CHAPTER IX

SELECTED NON-THERMAL MECHANISMS OF INTERACTION OF ULTRASOUND AND BIOLOGICAL MEDIA

F. Dunn and J. B. Pond

1. INTRODUCTION

There are numerous reasons for which the physical mechanisms of interaction of ultrasound and living systems should be available for analytical purposes.[1] As ultrasonic techniques become ever more widely employed in medical practice, ever larger fractions of the population have the opportunity to be exposed to this form of energy. In order that possible risks to patients can be assessed with accuracy, it is necessary to have available the acoustic exposure conditions at which reversible and irreversible structural and/or functional alterations occur in normal and pathological tissues and organs. Threshold-type responses have been demonstrated for tissues of the mammalian central nervous system,[2] but except for extremes in the dosage conditions, wherein cavitation and thermal processes are known to be involved, the physical mechanisms remain largely unknown. It would appear to be pertinent and necessary to determine the range of sensitivities, and to elucidate the mechanisms, of all tissue structures routinely exposed to ultrasound in clinical diagnostic and therapeutic situations.

Fabricators of diagnostic instruments and designers of safe and effective clinical procedures must require information on how tissues alter applied sound waves and this involves knowledge of the interacting mechanisms. Detailed knowledge of such effects are needed for a variety of tissues and organs since most regions of the body may be exposed to ultrasound.

For the purpose of this discussion, the mechanisms can be divided into three groups, viz., cavitation, thermal and mechanical. The presence and importance of cavitation in tissue under conditions relevant to medical ultrasound require special attention. While this mechanism has been studied extensively in water, virtually nothing is known of nucleating structures and thresholds of occurrence for more complex media. As this topic is treated in Chapter IV by Nyborg and Coakley, no further mention will be made here.

Thermal mechanisms of interaction of ultrasound and tissues are perhaps the most thoroughly studied and best understood of the three classes. The lower dose situations in which the observed effect arises from increases in temperature produced by ultrasound allow for the greatest success in prediction via physical theory,[3,4] and for this reason this topic will not be pursued further herein. Current problems in this area involve more detailed knowledge of heat transfer processes in tissues and on biological effects of short heat-producing pulses.

Non-thermal, non-cavitation damage may be produced in tissues at intermediate dosage conditions. An increase in temperature during ultrasonic exposure may be avoided, controlled or monitored, e.g., by keeping the dose below a specified time average intensity such that the temperature increase can never reach critical levels. Perhaps a similar statement can be made as regards the avoidance of cavitation since monitoring techniques have become relatively sensitive.[5] However, hazards may be presented when the physical mechanisms are not sufficiently well identified to permit crucial observation and the tissue is subject to accumulating alterations which may not decrease to insignificant values, as can be the case with proper design for thermal processes, between exposures or within a specified time after an exposure.

Thus, for discussion in this chapter, the mechanical non-thermal mechanism of wave distortion, those mechanisms arising from variation in mechanical properties of tissue structures, and thermodynamic effects have been selected. These are discussed relative to conditions of irradiation wherein ultrasound of frequencies 1, 2, 3, 5 and 6 MHz, extending into the kilowatt per square centimeter region at the beam focus, and produced at specified sites in mammalian brain.

2. WAVE DISTORTION

A study of the solution of the wave equation for initially sinusoidal wave motion of finite amplitude shows that points of high particle velocity in the wave are propagated more rapidly than those of lower velocity.[6] Distortion of the wave thus occurs which implies the addition of components of higher frequency in its Fourier representation. This wave distortion is resisted by the greater attenuation suffered by the higher frequency components and this results in a variation in wave shape with distance from the source. As the original monochromatic form of the wave takes on a special character, the waveform becomes stabilized at the distance from the source where the time rate of energy input into the harmonics equals the time rate of energy dissipated through absorption. Very rapid and extreme changes of temperature and pressure may be built up if shock fronts are produced and these might be expected to affect tissue. Further, the mechanical interference with the tissue would have to be treated somewhat differently. The following is a brief discussion on how far wave distortion may proceed in the tissue irradiation case.

An initially high amplitude sine wave will change towards the sawtooth (N wave) shape and the degree to which this process proceeds depends upon the initial wave amplitude. As the wave continues to propagate, attenuation processes become ever more important, the wave Mach number decreases and the wave shape returns to sinusoidal. The process is difficult to treat analytically and many approximations are used.[7,8] This is especially true when the additional attenuation of the high frequency components is an arbitrary characteristic of the field medium. An estimate of the harmonic distortion and the total absorption coefficient of the radiation is needed.

A relevant treatment has been given by Blackstock[8] who uses a modified version of "Burgers' equation" for which the solution is known and in terms of which the acoustical parameters of propagation for a finite amplitude dissipating wave can be expressed. Table I provides details for examples of the radiation parameters as might occur in ultrasonic neurosurgery -- a procedure requiring relatively high intensities. The parameter G is

$$G = \beta \times \frac{U}{c} \times \frac{4\pi}{\mu\lambda} \qquad (1)$$

where β is the second order coefficient in a pressure-density relationship

Table I Numerical Examples of Wave Distortion Parameters for Biological Tissues at 3 MHz.

I (w/cm^2)	U (cm/sec)	$U/c \times 10^3$ (Mach No.)	G	d (cm)
1000	365	2.43	2.6	0.92
2000	515	3.44	3.7	0.66
4000	730	4.85	5.2	0.46

for the medium and has the value of about 3.5 for water dominated media.[7] U is the particle velocity, c is the speed of sound, μ is the intensity absorption coefficient and λ is the wavelength.

The table contains example data for 3 MHz and three intensities. However, it is necessary to consider that the intensity of the beam is non-uniform and that it travels through a water path before entering the brain. For a specific example of a 7.2 cm path in water, the effect on the beam through this stage of its course is considered.

For the unattenuated intensity of 4000 w/cm^2, an approximation is considered as a "geometrical average" for the intensity (valid so long as the focus is not too closely approached). The discontinuity distance, d, defined by $d = \frac{c\lambda}{2\pi U\beta} \doteq \frac{29.4}{I^{1/2}}$, yields, for the above case, the geometrical average as the effective fraction of the discontinuity distance contributed by the water stage, 0.58. Thus, practically irrespective of the constant G for water, it is seen that little energy has been abstracted from the fundamental sine wave by the water stage of the total propagation path.

In the remaining 4 mm from the brain surface to the target, it is not permissible to use the above approximation on geometric averaging. However, the energy transferred to harmonics must be less than the amount arrived at by considering, for the whole 4 mm of travel, the final, focal values for G and d and also the "low intensity" value for the attenuation coefficient. Thus, for an unattenuated intensity of 4000 w/cm^2, a delivered intensity of 2880 w/cm^2 (α = 0.82 cm^{-1} at 3 MHz), G = 4.46 and d = 0.55 and Blackstock's analysis gives the consequent attenuation of the fundamental as in the region of half a decibel. It thus appears that the finite amplitude effects on both the overall absorption coefficient and the wave shape are relatively unimportant as mechanisms requiring serious attention.

3. MECHANICAL DISARRANGEMENT OF TISSUE STRUCTURES

There are a number of forces acting at media inhomogeneities in response to exposure to a mechanical wave field. The following four may be considered as most significant for the biological tissue case.

1. Buoyancy forces are produced on structures having densities different than the surroundings. These are magnified by the very large accelerations the media undergo in accord with the basic acoustic field relations. These forces are oscillatory and, they time-average to zero.

2. A radiation absorber or reflector will experience a displacing force and, since this force has a non-zero time-average, an appreciable relative velocity with the surrounding medium may develop over many wave cycles.

   The tendency to relative movement of contiguous structures, initially the result of the two above identified forces, will be opposed by any structural bounding present, whether rigid or flexible, and, in the case of flexibly bound or free flowing structures, by viscous forces at their boundaries. For the case of viscous forces, the following two additional factors must be considered.

3. "Viscosity-variation" force results from any variation of viscosity over the cycle of the applied radiation and, consequently, over the cycle of relative velocity of the structure in the medium.

4. Insofar as the relative velocity includes displacement flows and streaming (relatively steady flow induced by radiation pressure), the mean square may differ appreciably during the two halves of a cycle. Thus to the time-average drag caused by any time-average value in the relative velocity-viscosity product must be added another time-average force due to the dependence of drag on the second power of relative velocity. This is the Oseen force.

Due to time-averaging forces, flexible attachments are displaced and strained; thus membranes may be stretched, coiled polymers elongated. The new configuration may increase the effect of the primary displacing forces and the result may destroy the attachment. A time interval of many cycles may be needed for this process.

It should be remembered that the structures of living tissue comprise a complex dynamic system and some disarrangement can be accommodated and/or repaired.

3.1 Cyclic Tissue Movements

The particle velocity associated with an intensity as high as 4000 w/cm^{-2} in a waterlike medium is 730 cm/s. Now the mean thermal velocity of translation of a molecule at $37^{o}C$ is $\frac{0.26 \times 10^{6}}{M^{\frac{1}{2}}}$ cm/s where M is the molecular weight. For water molecules M = 18 and the mean thermal velocity is 6.1×10^{4} cm/s. Thus it cannot be expected that the extra forces due to mechanical wave movements would break bonds by individual impact, nor, a fortiori, to disturb structures en masse. Rather, it is necessary to consider the breaking of bonds when put under strain by the extra acoustic movements of a relatively large number of molecules. It will be seen below that the extra acoustic forces (drag) on volumes of micron dimensions and larger are needed to break single weak covalent bonds. The radiation field may, therefore, be considered as a continuum on the atomic (Ängstrom) scale, but must admit discontinuities on the macromolecular-structural (micron) scale. Biological structures have characteristic topologies but very variable geometries. To help appreciate the action of the field, some simple models are considered.

3.1.1 Structural Inclusion Rigidly Bound to Surroundings

Consider a spherical inclusion of radius r and density greater than its surroundings by the amount $(\rho-\sigma)$. The amplitude of the cyclic displacing force suffered by this will be $\frac{4}{3}\pi r^3(\rho-\sigma)$ multiplied by the acceleration. Thus the displacement force amplitude in dynes can be expressed as

$$F = 3.05 \times 10^8 \times f . I^{\frac{1}{2}} r^3 (\rho-\sigma) \qquad (2)$$

where f is frequency in megahertz, I is acoustic intensity in watts per square centimeter and all other quantities are in cgs units. The strength of weak covalent bonds is in the region of 10^{-3} dynes.[9,10] Further, for biological structures of micron size, $(\rho-\sigma)$ will differ little from zero. In fact $(\rho-\sigma)$ of 0.3 would appear to be a generous upper limit.[11] Thus, to generate sufficient force to break such a bond, where I = 1 and f = 1, r must be in the region of 2.2 μ and, since it enters the equation as the cube, must not be much smaller even for considerably weaker bonds.

3.1.2 Free Flowing Structural Inclusion

The forces on free flowing structures are expected to be less than those on similar structures constrained by some form of bonding. However, such motion allows the possibility of altered chemical reaction rates and it is conceivable that there may be inertia-impact effects with the destruction of stored energy at high rates. Further, there may also be large boundary shear stress, depending on the shape of the inclusion.

Consider again a spherical inclusion of radius r and having density difference $(\rho-\sigma)$ relative to the surrounding media. The liquid drag on a sphere moving relative to the surrounding fluid with simple harmonic motion at instantaneous velocity U and frequency $10^6 f$ Hertz is, from a relation given by Lamb,[6]

$$\frac{4}{3}\pi r^3 \sigma \left[\frac{1}{2} + \frac{9}{4r\left(\frac{10^6 f\sigma}{2\eta}\right)^{\frac{1}{2}}} \right] \frac{du}{dt} + 3\pi\sigma r^3 10^6 f \left[\frac{(2\eta)^{\frac{1}{2}}}{r\,(\sigma . 10^6 f)^{\frac{1}{2}}} + \frac{2\eta}{r^2 \sigma 10^6 f} \right] u \qquad (3)$$

where η and σ are the viscosity and density values of the suspending liquid medium, respectively. There is, in addition, an inertial force on the inclusion insofar as it moves with the medium. That part unbalanced by hydrostatic pressure is from elementary considerations,

$$\frac{4}{3}\pi r^3(\rho-\sigma) \times \left(0.73 \times 10^8\, I^{1/2} f \sin\omega t - \frac{du}{dt}\right) \text{dynes} \tag{4}$$

Relations 3 and 4 combine to yield

$$0.305(\rho-\sigma)\, r^3 I^{1/2} f \sin\omega t \times 10^9 - \left\{\frac{4}{3}\pi r^3 (\rho-\sigma) + \frac{4}{3}\pi r^3\sigma \left(\frac{1}{2} + \frac{9}{4r\left(\frac{10^6 f\sigma}{2\eta}\right)^{1/2}}\right)\right\}\frac{du}{dt} - \left\{3\,\pi\sigma r^3\cdot 10^6 f \left(\frac{(2\eta)^{1/2}}{r\,(\sigma.10^6 f)^{1/2}} + \frac{2\eta}{r^2\sigma.10^6 f}\right)\right\}u = 0 \tag{5}$$

or written as

$$C\sin\omega t - A\frac{du}{dt} - Bu = 0 \tag{6}$$

where the substitutions are obvious. By usual methods, e.g.,

$$V\sin\omega t - L\frac{di}{dt} - Ri = 0 \rightarrow |i| = \frac{V}{\left(\omega^2L^2+R^2\right)^{1/2}}$$

the velocity of the inclusion relative to the medium is considered sinusoidal, of angular frequency $\omega = 2\pi f 10^6$, and amplitude

$$|u| = \frac{C}{\left(\omega^2A^2+B^2\right)^{1/2}} \tag{7}$$

It follows that the amplitude of relative displacement of the structure is the velocity amplitude divided by the angular frequency.

The viscosity in the tissue exceeds that of water, viz., 0.01 poise, as values of 0.20 - 0.1 poise are quoted for nucleoplasm and cytoplasm.[12] Table II shows the magnitude of movement of free flowing inclusions relative to the surrounding medium for a specific set of parameters.

3.2 Streaming Movements, the Effect of the Summation of Cyclic and Streaming Velocities

As will be seen, the direct effect of radiation pressure is small. However, resulting streaming movements and the flow around structures in relative motion in the field, add to the primary cyclic movements. At the higher intensities, even small superimposed non-cyclic flows have an appreciable effect due to the involvement of the squared term, i.e., Oseen correction, of relative velocity in the expression for the drag coefficient. A time-averaging force is produced and a time developing "positive feedback" effect is promoted as those structures free to move do so, the fluid medium streaming is allowed to increase with a relatively large effect on neighboring fixed structures. The streaming induced by radiation pressure acting on relatively large volumes in the field is considered first.

It is helpful to visualize the action of radiation pressure, for example, as the following. Consider the generation of a plane beam of compressional waves by the impermeable rigid plane face of a transducer vibrating normally. The pressure at the face will be, to first approximation, the alternating pressure in the wave which is later experienced at points in the field along the direction of travel of the beam. The particle velocity is in phase with the pressure. However, the excess, e.g., acoustic, pressure at the face does not time-average to zero. As long as the medium has a finite value for phase velocity, the two halves of the pressure cycle are unequal. When, after several cycles have established equilibrium, the radiating face is forward of its mean position, extra mass, i.e., extra pressure, accumulates at the face due to its "catching up" to some extent with the wave motion. This situation is cancelled and reversed as the face moves back through its equilibrium position into the negative half of the pressure cycle. The same conditions obtain at "virtual" planes of equal phase in the transmitting medium. However, these planes are permeable to the thermal and drift velocities of the medium. A general thermodynamic argument, applicable to all forms of radiation, gives the value I/c, multiplied by a constant depending on the units, as the average pressure transmitted by such surfaces. For water, 67 mg/w are transmitted. Part of the force on a reflecting surface element dS is, therefore, $0.067\ \bar{I}.d\bar{S}$ but the remaining part, due to reflected energy, is complicated by the question of diffraction.

This direct "radiation pressure" force on a volume element is due to a redistribution of radiation momentum and is quite distinct from viscous drag forces. Crum[13] and Yosioka and Kawasima[14] give relevant treatments. As examples, we consider the force on a small sphere in standing and in progressive plane waves.

In plane progressive plane waves, the force in dynes on a sphere radius r cm and immersed in water may be written

$$F = 6.45 \times 10^{8} r^{6} f^{4} I F_1$$

where F_1 is a function of the density and compressibility of the sphere materia[l] relative to the surrounding medium. F_1 may be expected to be in the range 0.1 $\rightarrow$ 1 and, for a given force, its reciprocal effect in determining r is small since r enters as the sixth power. Taking F_1 as 1 we get a sphere radius of 108 microns to derive a force of 10^{-3} dynes. The sixth power dependence on r suggests the triviality of forces derived by micron sized structures except at very high frequencies.

In the plane standing wave case we consider an incident intensity of I W cm^{-2} completely reflected and so an energy density of 2I/c. The force varies sinusoidally with position in the field and may be put:

$$F_{max} = 1.75 \times 10^{4} r^{3} f I F_2$$

where F_2 is similar to F_1. Taking F_2 as 1 gives r = 38 microns to derive a force of 10^{-3} dynes. We note that in the standing wave case the forces only reduce as r^3 rather than r^6 so that the forces on micron sized structures are less trivial.

A volume element dV which merely absorbs will experience a force of $133 \cdot \alpha I \cdot dV$ dynes where α is the (amplitude) absorption coefficient and such force, in relatively large cell volumes, is mainly responsible for intracellular streaming. If the field is divergent rather than plane, all radiation pressure forces are much enhanced.[15]

Vigorous streaming has been observed in cells at relatively low intensities, viz., 0.03 w/cm^2 at 1 MHz.[16] However, the calculation of streaming in tissue presents many problems. Not only does the complex structure result in a primary cyclic intensity varying rapidly in both magnitude and direction, but the streaming movements are confined to labyrinthine channels. Displacement flow due to the presence of vibrating structures further complicates the picture. It is not intended here to go into detailed calculations, (for a review of some methods of attack see Nyborg[17]). Rather, a simplified model is used to give the order of magnitude results and the nature of the dependence of the effects on tissue structure and the radiation parameters.

Consider the duct in the tissue through which fluid can flow. Let a part of the duct be a circular cross-section of radius r, and with its axis in the direction of the local intensity vector. A non-slip condition is assumed at the wall but the whole structure follows, at least to first approximation, the primary cyclic movements of the free field. Let the part of the duct with thich we are concerned be of length l. Then, provided a critical Reynolds Number is not exceeded, Poiseuille flow obtains within l and the maximum, i.e., axial, flow rate may be stated in terms of the pressure fall per unit length. That is,

$$U_2 = \frac{r^2}{4\eta l} \times (p_1 - p_2)$$

But the $p_1 - p_2$ here is given by the decrease in pressure resulting from absorption in the medium of coefficient 2α over the path l, viz.,

$$p_1 - p_2 = 67\ I(1 - e^{-2\alpha l})$$

Characteristically, l is of the order of 10^{-3} cm and $2\alpha l \ll 1$ so that the final particle velocity is

$$U_2 = \frac{16.5\ r^2 2\alpha I}{\eta} \qquad (8)$$

For the case where r is 10 μ, $2\alpha = 0.82\ \text{cm}^{-1}$, $I = 4000\ \text{w/cm}^2$ and $\eta = 0.02$ poise, U_2 turns out to be about 2.7 cm/s which would no doubt be considered vigorous when observing tissue under the microscope at say, 100 x. Note that the Reynolds Number, in the present context for a circular pipe radius r, may be taken as $Re = r \times u_{max(central)} \times \frac{\sigma}{\eta}$ and turbulence does not occur for Re less than 1600. Thus turbulent flow (in the technical sense of the growth of a time-dependent eddying field) is not expected in tissue due to the small effective radii available for streaming.

The effect of a streaming (or at least non-cyclic) flow in producing a time-average drag on tissue structures is now considered. Again, simple spherical inclusions are treated.

3.2.1 Oseen Force

The usual expression for the "Stokes law" drag on a sphere only takes account of the first power of the relative velocity. Oseen point out that the velocity enters beyond the first power. Physically, this is recognizing the fact that a moving particle leaves a wake whose energy per unit path length increases with the relative velocity. The second power of the velocity may be introduced by replacing $\bar{u}$ with $\bar{u}(1 + \delta|u|)$. δ may be put $\frac{3r\sigma}{\delta\eta}$[18] for steady flow and should not be very different for time dependent flow. Thus at the higher intensities where $\bar{u}$ is large, an added unidirectional component to the velocity can have a relatively large effect in unbalancing the drag between half cycles of $\bar{u}$. A time average drag is produced and structures may thus be forced over relatively large distances. Let the velocity be expressed as $\bar{u}_2 + \bar{u}_o \sin\omega t$. From the foregoing, it may be expected that u_2/u_o will be small. Returning to Eq. (3), the first term represents an "effective" mass which may be neglected in view of the small radii being considered. If D denotes the drag coefficient of velocity, the drag force is

$$\bar{F} = D\left\{(\bar{u}_2 + \bar{u}_o \sin\omega t)\quad(1 + \delta\,|\,u_2 + u_o \sin\omega t\,|)\right\}$$

Thus the time average force is

$$|\bar{F}_{ta}| = \frac{D}{2\pi}\int_o^{2\pi}\left\{(u_2 + u_o \sin\omega t) + \delta(u_2 + u_o \sin\omega t)^2\right\} d(\omega t),$$

where, in forming the integral, the second term is to be considered negative when $(u_2 + u_o \sin\omega t)$ is negative. Thus

$$F_{ta} = \frac{D}{2\pi}\left\{2\pi x u_2 + \delta u_o^2\left(\int_a^b - \int_b^{a+2\pi}\right)\left(\frac{u_2}{u_o} + \sin\omega t\right)^2 \quad d(\omega t)\right\}$$

where $u_2/u_o + \sin\omega t$ is positive over that part of the cycle denoted by (a--b).

This is equivalent to

$$F_{ta} = \frac{D}{2\pi}\left\{2\pi x u_2 + \delta u_o^2\left(2\Big[^{b} - \Big[^{a} - \Big[^{a+2\pi}\right)\left(\left(\frac{u_2}{u_o}\right)^2 \omega t + \frac{\omega t}{2} - \frac{\sin(2\omega t)}{4}\right.\right.$$

$$\left.\left. - 2\left(\frac{u_2}{u_o}\right)\cos 2\omega t\right)\right\} \tag{9}$$

It remains to establish the limits a and b. Note that $b = \pi - a$ and that when $\frac{u_2}{u_o}$ is small, $a = \frac{u_2}{u_o}$.

As an example, consider the case where

$$\frac{u_2}{u_o} = 0.1$$

Then $a \doteq -0.1$ and $b \doteq (\pi + 0.1)$.

Thus

$$\frac{F_{ta}}{D} = \frac{1}{2\pi}\left\{2\pi u_2 + \delta u_o^2\ (0.51 \times 0.4 + 0.8)\right\}$$

For $\sigma = 1$, inserting δ and substituting for D from Eq. (3) gives

$$F_{ta} = 1.5 r^2 \eta\left(\frac{(2 \times 10^6 F)^{1/2}}{\eta^{1/2}} + \frac{2}{r}\right)\left(2\pi u_2 + \frac{3 r u_o^2}{8\eta}\right) \tag{10}$$

where u_o is the value obtained from Eq. (5). Strictly speaking, one should work from a differential equation analogous to Eq. (5) but taking δ into account. However, it may be seen from Eq. (5) and Table II that even at an intensity of 4000 w/cm^2, the effect of δ in forming u_o will be relatively small for inclusions as large as 2μ radii.

The drag force, including the Oseen component, on a free flowing inclusion of 2μ is calculated for I = 4000 w/cm^2, f = 3 MHz, $u_2/u_o = 0.1$, $\sigma = 1$ g/cm^3, $(\rho-\sigma) = 0.3$ g/cm^3 and, $\eta = 0.2$ poise. From Table II, $u_o = 104$ cm/sec and Eq. (10) then gives $F_{ta} = 3.5 \times 10^{-3}$ dynes.

3.2.2 <u>The Viscosity-Variation Effect</u>

Westervelt[18] introduced the concept of a time-average force on elements in the field subject to the relative oscillatory flow of a medium whose viscosity depends on the temperature which changes, in turn, in the flow

Table II Numerical Examples of Magnitude of Movement of Free Flowing Inclusions Relative to Surrounding Medium. (Field parameters: $f = 3$ MHz, $I = 4000$ w/cm^2, $\rho-\sigma$ = gm/cm^3, $\sigma = 1$ gm/cm^3, $\eta = 0.02$ poise).

0.3

Inclusion Radius (cm x 10^4)	Excursion Amplitude (cm x 10^4)	Velocity Amplitude (cm/sec)
0.5	2.0	37
1	3.4	64
2	5.2	104

cycle. Although with "perfect fluid" behaviour, where the viscosity is approximately proportional to the square root of absolute temperature, the resultant force is not significant under these conditions, a complex colloid such as living tissue, whose viscosity will probably vary greatly over a small temperature interval, may well generate significant forces by this mechanism.

For a perfect fluid whose equation of state may be simply characterized by γ,

$$\frac{T}{T_o} = \left(\frac{V_o}{V}\right)^{\gamma-1}$$

where T is the absolute temperature of a volume element V in the field. Note that the compressibility of the medium is $\frac{1}{\sigma c^2}$ and thus

$$\frac{V_o - V}{V_o} = \frac{p}{\sigma c^2}$$

Further $p = \sigma cu$ for plane travelling waves, so that $\frac{T}{T_o}$ becomes

$\left(\frac{1}{1-\frac{u}{c}}\right)^{\gamma-1}$ and, since u/c is small, this may be approximated as $(1 + (\gamma-1)\frac{u}{c})$.

In the real fluid of the present discussion, the increase in T is of the order of one percent. For $T = T_o(1 + Au)$ and referring to Sec. D, A is about 1.3×10^{-6}. For

$$\eta = \eta_o + B\left(\frac{T-T_o}{T_o}\right) = \eta_o + ABu$$

If $u = U\sin\omega t$, the time average of $u\eta$ is $\frac{1}{2}ABU^2$. Thus, the force on a sphere of radius r resulting from temperature variation of viscosity will be approximately

$$F_{ta(v-t)} = 3\pi rABU^2 \tag{11}$$

Note that the force is proportional to acoustic intensity whereas buoyancy forces are proportional to $I^{\frac{1}{2}}$. Also its dependence is on r, rather than r^2 and r^3 as is, respectively, with Oseen and buoyancy forces. A pressure-induced variation of viscosity may be treated similarly and will, of course, have a similar effect.

Note that, for free flowing inclusions and for flexibly bound ones, there is a time lag between the initiation of the radiation and the development of the maximum effect. Apart from the time required to establish streaming (see below), time is required in the first case to reach the streaming velocity and in the second case to stretch the bonds. These times should be of the same order, for inclusions of similar buoyancy and viscous drag. The initial acceleration for the inclusion discussed above would be of the order of 10^{-5} cm $\sec^{-2}$ so that expected time constants would be of the order of 10^{-4} sec.

The time required for the build up of streaming velocity, which must be added to these time constants for time-average viscosity effects, will now be discussed. A time-averaging force field superimposed on the cyclic field leads to a field of streaming velocity changing in magnitude (though not, to a first approximation, in disposition) from initiation until frictional forces balance the streaming forces. An analogy is the case of the particle moving under the condition $F = M\dot{u} + Ru$ which integrates to $u = (1-e^{-tR/M})F/R$, showing a build-up of velocity with time constant M/R independent of F.

Under the action of the mechanical wave field, fluid element experience a volume-proportional force of $\mu\frac{I}{c}$, where c is the wave (group) velocity, I is the acoustic intensity and μ is the intensity absorption coefficient. Biological media essentially restrain streaming flows to a collection of irregularly shaped cells resulting in a complex system of vortices. To obtain an estimate and a maximum of streaming build-up time under these conditions, consider the case of a beam of waves of intensity I propagating parallel to and filling a tube of radius a. Suppose the tube filled with fluid of density σ, viscosity η and attenuation coefficient μ, let it be indefinitely long, and allow a no-slip condition at its wall. The resulting equation and boundary conditions are

$$\frac{\partial^2 u}{\partial r^2} + \frac{1}{r}\frac{\partial u}{\partial r} = \frac{\sigma}{\eta}\frac{\partial u}{\partial t} - 10^7\,\frac{\mu I}{\eta c}$$

with $u = 0$ for all t, when $r = a$, also $u = 0$ for all r, when $t = 0$. This equation and boundary conditions are also an example of the diffusion equation applying to an infinitely long cylinder with its surface temperature maintained constant, suffering a uniform volume rate of heat production inside it after $t = 0$. The solution is given by Carslaw and Yaeger[19] and transforming their symbols gives

$$u(r,t) = \frac{10^7 \mu I}{4\eta c}\,(a^2 - r^2) - \frac{2 \times 10^7 \mu I}{a\eta} \sum_{1}^{\infty} e^{-\frac{\eta}{\sigma}\beta_i^2 t}\,\frac{J_o(r\beta_i)}{\beta_i^3 J_1(a\beta_i)} \qquad (12)$$

where the β_i are the positive roots of $J_o(a\beta) = 0$. It is found that u reaches 0.8 of its final value in a time $\tau \doteq 0.2a^2\,\frac{\sigma}{\eta}$, for all r. This timing also applies to the rise of $\frac{\partial u}{\partial r}$ at the wall of the tube (that is, to the shear force rise). Since any constraints such as tube blockages require the fluid to circulate rather than progress, and thus increase frictional loss relative to kinetic energy, this time constant may be taken as a maximum. In the case of a tube of 100 μ diameter, τ turns out to be $7.5\,\frac{\sigma}{\eta}$ μsec. A tube of 20 μ diameter with liquid of unity density and viscosity of 2 centipoise involves a time constant of some 15 μsec.

3.3 The Effect of Structure Shape on Viscous Forces

The viscous force per unit volume per unit relative velocity, and hence the displacing effect of buoyancy forces on free and "semi-free" structures, will depend on the shape of the structure. The viscosity/inertial ratio will be least for spheres and greatest for thin filaments. As spherical structures have been considered previously, the extent to which filaments may behave differently will now be treated. This is instructive because it provides the other extreme to the sphere in viscosity/inertial ratio and because thread-like long chain molecules, whether coiled or partially extended appear to be somewhat common place in cells.[11]

Approximations for the viscous forces on thin rods of length l and radius r "streamlining" through a fluid with speed u are

$$F_1 = \frac{2\pi\eta l u}{\ln(\frac{l}{r})-0.72}$$

for movement parallel to the rod axis and

$$F_2 = \frac{4\pi\eta l u}{\ln(\frac{l}{r})+0.5}$$

for movement normal to the rod axis.[20] With l/r large, an average for arbitrary translational movement may be taken as

$$F_{rod} = \frac{3\pi\eta l u}{\ln(\frac{l}{r})}$$

The force per unit volume per unit relative velocity is

$${}_{rel}F_{rod} = \frac{3r^{-2}}{\mathrm{in}(\frac{l}{r})}$$

Also ${}_{rel}F_{sphere} = 4.5\ r^{-2}$ where of course the radius of the rod will be less than the radius of the sphere for equal volumes. Then

$$\frac{{}_{rel}F_{rod}}{{}_{rel}F_{sphere}} = \frac{3}{4.5\ln\left(\frac{l}{r_{rod}}\right)} + \left(\frac{3}{4} \cdot \frac{l}{r_{rod}}\right)^{2/3}$$

When l/r is 20, the above ratio is 1.35. That is to say that a rod of length to radius ratio, 20, experiences 1.35 times the viscous drag of a sphere of the same volume and under similar conditions. When l/r = 1000, $\frac{{}_{rel}F_{rod}}{{}_{rel}F_{sphere}}$ becomes 8, though such relatively long filaments would probably not maintain the rigid rod thus reducing the factor. The main significance of the factor is in the increase of time-average forces on "semi-free" filaments.

4. THERMODYNAMIC EFFECTS

One of "Maxwells four thermodynamic relations" is

$$\left(\frac{\partial T}{\partial p}\right)_s = \left(\frac{\partial V}{\partial s}\right)_p$$

Then

$$\left(\frac{\partial T}{\partial p}\right)_s = T\left(\frac{\partial V}{\partial Q}\right)_p = \frac{TV\alpha}{cp}$$

where the symbols have the meanings conventional in thermodynamics. Thus the rate of change of temperature with pressure under isentropic conditions (such as reversible adiabatic) is equal to the absolute temperature times the thermal expansion coefficient divided by the specific heat per unit volume at constant pressure. Although the compressions in the mechanical waves are not quasi-static, they are reversible in that the extra energy given to a volume element as particle velocity is, in first approximation, returned from it and not degraded into heat. We ignore the relatively small effect of heat conduction and thus consider the compression as reversible adiabatic.

Consider values for water. The thermal expansion coefficient α is very small, viz., approximately $3.6 \times 10^{-4} \frac{1}{^{o}C}$ at $37^{o}C$. The compressibility is also small so that $\left(\frac{\partial T}{\partial p}\right)_s$ remains relatively constant so that

$$\left(\frac{\partial T}{\partial p}\right)_s = \frac{\Delta T}{\Delta p}$$

This value turns out to be 3.6×0.031 where p is in units of calories per centimeter^3. Alternatively this can be expressed in other units (I atm $\simeq$ I bar) and the ratio $\Delta T/\Delta p = 2.7 \times 10^{-3}$ ^{o}C/bar. Brain tissue is very largely water, free and bound. Taking the water value of the T-p ratio as above, considering the intensity to be 4000 w/cm^2, and from elementary acoustic consideration $\Delta T = 0.3^{o}C$ and $\Delta p = 110$ bar, these being the amplitudes of the sinusoidal excursions at the cyclic frequency of 3 MHz.

If structural or chemical alteration are influenced by these changes and if they can respond to proceed appreciably in a half period, there will, due to the rapid succession of such changes, be considerable dissipation of the wave energy (as heat) due to the molecular activity involved. This dissipation does not occur (relaxes out) if the cyclic frequency is made too high for the alteration to follow. Thus much can be learned of the liquid structure by ultrasonic absorption methods and this is treated in Chapter III. Since the present treatment considers heat as a damage factor without inquiry into its origins, it is pertinent to remark on two effects. Firstly, the shifting of the balance point of temperature or pressure sensitive reactions in step with the wave frequency may upset tissue metabolism. Secondly, the balance point of such reactions will be shifted in time-average insofar as their equations of state are non-linear in temperature or pressure.

The second effect will not be important if the tissue can be shown to bear the maximum values of the excursions of pressure and temperature for comparatively long times. This would seem to be the case. The temperatures are clearly trivial and as regards pressure, it seems that very much higher pressures are needed to cause effects in times comparable to dose times. For example, Belser and Vacquier[21] exposed developing larva of the copepod "Trigriopus Californicus" to 500 bars for two hours at $23^{\circ}C$. The ten percent of deaths would appear largely due to handling. The overt effect (depending on the growth stage of the larva) was the conversion of males to females. In another report, Weida and Gill,[22] examine the influence of pressure on the thermal denaturation of DNA (which may well be the most delicate chemical constituent of living tissue) as measured by optical rotation. Denaturation set in between 60 and $70^{\circ}C$ and the thermal stability was found slightly improved (2-$3^{\circ}C$) by the highest pressures employed, 1350 bars.

In view of the relatively large tolerance of living tissue, even the first effect (that of rapid adjustment of balance points) would not, at first sight, seem very likely at or below the excursions calculated above. But the principle is there. For example many cell types which can live at final low temperatures, are killed if they are brought down to these temperatures rapidly, the metabolism needs time to adjust.[23] There would seem to be a similar effect in the experiments on cooled frogs and mice,[24,25] viz., damage accompanied a temperature rise although a temperature which would be damaging in the static sense was avoided.

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