Ultrasonics

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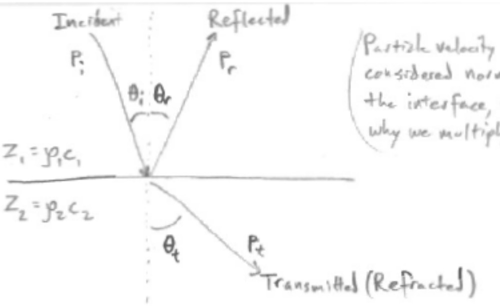
$c = \frac{1}{\sqrt{\kappa\rho}} = 1540\ m/s$ in tissue

(Like $R = \frac{V}{I}$)

$$* \boxed{p = \rho c u} \longrightarrow * \boxed{Z = \frac{p}{u} = \rho c} = \sqrt{\frac{\rho}{\kappa}}$$



(Particle velocity is only considered normal to the interface, so that's why we multiply by cos.)

κ = compressibility
ρ = density
p = pressure
u = particle velocity
Z = impedance
I = intensity
x = distance
w = pulse width
Z_R = Rayleigh distance (not impedance)
λ = wavelength
r = radius (below)
D = diameter

$\theta_i = \theta_r$

How to find θ_t from θ_i

$$* \boxed{\frac{\sin\theta_i}{\sin\theta_t} = \frac{c_1}{c_2}}$$

Noise = speckle & clutter (side lobes, grating lobes, motion)

Attenuation = sum of scattering & absorption.

$p = p_0 e^{-\alpha x}$ or $I = I_0 e^{-\mu x}$ where $\mu = 2\alpha$

In tissue, $\mu = 1 \frac{dB}{cm \cdot MHz}$.

Every 3 dB reduction is a factor of 2 reduction in Intensity.
(So 9 dB reduction = 2^3 = 8-fold reduction in Intensity.)

How to find reflection & transmission coefficients?

(Note that Z is always multiplied by the cosine of the opposing layer's angle)

$$* \boxed{R_p = \frac{P_r}{P_i} = \frac{Z_2\cos\theta_i - Z_1\cos\theta_t}{Z_2\cos\theta_i + Z_1\cos\theta_t} \qquad T_p = \frac{P_t}{P_i} = \frac{2Z_2\cos\theta_i}{Z_2\cos\theta_i + Z_1\cos\theta_t}}$$

Set $\theta_i = 0$ to solve direct wave problems.

$R_p = \frac{Z_2 - Z_1}{Z_2 + Z_1}$

$T_p = \frac{2Z_2}{Z_2 + Z_1}$

Derivation?

$R_I = R_p^2 = \frac{I_r}{I_i} = \ldots$

$T_I = \frac{I_t}{I_i} = \frac{4Z_1Z_2}{(Z_1+Z_2)^2}$

$T_p = R_p + 1$ (Pressure not conserved!)

$T_I + R_I = 1$ (Energy is conserved)

How to use: $P_r = P_i R_p$, $P_t = P_i T_p$ ✓

*This assumes plane wave behavior (constant frequ & amplitude, distance >> wavelength)

Device Setup ⇒ p. 157

Impedance matching of transducer to prevent internal reflection.

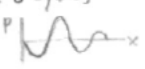
Ideal $Z = \sqrt{Z_1 Z_2}$
Ideal thickness $= \frac{\lambda}{4}$
Derivation

Axial Resolution (in mm) (Depth) $= \frac{1}{2} wc$ — b/c resolvable points are at $\frac{1}{2}$ the pulse width (same unit) (p. 164)

(Lower is better)

So make fast pulses (2-3 cycles) & also dampen the PZT crystal with epoxide.

Pulse width typically 2-3 cycles

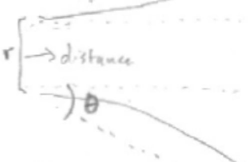


Near-field to Far-field Boundary (Distance):

$$\boxed{Z_R \simeq \frac{r^2}{\lambda}}$$

Axial Pressure Graph

Axial Beam width Graph



$\operatorname{sinc}\left(\frac{\theta_i}{\theta_o}\right) = 0.5$ when $\frac{\theta_i}{\theta_o} = 0.6$

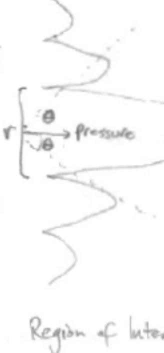
Maximum Angle of deviation of primary beam $\boxed{\theta = \operatorname{asin}\left(\frac{0.6\lambda}{r}\right)}$

Focused Array — Focal distance (F) ≈ radius of curvature (R)

Lateral Focal Resolution $= \frac{\lambda F}{D} = \frac{1}{\text{Beam width}}$

↓ diameter = ↑ resolution = ↓ beam width = ↓ penetration

In reality, it's not a single beam. "Lateral field in the focal plane"



So the angle thru the first zero point is $\theta = \operatorname{asin}\left(\frac{0.6\lambda}{r}\right)$

Phased (aka "Dynamic") Beam-forming, Beam-steering, & Beam aperature (↑ diameter = ↑ depth)

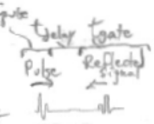
↳ The received signal can undergo "receiver beam-forming" to put the image back in focus.

↳ Apply time-gain compensation to compensate for the much weaker signals (delayed) from deeper tissue.

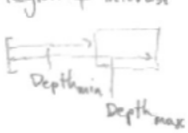
↳ The second harmonic is used from the receive signal → Increased lateral resolution, ↓ side lobe clutter → BUT does not reduce nonlinear scattering. So use pulse inversion instead.

↳ Pulse inversion: signals cancel out, the residual is nonlinear noise.

(Can be done by standard pulse mode or continuous mode.)



Region of Interest



$Depth_{min} = \frac{c(t_{delay} - t_{pulse})}{2}$

$Depth_{max} = \frac{c(t_{delay} - t_{gate})}{2}$

Doppler shift, Incident frequ., Sensed frequ., Velocity, Doppler Shift (Δf)

$$f_D = f_i - f_s = \frac{2f_i v\cos\theta}{c} + \underbrace{\frac{f_i v^2\cos^2\theta}{c^2}}_{\text{Small}} \approx \boxed{\frac{2f_i v\cos\theta}{c} = f_D}$$

If Velocity exceeds pulse rate $\left(\frac{\text{pulses}}{s}\right)$ then aliasing occurs & gives erroneous values.

Ultrasonics I

Small changes in pressure & density:

$$\begin{cases} p(r,t) = p_0 + p'(r,t) \\ \rho(r,t) = \rho_0 + \rho'(r,t) \end{cases}$$

where p' ← indicates small fluctuation

(Linear when $p' \ll p_0$)

Note $u(r,t) = 0 + u'(r,t)$

Conserv of Mass (Eq of Continuity) — Rate of change of mass is equal to mass flux in and out of the control volume

$$\frac{\partial \rho(r,t)}{\partial t} = -\nabla\cdot(\rho(r,t)\,u(r,t))$$

↓ Ignore small products, Assume linear

$$\frac{\partial \rho'(r,t)}{\partial t} = -\rho_0 \nabla\cdot u'(r,t) \quad (1)$$

Conserv of Momentum — Net change in momentum flux is equal to the net force acting on the control volume.

From same assumptions above...

$$\rho_0 \frac{\partial u'(r,t)}{\partial t} = \nabla p'(r,t) \quad (2)$$

Euler's equation of motion (net 3D force on fluid particle) $\rho \frac{\partial u}{\partial t} = -\nabla p$

(rate of change of momentum per unit volume.)

density $\cdot$ ΔVel = ∇press (Like $m\cdot a = F$)

Eq of State — Any thermodynamic quantity can be expressed as a function of any other two thermodynamic quantities

$$p = p(\rho, s) \text{ where } s = \text{entropy}$$

Sound speed c depends on density & bulk modulus (which is the inverse of compressibility k). ($B = 140$ kPa in air, 2 GPa in tissue)

$$B = \frac{1}{k} = \rho_0\left(\frac{\partial p}{\partial \rho}\right)$$

* Isentropic assumption (entropy constant)
* Adiabatic assumption (no heat change)

$$p'(r,t) = \frac{1}{k\rho_0}\rho'(r,t) \quad (3) \longrightarrow c^2 = \frac{p'}{\rho'} = \frac{1}{k\rho_0} \longrightarrow c = \sqrt{\frac{1}{k\rho_0}}$$

Combination of (1) (2) (3) gives the linear wave equation:

$$\frac{\partial^2 p'(r,t)}{\partial t^2} = c^2\nabla^2 p'(r,t)$$

↓ Drop the ' small fluctuations

$$\boxed{\frac{\partial^2 p(r,t)}{\partial t^2} = c^2\nabla^2 p(r,t)}$$

← 3D wave equation

1D wave equation → $\frac{\partial^2 p(x,t)}{\partial t^2} = c^2\frac{\partial^2 p(x,t)}{\partial x^2}$

↓ Integrate once

$$\frac{\partial p(x,t)}{\partial t} = \pm c\frac{\partial p(x,t)}{\partial x}$$

↓ D'Alembert's Solution

$$p(x,t) = \underbrace{f\left(t-\frac{x}{c}\right)}_{\text{Travels in } x\text{-direction}} + \underbrace{g\left(t+\frac{x}{c}\right)}_{\text{Travels in neg } x\text{-direction}}$$

$$p(x,t) = p\cos\left(\omega t \pm \frac{\omega}{c}x\right)$$

Instantaneous Intensity: $I = pu = \frac{p^2}{\rho c}$ Avg $I = \frac{p^2}{2\rho c}$

Acoustic Intensity = time avg of instantaneous $= \frac{1}{\tau}\int_t^{t+\tau} p\bar{u}\,dt$ ($I = \frac{pu}{2}$)

Energy $= E_{kin} + E_{pot} = \frac{1}{2}\rho_0 u^2 + \frac{1}{2}\frac{p^2}{(\rho_0 c)^2} = \frac{pu}{c} = \rho_0 u^2$ — See above!

z(tissue) $= 1.63$ MRayl
$c = 1480$ m/s
$P = 1$ MPa
$I = 667$ kW/m² $= .67$ W/cm²
$E = 447$ J/m³
$u_{max} = .67$ m/s

$$P_{RMS} = \frac{P_{max}}{\sqrt{2}}$$

All are complex but only consider the real component:

$$P = \mathrm{Re}\left[P_0 e^{-i\omega(t\pm\frac{x}{c})}\right] \quad \left(\text{Let } k = \frac{\omega}{c} = \frac{2\pi}{\lambda},\ \omega = 2\pi f\right)$$

$$U = \mathrm{Re}\left[U_0 e^{-i\omega t}\right] = \frac{P}{\rho_0 c} \quad (\rho_0 c \text{ is the characteristic impedance})$$

$$Z = \mathrm{Re}\left[\rho_0 c\cdot\cos\theta\cdot e^{-i\theta}\right] \quad \text{(Impedance is complex b/c it affects both amplitude \& phase)}$$

$$\cot\theta = \frac{\omega r}{c}$$

$$\boxed{p = \rho c u}, \quad \underbrace{\rho c}_{Z} \qquad Z = \rho c = \sqrt{\frac{\rho}{k}}$$

(u = particle displacement velocity)

$$\boxed{k = \frac{2\pi}{\lambda} = \frac{\omega}{c}} \quad \text{b/c } \omega = 2\pi f,\ f = \frac{c}{\lambda}$$

1

subst.

Instantaneous Intensity "Energy flux"

$$I = pu = \pm\frac{P_{peak}^2}{\rho_0 c}$$

Divide by RMS $= \frac{P_{max}}{\sqrt{2}}$, i.e., $P_{peak} = \sqrt{2}\,P_{rms}$

Avg. "Acoustic Intensity"

$$I_{rms} = \frac{p}{\sqrt{2}}\cdot\frac{u}{\sqrt{2}} = \frac{P_{peak}^2}{2\rho_0 c}$$

Instantaneous Energy Density

$$E = \frac{pu}{c} = \rho_0 u^2$$

Avg. "Acoustic Energy Density"

$$E = \frac{\frac{p}{\sqrt{2}}\frac{u}{\sqrt{2}}}{c} = \frac{\rho_0 u^2}{2}$$

Negative or Positive depending on whether Z_1 or Z_2 is greater (Often must be solved in the problem)

For perpendicular wave:

$$\begin{cases} P_r = P_i R_p \\ P_t = P_i T_p \end{cases}$$

The Meaning!

Best at $R = \pm 1$, $T = 1$ or 2

If no boundary, $R = 0$, $T = 1$.

$$\pm R_p = \frac{P_r}{P_i} = \frac{Z_2 - Z_1}{Z_2 + Z_1} \qquad R_I = R_p^2 = \frac{(Z_2-Z_1)^2}{(Z_2+Z_1)^2}$$

$$T_p = \frac{P_t}{P_i} = \frac{2Z_2}{Z_2+Z_1} \qquad T_I = \frac{I_t^2}{I_i^2} = \frac{Z_1}{Z_2}\frac{P_t^2}{P_i^2} = \dots \frac{4\frac{Z_1}{Z_2}}{\left(1+\frac{Z_1}{Z_2}\right)^2}$$

$\neq T_p^2$; $\frac{Z_1}{Z_2}T_p^2$ b/c $I = pu$ & $u = \frac{p}{z}$

Note that $T_p = R_p + 1$ (Pressure not conserved)

Note that $T_I + R_I = 1$ (Energy is conserved)

Hard Boundary ($Z_1 \ll Z_2$) — In phase reflection, transmits a lot of energy, pressure is doubled, velocity is zero. (think angle of intromission) If $R_p = 1$, $T_p = 2$, then $P_i = P_r$, so $P_t = 2P_i$. $\frac{P_t}{P_i} = 2 \to P_t = 2P_i$ & $Z_1 = 2Z_2 \to P_t = P_r \to Z_1u_1 = Z_2u_2 \Rightarrow u = 0$.

Soft Boundary ($Z_1 \gg Z_2$) — Out of phase reflection, reflects a lot of energy, pressure at boundary = 0. (Think critical angle) If $R_p = -1$, then $\frac{P_r}{P_i} = -1 \to P_r = -P_i \to P_r + P_i = 0$; $T_p = 0$; $\frac{P_t}{P_i} = 0 \to 0 = \rho c u_t \to u_t = 0$

"Transmission thru a Layer"

Z_1, Z_2 (L), Z_3; P_i, P_t

Use equations above to find formula for T_I. $T_I = \frac{Z_1}{Z_3}\left(\frac{P_t}{P_i}\right)^2$; $P_{t_2} = \frac{2Z_2}{Z_2+Z_1}$ & $P_{t_3} = \frac{2Z_3}{Z_3+Z_2}$

$$T_I = \frac{Z_1}{Z_2}\left(\frac{P_{t_2}}{P_i}\right)^2\frac{Z_2}{Z_3}\left(\frac{P_{t_3}}{P_i}\right)^2 = \frac{Z_1}{Z_3}\frac{4Z_2^2}{(Z_2+Z_1)^2}\cdot\frac{4Z_3^2}{(Z_3+Z_2)^2} \dots$$

From notes:

$$T_I = \frac{4}{2 + \left(\frac{Z_3}{Z_1}+\frac{Z_1}{Z_3}\right)\cos^2(k_2L) + \left(\frac{Z_2^2}{Z_1Z_3}+\frac{Z_1Z_3}{Z_2^2}\right)\sin^2(k_2L)}$$

If $Z_1 = Z_3$

$$T_I = \left[1 + \frac{1}{4}\left(\frac{Z_2}{Z_1}-\frac{Z_1}{Z_2}\right)^2\sin^2 k_2L\right]^{-1}$$

Best transmission occurs at $T_I = 1$

∴ Best when $L \ll \lambda$

$\frac{2\pi}{\lambda} = \frac{\omega}{c_2} = \frac{\omega\rho_2}{Z_2}$

For $k_2L = n\pi$, best at frequencies $\boxed{f_n = n\frac{c_2}{2L}}$ (Best at half natural frequ.)

$$\frac{\omega}{c_2}L = n\pi \to f = \frac{n\pi c_2}{2\pi L}$$

So n = harmonic or best at $L = \frac{1}{2}\lambda$

If $Z_1 \neq Z_3$

$$T_I = \frac{4Z_1Z_2}{\left(Z_2 + \frac{Z_1Z_3}{Z_2}\right)^2}$$

Set $T_I = 1$ → Best transmission when $\boxed{Z_2 = \sqrt{Z_1Z_3}}$

or quarter natural frequ. with

Set $k_2L = \frac{(2n-1)\pi}{2}$ → $\boxed{L = \left(\frac{2n-1}{4}\right)\lambda}$ $L = \frac{1}{4}\lambda$

Noise – aberration, reverberation

$\sin\theta_i = \sin\theta_r \rightarrow$ Angle of Incidence = Angle of Reflection (Snell's)

(1) $$\boxed{\frac{\sin\theta_i}{c_1} = \frac{\sin\theta_t}{c_2}}$$

Square both sides & remember $\sin^2\theta_t = 1-\cos^2\theta_t$

$$\cos\theta_t = \sqrt{1-\left(\frac{c_2}{c_1}\right)^2 \sin^2\theta_i}$$

10 ⊙

"Total Internal Reflection" occurs when θ_t is imaginary $\xrightarrow{\text{solve with}}$

$$\boxed{R_p = \frac{Z_2\cos\theta_i - Z_1\cos\theta_t}{Z_2\cos\theta_i + Z_1\cos\theta_t}} = \frac{\left(\frac{Z_2}{Z_1} - \frac{\cos\theta_t}{\cos\theta_i}\right)}{\left(\frac{Z_2}{Z_1} + \frac{\cos\theta_t}{\cos\theta_i}\right)}$$

since $Z = \rho c$, if $c_1 > c_2$, $\theta_t < \theta_i$

if $c_1 < c_2$, $\theta_t > \theta_i$ but only up to a point!

For $C_1 < C_2$ (or $Z_1 < Z_2$): At a critical incidence angle (θ_c), θ_t becomes imaginary! (propogates along interface)

$$\boxed{\sin\theta_c \equiv \frac{c_1}{c_2}}$$ "Total Internal Reflection" meaning that the reflected pressure

The "evanescent wave" decays perpendicular to boundary

$$P_t = P_{t_0} e^{-\gamma x} e^{-i(\omega t - K_1 y \sin\theta_i)}$$

where $\gamma = K_2\sqrt{\left(\frac{c_2}{c_1}\right)^2 \sin^2\theta_i - 1}$

(Only slow to fast) C_1 C_2 (imped ↓ imped) (not just c or ρ)

(Not necessarily just fast to slow!)

If $R_p = 0$, this means perfect transmission! $T = 1 - r^2$ "Angle of Intromission"

$$\frac{Z_2}{Z_1} = \frac{\cos\theta_t}{\cos\theta_i} \text{ (only if } R_p = 0\text{)}$$

$$Z_2^2\cos^2\theta_i = Z_1^2\cos^2\theta_t$$

10 ⊙

& Use Eq (1)

$$1-\sin^2\theta_i = \frac{Z_1^2}{Z_2^2}\cos^2\theta_t$$

$$\sin\theta_i = \sqrt{\frac{1-\left(\frac{Z_1}{Z_2}\right)^2}{1-\left(\frac{\rho_1}{\rho_2}\right)^2}}$$

θ_i will be the angle of intromission only when real, which is when both $Z_1 > Z_2$ & $\rho_1 > \rho_2$ or when both $Z_1 < Z_2$ & $\rho_1 < \rho_2$.

Sound Sources

Again, $\boxed{k = \frac{2\pi}{\lambda}}$. "$kr$" or "$ka$" is a good way of describing "acoustically small or large" by relating λ to distance r. At small r, pressure & particle velocity are out of phase, and ∴ $I = 0$. For large r, pressure & particle velocity are in phase, and $Z = Z_0$. At this point the Intensity declines $\propto \frac{1}{r^2}$ b/c energy is conserved.

Skipped lots of complex theory

$$I = \frac{\text{Power}}{\text{area}}$$

$$I = \frac{W}{\pi r^2}$$

Pressure $\propto \frac{1}{r}$!

Intensity $\propto \frac{1}{r^2}$!

(becomes the inner part of directivity equation)

$(\Delta r = d\sin\theta)$

Discrete Line Array

$L = (N-1)d$

N = # of elements

d = spacing distance between elements

a = radius of transducer

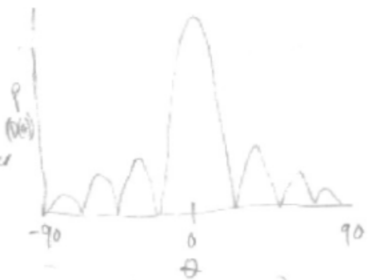
D = directivity

A = Pressure Amplitude?

r = distance from transducer

$k = \frac{2\pi}{\lambda}$

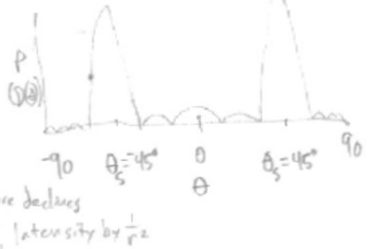
c = speed in medium



Steering

$$\boxed{P = P_{ax}(r)\cdot D(\theta)}$$

$$P_{ax} = \frac{NA}{r}$$ — Pressure declines by $\frac{1}{r}$, Intensity by $\frac{1}{r^2}$



If using time delay:

$$\boxed{\theta_s = \sin^{-1}\left(\frac{c\tau}{d}\right)}$$ where τ = time delay between adjacent elements

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↑N = Narrower primary beamwidth

# of side lobes (on both sides) $= (N-2)$

Angle of deviation of primary beam (for circular?)

$$\theta = \sin^{-1}\left(\frac{0.6\lambda}{a}\right)$$

Grating lobes (constructive interference) will occur at

$$\theta_g = \sin^{-1}\left(\pm m\frac{\lambda}{d}\right) \text{ where } m = 0,1,2\ldots$$

Therefore, make element spacing (d) no larger than $\frac{\lambda}{2}$! and there will be no grating lobes

If $D = 1$, normal. $0 < D < 1$ = angled.

$$\boxed{D(\theta) = \left|\frac{\sin\left(\frac{N}{2}kd\sin\theta_s\right)}{N\sin\left(\frac{1}{2}kd\sin\theta_s\right)}\right|}$$

Can use this to find θ of main lobes & θ of nodal points (zero values) by setting $D = 1$ and $D = 0$ respectively:

$$\theta_{lobes} = \sin^{-1}\left(m\frac{\lambda}{d}\right) \text{ where } m = 0,1,2\ldots\left(\frac{d}{\lambda}\right)$$

$$\theta_{nodes} = \sin^{-1}\left(\frac{n}{N}\frac{\lambda}{d}\right) \text{ where } n = 0,1,2\ldots$$

"Effective acoustic radius" of stone

$$\frac{a_{eff}}{(\text{actual radius})} = \sin(\theta_{crit}) = \text{ratio of acoustic energy that can actually enter}$$

$$\text{Effective Energy into sphere} = \frac{2r\sin(\theta_{crit})}{2r} = \%E$$

For discrete array: Rayleigh distance $Z_R = \frac{L}{2}$ where L = depth length of individual element (or "array length" of $L = (N-1)d$?!) (Far-field $= 2Z_R$? $= L$?)

(Derived from $p(r,\theta,t) = \sum \frac{A}{r} e^{-j(\omega t - kr)}$)

$$D(\theta) = \frac{\sin(N\varphi)}{N\sin(\varphi)} \text{ where } \varphi = \tfrac{1}{2}kd\sin\theta - \tfrac{1}{2}kd\sin\theta_s$$

θ = angle of lobes (e.g. primary lobe)

θ_s = steered beam angle

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→ To find zero points, set $D(\theta) = 0 \ldots \rightarrow \frac{1}{2}kd\sin\theta = m\pi$ $m = 0,1,2\ldots$

→ To find peak points, set $D'(\theta) = 0 \ldots \rightarrow D = \frac{\sin\theta}{\theta} \rightarrow D' = \frac{\cos\theta}{\theta} - \frac{\sin\theta}{\theta^2} = 0$

→ To find grating lobe θ, set $\varphi = 2\pi$ & solve θ.

$\theta = 7.7°$, & so on...

Ultrasonics II

Amplitude Detector / Contrast* Table / Resampling Filters / Hilbert* Wavemap / Envelope detection → Scan Converter $(r,\theta)\rightarrow(x,y)$ → Video Output

Grayscale Mapping to 256

TGC ← Beamformer (R/T/R switch) — Can refocus

Signal Generator → Beamformer

Phase Shifting → D/A convert. → Amplifier → Transducer

Transducer → Amplify → A/D convert → Phase shifting & Summation → Beamformer

Best to use second harmonic.

- Improves border outline
- Improves contrast
- Reduces (side-lobe) clutter

Is generated from nonlinear effects of tissue.

- Does not reduce scattering → need to use pulse inversion! (below)

Artefacts

I) Reverberation — strong reflecting layer (skin) near transducer causes (& refraction) harmonic internal reflections

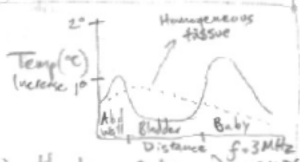
II) Aberration — we assume homogeneous sound speed, but inhomogeneous tissue causes distortions (increases with depth)

III) Side-lobes — strong scatterer (bone) aligned with side lobes causes repositioning of artificial image.

Attenuation = absorption & scatter & diffraction

Safety

(Remember Energy (J) = Power (W) · Time) — Intensity · Area



$f = 3\,MHz$, $c = 1540\,m/s$, $W = 225\,mW$, $\rho = 0.001\,kg/cm^3$

Thermal Index — cannot exceed 1 (tell machine the type of tissue)

$$T.I. = \frac{W_o}{W_{deg}}$$

W_o — avg. power

TI_S – soft

TI_B – bone

TI_C – cranium (fastest heating)

W_{deg} → the power to raise tissue 1°C

$$W_o = \frac{\rho_o u^2}{2} = \frac{p^2}{2\rho c^2}$$

from part I

$$M.I. = \frac{\dfrac{P_o}{(0.3\frac{dB}{MHz\cdot cm})(\text{measurement distance})(\text{freq (MHz)})}{2.5}}{\sqrt{f}}$$

P_o — Solved from $\bar{x} = \frac{\rho_o c_o^3}{\beta P_o 2\pi f}$ — Pressure at the shock formation distance

← Derating

Mechanical Index — cannot exceed 1.9 → If greater, cavitation and bubbles

$$\boxed{M.I. = \frac{P_{r.3}(z_{sp})}{\sqrt{f}}}$$ f in MHz

$P_{r.3}$ = Attenuated pressure: it's the peak negative pressure derated to $0.3\,\frac{dB}{MHz\cdot cm}$ to account for attenuation.

Z_{sp} = location of max negative pressure (after derating/attenuation) in cm

Something about pulse intensity integral (see p.4)

assume it occurs at the shockwave distance! $Z_{sp} = \bar{x} = \frac{\rho_o c_o^3}{\beta P_o 2\pi f}$ as above

Note lower f = ↑M.I. b/c longer time in negative pressure region so more damaging?!

Contrast Agents

Gas like spring, Water like damper

$$\ddot{r} + \frac{b}{4\pi R_o^3 \rho_l}\dot{r} + \frac{3\gamma P_o}{R_o^2 \rho_l} r = \frac{-F}{m} e^{-i\omega t}$$ (Gilmore Equation)

Equivalent of mass is 3x mass of bubble: $4\pi R_o^3 \rho_l$

Equiv of K is $12\pi\gamma R_o P_o$

Resonant $\omega_o = \sqrt{\frac{K}{m}}$ ...

↑K = ↑ resonant freq

↑viscosity = ↑damping = ↓amplitude

Bubbles — nonlinear oscillators

See next pg 6.

Linear resonant freq: $f_o a = \frac{1}{2\pi}\sqrt{\frac{3\gamma P_o}{\rho}}$

Simplified ↓

$f_o a = 3\,m/s$

- → So ↑ bubble size = ↓ resonant freq.
- → Can achieve amplification of signal, BBB delivery, release gas for perfusion imaging, targeted ligands, etc.
- → But SNR limitations, poor ligand adhesion, poor sensitivity

→ oscillating bubbles can cause microstreaming & shear forces, even jetting

Other Modalities

Intravascular U/S

U/S Tomography (for breast)

Elastography — Bulk modulus (compress – not helpful); Shear modulus (distinctive) } Press down probe, determine strain, Invert elasticity Eqs.

Doppler Shift

Shift in Frequ. (for continuous ultrasound)

$$\boxed{f_D = f_i - f_r \approx \frac{2 f_i (V\cos\theta)}{c}}$$

θ = angle b/w transducer beam & blood flow

V = blood velocity (0–5 m/s)

f_i = incident frequ (2–10 MHz)

$\therefore f_D = 0$–$15\,kHz$

(If perpendicular $\theta = 90°$, no signal)

For pulsed wave doppler

$$\boxed{f_D = \frac{1}{t_D} = \frac{c}{2T_{PRF}(V\cos\theta)}}$$

t_D — time between echoes; T_{PRF} — pulse separation time

Limitation is that the max measurable velocity is

$$V_{max} = \frac{c}{4T_{PRF} f_i}$$ @ c = 1500 m/s

b/c any movement above this velocity results in aliasing.

Also very sensitive to low velocities → must use wall filter to remove vessel motion.

Nonlinearity increases with:
Amplitude
Frequency
Tissue characteristics
Distance travelled

This generates harmonics

Nonlinearity

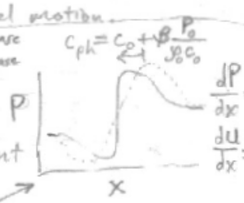
= $u > c$ during compression phase; $u < c$ during rarefaction phase

$c_{ph} = c_o + \beta \frac{P_o}{\rho_o c_o}$

If $\sigma << 1$, linear behavior

If $\sigma < 1$, nonlinearity is important

If $\sigma > 1$, shock wave formation



$\frac{dP}{dx} = \infty$, $\frac{du}{dx} = \infty$

$$\boxed{\sigma = (\beta \varepsilon k x) = \frac{x}{\bar{x}}}$$ (Not important)

x = propagation distance

$\bar{x}$ = shock formation distance

$\beta \varepsilon k = \frac{1}{\bar{x}}$

with $\beta\varepsilon k = \frac{\beta P_o 2\pi f}{\rho_o c_o^3}$

$$\boxed{\bar{x} = \frac{\rho_o c_o^3}{\beta P_o 2\pi f}}$$ Important

E.g. if wave is measured 5 cm (x) into tissue, and given that it's nonlinear ($\sigma = 1$), $\beta = 5$?, find P_o:

$$1 = \frac{0.05}{\left(\frac{\rho_o c_o^3}{\beta P_o 2\pi f}\right)} \rightarrow \frac{\rho_o c_o^3}{0.05} = \beta P_o 2\pi f$$ Solve for P_o.

- Nonlinear effects cause harmonics & reverberation, and also increased attenuation, which requires increased TGC. This can result in unwanted artefact & unwanted heating prior to focus area (e.g., esp. in fat).

Pulse Inversion Processing – used by all ultrasound

Send a pulse & its inverted equivalent — they should cancel, anything left over is noise/scatter, or if bubbles are used, is nonlinear response of bubbles.

HIFU (09)

Cancer, epilepsy, ablation (liver, prostate), hemostasis

Thermal lesion (cell death at 56°C for 1 sec; long time exposure, high duty cycles) or just mechanical (10 cycle pulses)

- boils/denatures in well-demarcated region (10-20 cell widths)
- forms hyperechoic region (start far, work towards)
- Also inertial cavitation & mechanical tissue disruption (less controllable) — if driven too hard, cav ↓ heating

$I = I_0 e^{-2\alpha(f)t}$ — 2/3 viscous & thermal damping

Ultimately, energy lost to absorption must go into heat:

$$\boxed{q_s = \frac{-dI}{dt} = 2\alpha(f)\cdot I} = \frac{dT}{dt}(\rho c) \quad (09\ldots13?)$$

(Heat Stored)

$\therefore \uparrow f = \uparrow$ heating but ↓ depth possible.

$\alpha(f)$ is the attenuation function

$\alpha(f) = \alpha \cdot f^n$ where $n = 1.1$ usually.

So even if 2 beams have same intensity ($\frac{W}{cm^2}$), ↑f causes ↑attenuation which means ↑ heating!

Nonlinear beams have more absorption & heat, as do harmonics

Characteristics

↑frequ = tighter focus (↑resolution)

↑Watts = faster ablation (↓time)

↓pulse cycle = ↑nonlinear effects = ↑ablation volume (assuming same time-averaged power (W)). = (briefer pulse of higher power, same energy)

Actually 3 Eqs — Tissue Domain — Blood Domain — Laminar flow

Pennes Bioheat Equation

$$\underbrace{\rho_t c_t \frac{dT}{dt}}_{\text{"Energy Stored Rate" or "Temp rise Rate"}} = \underbrace{2\alpha I_0}_{\text{"Acoustic Energy Applied Rate"}} + \underbrace{k_t \nabla^2 T}_{\text{"Energy Conducted Rate" or "Heat flux"}}$$

(often ignore)

$$\left[\frac{\partial T(r,t)}{\partial t} = \frac{1}{\rho_t c_t} q_{stored}\right]$$

$$\dot{Q}_{stored} = \int_V \rho_t c_t \frac{\partial T(r,t)}{\partial t}\, dV$$

$$\dot{Q}_{Conduction} = -\int_A k_t \vec{\nabla} T(r,t) \cdot n\, dA$$

temp gradient

$$\dot{Q}_{convection} = \int_V \rho_b c_b \left[\vec{u} \cdot \vec{\nabla} T(r,t)\right] dV$$

primarily blood

Heat loss due to:
- Conduction
- Convection
- Perfusion

$$\dot{Q}_{gained} = \int_V q(r,t)\, dV = \dot{Q}_{source}$$

heat in Volume = energy

energy/volume =

Q = Energy

$\dot{Q}$ = heat power

q = heat

V = Volume A = area

r = radius

t = time

C_t = specific heat

T = Temp

↑freq (f) = ↑ heating b/c higher chance of nonlinear harmonics & b/c greater attenuation.

Numerically:
Can also model with Westervelt Equation & KZK Equation
- Westervelt: 2 μm voxel F.E. model. Simplify to linear & quadratic terms.
- KZK: parabolic approximation

(09) (11)

U/S Contrast Agents (gas bubbles c̄ shell)
- Visualize perfusion in B-mode
- Harmonic imaging (perfusion) for nonlinear bubble harmonics
- In HIFU to decrease cavitation threshold for faster heating
- Drug delivery by placing drug in contrast agent, localized bubble rupture
- Drug delivery by enhancing sonoporation in cells.

Ultrasound Mechanical Uses

Use of U/S Mechanics

ESWL — kidney stones (10-20 mm), with pool or C-arm
- 1000-4000 SWs at 1-2 Hz
- primarily broken by shear stress → Makes stones into chunks
- (vs. the compressive & tensile stresses) → Makes chunks into fragments
- at least 1000 SWs for cavitation to begin
- These shock waves can cause bubble formation & jetting
- *Tissue repair & regeneration (tendon, ligament, muscle, bone, etc.) (3) See research studies!

1.
- (1) Inertial cavitation (Bubble) for HIFU — thermal ablation. 60-90 second signal, e.g. cancer
- (2) Inertial cavitation (Bubble) for non-thermal ablation (histotripsy). 10 cycle pulse, e.g. prostate, noncancer ablation (don't want spread)
- (3) Stable cavitation (Bubbles) for thrombolysis (aiding clot-busting drugs)
- (4) Shock wave to mechanically break up kidney stones (lithotripsy) (2)
- (5) Shock wave therapy for tissue repair (tendons, bones)
- (6) Stable cavitation (bubbles) to open BBB (e.g. Sonoporation)

Bone fractures, growth

Chronic fasciitis/epicondylitis, other ortho

Soft tissue revascularization/healing

Mechanotransduction →
- Cell proliferation & differentiation
- Collagen production & stronger crosslinking
- GF (VEGF, TGFβ1, IGF-1, BMP, etc.)
- Neovascularization

Sonoporation (cell drug delivery)

Opening BBB for drug delivery

Recannulization with tPA (cardiac/cerebral) = "Sonothrombolysis"

} Stable Cavitation

Mechanical Only

(09)

HIFU + Bubbles — dramatically increase tissue heating (cavitation-enhanced heating)

HIFU (without bubbles) for mechanical histotripsy (e.g. prostate, noncancer)

Shock wave lithotripsy (above) & tissue repair (above)

} Inertial Cavitation

1 MPa = 10 atm

Baffled Piston Source (Unfocused) 09

Rigid wall behind source doubles the pressure amplitude.
(Note unfocused beam)

$r_e = \sqrt{r^2 + a^2}$

$p(r,t) = \rho_0 c_0 \left[U\left(t - \frac{r}{c_0}\right) - U\left(t - \frac{r_e}{c_0}\right) \right]$

center wave — edge wave

(See back page)

Axial Far-field pressure P_{ax}

① $$\boxed{P_{ax} = 2\rho_0 c_0 U_0 \left(\frac{\frac{1}{2} k a^2}{r} \right)}$$

May ask RMS press

θ = angular width of beam $D(\theta)$ ③

② $$\boxed{D(\theta) = \frac{2 \sin (ka \sin\theta)}{(ka \sin\theta)} = \frac{\sin\left(\frac{\pi a}{\lambda}\sin\theta\right)}{\frac{\pi a}{\lambda}\sin\theta}}$$

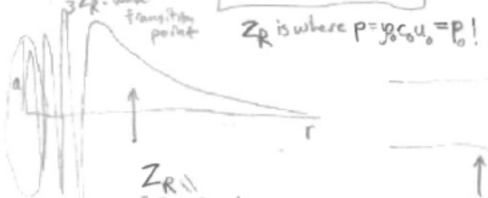
Total Pressure $$\boxed{P(r,\theta) = P_{ax}(r)\, D(\theta)}$$

For discrete array → $Z_R = \frac{L}{2}$ where L is the depth length of the individual element, from $Z_R = \frac{dL}{\lambda}$ and $d = \frac{\lambda}{2}$

Rayleigh Distance: $$\boxed{Z_R = \frac{1}{2} k a^2 = \frac{\pi a^2}{\lambda}}$$ — Determined only by transducer radius & sound wavelength

$\frac{1}{3} Z_R$ = wave transition point

Z_R is where $p = \rho_0 c_0 u_0 = P_0$!



$Z_R \gg$ "Far-field"

Z_R = field transition point

$\frac{1}{3} Z_R$ Near-field $\approx k \cdot a$

$P_{ax} = 2\rho_0 c_0 u_0 \left(\frac{Z_R}{r}\right)$ — Same as above

$P_{ax} = 2\rho_0 c_0 u_0 \left| \sin\left(\frac{1}{2} k r \left[\sqrt{1 + \frac{a^2}{r^2}} - 1\right] \right) \right|$

Z_R = point where distance to center & distance to edge is $< \frac{\lambda}{2}$ in difference!

$Z_R = \frac{D^2}{4\lambda}\left(1 - \frac{\lambda^2}{D^2}\right)$

e.g. use $\frac{P}{P_{ax}} = D(\theta)$ to find the ratio of the main lobe pressure after steering

$D(\theta) = \frac{\sin\theta}{\theta}$, maxima are found at $D'(\theta) = 0 = \frac{\cos\theta}{\theta} - \frac{\sin\theta}{\theta^2}$

$\theta = \pm 7.7° \rightarrow D(7.7) = 0.128$

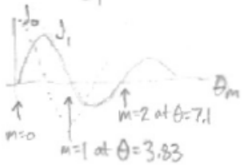
Z_r For field = sufficiently far that all wavelets are in phase (ideal plane wave)

Axial Field (Both show pressure) Lateral Field

Larger "ka" $\left(\frac{2\pi a}{\lambda}\right)$ = tighter primary beam

So larger a, or smaller λ (meaning higher freq.)

The $J_{1,m}$ Bessel function crosses at 0 for m=0, 3.83 for m=1, & so on. In other words, m is the # of the node where $J_1 = 0$



Maxima occur at $\theta = 0$
Nodes occur at $\theta = \theta_m$ where

$$\boxed{\theta_m = \sin^{-1}\left(\frac{J_{1,m}}{ka}\right)}$$

E.g. to find first nodal crossing point, $J_{1,1} = 3.83$, find $\theta_1 = \sin^{-1}\left(\frac{3.83}{ka}\right)$

To find # of crossings before distance r, (e.g. before Z_R) → use the k & a, and since $\left(\frac{J_{1,m}}{ka}\right)$ must be < 1 to be real, → find "m" where $J_{1,m} \le ka$, & that m = total # of nodes.

~~Note that θ is the beam width, and then we can also steer in direction θ_s. In this case, $D(\theta) = D_1(\theta) D_2(\theta)$ where D_1 represents beam width and D_2 represents steering;~~

$D_1 = \frac{\sin\left(\frac{\pi a}{\lambda}\sin\theta\right)}{\frac{\pi a}{\lambda}\sin\theta}$ (Same as above)

$D_2 = \frac{\sin\left(\frac{N\pi d}{\lambda}(\sin\theta_s - \sin\theta)\right)}{N \sin\left(\frac{\pi d}{\lambda}(\sin\theta_s - \sin\theta)\right)}$ = 1 if no steering (Same as prev. page)

So to find the distance where P = 50%, use Eq. ①. To find the angular beam width where P = 50%, set $D(\theta) = 0.50$ and solve for θ (difficult). Alternative forms:

$\theta = \sin^{-1}\left(\frac{0.6\lambda}{a}\right)$ (This θ = the angular beam width, which is also the angle to the first zero points.)

$\theta = \sin^{-1}\left(\sin\theta_s + \frac{\lambda}{Nd}\right) - \sin^{-1}\left(\sin\theta_s - \frac{\lambda}{Nd}\right)$ (See p. 2 formula. Easy to solve. θ_s usually given or equals zero.)

Focused Piston Source

$\downarrow$ diameter (aperture) = $\downarrow$ beam width = $\uparrow$ lateral resolution = $\downarrow$ penetration

Axial Solution 10 09

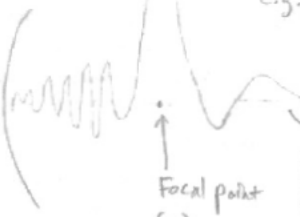
$$\boxed{P_{ax} = \rho_0 c_0 u_0 \cdot G}$$

R_c = radius of curvature

Where gain $G = \frac{\frac{1}{2} k a^2}{R_c}$

Ideal to have large G: $\downarrow\lambda$, $\uparrow f$, $\uparrow a$, $\downarrow R_c$

E.g., increasing a helps focus the pressure beam more directly at focus F.



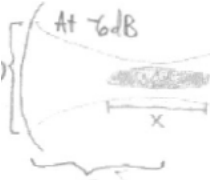
Focal point (F)

09 10

(Actual solution given by the complex Neil solution)

Intensity I (W/cm²) $= \frac{\text{Power (Watts)}}{\text{cross-sectional area}} = \frac{\text{Power (Watts)}}{\pi\left(\frac{\text{Beam Diam}}{2}\right)^2}$

$P_{inst} = \sqrt{2}\hat{P}$ $\left[\hat{P} = \sqrt{2\rho_0 c_0 I}\right]$ (P in Pa)



At −6dB

$X_{-6dB} = \lambda \frac{F}{D} = \frac{1}{\text{Beam width (diameter)}}$

$Y_{-6dB} = 7\lambda\left(\frac{F}{D}\right)^2$

$$\tau = \frac{r - \sqrt{(x_r - x_n)^2 + z_r^2}}{c} + t_0$$

x_r = diag. dist. b/w sound waves
r = focal distance (origin to focal point)
x_n = distance from origin to center of nth element,
t_0 = added to avoid neg. time delays
$Z_r = \frac{L}{2}$
$r = \sqrt{x_r^2 + z_r^2}$

Phased-Array Focusing

Eg. May need to solve for r

Dynamic focusing – keeps focus at $\frac{ct}{2}$

For steering in phased array (unfocused):

$$P(r, \theta_s) = \frac{P_0 N a}{r} \operatorname{sinc}\left(\frac{\pi a}{\lambda}\sin\theta_s\right) \quad \text{and} \quad \theta_s = \sin^{-1}\left(\frac{c\tau}{d}\right)$$

(Same as previous page)

$\frac{P}{P_0} = \frac{Na}{r}$ ← If this = 0, sinc = 1.

Attenuation

$\frac{P}{P_0} = e^{-\alpha x} \rightarrow \ln\left(\frac{P}{P_0}\right) = -\alpha x \rightarrow \frac{\log\left(\frac{P}{P_0}\right)}{\log e} = -\alpha x \ldots$

$\boxed{P(x) = P_0 e^{-\alpha(f)x}}$

$(I = I_0 e^{-2\alpha(f)x})$

(Remember $I \propto P^2$)

α is a function of frequency: $\boxed{\alpha = \alpha_0 (f)^n}$ (1 to 1.5 in tissue) e.g. $\alpha = X \frac{dB}{m \cdot MHz^{1.5}}$

$\alpha(f)$ in units of $\frac{Np}{m}$? $\rightarrow 1 \frac{Np}{m} = 0.087 \frac{dB}{cm}$

α often expressed as $\frac{dB}{cm}$

$\rightarrow 20 \log\left|\frac{P(x)}{P(0)}\right| = (dB)$ "Gain"

$\boxed{dB = 10 \log\left(\frac{I}{I_0}\right) = 20 \log\left(\frac{P}{P_0}\right)}$

Average α in tissue $= 0.5\ dB/_{cm}/_{MHz^{(n)}}$

(FDA assumes 0.3 to know greatest pressure possible)

Attenuation

Due to absorption + scattering! (speckle contrast of tissue (not imped mismatch))

Distorts the shape & amplitude of the pulse (↑ pulse length)

Imaging depth ≈ 400 wavelengths

Axial resolution relates to pulse width (2-3 cycles) →

Difference in echo time between 2 pulses > pulse duration (period T) $^{1}/_{f}$

$\boxed{\Delta d = \frac{c}{2f}(\#\text{ of pulses})}$ (Try to minimize Δd = axial res.)

Same $\Delta d = \frac{(\text{pulse width})(c)}{2}$

So ↑ with 2f harmonic imaging.

↑ frequ = ↑ resolution

↑ frequ = ↓ penetration (↑ attenuation)

Spherical Wave Instant. Intensity

$I = \left(\frac{1}{2}r\right)\left(\frac{P^2}{\rho_0 c_0}\right)$

Power of pulsating sphere

$P = I \cdot 4\pi r^2$

Intensity in focused beam

$I = \frac{\text{Power}}{\text{crosssect area}} \left(\frac{W}{cm^2}\right)$

Acoustic $I = \frac{P^2}{3\rho_0 c_0}$ $P_{rms} = \frac{P}{\sqrt{2}}$

Instant. Intensity for Pulses

$I = \frac{P^2}{3\rho_0 c_0}$ b/c $I = \frac{1}{T}\int_t^{t+T} \frac{P^2}{\rho c}\, dt$

Energy = [Intensity][Time][Area]

Time-Gain Compensation

To keep signal the same at all depths, gain is applied as function of time:

$\text{Attenuation (in dB)} = \alpha[2(X_2 - X_1)][f]^{3/2}$

To find attenuation difference between point 1 & 2 in mm!

$dB = 20 \log_{10}$

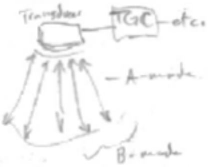
Required Gain $= 10^{\frac{\text{attenuation (dB)}}{20}}$

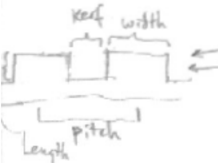
Ultrasound Function

A-mode - single line - time of reflected pulses translated into distance

$\boxed{d = \frac{t c_0}{2}}$

B-mode - image assembled from multiple A-lines.





C-mode - perpendicular to B-mode at specific depth.

M-mode - motion (A or B mode over time)

Doppler mode - color, PW, duplex, etc.

Pulse/Harmonic - taking advantage of harmonics & non-linearity

Apodization

reduces sidelobe clutter, thereby enhancing Contrast to Noise Ratio.

Reduce amplitude of outer elements (Hann weighting)

- This decreases the number of side lobes
- But main lobe becomes wider

Element width does not affect beam width, but can create grating lobes... keep $d < \lambda/2$

(↑ # of elements (N) causes narrower beam width) (Amplitude limited by side effects, nonlinearity, cavitation if present)

(↑ ka also causes narrower beam width ⇒ ↑f, ↓λ, ↑a) (Not applicable to discrete arrays)

Mach

$\text{Mach \#} = \frac{|U|}{c_0} = \frac{|P|}{\rho_0 c_0^2}$ } = B (Bulk modulus)

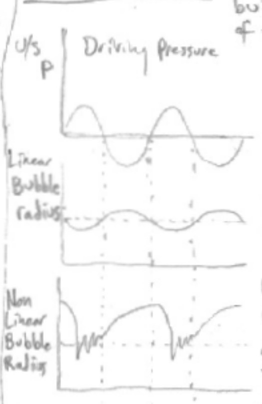
use $U = \frac{P}{Z}$ ← use $P_{ax} = \rho_0 c_0 u_0 \left(\frac{\frac{1}{2}ka^2}{r}\right)$

(Like particle velocity normalized to speed c)

Instant. Intensity for pulses $I = \frac{P^2}{3\rho_0 c_0}$ ← $E = I \cdot t \cdot \text{Area}$ → $\int_T^{T+\Delta T} I\, dt$ (ΔT)

Stable Cavitation - Linear or Nonlinear oscillations of bubbles where the bubble response is repeatable/periodic over hundreds of cycles.

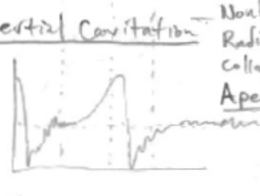
"We didn't know until bubble testing that tissue had any nonlinearity"



In phase with driving frequ. Stable

Multiple harmonics (ultraharmonics), Stable thousands of cycles. Radius reaches max at end of neg P, collapses and vibrates (can listen to subharmonics $\frac{f}{2}$ since these are only due to bubble resonance!)

Inertial Cavitation - Nonlinear response when driven hard. Radius enlarges over twice original, then violent collapse to < 1%, then wideband white noise. Aperiodic



also, high impedance means ↑ reflection in normal B-mode scanning.

Bubbles are very nonlinear (much more than tissue), so we can use harmonic imaging, listening for $2f_0$, in order to visualize primarily bubbles (↑ SNR) (e.g. for use in perfusion imaging)

See next pg. 5-6 for mechanical/thermal ultrasound uses & comparison of inertial vs. stable cavitation.

In HIFU inertial cavitation of bubbles enhances heating (from acoustic emissions)

Frame Rate

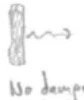
$\text{Frame time} = (\#\text{ lines})(\text{duration of each line})$

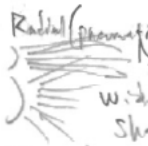
$\text{Frame Rate} = (\#\text{ lines})\left(\frac{\text{depth} \times 2}{\text{vel}}\right)$

3D Ultrasound

Hand movement + post-processing or Stacked 2D arrays (6 beams at once)

	Diagnostic	Therapeutic
Pulse	1-2 cycles (~10 for doppler)	Long or Continuous
Transducer Backing	lossy dampener to minimize back wave scatter (but causes ↓ amplitude)	Air; No dampening for higher amplitude
Freq	3-10 MHz	1 MHz (0.5-2) ↳ best regional penetration with little heating of shallow tissues
Bandwidth	As wide bandwidth as possible (50-100%) (Eg. if f_0 = 5 MHz & 100%, then range is 2.5 MHz - 7.5 MHz)	< 10% bandwidth (helps ↑ amplitude)
Transducer	Handheld, 50 x 20 mm, Phased array [illegible]	Wide diameter (10 cm), focused, single element.





Focused:
- Electrohydraulic
- Piezoelectric
- Electromagnetic
- Electroacoustic

* Can ↑ amplitude (& ↓ freq) to image deeper, but eventually will cause (1) nonlinear propagation & (2) acoustic cavitation.

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Mechanobiology

To find critical pipette pressure (P_p) when cell will enter:

Let P_{total} = difference in pressure across membrane

Now $P_{total} = P_c - P_p$

cell

Pipette (r_p) (P_p)

$P_c \cdot \pi r_c^2 = F_{outward}$

$T_c \cdot 2\pi r_c = F_{inward}$

$$P_c \pi r_c^2 = T_c 2\pi r_c \longrightarrow (P_c - P_p)\pi r_p^2 = T_c 2\pi r_c$$

Equilibrium of cell pressure, cell tension, pipette pressure.

This $r_c = r_p$ because it's inside cell.

$$P_c = \frac{2T_c}{r_c}$$

subst. (stays in original relation (r_c))

$$P_c \pi r_p^2 - P_p \pi r_p^2 = T_c 2\pi r_c$$

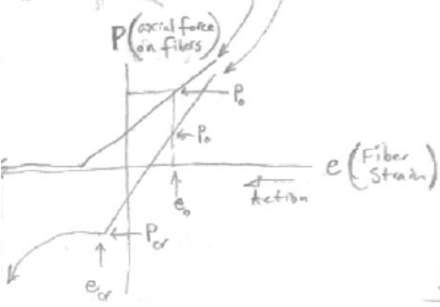
$$P_p = P_c - \frac{2T_c}{r_p} \longrightarrow \text{Threshold } P_p = 2T_c\left(\frac{1}{r_c} - \frac{1}{r_p}\right)$$

Tensigrity – Cell Architecture

10

Compression Fibers (microtubules – α/β tubulin dimers)
Tension Fibers (F-actin microfilaments)
} Bundled by IFs

Collagen ↓ Tropocollagen ↓ Fibrils



Arrows show direction of graph with external compression of the cell (thereby decreasing e)... Tensile fibers no longer exert any force b/c distance between compression fibers decreases.

Deflection $X = A\cos(\lambda x) + B\sin(\lambda x)$ where X has solutions of $X = n\pi$, etc.

n^2 appears occassionally, when solutions are complex, let $n=1$ for minimum P_{cr}.

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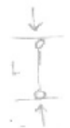
Find P_{cr} with Euler buckling formula:



$$\boxed{P_{cr} = \frac{\pi^2 E I (n^2)}{L^2}}$$

$\| \; \sigma \cdot L^2$

$\sigma = \frac{\pi^2 E I}{L^4}$ ← i.e.

E = modulus of elasticity
I = area moment of inertia (e.g. = (mg)(r)).
L = unsupported length
P_{cr} = critical force on beam (2.5 pN in cell)

in HRT – Must Know (Alsoin Biomechanics)

Note throughout: Stresses are always averaged diagonal sums, strains are diagonal sums but never averaged, except in the formulas.

PoroElastic Equation (Hookes')

Definitions →

Total & Dev. / Hydro / fluid (Δ)

*Assume Isotropic poroelastic

P = pore pressure (a result of applied stress σ_H) $\begin{bmatrix} P&P&P\\P&P&P\\P&P&P\end{bmatrix}$
α = elastic constant
ζ = flow
B = skempton Coefficient (relates p to σ_H cf. K)
H_A = Aggregate Modulus = $\frac{3}{3K+4G}$

Total Core Equation: Relates σ, ε / σ_H, $\epsilon_{\theta\theta}$

$$\boxed{\sigma_{ij} = 2G\epsilon_{ij} + \left(K - \frac{2G}{3}\right)\delta_{ij}\epsilon_{\theta\theta} - \alpha\delta_{ij}P}$$

Deviatoric & Total — Hydrostatic

Kronecker delta function

$$\begin{bmatrix}\sigma_{11}&\sigma_{12}&\sigma_{13}\\\sigma_{21}&\sigma_{22}&\sigma_{23}\\\sigma_{31}&\sigma_{32}&\sigma_{33}\end{bmatrix} = 2G\begin{bmatrix}\epsilon_{11}&\epsilon_{12}&\epsilon_{13}\\\epsilon_{21}&\epsilon_{22}&\epsilon_{23}\\\epsilon_{31}&\epsilon_{32}&\epsilon_{33}\end{bmatrix} + \left(K - \frac{2G}{3}\right)\begin{bmatrix}1&0&0\\0&1&0\\0&0&1\end{bmatrix}\epsilon_{\theta\theta} + \alpha\begin{bmatrix}1&0&0\\0&1&0\\0&0&1\end{bmatrix}\begin{bmatrix}P_{11}&P_{12}&P_{13}\\P_{21}&P_{22}&P_{23}\\P_{31}&P_{32}&P_{33}\end{bmatrix}$$

12

$$\begin{bmatrix}\epsilon&\epsilon&\epsilon\\\epsilon&\epsilon&\epsilon\\\epsilon&\epsilon&\epsilon\end{bmatrix} = \begin{bmatrix}e&e&e\\e&e&e\\e&e&e\end{bmatrix} + \frac{1}{3}\begin{bmatrix}\Delta&&\\&\Delta&\\&&\Delta\end{bmatrix}$$

$$\begin{bmatrix}\sigma&\sigma&\sigma\\\sigma&\sigma&\sigma\\\sigma&\sigma&\sigma\end{bmatrix} = \begin{bmatrix}S&S&S\\S&S&S\\S&S&S\end{bmatrix} + \begin{bmatrix}\sigma_H&&\\&\sigma_H&\\&&\sigma_H\end{bmatrix}$$

(Deviatoric can still include diagonal component)

$\begin{bmatrix}\Delta&0&0\\0&\Delta&0\\0&0&\Delta\end{bmatrix}$ b/c $\epsilon_{\theta\theta} = \epsilon_{11}+\epsilon_{22}+\epsilon_{33} = \Delta$ $\quad \begin{bmatrix}P&0&0\\0&P&0\\0&0&P\end{bmatrix}$

E.g. So if $\sigma = \begin{bmatrix}-1&2&0\\2&-3&0\\0&0&-2\end{bmatrix}$ then

$\sigma = \begin{bmatrix}-2&0&0\\0&-2&0\\0&0&-2\end{bmatrix} + \begin{bmatrix}1&2&0\\2&-1&0\\0&0&0\end{bmatrix}$
$\quad\;\; \sigma_H \qquad\qquad\quad S$

Will be averaged later (Δ = dilation)

To find principle stress, find eigenvalue of deviatoric stress (S): $\det\begin{bmatrix}1-\lambda&2&0\\2&-1-\lambda&0\\0&0&-\lambda\end{bmatrix} = 0$

*Note: Work = $\sigma\epsilon + p\zeta$ or $dW = \sigma d\epsilon + p d\zeta$

"Work conjugate" of ζ is p.

Relation of deviatoric to total:

$$\begin{cases}\sigma_{ij} = S_{ij} + \sigma_H\delta_{ij}\\ \epsilon_{ij} = e_{ij} + \frac{1}{3}\Delta\end{cases}$$

→ If substituted above, can show poroelastic materials behave entirely elastically in shear loading (meaning only deviatoric component). ⋯⋯> $\boxed{S_{ij} = (2G)e_{ij}}$

12

Note $\frac{1}{3}\Delta$ is the average ε of $\epsilon_{\theta\theta}$ above.

$\begin{bmatrix}\sigma&\sigma&\sigma\\\sigma&\sigma&\sigma\\\sigma&\sigma&\sigma\end{bmatrix}$ σ = total (Pressure) / stress (e.g. stress applied) = $S + \sigma_H$ (Actually the eigenvalues!)

$\begin{bmatrix}\epsilon&\epsilon&\epsilon\\\epsilon&\epsilon&\epsilon\\\epsilon&\epsilon&\epsilon\end{bmatrix}$ ϵ = total strain = $e + \frac{1}{3}\Delta$ (so if no deviatoric, just equals $\frac{1}{3}\Delta$ and modulus is just K.)

$\begin{bmatrix}S&S&S\\S&S&S\\S&S&S\end{bmatrix}$ S = deviatoric (Shear) Stress

$\begin{bmatrix}e&e&e\\e&e&e\\e&e&e\end{bmatrix}$ e = deviatoric (Shear) Strain

Deviatoric (Shear) only affects shape. $E/2(1+\nu)$ (in HRT)
G = Elastic Shear Modulus

$\begin{bmatrix}\sigma_H&&\\&\sigma_H&\\&&\sigma_H\end{bmatrix}$ σ_H = hydrostatic stress (Each σ_H is equal (each value) (average)) see below; $\sigma_H = \text{avg}(\text{diag}(\sigma))$

$\begin{bmatrix}\Delta&&\\&\Delta&\\&&\Delta\end{bmatrix}$ Δ = hydrostatic strain (dilation) $\Leftarrow \epsilon_{11}+\epsilon_{22}+\epsilon_{33} = \Delta = \epsilon_{\theta\theta}$

Hydrostatic = "Spherical" (only affects volume) Only these components are affected by the presence of fluid:

$\left(\Delta = \frac{\sigma_H + \alpha P}{K}\right)$ K_u = Undrained Bulk Modulus (Relates σ_H to Δ when fluid flow $\zeta = 0$): $\boxed{\sigma_H = K\Delta - \alpha p}$ (just know both forms)

↑P results in ↓ of [αP] in σ in order to keep ε constant. Or applied stress σ changes p.

K = Bulk Modulus (drained) (Relates σ_H to Δ when $p = 0$) $\boxed{\sigma_H = K\Delta}$

(When undrained, $\sigma_H = K_u\Delta$ see below)

K_u has long bizarre relation to K, found by setting $p = -\sigma_H$ (Pi Loading) see next pg.

$$\epsilon_{\theta\theta} = \Delta = \frac{(\sigma_H + \alpha P)}{K} \quad \text{or} \quad \boxed{\sigma_H = K\Delta - \alpha p} \text{ both when } \zeta = 0$$

(simple derivation above)

Core 1: Flow due to σ_H & P

Flow
$$\boxed{\zeta = \frac{\alpha}{K}\sigma_H + \frac{\alpha}{KB}P}$$

B = skempton coeff., where $\boxed{p = -B\sigma_H}$ only when $\zeta = 0$ (Undrained)

$$\boxed{B = \frac{K_u - K}{\alpha K}}$$

12

subst. $P = \frac{K\Delta}{\alpha} - \frac{\sigma_H}{\alpha}$ or subst. σ_H

Not derived, just set up already knowing the solution and setting $\zeta = 0$.

Eq. 1A
$$\sigma_H = \frac{-K_u - K}{\alpha}\zeta + K_u\Delta$$

E.g. ∴ This is how σ_H or P can be expressed as functions of ζ & Δ!

Undrained ⇒ ζ = 0, p varies

Drained ⇒ p = 0, ζ varies

see next page for P

$$\left(\zeta = \frac{\alpha^2}{K_u - K}P + \alpha\epsilon_{\theta\theta}\right) \xleftrightarrow{\text{subst } (\alpha B)} \sigma_H = K_u\epsilon_{\theta\theta} \text{ when } \zeta = 0.$$

σ = Total Stress Tensor — ε = Total Strain Tensor

S = Deviatoric (Shear) Stress Tensor — e = Deviatoric (Shear) Strain Tensor

$S = \sigma_{total} - \delta\sigma_H$ — $S = 2Ge$ ↳ "Elastic (Shear) Modulus"

$\sigma_{\theta\theta}$ = summing; $\frac{1}{3}\sigma_{\theta\theta} = P_A$ (applied pressure, not pore pressure) — $e = \epsilon_{total} - \frac{\Delta}{3}\delta$

σ_H = Hydrostatic (Spherical) Stress — $\epsilon_{\theta\theta}$ or Δ = Hydrostatic Strain (Dilation)

$\sigma_H = K\Delta - \alpha P$ if $\zeta = 0$ ↳ Bulk Modulus (Hydrostatic, Drained) — Sum of diag(ε) = $\epsilon_1+\epsilon_2+\epsilon_3$

Can be expressed as P or ζ, Δ

$\sigma_H = -P/B = \frac{-K_u - K}{\alpha}\zeta + K_u\Delta$ — $\left(K = \frac{E}{3(1-2\nu)}\right)$ (in HRT)

***Total Stress = Eigenvalues of σ
Principal Stress = Eigenvalues of S (see center bubble)

Total Strain = Eigvalues of ε
Principal Strain = Eigvalues of e

Direct Stress = sum of diag(σ) = $\sigma_H \times 3$

Direct Strain = sum of diag(ε)? = $\frac{1}{3}\epsilon$?? (like in quant. phys.?)

Hooke's Isotropic elastic behavior derivations: $\epsilon_{ij} = \frac{1}{2}\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}\right)$ Also see HRT p.127 ②

E = Elastic modulus

ν = Poisson's ratio $\left(\frac{\Delta y}{\Delta x}\right)$

Mathematical definition of (deviatoric) shear: $2\epsilon = \gamma$ (total strain, shear strain)

$\epsilon_{ij} = \left(\frac{1+\nu}{E}\right)\sigma_{ij} - \left(\frac{\nu}{E}\right)\delta_{ij}(\sigma_{11}+\sigma_{22}+\sigma_{33})$

E.g. So this is zero except $i=j$ $(\epsilon_{11}, \epsilon_{22}, \epsilon_{33})$

E.g. for ϵ_{12}

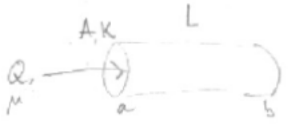
Whole Eq. eventually becomes the total core equation

$\epsilon_{12} = \left(\frac{1+\nu}{E}\right)\sigma_{12}$

$\sigma_{12} = \underbrace{\frac{E}{2(1+\nu)}}_{G}\epsilon_{12}$

Hence deviatoric behaves entirely elastically.

$\boxed{S_{ij} = G e_{ij}}$



perm. area pressure

Thin film assumed: $Q = \frac{-KA}{\mu}\frac{(P_b - P_a)}{L}$ (visc, length)

↓ 1-D

*Darcy's law

$\boxed{q_i = \frac{-K}{\mu}\frac{\partial P}{\partial x_i}}$

Note flow (like strain) relates to change in pressure (like stress) (pressure gradient) vs. solids (Similar to Fick's 1st law in Quant Phys J=q)

↓ deriv.

$\frac{\partial q_i}{\partial x_i} = \frac{-K}{\mu}\frac{\partial^2 P}{\partial x_i^2}$

(would result in Navier Eq. where solutions are harmonic functions)

12 ⊙

[3 Assumptions]

*Assume Equilibrium $\frac{\partial \sigma}{\partial x_i} = 0$ (So fx of time only)

12 ⊙

*Continuity of Mass

$\frac{\partial \zeta}{\partial t} + \frac{\partial q_i}{\partial x_i} = 0$

subst.

$\frac{\partial \zeta}{\partial t} - \frac{K}{\mu}\nabla^2 P = 0$ } Important result

Eq 1B

$P = \frac{K_u - K}{\alpha^2}(\zeta - \alpha\Delta)$

↓ deriv.

$\frac{\partial P}{\partial t} = \frac{K_u - K}{\alpha^2}\left(\frac{\partial \zeta}{\partial t} - \alpha\frac{\partial \Delta}{\partial t}\right)$

Use pressure flow equation from pg ① bottom left. Multiply by $\frac{K_u - K}{\alpha^2}$ here

$\frac{K_u - K}{\alpha^2}\frac{\partial \zeta}{\partial t} - \frac{K}{\mu}\left(\frac{K_u - K}{\alpha^2}\right)\nabla^2 P$

subst.

Pore Pressure Diffusion Eq.:

$\frac{\partial P}{\partial t} = \frac{K_u - K}{\alpha^2}\left(\frac{\partial \zeta}{\partial t} - \alpha\frac{\partial \Delta}{\partial t}\right)$

$p(t=0) = -\left(\frac{K_u - K}{\alpha}\right)\Delta$

$\Delta = \epsilon_{zz}$ in 1D

Since we assumed undrained condition of $\zeta = 0$, $K \to K_u$ ("Pi loading")

$\therefore p(t=0)$ must $= 0$

*E.g. Derive 1D analytical solution i.e. show behavior (formula) of pressure at instant (t=0).

Assume at t=0, $\zeta = 0$, and simply plug into

Plug into "Total core Equation" on front pg. (in 1D)

↓

$\sigma_{zz} = 2G\epsilon_{zz} + \left(K - \frac{2G}{3}\right)\epsilon_{zz} - \alpha P_{zz}$ ← plug in

*Assume no fluid exit at t=0 ($\zeta = 0$)

σ_{zz} is applied pressure ($-P_A$). $K \to K_u$

This relationship applies, subst. for $\epsilon_{zz} = \frac{P}{-\left(\frac{K_u - K}{\alpha}\right)}$

$-P_A = \left(K_u + \frac{4G}{3}\right)\epsilon_{zz}$

↓ *Assume uniform pore pressure

$P_A = \left(K_u + \frac{4G}{3}\right)\left(\frac{\alpha}{K_u - K}\right)P_{zz}$

↓ Rearrange

1D analytical solution

$P(z, t=0) = \frac{3(K_u - K)}{\alpha(4G + 3K_u)}P_A$ Solve for P_A

pore pressure   applied stress in 1D $P_A = \sigma_{zz}$

Loading activates osteoblasts, chondrocytes, which ↑ growth & nutrients to avascular cartilage.

GAGs (negative charge) = proteoglycans (hydrophilic), collagen

$[Na^+]$ = osmotic pressure

H_A = aggregate modulus = $\frac{3}{3K + 4G}$ Given in problems.

Diffusivity = $c = \frac{H_A K}{\eta}$ where K = perm. & η = visc.

In reality, permeability varies with pore geometry as K^n where $3 < n < 8$, but just assume constant.

If $p = -\sigma_H$ ("Pi loading"), $\epsilon = \frac{P}{3K_s}\delta_{ij}$

Notes & SUMMARY

Eq 1A (Derived on 1st pg)

$\sigma_H = -\frac{K_u - K}{\alpha}\zeta + K_u\Delta$

Eq 1B (b/c $p = -B\sigma_H$)

$p = \frac{K_u - K}{\alpha^2}(\zeta - \alpha\Delta)$

Ⓐ $[\zeta, \sigma_H, \Delta]$ ζ couples stress & strain: $\left[\epsilon - \frac{B}{3}\zeta\delta_{ij} = \frac{\sigma}{2G} + \left(\frac{1}{6G} - \frac{1}{9K_u}\right)\sigma_{kk}\delta_{ij}\right]$

The Pore Pressure Diffusion Eq. is also written as:

$\left[\frac{\partial P}{\partial t} = \frac{K}{\mu}\left(\frac{K_u - K}{\alpha^2}\right)\nabla^2 P + -\frac{K_u - K}{\alpha}\frac{\partial \Delta}{\partial t}\right]$

b/c $\zeta \Leftrightarrow q$ is given by Cont. of Mass, and $q \Leftrightarrow P$ is given by Darcy's law, so $\left[\frac{\partial \zeta}{\partial t} = \frac{K}{\mu}\nabla^2 P\right]$ was substituted.

Ⓑ $[P, \sigma, \epsilon]$ P can couple stress & strain (see Total Core Eq on front)

Ⓒ $[P, \zeta, \sigma_H]$ P can couple ζ and σ_H (core 1) or $[P, \zeta, \Delta]$ ζ and Δ (Eq 1B)

Ⓓ P can couple σ in 1D (1D analyt solution at t=0)

Drained ⇒ P=0

Undrained ⇒ $\zeta = 0$

From Total Core Eq., we could just say the "effective" stress is

$\sigma_{eff} = \sigma_{ij} + \alpha\delta_{ij}P$

and

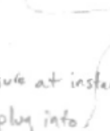
$\epsilon_{eff} = \epsilon_{ij} - \frac{B}{3}\zeta\delta_{ij}$

Not used in problems

Use $\epsilon_{zz} = \frac{\partial U_z}{\partial z} = \frac{3}{(3K + 4G)}(-P_A + \alpha p)$ to find solution for $U_z = \cdots P_A z \cdot$ [Harmonic Solns] Cf. Biomechanics – stress, strain, Porous, etc.

⊙

Creep test – constant stress



Boundary Conditions: $p(z,t)\Big|_{z=h} = 0$ (press at surface)

(Displacement U along z at the base) $U(z,t)\Big|_{z=0} = 0$

(Base is impermeable) $\frac{\partial P}{\partial z}\Big|_{z=0} = 0$

*Assume

*Assume incompressible fluid itself ($K_u >> K$)

*Assume $\epsilon_{xx} = \epsilon_{yy} = 0$ (1D)

*Use Pore Press Diff Eq. above with Darcy's/Cont. of Mass result on right

$\frac{\partial P}{\partial t} = \frac{K_u - K}{\alpha^2}\left(\frac{\partial \zeta}{\partial t} - \alpha\frac{\partial \Delta}{\partial t}\right)$ per above, if $\frac{\partial P}{\partial t} = 0$ and $\frac{\partial \zeta}{\partial t} = 0$, then $\frac{\partial \Delta}{\partial t} = 0$.

*Constant stress

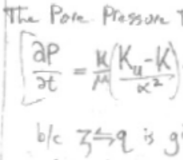
$\frac{\partial \zeta}{\partial t} = \frac{K}{\mu}\nabla^2 P$ from mid-right of pg.

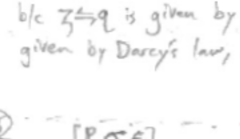
$\therefore \boxed{\frac{\partial P}{\partial t} = \left(\frac{K}{\mu}\right)\left(\frac{K_u - K}{\alpha^2}\right)\frac{\partial^2 P}{\partial z^2} = 0}$

Harmonic (Fourier series) Solutions for U(z) → Tissue Eng (Diffusion) → Quant Phys (Diffusion)

Max P at t=0

Pore press first carries load, then solid matrix (b/c fluid flows out)

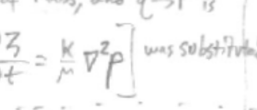




$\left(\begin{matrix} K_u \to \infty \\ \alpha = 1 \end{matrix}\right)$ U_z

$p(h) = 0$ B.C.

Displacement over time:



Shape ⇒ Deviatoric = Shear =

Volume ⇒ Hydrostatic = Spherical = Dilatation

Tissue Engineering

Cellular — Materials — Process — Bioreactor, Monitoring, Preservation

Cells: Autologous vs Allogenic (Immunity?)

Stem vs Mature

Adult vs Embryonic (ethical?)

Autologous: Accesible but Limited differentiation, Limited self renewal

(Stem = selfrenewal + differentiation)

First Products → Transcyte (cartilage/collagen)

Apligraf / Dermagraft

Collagen Matrix + Dermal Fibroblasts + Epidermal Keratinocytes

Now — (Still limited in thickness by mass tansfer)

- Skin
- Cartilage
- Bone
- Valves
- Nerve conduits
- Tendon
- Ligament
- Muscle

Encapsulated cells (pancreas)

Etc.

① Isolate Cells

Enzyme digestion

Flow cytometry

② Scaffolding

First optimize scaffold, then scale-up

Matrix size must always be within mass transfer limit

(Consider cell adhesion, strength, drug delivery, biodegradation, topography, etc.)

(Some have surface erosion (mass loss > H_2O ingress) while others have bulk erosion (H_2O ingress > mass loss).)

Conventional vs. Rapid Prototyping

- solvent casting
- electrospinning
- fibre bonding
- phase separation
- freeze drying (pores depend on cooling rate)
- 3D printing
- Fused deposition modeling

Synthetic — PLA, PGA

Natural — Collagen, gelatin, agarose, etc. — low toxic, low inflamm

③ Bioreactor (Controls & automates conditions — seeding, proliferation, mass tansfer (perfusion), mechanical stimulation)

(Consider mass transfer, hydrodynamics, Monitoring & control, Stimuli, scale-up, biocompat, Sterilisation, etc.)

- Spinner flask — stirring (great mass transfer/convection) but high shear stress
- Rotating Wall — good dynamic mass transfer with low shear stress
  - Balances drag force, centrifugal force, gravitational force
  - laminar flow with low shear.
- Hollow-fibre — protects sensitive cells in hollow fibers while still enabling mass transfer (good mass transfer)
- Direct Perfusion — direct flow onto scaffold evenly seeds cells & provides even mass transfer (but shear stress? & erosion)
- Specialized Mechanical — dynamic compression, physiologic simulation, functionalization, tension, torsion, (shaken — for bacteria)

Also microreactors, pneumatic pumps, etc.

ECM — support, regulate, development, receptors

Proteoglycans

Collagen, Elastin, Etc. } Structural ... Multistage/Multimodal assembly ...

Enzymatic

Biomechanical

Cofactors/Nutrients

Cellular/Extracellular

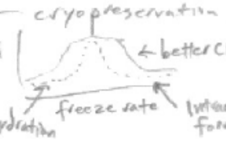
⋮

Fibronectin, Laminin } Adhesive

④ Preservation — cryopreservation (liquid nitrogen) or $-80°$ with cryopreserv. agent (CPA)

Try to ↑ survival, not lose function, reduce toxicity, make simple.

① CPA loading ② Freeze rate ③ Thaw rate ④ CPA removal



Called "localized shear damage"

Collagen + Abundant

+ Biocompatible

+ Crosslinking to prevent degradation

— Poor mechanical properties

— Batch variability

— gel contraction

HA

+ Abundant

— Fast degradation

— Poor mechanical

Enhance via stem cell/molecular signaling, biomechanical stimulation, cofactors/nutrient solutions

Mixing Considerations

Vortex is bad — collisions lead to cell damage & lines of flow still lead to poor mixing.

→ So use off-centre impellers & baffles!

Alginate + Gels with Ca^{++} (cell delivery)

+/- Same as collagen

— Poor cell adhesion

Chitosan

+ Reactive groups

— Poor cell adhesion

+ Biocompatible

Eddies shouldn't be too small or too large (Kolmogorov eddy = smallest eddy size)

b/c too little mixing & cells break

b/c too much shear

cells larger than this size are damaged by shear in the flow lines.

Axial Flow

Radial flow Impellers have high shear (better mixing, eg. immiscibles) — good to minimize bubbles/foam, but it damages the cells

PGA/PLA/PCL

+ Biocompatible

— Metab acidic ($CO_2 + H_2O$)

Synthetics

+ More functional

— Less biocompatible

O_2 rarely diffuses > 0.2 mm (cartilage cell survive 1 mm!)

Oxygenation — The main limiting factor (more than nutrients)

(can also use headspace oxygenation)

- Use membrane oxygenation, external oxygenation to minimize bubbles.
- Consider impeller design to minimize cell damage

Bubbles on surface can also cause shear damage to cells on surface. (bigger bubbles worse than small.) Foam damage does the same thing, resulting in damaged cells. Therefore, the size of the "disengagement zone" is important.

⑤ Implantation ...

Sensors in Bioreactors

Physiochem — pH, temp, O_2, CO_2

Nutrients — Gluc, a.a., lactate, ammonia

Cytokines

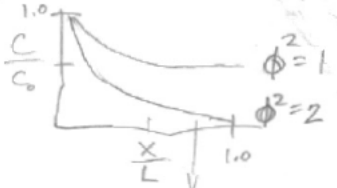
Can use micromembrane probes

Oxygen transfer

$$\frac{\partial C}{\partial x} \propto \frac{d\left(\frac{C}{C_0}\right)}{d\left(\frac{x}{L}\right)} = \phi^2 = \frac{Q_{O_2} L^2 [\text{cells}]}{C_0 D_{O_2}} \approx \frac{\text{reaction rate}}{\text{delivery rate}} \approx \frac{\text{consumption}}{\text{delivery}}$$

Metab rate

Generally assume that metabolic rate is constant (see below on bottom left.)



Lower b/c consumption > delivery.

Q_{O_2} = O_2 flow (consumption!)

D_{O_2} = O_2 diffus

C_0 = O_2 concent. at surface $\left(\frac{mol}{L}\right)$

$$\frac{\left(\frac{mol}{cells \cdot s}\right)(cm^2)\left(\frac{cells}{L}\right)}{\left(\frac{mol}{L}\right)\left(\frac{cm^2}{s}\right)} = \text{unitless}$$

*If $\phi^2 = 1$, then consumption equals delivery, meaning this is the condition for no necrosis yet maximal # of cells!!

ϕ^2 (units of cells/cm³)

Eg. $L = 1\,cm$

$Q_{O_2} = 4e^{-17} \frac{mol}{L}/s$

$D_{O_2} = 2e^{-5}\ cm^2/s$

$C_0 = 0.07e^{-3} \frac{mol}{L}$

all units cancelled

$$\frac{(4e^{-17})(1)^2 [\text{cells}]}{(0.07e^{-3})(2e^{-5})} = (2.85e^{-8})[\text{cells}]_{max} = 1$$

$\therefore$ Max cells / cm³ = 35 million

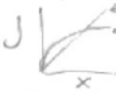
If L=2 instead of 1, Max cells / cm³ = 8.7 million

$\therefore$ *There is an inverse square relationship between cell max & diffusion distance.

(Increasing size 3x reduces cell capacity 9x)

Note D is always times $\frac{C}{x}$ or $\frac{dC}{dx}$!

$D\frac{\partial C}{\partial x} = J$



pg 9

Diffusion — Passive

Fick's 1st Law (1-D)

$$\boxed{J = -D_A \frac{\partial C_A}{\partial x}}$$

like $\frac{\partial C}{\partial t}$

$J = \left(\frac{mol}{L}\right)\left(\frac{m}{s}\right)$

Negative b/c flux flows towards decreasing concent.

D = Diffusivity of A $\left(\frac{m^2}{s}\right)$ — if 1D instead of 3D area, D = ...

C_A = Concentration of A $\left(\frac{mol}{L}\right)$

Convective Mass Transfer ("Film Theory") *** (Assume very thin film)

$$\boxed{J = \frac{D(C_1 - C_2)}{L}}$$

$\frac{D}{L}$ = mass transfer coefficient (↑turbulence in film = ↑D) (like k below)

Same as $J = \frac{D}{A}(C_1 - C_2)$ Used in example problem

Same as $J = PA(C_1 - C_2)$ (2-dimensional assumption?)

Net flow; Perm. (m/s); area (m²)

Partial Pressure in Liquid determines Concentration in Liquid: Partial Pressure $P_c = P_{Total}$(% composition)

Henry's Law

$$\boxed{P_c = H[C]}$$

In ideal gas $H = RT$, but $H \neq RT$ in the liquid!

i.e. for given P, if H↑, [C]↓.

If large H (low solubility), resistance is in the liquid phase

If small H (high solubility*) resistance is in the gas phase.

*still in terms of concentration!

O_2: Air P_0 → P_i; C_i → Liquid C_0

$$J_{Air} = \frac{D_g}{L_1}\left(\frac{P_0 - P_i}{RT}\right) \quad (K_g)$$

$$J_{Liquid} = \frac{D_L}{L_2}(C_i - C_0) \quad (\text{"}K_L\text{"})$$

In equilibrium → $\frac{D_g}{L_1}\left(\frac{P_0}{RT} - \frac{HC_i}{RT}\right) = \frac{D_L}{L_2}\left(\frac{P_i}{H} - C_0\right)$ (substituted P_i; ⇑subst. C_i)

Substitute

→ $P_i = HC_i$

→ $\frac{P_i}{RT} = C_i$

→ $C_i = \frac{P_i}{H}$

all the same

Can solve for C_0

$$C_0 = \left(1 + \frac{L_1 D_g}{L_2 D_L}\right) C_i - \left(\frac{L_1 D_g}{L_2 D_L}\right)\left(\frac{P_0}{RT}\right)$$

Diffusion in Alginate Bead $\left(D = \frac{cm^2}{s}\right)$

$D\frac{\partial^2 C}{\partial x^2} - \left(\begin{smallmatrix}\text{consumed}\\ \text{rate}\end{smallmatrix}\right) = 0$

In sphere:

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$D_e\left[\frac{\partial^2 C}{\partial r^2} + \frac{2}{r}\frac{\partial C}{\partial r}\right] = \left(\begin{smallmatrix}\text{consumed}\\ \text{rate}\end{smallmatrix}\right)$

$D_e\left[\frac{d\left(r^2 \frac{dC}{dr}\right)}{dr}\right] = r^2\left(\begin{smallmatrix}\text{consumed}\\ \text{rate}\end{smallmatrix}\right)$ Makes much more sense.

Eg. $\int \frac{dC}{[C_t - C_\infty]} = \int \frac{D}{r^2}\, dt$ ← origin?

$\therefore C_t = Ce^{\frac{-Dt}{r^2}} + C_\infty$

can normalize by $\frac{[C_t - C_\infty]}{[C_0 - C_\infty]}$

↳ Can calculate D from natural log regression.

Can also create an overall mass transfer eq. for air + liquid.

$$J_{Combined} = K^*\left(\frac{P_0}{H} - C_0\right)$$

where K^* is found by law of parallel resistance: $\frac{1}{K^*} = \frac{1}{K_L} + \frac{RT}{K_g H}$ (liquid; gas)

(why? similar to how ΔV is same across all circuits in parallel?)

can also put in terms of H

① = Lumen

② = Fibre

③ = Matrix

R_1, H; R_2; R_3

Model of Hollow Fibre Membrane Bound. Cond.

① At $r = 0$, $\frac{\partial C}{\partial r} = 0$ Ah!

At $r = R_1$, $J_1 = J_2$ → $D_1\frac{\partial C}{\partial r} = D_2\frac{\partial C}{\partial r}$ Ah!

② At $r = R_2$, $D_2\frac{\partial C}{\partial r} = D_3\frac{\partial C}{\partial r}$ ($J_2 = J_3$)

③ At $r = R_3$, $\frac{\partial C}{\partial r} = 0$ ✓

Facilitated Diffusion

(See Quant Phys II) 1D Fick's 2nd Law

$$\left(\frac{\partial C}{\partial t} = \cancel{} = D_A \frac{\partial^2 C}{\partial x^2}\right)$$

Apparently, this can be written as

(Diffusion Rate)

$$\boxed{\frac{\partial C}{\partial t} = \frac{V_{max}}{1 + K/\left(\frac{\partial C}{\partial x}\right)}}$$

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like:

$$D\frac{\partial^2 C}{\partial x^2} - \frac{\partial C}{\partial t} = 0$$

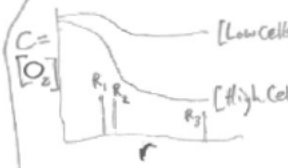
→ Harmonic Solutions

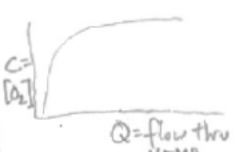
↳ See Mechanobio Creep; Quant Phys Diffusion

Metabolic rate is usually assumed to be constant = r

*Note that as the gradient approaches ∞, diffusion rate → V_{max}

*Note that K determines how quickly we approach V_{max} (channel saturation), and K is determined by particle properties, permeability, surface area





Q = flow thru HFMB