the skin. Epithe during embryological to form muscle tissu

Collagen is clc brates. It turns ou single protein in th entire animal kingdo quarter to one-third therefore about six 1968). One reason f aging process is int as aging proceeds, π tween cells. Injury due to its abundance that collagen would ${\begin{tabular}{c}} {\begin{tabular}{c}} {\begin{t$ properties of tissue more investigators (collagen may have and pagation properties imaging. Therefore, sonic propagation pr constituent propertie and collagen, and so

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There are principally three skeletal support systems in living organisms. These are the cellulosic system in plants, the collagenous system in animals and the chitunous system in both plants and animals. The basis of these three systems is found at the macromolecular level. The major fibrose elements are, respectively, the linear polysaccharide cellulose and the asymmetric protein molecule collagen in the cellulosic and collagenous systems. Chitin provides an alternative to cellulose in plants and collagen in animals. (Mathews, 1975).

Animal tissues are usually classified into one of five catagories, viz., epithelial, connective, muscular, nervous and blood (Giese, 1962). Epithelial tissue is an aggregration of cells which cover the surfaces of organs. The epithelial cells lie on a noncellular basal membrane which is composed of collagen fibers embedded in a matrix. Epithelial tissue is found throughout the body such as the lining of the digestive tract, windpipe, lungs, mouth, esophagus, kidney tubules and urinary bladdar and the outer layer of the skin. Epithelial cells specialize to form nervous tissue during embryological development. Other epithelial cells specialize to form muscle tissue (Biology Today, 1972).

Collagen is closely associated in connective tissue of vertebrates. It turns out, in fact, that collagen is the most abundant single protein in the human body and the most common protein in the entire animal kingdom. Collagen comprises somewhere between onequarter to one-third of the total protein in the human body and therefore about six percent of the total body weight (White et al., 1968). One reason for the wide variation in collagen is that the aging process is intimately involved in intercellular changes and as aging proceeds, more and more collagen fibers are developed between cells. Injury and disease are additional causes. Thus, simply due to its abundance within the human body, it would seem logical that collagen would play an important role in determining ultrasonic properties of tissue. In addition, within recent time, more and more investigators (Fields and Dunn, 1973) have been suggesting that collagen may have an important role in determining ultrasonic propagation properties in tissue, especially in terms of echographic imaging. Therefore, this article is an attempt to compile the ultrasonic propagation properties of tissue, compare them to the tissue constituent properties such as percentages of water, total protein and collagen, and suggest some general observations.

In the early 1950's, at the time when pulse-echo diagnostic ultrasound was in its infancy, the observation was made that very few reflections were observed from breast fat alone but these reflections were much more pronounced from connective tissue sheets in lobulated fat (Wild and Reid, 1954). They (Wild and Reid, 1953)

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also examined the ultrasonic reflection from an in vitro cube of striated muscle wherein it was observed that no echos were detected when the sound beam was directed parallel to the muscle fibers and many echos were received when the orientation was changed by 90°. This anisotropy in echo return was disrupted by mechanically rupturing the cube of muscle in order to break up the connective tissue but the rupture procedure was not detailed.

In the mid 1950's the ultrasonic propagation properties of articular tissue were examined (Dussik and Fritch, 1955, 1956; Dussik et al., 1958) and it was concluded that tissues with higher collagen content exhibited higher values of ultrasonic attenuation and velocity, for the most part, as compared to soft tissue with lesser amounts of collagen. These values have been included in Table 1.

Dussik and Fritch (1955, 1956) also suggested that aging of dense fibrose tissue is accompanied by an increase in the ultrasonic attenuation.

Examination of the human female breast, pre- and post-menopausal, with fibrosing adenosis exhibited an increase in the ultrasonic reflectivity over normal breast tissue. This condition is characterized by a proliferation of connective tissue which is replacing the normal glandular breast tissue (Fry et al., 1972). The post-menopausal breast has been shown to exhibit a three to four percent lower ultrasonic velocity than that of the pre-menopausal breast. This velocity difference has been attributed to the proliferation of fatty tissue interlaced with an increased amount of connective tissue (Kossoff et al., 1973).

Greenleaf and his colleagues (Greenleaf et al., 1975, 1976) have shown in excised, unfixed breast specimens, that fat yields the lowest attenuation and lowest velocity as compared to all other surrounding tissue. Additional relative comparisons of the ultrasonic propagation properties of breast showed the following: normal parenchymal breast tissue exhibited relatively high attenuation and medium high velocity, infiltrating medullary carcinoma exhibited an attenuation between fat and normal breast tissue and a high velocity, and connective tissue associated with muscle boundaries of a scirrhous carcinoma clearly exhibited the highest attenuation and velocity.

Measurements of ultrasonic attenuation in the aqueous and vitreous humor indicate it to be from 50 to 100% greater than water at 30 MHz (Begui, 1954). While both are extremely high water content materials, the vitreous contains vitrosin, a basement membrane-like collagen (Mathews, 1975) which may account for the slightly higher ultrasonic velocity.

Cerebrospinal fluid, CSF, also an extremely high water content

material, is a clear, colorless liquid which contains small amounts of protein, glucose, urea, salts and leukocytes (Schneidermann and Hosek, 1976).

The early studies that examined the ultrasonic properties of blood and plasma are largely responsible for our understanding of the importance of protein in that the protein content largely determines the ultrasonic properties and that the absorption is directly proportional to the protein concentration (Carstensen et al., 1953; Carstensen, 1960). Over the frequency range from 1 to 10 MHz, the absorption of blood and plasma exhibit a frequency dependence to the 1.3 power (Carstensen, 1960). Hemoglobin, the major protein in red blood cells, in aqueous solution exhibits a similar frequency dependence over a much wider frequency range (O'Brien and Dunn, 1972).

Mammalian testicular tissue, a relatively high water content tissue, exhibits an ultrasonic absorption lower than any other intract parenchymal tissue and, additionally, appears to exhibit a frequency dependence similar to that of a single relaxation phenomenon, over the frequency range from 0.7 to 7 MHz (Brady et al., 1976).

Milk, a suspension of fat particles and hydrated casein complexes, exhibits an ultrasonic absorption which is proportional to frequency to the 1.1 power (Hueter, 1958; Maynard and Goss, 1976). Cow milk is composed of 87.4% water, 3.5% protein, 3.5% fat and 4.9% total carbohydrates. In comparison, human milk contains about one-third the concentration of protein, twice the concentration of total carbohydrates with water and fat approximately the same (Watt and Merrill, 1963).

Fat is an almost water free tissue. Total body water is dependent upon the total amount of body fat. On the average, babies have less fat than young males, and young males have less fat than young females and this is reflected in the average total body water, viz., 76%, 60% and 50%, respectively (Wolf, 1976). Fat develops in loose connective tissue and consists of numerous fat cells lying in close contact with one another (Bradley, 1972). For most fat tissue, the frequency dependence of attenuation is between the 0.93 and 1.3 power over the frequency range from 1 to 10 MHz (Goldman and Hueter, 1956; Dussik and Fritch, 1956; Chivers and Hill, 1975). The low ultrasonic velocity may be attributed to the low water content.

Dussik and Fritch (1956) indicated that the attenuation of fat tissue located in the sole of the foot yielded a consistently higher value than from other body areas such as the abdomen. It is interesting to observe that the fat in the sole serves one of the few structural and protective functions whereas most fat tissue serves primarily the function of energy storage (Windle, 1976).

Orbital fat tissue has been measured by a backscatter spectral analysis technique and has yielded an ultrasonic attenuation of 0.3/(MHz-cm) over the frequency range from 6 to 12 MHz (Lizzi and Laviola, 1975). More recent measurements indicate the attenuation is 0.17/(MHz-cm) over the frequency range from 5 to 15 MHz and, additionally, when compared with abnormal orbital fat (Graves' disease), is increased to 0.20/(MHz-cm). Histology showed that the abnormal tissue was infiltrated with connective tissue (Coleman et al., 1976).

For purposes of examining the ultrasonic propagation properties, spleen, liver and kidney may be grouped together principally because the scatter in the data does not permit extraction of trends between them. On the average, all three have approximately the same percentages of water, total protein and collagen. The spleen contains a connective tissue framework in which the lymphatic vessels are found. For its large size the liver has relatively little connective tissue. The interlobular septa, called Glisson's capsule, accounts for the major fraction of connective tissue. The kidney is a highly heterogeneous organ. On the average, the cortex has a lesser amount of collagen than the kidney as a whole (Chvapil, 1967; Bloom and Fawcett, 1968).

The frequency dependence of attenuation for spleen is approximately to the 1.5 power over the frequency range 1 to 8 MHz (Chivers and Hill, 1975). For liver, over the frequency range 200 kHz to 10 MHz, and kidney, 200 kHz to 100 MHz, the frequency dependence of attenuation is approximately a linear relationship (Goldman and Hueter, 1956; Kessler, 1973). Acoustic microscopic images of the kidney appear to yield details of connective tissue boundaries (Lemons and Quate, 1974; Kessler et al., 1974). Both cirrhotic and fibrotic livers have a greater acoustic impedance than normal livers, with an average increase of about 8 percent (Yamakawa et al., 1964).

Hueter (1958) showed that the attenuation of ultrasound in liver decreased markedly during the period from 1 hour post mortum to 2 days post mortum. At 1.5 MHz, the attenuation changed from 0.26 cm to 0.06 cm $^{-1}$. Chivers and Hill (1975) measured the attenuation of ultrasound in liver tissue which was several weeks post mortum and obtained approximately the same value that Mountford and Wells (1972) determined under in vivo conditions at 1.5 MHz, viz., 0.20 cm $^{-1}$. Thus in relatively high water parenchymal tissue, details of the state of preservation are necessary for analysis.

Except for the membranes which surround the brain and the stroma of fibrous connective tissue associated with the main blood vessels, the brain is relatively free of connective tissue. It is assumed that the spinal cord also possesses relatively little connective tissue. It is interesting to observe that while the percentages of

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total protein and collagen are at least half those of spleen, liver and kidney, the ultrasonic attenuation and velocity do not appear to be different.

Water, however, appears to appreciably affect the ultrasonic propagation properties in brain tissue. Kremkau et al. (1976) observed that the ultrasonic attenuation in infant brain was approximately one-third that of adult brain. Infant brain exhibits one of the highest, if not the highest water content for intact tissue, somewhere around 90% as compared to 76-79% for adult brain (Altman and Dittmer, 1961). Also, the ultrasonic attenuation of an adult hydrocyphalic brain was slightly less than that of the infant brain (Kremkau et al., 1976). Oka and Yosioka (1976) reported that the attenuation of an edematose brain was less than that of normal adult brain. Wladimiroff et al. (1975) measured the speed of sound in infant brain from the sixteenth day of gestation to term and observed an increase with age in the velocity from 1513 to 1540 m/s. This change was attributed to the content of solids, or conversely, to the content of water.

Johnston and Dunn (1976) developed a model to describe the transmission of ultrasonic energy into the brain, through the meninges from physiological saline. The meninges consists of the three membranes which envelop the brain, viz., the outer dura mater, the intermediate arachnoid and the pia mater. The model assumed was a three transmission—layer model (Kinsler and Fry, 1962). The two outer media, the brain and the physiological saline, were assumed to possess the same impedance. In order for the model to then fit the transmission data as a function of frequency, the intermediate layer was assigned a thickness of 250µm and a speed of sound of 1800 m/s, 300 m/s greater than the other two media. An examination of Table I indicates that such a high velocity would correspond to a very high collagen content material which, in fact, the meninges is.

The data on striated muscle provides some confusion in terms of the affect of attenuation as a function of grain. This would also include tongue since the deep tissue is striated muscle. For striated muscle, it was found that the attenuation coefficient was lower against the grain (Dussik and Fritch, 1955, 1956) whereas the opposite has been observed for tongue (Hueter, 1948). The same contradiction exists for the velocity. Tongue tissue consists of much more than striated muscle (Bradley, 1972). Therefore, it may not be proper to compare tongue directly with striated muscle.

The density of connective tissue is always greater in the right ventricle as compared to the left ventricle, in the range of 2 to 5% dry weight in the left ventricle and 4 to 7% in the right ventricle, and the density in the atrium is approximately twice that of the ventricles (Chavpil, 1967). On the average, heart tissue has a

slightly greater percentage of collagen than the other tissues above it in Table II. Correspondingly, it also has the greatest attenuation coefficient.

Namery and Lele (1972) reported that the acoustic impedance of infarcted myocardium is lower than normal myocardium. This would indicate that the velocity decreased and may be explained in terms of increased fluid in the area of the infarct since the ultrasonic measurements were performed 20 to 30 minutes after ligation. A quantitative study of the ultrasonic attenuation on normal and infarcted canine myocardium, around 2 months after the infarct, over the frequency range from 2 to 10 MHz clearly indicates that the attenuation is increased in the infarcted tissue (Yuhas et al., 1976; Mimbs et al., 1976). The pathology of an infarct indicates that within 24 hours fibroblasts and capillaries appear. Within a few days, the fibrin is replaced by collagen and eventually, within a couple of months, becomes dense collagenous tissue (Friedberg, 1966). Thus, the increase in ultrasonic attenuation can be correlated with an increase in collagen.

The ultrasonic attenuation in lenticular tissue, if extrapolated to a frequency of 1 MHz by assuming a linear dependence upon frequency, would be between 0.09 and 0.23 cm⁻¹. Begiu's (1954) measurement at 3 MHz yielded an attenuation in the range of 0.59 to 0.69 cm⁻¹ and the data of Lizzi and colleagues (Lizzi et al., 1976) reported a value of 0.92/(MHz-cm) in enucleated human eye over the frequency range from 10 to 17 MHz. The latter report also qualitatively indicated that the lenticular attenuation was greater in the rabbit. Lenticular tissue is a high protein material with a varied spatial distribution of water. The innermost zone of the lens typically has less than half the water concentration of the outermost zone (Davson, 1972).

The balance of the tissues in Table I and II are high collagen content materials. These include articular capsule, integrument, cartilage and tendon which typically have collagen contents in the range from 7 to 30 percent wet weight. This is at least a factor of five greater than the other tissues listed in the two tables; those values of collagen content range from 0.04 to 1.6 percent wet weight. Yet it is unmistakable that the high collagen content materials exhibit a greater attenuation than the low collagen content materials. Thus, it must be suggested that the scatter in the data does not permit more than a qualitative observation on the role which collagen plays to influence attenuation. If one were to question the accuracy of the velocity of sound in integument, and use the velocity range from 1665 to 1750 m/s to describe high collagen content tissues, then it could be strongly suggested that collagen has a marked influence on velocity. At 1700 m/s, this is around a 10 percent increase in the velocity as compared to the low collagen content tissues. This is highly supportive of the Fields and Dunn's

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(1973) hypothesis that the structural collagen-containing components of tissue are largely responsible for echographic visualizability.

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