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Treatise on New Physical Mechanism of Medical Diagnostic Ultrasound (MDU) for Bio-effects from Shear Stress/Strain Resolved from Longitudinal and Extensional Waves

Abstract: Over 2005-2020 *pro bono* research was carried out on the evidently overlooked but simple origins, action and implications of resolved shear stress and shear strain predicted to occur in biological tissue and human patients in clinical settings via exposure to MDU as MHz longitudinal plane waves and focused beams, either emitted by medical devices like ultrasound scanners and imaging machines. Termed (purely) solid state mechanical shear strain and stress (SSMSSS), discovery of this effect – first observed and measured photoviscoelastically in soft solids in the 1970's by Frost – resulted from insight gained from analyzing a cause-and-effect chain beginning with emission at time t=0 of elastodynamic radiation from a point or line source on the plane surface of a solid half-space or solid half-plate, with waves or particles observed at t>0 at a field point in the far field. Much math analysis of this type "is concerned with an initially undisturbed body which in its interior, and at a specified time, say t = 0, is subjected to external disturbances" which "give rise to wave motions propagating away from the disturbed region."[1] With relatively simple math, Part 1 sets up this treatise plus the tensor calculus and analysis of Part 2 whose own math climaxes in Addendum A for calculating critical values of observables related to possible tissue damage thresholds from MDU. Both Parts move a rational argument towards a tensor-based continuum mechanics and dynamics model for critical resolved time-averaged principal shear stress or strain for calculating damage thresholds for exposure of biological tissue to plane waves of MDU under conditions of mechanical creep and wave absorption without cavitation or strong heating. Featured are simple models of uniaxial stress (extensional waves) and uniaxial strain (longitudinal waves) in a half-space or a half-plate of a dry isotropic homogeneous viscoelastic solid with small amplitude-attenuation coefficients based on a relaxation or retardation process. The Postscript of Addendum E indicates how this analysis is pertinent to searches for causes of ASD and other early-in-life neurocognitive developmental disorders, taking account of special vulnerability to damage of the CNS from MDU including the prenatal & neonatal brain and blood brain barrier even in adults.

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[1] J. D. Achenbach, *Wave Propagation in Elastic Solids* (North-Holland Publishing Co., Amsterdam, et al., 1975 & later for paperback edition), p.89.

PART 1: SIMPLE NONCAVITATIONAL NONTHERMAL PHYSICS MODEL FOR ULTRASONIC SSMSSS BIOEFFECTS

General:

Scientific and product information on medical diagnostic ultrasound (MDU) use on the *in utero* fetus, embryo and ovum and on the *in vivo* uterus, has themes like exposimetry,[2] efficacy[3] and bioeffects[4] in OB-GYN practice for fetal, postnatal and early childhood screening, diagnosis and

2 Viz., see http://www.brl.uiuc.edu/Projects/in_vivo_ultrasound_exposimetry.php for profile "In Vivo Ultrasound Exposimetry," Bioacoustics Research Lab (BRL) at the University of Illinois, Urbana-Champaign. An important FDA regulatory document issued June 27, 2019 is "Guidance for Industry and FDA Staff" (as on ultrasound transducers) at https://www.fda.gov/media/71100/download. Its App. A lists symbols, definitions & formulae used. Track 3 recommendations for those following the Output Display Standard (ODS) limit the "global maximum derated" spatial-peak time-average ultrasound intensities to 720 mW/cm2 save for 50 mW/cm2 for ophthalmic use. These "Ispta.3" values are linked to values for thermal index (TI) and mechanical index (MI).

3 E.g., L. Bricker, N. Medley & J.J. Pratt (2015), "Routine ultrasound in late pregnancy (after 24 weeks' gestation)," 81-pp., Cochrane Database of Systematic Reviews, Issue 6, Art. No. CD001451. Quote: "...34,980 women were included in the systematic review...There was no difference in antenatal, obstetric and neonatal outcome or morbidity in screened versus control groups. There is little information on long-term substantive outcomes such as neurodevelopment".

4 Hal's concern since 1970's. Former BRH/FDA colleague, M. E. Stratmeyer, presented paper, "Ultrasound-Induced Fetal Bioeffects" at *World Congress on Ultrasonics*, Paris, France, September 7-10, 2003, pp.1145-1146 in conference proceedings available at: **http://www.conforg.fr/wcu2003/procs/cd1/**.

therapy. In the *medical ultrasound research and practice* (*MURP*) *community*, MDU is thus a beginning-of-life and childhood neuroethics issue, with a fetus' or toddler's central nervous system (CNS) most sensitive to exposure to ultrasound. Medical disciplines' focus on "ALARA" (*vide next para.*) while improving image contrast mechanisms for the pulse-echo technique using reflections from acoustic-impedance discontinuities in tissue can inspire well-posed physics-based calculations to reframe the discussion on adverse vs. benign effects of medical ultrasound.[5] In typical B-Mode scans, an external ultrasound transducer (or probe or unit) transmits in the forward (say, $+x_1$) direction a pulsed beam into tissue and receives and time-gates multiple echoes returning in the opposite ($-x_1$) direction via reflections from tissue heterogeneities located on various planes (denoted by x_1=constant), feeding data to a computer to process it into images. Associated *medical ultrasound bioeffects mechanisms* (MUBEMs) entail known thermal and mechanical effects, respectively, of wave absorption and hydrodynamic shear flow from cavitating gas bubbles in lossy tissue (FSMSS, p.1) exceeding known thresholds for irrecoverable damage like protein denaturation and cell lysis. But scant attention is paid to nearly isothermal, purely solid-state mechanical shear strain or stress (SSMSSS), a 2nd (non-FSMSS) *mechanical* effect of longitudinal waves but in *fluid-free* soft solids. Though sought, the MURP community has provided no critique on his analysis while still promoting technology trends of growing mechanical energy, power or intensity levels from ultrasound units to improve image quality and facilitate hand-held use. So for the record a case is made here for solid-state bioeffects like residual SSMSS undetected in a susceptible *in utero* fetus at time of ultrasonic exposure, but possibly appearing in childhood as stunted CNS growth/development as of a brain's neurocircuitry, via subtle delayed functional bioeffects of cognition like memory and learning.

Such analysis is important, given nearly universal use of "ultrasounds" to manage pregnancies in all 3 trimesters[6] as for the 3.7 million births in 2019 in the U.S. Yet physicians generally believe ultrasound exposures are safe if kept "as low as (is) reasonably achievable" (ALARA) by using thermal and mechanical indexes like MI and TI in the output display standard (ODS) of ultrasound imagers, based on known, accepted *dose-bioeffect laws* and no "specific reason known" to suspect there is a significant health risk to fetus or mother from exposure to MDU in obstetrics."[7] But Hal's math does identify a "specific reason," linked to SSMSSS, to show this view lacks scientific rigor, is flawed by a fallacy of exclusion on the role of shear in deformation caused by longitudinal waves, and suffers from financial and other conflicts of interest. Also, if improperly used, FDA-approved medical devices can be unsafe.[8]

A broader physics framework may yield more truthful safety-vs.-efficacy assessments on MDU use via new dose-bioeffect laws incl. irreversible-bioeffect dose thresholds for elements of tensors of rank≥2. Such laws may be missed in MURP's assumption of ultrasound waves as disturbances in just particle displacement **u**, a vector, or excess pressure, p, a scalar invariant.

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[5] See, for ex., Eugenius S. B. C. Ang Jr, Vicko Gluncic, Alvaro Duque, Mark E. Schafer and Pasko Rakic (2006), "Prenatal exposure to ultrasound waves impacts neuronal migration in mice," Proc. Nat'l Academy of Sciences [NAS] of the U.S.A. **103 (34):**12903-12910; cited by over 200. Rakic is NAS member.

[6] E.g. visit U.S. Centers for Disease Control and Prevention online as at: **https://www.cdc.gov/pregnancy/zika/testing-follow-up/prenatal-care.html** and **https://www.cdc.gov/ncbddd/birthdefects/diagnosis.html**. Rapidly evolving use of ultrasound in obstetrics & gynecology is evident in a medical textbook in 3rd ed., *Ultrasound – The Requisites* by Barbara S. Hertzberg & William D. Middleton (Elsevier, 2015; 612pp.). Another recent book is *First-Trimester Ultrasound: A Comprehensive Guide* (Springer, 2016), 408pp., edited by Jacques S. Abramowicz of the Wayne State University School of Medicine..

[7] Douglas L. Miller (2008), "Safety Assurance in Obstetrical Ultrasound," *Seminars in Ultrasound, CT and MRI* **29(2):** 156–164. (Author was fellow physics graduate student of Hal at UVM; dissertation advisor for both was W. L. Nyborg.) Full text at **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2390856/**.

[8] For ex. via Medsun Reports database at **https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/Medsun/medsun_details.cfm?id=29420**, see report of 03/09/2012 on "Ultrasound Unit, PT." Incident reports are logged by medical-ultrasound users with the Center for Devices and Radiological Health (CDRH).

That comes from the math used that describes much biological tissue as liquid, with MDU seen mainly as *dilatational* or *longitudinal* plane waves of scalar or vector disturbances traveling in unbounded isotropic homogeneous solids with shear moduli of elasticity μ. To illustrate, ideal plane wave propagation in a lossy isotropic homogeneous solid is often taken to be governed by a 2-term 2^{nd}-order partial differential equation (PDE) or "wave equation" (WE) with constant coefficients for small-amplitude harmonic waves traveling in the direction of unit vector $\boldsymbol{p}$, with uniaxial motion in the direction of unit vector $\boldsymbol{d}$. (For longitudinal waves traveling in the x_1 direction, the motion is coaxial, so $\mathbf{u}=u_i\hat{\mathbf{e}}_1=\boldsymbol{d}_L$, with $\hat{\mathbf{e}}_1$ an RCC unit vector in the "1" direction.) Here, WE-solutions of damped harmonic fields are real *dependent* variables with arguments $(-\omega t \pm k_1x_1+\Omega_\mu)$ and $(-\alpha x_1)$, Ω_μ a constant phase angle for dependent variable of type μ. *Independent* variables are time t and component x_1 of field point vector $\mathbf{x}=x_i\hat{\mathbf{e}}_i$ (sum on i; unit vectors $\hat{\mathbf{e}}_i$ on RCC system axes), including $(\Pi_\pm)_p=[(\Pi_o)_\pm]_p\exp[-\alpha x_1]\sin[-\omega t\pm(k_1)_p x_1+\Omega_p]$ for p, and $(\Pi_\pm)_{u1}=[(\Pi_o)_\pm]_{u1}\exp[-\alpha x_1]\sin[-\omega t\pm(k_1)_{u1} x_1+\Omega_{u1}]$ for u_1, with subscript 1 for x_1 direction; $\boldsymbol{p}=k\hat{\mathbf{e}}_1$ for propagation in $+x_1$ direction; k and α real; both $[(\Pi_o)_\pm]u_1$ and $[(\Pi_o)_\pm]_p$ real; and by convention $\Omega_{u1}=0$ so that, for ex., $\Omega_p=-\pi/2$. Here $\omega=2\pi f$ of frequency f (like 1-20 MHz), $k_1=2\pi/\Lambda_1$ the propagation constant, k_1x_1 part of $\mathbf{k\cdot x}=k_ix_i$ for off-axis propagation denoted by $\boldsymbol{p}\equiv\mathbf{k}/k$, $c=\omega/k=f\Lambda$ the phase velocity, $\Lambda_1\equiv\Lambda$ the elastodynamic wavelength, and $\alpha_1\equiv\alpha$ an amplitude attenuation coefficient (α=0 if no losses). For longitudinal waves, the dot product is $\boldsymbol{p}_L\bullet\boldsymbol{d}_L=1$, and for shear waves $\boldsymbol{p}_s\bullet\boldsymbol{d}_s=0$. (For complex $\boldsymbol{p}$, see Addendum A in Part 2.) For context, the FDA guidance document cited elsewhere in this treatise recommends using a general value for biological tissue of $\alpha= 0.3\text{dB cm}^{-1}\text{Mhz}^{-1}=0.03454 \text{ neper cm}^{-1}\text{Mhz}^{-1}$.

But also useful WE dependent variables are rank-2 tensor functions like $(\Pi_\pm)_{\check{T}ij}=[(\Pi_o)_\pm]_{\check{T}ij}\exp[-\alpha x_1]\sin(-\omega t\pm k_1x_1+\Omega_{\check{T}ij})$ for a stress tensor (no indicial sum) and $(\Pi_\pm)_{\check{S}ij}=[(\Pi_o)_\pm]_{\check{S}ij}\exp[-\alpha x_1]\sin(-\omega t\pm k_1x_1+\Omega_{\check{S}ij})$ for a strain tensor. Important tensor element solutions include a sole uniaxial (principal) component either of stress $(\Pi\pm)_{\check{T}11}$ or strain $(\Pi\pm)_{\check{S}11}$, with Hooke's law $\check{T}_{11}=(\lambda+2\mu)\check{S}_{11}$ and phase-constant values $\Omega_{\check{T}11}=\Omega_{\check{S}11}=\pm\pi/2$. Though the frame-invariant trace is $Tr(\check{T}_{ij})=\check{T}_{11}$ or $Tr(\check{S}_{ij})=\check{S}_{11}$ for these uniaxial cases, neither $\check{T}_{11}$ nor $\check{S}_{11}$ is a scalar but transforms by the tensor rule). Even in unbounded media uniaxial stress creates triaxial strain, and uniaxial strain, triaxial stress. Another reason to analyze *triaxial* $\check{T}_{ij}$ or $\check{S}_{ij}$, though the math is more complex than for p, u_1, $\check{T}_{11}$ or $\check{S}_{11}$, is its power to faithfully model MDU's locally complex spatiotemporal patterns of *vibration* in a sampling volume V enclosing $\mathbf{x}$ of bounded lossy (α>0) anisotropic and inhomogeneous biological tissue. Here $\sqrt[3]{V}$ can span lengths of several multiples of Λ/4. In an unbounded to bounded transition, wave disturbances at $\mathbf{x}$ couple more strongly to effects of a sample's boundaries to add Poisson's ratio ν to expressions for new elements in $Tr(\check{S}_{ij})$. Also, reflection and mode conversion in or on V at echogenic discontinuities in 'acoustic' impedance (e.g., ρ_oc_L for longitudinal waves in solid with mass density ρ_o) enable B-mode imaging via pulse echoes returning in the $-x_1$ direction from them to the ultrasound unit sending them out in $+x_1$ direction, but may build up vibrations as standing waves damped by scattering and absorption creating many local spherical and other secondary disturbances with off-axis propagation in the 'near field' over tiny radial distances from small scatterers to observation point $\mathbf{x}$. Theory for continuum and contact mechanics for deforming solids, incl. boundary conditions (BC's) and continuity equations for $\check{T}_{ij}$ and u_i across interfaces can extend solutions for uniaxial principal stress or strain in an *unbounded* isotropic homogeneous perfect solid free of inhomogeneities and with distortion coupled to a constant scalar μ, to a case of *bounded* inhomogeneous aniso-tropic solid and nonlinear shear moduli of elasticity as elements of tensors of rank≥4. There are now 3 principal strains and 3 principal stresses, with 3 principal strain *differences* and 3 principal stress differences, plus interplay between shear strain and principal strain difference at **x**, depending on direction of the normal of the chosen plane intersecting **x** and so of both tangential and normal stresses deforming the solid there. An infinite no. of planes intersecting **x** can arise via a continuum of tilt angles with respect to the RCC axes (x_1, x_2, x_3). Instantaneous or time-ave. ultrasonic shear ($\check{T}_{i\neq j}$) or ($\check{S}_{i\neq j}$) at **x** ("dose") on one coinciding with a distortion-vulnerable material plane also at **x**, in a given in-plane direction, may cause slip via softened nonlinear shear compliance $J=\mu^{-1}=[\mu(\mathbf{x};\ \check{S}_{i\neq j})]^{-1}$. Then material damage and residual shear strain ("bioeffect") may result. With anisotropy, directions of principal stress and principal strain may no longer coin-cide. New epidemiological studies and physical and animal-model experiments preceded by computation and simulation studies are needed to test this model.

On the status of dose-bioeffect laws:

A dose/***immediate***-effect law for single-cell *mortality* exists for ultrasonic cavitation in liquid suspensions of red blood cells (RBC's), expressible in an x-y plot of shear stress as dependent variable or ordinate "y," with optically detected concentrations of released hemoglobin as independent variable or abscissa "x". For ex., see two research journal papers cited in Rooney's profile on p.16 alluding to a threshold for hydrodynamic shear stress (FSMSS) at which RBC lysis begins in a viscous liquid. Trial dose/immediate-effect laws for mortality are scarce when ultrasonic cavitation or heating from absorption of ultrasonic-wave energy severe enough to damage plasma membranes or denature proteins is absent and ultrasound creates solid-state effects only. Laws for *morbidity* are rare for either cavitational mechanical or thermal category – rarer still for nonthermal solid-state mechanical. MURP tends to ignore reports of dose-vs.-**delayed-effect** laws with subtle morbidity like altered neurodevelopment based on functional lesions seen in learning/memory deficits after long time delays. However, Hal, while investigating ultrasound-induced, purely solid-state mechanical effects in dry monolithic viscoelastic solids undergoing creep with only small temperature rises from sonication but without trapped bubbles, did observe an unpredicted but reproducible reversible residual SSMSS effect not seen with solely thermal methods. Accordingly, he hypothesizes a residual SSMSSS, a rank-2 strain tensor component, can be featured in dose/bioeffect laws either as bioeffect or as a dose with an as-of-yet confirmed biochemical, anatomical or other biomarker in a cellular mechano-transduction system or in excised tissue taken as nonlinear viscoelastic. Indeed, looking ahead through the lens of Part 2 to understand its significance, a clue to such a biomarker is in the 1969 Physiology and Biophysics dissertation at UVM by R. M. Schnitzler[9] who used experimental methods for ultrasound exposure (of excised muscle tissue) that Hal adopted, improved and applied to a thermoplastic epoxy 'phantom' in his own 1974 Physics dissertation at UVM [1st #2, p.8]. For ex., the striated muscle tissue sonicated by Schnitzler, whose report was noted by Hal [per # (12) on p.325 of "Footnotes and References" in his dissertation], revealed such a biomarker may be the "Z-line" in the sarcomere, a basic repeating unit in the banded structure found by post-irradiation TEM to have elongated irreversibly. Hal conjectured that, under severe ultrasound conditions, the "yield strength" of the contractile proteins as a solid "may be exceeded by the steady stresses [with ultrasound "on"]; when the sound is turned off, a permanent set or strain in the protein filaments remains" [pp.5-6 of Hal's

[9] Ronald M. Schnitzler, *The Effect of Highly Localized Ultrasonic Vibration on Skeletal Muscle*, February 1969 Physiology and Biophysics dissertation, The University of Vermont (UVM), Burlington, Vermont, USA. Hal developed theory on basis of his 1974 physics dissertation at UVM [1st #2, p.8] to explain ultrasound effects Dr. Schnitzler saw in *his* research. Prof. W. L. Nyborg [p.16] was the advisor on faculty committees for both dissertations. To get abstracts for both dissertations and some of their other works, enter "Schnitzler" or "Frost" in search engine at: **http://www.brl.uiuc.edu/Abstracts/**.

dissertation]. This may be an *ex situ* tissue precursor of aforementioned residual SSMMSS effect in epoxy Hal reported 4 and 5 years later.

Sensing/measuring usually hidden variable of orientational dependence of rank-2 strain tensor vs. pressure's orientation-invariant scalar effects:

Data from many types of contact probes, like thermocouples and hydrophones directly sensing temperature T and pressure p, respectively, as rank-0 tensors called scalars, tend to be insensitive to shear interactions of ultrasound in solids including soft ones like thermoplastics, gels, wax, biological tissue and exposimetry 'phantoms' mimicking tissue's low values of μ. Transducer elements built into 1D and 2D arrays of handheld front ends of medical ultrasonic imaging systems generally fail to monitor for SSMSSS-related dose bioeffects whether immediate or delayed. When used on human patients, such transducers, constructed of rigid solid materials, emit and detect *longitudinal* waves with wave propagation speed $c_L=\sqrt{[(\lambda+2\mu)\rho_o]}$, with λ the first Lamé constant (not wavelength) an ρ_o the initial, unstrained mass density. These waves have *longitudinal* axes for polarization and propagation direction in solids, even solid-like biological tissue with weak rigidity denoted by $\mu<<B$, with $B=\lambda+(2/3)\mu$ the bulk modulus and $B\rightarrow\lambda$ when $\mu\rightarrow0$. But, as B for much of biological tissue has a value close to water's (λ_{water}), many in the MURP community regard ultrasound's action as just that of p, the excess pressure, or of particle displacement component u_1. That POV assumes the strain or stress tensor at **x** [viz., Eq.(1), Part 2] has a *spherical* part large enough to ignore the small *deviatoric* part when $\mu<<B$. That then wrongly implies that deformation caused by longitudinal waves in soft tissue is only *volumetric* in nature, dismissing their small but important *isochoric* power to iso-volumetrically distort shapes or change orientations of particle pairs in their propagation paths.

Ultrasound from MDU transducers, though, can deform tissue with significant volumetric and isochoric contributions. So it is important to make clearer the role of shear rigidity in ultrasound's action on soft tissue. To start, the pair of Lamé parameters, $M\equiv\lambda+2\mu$, has a general significance as the elastic modulus for waves of dilatation given as the sum of the on-diagonal components of the strain tensor which in the 3D case has 3 terms but for longitudinal waves has just one, e.g., $\check{S}_{11}$. Dilatation in a rectangular Cartesian coordinate (RCC) system equals the trace Θ of the strain tensor Š given by $\Theta\equiv Tr[\check{S}_{ii}]=\check{S}_{11}+\check{S}_{22}+\check{S}_{33}$, invariant under coordinate transformation. So, longitudinal waves of uniaxial strain with speed c_L in a solid is a special case of dilatational waves with triaxial strain traveling as waves of pressure $p=-\lambda\Theta$ for liquid ($\mu=0$) at frequencies not too high; with wave speed $c_L=c_D=\sqrt{[(\lambda+2\mu)/\rho_o]}=\sqrt{(M/\rho_o)}$ and $\mu>0$.

Ideally, sinusoidal and other time-varying field disturbances are governed by simple WE's, 5 given here for waves of infinitesimal amplitude propagating in the $+x_1$ direction in unbounded media, with no attenuation losses ($\alpha=0$) and no change in mass density ρ from ρ_o. For waves in liquids of excess pressure "p" with speed $c_p\equiv\sqrt{(\lambda/\rho_o)}$ the WE is: $\partial^2p^o/\partial t^2=(\lambda/\rho_o)\partial^2p^o/\partial x_1^2$. For longitudinal waves, the WE for particle displacement u^o_1 as the dependent variable, the WE is: $\partial^2u^o_1/\partial t^2=[(c_D)_o]^2\partial^2u^o_1/\partial x_1^2$. Paired with u^o_1 (with superscript "o" still denoting an infinitesimal disturbance) are alternate dependent variables $\check{T}^o_{11}$ and $\check{S}^o_{11}$ (both out of phase with u^o_1) for longitudinal stress with WE of $\partial^2\check{T}^o_{11}/\partial t^2=[(c_D)_o]^2\partial^2\check{T}^o_{11}/\partial x_1^2$ and longitudinal strain with WE $\partial^2\check{S}^o_{11}/\partial t^2=[(c_D)_o]^2\,\partial^2\check{S}^o_{11}/\partial x_1^2$. So elastodynamic disturbances can be stress or strain waves, too, with a work density $\check{T}^o_{11}\check{S}^o_{11}$ having a time average $\langle\check{T}^o_{11}\check{S}^o_{11}\rangle>0$. For dilatational waves (called P-waves in geophysics), the WE is:

$$\partial^2\Theta^o/\partial t^2=[(c_D)_o]^2\nabla^2\Theta^o=[(c_D)_o]^2\,[\partial^2\check{S}^o{}_{11}/\partial x_1{}^2+\partial^2\check{S}^o{}_{22}/\partial x_2{}^2+\partial^2\check{S}^o{}_{33}/\partial x_3{}^2].$$

In MURP despite such differences, longitudinal waves are typically but erroneously regarded as pressure waves exerting only normal forces on *planes* of *any* orientation they pass through at tissue interaction sites, with tangential (in-plane) forces assumed absent. But important isochoric deformation information hides behind the small departure of $(c_L)_{solid}$ from $(c_D)_{fluid}$ for $\mu<<\lambda$, as expressed in the Taylor series approximation $c_L\approx[1+(\mu/\lambda)]\sqrt{(\lambda/\rho_o)}$ when $\mu<<\lambda\approx B\approx M$, as for shear-soft and/or shear-weak biological media. a stark reality of shear in solids is the overlooked plane-orientational dependence of $\check{T}_{ij}$ and $\check{S}_{ij}$ expressed by their coordinate transformation properties per the rank-2 tensor rule, as seen in the context of longitudinal, extensional and related wave equations with axial polarization. For ex., consider at ($\mathbf{x}$, t) in an RCC system with coordinate axes $[x_1, x_2, x_3]$, a plane ultrasound wave with associated triaxial principal stress components $\check{T}_{11}$, $\check{T}_{22}$ and $\check{T}_{33}$ traveling along the x_1-axis to produce a volumetric (compressional/rarefactional) uniaxial strain $\check{S}_{11}=\partial u_1/\partial x_1=\check{T}_{11}/M$ of direction coaxial with wave propagation direction $\hat{\mathbf{e}}_\mathbf{k}=\hat{\mathbf{e}}_\mathbf{n}$, with $\hat{\mathbf{e}}_\mathbf{n}$ the normal to the plane the wave passes through at normal incidence. Here, tangential stress is zero on any face of a tiny volume element $\Delta V=\Delta x_1\Delta x_2\Delta x_3$ with centroid at $\mathbf{x}$ and pre-ultrasound undeformed shape of a cube of volume $\Delta V_o=[(\Delta x_1)_o]^3$ with co-equal sides $(\Delta x_1)_o=(\Delta x_2)_o=(\Delta x_3)_o$, with 6 square faces with each normal coaxial with the normal to its respective coordinate plane, viz., x_2-x_3 plane for 2 surfaces with normals coaxial with x_1 axis.

In the solid geometry of 3D Euclidean space, volumetric deformation represented by $\check{S}_{11}$ changes an initial cubical ΔV_o into a rectangular parallelepiped of volume $\Delta V\neq\Delta V_o$. However, in a newly oriented, deformed volume element $\Delta V'=(\Delta x_1)'(\Delta x_2)'(\Delta x_3)'$ in the space of an RCC' system with coordinate axes $[(x_1)',(x_2)',(x_3)']$, one or more of which may be tilted (in pairs) via coordinate transformation with respect to $[x_1, x_2, x_3]$ axes, shear stress arises on one or more pairs of the 6 new faces on which up to 9 non-zero components (like the 3 new on-diagonal ones) of transformed stress tensor $\check{T}'$ act to produce a new strain tensor $\check{S}'$. Here, action of $\check{T}'$ changes a rectangular parallelepiped (volume ΔV) into a parallelepiped (volume $\Delta V'$), with each face (in 1, 2 or 3 pairs) now shaped as a parallelogram (but remaining faces in 2, 1 or 0 pairs, respectively, as rectangles) and $\Delta V'=\Delta V$ as a (deformed) volume and scalar quantity invariant under a coordinate transformation. A normal stress acts on all 6 faces of ΔV and $\Delta V'$. In the example of longitudinal waves propagating in the x_1 direction in an RCC system, no change occurs in the 'angular' shape of ΔV, as all edges of ΔV of the volumetrically deformed solid remain parallel or perpendicular to each other. But longitudinal waves seen in an RCC' system yield a deformed volume $\Delta V'$ with some edges tilted, revealing *isochoric* strain.

In an isotropic solid, a tilt by any angle resolves an exclusively normal stress into two parts, a normal stress and a tangential stress, the latter of which can produce a shear strain such as SSMSS. This shear strain becomes an extremum of absolute value $\frac{1}{2}|\check{\mathbf{S}}|$ when, for ex., the RCC' system is formed by rotation of the x_1-axis in the x_1-x_3 plane about the x_2-axis by angle $\Theta=\pm45°$ or $\pm135°$ to form a new $(x_1)'-(x_3)'$ plane [with $(x_2)'=x_2$]. Here the associated extremal component of $\check{\mathbf{S}}$ is a tangential strain in any plane with normal $\hat{\mathbf{e}}_{\mathbf{n'}}$ so inclined to $\hat{\mathbf{e}}_\mathbf{k}=\hat{\mathbf{e}}_{\mathbf{x1}}$, per dot product, $\hat{\mathbf{e}}_\mathbf{n}\bullet\hat{\mathbf{e}}_{\mathbf{n'}}=\pm1/\sqrt{2}$. This POV is borrowed from rock mechanics. For equations and the useful interpretive tool of Mohr's circle diagrams, see, for ex., Sec. 2.3, "Stress in two dimensions," pp.11-17 in FRM (cited in Footnote [21] and included in the list of acronyms).

This continuum-mechanics POV is missed when misconstruing longitudinal waves as p, not $\check{T}_{11}$, waves, as in modeling B-scans of medical imaging enabled by tissue's echogenic acoustic-impedance (Z) discontinuities that reflect ultrasound waves. (For plane waves, $Z=\rho c_L$.) Isochoric effects of shape distortion in solid-like tissue from purely solid-state mechanical deformation effects controlled by μ are known to exist in MDU use. But ignoring the origins of their true potential for solid-state bioeffects exclusive of cavitation or severe heating comprises a serious error in safety-vs.-efficacy judgments, assuming tissue damage from ultrasound in some important cases is more of a shear rather than compression or tension effect.[10] Also, shear is a universal phenomenon not limited to effects from fluid flow. Posing and doing new experiments, theoretical calculations and computer simulations is important, then, to see if the shearing stresses available from longitudinal waves[11] are strong enough to produce an observable SSMSSS-type effect in fragile parts of biological tissue that have low values of shear yield, plastic flow threshold or breaking strength on vulnerable planes.

There is uncertainty over what type of stress (tensile, compressive , shear) acts in the system of chemical and biochemical processes, intra- and inter-cellular dynamics & mechanotransduction of applied mechanical forces initiating signaling to control protein synthesis & DNA transcription for growth processes and tissue remodeling after damage or injury. Stresses do produce exogenous strains that disturb endogenous strains homeostatically controlled to optimize performance of that system. Except for rare use of optical methods like polarization-sensitive photoelasticity and optical coherence tomography, though, such *pre*-strains go undetected and thus may change in uncontrolled fashion by unaware use of MDU imaging transducers in clinics. In that regard, present models generally used in MURP to describe operation of an ultrasound imager or its effects on tissue in general fail to incorporate hidden, shear-related or orientation-dependent variables whose measurement has potential to show how immediate, 'innocuous' and undetected effects of ultrasound at microscopic size levels in the ovum, embryo or fetus may evolve over time to observation finally of delayed adverse effects in an organ or the whole body of a human person as child, teenager or adult. Thus there seems to be a need to investigate a new, shear-strain-related mechanical index or MI for soft solids.

Need for 'time-longitudinal' studies of medical diagnostic ultrasound (MDU) bioeffects and experiments on purely solid-state MUBEM's:

Oversight in the MURP community pays scant attention to revising past MDU risk-vs.-benefit assessments by better embracing (1) all of the literature in old (print) and new (digital) formats describing the physical action of ultrasound in man-made or natural materials and then (2) testing of alternative (as opposed to null) hypotheses that physical effects of ultrasound observed in the lab may lead to adverse bioeffects of ultrasound in the clinic, whether or not there are present means to detect and measure them at times of exposures or after long time delays. The technology in this area is tracked well, but not the science. Letting the science catch up can mean better linking known but overlooked persistent local mechanical effects of

[10] See Ch.14, "Bioeffects of the Physical Environment," pp.454-516 in Wesley L. Nyborg, *Intermediate Biophysical Mechanics* [*IBM*] (Cummings Publ. Co., Menlo Park, CA, 1975; a *vade mecum* for this treatise), incl."Ch./Sec. 14.9.9, "Other Bioeffects" referring on p.513 to Hal's 1974 physics dissertation & their UI73 paper cited on p.587 + Ch./Sec. 6.4.1, "Shear-Stress Hypothesis" (pp.165-167) & "Applications of the Shear-Stress Hypothesis (pp.167-169) in NCRP Report No. 140, *Exposure Criteria for Medical Diagnostic Ultrasound: II. Criteria Based on All Known Mechanisms* issued December 31, 2002 by the National Council on Radiation Protection and Measurements (NCRP), as prepared by Scientific Committee 66 chaired by Prof. Nyborg.

[11] At field point **x** solid-state shear stress from longitudinal waves with only one stress component $\check{T}_{11}(\mathbf{x})$ is a maximum or a minimum, viz., an extremum, with absolute value of ½ $|\check{T}_{11}(\mathbf{x})|$, on any plane cutting the propagation axis (PA) at angles of ±45˚ or ±135˚ in any plan view. See Part 2 for extra details.

purely solid-state origins in phantoms to potential adverse bioeffects as in CNS tissue, as seen in *ex situ* and *in situ* exposures to MDU; supporting computation and simulation; physical experiments; and animal-model studies to test concerns arising from prior math analysis such as in this treatise. Furthermore, ultrasound bioeffects studies usually do not longitudinally track large cohorts of patients or test animals from prenatal exposures and epidemiological analyses are outdated. For ex., internal SSMSSS from MDU exposure is not clinically tracked, nor neuronal-distortion correlates of it for-delayed effects in humans like learning and memory anomalies detected by psychological testing years after birth.[12] Thus Hal advocated with leadership of an ultrasound bioeffects committee[13] and regulatory agency managers[14] to extend his math calculations based on old physics and animal-model experiments to uncover overlooked evidence for ultrasound bioeffects of immediate residual SSMSSS or softening of μ in fetal-CNS and child-BBB tissue at microscopic levels and corresponding delayed effects on learning and thinking.

PART 2: TENSOR PARADIGM OF ENTROPY PRODUCTION, HOOKE'S LAWS AND EQUATIONS OF MOTION NEEDED TO REFORM MATH FRAMEWORK USED TO ASSESS MEDICAL DIAGNOSTIC ULTRASOUND (MDU) RISK-V.-BENEFIT

Summary, Scope and Perspective:

A compelling need exists for a deeper level of math to more completely specify and measure thermodynamically relevant states like physical, condition, material and dynamic of living human tissue as an anisotropic and inhomogeneous soft solid, either elastic -- or viscoelastic (VE) or other deformation-rate-dependent type. Such math can integrate knowledge from STEM topics including the oft overlooked one of non-equilibrium thermodynamics to develop a suitably broad framework encompassing elastodynamic wave propagation in solids undergoing relaxation or creep. Such waves can induce or be perturbed in conjunction with changes in internal energy ΔU of a system of mutually interacting atoms and molecules with kinetic and potential terms exclusive of intra-nuclear contributions. *Physical state* is for matter as gas, liquid or solid. *Condition state* denotes reference (e.g., perfect crystal at absolute zero tempera-ture, or room-temperature solid free of residual stress or strain), initial (viz., undeformed) or final (e.g., deformed) states with applicable initial and boundary conditions in the flow or deformation history of matter with pre-strain, residual strain and memory in solids and ambient pressure in liquids. *Material state* refers, for ex., to presence of matter (e.g., microbubbles or tiny solid particles) suspended in a liquid or of natural structural features or of unwanted flaws or defects embedded in a solid matrix, or of anatomical and physiological (i.e., structural and functional) features, defects or damage in biological matter of indeter-minate physical state. Such inhomogeneities in tissue can limit as well as facilitate functioning, performance and lifetime of a body or organ. Finally, *dynamic state* specifies the type of time evolution a system undergoes, as in stationary and non-stationary states of equilibrium. Dynamic states for closed or open

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[12] See, for ex., the well cited paper, "Effect of diagnostic ultrasound during the fetal period on learning and memory in mice" by R. Suresh, Rao T. Ramesh, E.M. Davis, N. Ovchinnikov and A. McRae (2008), *A. Ann Anat.* **190(1):** 37-45. Abstract is at: **https://www.ncbi.nlm.nih.gov/pubmed/18342141**.

[13] This includes e-mail exchanges in 2016--2018 with J. S. Abramowicz, MD, AIUM Bioeffects Committee (BC) Vice Chair (now Chair) that "provides information to the AIUM membership on matters relating to the biological effects of ultrasound...," per **https://www.aium.org/aboutUs/committees.aspx**.

[14] Incl. e-mail exchanges in 2018 with Dr. Keith Wear, Acoustics Lab Leader, Applied Mechanics Div., CDRH, FDA + now AIUM-BC Vice-Chair. Hal's CV with Apps. II-III, the basis of this treatise, were also sent, as on July 26, 2020 to CDRH Director Jeffrey Shuren, M.D. (Dr. Wear Cc'd). Later e-mail to Dr. Shuren incl. "Rebuttal to your reply," July 30, 2020, with 15 "Cc's" incl. Dr. Wear. FDA information on medical ultrasound devices is provided at **https://www.fda.gov/Radiation-EmittingProducts/default.htm**. This present document was not sent to the FDA.

thermodynamic systems are thermal, mechanical or chemical, for example – with static, dynamic and stable as equilibrium cases and unstable for non-equilibrium.
An extensive thermodynamic variable included in Part 2 is entropy, denoted by symbol S. Its total incremental variation ΔS (akin to differential dS) is $\Delta S = \Delta S_1 + \Delta S_2$. The 1st term is for entropy introduced to the system by its surroundings as a heat increment ΔQ, described by the 2nd Law of Thermodynamics for a reversible process in a closed system, as $\Delta S_1=\Delta Q/T$ with T>0. Term ΔS_2 is the entropy produced inside the system, as by an ultrasonic elastodynamic wave propagating in a soft solid inducing in it a local solid-solid order/disorder transition with a small or zero heat of transition and so at most a small change in temperature. (For example of ΔS_2 from rubber elasticity with no change in internal energy, see Footnote [24].) In a reversible process, ΔS=0: for an irreversible one, ΔS>0. In irreversible non-equilibrium thermodynamics, entropy can be interpreted as disorder or randomness; increasing as either does.

In the *scalar* paradigm for ultrasound bioeffects, whether adverse or benign, knowledge of state status is specified via observables as *rank-0 tensors* or "scalars" (e.g., temperature T, mass density ρ, or excess acoustic pressure p) or *rank-1 tensors* or "vectors" (as with field point components x_i or particle displacement components u_i i), but not *rank-2 tensors* (e.g., with shear stress components $\check{T}_{i\neq j}$, or shear strain components $\check{S}_{i\neq j}$ as examples of SSMSSS), nor rank-4 tensors (e.g., the elastic constants $\check{C}_{ijkl}$). This *status quo* view tends to favor simplistic math models for ultrasound's action on tissue often thus taken as liquid (pure, or one suspending particles) with condition and material states based mostly on dissolved or free gas and suspended solids content -- and no internal entropy production. This usual view also tends to limit inclusion of conservation laws to just those for mass, linear momentum (equation of motion or EOM and total energy, while omitting those for entropy production and angular momentum motion, including roles of chemical reactions in the solid.

A broadened perspective of all three conservation laws and ones for mass and angular momentum, as either just assumed (mass) or simply incorporated by using *symmetric* strain tensors $\check{S}_{ij} = \check{S}_{ji}$ (rank 2), plus *antisymmetric* rotation tensors $\check{R}_{ij} = -\check{R}_{ji}$ important for describing pure-shear and simple-shear fields of u_i, is facilitated in an organic way by adopting a *tensor-based* paradigm in the context of linear partial differential equations (PDE's) with variable coefficients and PDE's for nonlinear effects in strain – for elastodynamic waves in solids in both Eulerian and Lagrangian frames. Concepts treated in the classic work of de Groot and Mazur are used here while others are just identified for the reader's follow-up.[15] From p.6 of that classic work is this happy support: "The theory of non-equilibrium thermodynamics has found a great variety of applications in physics and chemistry. For systematic classification of these applications one may group the various irreversible phenomena according to their "tensorial character" like rank 0, 1, 2.

As a start in that regard, Eq.(1) *infra* is presented in the Eulerian frame with physical state subscript "β" for a *rate-independent* form of Hooke's law for tissue exposed to an external force

[15] S. R. de Groot & P. Mazur (1984). *Non-Equilibrium Thermodynamics* (Dover Publications, Inc., New York) 510pp., 1st published by North-Holland Publishing Co. in 1962. From Dover ed. Preface: The "domain of validity" of book "is essentially the one for which the hypothesis of local equilibrium is valid, and includes, as far as transport processes are concerned, those phenomena for which the dissipative thermodynamic fluxes are linear functions of the gradients of the thermodynamic-state variables." Important follow-up reading includes: Ch. I (Introduction), Ch. II (Conservation Laws); Ch. III (Entropy Law & Entropy Balance); Ch. V (Stationary States or 'SS') incl. mechanical equilibrium & SS (equilibrium or non-equilibrium) with minimum entropy production in non-equilibrium SS for continuous system; Ch. 6 (Elastic Relaxation [in anisotropic solid]) incl. Eqs. (177)-(179) for "the EOM, the energy law and the entropy law"; sections in Ch. XII (Viscous Flow and Relaxation Phenomena) = 3 (Propagation of Sound [in a fluid]), 4 (Acoustical Relaxation); and pp. II (On Thermodynamic Relations [for Gibbs function or free energy "G"].

(e.g., of ultrasound) and modeled variously as *liquid* (β=1), *solid* (β=2), or *biological condensed matter* of indeterminate or mixed physical state (β=3) -- all with flow absent. In section following are discussed important distinctions between: *Pressure p in a liquid* with a 1-term scalar Hooke's law with bulk modulus B=λ (1st Lamé parameter) independent of shear modulus of elasticity μ (2nd Lamé parameter), and bulk *elastodynamic stress tensor components* $(\check{T}_{be})_{ij}$ in a solid with a 2-term Hooke's law including coefficient of 2μ. Developing a paradigm with tensors of rank-2 or higher rank better incorporating orientational and co-alignment effects is vital to understanding purely solid-state bioeffects of ultrasound; such 'dry' nearly nonthermal effects tend to decrease with decreasing rank order (2→1→0) for observables. Then Eq.(2) adds *flow* and rate processes in relaxation and creep phenomena with associated time dependence per a VE *linear* Hooke's law. Equation (3) is for a 3D frame-invariant shear quantity, octahedral shear stress (symbol, τ_{oct}),[16] placing FSMSS and SSMSSS MUBEM's on the same footing and including a criterion for material damage from applied stress. Equation (4) describes a *nonlinear* Hooke's law for an excess elastodynamic stress tensor $\Delta(\check{T}_{be})_{ij} \equiv (\check{T}_{be})_{ij} - (\check{T}_{o})_{ij}$ defined in analogy with excess pressure as the difference between total pressure and ambient pressure. Then nonlinear analogs of [Eq.(3)] are given with non-zero time averages, for cases of deformation as simple shear or uniaxial principal strain from a longitudinal plane wave. Equations (5)-(6) in a Lagrangian frame give the balance of linear momentum, followed by a section on *spatial* averages of tensor components as a function of local anisotropy arising from their orientational dependence on coordinate transformation used. Next are sections for emerging trends and gaps in ultrasonic imaging performance vs. safety; national health policy analysis and epidemiology to assess and manage uncertainty of risk of harm from ultrasonic SSMSSS; "Going Forward from Here...;" dedication, acknowledgments and advisory sections; and 5 Addenda.

As MDU is hypothesized to create SSMSSS in tissue without having to transmit shear waves directly into the human body via external transducer, the latter topic is omitted to better focus on unintended, uncontrolled exposure of patients to shear stress and strain that can be resolved from *longitudinal* strain and stress when μ>0, as evident in the following sections. The principles for this hypothesis draw from the theory of continuum mechanics and elasticity of solids and so, from the perspectives of Addenda A, B, D and E of this Part 2, Hal applied them to predicting the action that ultrasound produces in phantoms and biological tissue but are left out in *status quo* analyses such as behind the 2002 result given in Addendum C. Nonetheless, he has only scratched the surface here in this incomplete draft of a treatise on the subject.

Linear rate-independent Hooke's law as constitutive equation in absence of relaxation:

Rate-independence between stress and strain in condensed matter at a field point "**x**" and time "t" is made explicit in Eq.(1) and then *rate-dependence* in Eq.(2), both in the Eulerian frame for infinitesimal strain amplitudes in the absence of pre-strain and spatial gradients in mass density, and thus for linear deformation and property behavior. Both tensors are symmetric. For simplicity, the rotation tensor is assumed to be zero.[17] Equation (1) follows:

Eq.(1) $\{[\check{T}_{be}{}^{0}(\mathbf{x},t)]_{ij}\}_{\beta} = (\lambda_{be}{}^{0})_{\beta}\, [(\Theta_{be}{}^{0}(\mathbf{x})]_{\beta}\, \delta_{ij} + 2(\mu_{be}{}^{0})_{\beta}\, \{[\check{S}_{be}{}^{0}(\mathbf{x},t)]_{ij}\}_{\beta}$.

[16] Eqs.(49)-(51), p.24, *FRM*. Eq.(52) give the "direction ratios" for octahedral shear stress, as based on Eqs.(36)-(38) for the direction of the shear stress.

[17] The rotation tensor, ignored in Part 2 though important for treating multiscale complexity of shear deformation in biological tissue, can be studied via the theory of micropolar elasticity based on the development of Cosserat theory reprised in the book chapter of A. Cemal Eringen, "Theory of Micropolar Elasticity," pp. 101-248 in *Microcontinuum Field Theories, Vol I. Foundations and Solids* ed. by A. Cemal Eringen (Springer-Verlag, New York, 1999).

Generally suppressed until Eq.(2), superscript "0" makes explicit the assumption of infinitesimal strain amplitude. Eq.(1) uses the Kronecker delta function δ_{ij}, dilatation $\Theta=Tr(\check{S}_{be})$, Lamé parameters λ and μ, symmetric rank-2 Cauchy stress tensor $\check{T}_{be}$, symmetric rank-2 strain tensor $\check{S}_{be}{}^0$ and the rank-2 identity tensor δ_{ij} called the Kronecker delta function equal to 0 if i≠j but 1 if i=j. Six elements (i≠j) of the strain tensor provide by simple identity three independent SSMSS components, $(\check{S}_{be}{}^0)_{12}=(\check{S}_{be}{}^0)_{21}$, $(\check{S}_{be}{}^0)_{23}=(\check{S}_{be}{}^0)_{32}$ and $(\check{S}_{be}{}^0)_{31}=(\check{S}_{be}{}^0)_{13}$. The Eulerian-Almansi finite (i.e., linear) strain tensor in the Eulerian or spatial frame is given by:

$$(\check{S}_{be})_{ij}\equiv(1/2)[(\partial u_i/\partial x_j)+(\partial u_j/\partial x_i)+(\partial u_k/\partial x_i)(\partial u_k/\partial x_j)],$$ [18]

with infinitesimal strain $(\check{S}_{be}{}^0)_{ij}=(1/2)[(\partial u_k/\partial x_i)+(\partial u_k/\partial x_j)]=(\check{S}_{be}{}^0)_{ji}$. Here the particle displacement vector $\mathbf{u}=u_i\hat{\mathbf{e}}_i$ has components u_i at vector field point $\mathbf{x}=x_i\,\hat{\mathbf{e}}_i$ with components x_i. All components are defined in an orthonormal RCC frame with the three unit vectors $\hat{\mathbf{e}}_i$ lying on the coordinate axes. All 3 rank-2 tensors can be represented as 3x3 symmetric matrices, each with 9 components, 3 independent *on-diagonal* plus 6 *off-diagonal* for another 3 independent for a total of 6 independent components. Lamé parameters λ and μ constitute one of many pairs representing the 2 independent material properties of an isotropic and homogeneous liquid or solid, with μ the shear modulus of elasticity and λ in the bulk modulus $B=\lambda+(2/3)\mu$, with $\lambda=B$ for a liquid with $\mu=0$ (except at very high ultrasonic frequency). Other common parameter pairs are Young's modulus Y and Poisson's ratio v (Greek letter "nu," lower case) as in $Y=2\mu(1+v)$ for extensional waves and S_o plate waves, plus $M\equiv\lambda+2\mu=\lambda[v^{-1}-1]$ for P-waves and longitudinal waves. For incompressible solids, v is highest at value of ½, with $Y=3\mu$. Both λ and μ at macroscopic size scales can be spatially uniform or not. They are rank-0 tensors called scalars invariant with choice of the coordinate axes that transforms, for example, an RCC frame with initial $\hat{\mathbf{e}}_i$ into an RCC' frame with final unit vectors $\hat{\mathbf{e}}_i'$ for its coordinate axes. In contrast, vectors like $\mathbf{x}$ are rank-1 tensors with 2 invariants, their length $|\mathbf{x}|=+\surd(x_i\,x_i)$ and direction $\mathbf{x}/|\mathbf{x}|\equiv\hat{\mathbf{e}}_{\mathbf{x}}$, both independent of coordinate transformation like a pure rotation about a coordinate axis that changes x_i. A wave equation corresponding to Eq.(1) accounting for losses is $Mu_{1,11}=\rho_o u_{1,tt}$, with a shorthand subscript notation used for differentiation, e.g., $u_{1,tt}\equiv\partial^2u_1/\partial t^2$ and $u_{1,11}=\partial^2u_1/\partial x_1{}^2$. For these particle-displacement waves along the x_1-axis, only one component of the strain tensor $\check{S}_{be}{}^0$ is non-zero, $(\check{S}_{be}{}^0)_{11}=\partial u_1/\partial x_1=u_{1,1}$.

Use of linear Hooke's law to distinguish scalar-invariance from tensor-invariance concepts used in descriptions of action of MDU:

In further contrast, rank-2 tensors of stress and strain each have 3 invariants I_I, I_{II} and I_{III}, with I_I the trace of a tensor, which in the matrix representation is the sum of the three diagonal components (i=j). With symbol "Tr," this operation for strain is denoted as $[Tr(\check{S}_{be})]_\beta=[(\check{S}_{be})_{11}]_\beta+[(\check{S}_{be})_{22}]_\beta+[(\check{S}_{be})_{33}]_\beta=\Theta_\beta=[(I_I)_{\check{S}be}]_\beta$, with Θ_β a generalized form of the dilatation appearing in Eq.(1). For stress, that sum is given by

$$Tr(\check{T}_{be})]_\beta=[(\check{T}_{be})_{11}]_\beta+[(\check{T}_{be})_{22}]_\beta+[(\check{T}_{be})_{33}]_\beta=[(I_I)_{\check{T}be}]_\beta,$$

[18] The Einstein sum convention is applied for repeated Roman subscripts but not for repeated Greek subscripts (like α). Superscript 0 was restored for this statement. Anticipating Eqs.(5)–(6) for deformation in the Lagrangian or material frame with position coordinates a_i embedded in the test sample, the finite or nonlinear Green strain tensor in that frame is $(\check{E}_{be})_{ij}\equiv(1/2)[(\partial u_i/\partial a_j)+(\partial u_j/\partial a_i)+(\partial u_k/\partial a_i)(\partial u_k/\partial a_j)]$. Position coordinates x_i and a_i are related by means of the particle displacement vector $u_i = x_i - a_i$. If strain is infinitesimal, the Eulerian strain tensor equals the Lagrangian strain tensor.

so that Eq.(1) yields $[Tr(\check{T}_{be})]_\beta=(3\lambda+2\mu)_\beta\Theta_\beta=(3\lambda+2\mu)_\beta[Tr(\check{S}_{be})]_\beta$. So, $[Tr(\check{T}_{be})]_\beta=3B_\beta [Tr(\check{S}_{be})]_\beta$. For solids, the quantity $I_1([\check{T}_{be}]_{\beta=2})=[Tr(\check{T}_{be})]_{\beta=2}$ has no common name in MURP, but for liquids $I_1([\check{T}_{be}]_{\beta=1})= [Tr(\check{T}_{be})]_{\beta=1}$ is well-defined as pressure in a fluid, $p= -(1/3)[Tr(\check{T}_{be})]_{\beta=1}= -\lambda\Theta$. This is hydrostatic pressure in the absence of ultrasound or excess pressure in its presence. Pressure as a function of field point **x** and time t, viz., p=p(**x**,t), is linear when ultrasound levels are low, as in tonebursts with harmonic time dependence and zero time-average over one ultrasound cycle. In nonlinear cases at high ultrasound level, p accretes higher-order terms such as quadratic when "radiation pressure" exists with non-zero ultrasonic time average. "Radiation force" arises from (1) radiation pressure in a liquid and is called acoustic radiation force (**ARF**, a vector), and (2) radiation stress in a solid as called elastodynamic radiation force (**ERF**, a vector).

Pressure, a scalar, is a typical dependent variable in many published wave equations for generation, propagation, absorption, scattering and detection of ultrasound in medical use. For an important ex., pressure is a wave emitted as mechanical radiation from gaseous or vapor cavitation of a microbubble in a viscous liquid like water. Ultrasonic cavitation, especially inertial, has a high profile in the MURP community including regulators of medical (and dental) ultrasound devices, as a known MUBEM for damaging biological tissue. Along with prevalent use of pressure as a dynamic variable in equations presented in book chapters on the physics of ultrasound in it medical applications, the ease for visually observing dramatic liquid flow and electronically detecting sub-harmonic and harmonic emissions associated with cavitation in liquids may have contributed to an unwritten belief of biological tissue except the skeletal system as basically liquid solid. Perhaps further contributing to that bias is that until recently, generation and propagation of shear waves in biological tissue was impracticable due to difficulty in designing transducers generating them, plus high attenuation coefficients of shear waves in tissue compared to those for longitudinal or dilatational waves. Also, safety concerns tend to arise more when focused, high-power longitudinal waves are used to locally and internally generate supersonic shear-wave shock fronts at the focus [SSMSS]. For these and other reasons, the MURP mechanically regards soft biological tissue more like water or other liquid in only excess *pressure* p arises in a patient being exposed to ultrasound.

Though convenient, this choice of p or even u_i can be disenabling, as $\check{T}_{ij}$ has more power for correctly modeling ultrasound bioeffects though requiring more advanced math to master and more attention to keep track of principal stress and principal strain axis orientations, plus those of principal shear stress and principal strain, with respect to normals of planes tangent to adverse-bioeffect-prone or damage-vulnerable surfaces and interfaces in human tissue like curved *plasma membranes* of individual cells and their *junctions* when adjacent or separated by an extracellular matrix. Such areal segments or 'faces' may not be vulnerable to shear damage just from cavitation's microstreaming (viz., FSMSS). That is, not only velocity gradients in flows in a liquid with shear viscosity η or η^o [equal to $(\mu^0)'$ in Eq.(2) next] can lead to a shear stress on a damage-prone biosurface but also just strain itself in a dry solid with a shear modulus of elasticity μ [per Eq.(1), for no flow]. In a soft solid, the effect of μ on *on-diagonal* stress components is small due to the small 2nd term with coefficient (2/3)μ in the 2-term coefficients for bulk modulus B, per Eq.(1) and $B_{\beta=2}=\lambda_{\beta=2}+(2/3)\mu_{\beta=2}$ with $\mu_{\beta=2}<<\lambda_{\beta=2}$. But the coefficient is 2μ in the 1-term expressions for the six *off-diagonal* stress components. Thus, adopting a tensor paradigm means in effect dealing with local tensorial anisotropy in tissue.
That is, in a viscous liquid or solid, $\check{T}_{ij}$ and strain $\check{S}_{ij}$ are chameleon-like math objects changing values in a coordinate transformation in a more complex way than u_i does and thus more than p

does. To see this, first consider sums of all on-diagonal stress or strain components per $[\mathrm{Tr}(\check{T}_{be})]_\beta=(3\lambda+2\mu)\Theta_\beta$, with β≡1 or 2, invariant with coordinate transformation (e.g., RCC to RCC'). In an inviscid liquid (β=1), a single component $[(\check{T}_{be})_{ii;\ no\ sum}]_{\beta=1}$ is rotation invariant, equaling each of the other two, viz., $[(\check{T}_{be})_{11}]_{\beta=1}=[(\check{T}_{be})_{22}]_{\beta=1}=[(\check{T}_{be})_{33}]_{\beta=1}=\lambda\Theta_{\beta=1}\equiv-p$. Here, pressure p as a measure of any of the 3 on-diagonal stress components is always normal to the plane chosen to define it. Thus at any point on a liquid-solid boundary surface, p still acts over an infinitesimal area as a force directed coaxially with the surface normal. With no shear viscosity in the liquid and thus no tangential force acting on that surface, p is a principal stress. In contrast, for a viscous liquid in which flow occurs as well as for a solid in the absence of flow, a double coordinate transformation[19] is required to find the planes on which the stresses are entirely normal as principal stresses.[20] Such a principal stress integrated over an area on such a surface exerts a normal but no tangential force. On-diagonal stress components in a solid, even principal values, thus behave differently than those for an inviscid liquid, varying at a given field point **x** on a surface on either side of which there is no stress release. However, the trajectory of one of the 3 orthogonal directions of the 3 principal values of stress in a solid (β=2) still meets a free surface at right angles to it,[21] similar for the case of pressure in liquids with no viscosity. Each of the 3 principal stresses, given symbol P, in a 3D solid or liquid yields three non-zero principal stress differences. Suppressing the β subscript, these are given as $P(\check{T}_{be})_{11}-P(\check{T}_{be})_{22} \geq P(\check{T}_{be})_{22}-P(\check{T}_{be})_{33} \geq P(\check{T}_{be})_{33}-P(\check{T}_{be})_{11}$, the order in the inequality rule being an engineering convention. Shorthand notation for principal stress differences, suppressing the "be" subscript, is $\check{T}_1-\check{T}_2\geq\check{T}_2-\check{T}_3\geq\check{T}_3-\check{T}_1$. In contrast, all three principal stress differences in an inviscid liquid are zero.

Suppose in an RCC system frame $[x_1, x_2, x_3]$ an imaginary tetrahedron with 4 triangular faces is formed in an isotropic homogeneous solid, with the corner opposite the inclined face at the origin and a field point defined by position vector **x** taken to be normal to the inclined face and itself inclined to the coordinate axes by angles θ_i for direction cosines $\cos(\theta_i)$. Then $\mathbf{x}=|\mathbf{x}|\ \hat{\mathbf{e}}_\mathbf{x} \equiv x_i\ \hat{\mathbf{e}}_\mathbf{i}$ with $\hat{\mathbf{e}}_\mathbf{x}=\cos(\theta_i)\hat{\mathbf{e}}_\mathbf{i}$ the unit normal vector to the inclined face, and the stress *vector* $\mathbf{T}=\mathbf{T_i}\ \hat{\mathbf{e}}_\mathbf{i}$ for the 6 independent stress components across the inclined face is given by $\mathbf{T_i}=\check{T}_{ij}\cos(\theta_j)$. To simplify the math let $[x_1, x_2, x_3]$ be the reference frame with coordinate axes coaxial with the principal stress directions, via a shorthand notation of $P(\check{T}_{be})_{ii}\equiv\sigma_i$. Then $\mathbf{T}_i=\cos(\theta_j)\ \sigma_i$ (no sum on repeated indices). The magnitude $\mathrm{T}\equiv|\mathbf{T}|$ of the resultant stress across the inclined plane is $\mathrm{T}=\sqrt{(\mathbf{T_I\ T_i})}=\sqrt{[(\cos^2(\theta_j)(\sigma_i)^2]}$ and the normal stress to it is $\sigma=\sigma_i\cos^2(\theta_j)$. The magnitude τ of the shear stress across the inclined plane is given by $\tau^2 = \mathrm{T}^2 - \sigma^2$. The calculation to find the extremal values of τ involves many terms (viz., pp.21-22, FRM cited in Footnote [21]) but some of the results are simple. If $\cos(\theta_1)=0$ and $\cos(\theta_2)=\cos(\theta_3)=2^{-1/2}$, then $\tau=½\ (\sigma_2-\sigma_3)\equiv\tau_1$. If $\cos(\theta_1)=\cos(\theta_3)=2^{-1/2}$ and $\cos(\theta_2)=0$, then $\tau=½\ (\sigma_1-\sigma_3)\equiv-\tau_2$. Or if $\cos(\theta_1)=\cos(\theta_2)=2^{-1/2}$ and $\cos(\theta_3)=0$, then $\tau=½(\sigma_1-\sigma_2)\equiv\tau_3$. The three extremal shear stresses τ_i are called the principal shear stresses. Preceding values of $1/\sqrt{2}$ for the $\cos(\theta_i)$ correspond to angles of ±π/4 radians

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[19] Components of rank-2 Cartesian tensor Ň can be changed vi coordinate transformation $(\check{N}')_{mn}=a_{mi}a_{nj}(\check{N})_{ij}$, viz., Cauchy stress tensor $([\check{T}]_{be}')_{mn}=a_{mi}a_{nj}([\check{T}]_{be})_{ij}$, with direction cosines a_{pq}. Infinitesimal strain tensor rule is $(\check{S}^0)'_{mn}=a_{mi}a_{nj}(\check{S}^0)_{ij}$, given in Chs. 2 & 3 of *IBM* like Eq.(2.8), p.36 as double sum for Nyborg's stress tensor "S". Vector **A** as a *rank-1 tensor* has RCC components obeying the coordinate transformation $A_j'=a_{ji}A_i$ giving new components A_j' in RCC'. A scalar is *a rank-0 tensor* like pressure p=p' in a liquid, or rank-4 tensor norm $||\mu'||=||\mu||$ of shear modulus of elasticity μ in an isotropic and homogeneous solid.

[20] Principal values of the norm & direction of a rank-2 tensor can be found by solving its eigenvalue problem via spectral decomposition, as described in curvilinear coordinates on pp.23-27 of Yavuz Başar & Dieter Weichert's book, *Nonlinear Continuum Mechanics of Solids – Fundamental mathematical and physical concepts* [*NCMS*] (Springer Verlag, Berlin, et al., 2000).

[21] Viz., *Fundamentals of Rock Mechanics*[*FRM*], 3rd Ed., by J. C. Jaeger and N. G. W. Cook (Chapman and Hall, London and New York, 1979), paperback, 593 pp. Items (iv) and (vi) in list on p.17 distinguish between principal stress directions and isoclinics observed in solids via photoelasticity such as reported in Hal's 1973 UI73 paper and 1974 physics dissertation research on action of ultrasound on a viscoelastic solid.

with respect to the associated RCC axes and thus here with the directions of the principal stresses. (Associated with each principal shear stress is the corresponding normal stress expressed in terms of the isopachic or sum of the same principal stresses, that is, $½(σ_2+σ_3)$ paired with τ_1, $½(σ_3+σ_1)$ paired with τ_2, and $½(σ_1+σ_2)$ paired with τ_3.) So, for ex., in a longitudinal plane (x_1, x_2), extremal shear $|\tau_3|=½|\check{T}_{11}-\check{T}_{22}|$ for a plane longitudinal wave propagating in the "1" direction with stress $\check{T}_{11}$ is resolved on the plane that bisects the x_1 and x_2 axes. (More detail on this problem is provided in Addendum A to Part 2.) With a shear stress damage threshold of 1500 dyn/cm^2 for a red blood cell in a viscometer,[22] then a longitudinal stress value of 3000 dyn/cm^2 that is normal to planes transverse to the x_1-axis may be enough on planes with normals tilted by π/4 radians from the x_1=axis to cause release of hemoglobin from red blood cells moving in a system of capillaries, for example.

This action of resolving shear stress from normal or longitudinal stress can be seen more simply in a transformed RCC' system with axes $[x_1', x_2', x_3'=x_3]$ secured by rotating the x_1'-axis by angle Θ around the x_3 axis, with Θ positive when CCW from the x_1-axis. Using the stress tensor rule $(\check{T}_{ij})'=a_{im}a_{jn}\check{T}_{mn}$ then allows one to find planes on which shear stress is extremal and normal stress is zero, as at Θ=±π/4 radians for $\tau_3=-½(\check{T}_1-\check{T}_2)\sin(2Θ)$ [per Eq.(17), p.14, FRM cited in Footnote 21]. The same reasoning applies to the strain tensor, with the absolute value of principal shear strain being one half the principal strain difference, viz., $|P[(\check{S}_{be})_{12}]= ½|P(\check{S}_{be})_{11}-P(\check{S}_{be})_{22}|\equiv½(\check{S}_1-\check{S}_2)$. Further, in an isotropic homogenous solid the principal axes for $\check{T}_{ij}$ coincide with those for $\check{S}_{ij}$. Such physical insights do not normally come from equations arising from a coordinate transformation of, say, u_i, the components of a vector, a rank-1 tensor.

So there is concern that past *safety-vs.-efficacy assessments* overlooked μ-based solid-state tissue stiffness depending on atomic, molecular, electronic and other features of (1) the structure of elastic or viscoelastic solids[23] or (2) biological tissue at the cellular level, in or through which ultrasound propagates and whose initial physical state is a soft solid, not a liquid. Logic indicates this is an error since such properties of a solid are controlled by its internal energy which for a soft solid (μ<<B) has both energetic and entropic contributions. In this respect, entropy can be important in calculating an elastic constant of a soft solid or biological tissue, due to solid-solid order↔ disorder transitions and associated rate processes for bond breakage and restoration occurring in polymers and their states of configuration of macromolecular chains absent or weak in unpolymerized media. For ex., configurational entropy can give rise to proportionality of elastic moduli μ and Y to the number of chain segments per unit volume in a high molecular-weight soft solid like natural rubber or vulcanized rubber with covalent crosslink bonds between long molecules, even without a change in the internal energy.[24] Entropy production is also a factor in ultrasonically-induced rate-dependent

[22] L. B. Leverett, J. D. Hellums, C. P. Alfrey and E. C. Lynch (1972). "Red Blood Cell Damage By Shear Stress," *Biophysical Journal* **12:**257-273. Per the Abstract: " ...there is a threshold shear stress, 1500 dynes/cm^2, above which extensive cell damage [hemoglobin release] is directly due to shear stress."

[23] Viz., see Ch. 30, "Mechanical Properties," pp.563-595 of *Materials Engineering – Bonding, Structure, and Structure-Property Relationships* by Susan Trolier-McKinstry and Robert E. Newham (Cambridge University Press, Cambridge, UK, 2018). From p.575, for example, "Many polymers are viscoelastic, such that the rate at which stress is applied is also important to the mechanical response. This occurs because when [molecular or macromolecular] chains try to move, it takes time. Thus the strain rate matters." Bracketed words added by Hal. Strain effects are added in this Part 2, as via its Eqs.(2)-(3), (4) and (6).

[24] Ch.12, "Bioelasticity," pp.367-401, *IBM* (book) of W.L. Nyborg cited in Footnote [10]. Eqs. (12.35)-(12.38) give entropy-based shear modulus of elasticity μ, Poisson's ratio ν & Young's modulus Y=2μ(1+ν) for natural rubber, , citing the 1958 ed. of classic *The Physics of Rubber Elasticity* by L. R. G. Treloar (3rd ed.: Clarendon Press. Oxford, 1975). Per p.64 in its Ch. 4, "The Elasticity of a Molecular Network," Helmholtz free energy or work of deformation W is given by $W=-TΔS=(1/2)NkT\,[(\check{S}_{11})^2+(\check{S}_{22})^2+(\check{S}_{33})^2-3]) = (1/2)μ[(\check{S}_{11})^2+(\check{S}_{22})^2+(\check{S}_{33})^2]$ for elastomeric network with N chains per unit volume & Boltzmann's constant k.

shear deformation and disruption of the red blood cell plasma membrane.[25] Indeed, *off-diagonal* components of $(\check{T}_{be})_{\beta=2}$ have not received the attention deserved in safety-vs.-efficacy assessments on MDU, as on the viable *in utero* fetus. Thus, ultrasound safety studies informed on such matters may better identify relative or absolute contraindications, e.g., whether ultrasound use is to be moderated or avoided in particular medical cases, such as exposure of the fetus early in the first trimester of a human pregnancy or of the BBB of a child or adult to open it up for administration of drugs into the brain, or of transcranial high-intensity focused ultrasound for neuromodulation in the brain.

Linear Hooke's law as constitutive equation in the presence of a rate process:

The preceding provides basic observations and reasoning for why strains like SSMSS and their time derivatives, e.g., $[(\check{S}_{be})_{12}]_{\beta=2}$ and $\partial[(\check{S}_{be})_{12}]_{\beta=2}/\partial t$, may have been missed in ultrasound safety-vs.-efficacy assessments and in ultrasonographers' cautionary judgments that what they do is safe, exposing patients to ultrasound to secure a medical benefit. Indeed, a more universal framework than Eq.(1) helps to examine this matter, such as by adding to its instantaneous or purely elastic response two time-derivative terms[26] to account for a delayed response to an applied ultrasonic force that allows flow, viz.,

Eq. (2) $[(\check{T}_{be}{}^0)_{ij}]_\beta = (\lambda^0)_\beta[(\Theta_{be}{}^0)]_\beta\delta_{ij} + 2(\mu^0)_\beta[(\check{S}_{be}{}^0)_{ij}]_\beta + [(\lambda^0)']_\beta[\partial[(\Theta_{be}{}^0)_\beta/\partial t]\delta_{ij} + 2[(\mu^0)']_\beta[\partial[(\check{S}_{be}{}^0)_{ij}]_\beta/\partial t].$

Here λ' is a bulk viscosity and μ' a shear viscosity (usually given symbol η). Superscript "0" means that strain amplitude is taken as infinitesimal. If the order of time and spatial derivatives can be reversed, then in the third and fourth terms on the right hand side of Eq.(2) appear velocity gradients of type $\partial v_i/\partial x_j$, with velocity $v_i=\partial u_i/\partial t$. For steady flow in a liquid, with $\partial(\Theta_{be}{}^0)/\partial t=0$ and $\mu=0$, Eq.(2) reduces to the usual form for a linear Hookean response of a sonicated viscous liquid, viz., $[(\check{T}_{be}{}^0)_{ij}]_{\beta=1}=\lambda(\Theta_{be}{}^0)_{\beta=1}\delta_{ij}+2\mu'[\partial(\check{S}_{be}{}^0)_{ij}/\partial t]_{\beta=1}$ with off-diagonal terms of $[(\check{T}_{be}{}^0)_{i\neq j}]_{\beta=1}=2\mu'[\partial(\check{S}_{be}{}^0)_{i\neq j}/\partial t]_{\beta=1}$, in contrast to the off-diagonal terms $[(\check{T}_{be}{}^0)_{i\neq j}]_{\beta=2}=2\mu^0[(\check{S}_{be}{}^0)_{i\neq j}]_{\beta=2}$ of $[(\check{T}_{be}{}^0)_{ij}]_{\beta=2}$ for a solid with no macroscopic flow, per Eq.(1). Equation (2) improves upon Eq.(1) by adding two terms to the constitutive equation, as partial derivatives with respect to time, to yield a viscoelastic Hooke's law. A derivation then yields a third term in the plane longitudinal wave equation for particle displacement u_i as the dependent variable,[27] in contrast to the two-term wave equations for no propagation losses for either u_1 or $\check{T}_{11}$ per Part 1 for a solid ($\beta=2$ here). The wave equation in u_1 with a solution accounting for losses is given by $Mu_{1,11}+[(\lambda^0)'+2(\mu^0)']u_{1,11t} = \rho_o u_{1,tt}$. Solutions for the corresponding propagation constant k, amplitude attenuation coefficient α, and phase velocity c are given in a subsequent section.

Frame-invariant octahedral shear stress:

The tensor paradigm is now applied to 2 infinitesimal-amplitude steady-state cases via Eq.(2): Ultrasonically induced strain in a compressible solid and flow in a viscous liquid, whose Hooke's laws are $[(\check{T}_{be}{}^0)_{ij}]_{\beta=1} = [\lambda^0\Theta^0]_{\beta=1}\delta_{ij}+2[(\mu')^0]_{\beta=1}(\partial/\partial t)[(\check{S}_{be})_{ij}]_{\beta=1}$ and $[(\check{T}_{be}{}^0)_{ij}]_{\beta=2} =$

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[25] See Ch./Sec. 14.7.6., pp.482-484 in Nyborg's *IBM* cited in Footnote [10] for a review of scientific literature prior to 1975 on effects of shear on biological cells, especially erythrocytes. An inadvertent connection this review makes to entropy production by ultrasound is provided by Nyborg's description of the seminal paper, J. Krizan & A.R. Williams (1973), "Biological membrane rupture and a phase transition model," *Nature New Biology* **246:** 121-123.

[26] Such as done by Nyborg, p.89 in his *IBM* (book) cited in Footnote [10], via Eq.(4.22) [while correcting Eq.(4.23)].

[27] Ch.13, *IBM*, pp.402-409, incl. Eq.(13.18) for plane longitudinal wave equation, with particle-displacement solutions $u_i = (ui)_o \exp(-\alpha x)\sin(\omega t-kx)$, not solutions (unless $\alpha=0$) of wave eq. in Part 1 for no losses. Here $(ui)_o$ = constant, α = amplitude attenuation coefficient, $\omega=2\pi f$ and k = propagation constant.

$[\lambda^0\Theta^0]_{\beta=2}\delta_{ij}+2[\mu^0]_{\beta=2}[(\check{S}_{be}{}^0)_{ij})]_{\beta=2}$, respectively. Tensor components are defined in an RCC system, simple shear acting in the 1-2 plane such as by flow in the liquid or by a plane shear wave traveling in the $+x_3$ direction in the solid. However, here ultrasound in the solid is taken as a traveling longitudinal plane wave propagating in the $+x_1$ direction with thus just one non-zero strain component, $[(\check{S}_{be}{}^0)_{11}]_{\beta=2}$. For β=1, the principal stresses $[\check{T}_i]_\beta$ can be found by solving the eigenvalue problem for the aforementioned simple case of a pure rotation by angle Θ about the x_3-axis that generates a new RCC' in which the stress components $[(\check{T}_{be}{}^0)_{ij}]_{\beta=1}$ in the x_1-x_2 plane are transformed into their components $[(\check{T}_{be}{}^0)_{ij}]'_{\beta=1}$ in the $(x_1)'$-$(x_2)'$ plane, expressed as factors of circular functions with argument Θ. Accordingly, with $[\lambda^0\Theta^0]_{\beta=1}\equiv-p_{\beta=1}$, one has $[\check{T}_1]_{\beta=1}=-p_1(1-\gamma_{\beta=1})$, $[\check{T}_2]_{\beta=1}=-p_{\beta=1}(1+\gamma_{\beta=1})$ and $[\check{T}_3]_{\beta=1}=-p_{\beta=1}=[(\check{T}_{be}{}^0)_{33}]_{\beta=1}$ where $\gamma_{\beta=1}\equiv2[(\mu')^0]_{\beta=1}\{(\partial/\partial t)[(\check{S}_{be})_{12}]_{\beta=1}\}/p_{\beta=1}$. For longitudinal waves in a *solid*, the principal stresses are already known through use of the applicable Hooke's law, viz., $[\check{T}_1]_{\beta=2}=-p_{\beta=2}(1-\gamma_{\beta=2})$ and $[\check{T}_2]_{\beta=2}=[\check{T}_3]_{\beta=2}=-p_{\beta=2}$, where $\gamma_{\beta=2}=2(\mu_{\beta=2}/p_{\beta=2})[(\check{S}_{be}{}^0)_{11}]_{\beta=2}$ and $-p_{\beta=2}\equiv[\lambda^0\Theta^0]_{\beta=2}=(\lambda^0)_{\beta=2}[(\check{S}_{be}{}^0)_{11}]_{\beta=2}$. Now octahedral shear stress τ_{oct} for infinitesimal amplitudes can be calculated:

Eq.(3) $3([\tau_{oct}{}^0]_\beta)^2 = \{[(T_1)^0 - (T_2)^0]_\beta\}^2 + \{[(T_2)^0 - (T_3)^0]_\beta\}^2 + \{[(T_3)^0 - (T_1)^0]_\beta\}^2$

invariant with coordinate transformation as it is also expressible as a function of the first and second invariants I_1 and II_2 of the stress tensor in either medium.[28] For a liquid, $[\tau_{oct}]_{\beta=1}=\pm\sqrt{(2/3)}[(\mu')^0]_{\beta=1}(\partial/\partial t)[(\check{S}_{be})_{12}]_{\beta=1}$ and for a solid $[\tau_{oct}]_{\beta=2} =\pm(2/3)\sqrt{2}[\mu^0]_{\beta=2}[(\check{S}_{be}{}^0)_{11}]_{\beta=2}$. With use of the more intuitive subscripts L and S for liquid and solid, and using subscripts for what types of deformation are involved, these equations become $[\tau_{oct}]_L=\pm(\sqrt{(8/3)}[(\mu')^0]_L\{\partial/\partial t[(\check{S}_{simple\ shear})_{12}]_L\}$ and $[\tau_{oct}]_S=\pm(\sqrt{(8/9)}(\mu^0)_S[(\check{S}_{long\ wave})_{11}]_S$. In terms of the MUBEM's of fluid state mechanical shear stress (FSMSS) and solid-state mechanical shear strain (SSMSS) [both SSMSS and FSMSS], examples of octahedral shear stress are, respectively,

$[\tau_{oct}]_{FSMSS}=\pm(\sqrt{(2/3)}[\partial/\partial t(FSMSS)]$, and
$[\tau_{oct}]_{SSMSSS}=\pm(\sqrt{8/9})(\mu^o)_S[(SSMSSS]$.

With a simple harmonic time dependence, then time averages of $[\tau_{oct}{}^0]_\beta$ are zero though not for its square, $([\tau_{oct}{}^0]_\beta)^2$.

Nonlinear Hooke's law as the constitutive equation in presence of a rate process, and equation of motion (EOM) as balance of linear momentum:

An explicitly nonlinear rate-depended stress-strain law in the Eulerian frame is now presented, in terms of *excess* elastodynamic stress $\Delta(\check{T}_{be})_{ij}\equiv(\check{T}_{be})_{ij}-(\check{T}_o)_{ij}$ defined in parallel with the steady-state excess acoustic pressure $p-p_o$ with p_o the ambient pressure:

Eq.(4) $\Delta(\check{T}_{be})_{ij} = \lambda\Theta_{be}\delta_{ij} + 2\mu(\check{S}_{be})_{ij} + \lambda'[\partial\Theta_{be}/\partial t]\delta_{ij} + 2\mu'[\partial(\check{S}_{be})_{ij}/\partial t]$.

The superscript "0" is now 'missing," as finite strain is assumed, with

$$(\check{S}_{be})_{ij}\equiv(1/2)[(\partial u_i/\partial x_j)+(\partial u_j/\partial x_i)+(\partial u_k/\partial x_i)(\partial u_k/\partial x_j)] \equiv (\check{S}_{be}{}^0)_{ij} + (1/2)(\partial u_k/\partial x_i)(\partial u_k/\partial x_j).$$

[28] Eqs.(47)-(51) on pp.23-24 of *FRM*.

Thus the time average is now positive definite in value, viz.,

$$\langle[\tau_{oct}]_L\rangle = \pm(\sqrt{(8/3)}[(\mu')^0]_L \langle\{\partial/\partial t[(\check{S}_{simple\ shear})_{12}]_L\}\rangle > 0 \text{ and}$$
$$\langle[\tau_{oct}]_S\rangle = \pm(\sqrt{(8/9)}(\mu^o)_S \langle[(\check{S}_{long\ wave})_{11}]_S\rangle > 0.$$

The maximum octahedral shear stress is related to a failure criterion for solids for when $(\tau_{oct})^2$ reaches a value of k^2. [29]

In an Eulerian frame the EOM for balancing linear momentum of nonlinear bulk waves in an unbounded homogeneous solid is $\rho Dv_i/dt=(\check{T}_{be})_{ij,j}+f_i$, with mass density ρ, particle velocity $v_i=u_{i,t}$, total (or material) time derivative $D/Dt=\partial/\partial t+v_j\partial/\partial x_j$, $u_i=x_i-a_i$ for material coordinates a_i specifying original field point coordi-nates $(x_i)_o$, and f_i the sum over j of body forces f_{ij}. It is important to recall that this expression, just for $f_i=0$, small u_i and no dissipation ($\lambda'= \mu'=0$), as indicated in Addendum D to Part 2, is formally derived by integrating the Lagrangian density ***L*** over an entire anisotropic system while applying Hamilton's principle to get homogeneous wave equations with many terms on the RHS due to the general elastic constitutive eq. $(\check{T}_{be})_{ij}=C_{ijkl}\,(\check{S}_{be})_{kl}$ with a rank-4 tensor C_{ijkl} for the elastic constants. Such WE's have harmonic plane-wave solutions. Also, body forces can lead to inhomogeneous WE's with forcing terms, with spherical-wave solutions solved by means of the Green's tensor (Addendum D). However, just the EOM of $\rho_o(\partial v_i/\partial t)=(\check{T}_{be})_{ij,j}$ is useful for deriving wave equations for small strain in lossy media. This is not only with the typical dependent variable of particle displacement u_1 and independent position variable x_1 given by:

$$Mu_{1,11} + [(\lambda^0)'+2(\mu')^o]u_{1,11t} = \rho_o u_{,tt} \text{ or } u_{,tt}=(c_D)^2u_{1,11}+(1/\rho_o)[(\lambda'+2\mu')/(\lambda+2\mu)]u_{1,11t},$$

but also in uniaxial stress $\check{T}_{11}$, i.e., $\check{T}_{11,tt} = (c_D)^2\check{T}_{11,11} + [(\lambda'+2\mu')/\rho_o]\,\check{T}_{11,11t}$. Besides the concept of stress waves [viz., Herbert Kolsky, *Stress Waves in Solids*, 2nd ed. (Dover Publications, 2012)], however, a tensor paradigm yields other physical insight, as the WE in u_1 via the EOM yields a surge damping term in strain facilitated by flow, of: $\check{T}_{11,tt} = (c_D)^2\check{T}_{11,11} + (\lambda'+2\mu')\check{S}_{11,ttt}$.

Going to the Lagrangian frame, however, has the advantage of eliminating the deformed mass density ρ even for finite strain, with volume forces ignored: [30]

Eq.(5) $\rho_o\partial^2u_i/\partial t^2 = (\nabla_a \bullet \mathbf{P}_{be})_i = (\mathbf{P}_{be})_{ij,j'}$.

Partial differentiation with respect to material coordinates a_n in the 'tensor dot product' here is denoted by a prime on the superscript index. The first Piola-Kirchoff stress tensor is $\mathbf{P}_{ij}$ (not the pressure p nor principal value of a tensor) It is non-symmetric rank-2, defined as $(\mathbf{P}_{be})_{ij}=(\rho_o/\rho)(\check{T}_{be})_{im}[(F^{-1})^T]_{mj}$, with the rank-2 deformation gradient tensor $F\equiv F_{be}$ given in component notation as $F_{ij}=x_{i,j'}=\delta_{ij}+u_{i,j'}$ and superscripts T and −1 denoting the transpose and inverse of the tensor. Substitution of $(\check{T}_{be})_{ij}$ from Eq.(4) along with the determinant property $\det|F|=\rho_o/\rho$, a scalar, gives this EOM as 3 PDE's with variable coefficients:

Eq.(6) $\rho_o\partial^2u_i/\partial t^2 = \{[(\check{T}_o)_{im} + \lambda_{be}\Theta_{be}\delta_{im} + 2\mu_{be}(\check{S}_{be})_{im} + \lambda_{be}'[\partial\Theta_{be}/\partial t]\delta_{im} + 2\mu_{be}'[\partial(\check{S}_{be})_{im}/\partial t]\,\det|F|\,[(F^{-1})^T]_{mj}\}_{,j'}$

[29] Viz., p.91, *FRM*, with reference to citations of two papers from 1962 and 1965 on rock failure under stress. Pertinent papers with a biomechanics view include three: (1) Yuan-Cheng Fung (1995), "Stress, Strain, growth, and remodeling of living organisms," pp. 469-482 in *Theoretical, Experimental, and Numerical Contributions to the Mechanics of Fluids and Solids* edited by J. Casey and M. J. Crochet (Birkhäuser Basel, Switzerland), with a tissue engineering view. (2) J. D. Humphrey (2003), "Continuum biomechanics of soft biological tissues" (Review Paper), *Proc. R. Soc. Lond. A* **459:**3-46. (3) Cora Wex, Susann Arndt, Anke Stoll, Christiane Bruns and Yuliya Kupriyanova (2015), "Isotropic incompressible hyperelastic models for modelling the mechanical behaviour of biological tissues: a review," *Biomed. Eng.-Biomed. Tech.* **60(6):** 577–592, with some comments on medical ultrasound.

[30] Eq.(6) on p.265, Ch.9, "Finite-Amplitude Waves in Solids" [FAWS] by Andrew N. Norris in *Nonlinear Acoustics* [NA] ed. by Mark F. Hamilton & David T. Blackstock (Academic Press, San Diego, 1998). Hal's physics dissertation advisor Wesley L. Nyborg wrote Ch.7, "Acoustic Streaming."

$$= \{[(\check{T}_o)_{im} + \lambda_{be}\Theta_{be}\delta_{im} + 2\mu_{be}(\check{S}_{be})_{im} + \lambda_{be}'[\partial\Theta_{be}/\partial t]\delta_{im} + 2\mu_{be}'[\partial(\check{S}_{be})_{im}/\partial t]\}\ \{\det|F|\ [(F^{-1})^T]_{mj}\}_{,j'} + \{\det|F|[(F^{-1})^T]_{ij}\}\{[(\check{T}_o)_{jm} + \delta_{jm}\lambda_{be}(\Theta_{be}) + 2\mu_{be}(\check{S}_{be})_{jm} + \lambda_{be}'[\partial\Theta_{be}/\partial t]\delta_{jm} + 2\mu_{be}'[\partial(\check{S}_{be})_{jm}/\partial t]\}_{,m'}.$$

Variable coefficients have factors of spatially-dependent material parameters λ_{be}, μ_{be}, λ_{be}' and μ_{be}' with non-zero spatial derivatives. Stress superposition, viz., $(\check{T}_o)_{im} \equiv (\check{T}_{oa})_{im} + (\check{T}_{ob})_{im} + (\check{T}_{oc})_{im}$, applies, with pre-stress $(\check{T}_{oa})_{im}$ left from prior deformation and coupling stress $(\check{T}_{oc})_{im}$ like residual stress. Paired with $(\check{T}_{ob})_{im}$ are bias strain $(\check{S}_{ob})_{im}$ and coupling strain $(\check{S}_{oc})_{im}$ like residual strain. To derive wave equations, Norris simplified Eq.(6) by making elastic constants depend on specific strain energy, but excluded softening of constants like μ [e.g., $\mu_{be} < \mu^0$ of Eq.(2)] by entropic alteration of a soft solid, even to liquefying cytoskeletal contents with macromolecular configuration states, making $\mu_{be}=0$.[31] The 1st and 2nd laws of reversible thermodynamics do not govern ultrasonic production of entropy there nor in benignly treating cancers by ultrasonic differential softening of tissue. Ultrasound changes a soft solid's internal energy via not only the strain energy density but also the entropy density, with entropy flow related to information flow, as with ultrasound attenuation of via the Beer-Lambert law.[32]

Discussion including co-alignment facilitated by entropic and other thermodynamic matters, with frame-dependent effects:

Such configurational (or conformational) states for a single macromolecule or an intracellular actin filament encompass a wide range of orientations ranging from ordered (viz., folded DNA inside the nucleolus) to disordered (viz., coiled DNA). Further, the entropic part of the internal energy of a soft solid may more likely change than its strain energy when a solid experiences a nonlinear strain over a period of time commensurate with a viscoelastic relaxation or retardation time or the inverse of a rate constant for a reaction of the type A⇌B such as the breaking and reforming of weak intra-macromolecular bonds during a transition between coiled and folded configurations of DNA or other macromolecule. Inter-molecular effects can also occur. Entropic energy may preferentially change if a stress or strain threshold governs onset of a solid-state phase transition and thus perturbs the steady state for A⇌B.

So it is hypothesized that measurement of components of a rank-2 tensor like finite strain is more sensitive and selective to ultrasonically induced entropy changes than that of components of a rank-1 tensor (vector) or rank-0 tensor (scalar), due to greater orientational dependence with increasing rank number of a tensor. In the case of shear-based damage mechanisms, this is because probability-based statistics govern the occurrence frequency for orientational co-alignment effects between the principal shear strain axes[33] and the in-plane axes for susceptible planes on which easy internal motion in solids like glide, yielding, slip, hydrogen-bond breakage, and plastic flow occur as facilitated by specific on-plane microscopic flaws, rate processes for in-plane weak bond breakage, and anisotropic contributions to elastic strain energy, for example. In sum, frequency and occurrence of co-alignment effects between principal-shear axes and material-defect axes may increase with the rank order of the tensor quantity chosen to detect and measure them. A rank number of 2 may then confer local anisotropy on the elastic constants regarded as isotropic at macroscopic size scales.

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[31] N. Mizrahi, E. H. Zhou, G. Lenormand, R. Krishnan, D. Weihs, J. P Butler, D. A. Weitz, J. J. Fredberg, and E. Kimmel (2012). "Low intensity ultrasound perturbs cytoskeleton dynamics." *Soft Matter* **8(8):** 2438-2443.

[32] L. Luo, et al. (2006). "Ultrasound absorption & entropy production in biological tissue: a novel approach to anticancer therapy." *Diagnostic Pathology* 1, 35.

[33] At ±45° and ±135° with respect to the principal strain axes in an isotropic, homogeneous solid.

At the spatial level of one mammalian cell or a pair of them, the total set of its many internal micro-forces, with just one denoted by $\mathbf{\delta F}$ with direction unit vector $\hat{\mathbf{e}}_{\delta F}$, are randomly oriented with respect to the total set of directions, with just one of them denoted by $\hat{\mathbf{e}}_{DV}$, associated with damage-vulnerable (DV) features of tissue due to the randomness of cellular microstructural orientations with respect to the coordinate axes of a chosen RCC system. Thus, evaluation of the spatial average of the vector dot product, $\langle \hat{\mathbf{e}}_{\delta F} \bullet \hat{\mathbf{e}}_{DV} \rangle_{spatial}$, can require a detailed calculation in irreversible statistical mechanics that includes analysis of orientationally dependent contributions to spatial averages of material properties as well as of rank-2 tensor components in either the Eulerian or Lagrangian frame. Such orientations can be assigned angles $\psi_{\delta F,DV}$ that determine the value of the dot product $\hat{\mathbf{e}}_{\delta F} \bullet \hat{\mathbf{e}}_{DV} = \cos(\psi_{\delta F,DV})$. Further, the work required at a local level for an applied stress to displace a cellular or other microscopic feature by the vector length $\mathbf{\delta L}$ is $\delta W = \int_o^{Lmax} [\mathbf{\delta F} \bullet d\mathbf{\delta L}] = \int dA_{DV} \int_o^{Lmax} [\mathbf{T_{shear}} \bullet d\mathbf{\delta L}]$, where L_{max} is the maximum extension that occurs before a threshold for feature failure is reached on the damage-vulnerable surface area δA_{DV} due to action of a force $\mathbf{\delta F}$ within its tangent plane on which $\mathbf{\delta L}$ lies; $\mathbf{T_{shear}}$ is the shear stress vector $\mathbf{T_{shear}} = \text{limit}[\mathbf{\delta F}/\delta A]_{\delta A \to 0}$ (p.10, *FRM* cited in Footnote [21]).

Space limitations here prevent a detailed description. For anisotropic solid media containing shear strains, however, one can start with recent papers of S. J. Burns,[34] such as Eqs.(1) – (7) in “Burns 2” starting with an expression for an increment in the internal energy per unit mass [as Eq.(1)] and ending up with an expression for du, a "Gibbs like free energy in incremental form for a stressed solid" [as Eq.(7)]. Eq.(1) gives “du” as the sum of two terms: The heat (dq) added per unit mass to the stressed solid, dq=Tds with T the absolute temperature and ds the incremental entropy per unit mass, plus the incremental work done per unit mass on the stressed solid, $dw = v\check{T}_{ij}\check{S}_{ji}$ (double sum on indices i and j, each from 1 to 3), where v is the volume per unit mass and stress $\check{T}_{ij}$ and strain $\check{S}_{ji.}$ are symmetric rank-2 tensors. An expression for entropy is available as Eq.(20) in “Burns 1” with Eqs.(9)-(11) in that paper serving the same purpose as parallel Eqs. (1), (6)-(7) in “Burns 2” but with quantities in “Burns 1” defined in terms of unit volume (rather than unit mass).

Practical example of the Blood Brain Barrier (BBB) in which co-alignment-related damage effects may multiply in presence of ultrasound:

The BBB is a microcirculatory network of highly differentiated, specialized-function capillaries in the mammalian brain joining the smallest arteries or arterioles to the smallest veins or venules as connective or stromal tissue embedded in a parenchymal matrix of neurons and glial cells. As a barrier of specialized cerebral endothelial cells (EC’s) lining the internal wall of the lumen as part of its effective endothelium (along with a basement membrane), the BBB limits passage of blood-borne molecular toxins into the functional tissue or parenchyma. The EC’s tight junctions forming a diffusion barrier consist of inter-EC protein bridges tending to reduce transverse lumenal permeability and diffusivity to most proteins, in parallel with a transport system for passage of adequate amounts of oxygen, needed ions and other nutrients into the parenchyma. Parallel alignment of the apical or acicular axes of the long EC’s with the longitudinal axis of the capillary is maintained in part by shear stress resulting from *in vitro*

[34] Two papers: [“Burns 1”] S. J. Burns (2018). "Elastic shear modulus constitutive law found from entropy considerations." *J. Appl. Phys.* **124(8):** 085904-1 to 085904-9. Published Online: 30 Aug. 2018 + [“Burns 2”] S. J. Burns, “77 new thermodynamic identities among crystalline elastic material properties leading to a shear modulus constitutive law in isotropic solids,” J. Appl. Phys. **124(8):** 085114 (29 pp. for arXiv version). Published Online: 29 Aug. 2018.

viscous flow.[35] Such flow in cerebral capillaries obeys with little error Poiseuille's Law predicting zero flow velocity at the EC surface exposed to flowing blood, where shear stress is a maximum. This law was featured in a report indicating that pericytes, mesenchymal-like cells adhering apparent ly randomly to the external surfaces of cerebral capillaries, regulate the volume of cerebral blood flow via dilation via increase in lumen radius R initiated by neuronal activity and messenger signaling causing pericytes to relax their grip.[36]

A small change in that grip's force and thus in R can lead to a large change in the volume rate of blood flow which, according to Poiseuille's Law, is proportional to R^4. A continuum mechanics representation of the corresponding deformation can thus require use of tensors for large strain in the Lagrangian frame rather than small strain tensors in the Eulerian frame. This deformation mechanism can be more important than the usually cited one of contraction of smooth musculature of arterioles which branch out from arteries to capillaries and hence to venules and veins. However, both mechanisms can set up and modify complex non-axisymmetric fields of mechanical stress and strain in a capillary including circumferential, axial and shear tensor components. If deformability of the capillary tissue can be modeled as a nonlinear VE, hyperelastic or related soft solid and if arteriole contraction changes the mechanical tension by which a capillary is elongated or straightened out, then residual strains or pre-strains in the Lagrangian frame can exist in the capillary tissue as part of the homeostasis system optimizing blood flow and transport of nutrients for given physiological and environmental conditions.

Such persistent, residual strains can be attributed to corresponding residual stresses that can do work (and then trap internal elastic energy) of the type δW mentioned in the preceding section, such as required to induce a first change or deviation in tissue structure that is not completely reversible upon release of the applied forces, or even lysis of a cell like an RBC. Here, W, the work that a test sample does on its surroundings, can equal the volume integral of the negative of the product of a symmetric stress tensor with a symmetric strain tensor for a solid, assuming an initial state of zero strain. In the small strain regime, the tensor product is given as an internal energy density of $\boldsymbol{W} = (1/2)\, [(\check{T}_{be}{}^{0})_{ij}]_2\, [(\check{S}_{be}{}^{0})_{ji}]_2$, for infinitesimal strains in a linear solid where the stress tensor is given by Eq. (2) and the First Law of Thermodynamics is invoked but in the special equilibrium case of no heat supplied to the test sample taken as the thermodynamic system. (For an ultrasonic time average, $<\boldsymbol{W}>$ is greater than zero.) The Einstein convention for summing products of factors with repeated indices is used here for the relatively simple case of deformation governed by a linear but rate-dependent Hooke's Law involving first-order partial derivatives of strain with respect to time because of the presence of one or more rate processes which can also have an important temperature dependence. A systematic framework for calculating δW isentropically as the internal virtual work for small or large deformation is given in terms of the principle of virtual work for which the preceding restriction of zero initial strain is removed.[37] A more general framework is needed if a change in

[35] Luca Cucullo, Mohammed Hossain, Vikram Puvenna, Nicola Marchi & Damir Janigro (2011). "The role of shear stress in Blood-Brain Barrier endothelial physiology" *BMC Neuroscience* **12:**40 (15pp.) Quoted from Abstract: "One of the most important and often neglected physiological stimuli contributing to the differentiation of vascular endothelial cells (ECs) into a blood-brain barrier (BBB) phenotype is shear stress (SS). With the use of a well established humanized dynamic in vitro BBB model and cDNA microarrays, we have profiled the effect of SS [shear stress] in the induction/suppression of ECs genes and related functions." Such genes impact developing BBB properties & functions. Applied laminar shear stress reached capillary-like levels of ~ 6.2 dynes/cm^2.

[36] Catherine N. Hall, Clare Reynell, Bodil Gesslein, Nicola B. Hamilton, Anusha Mishra, Brad A. Sutherland, Fergus M. O'Farrell, Alastair M. Buchan, Martin Lauritzen and David Attwell (2014). "Capillary pericytes regulate cerebral blood flow in health and disease," *Nature* **508** (7494): 55–60.

[37] E.g., Section 5.6, "Principle of virtual work," pp.134-137 in Yavuz Başar and Dieter Weichert's book cited in Footnote [20].

entropy accompanies deformation of the test sample.[38] Such an entropy change may come about from ultrasound-induced reconfiguration of coiled or uncoiled macromolecules like the bridge proteins in the tight junctions between EC's, or from shear-stress induced release of free gas (e.g., O_2) or of ATP from red blood cells.

It seems to be relevant to specialize the preceding picture to the case of shear deformation represented by a large shear strain, such as SSMSS as an off-diagonal component of the Green strain tensor in the Lagrangian frame, and thus a corresponding shear stress as an off-diagonal component of the first Piola-Kirchoff stress tensor presented in Eq. (5). This is because shear stress can be an important contributor to BBB failure.[39] Further, another report in that vein considers the BBB to be "additionally comprised of the basal lamina, surrounded by the end-foot processes of [nearby] astrocytes.[40] The basal lamina is secreted by the EC's as an extracellular matrix outside the capillary as a buffer with connecting astrocyte end-feet and the parenchymal tissue itself of the brain. Thus the structural picture is more complex than just that of isolated EC's in much of the *in silico* and other research reported in the scientific literature. But returning to a focus just on the EC's, it is further noted that deterioration of the BBB by high stress levels in response to "aberrant force" has been reported.[41] Quoting from first part of paper's Abstract:

> "Microvascular endothelial cells at the blood–brain barrier exhibit a protective phenotype, which is highly induced by biochemical and biomechanical stimuli. Amongst them, shear stress enhances junctional tightness and limits transport at capillary-like levels. Abnormal flow patterns can reduce functional features of macrovascular endothelium. We now examine if this is true in brain microvascular endothelial cells. We suggest in this paper a complex response of endothelial cells to aberrant forces under different flow domains. Human brain microvascular endothelial cells were exposed to physiological or abnormal flow patterns. Physiologic shear (10–20 dyn/cm^2) upregulates expression of tight junction markers Zona Occludens 1 (1.7-fold) and Claudin-5 (more than 2-fold). High shear stress (40 dyn/cm^2) and/or pulsatility decreased their expression to basal levels and altered junctional morphology."

The quoted high shear stress level of 40 dyn.cm^2 is almost 1/40th of the 1500 dyn/cm^2 mentioned in Footnote [22] for lysis of red blood cells (RBC's), as based on steady-state viscometer data, and almost 1/80th of the lysing level of 3000 dyn/cm^2 based on an ultrasonic FSMSS interaction with longitudinal waves of ultrasound. Even at room or elevated temperatures, the threshold values from acoustic microstreaming data tend to be high due to measurement of transient rather than steady-state effects. The former are due to small residence times of the RBC in the HBL of a viscous liquid in which an ultrasonically oscillating microbubble or vibrating thin wire is immersed and acts. Thus, steady-state deformation of the plasma membrane is far from being realized due to the relatively slow strain rate processes involved. This is true even at elevated temperatures like 45°C reached by heating effects, at which about 5000 dyn/cm^2 was required for first release of hemoglobin, with this value reducing

[38] A more general framework is given by Clifford Truesdell and Walter Noll, *The Non-Linear Field Theories of Mechanics [NLFTM]*, 3rd Edition, ed. Stuart S. Antman (Springer, Berlin, et al., 2004). For example, see the three work theorems and the strain energy function described on pp.304-319 of that book.

[39] Ljiljana Krizanac-Bengez, Marc R. Mayberg, Edwin Cunningham, Mohammed Hossain, Stephen Ponnampalam, Fiona E. Parkinson, Damir Janigro (2006). "Loss of Shear Stress Induces Leukocyte-Mediated Cytokine Release and Blood–Brain Barrier Failure in Dynamic In Vitro Blood–Brain Barrier Model," *Journal of Cellular Physiology* **206:**68–77.

[40] G.J. del Zoppo, R. von Kummer and G.F. Hamann (1998). "Ischaemic damage of brain microvessels: Inherent risks for thrombolytic treatment in stroke," *Journal of Neurology, Neurosurgery, and Psychiatry* 65:1–9.

[41] Fernando Garcia-Polite, Jordi Martorell, Paula Del Rey-Puech, Pedro Melgar-Lesmes, Caroline C O'Brien, Jaume Roquer, Angel Ois, Alessandro Principe, Elazer R Edelman and Mercedes Balcells (2017). "Pulsatility and high shear stress deteriorate barrier phenotype in brain microvascular endothelium," Journal of Cerebral Blood Flow & Metabolism **37(7):** 2614–2625.

to zero at 56°C.[42] Thus detection of hemoglobin release from RBC's as induced by transient ultrasound far over-estimates the steady-state threshold for first alteration or damage of tissue. A more realistic approach is to measure the threshold for ischaemic process initiation in pericytes, EC's or other micro- or even nano-anatomical features of capillaries at low-amplitude ultrasound levels, as from *plane* longitudinal waves of ultrasound. Progressive increments in ultrasound *pressure* level could then lead to oxygen deprivation and hypoxia plus cell death at high-amplitude levels, as from *focused* longitudinal ultrasound waves. Alternatively, closer estimation of the ultrasonic *shear stress* level needed to produce first changes in cellular structure can come from sonoporation data, such as a mean critical threshold of 120 dyn/cm^2 at 21.4 kHz which translates, after a numerical calculation is carried out to an excess pressure amplitude of 1x10^6 dyn/cm^2 at the frequencies of 1-2 MHz typical for devices or transducers emitting MDU.[43] Finally, published studies for opening up the BBB by focused ultrasound can be mined to quantify paracellular and transcellular thresholds, as for opening tight junctions of EC's for given macromolecules or nanoparticles. However, a Review paper in this area[44] indicates the difficulty encountered in finding actual ultrasound levels (as in dyn/cm^2 or Pa) for actual components of a stress tensor. That Review did not provide those details. The research paper cited in it as Ref. 77 provides only part of that information, for an animal model study on gold-nanoparticle passage through the BBB brain of anaesthetized Wistar rats infused with microbubbles and insonated at 558 KHz by a spherically focused projector.[45] Thresholds for tight-junction opening were evidently far exceeded, in view of the gross "BBB disruption" of extravasation observed within the right paramedian hemispheric surface, by means of optical histology images provided in the Supplementary Material available online. The latest information published in this vein appears to be a pair of 2019 review papers.[46] Data on effects on the BBB of the fetus of MDU scans in Ob-Gyn practice appear to be lacking. This is an area for concern on safety, as the fetal skull is much thinner and less stiff mechanically than in adults and has openings (fontanelles), and so transmission of longitudinal ultrasound waves can be stronger into the fetal brain vs. adult's for a given intensity of ultrasound emitted from a

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[42] Viz.: J. A. Rooney (1972), "Shear as a Mechanism for Sonically Induced Biological Effects," *Journal of the Acoustical Society of America* 52: 1718-1724..

[43] Junru Wu (2007). "Shear stress in cells generated by ultrasound," Review paper in *Progress in Biophysics and Molecular Biology* **93(1–3):** 363-373. Abstract: "An experimental study using a mason horn of 21.4 kHz indicated that the threshold shear stress for cell sonoporation was 12±4 Pa for ultrasound exposure time up to 7 min. Numerical calculations have shown that shear stress associated with microstreaming surrounding encapsulated bubbles may be large enough to generate sonoporation at 0.1 MPa of 1 or 2 MHz ultrasound."

[44] See the Review paper, Maksymilian Nowak, Matthew E. Helgeson, and Samir Mitragotri (2019). "Delivery of Nanoparticles and Macromolecules across the Blood–Brain Barrier," *Advanced Therapeutics* 1900073 (14 pp.). From the first part of the Abstract: "Treatment of brain-related diseases is challenging due to the presence of the blood–brain barrier (BBB), a hurdle that prevents most foreign matter from entering the brain. While macromolecules and nanoparticles represent an increasing fraction of the therapeutic landscape in general, their limited ability to cross the BBB has hindered their clinical impact in treating diseases of the central nervous system. Here, the various routes for entry of macromolecular therapeutics into the brain are discussed, as well as the methods used to enhance their transport." From Conclusions and Future Outlook section of paper: "Delivery enhancement via focused ultrasound combined with microbubbles has demonstrated promise for a wide range of therapeutics and has undergone a number of preliminary safety studies. Many of the major technological hurdles have been overcome, with spatial and temporal control of BBB opening now possible, but identifying optimal operating parameters with regards to the acoustic components, the microbubbles, and the therapeutic[s] all still require additional investigation. Moreover, with this technique entering the clinic the long-term safety and effects will be critical to evaluate."

[45] Arnold B. Etame, MD, Roberto J. Diaz, MD, Meaghan A. O'Reilly, MS, Christian A. Smith, PhD, Todd G. Mainprize, MD, Kullervo Hynynen, PhD, and James T. Rutka, MD, PhD (2012). "Enhanced Delivery of Gold Nanoparticles with Therapeutic Potential into the Brain using MRI-Guided Focused Ultrasound," *Nanomedicine* **8(7):** 1133–1142. Supplementary Material is available online as is full text of article in Web version on PubMed Central. From p.4 of article is quoted: "The BBB was disrupted using 0.42W acoustic power (approximately 0.26 MPa peak acoustic pressure) in 10 ms bursts at 1 Hz periodic repeat frequency for 2 minutes." The ultrasound was emitted into a degassed water tank in which was immersed the exposed scalp of an anaesthetized rat in the supine position. No data were presented, such as photos of oscilloscope waveforms for the ultrasound.

[46] Ying Meng, Christopher B. Pople, Harriet Lea-Banks, Agessandro Abrahao, Benjamin Davidson, Suganth Suppiah, Laura M. Vecchio, et al. (2019). "Safety and efficacy of focused ultrasound induced blood-brain barrier opening, an integrative review of animal and human studies" *Journal of controlled release* **309(1):** 25-36. Also, Dallan McMahon, Charissa Poon, and Kullervo Hynynen (2019). "Increasing BBB Permeability via Focused Ultrasound: Current Methods in Preclinical Research," Current Methods in Preclinical Research in T. Barichello (ed), Blood-Brain Barrier. Neuromethods, Vol. 142 (Humana Press, New York, NY). Abstract at: https://link.springer.com/protocol/10.1007/978-1-4939-8946-1_16. Quoted from Abstract: "While this approach continues to show great promise and has entered clinical testing, there remains a need for preclinical research to investigate the long-term effects of single and repeated FUS treatment on cerebrovascular health and neurological function, as well the pharmacokinetics of specific drugs following FUS. Additionally, there is a need for improved monitoring strategies that can precisely predict resulting bio-effects."

transmitter transducer. Routine ultrasound scans to manage pregnancies are not used to open up the fetal BBB but that could be an unintended bioeffect. As the anatomy and physiology of the fetal brain is in a stage of rapid development, study of this matter is needed as a function of gestational age.

Spatial averages of tensor quantities of increasing rank number:

Any tensor quantity such as a BBB-opening threshold of ultrasonic shear strain (or SSMSS) as an off-diagonal component measured in a solid at field point **x** is actually a spatial average over a small sampling volume ΔV. An example is $\Delta V \equiv \Delta x_1 \Delta x_2 \Delta x_3$ in an RCC system, with centroid coinciding with **x**, but usually without orientational averaging which can be done over all 4π steradians of an angle φ subtended by the surface of a unit sphere also centered on **x**. One ray for this angle is represented by the unit vector $\mathbf{\hat{e}_R}$ for the direction of a reference axis taken for convenience as a coordinate axis of an RCC system (from whose origin both $\mathbf{\hat{e}_R}$ and x extend) but as translated to the point defined by **x**. The second ray is represented by the normal $\mathbf{\hat{e}}_{\mathbf{n(x;}\, x_a, x_b, x_c\mathbf{)}}$ also based at the sphere's origin and extending to any point on its surface. The direction of this normal, acting as a vector radius for the unit sphere, is variable as it is the normal to any one of an infinite number of planes on which **x** lies, any plane being specified by the equation $(x_1/x_a)+(x_2/x_b)+(x_3/x_c)=1$, with x_a, x_b, x_c being its intercepts on the x_1, x_2 and x_3 axes, respectively, of the RCC system. The intercepts range over all possible values. The two rays connect at their shared endpoint **x** located at the center of the unit sphere to form the angle φ defined in terms of its Cartesian dot product $\mathbf{\hat{e}_R} \bullet \mathbf{\hat{e}}_{\mathbf{n(x;}\, xa,\, xb,\, xc\mathbf{)}} = \cos(\varphi)$.

An observable scalar has no orientation dependence, so the orientational average is specified by just the value of the scalar itself. For ex., an infinitesimal ultrasonic disturbance taken as excess pressure p produces in an inviscid liquid only a volume strain $\check{S}_{ii}=\Theta$, with Θ the dilatation, so that $p=-\lambda\Theta$ is a negative stress. However, as tensor rank order increases, complexity increases. For a rank-2 tensor like stress or strain, three generally unequal numbers are required to specify that orientational average given then as the mean of all three on-diagonal components. That mean is equal in 3D space to one third of the trace, itself the tensor's first invariant, I_1. And, because of the tensor rule for coordinate transformations, an infinite number of planes are associated with a rank-2 tensor such as strain or stress evaluated at field point **x**, the components of each tensor depending on plane orientation specified by the intercepts.

The situation is more complex for a rank-4 tensor like the rank-4 elastic constant tensor C_{ijkl} for an isotropic homogeneous solid via $\check{C}_{ijkl}=\lambda\delta_{ij}\delta_{kl}+2\mu I_{ijkl}$ with the rank-4 identity tensor $\check{I}_{ijkl}\equiv(\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk})/2$.[47] So one can define a rank-4 isotropic shear elastic modulus tensor $(\check{C}_{shear})_{ijkl} \equiv \frac{1}{2}[(\check{C}_{ijkl})-\lambda\delta_{ij}\delta_{kl}) = \mu \mathbf{I}_{ijkl} \equiv \mu_{ijkl}$. Thus it is inaccurate to consider the magnitude μ as a complete specification of stiffness of an isotropic solid at any field point **x** since four directions are associated with μ due to its role simply as a coefficient factor scaling the rank-4 identity tensor. These 4 directions include a pair associated with a stress tensor element and another pair associated with a strain tensor element. In an RCC system, one direction in each pair can be taken as that of a normal to the plane [e.g., $\mathbf{\hat{e}}_{\mathbf{n(x;}\, xa,xb,xc\mathbf{)}}$] on which the stress or strain component acts. The other direction in each pair defines the direction in which that component acts, either

[47] Eq. (12) on p.266 in FAWS. The third-order elastic constant tensor is also defined on p.266 as a rank-6 tensor, C_{ijklmn}.

normal to that plane or tangent to it. The distinction between a rank-4 tensor component and its magnitude cannot be ignored in a solid with anisotropy.

If the solid is spatially inhomogeneous as is the natural case for soft biological tissue such as the human BBB or as due in engineering materials to microscopic flaws like microcracks, voids, inclusions and locally graded values of μ, viz., $\mu=\mu(\mathbf{x})$, then orientational averages of material properties as components of rank-4 tensors (and rank-6 tensors for lowest-order nonlinear contributions) will be skewed by orientations associated with EC surfaces and flaws, for example. Orientation examples include the normal vector to a microcrack surface or a unit vector for the direction of, for example, the semi-major axis of an ellipsoidal inclusion, a given crystallographic axis for an anisotropic spherical inclusion, or a gradient in μ [viz., $\nabla(\mu)$]. Such microscopic orientational features give the solid an anisotropy on a local level even if on a macroscopic level the solid can be taken as isotropic. The angles between these thus specified axes fixed in the material frame and axes of an RCC' system rotated over all three Euler angles from a reference RCC system to perform the orientational average over 4π steradians, can be time dependent due to the ultrasound realigning flaw axes to new directions. This action can be rate-dependent due to constitutive equations like Eq.(2). So a time average may also be needed to do the orientational average when ultrasonic elastodynamic radiation is present. Further, if ultrasound creates more than just excess pressure, e.g., $p=-(1/3)\mathrm{Tr}(\check{T}_{be})$, but also excess deviatoric or shear-related stress-component disturbance with associated direction(s) of normals of fictitious surfaces their extremal values act on, that time average IS affected as well.

This penultimate section is as far as Hal can go with online searches of the literature and with the mathematics due to his (1) lack of background at this deeper level and (2) inability to function well cognitively now after the wear and tear of decades of chronic stress due to a major disability. Also, he does not have any institutional access to the full text of published research papers in either print or digital format, and so is limited to what can be found for free without having to register an account. It is important, though, that MUBEM research be done along more rigorous lines like those in the foregoing and then its results be disseminated within the MURP community. This is because the gap continues to increase, even with apparent abandon, between, *on one hand*, the typically relatively low level of mathematical analysis, with its frequent assumptions of low strain amplitude and of spherical stress (viz., $\check{T}$ taken as just the scalar pressure p), and *on the other hand*, increasing levels of mechanical power and energy manufacturers build into their ultrasonic imaging systems to maintain and grow market share. This unbridged gap raises grave concerns over safety of MDU use on statistically vulnerable patients like the tiny, totally dependent human persons *in utero* whose CNS, e.g., neural tube or the hypothalamus-pituitary-adrenal-thyroid (HPAT) axis in the brain, is especially sensitive to ultrasonic mechanical force as prenatal stress – even that of the audible sound from the pulse repetition frequency (e.g., 1 kHz). Context for that gap follows.

<u>Context of emerging trends and gaps and the future of possible research on a purely solid-state bioeffect mechanism or MUBEM like SSMSSS:</u>

Efforts are made in the clinic to keep ultrasound power levels low to minimize exposures and avoid harm to the patient. Yet users and manufacturers succumb to an unrestrained drive to progressively (1) miniaturize the front end of an ultrasonic imager like a compact hand-held ultrasonic transducer array pressed with a manual holding force by physician or technician against the coupling gel on a patient's skin, and (2) improve HD images to make tissue features 'pop out' for quick, reliable interpretation by radiographer or physician doing a clinical screening or diagnosis procedure. The holding action of (1) exerts in effect a mechanical bias force that produces a creep deformation in VE tissue akin to that produced in Hal's graduate thesis research. Higher contrast comes from increasing mechanical power or intensity of single and multiple ultrasound scans of a patient performed by electronically steerable 1D and 2D arrays of ultrasound transducer elements each acting as a high-bandwidth transmitter, receiver or transceiver that accepts high amplitude pulses of steep rise times and narrow width at increasingly higher frequencies. Computer processing converts front-end data into 3D images and 4D movies.[48] Higher contrast also arises by (A) increasing the accumulated energy absorbed by the patient via multiple ultrasound scans computer-averaged to increase signal-to-noise ratios to sharpen image detail, and (B) enhancing echogenecity of acoustic wave impedance discontinuities in tissue by reflecting stronger echoes.

The enhancement per (B) comes from deliberate introduction into the bloodstream of ultrasonic contrast agents (UCA's) as microspheres of gas trapped within VE shells that resonantly scatter longitudinal waves due to UCA radii tuned to radial oscillation resonance at the MDU frequency. As with any cavitating bubble in contact with liquid, microstreaming can occur near an oscillating exogenous UCA or endogenous microbubble. Tissue like the solid endothelium of a blood vessel's lumen can then be deformed and damaged by hydrodynamic shear induced by microstreaming from cavitating bubbles. Such UCA's can open up the BBB. Circumferential pre-strain $(\check{S}_{oa})_{ij}$ [see Part 2] in the lumen wall can then relax, increasing damage. Bias strain $(\check{S}_{ob})_{ij}$ arises by applying a bias stress $(\check{T}_{ob})_{ij}$ inducing creep deformation as in ultrasonic elastography but also in intraoperative use of an ultrasound transducer array pressed by hand on an organ exposed by surgery. Coupling strain $(\check{S}_{oc})_{ij}$ [per Part 2] can be a residual strain induced by ultrasonic indentation of a nonlinear VE solid; for example, see photos x-z and aa-bb in Fig.5 of the UI73 conference proceedings paper cited in the bibliography.

The gap between device performance and protection of patient safety from adverse bioeffects (including delayed ones) can be bridged by a new generation of better-prepared scientists and engineers entering the MURP community via committed university faculty advisors who allow their physics, mechanical-engineering, physiology, molecular-biology and related dissertation students to pose high-risk but high payoff thesis statements *inspired* by success with core graduate courses with high-level textbooks like *NLFTM*[49] and then *tested* by rigorous, reviewed investigation. A higher level of tensor analysis and physics integration is needed such as the Lagrangian EOM for balance of linear momentum [Eqs.(5)-(6)], including body forces, in curvilinear coordinates (in the undeformed state) plus *covariant* differentiation so that derivatives of tensors still yield tensors, in contrast to the non-covariant formulations here. But in addition, a renewed respect for the "old" scientific literature could help such future graduate students come

[48] Feature in online October 2012 issue of ITN (Imaging Technology News), "Emerging Trends in Ultrasonic Imaging -- Ultrasound technology continues to improve, and the market is growing" by Darshana De, at: **https://www.itnonline.com/article/emerging-trends-ultrasound-imaging**. Updated 03-02-16 by Jeff Zagoudis, "Advances in Ultrasound," pp.14-15 in ITN Digital Ed. of March 2016, at: **https://www.itnonline.com/article/advances-ultrasound**.

[49] E.g., Josef Betten, *Creep Mechanics* (Springer Verlag, Berlin, 2008), with CD. Also, along with *NLFTM* cited in Footnote [38], a book holistically adding entropy production to a broad framework is the classic book by de Groot & P. Mazur, *Non-Equilibrium Thermodynamics* cited in Footnote [24]. The more integrated approach needed comes by combining statistical mechanics, thermodynamics and continuum mechanics of solids incl. elastodynamics and Hertzian contact. For ex., a structural framework for MUBEM's can be a set of fluxes & thermodynamic forces related by the Onsager relations for the phenomenological equations for flow of heat, particles & stress power, the last calculated by integrating over a volume the EOM, e.g., Eq.(5) *supra* without external volume forces, or with them per Eqs.(5.2.8) & (5.2.16) for Eulerian & Lagrangian expressions, resp., on pp.126-127 of *NCMS* (Footnote [29]) – and applying the Gauss-Green theorem (*NCMS*, p.19) to convert a volume integral to a surface integral for stress power flux.

up with new ideas and the passion to pursue them long enough to achieve decisive outcomes benefitting the common good of all including the MURP community, it being a matter of intellectual honesty and strength to build upon past results and findings so that the student or young investigator has a solid footing for his or her own career. In that vein, Part 2 was written out of concern for safety and future of the unborn human person alive in his or her mothers' womb when exposed to MDU without control of mechanical shear deformation caused in tissue by solely solid-state, mainly nonthermal bioeffects of ultrasonic mechanical power and energy.

That POV builds on Hal's joint statement of over 40 years ago with Dr. Mel Stratmeyer of the FDA [per 2nd #1, p.8]: "...several independent groups have found that diagnostic ultrasound produces biochemical, E.E.G., and behavioural effects connected with C.N.S. tissue in mammals. We cannot yet comment on the significance of delayed or reversible biological effects for the safety of diagnostic ultrasound; we believe that more work is needed on effects of low-level ultrasound on nervous tissue, with particular emphasis on functional vs. anatomical lesions." The proposed ultrasonic SSMSSS MUBEM arising from recent studies based on Hal's physics dissertation [per 1st #2, p.8] can be included in models for either lesion type.

<u>Context of national health policy, policy analysis and epidemiology on assessing and managing uncertainty of risk of harm from ultrasonic SSMSSS:</u>

In the U.S. there is no federal health-related policy on the use of ultrasound in medicine. The applicable part of the U.S. Code, Chapter 9 of Title 21 relating to the FDA does not mention one, nor does the FDA Policy Office provide online a policy on radiation-emitting medical devices including those emitting ultrasound, a form of mechanical radiation. Online information at the part of FDA dealing with radiation-emitting medical devices, the Center for Devices and Radiological Heath (CDRH), does mention incident reports on mishaps that occur in the field with actual medical devices.[50] The CDRH itself does not mention policy save the overly general one of "Protecting and promoting the public health," [51] viz.:

> "In keeping with our mission, the Center for Devices and Radiological Health (CDRH) is responsible for protecting and promoting the public health. We assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products. We provide consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee. We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S."..."We seek to continually improve our effectiveness in fulfilling our mission by planning strategically and regularly monitoring our progress."

Applicable scientific literature on safe (e.g., benign)-vs.-adverse bioeffects of ultrasound from medical devices does not refer to the discipline of *policy analysis* such as Benefit-Cost Analysis or Risk Analysis couched within a larger framework such as the reality of uncertainty in risks and

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[50] E.g., "Recent Medical Device Safety Communications -- The FDA's analyses and recommendations for patients and health care providers about ongoing medical device safety issues" at: **https://www.fda.gov/medical-devices/medical-device-safety**. Two other report formats are included at this source URL.
[51] Source URL as of May 12, 2020 for statements: **https://www.fda.gov/about-fda/fda-organization/center-devices-and-radiological-health**.

in the costs to avoid them.[52] A pertinent policy context for such policy analysis books is that for children's health:[53]

> "The foundations of health and well-being are laid down in pregnancy and the early years. *Health for all Children* takes a life course approach to child health, starting in pregnancy and extending to the age of seven to include transition into school, and to cover the foundation years in education...The fifth edition starts in pregnancy and runs until age seven taking into account government policies and different models of delivery of the child health programme. Evidence from all over the world is critically appraised and referenced to UK policy and practice."

Epidemiological studies on ultrasound effects on human populations, studies both retrospective and prospective, are essential for grounding in a statistically based reality the tetrad of policy analysis, promulgation of policy, its practice, and its management. However, even at the time that a seminal report was issued on exposimetry for mechanisms for the action of ultrasound on biological tissue, that such studies had not kept pace with advances in the technology for the medical devices emitting ultrasound as used in clinical settings. For example, nearly a decade had passed since the important epidemiological studies published in the mid-1990's (RADIUS, 1993; Newnham, et al.,1993; Campbell, 1993; Salvesen, et al., 1994) per NCRP Report No. 140 issued in 2002.[54] Also, from Section 13.12.2 (pp.426-427) in that report are these statements:

> "A number of epidemiological studies of the use of ultrasound in pregnancy, including several case-control and randomized-control studies, have been performed over the past 20 y. Based on the epidemiological evidence to date, there is insufficient justification to warrant a conclusion there is a causal relationship between diagnostic ultrasound and any adverse effect. (para. break) It is necessary, however, to realize that the entire database of the epidemiological evidence of humane exposure to diagnostic ultrasound is limited to the time prior to 1991, when the FDA relaxed the permissible upper limit of acoustic outputs. Current (i.e., as of 2002) exposures to the fetus, for example, could be considerably greater than those occurring before 1991. Also, other important changes in the practice of diagnostic ultrasound have been introduced during the past decade, such as the widespread use of contrast agents. Furthermore, it must be recognized that very large sample sizes would be required in order for epidemiological studies to reveal a small increment in the occurrence of an adverse effect. (para. break) Therefore, the comfort obtained from the absence to date of any harm based on epidemiological evidence must be tempered by the fact that there are no epidemiological studies appropriate and adequate for current clinical practice."

Part 2 was written 18 years after publication of NCRP Report No. 140 predating marked ultrasound energy, power and intensity exposure level increases since then as in routine fetal ultrasound scans in OB/GYN medical practice. And ultrasound scans are now used for non-medical purposes like 'baby pictures' for parents-to-be. Further, the FDA logs incident reports

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[52] A good recent book on this topic is M. Granger Morgan (2017), *Theory and Practice in Policy Analysis – Including Applications in Science and Technology* (Cambridge University Press, Cambridge, England, UK), hardcover, 590 pp.

[53] Alan Emond (editor) (2019), *Health for All Children*, 5th edition (Oxford University Press, Oxford, England, UK), paperback, 480 pp. This book gives a United Kingdom perspective as represented by the quotation presented on the back cover of this book.

[54] Chapter 12, "Epidemiology of Ultrasound Exposure," pp. 379-403 in *Exposure Criteria for Medical Diagnostic Ultrasound: II. Criteria Based n all Known Mechanisms*, NCRP Report No. 140 issued December 31, 2002, as Recommendations of the National Council on Radiation Protection and Measurements (NCRP, Bethesda, Maryland USA, 2002). The first paragraph of Ch. 12 in this report states: "Particular attention is given to the potential risks of fetal exposure to diagnostic ultrasound." And, from first paragraph in the Preface (p. iii): "This report is the third in a series that includes NCRP Report No. 74, *Biological Effects of Ultrasound: Mechanisms and Clinical Implications* and NCRP Report No. 113, *Exposure Criteria for Medical Diagnostic Ultrasound: I. Criteria Based on Thermal Mechanisms*. The 3 reports were prepared by scientific Committee 66 chaired by Wesley L. Nyborg." Over 1969-1974, Prof. Nyborg advised the successful physics dissertation of Hal and was a co-investigator at BRH with Hal there over 1975-1977.

on improper use or poor condition of ultrasound scanning machines, while not updating new epidemiological studies on diagnostic ultrasound bioeffects. No study has considered any possible adverse effect from ultrasonic SSMSSS including residual shear strain ultrasonically left or removed from tissue (e.g., inside the single cell). For that matter, unknown in clinical practice are the exposimetry physics and engineering needed to quantify the presence of shear strain as in soft solids, such as tissue or phantom materials, from use of longitudinal waves emitted from medical devices, with knowledge these waves are elastodynamic in nature, not acoustic. Finally, since ultrasound is routinely used in medical diagnoses for managing human pregnancies, no null-control population is available in developed countries like the U.S. for use in any prospectively designed epidemiological study. Such a study, having to thus include stratified levels of exposure to ultrasound, would be even more expensive to carry out, even in the unlikely scenario of a recovery of shear strain exposure data from published papers. For the preceding and other reasons, then, Hal has concluded a significant enough percentage of the total U.S. membership in the MURP community has so intentionally avoided the scientific rigor typical of the three NCRP Reports cited in Footnote [54] as still essential today for gaining truly objective assessments for safe use of ultrasound in medicine, that he has real concern the brain health of myriads of vulnerable Americans born each year after routine gestational exposure to ultrasound has been put at risk.

Going forward from here – Simple steps to take to start process of uncovering overlooked evidence for SSMSSS bioeffects of ultrasound:

Preliminary Matters:

One such step is to compare details for the physics and animal-model lab experiments conducted for both the 1969 physiology and 1974 physics dissertations at UVM, with both supervised under the same advisor and using nearly identical though separate ultrasonic stepped horns to, respectively, (1) induce bioeffects in whole *ex situ* muscle tissue from the frog *Rana pipiens* but observe them via post-irradiation data such as transmission electron micrographs, and (2) induce and *in situ* observe physical effects in a phantom material (a soft epoxy plastic). This comparison is made in the "Background" section following. Opportunities for future research experiments then can be identified from this comparison in the subsequent section, "Suggested New *in Situ* and *Ex Situ* Experiments with Quantitative Exposimetry of Induced stress and Strain." Firm decisions about what actual laboratory experiments to conduct, though, will depend on securing awareness of a better theoretical physics framework within which to design them and interpret their results. Such awareness has to extend beyond that developed by Hal, as described in his *pro bono* Technical Report issued by his former scientific consulting firm but does not mention the topic of residual stress or strain.[55] However, that TR plus Hal's UI73 paper cited in the bibliography section can be used as a guide for re-examining the original transmission electron micrographs (TEM's) taken by RMS at UVM to look for evidence of ultrasonically induced residual shear strain, through an optical comparison of registered pre-irradiation and post-irradiation TEM's. Also, experiments could be done with inclined contact forces to facilitate studies of threshold values for creating residual stress, annealing of pre-stress, and observing onset of damage via transmission electron microscopy,

[55] Harold M. Frost, III (2013). "Contact Mechanics and Dynamics of a Special Type of Vibrating Indenter Acting on a Soft Solid," Technical Report 2011-1 (ver 04), Aug. 5), Frosty's Physics, LLC, Sheffield, Vermont 05866 U.S.A. In this work, the acronym "SSMSS" means solid-state mechanical shear stress" in contrast to "solid-state mechanical shear strain" here. Awareness of importance of residual stress or residual strain (for ex.) came after this report was issued.

scanning electron microscopy with analytic features, atomic force microscopy, or related high-resolution nondestructive imaging method.

Pertinent Background for Preliminary Matters:

In the Spring of 1976, Professor Nyborg (WL**N**, p.16) gave a series of four lectures on bioeffects of ultrasound, at the Bureau of Radiological Health (BRH) located in Rockville, MD and directed by John C. Villforth when Hal was working there as a Health Physicist and the in-house ultrasound expert. (For citation of and online full-text access to the pertinent *HEW Publication (FDA) 78 – 8062*. Due to a Memorandum of Understanding between DHEW and the World Health Organization (WHO), three WHO Collaborating Centers had been established in BRH, one of which co-produced that book, the WHO Collaborating Center for Standardization of Protection Against Nonionizing Radiations. The other co-producer of the book was BRH's Division of Biological Effects as led by Moris L. Shore, Ph.D., where Hal worked. The following sub-sections of this Part 2 are based in part on Section 4.8 of the preceding book, "Response of a Semi-Solid Medium" (pp. 37-39). Full text of this book was accessed as a "Google Books" scan but unfortunately, due to a scanning error, not all of p.33 is available. Key statements from p. 37 of the book are quoted: "Much of the foregoing discussion of mechanisms for bioeffects is based on the assumption that the biological medium is a liquid or a suspension. This liquid model is surprisingly useful" but "it is obvious that a liquid model is inadequate for biomedia, and that solid-like properties of tissues should be taken into account. At present there has been little done in accounting for changes produced by ultrasound in tissues by models for solids."

Nyborg briefly reviewed some of the literature for possible models in this area such as cyclic fatigue leading to material failure at some critical threshold of experimental parameter like intensity or number of cycles in a pulse. One example is a paper by Welkowitz[56] for explaining certain bioeffects of unidirectional CW ultrasound on frog muscle tissue as nonlinear in nature, with a threshold value in intensity. Other workers investigated the matter by exposing mammalian brain tissue with pulses of ultrasound, each with a given number of cycles N.[57] Based on an observed change occurring after a given number of cycles (as described in papers cited in Footnote [57] of this treatise, Prof. Nyborg on p.38 of his book of lectures suggested that (1) "A certain amount of damage is done during each cycle," and (2) "The damage accumulates cycle by cycle until the total reaches a level required for the observed change which may be fracture of a solid, or lesion formation in the brain." He commented that "questions remain as to the basic prosess(es) [sic] leading to the damage." Both criteria (1) and (2) were met in two closely related sets of works of action of ultrasound on soft solids, as mentioned in Professor's Nyborg's lectures at BRH, each set comprising a dissertation and at least one published paper. The first set describes research on *ex situ* bioeffects of ultrasound on either the sartorius or the semitendinosus muscle of the frog *Rana pipiens*, via the 1969 UVM Physiology and Biophysics dissertation of Ronald M. Schnitzler (RMS) cited in Footnote [9] -- and in Ref. [80] in *HEW Publication (FDA) 78 – 8062* citing a sequel 1970 paper.[58] The second set describes the action

[56] Ref. [78] in Nyborg's HEW) Publication (FDA 78 – 8062: W. Welkowitz (1955). "Mechanical mechanism of destructive effects of sound on tissue." *J. Acoust. Soc. Am.* **27:** 1142-1144.

[57] Per Refs. [76] and [77] in Nyborg's HEW Publication (FDA) 78 – 8062 (cited in 1st item #2 on p.8 of Hal's CV): P.P. Lele, et al. (1974). "Mechanisms of tissue-ultrasound interaction, pp. 345-352 in *Proc. Second World Congress on Ultrasonics in Medicine*, Rotterdam 1973 (Int. Congress Series No. 309, *Excerpta Medica*, Amsterdam) for [76], and F. Dunn, et al. (1975). "Frequency dependence of threshold ultrasonic dosages for irreversible structural changes in mammalian brain," *J. Acoust. Soc. Am.* **58:** 512-514 for [77].

[58] M. Ravitz and R.M. Schnitzler (1970). "Morphological changes induced in the frog semitendinosus muscle fiber by localized ultrasound." *Experimental Cell Research* **60(1):**78-85. Cited in Ref. [80] on p. 57 in Nyborg's HEW Publication (FDA) 78 – 8062 (cited in 1st item #2 on p.8 of Hal's CV.

of ultrasound on a phantom solid material, a soft epoxy plastic described in Hal's 1974 UVM Physics dissertation and his UI73 prequel paper, cited in this treatise and also as Ref. [81] in the same HEW Publication.

Both dissertations, supervised at UVM by Prof. Nyborg [WL**N**, p.16], presented observations of strictly noncavitational and essentially nonthermal effects of the action of the same type of ultrasonic composite transducer [design including a stepped horn resonating at 85-90 kHz as made from stainless steel. per RMS's work + Hal and WLN's UI73 paper), or titanium to reduce internal heating (from a metal's internal friction) at the step transition (Hal's dissertation). Both RMS and Hal brought the same kind of dynamic indenter tip (e.g., wedge-shaped, with cylindrical curvature) into normal contact with a plane or curved edge surface of a solid test sample or object to locally create in it near the tip under static and other load conditions probably the same type of simple radial stress distribution first observed photoelastically in glass.[59] The test sample in the research of RMS was either a muscle fiber insonated with a spherically shaped tip at the free end of an exponential Mason horn or a whole muscle insonated with the wedge-shaped tip with cylindrical curvature on the end of the stepped horn. In the research of Hal, the test sample was PS-3 flexibilized epoxy insonated with the wedge-shaped tip. Contact for the latter was taken by Hal in his dissertation as Hertzian contact (thus, without adhesion), but as Hertzian-like contact with slight adhesion in RMS's dissertation. The test specimen was insonated when the piezoelectric transducer was energized harmonically for short periods like a minute. (However, RMS used irradiation times of up to 30 minutes.) For both dissertations, the tip oscillated ultrasonically at about the same values of displacement amplitude u_o (typically $u_o \leq 5\mu m$) along the axis normal to an edge surface of a solid to thus exert a dynamic force $\mathbf{F_d}$ coaxial with the static force $\mathbf{F_s}$.

A significant difference between the two dissertations was that in the research of RMS the static contact force $\mathbf{F_s}$ was uncontrolled and unmeasured, and so was probably variable, relatively small (compared to Hal's $\mathbf{F_s}$), and due to *continuous* contact (in contrast to Hal's *intermittent* contact as well) perhaps due to attractive capillary or acoustic-radiation force. But in Hal's research $\mathbf{F_s}$ was applied externally as a constant, calibrated and relatively large force via a small, on-stage balance beam with a small weight whose position was adjustable by hand to produce various torques and thus various values of $\mathbf{F_s}$ fixed in a sonication 'run' or varied from run to run. Also, in RMS's work, $\mathbf{F_s}$ as a transverse force on a muscle fiber or bundle, though coaxial with a small dynamic force $\mathbf{F_d}$ (as in Hal's research), was at right angles to a separate, independent nonlocal longitudinal tensile force $\mathbf{F}$ required on the end of the muscle tissue sample to stretch it into a rigid enough state to resist a transverse deflection. So $\mathbf{F}$ and $\mathbf{F_d}$ or $\mathbf{F}$ and $\mathbf{F_s}$ in RMS's work comprised two sets of biaxial stresses, with zero dot products, viz., $\mathbf{F}\cdot\mathbf{F_s} = \mathbf{F}\cdot\mathbf{F_d} = \mathbf{0}$. In the work of Hal, $\mathbf{F_s}$ was coaxial with $\mathbf{F_d}$, the dynamic force exerted by the oscillation of the tip; here, $\mathbf{F_s}\cdot\mathbf{F_d} = F_s\, F_d$. No other force was exerted so that the loading scheme here was uniaxial. Another important difference was that the resonant frequency was essentially constant in RMS's work, due to minimal loading effects on the tip and direct connection of an adjustable, commercially available oscillator to a power amplifier driving the Mason horn. But in Hal's work it varied by small amounts as a function of time, due to using a self-excited oscillator embedded in automatic gain control circuitry designed and fabricated to Hal's specifications so that the resonant frequency shifted with change in loading conditions in such a way as to keep u_o

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[59] Carus Wilson (1891). *Phil. Mag* **32:** 481, as cited in Footnote [2] on p.85 of book in 2nd ed., *Theory of Elasticity* by S. Timoshenko and J. M. Goodier (McGraw-Hill Book Co., Inc. New York et al., 1951).

constant via use of a negative feedback loop and special capacitance bridge. Also, contact of the indenter tip with test object was probably continuous over entire ultrasound cycles in RMS's work, but in much of Hal's work was intermittent from cycle to cycle.
The observed material deformation effects in the dissertations were complementary, with RMS's involving morphological changes in anatomy observed *after* irradiation at high spatial resolution with a transmission electron microscope (TEM), and Hal's involving changes in the in-plane principal strain difference as a solid-state mechanical shear strain SSMSS observed *during* irradiation at low spatial resolution with a polarizing microscope. The two workers offered different models to explain the observations, with RMS picking a Nyborg-like nonlinear acoustic model including microstreaming phenomena but Hal invoking an alternative elastodynamic model with microstreaming absent but with deformation of a nonlinear solid satisfying a linear Hooke's law for the relationship between composite contact force and tip displacement amplitude. (However, microstreaming may have occurred in either RMS's or Hal's research if plastic deformation and then plastic flow had occurred near the respective solid near the contacting tip.) Also, Hal observed residual strains which could be recorded or erased at will depending on the manner of turning the ultrasound off (there were two ways); RMS did not have this capability.

Incidentally, atomic force microscopy (AFM), introduced to complement specimen-destructive TEM as a nondestructive *in situ* imaging method, features static and dynamic nanoindentation via a cantilevered, sharp tip used to image surface properties of solids via raster or other scanning in either continuous or tapping contact mode. Hertzian contact theory akin to what Hal used is extended to include action of adhesion forces. In contrast to Hal's side indentation of an edge surface, though, AFM generally images effectively unbounded 'top' surfaces of solid objects with 3D extension (e.g., blocks) or 2D (e.g., thin films). Besides the *in situ* nondestructive feature, though, AFM usefully provides some of the input data needed for finite element models (FEM's) of biological tissue at microscopic size scales, such as single-cell surface topography and indentation-force-vs.-displacement curves. Strain hardening in the latter can indicate the presence of internal compressive residual stress. Types of models used in finite element analysis (FEA) of mammalian cell nuclei include schematic (e.g., Kelvin-Voigt), continuum mechanics, Hertzian contact and molecular dynamics.[60]

Suggested New in Situ and Ex Situ Experiments with Quantitative Exposimetry of Induced Localized Stress and Strain, With Some Theoretical Considerations:

A look for initial exploratory research experiments providing new but semi-quantitative data can start with a straightforward synthesis of the two approaches taken in the dissertations of RMS and Hal. Experimental design, methods, data processing, and data interpretation could be further refined later on by adopting for now a manageable form of classical physics theory incorporating an intermediate level of non-equilibrium thermodynamics. (Such an approach could spade the groundwork needed for the decisive results demanded by the wider MURP community.) A middle level of non-equilibrium thermodynamics has been published by workers in the de Groot and Mazur school of analysis going back to the 1960's.[61] Ideally, such

[60] Chad M. Hobson & Andrew D. Stephens (2020), "Modeling of Cell Nuclear Mechanics: Classes, Components, and Applications" (Review), *Cells* **9,** 1623; doi:10.3390/cells9071623 + Lili Wang, Li Wang, Limeng Xu & Weiyi Chen (2019), "Finite Element Modelling of Single Cell Based on Atomic Force Microscope Indentation Method," *Computational and Mathematical Methods in Medicine*, Vol. 2019, Article ID 7895061, 10 pp., doi:10.1155/2019/7895061.
[61] A starting point for developing a new theory or for finding one already in the literature is the paper, Francesco Farsaci, Silvana Ficarra, Antonio Galtieri, and Ester Tellone (2017), "A New Non-Equilibrium Thermodynamic Fractional Visco-Inelastic Model to Predict Experimentally Inaccessible Processes and

refinements in the theory need to be assembled from the technical literature if already done, or failing that, to be developed and published before any formal quantitative experiments are conducted. A key insight to this end is that RMS's *ex situ* experiments on mammalian muscle fibers or fiber bundles comprised a biaxial version of the uniaxial experiments that Hal conducted on a soft or flexibilized epoxy, PhotoStress® "PS-3" later shown to exhibit a nonlinear viscoelastic compliance.[62] Thus the needed theory would have to include biaxial or even triaxial stress systems with both static and dynamic components. Another insight is that of residual shear strain as induced by the ultrasound exposures, measured in the work of Hal and deduced by him as probably present in the work of RMS.

As an initial realization of the needed new *exploratory* experiments, the investigator could adopt the following plan. That is, a known dynamic compressive contact line force directed transverse to the longitudinal axis of the muscle sample and acting with an ultrasonic time dependence could be superposed coaxially with a known and coaxial static version of contact line force, both acting transversely at a given point along the length of a muscle tissue sample (even a single fiber) held in a suitable test fixture to allow two-dimensional surface scanning, one dimension being rectilinear along the longitudinal axis of the fiber, the other dimension being curvilinear (azimuthal) around the circumference of the essentially cylindrically shaped test sample, with the wedge axis of the sharp indenter tip (of different radii of cylindrical curvature) always being transverse to the longitudinal axis. The stretch of the muscle sample and thus its rigidity to transverse deflection by the applied transverse forces could be modified by a separate static longitudinal force applied to one end of the sample and on which could be superposed a small dynamic force for measuring, for example, longitudinal wave speed and attenuation. All forces would be applied by and measured via force or pressure transducers such as piezoelectric, with adequate frequency responses from 0 to 200 kHz. The associated transverse and longitudinal displacements, taken to be time-dependent in response to the applied forces, would also be known via measurements in quadrature with adequate frequency responses from 0 to 600 kHz, via displacement transducers or laser interferometry methods for both in-phase (recoverable) and out-of-phase (loss) parts could then both be calculated. With the transverse forces and longitudinal forces applied at different locations, they then could be removed or 'turned off' in two separate ways denoted as A and B, depending on the time order of removal that governs whether a shear or other strain is recorded or erased. Because a viscoelastic solid has memory at any given time of a past deformation, qualitative features of such effects may be affected by choice of the two different ways for 'turning on' the applied static and dynamic forces, via ways denoted by, say, C and D.

The preceding apparatus or perhaps a better and simpler one later on could be calibrated via use of theory already described in Hal's physics dissertation and papers cited in the bibliography section, plus by substitution use of a muscle phantom with roughly the same geometry as the muscle sample itself, as a long aspect-ratio rod of rectangular cross section precision cut or sawn from a commercially available isotropic PhotoStress® epoxy sheet of 2-3 mm thickness

Investigate Pathophysiological Cellular Structures," *Fluids* **2,** 59 (13 pp.) – in the Special Issue for "Non-Equilibrium Thermodynamics in Multiphase Flows." From p.2: "Following the De Groot and Mazur school, a remarkable step forward was made by Kluitenberg, who introduced and developed non-equilibrium thermodynamics with internal variables, the theory to which we will refer [2–7]. This theory has been developed both in the mechanical continuous and electrodynamic fields." Ref. [2] is for the de Groot and Mazur book cited in Footnote [15]. For full text of article, click on "Download PDF" icon at: **https://www.mdpi.com/2311-5521/2/4/59/htm**. This starting point of the work of Farsaci, et al., only for liquids, then might lead to a later derivative or citing paper in the literature presenting a formalism for soft solids such as much of biological tissue, include its inhomogeneity of structure and of corresponding macroscopic properties including nonlinear effects of pre-stress & residual stress, for example.

[62] Michelle L. Oyen (2007). "Sensitivity of polymer nanoindentation creep measurements to experimental variables." *Acta Materialia* **55:** 3633-3639.

mounted and instrumented on the stage of a polarizing microscope. Then isoclinics and isochromatics could be observed in the region of transverse contact, either as time-averaged fringes captured by a time-lapse series of photos taken by a still camera or as instantaneous fringes captured by high-speed cinematography. Two types of epoxy would be used, one with *linear* stress-strain constitutive equations (such as “PS-1” and “PS-4”) that thus cannot model recording or erasing of ultrasonic residual SSMSS fields depending on whether the ultrasound is turned off by way A or by way B, the other with *nonlinear* stress-strain constitutive equations (such as “PS-3”) that can accommodate residual strains. These choices of candidate viscoelastic photoelastic materials are based on compliance-related data reported in the paper cited in Footnote [62], for example, as well as on their present commercial availability maintained from at least as far back as the 1970’s so that there is a record of their use in the technical literature.[63]

Then it would be possible to quantitatively test the idea of recording residual shear strain (as SSMSS) if the forces are removed one way, denoted by A for removing the dynamic force before removing the static force , but erasing them if removed in the opposite way denoted by B, assuming that the constitutive equation for the tissue models a *nonlinear* viscoelasticity in which the compliance is a function of the mechanical stress arising from applied forces – in analogy with the shear strain recording and erasing phenomena observed by Hal in the sample of a nonlinear soft epoxy “PS-3.” Then changes in morphological features of the excised tissue could be captured by electron microscopy and compared with those for unirradiated samples, to see what structural differences if any might occur in the presence of vs. in the absence of residual strain. Details on such deformation related to specific anatomical features are provided by the abstract to the 1970 paper by Ravitz and Schnitzler cited in Footnote [58], viz.:

> “A spectrum of structural changes was observed which depended on amplitude and duration of sonation. The mitochondrial cristae and components of the sarcotubular system appear most sensitive to ultrasound. With increasing amplitudes and treatment durations, decrease in glycogen content, Z and M line disruption, and misalignment of the filaments within the myofibrils occur. In the most severely treated fibers, there is a complete breakdown of band structure. The generation of steady intracellular stresses produced by the sound field ... is postulated to explain these results. The results provide evidence that many effects of sound on muscle reported in the literature and ascribed to heating or cavitation can be produced in the absence of these factors.”

Image digitization and then processing and re-display of Dr. Schnitzler’s TEM’s could reveal and map the presence of residual strain if induced by localized ultrasound. If created at important microstructural features of the sonicated tissue, then one could investigate whether a functional change or even lesion involving a biochemical, chemical, or action-potential process also occurred there such as by mechanotransduction as in the cytoskeletal network. With an hypothesis that residual strain is most likely to occur on the most vulnerable planes in a biological tissue specimen, the following new approach could then be taken to get better data on threshold values for tissue damage from ultrasound. That is, one could incline the indentation force at some angle “Φ” with respect to the axis normal to the surface of the specimen which could be taken as the “y” axis in an (x, y, z) RCC, with the “z” axis in the thickness direction.

[63] "PhotoStress Coating Materials and Adhesives," a datasheet available from Micro-Measurements (a Vishay Precision Group brand) as a 5-page document including reference literature citations plus tables of optical, mechanical, geometric and thermal properties (such as but not limited to precast PS-1, PS-3 & PS-4 free-standing sheets) last revised August 6, 2015. FT: **http://www.vishaypg.com/docs/11222/11222BPhoto.pdf**. Hal has no vested interest in this firm.

(For perpendicular, indentation, Φ=0.) Then the expressions for the radial stress and radial strain for the case of normal inclination are:

$$[(\check{T}_{be})_{ij}]_{\Phi=0} = \delta_{i1}\delta_{j1}\ [(\check{T}_{be})_{11}]_{\Phi=0},\ [(\check{T}_{be})_{11}]_{\Phi=0} \equiv \sigma_{rro} = (-2/\pi)(F_T/hr)\cos(\theta),\ [(\check{S}_{be})_{11}]_{\Phi=0} \equiv [\varepsilon_{rr}(t)]\Phi_{=0} = \sigma_{rro}/Y(t), \text{ and } F_T = F_s + F_d.$$

For any inclination angle in general of applied force, denoted by Φ, these relations change to:

$$[(\check{T}_{be})_{ij}]_{\Phi} = \delta_{i1}\delta_{j1}\ [(\check{T}_{be})_{11}]_{\Phi}, [(\check{T}_{be})_{11}]_{\Phi} \equiv \sigma_{rr\Phi} = (-2/\pi)(F_T/hr)\cos(\theta+\Phi), \text{ and } [(\check{S}_{be})_{11}]_{\Phi=0} \equiv [\varepsilon_{rr}(t)]_{\Phi=0} = \sigma_{rro}/Y(t).$$

For an incompressible solid, the time-dependent VE Young's modulus can be expressed in terms of the creep compliance characterized by one or more retardation times such as per Eq. (D28) on p.271 of Hal's physics dissertation:

$$[Y(t)]^{-1} = (3/2)J(t);\ Y(0)]^{-1} \equiv [Y_o]^{-1} = (2/3)J(0) \equiv (2/3)J_o = (1/3)\ [\mu(0)]^{-1} \equiv (1/3)\ [\mu_o]^{-1},$$

with instantaneous (initial or t=0) values denoted by argument 0 or subscript o, with symbols already defined. For sense of angles θ and Φ, see contents in Timoshenko and Goodier cited in Footnote [59], e.g., illustrations of geometries per Figs. 52 (a) and 52 (b) on p. 85 for normal indentation force ($\mathbf{F_T}$ inclined at Φ=0), Fig. 54 on p.88 for tangential alignment ($\mathbf{F_T}$ at $\Phi=\pm\pi/2$), and Fig. 55 on p.88 for $\mathbf{F_T}$ at any angle Φ over $-\pi/2 \le \Phi \le \pi/2$, generally measured from the axis of symmetry (θ=0) of the contact problem, as also shown in Figs. 1-2 of the UI73 paper cited.

To return to the co-alignment theme, consider case 1 for normal force vs. case 2 for arbitrarily aligned force for photoelastic observations made in a polarizing microscope configured so the first integral (n=1) optical retardation isochromatics is visible but the isoclinics are not.. (Many n=1 circular fringes are shown in photos in Fig. 5 of the UI73 paper cited.) For case 1, the largest extremal shear strain appearing at a field point in polar coordinates (r, θ) on that circle but on r-z planes passing through that point while oriented at $\pm\pi/4$ radians relative to the on-axis r-z plane θ=0 occurs at (D, 0), while the largest extremal shear strain appearing at a field point on that circle but on r-z planes passing through that point while oriented parallel and perpendicular to the edge of the plate coincident with the x-axis and thus with the axis of symmetry (θ=0, or the y-axis in the x-y-z RCC system) occurs at ($D/\sqrt{2}$, $\pm\pi/4$).

But what if a plane for an interface in the anatomical structure for the tissue sample has other orientation? Then case 2 is useful, with an extremal analysis showing $\sigma_{r\Phi\ r\Phi}$ exerts, with choice $\Phi=-\theta$, a maximum compression stress at the field point (r_Φ, $-\Phi$) and thus extremal shear strain within r-z planes oriented at angles $\pm\pi/4$ radians relative to the r_Φ-z plane. Thus planes other than the preceding two sets on which the shear strain is extremal (i.e., either a maximum or a minimum) can be selected to yield more opportunities for co-alignment at a given field point of a plane of extremal shear strain with a plane associated with a weak or damage-vulnerable interface or other feature in the anatomical structure of the biological tissue being examined. Once that angle is selected, along with an optimal location on the x-axis of the inclined line force, then a series of TEM's or of high-resolution images via AFM or related scanning technique could be taken in test runs of gradually increasing u_o for the indenter tip until a damage threshold is reached or a residual shear strain is left at that field point. The radial coordinate r_Φ can be easily calculated from trigonometry associated with two right triangles inscribed inside the isochromatic circle (tangent to edge of plate and so to the x-axis, at the line of contact with the indenter tip). The equations $\cos(\Phi)/r_\Phi = \cos(\theta)/r = 1/D$ result.

A localized source on the external boundary of a solid like the line force used to model action of a wedge-shaped indenter tip on the straight edge of a semi-infinite elastic or VE plate is relevant to the exposimetry details for standard uses of plane-wave or focused MHz ultrasound (elastodynamic, not acoustic) in medicine for diagnosis, therapy and surgery. That is, restricting comments to 2D stress fields, the theoretical derivation for the spatial distribution of, for ex., stress and strain fields arising from a point force acting within the middle plane of an infinite elastic plate makes use of the solution for a point force acting on the straight edge of a semi-infinite plate.[64] Such a solution could likewise model the action of the localized elastodynamic radiation force created by an external ultrasound projector's small focal volume, whether fixed in location, oscillating, or raster scanned. Or the internal point force could be provided internally, as by a single embedded magnetic bead forced to move statically and dynamically via an applied magnetic induction field or by a single embedded ultrasonic contrast agent. Such 'dry' exposure to internal point sources of ultrasound could occur in living or in *ex situ* tissue.

Indeed, methods presented in this sub-section can help the researcher formulate and test new cause-and-effect laws for ultrasound bioeffects that are non-cavitational and essentially nonthermal in character, partly as localized stress creates a nonuniform field of strain so that at an instant in time the spatial dependence of stress or strain varies markedly from point to point. This geometric variation can be exploited experimentally when a localized dynamic component is added, usually with a different spatial dependence than for the static case only. (For ex., for the preceding case of a line force on the plane edge of a thin plate, with radial coordinates r (for observation points in the plate) greater than those for the region of plastic flow and as located in the far field of either source, the static force (either F_s, or F_s' for intermittent contact) creates a stress proportional to 1/r and the dynamic force a stress proportional to $1/\sqrt{r}$. Both static and dynamic stress also have a $\cos(\theta)$ dependence, with θ the pertinent polar angle.) So if applied forces do not change the elastic or VE moduli of the material, the strain fields have the same radial dependence as for stress.

Considerations Directly Related to Medical Diagnostic Ultrasound (MDU) with Plane Longitudinal Waves, with Comments on Attenuation and Intensity:

The preceding sub-section features line or point sources of ultrasound and their advantages for doing ER on ultrasound bioeffects, but along with a hypothesis that the lowest threshold for producing damage or creating residual strain involves a resolved shear strain within a vulnerable plane at given field point in the biological tissue sample. (Reasoning can be modified in a simple way should the damage or residual strain first occur on a given vulnerable plane as a result of tension.) This viewpoint comprises an innovation in the ultrasound bioeffects literature, in that nothing like the recording of a residual strain or the erasing of pre-strain is mentioned in a recent review paper assembling all the known ultrasound bioeffects mechanisms on living cells.[65] That may well be because the use of photoelasticity on living or even *ex situ* tissue only very rarely appears in the contemporary literature if at all (as on dental tissue). So such an

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[64] E.g., Sec. 38, "Force at a Point of an Infinite Plate," pp. 112-118 in Timoshenko and Goodier's classic book cited in Footnote [59].

[65] *Vide* "Table 1. Overview of publications on cellular ultrasonics in chronological order," in paper of David M. Rubin, Nicole Anderton, Charl Smalberger, Jethro Polliack, Malavika Nathan and Michiel Postema (2018), "On the Behaviour of Living Cells under the Influence of Ultrasound," in *Fluids* **3:** 82 (19 pp.).

effect tends to be invisible even if it does exist. Eventually, then, a search is also needed in new investigations for such effects but now from *plane-wave* or *focused* MDU creating residual strain or eliminating or reducing pre-strain in living biological tissue. A plane wave or a diverging or converging wave of $\check{T}_{ij}$, $\check{S}_{ij}$ or u_i of some type (e.g., plate wave) experiences attenuation incl. absorption by various processes (e.g., thermal, viscous and chemical relaxation). For a homogeneous solid, intensity is $I_r = I_{ro}\,(r_o/r)\exp[-2\alpha r]$ with I_{ro} measured at r_o and α the constant amplitude attenuation coefficient of cylindrical waves that a localized dynamic force launches to propagate as diverging ultrasonic waves of a field variable like $u_1=u_r$ or $(\check{T}_{be})_{11}\equiv(\check{T}_{be})_{rr}$. For plane waves in $u1=u_{x1}$ or in $(\check{T}_{be})_{11}\equiv(\check{T}_{be})_{x1\,x1}$, either traveling in the +x1 direction, the intensity is $I_1=I_{1o}\exp[-2\alpha x_1]$. Attenuation in a solid by either scattering or absorption as α_s or α_a (with $\alpha\equiv\alpha_s+\alpha_a$), respectively, can result in both elastodynamic radiation forces and heating, via action of the attenuation force density. In the EOM first stated just below Eq.(4), viz., $\rho Dv_i/dt=(\check{T}_{be})_{ij,j}+f_{ij,j}$ where $D/Dt=\partial/\partial t+(v_j)\partial/\partial x_j$ and $v_i=\partial/\partial t(u_i)=\partial/\partial t(x_i-a_i)$, this force density gradient is $f_{11}= I_{,11}$.

Such atypical calculations transforming the EOM into wave equations can be important, as material properties in tissue vary with field point **x** at cellular to organ levels (for ex.), as all in Eq.(6), or shear modulus and shear viscosity in Eq.(2). This can be shown by deriving a wave equation in longitudinal strain $\check{S}_{11}$ by taking the spatial gradient of both sides of the two-term EOM for infinitesimal u_1 and no losses (α=0), e.g., of $\rho_o\,\partial^2u_1/\partial t^2=(M\check{S}_{11})_{,1}$ where $[(c_L)_o]^2=M(x_1)/\rho_o$, with ρ_o the constant mass density, $M\equiv\lambda+2\mu=M_o+\Delta M$, and $\Delta M\equiv M_og(x_1)\equiv M_og(x)$. A calculation using a Taylor series expansion for M at closely spaced points $x_1\equiv x$, $x_2=x+\Delta x$ and $|\Delta x|<<1$, and a variational analysis on results locally converts a starting PDE with *variable* coefficients at x_1 into one with *constant* ones, viz., $\rho_o(\partial^2/\partial t^2)[\check{S}_{be}]_{11}-M_o[\check{S}_{be}]_{11,11}=(f_{eff})_{,1}$ with $(f_{eff})_{,1}=\psi(x,t)\Delta x$ an effective volume force gradient with volume force $\psi=(M_{,111})_o(S_{11})_x+2(M_{,11})_o(S_{11,1})_x+(M_{11})_o(S_{11,11})_x$. This result could be extended by assuming inhomogeneous mass density ρ_o. Also, with finite strain, mass density is $\rho\neq\rho_o$. Such computational complexity from material inhomogeneity as in Eq.(6), via proliferation of large numbers of terms with variable coefficients whose concise physical meaning may be unknown, may mean that longitudinal waves do not decouple from shear waves in the sample volume of interest. So achieving the gold standard of utility and elegance of wave equations may be elusive unless a deeper level of mathematics is used to model losses. Reframing the problem as one of strain or stress analysis, helps in this vein as well as seeming to offer practical advantages.

A more reliable way to solve this problem with a demonstrable solution of a WE is to use a unified formal theory to model wave attenuation from multiple scattering events in heterogeneous solids, as inspired by the microstructure of metals and alloys solids, with particle displacement **u** as the field variable.[66] That is, instead of differentiating the EOM with respect to spatial coordinates, such as done in Eq.(6) in this Part 2, one can find a solution via a (volume) integral equation of $u_i(\mathbf{r}) = u^o_i(\mathbf{r}) + \int d\mathbf{r'}\, g^o_{ij}(\mathbf{r}-\mathbf{r'})\, v_{jk}(\mathbf{r'})\, u_k(\mathbf{r'})$, where $u^o_i(\mathbf{r})$ is the solution of the wave equation for a uniform or homogeneous isotropic solid obeying the constitutive equation given in this Part 2 (as Eq. (2)), $g^o_{ij}(\mathbf{r}-\mathbf{r'})$ is a Green's function for the homogeneous material, and $v_{jk}(\mathbf{r'})$ contains all the details of material inhomogeneity in mass density $\rho(\mathbf{r})$ and elastic constants $C_{ijkl}(\mathbf{r})$ relative to homogeneous fields $\rho^o(\mathbf{r})$ and $C^o_{ijkl}(\mathbf{r})$.

[66] J. E. Gubernatis and E. Domany (1983). "Effects of microstructure on the speed and attenuation of elastic waves: Formal theory and simple approximations" (with discussion), pp.833-850 in Section 13: Ultrasonic Multiple Scattering in Review of Progress in Quantitative Nondestructive Evaluation, Vol. 2A, edited by D. O. Thompson and D. E. Chimenti (Plenum Press, New York). Full text pdf via: **https://lib.dr.iastate.edu/qnde/1983/allcontent/53/**. Follow-up research journal paper by same authors: "Effects of microstructure on the speed and attenuation of elastic waves in porous materials," *Wave Motion* **6(6):** 579-589 (November 1984).

This approach facilitates a formal definition of attenuation from scattering (per prior symbol in this Part 2 of $\alpha=\alpha_s$). It can incorporate statistics and probability for random and other distributions of material defects while taking advantage of the practical fact of ultrasonic attenuation data being more sensitive to temperature and frequency effects than data for ultrasonic speed of propagation. Also, it couples attenuation to tensor effects via an effective complex wave number operator $K_{ij}(k)$, a rank-two tensor, whose real part is related to a shift in the phase velocity of a longitudinal wave and whose imaginary part relates to the attenuation. (See Add. A *infra* for complex solutions of elastodynamic wave equations.) This operator is a factor in a term in an expression for the longitudinal-wave propagation constant k whose modulus $k^2=|\mathbf{k}|^2=kk^*$ is given in the cited paper by $k^2=(k^o)^2+(k^o)^{-2}K_{ij}(k)(\boldsymbol{p})_i(\ \ )_j$, with $(\boldsymbol{p})_i(\boldsymbol{d})_j$ a tensor product for the direction cosines for the unit vectors denoting the directions of propagation ($\boldsymbol{p}$) and motion ($\boldsymbol{d}$) introduced in Part 1, while $k^o=\omega/(c^o)_L$ is the propagation constant for a homogeneous solid, with $M^o = \lambda^o + 2\mu^o = \rho^o[(c^o)_L)]^2$. The presence of repeated indices i and j in the quantity of $(k^o)^{-2}K_{ij}(k)(\boldsymbol{p})_i(\boldsymbol{d})_j$, summed according to the Einstein convention, denotes a double contraction of the tensors to a scalar. Such a formal approach might be well extended to include contributions from rate processes due to bulk viscosity and shear viscosity for internal friction effects associated with time derivatives of strain in the constitutive equation such as modeled by Eq. (2) as well as to connect residual stress and strain to scattering of ultrasound in an inhomogeneous solid like soft biological tissue, by using the theory of ultrasonic NDE of metals and alloys whose material inhomogeneity is also due to heterogeneous microstructure.[67]

For a globally inhomogeneous solid, a form of the Beer-Lambert law can be used, with far-field intensity $I_r=I_{ro}\,(r_o/r)\exp[-2\langle\alpha(r,\theta)\rangle r]$ and $I_1=I_{1o}\exp[-2\langle\alpha(\mathbf{x})\rangle x_1]$, with $\langle...\rangle_{sp}$ indicating spatial averaging of the total attenuation coefficient, viz., $\langle\alpha(\mathbf{r})\rangle_{sp}$ or $\langle\alpha(\mathbf{x})\rangle_{sp}$, respectively, over, for example, a portion Δr of the radial domain $r_o\le r\le R$ in which cylindrical ultrasound waves propagate, or Δx in a linear domain $x_{1o}\le x_1\le X_1$ where plane waves do, in the far field of either source and with a decomposition of the inhomogeneous total attenuation along the propagation path of $\alpha_T(\mathbf{r})=\alpha_a(\mathbf{r})+\alpha_s(\mathbf{r})$ or $\alpha_T(\mathbf{x})=\alpha_a(\mathbf{x})+\alpha_s(\mathbf{x})$ in terms of randomly varying (for ex.) local absorption and scattering events, respectively. For wave propagation along the x_1 axis in an RCC, $\langle\alpha(\mathbf{x})\rangle=[X_1-x_{1o}]^{-1}\int\alpha(\mathbf{x})dx_1$ in terms of a definite line integral with upper and lower integration limits of X_1 and x_{1o}, respectively. For a small path length of interest $\Delta x=|(x_1)_2-(x_1)_1|<<|X_1-x_{1o}|$ along the x_1 axis, $I_2=I_1\exp[-(2\alpha\Delta x)]$, with reference intensity at x_1 of $I_1=\langle(\check{T}_{be})_{11}(\partial/\partial t)(u_{be})_1\rangle_{a=0}$ $\{\exp[-2\alpha x_1]\}$ in terms of elastodynamic power flux temporally time-averaged in the real-variable frame as $[\langle(\check{T}_{be})_{11}(\partial/\partial t)(u_{be})_1\rangle_{temp}]_{\alpha=0} = (2\rho_o c)^{-1}\{[(\check{T}_{be})_{11}]_{sp.\ peak}\}^2$ for waves of infinitesimal stress amplitude $[(\check{T}_{be})_{11}]_{sp\ peak} = [(\Pi_o)_\pm]_{\check{T}ij}$ introduced in Part 1 via the stress-tensor wave-equation solution $(\Pi_\pm)_{\check{T}ij}=[(\Pi_o)_\pm]_{\check{T}ij}\exp[-(\alpha_{\check{T}ij})_1x_1]\sin(-\omega t\pm k_1x_1+\Omega_{\check{T}ij})$ with convention of $\Omega_{\check{T}ij}=\pm\pi/2$. Functional dependences for quantities k, c and α depend on the constitutive equation involved. If Eq. (2) preceding is used plus the type of complex exponential WE solutions featured in Addendum A *infra*, then $k^2=(1/2)\zeta\,[1+(1+\epsilon^2)^{1/2}]$, $\alpha=\zeta\epsilon/(2k)$, $c=\omega/k$ (as the phase velocity), and $c_g=(dk/d\omega)^{-1}$ as the group velocity. If rate processes contribute weakly to values of stress in a solid so that the

[67] E. Domany & J. E. Gubernatis (1983). "Residual Stress Characterization by Use of Elastic Wave Scattering Measurements," pp.1309-1326, Sec. 20: Residual Stress and Acoustoelasticity in *Review of Progress in Quantitative Nondestructive Evaluation* , Vol. 2A, edited by D. O. Thompson and D. E. Chimenti (Plenum Press, New York). FT pdf via: **https://lib.dr.iastate.edu/qnde/1983/ResidualStress/**. Also in that sec.: A. F. Emery & G. H. Thomas (1983), "The Use of Acoustic Signal Attenuation in the Examination of Residual Strains: Part B — The Use of Experimentally Derived Acoustic Strain Correlations in the Evaluation of Residual Strains and Stresses," pp. 1381-1387. A review as prequel to that paper by same authors to characterize residual stress: A.F. Emery and G.H. Thomas (1982), "The Use of Analytical Mechanics in Defining Acoustic Test Methodology," RPQNDE, Vol. 1 (Plenum Publishing Corp., NY).

dimensionless quantity $\epsilon_{\beta=}2=\omega\{[(\lambda^0)']_{\beta=2}+2[(\mu^0)']_{\beta=2}\}/[(\lambda^0)_{\beta=2}+2(\mu^0)_{\beta=2}]\}\equiv\epsilon<<1$ is small, then $k\approx k_o[1-(3/8)\epsilon^2]$ with $k_o=\omega/c_L$; $c_L=(M/\rho_o)$; $\alpha\approx k_o\epsilon_2/2$ and $c\approx c_L\{1-[3\alpha^2/[2(k_o)^2]\}^{-1}$ – per Nyborg.[68]

Advisory Notice:

Hal has a disability limiting ability to process information and focus and concentrate on a writing or math task. So, as the subject of this treatise is complex, he has only 'scratched the surface' of its mathematical reality, devoting much of his energy to detecting and correcting errors cropping up in the many revisions of this treatise, due in part to a burgeoning number of math symbols, sometimes with multiple uses of the same character. Errors undoubtedly remain as well as gaps in needed theory and so the expert reader interested in the physical truth is advised this treatise can only accompany his or her own study, calculations and writing to go beyond the ground covered here and embrace the depths of this ultrasound topic. Yet at this late stage Hal is confident that such an investigator can find much to occupy him or her, a confidence coming from a specific technical vision that has been his own guide to what else needs to be done. It is then his hope that other workers can, through their own research, finally bring emergent clarity and credibility to the meaning and meaningfulness of the SSMSSS hypothesis posited here. He cannot realize this vision himself, due to reasons given, and so at this point, he stops and hands the task over to someone unknown but certainly more competent and able than he to prosecute it.

Acknowledgements:

Indeed, there are many reasons why Hal was able to do *something* to bring this topic far enough along to plausibly elicit interest in experts who might read this Part 1 (and Part 2) and then take up the challenge of a physical argument, even if he or she think it is only for testing and trying to knock down a 'strawman' proposal or hypothesis. So acknowledgements are in order, including those for the patience of and assistance rendered by his wife Bev (since 1964) to allow Hal to have enough hours daily in his own private office at their residence connected to the Internet to do the work necessary. And that would not have been possible without the small pension from the University of California Office of the President (UCOP) that Hal has had since retiring in mid-2008 but which would have been much smaller still without the personal intervention of the UC President at the time, Dr. Robert C. Dynes, a fellow physicist (*vide* p.4 of Hal's CV, a separate document). And during the trying time for everyone experiencing the COVID-19 coronavirus outbreak, the owners Johnny and Linda Lotti of Café Lotti in East Burke, Vermont have given Hal a nice and accommodating way to get out of his house in Sheffield with a solo drive daily to their shop for a lunch (curb-side, take-out ,or dine-in) and then a relaxing walk nearby in some of the beautiful fields and woods of the Northeast Kingdom where they all live.

The preceding came to mind immediately upon realizing that this section had to be included in Part 2. Others that Hal then recollected include his professional organization of IEEE which gave him some scope for connecting with other members plus some badly needed confidence when in October 2017 it elevated his membership status from Life to Life Senior, due in part to an initiative of the Ottawa (Ontario, Canada) Section of IEEE to help out in this respect. Besides IEEE, the Foundation for Science and Disability and its President , Dr. Richard Mankin whom

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[68] Source: Pages 408-409 of WLN's book *IBM* (cited in Footnote [10] and acronyms list]. The quantity "ζ" used here is for the quantity "β" used by Nyborg.

Hal has known since February 2008, gave Hal an outlet for his advocacy for the rights and dignity of the disabled person and a platform at **www.stemd.org** for posting a much shorter (10-p.) August 2015 version of his CV. And the scientific thinking that has evolved into this treatise was kick-started in October 2005 after Hal emerged from the darkest part of a long bout with major depression (since 1999) and accepted the offer of a two-year term appointment as an unpaid Research Associate in the Department of Physics at The University of Vermont. The initiator of this offer was his mentor, Prof. (emeritus) Wesley L. Nyborg, who earlier reached out to Hal to support him in his then ongoing recovery, and then with whom from 2005 Hal worked off and on until late 2010, about a year before "Wes's" death in September 2011. Contributions of Dartmouth College and Edward Zuccaro, attorney-at-law, are also acknowledged.

Dedication:

Part 2 is dedicated to young investigators embarking on physics, physiology and related Master's and Doctoral theses researching uncovered ground relating to the safety and efficacy of MDU. Others who might derive benefit include (1) double-degreed researchers with both M.D. and STEM-related degrees as in physics and engineering (e.g., continuum mechanics of solids) who are looking for new investigative challenges, plus (2) qualified and imaginative program managers and directors at federal agencies, private foundations, and other research-project sponsoring entities wishing to understand trends and needs of current and past research in order to strategize the future growth of their portfolios of next-generation grant offerings to be developed and awarded on a competitive, peer-reviewed basis. A starting point for all interested could be an immersion in the technical literature on the important topic of residual stress and strain[69] (SSMSS or otherwise) to gain an understanding of its universal prevalence in *solid* materials including soft living tissue and solids.

Addendum A – Math Framework of Complex Numbers Including Conventions for Elastodynamic Waves:

The vector propagation constant $\mathbf{K}_{\kappa\lambda}$ ("kay," upper case) is generally *complex* for a given wave of type κλμ (lower-case Greek letters kappa, lambda, mu) in the complex-variable frame, with subscript κ denoting the wave type. For example, $\kappa\equiv0$ for pressure waves, $\kappa\equiv1$ for longitudinal waves (including dilatational waves) in a solid whether isotropic and homogeneous or not, plus $\lambda\equiv0$ and $\lambda\equiv1$ for corresponding constitutive equations with real elastic moduli λ and M, respectively, between stress and strain such as per Eq. (1) here for $\lambda\equiv1$ (depending on the values of principal strain involved). If the constitutive equation to be used is Eq. (2) in this Part 2, then $\lambda\equiv2$. The type of dependent variable featured in the EOM or the corresponding WE is denoted by μ, with $\mu=0$ for excess pressure p, $\mu=1$ for u_i, $\mu=2$ for $\check{T}_{ij}$, $\mu=3$ for $\check{S}_{ij}$, and so on. The constant $\mathbf{K}_{\kappa\lambda}$ is given in the vector equation $\mathbf{K}_{\kappa\lambda}=(k_{\kappa\lambda}+i\alpha_{\kappa\lambda})\boldsymbol{p}_{\kappa}$, with $\boldsymbol{p}_{\kappa}$ a unit vector denoting the direction of propagation in a solid or other material, and $k_{\kappa\lambda}$ ("kay" with subscripts) and $\alpha_{\kappa\lambda} > 0$ being real numbers for the real and imaginary parts of $\mathbf{K}_{\kappa\lambda}$. (Here it is assumed that $k_{\kappa\lambda}$ and $\alpha_{\kappa\lambda}$ do not depend on dependent variable type μ in the WE.)

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[69] *Vide* paper of Yoram Lanir (2009). "Mechanisms of Residual Stress in Soft Tissues " (a "Technical Brief"). *Journal of Biomechanical Engineering* **131(4):** 044506 (5 pages) (April). DOI: **https://doi.org/10.1115/1.3049863**. Last sentence of abstract: "The analysis also suggests that a true stress-free configuration can be obtained only if all RS [residual stress] producing mechanisms are relieved, and outlines a manner by which this may be achieved."

Other values of the subscripts can be assigned. For kappa, these include, say, $\kappa=2$ for extensional waves, $\kappa=3$ for plate waves, $\kappa=4$ for torsional waves, $\kappa=5$ for SV shear waves, $\kappa=6$ for SH shear waves, $\kappa=7$ for Rayleigh waves, and so on. Such waves also have various modes, as for $\kappa=2$, 3, and 4, with lowest order modes being non-dispersive in $K_{\kappa\lambda}\equiv|\mathbf{K}_{\kappa\lambda}|=+\sqrt{(\mathbf{K}_{\kappa\lambda}\bullet\mathbf{K}_{\kappa\lambda}^{*})}$ in terms of the 'dot product' between two vectors in an RCC system. (In this Part 2, repeated Greek indices does not imply a sum, while repeated Roman indices do indicate the Einstein sum convention.) A superscript * denotes the complex conjugate, typically used for *complex* solutions of elastodynamic wave equations, even in isotropic homogeneous solids, to facilitate calculations for $\mathbf{K}_{\kappa\lambda}$ and $\alpha_{\kappa\lambda}$ by providing a simple way to eliminate the time dependences from each side of each equation cropping up in a detailed calculation and to preserve phase relationships among dependent variables *within* a given frame (per function type μ) and *between* frames (real variable or complex variable).
In general, WE solutions for wave type ($\kappa\lambda\mu$) are:

$$(\underline{\Pi}_{\pm})_{\kappa\lambda\mu} =[(\underline{\Pi}_{o})_{\pm}]_{\kappa\lambda\mu} \exp[-\alpha_{\lambda\mu}x_1] \exp[i\Psi_{\kappa\lambda\mu}] \exp[i(\pm\mathbf{K}_{\lambda\mu}\bullet\mathbf{x}-\omega t)],$$

Here, it is assumed that the propagation constant $\mathbf{K}_{\lambda\mu}$ for a particular combination of ($\kappa\lambda\mu$) does not depend on choice of the WE's dependent variable of type μ. Also, "i" is the pure imaginary number of $i=\sqrt{(-1)}=e^{-i\pi 2}$ and $[(\underline{\Pi}_{o})_{\pm}]_{\kappa\lambda\mu}$ can be complex, viz., $[(\underline{\Pi}_{o})_{\pm}]_{\kappa\lambda\mu} \equiv$ ***Re*{**$[(\underline{\Pi}_{o})_{\pm}]_{\kappa\lambda\mu}$**}** + i ***Im*{**$[(\underline{\Pi}_{o})_{\pm}]_{\kappa\lambda\mu}$**}**. So, for example, the excess pressure amplitude $[(\underline{\Pi}_{o})_{\pm}]_{\mu=0\equiv p}$ (frequently denoted by symbol p) is now complex, in contrast to real for the sinusoidal solutions presented in Part 1. Also complex is $[(\underline{\Pi}_{o})_{\pm}]_{\kappa=1,\, \lambda=1,\, \mu}$.. However, in the limit as $\alpha_{\kappa\lambda}\rightarrow 0$, $[(\underline{\Pi}_{o})_{\pm}]_{\kappa=1,\lambda=1,\mu} \rightarrow [(\Pi_{o})_{\pm}]_{\kappa=1,\lambda=1,\mu;\alpha=0}$ is a real number.

Examples of dependent variables of type μ for longitudinal wave propagation ($\boldsymbol{p}_{\kappa=1} \equiv \pm\, \hat{\mathbf{e}}_{x1}$) include u_1 ($\mu=1$) and T_{11} ($\mu=2$), whose importance as a pair for (1) specifying boundary conditions of a bounded body in an elastodynamic problem and for (2) calculating work[70] is described subsequently. Particle velocity $u_{1,t}$ is also considered, for calculating power flux. Here shorthand subscript notation of ",t" is used in place of the usual operator notation $\partial/\partial t$ for partial derivatives with respect to time. These variables as physical observables modeled in a WE solution given in complex form are expressed as $Re\{\underline{\Pi}_{\pm}\}_{\kappa}$ to give formulas in Part 2 that are consistent those in Part 1 for dependent variables in the real-variable frame. Here ***Re*{**$\mathbf{K}_{\kappa\lambda}\bullet\mathbf{x}$**}**=[***Re*{**$\mathbf{K}_{\kappa\lambda}$**}**$\bullet\mathbf{x}$**]** is restricted to the uniaxial case in an RCC system via ***Re*{**$\mathbf{K}_{\kappa\lambda}$**}**$\bullet\boldsymbol{p}_{\kappa=1}=k_{\kappa=1}\equiv k_1\equiv k=\omega/c_L$ (so that $k_1x_1 \equiv kx_1$ in this instance), and, when $\alpha_{\kappa\lambda}\rightarrow 0$, the phase velocity $c_L\rightarrow c_{Lo}=\sqrt{(M/\rho_o)}$, the phase velocity for propagation in an unbounded lossless solid medium of a plane infinitesimal longitudinal-wave disturbance ($\kappa=1$) of constant phase on planes with normals parallel to the x_1 axis, traveling in either the $+x_1$ or $-x_1$ direction. (Superscript "o" and subscript "be" designations for infinitesimal amplitude and bulk elastodynamic waves, respectively, are suppressed to reduce symbol clutter.)

Phases are adjusted for consistency between the real- and complex-variable frame expressions via the correspondence condition implemented in the following equations of $Re\{\underline{\Pi}_{\pm}\}_{\kappa\lambda\mu} \equiv (\Pi_{\pm})_{\mu} = [(\Pi_{o})_{\pm}]_{\mu} \exp[-\alpha x_1] \sin[-\omega t \pm kx_1+\Omega_{\mu}]$, with the subscript $\pm$ to the variables $\{\underline{\Pi}_{\pm}\}_{\kappa\lambda\mu}$, $(\Pi_{\pm})_{\mu}$, and $[(\Pi_{o})_{\pm}]_{\mu}$ meaning propagation in either the $+x_1$ or $-x_1$ direction. So, for the index cases of $\mu=1\equiv u_1$ and $\mu=2\equiv\check{T}_{11}$ plus the case of real M:

[70] For both topics, v*ide* Sec. 2.9.2, "Variational equation of motion," pp. 63-65 in Achenbach (1973; 1984) cited in Footnote [76]

$$
\begin{aligned}
\boldsymbol{Re}\{\underline{\Pi}_\pm\}_{\kappa=1,\,\lambda=1,\,\mu=u1} &= \exp(-\alpha x_1)\,[(\underline{\Pi}_o)_\pm]_{\mu=u1}\,\boldsymbol{Re}\{\exp(i\Psi_{\kappa=1,\,\lambda=1,\,\mu=u1})\exp[i(-\omega t \pm kx_1)]\}\\
&= \exp(-\alpha x_1)\,[(\underline{\Pi}_o)_\pm]_{\mu=u1}\,[\cos(\Omega_{u1}\pm\pi/2)\cos(-\omega t\pm kx_1) - \sin(\Omega_{u1}\pm\pi/2)\sin(-\omega t\pm kx_1)]\\
&\equiv (\Pi_\pm)_{u1} = \exp(-\alpha x_1)\,[(\Pi_o)_\pm]_{u1}\sin[-\omega t \pm kx_1 + \Omega_{u1}]\\
&\equiv \exp(-\alpha x_1)\,[(\Pi_o)_\pm]_{u1}\sin[-\omega t \pm kx_1],\\
\boldsymbol{Re}\{\underline{\Pi}_\pm\}_{k=1,\,\lambda=1,\,\mu=T11} &= \exp(-\alpha x_1)\boldsymbol{Re}\{[(\underline{\Pi}_o)_\pm]_{\mu=T11}\exp(i\Psi_{\kappa=1,\,\lambda=1,\,\mu=T11})\exp[i(-\omega t \pm kx_1)]\}_{\mu=T11}\\
&= \exp(-\alpha x_1)\boldsymbol{Re}\{\exp(i\,\Psi_{\kappa=1,\,\lambda=1,\,\mu=T11})[[(\underline{\Pi}_o)_\pm]_{\mu=T11}\,[\cos(-\omega t \pm kx_1) + i\sin(-\omega t \pm kx_1)]\}\\
&= \exp(-\alpha x_1)\boldsymbol{Re}\{[(\underline{\Pi}_o)_\pm]_{\mu=T11}\,[\cos(\Psi_{\mu=T11})\cos(-\omega t\pm kx_1) - \sin(\Psi_{\mu=T11})\sin(-\omega t\pm kx_1)]\\
&\quad + i\,[(\underline{\Pi}_o)_\pm]_{\mu=T11}\,[\sin(\Psi_{\mu=T11})\cos(-\omega t \pm kx_1) + \cos(\Psi_{\mu=T11})\sin(-\omega t \pm kx_1)]\}.
\end{aligned}
$$

In the lines on the RHS of the preceding equations, a shorthand notation of $\Psi_{\mu=T11}$ and $[(\underline{\Pi}_o)_\pm]_{\mu=T11}$ was substituted for the fully subscripted quantities. The phase angle in the complex-variable frame is chosen as $\Psi_{\mu=T11} = \Psi_{\mu=u1} \pm \pi/2$, so that a second 'plus/minus' symbol of "±" is introduced -- in a different font style. Also, the complex quantity $(\underline{\Pi}_o)_\pm]_{\mu=T11}$ can be evaluated in the complex-variable frame in terms of the (real) particle displacement amplitude $(u_i)_o$ as $(\underline{\Pi}_o)_\pm]_{\mu=T11} = \pm\,(ik_{\kappa\lambda} - \alpha_{\kappa\lambda})$ □ $(u_i)_o$ where, for the more general ultrasonic viscoelastic case per Hal's calculations based on Eq. (2), □= (M + iM'), with M=λ+2μ and M'=–ω(λ'+2μ'). Taking □=M gives the following lines:

$$
\begin{aligned}
\boldsymbol{Re}\{\underline{\Pi}_\pm\}_{k=1,\,\lambda=1,\,\mu=T11} &= -\,\alpha M(u_1)_o\,e^{-\alpha x1}\,[\cos(\Psi_{\mu=u1}\pm\pi/2)\cos(-\omega t \pm kx_1) - \sin(\Psi_{\mu=u1}\pm\pi/2)\sin(-\omega t \pm kx_1)]\\
&\quad - kM(u_1)_o\,e^{-\alpha x1}\,[\sin(\Psi_{\mu=u1}\pm\pi/2)\cos(-\omega t \pm kx_1) + \cos(\Psi_{\mu=u1}\pm\pi/2)\sin(-\omega t \pm kx_1)]\\
&= -\,\alpha M(u_1)_o\,e^{-\alpha x1}\,[\mp\sin(\Psi_{\mu=u1})\cos(-\omega t\pm kx_1) \mp \cos(\Psi_{\mu=u1})\sin(-\omega t\pm kx_1)]\\
&\quad - kM(u_1)_o\,e^{-\alpha x1}\,[\pm\cos(\Psi_{\mu=u1})\cos(-\omega t \pm kx_1) \mp \sin(\Psi_{\mu=u1})\sin(-\omega t \pm kx_1)]\\
&= e^{-\alpha x1}\,[\pm\alpha Mu_1\sin(-\omega t\pm kx_1) \mp kMu_1\cos(-\omega t \pm kx_1)].\\
&\equiv (\Pi_\pm)_{\check{T}11} = [(\Pi_o)_\pm]_{\check{T}11}\exp[-\alpha x_1]\sin(-\omega t \pm k_1x_1 + \Omega_{\check{T}11})\\
&\equiv [(\Pi_o)_\pm]_{\check{T}11}\exp[-\alpha x_1]\sin(-\omega t \pm k_1x_1 + \Omega_{u1} \pm \pi/2)\\
&= \pm\,[(\Pi_o)_\pm]_{\check{T}11}\exp[-\alpha x_1]\cos(-\omega t \pm k_1x_1 + \Omega_{u1})\\
&= \pm\,[(\Pi_o)_+]_{\check{T}11}\exp[-\alpha x_1]\cos(-\omega t + k_1x_1 + \Omega_{u1})\\
&= \pm\,kM(u_1)_o\exp[-\alpha x_1]\cos(-\omega t + k_1x_1 + \Omega_{u1}),
\end{aligned}
$$

the last two being for a wave traveling in the $+x_1$ direction in an elastic solid with real modulus, with complex $\boldsymbol{M} \equiv (M + iM')$ in general, then $\boldsymbol{M}$= M=λ+2μ. If the solid is viscoelastic on an ultrasonic time scale as represented by the constitutive equation of Eq. (2) in this Part 2, then $\boldsymbol{M}$ = M+iM' with M' ≡ –ω(λ'+2μ'). Taking M'=0 as the absence of any relaxation or retardation processes associated with strain-rate terms if present in a constitutive equation, $[(\underline{\Pi}_o)_\pm]_{\mu=T11}$, though with $\boldsymbol{M}$≡ M, is still complex as it is based on a spatial derivative of u_i. However,

$$\boldsymbol{Re}\{\underline{\Pi}_\pm\}_{\mu=T11} = Mu_1\exp(-\alpha x_1)[\pm\alpha\sin(-\omega t\pm kx_1) \mp k\cos(-\omega t \pm kx_1)],$$

with RHS of this equation derived in the real-variable frame, the bi-choice of $\Omega_{\check{T}11} = \Omega_{u1} \pm \pi/2$ complementing the bi-choice in the complex-variable frame of $\Psi_{\mu=T11} = \Psi_{\mu=u1} \pm \pi/2$. In the limit of vanishing attenuation in the complex-variable frame, i.e., α→0, then

$$\boldsymbol{Re}\{\,\underline{\Pi}_\pm\}_{\mu=T11}\rightarrow kMu_1\cos(-\omega t\pm kx_1),$$

with phase angle choice $\Psi_{\mu=\check{T}11} = \Omega_{u1} - \pi/2$ then selected (the other possibility introduced into the preceding calculation being $\Psi_{\mu=T11} = \Omega_{u1}+\pi/2$), consistent with the definition not only given in the real-variable frame (per Part 1) that $(\Pi_\pm)_{\check{T}ij}=[(\Pi_o)_\pm]_{\check{T}ij}\exp[-\alpha x_1]\sin(-\omega t\pm k_1x_1+\Omega_{\check{T}ij})]$, but also with other WE solutions like the one given by Nyborg (1975) in terms of his symbol ξ for particle displacement.[71]

Underpinning all this is the base convention that $[(\Pi_o)_\pm]_{\kappa=1,\ \lambda=1,\ \mu=u1} = [(\Pi_o)_\pm]_{u1} = (u^o{}_1)_o$ are real spatial-peak numbers, while $[(\Pi_o)_\pm]_{T11} = (-\alpha \pm ik)Mu_1 \exp(-\alpha x_1)$ is complex (with □ real in this case). With $\Omega_{u1} \equiv 0$, as substituted in the preceding calculation, then one has $\Psi_{\kappa=\check{T}11} = -\pi/2$. Such care with definitions and signs is important in the complex topic of higher-order wave equations mentioned specifically in the context of WE's in $u^o{}_i$ by Truesdell and Noll (2004) [72], so their mathematical connection with the fundamental equations in which u_i is the dependent variable is clear.

Many important quantities such as work, intensity, power, and **ERF** (or **ARF**) arise in terms of the product of two dependent complex variables, as for the intensity of plane waves in an isotropic homogeneous solid – as already given. In general, such an approach is needed to calculate physically correct expressions, a problematic goal with use of just real functions with sinusoidal time- and space-dependent factors to calculate time averages of function products that are not squares of functions. The real variable method *can* work, but only in limited circumstances such as for squares or for the following example of inhomogeneous uniaxial elastodynamic waves propagating in the $+x_1$ direction over a small path length $\Delta x = |(x_1)_2 - (x_1)_1|$ in a lossy material ($\alpha > 0$). Here, intensity at $x_1 = x_{b1}$ is $I_b = I_a \exp[-(2\alpha\Delta x)]$, with reference intensity at $x_1 = x_{a1}$ of $I_a = \langle(\check{T}_{be})_{11}\ (u_{be})_{1,t}\rangle_{\alpha=0} \{\exp[-2\alpha x_1]\}$ in terms of temporally or time averaged *real* elastodynamic power flux ***P***. For waves of infinitesimal amplitude,

$$I_a = [\langle(\check{T}^o{}_{be})_{11})(u^o{}_{be})_{1,t}\rangle_{temp}]_{\alpha=0} = (2\rho_o c)^{-1}\{[(\check{T}^o{}_{be})_{11}]_{sp.\ peak}\}^2 \exp[-2\alpha x_1].$$

The complex-variable approach for obtaining the power flux is to use the relation:

Eq. (7) $$\boldsymbol{P} = \langle \boldsymbol{Re}\{(\check{T}_{be})_{11}\}\ \boldsymbol{Re}\{[(u_{be})_{1,t}]\}\rangle_{\alpha>0} = ½\ \boldsymbol{Re}\{[(\check{T}_{be})_{11}](u_{be})_{1,t}]^*\} = ½\ \boldsymbol{Re}\{[(\check{T}_{be})_{11}]^*\ [(u_{be})_{1,t}]\}.$$

The real-variable method does not give correct results when calculating dependent variables in a standing-wave elastodynamic field, nor does it for the work per unit area, since calculating that way yields a false result, with the time average over a single ultrasound period and on the correct plane for the corresponding product of stress times particle displacement being zero. Instead, the areal work density $\boldsymbol{W}_{areal}$ on the plane whose normal is coaxial with the direction of propagation (given by $\boldsymbol{p}_\kappa$) is:

Eq. (8) $$\boldsymbol{W}_{areal} = \langle \boldsymbol{Re}\{(\check{T}_{be})_{11}\}\ \boldsymbol{Re}\{(u_{be})_1\}\rangle_{\alpha>0} = ½\ \boldsymbol{Re}\{(\check{T}_{be})_{11}\ [(u_{be})_1]^*\} = ½\ \boldsymbol{Re}\{[(\check{T}_{be})_{11}]^*\ (u_{be})_1\}.$$

For the case of $\kappa=1$ and $\lambda=1$, when the stress wave travels in the $+x_1$ direction and $\boldsymbol{M}$ is real and thus there are no bulk nor shear viscosity effects,

Eq. (9) $$(\boldsymbol{W}_{areal})_{Re\{□)} = -\ ½\ \alpha_{\kappa=1,\ \lambda=1}\ M\ e^{-2\alpha x1}\ (u^o{}_1)^2.$$

---

[71] That is, $\xi = A \exp[-\alpha x]\sin[\omega t - k\ x_1]$, with A the displacement amplitude at x=0, per p.402 of WLN's book *IBM* cited in Footnote [10] of CV and in which he uses the symbol u for particle *velocity*.

[72] Sec. 72, "Waves of higher order," pp.272-273 in NLFTM cited in Footnote [47]; see also Sec. 73, "General theory of plane infinitesimal progressive waves."

No model is presented here for a non-viscous amplitude attenuation coefficient which may depend instead on other effects such as thermal conduction or scattering from inhomogeneities in the solid. For the case of κ=1 and λ=2, when $\boldsymbol{M}$ instead is complex and thus there *are* bulk and shear viscosity effects but no other contributions to the attenuation coefficient,

Eq. (10) $(\boldsymbol{W}_{areal})_{\boldsymbol{M}} = ½ (k\omega M' - \alpha_{\kappa=1,\lambda=2}M)\, e^{-2\alpha x1} (u^o{}_1)^2$.

(Here, $\boldsymbol{M} \equiv M - i\omega M'$.) There is a model for $\alpha_{\kappa=1,\lambda=2}$ here, that can be calculated from the WE,

$$Mu^o{}_{1,11} + M'u^o{}_{1,11t} = \rho_o u^o{}_{i,tt}$$

plus use of Eq. (2), to yield this exact result:

Eq. (11) $\alpha_{\kappa=1,\lambda=2} = ½ [(k_o)^2/k]\, \gamma\, [1 + \gamma^2]^{-1}$,

where $\gamma \equiv \omega M'/M \geq 0$. For weak losses, γ<<1. They can include internal friction in the solid, such as shear friction effects on vulnerable, high-compliance internal surfaces where slip may occur relatively easily -- for example, in a soft solid. When γ<<1, the propagation constant is given approximately by:

Eq. (12) $k_{\kappa=1,\lambda=2} \approx k_o [1 - (3\gamma^2/8)]$.

As $\check{T}_{22}=\check{T}_{33}$ for the principal stresses in the transverse x_2-x_3 planes (specified by x_1 = constant), with normals thus coaxial with $\pm\mathbf{\hat{e}_1}$ for propagation directions of longitudinal waves, no shear stress can be resolved within them, due to the identically zero principal-stress difference. But in any two sets of *longitudinal* orthogonal planes with normals orthogonal to the x_1-axis, they are non–zero, for $\check{T}_{11}-\check{T}_{22}$ (in x_1-x_2 planes at x_3 = constant), and $\check{T}_{33}-\check{T}_{11}$ (in x_3-x_1 planes at x_2 = constant). On these planes, shear stress can be resolved. To illustrate once again with harmonic solutions to the WE for the case of ($\kappa=1$, $\lambda=2$, $\mu=\check{T}_{ij}$):

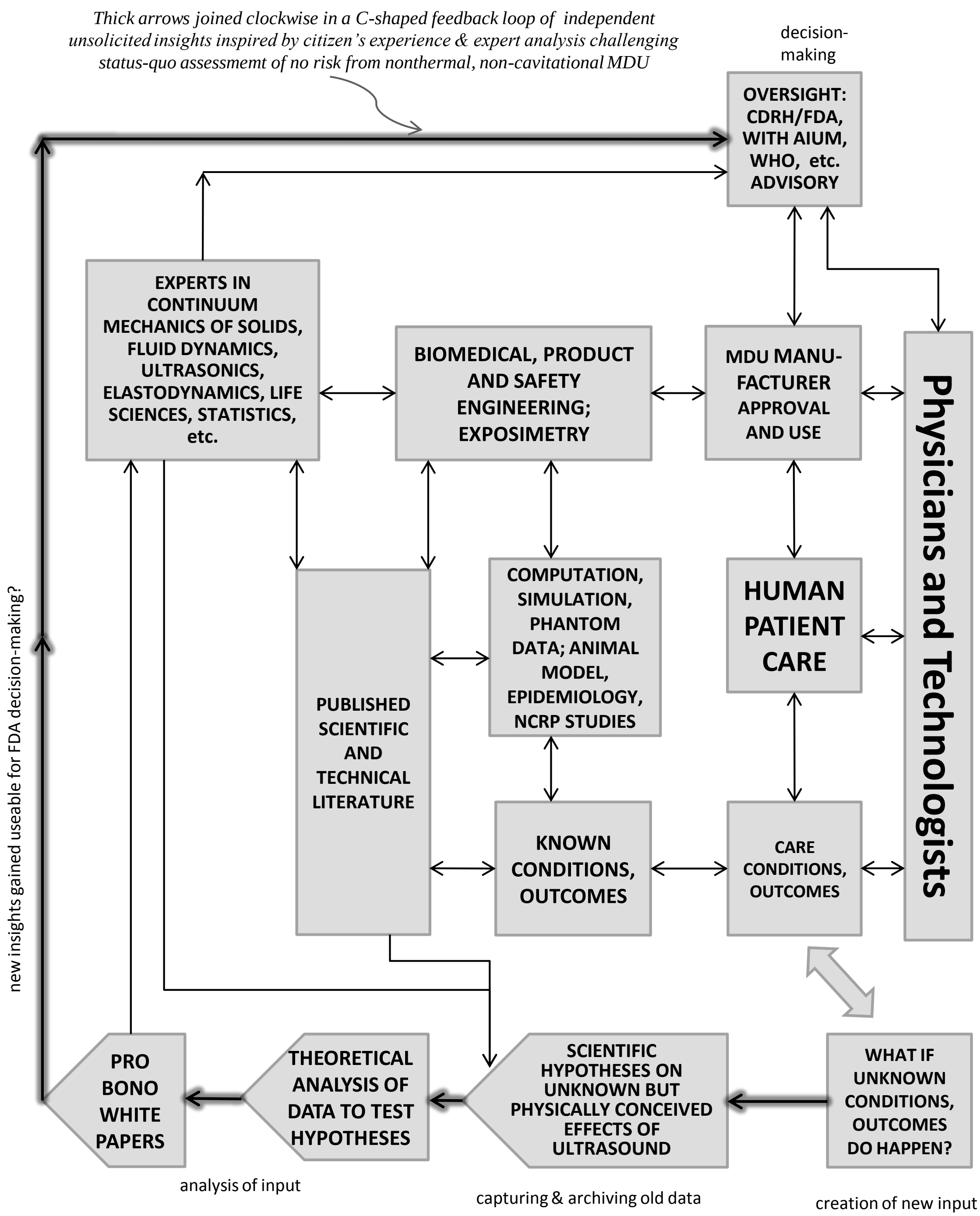
$\check{T}_{11}=(M-\omega M')\,\check{S}_{11}$, $\check{T}_{22} = (\lambda-\omega\lambda')\check{S}_{11}$, and $\check{T}_{33}=(\lambda-\omega\lambda')\check{S}_{11}$, with
$\check{T}_{11}-\check{T}_{22}=[(M-\omega M')-(\lambda - \omega\lambda')]\check{S}_{11}=2(\mu-\omega\mu')\check{S}_{11}$, and
$\check{T}_{33}-\check{T}_{11}=[(\lambda-\omega\lambda')-(M-\omega M')]\check{S}_{11}=-2(\mu-\omega\mu')\check{S}_{11}$.

According to a 'tetrahedral' argument for an isotropic homogeneous solid, then, sets of planes with normals tilted by ±π/4 or ±3π/4 radians to x_1-axis have zero normal stress and extremal, that is, minimum or maximum, shear stress whose modulus value is $½|\check{T}_{11}-\check{T}_{22}|$ or $½|\check{T}_{33}-\check{T}_{11}|$.

At any field point **x** in solid on an imaginary plane with a non-zero projection onto the x_1-axis, 2 shear stresses will be a resolved. In fact, any of an infinite number of planes can pass through **x** as the vertex of a right circular bi-cone whose axis of symmetry is the x_1-axis and whose surface is given by the condition $(x_1)^2+(x_2)^2+(x_3)^2= 0$, while also being tangent to a single generatrix or 'double line' on the conical surface that also passes though the vertex. With the cone half-angle less than π/2 radians, then shear stress is resolved on any of these tangent planes, expressible as 2 terms in the stress vector $\mathbf{T}=\mathbf{T_i\hat{e}_i}$. With a cone half angle of π/4 radians on the surface given, the resolved shear stress is extremal. That's SSMSSS!

Addendum B –Chart for Information Flow on Ultrasound's Action on Biological Tissue:

The following flow chart gives a perspective on the Medical Ultrasound and Practice (MURP) community, to which over 1975-1977 he once belonged at the 'old' BRH now replaced by the CDRH, both at the FDA. (See block in upper right hand corner of chart.)



FLOW CHART FOR INFO ON ACTION OF ULTRASOUND ON SOFT BIOLOGICAL TISSUE BEARING ON PUBLIC HEALTH SIGNIFICANCE AND IMPORTANCE OF SAFETY AND EFFICACY OF MEDICAL USE

This chart acknowledges a possible independent unsolicited 3rd-party or *pro bono* input, as from retirees or former federal employees of FDA, for ex., per thick arrows constituting a feedback loop for the benefit of those with regulatory, advisory and other oversight responsibilities on ultrasound-emitting medical devices: In recent years, Hal has been providing such input, but with no constructive criticism or other substantive response. (See Footnote [14], plus the first section, "General," of Part 1 for some details.) In part Hal sees the need of society to protect its most vulnerable members, those human persons whose growth and development in the fetal state may be susceptible to overlooked nonthermal, noncavitational bioeffects of ultrasound that the MURP community essentially denies as existing.

But also he believes there needs to be a counterweight to the conflicts of interest built up within its infrastructure, as evident from the dependent relationships that may result, as when the Director of a major lab at the FDA that is responsible for regulating ultrasound-emitting medical devices is also the vice-chair of an important professional physician-centered MDU safety committee, per Footnote [14] again.

That counterweight was heavier when his mentor, Prof. Wesley L. Nyborg, served as a temporary investigator at BRH in Rockville, MD when Hal worked there and consulted with him as "Wes." Hal also helped him in small ways to set up and give his four lectures in the spring of 1976 that were transcribed and compiled into an official report that was then converted into a slim hardcover book.[73] Most substantially, though, Prof. Nyborg chaired Scientific Committee #66 at the NCRP headquartered nearby in Bethesda, MD. This committee produced three reports that were issued by the NCRP as hardcover volumes on exposimetry, bioeffects and epidemiology of ultrasound use in medicine, as mentioned in the "Preface" [74] on p.iii of his NCRP Report No. 140 cited in Footnote [54] and in the memorial tribute on Wes as produced by the NAE of which he was a member, as published by the NAP in 2012 [cited in Bibliography].

That Preface makes statements with which the following flow chart is consistent. That is, Prof. Nyborg and colleagues at NCRP dealt with known conditions for and outcomes to patient care, while Hal speculated on informed, rational grounds on what unknown conditions and outcomes might pertain to patient care as understood and seen through the lens of his own exploratory research experience of over a half century on the action of ultrasound on solids and liquids.

[73] The book of lectures is: *Physical Mechanisms for Biological Effects of Ultrasound -- Based on a Series of Lectures Delivered by Dr. Wesley L. Nyborg*, Investigator, Division of Biological Effects, BRH, FDA, 59 pp., ed. by Evelyn Byers Surles, **Sept. 1977**, printed as a book **in May 1978** [HEW (FDA) Publication 78-8062].

[74] Quoted from that Preface: "This Report is the third in a series that includes NCRP Report No. 74, *Biological Effects of Ultrasound: Mechanisms and Clinical Implications* and NCRP Report No. 113, *Exposure Criteria for Medical Diagnostic Ultrasound: I. Criteria Based on Thermal Mechanisms*. These three reports were prepared by Scientific Committee 66 under the chairmanship of Wesley L. Nyborg. Dr. Nyborg and the Committee responded admirably to its mandate to address the topic ''Biological Effects of Ultrasound and Exposure Criteria.'' As has been pointed out in the earlier reports, the use of diagnostic ultrasound in medicine has an enviable record for safety. However, new applications, new procedures, and new kinds of equipment are continually being introduced, higher output levels have become available for some applications, and the extent of usage continues to increase. Hence, it is important that users be informed as well as possible for judging conditions under which the benefit/risk ratio is or is not favorable. It is the purpose of this Report, and its two predecessors, to present background for a scientifically based approach to safety assessment for diagnostic ultrasound. These three reports are intended to help the medical community take advantage of new developments in clinical practice, while maintaining its safety record."

Addendum C – 2002 Classification Scheme for Known Physical Mechanisms for Changes Produced by Ultrasound in Biological Systems:

This chart gives a 2002 scheme of physical mechanisms for ultrasound in biological systems:[75]

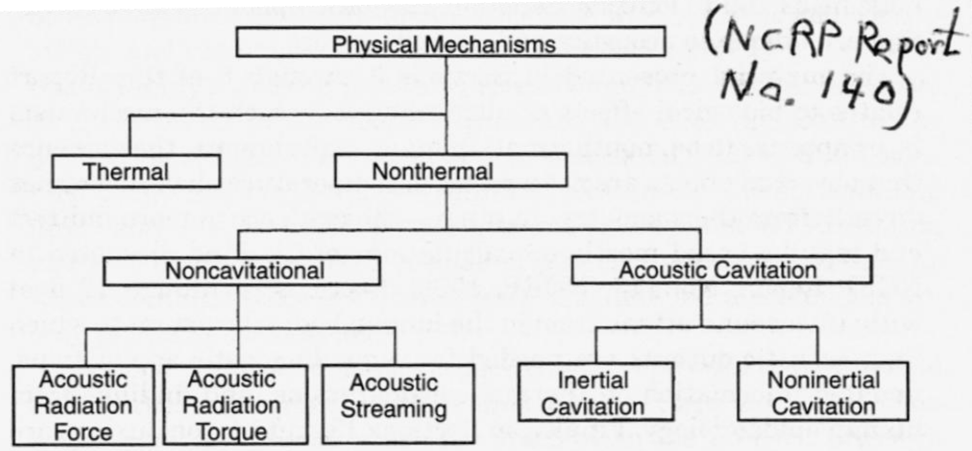


Fig. 2.1. Classification of physical mechanisms by which ultrasound can produce changes in biological systems.

The various SSMSSS mechanisms that Hal understands on the basis of his recent analyses to possibly operate in a patient exposed to MDU can be added to the classification scheme *supra*, under the "Noncavitational" category and in the same row as "Acoustic Radiation Force," Acoustic Radiation Torque," and "Acoustic Streaming" generally pertaining to biological tissue analyzed in mathematical terms to look more like a liquid, not a solid. On that row, then, Hal asserts one can provisionally add 4 more physical mechanisms for dry solids: "Elastodynamic Radiation Force," ""Elastodynamic Radiation Torque," "Instantaneous, Time-Averaged and Residual Stress or Strain," and "Softening of Shear Modulus of Elasticity."

Addendum D – Snapshot of Formal Derivation of Equation of Motion (EOM) for Wave Propagation in Elastic Solids (incomplete):

Part of that deeper level of mathematics that Part 2 states is needed for next-generation contributions, like new original papers published in peer-reviewed research journals by the MURP community that report on revised risk-vs.-benefit assessments of MDU considering the proposed new MUBEM of SSMSSS, entails more formal definitions of the (excess) elastodynamic stress and strain tensors for a homogeneous anisotropic elastic solid as a conservative system framed by a Lagrangian density $\boldsymbol{L_c} = \boldsymbol{W_{KE}} - \boldsymbol{W_{PE}}$ with kinetic energy density $\boldsymbol{W_{KE}} = (½)\rho(u^o)_{i,t}(u^o)_{i,t}$ and internal potential energy density $\boldsymbol{W_{PE}} = (½)C_{ijkl}\check{S}_{ij}\check{S}_{kl}$.[76] Here, particle

[75] This chart is a scan of Figure 2.1 on p.7 in the Introduction to NCRP Report No. 140, a hardcover book cited in Footnote [63] of CV.

[76] Three books *cum* specific chapters consulted for writing this Addendum D include: **[1]** Ch.1, "Kinematics and Dynamics" by E. U. Condon, pp.3-3 to 3-13 + Ch.7, "Vibrations of Elastic Bodies; Wave Propagation in Solids" by Philip M. Morse, pp. 3-97 to 3-111 + Ch.8, "Acoustics" by Uno Ingard, pp. 3-112 to 3-133 – all in Part 3, "Mechanics of Deformable Bodies" of *Handbook of Physics* edited by E. U. Condon and Hugh Odishaw (McGraw-Hill Book Co., Inc., New York et al., 1958); **[2]** Ch.2, "The Linearized Theory of Elasticity," pp. 46-78; Ch.3, "Elastodynamic Theory," pp.79-121; and Ch.4, "Elastic Waves in an Unbounded Medium, pp.122-164 – all in *Wave Propagation in Elastic Solids* by J.D. Achenbach (North-Holland Publishing Co., Amsterdam, et al., 1984 for 4th printing of pbk. ed. but 1973 for 1st ed.) already cited in Footnote [7]; and **[3]** Ch. 3f, "Acoustic Properties of Solids" by W. P. Mason, pp.3-82 to 3-97 in Sec. 3, "Acoustics" ed. by Richard K. Cook -- in *AIP Handbook*, 2nd ed, coordinating editor Dwight E. Gray (McGraw-Hill Book Co., New York et al., 1963).

displacements are taken as infinitesimal; the elastic constants have the symmetries of $C_{ijkl}=C_{ijlk}=C_{jikl}=C_{jilk}=C_{klij}=C_{klji}=C_{lkij}=C_{lkji}$; and the potential energy density is given by

$$\boldsymbol{W_{PE}} = (½)\lambda(\Theta^o)^2+\mu[(\check{S}^o{}_{11})^2+(\check{S}^o{}_{22})^2+(\check{S}^o{}_{33})^2+2(\check{S}^o{}_{12})^2+ 2(\check{S}^o{}_{13})^2+(2\check{S}^o{}_{23})^2]$$

with Lamé constants λ and μ for an isotropic solid. At the most, the 81 elastic constants from C_{ijkl} depend at most on 21 independent moduli for the least symmetric case, the triclinic crystal class, but which in the most symmetric case of isotropy reduce to three. And, due to the property of an isotropic solid having no preferred RCC in the material *per se*, only two of these three (λ and μ) are independent per a separate relation based on that property of type $C_{1111}=C_{1122}+2C_{2323}$, with $C_{1111} = M = \lambda+2\mu$ and $C_{2323}=\mu$, for example. (The two-index system for notating elements of rank-4 tensors is not used here.) The Lagrangian density $\boldsymbol{L}$ has 3 independent variables u_i, $u_{i,t}$ and $u_{i,j}$ in its argument, viz., $\boldsymbol{L} = \boldsymbol{L}(u_i\ ;\ u_{i,t\ ;}\ u_{i,j})$. If a system is conservative as denoted by $\boldsymbol{L}\equiv \boldsymbol{L_c}$, it satisfies the three Euler -Lagrange (or just Euler) field equations of motion (EOM's): $[\partial\boldsymbol{L_c}/\partial(u_{i,t})]_{,t}\ +\ [\partial\boldsymbol{L_c}/\partial(u_{i,j})]_{,j} = [\boldsymbol{L_c}]_{,i}$. Here, i is 1, 2 or 3. The first bracketed term [...] on the LHS is the momentum density $\boldsymbol{P_i}=\rho u_{i,t}$ set up in the solid by the motion, and the second bracketed term [...] is the negative of the (symmetric) stress tensor $\check{T}_{ij}$. The momentum density $\boldsymbol{P}_i$ and the coordinate u_i are generalized conjugate variables in configuration space (u_i, $\boldsymbol{P}_i$).

This EOM is derived by applying Hamilton's principle to the definite integral of $\boldsymbol{L_c}$ over the positive-definite time interval $\Delta t=t_2-t_1$ in which the entire system evolves, viz., $\boldsymbol{A}=\int_t [\boldsymbol{L}]dt$, where the upper limit of integration is t_2 and the lower limit is t_1, and $\boldsymbol{A}$ is a scalar "action density" with units of angular momentum density. Integrating $\boldsymbol{A}$ over a system volume V in an unbounded medium then gives its "action" $L_c=\int_V[\boldsymbol{A}]dV$ with units of angular momentum or energy times time. If V is that of a rectangular parallelepiped in an RCC system of $\Delta x_i=x_{bi}-x_{ai}$ in an unbounded medium, with $dV=dx_1dx_2dx_3$, then the volume integral is $L_c=\iiint[\boldsymbol{A}]dx_1dx_2dx_3$, each definite integral having upper and lower limits of x_{bi} and x_{ai}, respectively (with $\Delta x_i>0$).

Hamilton's principle is expressed mathematically by the variational statement δL=0. In words it "states that of all possible paths of motion between two instants t_1 and t_2, the actual path taken by the system is such that the integral over time and space of the Lagrangian density $\boldsymbol{L}$ is stationary. An analogous but more usual statement of the principle is that the variation of the integral vanishes for any changes δx_i which vanish at $t=t_1$ and $t=t_2$, and on the boundary of the arbitrary volume V." [77] In more geometric terms, though, this principle means that the trajectory of the system in configuration space remains stationary, i.e., unchanged, with small changes or perturbations in particle displacement u_i. By means of the calculus of variations, the stationary condition for which the 4 independent variables (x_i, t) have an unchanged range of integration requires choosing for an EOM the one already stated if the system is conservative.

If the medium is bounded and thus itself has boundaries, then the equation of $\delta L_c=0$ has to be replaced by $\delta L_c=-\int_t W_e\, dt$, with the definite integral having the limits of t_2 and t_1. Here, W_e is the work done on the system by the body forces and surface tractions when the u_i are varied. This result is known as Hamilton's principle, valid for a perfectly elastic body and invariant under a coordinate transformation. (If the system is not conservative, another choice is needed for $\boldsymbol{L}$.)

[77] Quoted from p.61 of Achenbach (1984) cited in Footnote [76].

Addendum E – Postscript:

When HMF and his mentor Prof. Wesley L. Nyborg (1917-2011) did the work for their UI73 paper cited in the Bibliography and HMF finished in the following year his physics dissertation (advised by "Wes") as a sequel to that paper, neither saw a connection to ASD or to any other neurocognitive developmental disorder. Now, HMF sees and argues that residual strain (or stress) imparted by ultrasound as shown by just a few of the photos displayed in Fig. 5 of the UI73 paper can be a physical though almost always invisible correlate of a biomarker of irrecoverable immediate and apparently benign CNS tissue damage at small size scales in medical practice like Obstetrics/Gynecology and Pediatrics, or long-delayed functional and even anatomical distortion or mal-direction effects in tissue development at much larger size scales, as in a lobe in the brain or the BBB of a vulnerable population, due to mechanotransduction effects from mechanical force signaling known in the eukaryotic single cell's cytoplasm and the cytoskeletal network (such as actin filaments) embedded in it that affect protein synthesis, movement, transcription error correction and so on.

While laser-based methods can measure acoustic stress and strain fields, they are generally sensitive only to the fast changes in time in those fields that are caused by the action of ultrasound waves on the surface or near the surface of the test object. Further, the time window chosen for making those kinds of measurements is usually too short to pick up any 'recording' or 'erasure' of a constant residual stress or pre-stress, for example, that stays essentially the same over long time intervals. Acoustoelasticity as an acoustic (actually, elastodynamic) analogue of photoelasticity could be used, and is in nondestructive testing of metals and alloys, but that requires use of shear waves of orthogonal transverse polarizations which are attenuated much more in tissue than longitudinal waves (with degree of tissue damage correlating with value of the attenuation coefficient).

There are cutting-edge techniques that could be used in the clinical setting such as polarization-sensitive optical coherence tomography, infrared photoelasticity in reflection mode, and so on. Advanced methods with use of polarized x-rays in CT (e.g., XFCT) are also emerging, but they carry with them additional risks to a patient in a clinical setting. In sum then, no suitable 'eye' is being used in the clinic to make visible any residual stress/strain imparted by ultrasound or any pre-existing pre-stress/pre-strain fields present in biological tissue, as a clinician may not think it is necessary to monitor and control resolved shear effects from longitudinal waves inside 'dry' test objects such as tissue regarded as solid, not liquid -- with those waves usually incorrectly treated as just pressure waves in a solid with a shear modulus of elasticity taken to be so small that it can be regarded as negligible. With that invalid assumption, then the 3 by 3 stress tensor is always diagonalized with co-equal components so that in turn no shear stress is resolved upon imposition of any 3D coordinate transformation.

In closing, there is no 'RS' index (for example) for resolved shear to complement the known MI and TI indices indicated in the Output Display Standard (ODS) of an ultrasound imaging machine to track and avoid known dangerous levels producing cavitation and heating. So, this treatise could be the start of a long effort to propose and then establish the use of an 'RS' index to add to the ODS. However, that may happen only after proof is provided like demonstrating a cause-and-effect law for ultrasound causing tissue damage that can be directly related to onset of ASD years later, such as the action of resolved shear (the cause) to uncoil a folded protein or to add a topological defect to an already unfolded protein.

BIBLIOGRAPHY: ANNOTATED EXAMPLES OF PERTINENT PUBLICATIONS OF HMF:

H.M. Frost [UVM Physics Dep't] (1969). *Interactions between a vibrating object and the surface of a soft solid*. M.S. thesis; W. L. Nyborg [WLN, p.16], advisor. In simple VEDIP experiments, a DC displacement transducer connected to a Sanborn chart recorder measured penetration-depth-vs.-time profiles for ultrasonically time-averaged separations between (a) the vertical coordinate for an initially undisturbed top surface of a small block of soft solid (gel; wax; plastic; or Pb) and (b) the fixed vertical coordinate of the apex of a small, rigid object machined as an indenter tip on the free end of a Mason horn resonantly oscillating longitudinally along the vertical axis. Mason horn was driven by a resonant $BaTiO_3$ piezoelectric cylinder bonded to horn's other end, and clamped at its particle-displacement antinode. The resonant frequency of high-Q composite system was fixed at f_{RC}≈20kHz (despite changing load conditions). The sample was forced into contact with tip by applying static force $\mathbf{F_s}$ with $|\mathbf{F_s}|>0$ for either continuous or intermittent contact, and $|\mathbf{F_s}|=0$ for no contact. Besides penetrations of both fast and slow phases of tip into soft solid under action of $\mathbf{F_s}$ as a creep force combined with ultrasonic dynamic force $\mathbf{F_d}$ during *continuous* contact (with $\mathbf{F_d}=\mathbf{0}$ if $|\mathbf{F_s}|=0$), repulsion between tip and sample surface was also observed as due to *intermittent* contact, a condition later exploited in sequel of Hal's dissertation (#2, *infra*) as next VEDIP item. Abstract: Navigate on Frost at **http://library.uvm.edu/collections/theses?search_type=dept&dept=35** or at **www.brl.uiuc.edu/Abstracts**.

H.M. Frost and W.L. Nyborg [both, UVM Physics Dep't] (1973). *Action of ultrasound on a viscoelastic (VE) solid*. *Ultrasonics International 1973 (UI73): Conference Proceedings*, pp.81-88 (IPC Science & Technology Press Ltd., Guildford, Surrey, UK, 1973).

H.M. Frost [UVM Physics Dep't] (1974). *Action of ultrasound on a viscoelastic (VE) solid*. Dissertation (347 pp.); advisor, W.L. Nyborg. Abstract via URL's for M.D. thesis *supra*. Sequel: "Ultrasonic indentation of plastics and bioeffects applications," Hal's talk II9, 91st ASA meeting [*JASA* **59, Suppl. No.1,** p. S76 (1976)], with playback of video tape of time-dependent growth of isochromatics, plus simultaneous audio track for time-varying difference tone of freq. f--$f_{RU}=\Delta f_R(t)$, with f_{RU} at about 90 kHz via AGC action in electronic negative feedback loop designed to fix axial displacement amplitude u_o of ultrasonic vibrator despite changing load conditions. Such and like work [#12-14, p.9] mimics some imaging conditions for MHz beams of ultrasound in elastography, step/impulse **ARF**, shear wave (sw), push/track and intra-operative usage, via oscillating **ERF** like $\mathbf{F_d}$, applied creep force $\mathbf{F_s}$, static **ERF** like $\mathbf{F_s'}=\mathbf{F_s'}(F_s, F_d)$, oscillating and static radial strains $(\varepsilon_{rr})_d$ and $(\varepsilon_{rr})_s$ in test sample proportional to F_d and F_s, resp., and constant residual radial strain $(\varepsilon_{rr})_R$ reproducibly set up and annealed out at will due to still unknown physical mechanism. Irradiation details: Harmonic ultrasonic line source of fixed amplitude u_o acted normal to free edge surface of small, thin, rectangular plate of soft epoxy ("PS-3") of time-dependent nonlinear viscoelastic (VE) Young's modulus Y(t) to boost in-plane creep as function of u_o under intermittent (i.e., tapping-contact) conditions. To do this, Hal adapted extensional-wave exposure system of W. P. Mason [p.16] of stepped metal horn bonded to end of piezoelectric (PE) driver to adopt related method in 1969 UVM Physiology and Biophysics dissertation of R.M. Schnitzler on excised muscle tissue [per Footnote [9]. Unlike Mason's bonding of small metal test sample to *flat* free horn tip, Hal pressed via calibrated $\mathbf{F_s}$ a free end of small VE epoxy plate into Hertzian contact with oscillating *wedge-shaped* tip acting as ultrasonic line source. (PE driver was clamped.) Unlike WPM's shifts $\Delta(u_o)$ at fixed f_{RU}

(20kHz), Hal measured $\Delta(f)$'s from unloaded f_{RU} (90kHz) with u_o fixed. Total force $F_s' = |\langle F_d \rangle + F_s|$ for time-ave. dynamic force $\langle F_d \rangle$ was normal to the straight plate edge (on-axis at θ=0) to give in-plane uniaxial stress field $(\check{T}_{be})_{ij} = \delta_{i1}\delta_{j1}(\check{T}_{be})_{11}$, with

$$(\check{T}_{be})_{11} = (-2/\pi)(F_T/hr)\cos(\theta) \equiv \sigma_{rr} = (Y_o\check{S}_{be})_{11} \equiv Y_o\varepsilon_{rr}(t),\ \varepsilon_{rr}(t) = \sigma_{rr}/Y(t)$$

and compliance $J(t) = [Y(t)/Y_o]^{-1}J_o$ measured photoelastically in Zeiss polarizing microscope as in-plane principal strain difference $\varepsilon_{rr}(t) - \varepsilon_{\theta\theta}(t) = (1+\nu)\varepsilon_{rr}(t)$ evolving in time t at fixed field point but constant on growing circular isochromatic diameter D(t)=r(t)/cos(θ). For tapping-contact with $(u_o)_1 \le u_o \le (u_o)_2$, a Hooke's law $F_s' = F_s + ku_o$ was found for an effective static force F_s' even if $\langle F_d \rangle >> F_s$. Thermal and nonthermal effects were separated. Line source probably generated symmetric S_o plate waves at frequencies below cutoff for S_1 waves but above cutoff for anti-symmetric A_1 waves, per the Rayleigh-Lamb dispersion relations for a 2-mm thick epoxy plate with $Y_o = 2.1\times10^9$ dyn/cm^2, Poisson's ratio v=0.42 and S_o wave speed of ~4.6×10^4 cm/s, between its longitudinal and shear wave speeds of ~8×10^4cm/s and ~3×10^4cm/s. WLN cited Hal's dissertation and their UI73 paper, for example, in Ref. 14.71 [78] in WLN's *Intermediate Biophysical Mechanics* (*IBM*) (Cummings Publ. Co., Menlo Park, CA, **1975**); in Ref. [81] in *Physical Mechanisms for Biological Effects of Ultrasound -- Based on a Series of Lectures Delivered by Dr. Wesley L. Nyborg*, Investigator, Division of Biological Effects, BRH, FDA, 59 pp., ed. by Evelyn Byers Surles, **Sept. 1977**, printed as book **May 1978** [HEW (FDA) Publication 78-8062 co-sponsored by School of Engineering Acoustics Program at Catholic University of America, Washington, D.C]; and in Ref.[12] of WLN's Ch.1, "Basic Physics of Low Frequency Therapeutic Ultrasound," pp.1-23 in *Ultrasound Angioplasty* ed. by R.J. Siegel (Kluwer Academic Publishers, Boston, **1996**); #4, p.8 of Hal's CV (**2006**). Hal's dissertation was starting point for his much later SSMSSS hypothesis of purely solid-state, non-cavitational, nearly nonthermal effect for new 6th MUBEM to be added to 5 reported in NCRP Report No. 140.

Note: *HEW (FDA) Publication 78-8062* is an edited compilation of 4 seminars WLN gave in March-April 1976 at BRH where/when Hal was employed (1975-1977) as Health Physicist (GS-12/GS-13) and resident ultrasound expert. (FT of *HEW Publication 78-8062* at: **https://babel.hathitrust.org/cgi/pt?id=mdp.39015003215715&view=1up&seq=3**.

H.M. Frost (1976). "Ultrasonic indentation of plastics and bioeffects applications," talk II9, 91st ASA meeting. Abstract in *Journal of the Acoustical Society of America* **59, Suppl. No.1,** p. S76,

H.M. Frost and M.E. Stratmeyer [both, BRH] (1977). Letter to Editor, "In-vivo effects of diagnostic ultrasound." *The Lancet* 309 (No. 8019): 999 (May 7); first published as Vol. 1, Issue 8019. Survey of known mammalian CNS bioeffects at low MHz frequencies.

H.M. Frost [UVM] (2005). "Past and future of ultrasonic indenter physics and engineering at UVM, including new research directions and possible clinical applications for bone." UVM Physics Dep't Colloquium, Dec 14. Orthopedic "indentoscope" idea was based on Hal's dissertation [1st #2, p.8] as applied to ultrasonic guided waves in long bone to assess damage and strength for medical diagnosis of disease.

[78] To support his p.513 comment (in *IBM*) on microindenter deformation in tissue like single plant cells: "A study of strains produced by microvibration in soft plastic solids has been carried out by Frost (1974), from which insight is gained on effects in solid-like tissue."

W.L. Nyborg and H.M. Frost [both, UVM] (2006). "Stress, strain and flow produced by a vibrator in or on the surface of a soft solid." June 8 invited talk in session honoring Edwin L. Carstensen (Univ. of Rochester), 151st ASA Meeting, Providence, RI. Based on Hal's ultrasonic VEDIP dissertation. Abstract: **scitation.aip.org/content/asa/journal/jasa/119/5/10.1121/1.4786586**.

H.M. Frost [Frosty's Physics, LLC] (2011). *Contact Mechanics and Dynamics of a Special Type of Vibrating Indenter Acting on a Soft Solid*, 11 pp., May 9. *Pro bono* FP TR 2011-1 (ver 04). Abstract: **www.brl.uiuc.edu/Abstracts**. Extends Hal's dissertation on VEDIP physics towards proposing new MUBEM of ultrasonic solid-state mechanical shear strain (SSMSS). Hal derived nonlinear laws between ultrasonic forces and contact stresses (incl. averaging over times t) for both continuous and intermittent (tapping) contact. Pairs of intermittent-impact impulse forces $\mathbf{IF_B}(t)$ and $\mathbf{IF_R}(t+\Delta t)$ to break and restore contact in one cycle of ultrasound harmonic at freq. f were assumed via EDIP to *elastically* deform soft solid (low-Y epoxy) and so obey $\langle \mathbf{IF_B}+\mathbf{IF_R}\rangle=\mathbf{0}$, with $\langle ... \rangle$ denoting time average in ultrasonic period $f^{-1} = T > |\Delta t|$. In sequel (#13, p.9), Hal included *viscoelastic* creep compliance J(t) in calculations, to find that both the sum $\langle \mathbf{IF_B} + \mathbf{IF_R}\rangle$ and $\langle$work$\rangle$ are nonzero.

H. M. Frost [retired from UC] (2012). "Wesley L. Nyborg: 1917-2011," pp.196-205, *Memorial Tributes*, Vol.16 (NAP, Washington, DC). NAE Membership Committee asked Hal to write draft, with family input. Article recognizes "Wes" as a bioacoustics pioneer and honors his memory as Hal's former mentor. Full text of tribute is accessible via **www.nae.edu** or **www.nap.edu**.

H.M. Frost [at Frosty's Physics, LLC] (2014). *Residual stress induced ultrasonically and nonthermally in thin epoxy plates at room temperature and under creep-loading conditions*, 4 pp., Jan 28. *Pro bono* FP TR 2014-1. This TR focuses on one finding from Hal's dissertation and its prequel UI73 conference proceedings paper [1st #2, p.8], the nonthermal 'recording' and 'erasing' of residual SSMSS in a soft epoxy observed photoviscoelastically as isochromatics arising from strain birefringence in test samples subject to both static and dynamic line-force loading. Data include: (1) Photos x-z and aa-ee from Fig.5, p.80, UI73 paper, plus (2) 11 new photos in Figs. 25-26, pp. 300-301 of 1974 dissertation [reproducing data of (1)]. Effect changes when time order of removing static and dynamic force is reversed; relevant today to ultrasound imaging for medical diagnosis, as illustrated in parts A-C of graphic "technique of graded compression," p.B10 ("Ultrasonography") in *Stedman's Medical Dictionary, 28th ed.* (Lippincott Williams and Wilkins, Philadelphia, 2006).

H.M. Frost [VT] (2015). *Rationale for Developing a New Physical Model for a Medical Ultrasound Bioeffects Mechanism (MUBEM), Solid-State Mechanical Shear Strain (*SSMSS*)*, 43 pp., Nov 4 (ver07; draft). *Pro bono* private technical report. SSMSS [pp.1, 14] is distinct from Fluid-State Mechanical Shear Stress (FSMSS) [pp.1,13]. Concepts are at mechanisms level, encompassing broad array of topics like ARF, residual strain, and softening of viscoelastic moduli via entropic solid/solid order/disorder phase transition.

SELECTED ACRONYMS, ABBREVIATIONS AND SYMBOLS USED)

AIUM	American Institute of Ultrasound in Medicine (**www.aium.org**, professional non-profit organization). Hal is a former member.
ARF	Acoustic radiation force (p.1). Nonlinear acoustic effect in fluids (μ=Y=0); often time constant. Used for solids (μ >0,Y>0) but see **ERF**.
BRH; CDRH	Bureau of Radiological Health, former bureau in FDA, U.S. DHEW, Rockville, MD where Hal was employed. Today this is Center for Devices & Radiological Health (info via **www.fda.gov/MedicalDevices/default.htm**), part of the FDA in the now-named (U.S.) DHHS.
CPC	Cylindrical polar coordinates with mixed curved cord. axes compared to Rectangular Cartesian coord's (RCC) all on rectilinear axes.
DHEW; DHHS (US)	Department of Health, Education & Welfare; preceded Dep't of Health & Human Services. Funded Hal's R&D at BRH in 1975-1977.
EDIP	*Elastic Dynamic Indentation/Penetrometry*; solid-mechanics topic; precursor of quasistatic, harmonic & transient methods in elastography [M.M. Doyley (2012), *Phys Med Biol.* 57(3): R35–R73]. Ex: Wedge-shaped tip of Mason-horn oscillating with stroke $2u_o$ as line source on elastic solid plate's edge surface exerts force $F=F_d+F_s$, indenting it. F_d is AC force; $\langle F_d\rangle+F_s$ acts as DC load. See VEDIP.
ERF	Elastodynamic radiation force as nonlinear effect in solids (μ>0, Y>0); often constant in time (p.1; Table Pre-Col., Row 2, p.10). Ultrasonic **ERF**, often wrongly called **ARF**, sets up strain field in and even fractures *constrained* solid part, or propels it as small *rigid* body, like kidney stone (videos of both by Univ. of Washington's Center for Industrial & Medical Ultrasound, via **www.apl.washington.edu**).
ext. *(2 senses)*	*External*. Or, *extensional* elastodynamic wave, as in wire with phase velocity $\sqrt{[Y/\rho]}$; ρ = mass density) or in thin plate.
F, $\mathbf{F_d}$, or $\mathbf{F_s}$	**D**ynamic (AC) or static (DC) vector force $\mathbf{F_d}$ or $\mathbf{F_s}$ on local surface of solid sample pushed by $\mathbf{F_s}$ to contact Mason horn tip osc. as dipole. In EDIP, $\mathbf{F_s}$ is force akin to **ARF** or **ERF**. Total force $\langle \mathbf{F_T}\rangle=\langle \mathbf{F_d}\rangle+\mathbf{F_s}$; ⟨ ⟩ = ultrasonic time ave. $\mathbf{F}=F\hat{\mathbf{e}}_F$, $F\equiv\|\mathbf{F}\|$ & $\hat{\mathbf{e}}_F$ is unit vector. .
FDA	Food and Drug Administration (**www.fda.gov**), in past (U.S.) DHEW in whose past BRH (CDRH today in DHHS) Hal once worked.
FRM	J.C. Jaeger and N.G.W. Cook, *Fundamentals of Rock Mechanics*, 3rd edition. (Chapman and Hall, London, 1979).
FSMSS	Fluid-State Mechanical Shear Stress [compare SSMSS, p.14]. Developed in 1970's by JAR [pp.1,16] as *acoustic [p.10]* MUBEM.
IBM	Hardcover book: Wesley L. Nyborg (1975), *Intermediate Biophysical Mechanics* (Cummings Publishing Co., Menlo Park, CA, et al.).
IEEE	Institute of Electrical and Electronics Engineers (**www.ieee.org**). Hal has been member since 1977; today is Life Senior member.
MUBEM	Medical Ultrasound Bioeffect Mechanism. Hal modeled one as solid-state mechanical shear strain and stress [SSMSSS; pp.1,14].
MURP	Medical Ultrasound Research And Practice, as in MURP community of researchers, physicians, manufacturers, regulators & patients.
NAE; NAP; NAS	Nat'l Academy of Eng. (**www.nae.edu**); Nat'l Academies Press (**www.nap.edu**); Nat'l Academy of Sciences (**www.nasonline.org**).
NIH; NIST	National Institutes of Health; National Institute of Standards and Technology (once, NBS), with campuses in Maryland and Colorado.
PI	Principal investigator (leader and manager of federally funded or other sponsored R&D or related project.
RCC	Rectangular Cartesian coordinates (RCC), all on rectilinear axes. Compare with CPC.
SSMSS; SSMSSS	Solid-State Mechanical Shear Strain (or Stress). Elastodynamic (e-d) MUBEM* via shear strain on planes with normals *off-axis* to propagation constants $\mathbf{k}_L$ or $\mathbf{k}_e$ for travel directions of longitudinal (or extensional) waves in ultrasound beams or plate waves if separate forces, like $\mathbf{F_s}$ as **ARF**, **ERF**, or indenter force, & $\mathbf{F_d}$ as dynamic force, exist at 2 frequencies and 2 sites via dual-beam MHz ultrasound or 1 site via DC & AC forces in VEDIP*. (Shear waves with travel direction given by $\mathbf{k}_S$ exist.) Residual shear strain arises in nonlinear VE solid if $\langle F_d\rangle\to 0$, *then* $F_s\to 0$. SSMSS & FSMSS differ in effects though couple [P.A. Lewin & L. Bjørnø, *JASA* **71(3):**726-734(1982)]. *2D problem:* Harmonic osc. line source, with radial stress $(\check{T}_{be})_{11}=(\check{T}_{be})_{ij}\delta_{i1}\delta_{j1}\equiv\sigma_{rr}$ & strain $(\check{S}_{be})_{11}\equiv\epsilon_{rr}=\partial u_r/\partial r$ in solid, emits e-d waves of small particle displacement u_{io} governed by *linear* d'Alembertian wave eq. (WE), $\Box u_{ro}=0$, with CPC axes parallel to principal stress axes in plate with thickness $h<\Lambda_{eo}$ & Young's modulus Y_o. Harmonic elastic-case Hooke's law is $(\sigma_{rr})_o=Y_o(\epsilon_{rr})_o$, with incompressible $Y_o=3\mu_o$, shear elasticity modulus $\mu_o<<K_o$, bulk modulus K_o, Lamé parameters $\lambda_o>>\mu_o>0$, shear-wave speed $v_{so}=\sqrt{[\mu_o/\rho_o]}$, extensional-wave speed $v_{eo}=\sqrt{[Y_o/\rho_o]}>v_{so}$, longitudinal-wave speed $v_{Lo}=\sqrt{[(\lambda_o+2\mu_o)/\rho_o]}>v_{eo}$, mass density ρ_o, freq. f, wavelength Λ_o, phase velocity $v=f\Lambda_o$. Ultrasonic time-ave. of pulsed VE-case for Hooke's law: Total force $F\propto Y_o\, u_o$, with $2u_o$ = displacement stroke of harmonic line source. Linear laws of line force $\propto u_o$ are derived by Hertzian contact theory in the absence of adhesion, and force acts at point on isotropic-plate edge to yield tangential in-plane circles as loci for constant extremal shear strain $\varepsilon_E=[(\check{S}_{be})_{i\neq j}]_E$ in vertical planes with normals ±45º, ±135º to principal strain axes. Non-linear constitutive eq. $\sigma_{rr}=Y(\epsilon_{rr};\, S_i)\epsilon_{rr}$ models Y softening via ultrasonic change in conformation (i=1) & configuration (i=2) parts of internal entropy $S=S_1+S_2$ for order-disorder phase change via action of extremal shear in same plane as damage-vulnerable plane at given field point. Nonlinear *variable*-coefficient WE with *dispersive* wave speeds arises, mathematically transformable into forced harmonic oscillator eq. Derived WE for ERF-forced shear motion has effects like creep via supersonic shear-wave shock-front-induced softening of Y or μ at size scales of $v_e/f\equiv\Lambda<<h<\Lambda_o$ if $\partial u_r/\partial t>\sqrt{[\mu_o/\rho]}$ – akin to Khokhlov-Zabolotskaya-Kuznetsov equation in σ_{rr}. Photoelastic gels can serve as calibration phantoms to do precision SSMSS exposimetry.
TOP	Test of principle suggested by asking question or posing new idea or hypothesis. Testing is done as Exploratory Research (ER), as by experiments with new prototype device, calculations in analytic theory or white paper marshaling evidence from the literature & making logical arguments. TOP approach is based on Hal's 2008 white paper, *A New Learning Model for Struggling Students in the STEM Educational System* (67 pp.; Dec 19). leading in 2010 to discovering a Double Hypothesis method [FP *infra*, 2nd sense].
UVM	University of Vermont, Burlington, VT where Hal earned 3 physics degrees & held 2 Research Associate posts, 1st paid (1974) & 2nd unpaid (2005-2007). His triple-alumnus bio is at: **https://www.uvm.edu/cas/physics/dr-harold-m-frost-ba-ms-phd-physics-1974**.
VE; VEDIP	*VE=Viscoelastic* [e.g., *Recent ER Success, Ex.1*, p.1; 1st #2, p.8]. *VEDIP=Viscoelastic dynamic indentation/penetrometry* (see EDIP).
WE	*Wave equation* [e.g., #14, p.9]. See "SSMSS.". Also, VEDIP & EDIP can generate waves in solids, e.g., S_o plate waves in thin plates.
Y	*Young's modulus*. In isotropic solid, Y=2μ(1+v) with shear modulus μ & Poisson's ratio v. Mason-horn tip oscillating normal to edge surface of thin isotropic strain-birefringent viscoelastic (VE) plate of Y, exerts total ultrasonic time-averaged line force $\langle\|F\|\rangle\propto u_o$ for isothermal intermittent contact conditions, ∴ uniaxial radial creep stress $\langle\sigma_{rr}\rangle$ & strain $\langle\varepsilon_{rr}(t)\rangle=\langle\sigma_{rr}/Y(t)\rangle\cong\langle\sigma_{rr}\rangle/Y(t)$. Via F_d, elastodynamic S_o-Lamb waves radiate at phase velocity $\sqrt{(Y/[\rho(1-v^2)])}$ for mass density ρ. ($\sqrt{[Y/\rho]}$= ext. wave speed in wire; $\sqrt{[\mu/\rho]}$ = bulk hear-wave speed.) $Y(t)/Y_o=[J(t)/J_o]^{-1}$ via creep compliance $J(t)\equiv[2\mu(t)]^{-1}$ measured photoelastically in a fixed, Eulerian coordinate frame with $d\langle F\rangle/dt=0$ & stress-relaxation Y(t) based on loci of $\langle d\varepsilon_{rr}/dt\rangle=0$ in moving, Lagrangian-like frame. If v=½ (incompressibility), $Y_oJ_o=Y_\infty J_\infty=3/2$ for initial & final values. $\partial J_o/\partial\sigma_{rr}=\partial Y_o/\partial\sigma_{rr}=0$ in $0\leq\langle\|\sigma_{rr}\|\rangle<\langle\|\sigma_{rr}\|_o\rangle_T]$, with like equations for $Y_\infty\equiv Y(t\to\infty)$ & $J_\infty\equiv J(t\to\infty)$. Above thresholds $\langle\|\sigma_{rr}\|_o\rangle_{TH}$ & $\langle\|\sigma_{rr}\|_\infty\rangle_{TH}$, Y_o & Y_∞ can soften, J_o and J_∞ can increase, and hysteresis can occur in stress/strain curve.