(Thermal) mechanisms of interaction between HF and biological systems

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REVIEW ARTICLE

Thermal aspects of exposure to radiofrequency energy: Report of a workshop

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Mechanism" is defined by IEEE (2006) as a theoretical formulation that:

- can be used to predict a biological effect in humans;
- can be formulated in an explicit model using equations or parametric relationships;
- is supported by data from humans, or by animal data and can be extrapolated confidently to humans;
- is supported by strong evidence; and
- is widely accepted among experts in the scientific community.

Mechanism 1

(metric: temperature increase)

Thermal Dependence of Biological Processes

Arrhenius' equation

$$k = Ae^{-E_a/(RT)}$$

k = rate constant of a chemical reaction

T = absolute temperature (in K)

A = pre-exponential factor (or simply the prefactor),

E_a = activation energy

R = universal gas constant

For most biological systems, Q_{10} ~ 2 to 3

Q_{10} - Practical characterization of temperature dependence

$$Q_{10} = \left(\frac{R_2}{R_1}\right)^{10/(T_2 - T_1)}$$

where

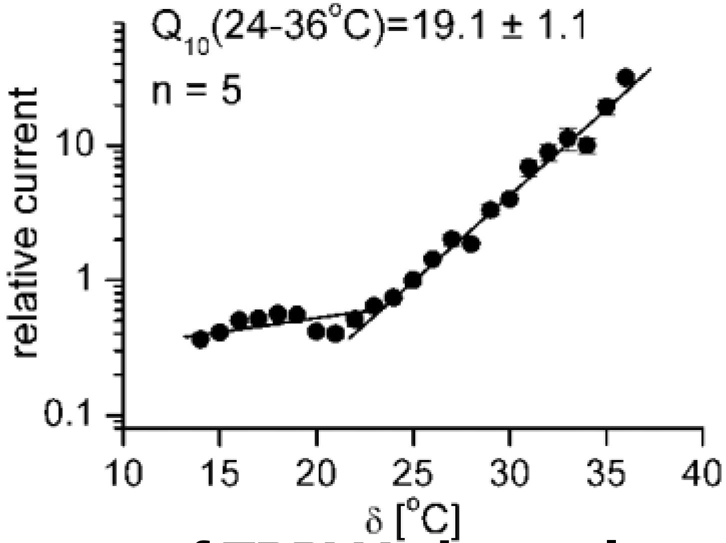
R is the rate

T is the temperature in Celsius degrees or kelvins.

Q_{10} of 2 means that a 10°C increase in temperature doubles the reaction rate

Typical range 1.5-3

More sensitive systems exist:



Membrane conductance of TRPV4 channels

“TRPV4 is a functional temperature-sensing channel in native endothelium”

(Watanabe, Hiroyuki, et al. "Heat-evoked activation of TRPV4 channels in a HEK293 cell expression system and in native mouse aorta endothelial cells." *Journal of Biological Chemistry* 277.49 (2002): 47044-47051.)

Fun Fact

de Pomerai et al. (2000, 2006) reported induction of heat shock proteins in the nematode *C. elegans* after extended (2 to 24 h) exposures to microwave energy.

This effect was eventually found to be associated with a small (0.2°C) temperature increase in
the irradiated samples (de Pomerai et al. 2006).

Relevance to Exposure Guidelines

- Arrhenius equation says that *any* temperature change will produce biological effects
  - some may be adaptive or not adverse to health
  - Some reported “nonthermal” effects might be thermally induced after all
- But… difficult to extrapolate to low exposures (no data)

Mechanism 2

(metric: temperature increase)

Thermal Damage

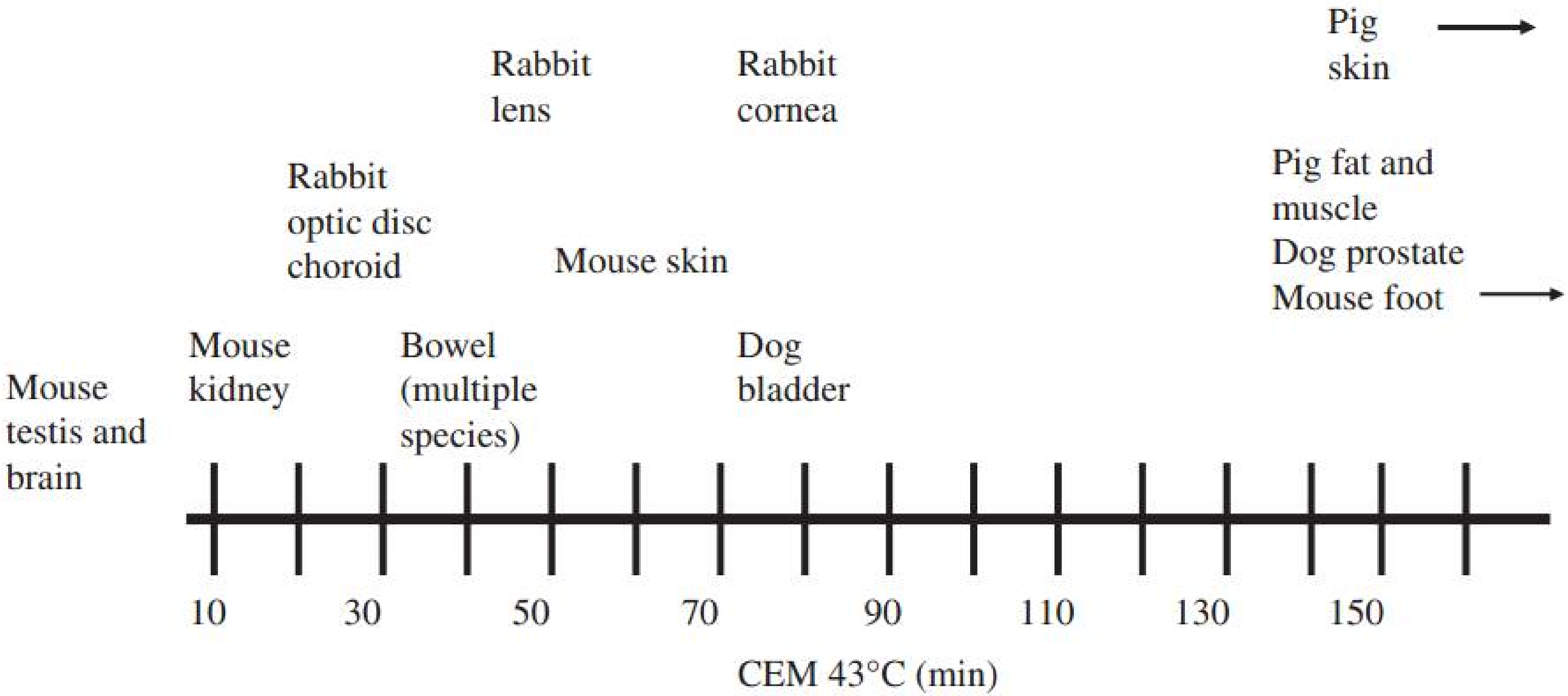
$$\frac{d\Omega}{dt} = A \exp\left(\frac{-E_a}{R_b T(t)}\right) \qquad \Omega = \int_0^{\tau} A \exp\left(\frac{-E_a}{R_b T(t)}\right) dt$$

Ω is the thermal damage index

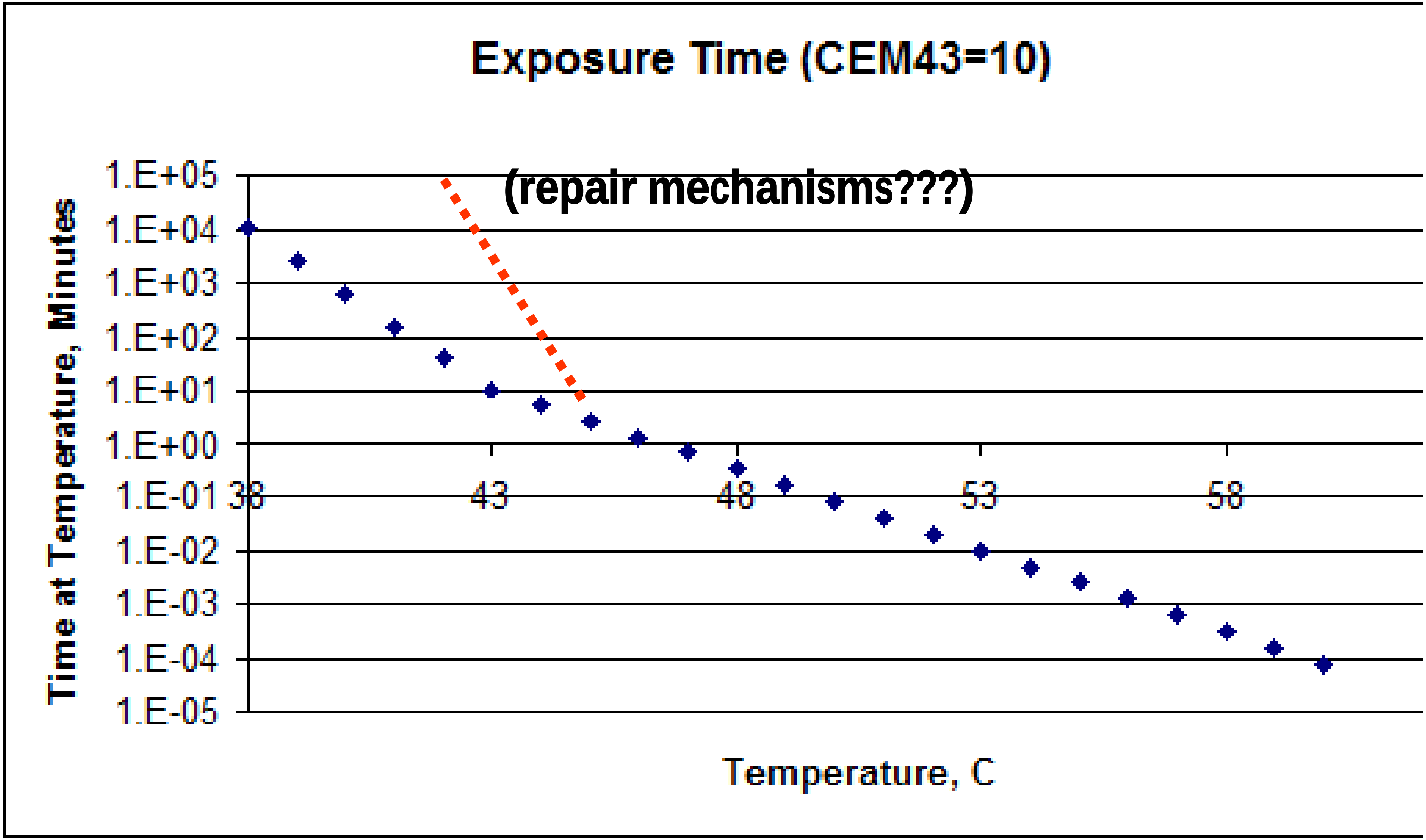
isoeffect dose cumulative equivalent min 43 (CEM43)

$$CEM43 = \Delta t R^{43-T_c}$$

R = 0.25 for T < 43 C
= 0.5 for T > 43 C



proximate ranking of thresholds for thermal damage of various tissues. Adapted from a figure c


Exposure Time (CEM43=10)
(repair mechanisms???)
Time at Temperature, Minutes
1.E+05
1.E+04
1.E+03
1.E+02
1.E+01
1.E+00
1.E-01
1.E-02
1.E-03
1.E-04
1.E-05
38
43
48
53
58
Temperature, C

Fun Fact

Tissues can sustain high temperature increases for short time periods

Gaps in Knowledge

- Data for thermal injury very scattered, not collected using consistent protocols
- Most data at thermal exposures far above safety limits
- Little (no?) basis to extrapolate to low thermal exposures.

Relevance to Guidelines

Nil unless limits are raised considerably

Mechanism 3

(metric: time rate of change of temperature)

Microwave Auditory Effect/Thermoelastic expansion

$$P_o = \frac{c_s \beta R \rho S}{CJ},$$

Po = sound pressure
R is the diameter of the heated region
S is the SAR in the exposed region,
β= volumetric thermal expansion coefficient of the tissue, c = velocity of sound
C is the heat capacity of the tissue, and J is the
mechanical equivalent of heat.

Microwave auditory effect

- Typical pulse intensity W/cm^2, μs pulses

Implications for Guidelines

Threshold hearing phenomenon - no apparent hazard.

Might be considered as an annoyance

Mechanism 4

(metric: time rate of change of temperature)

Thermally-induced membrane depolarization

High dT/dt will affect membrane activity (Wachtel)

Very high peak SAR's needed (tens of W/kg)

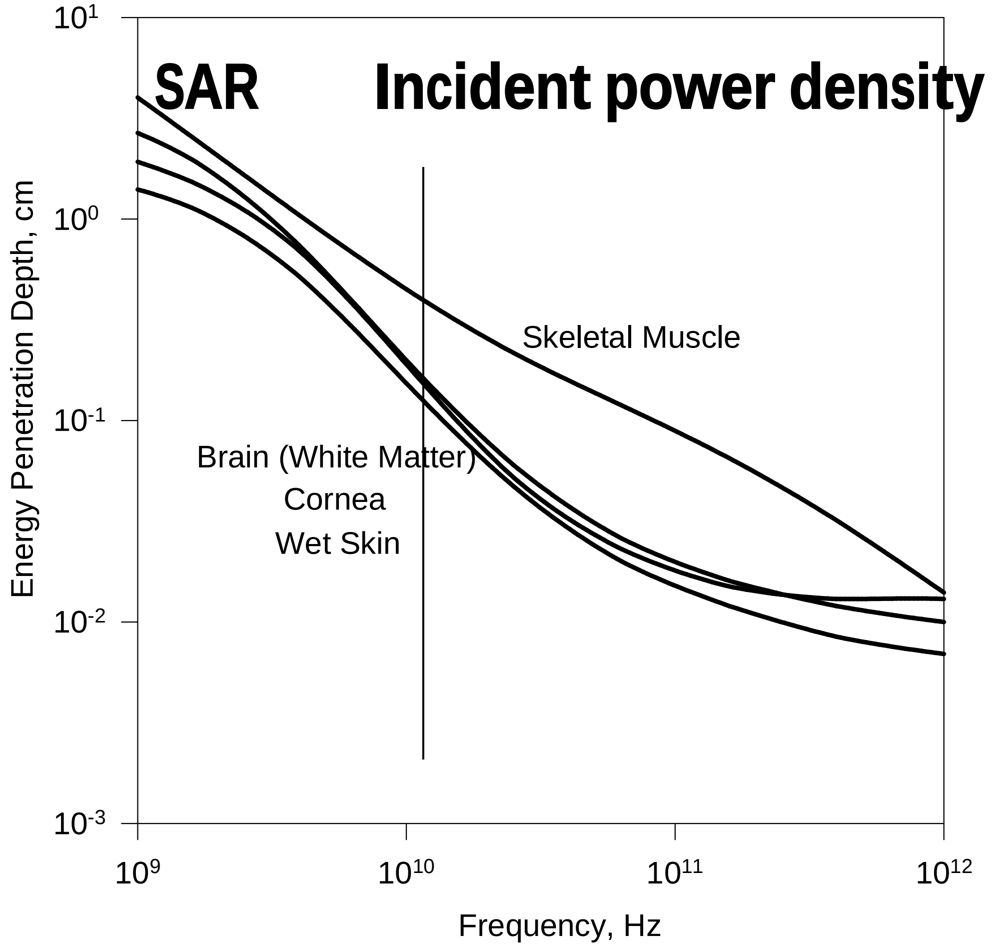
Not relevant to exposure limits

Thermal and Spatial Averaging

WHENCE 6 MINUTES?

"Our early C-95.4 Committee needed to recommend a time constant. My suggestion was 0.1 h. I was trying to come up with a number with as few significant figures as I could, considering the precision of what we were dealing with. A minute was too short — an hour was too long. But, alas, 0.1 h turned into 6 min, and 6 min implies an accuracy beyond the art…"

Tom Ely (1998) quoted in Foster et al, Bioelectromgnetics 19:420 – 428 (1998)


SAR
Incident power density
Energy Penetration Depth, cm
10^1
10^0
10^-1
10^-2
10^-3
Skeletal Muscle
Brain (White Matter)
Cornea
Wet Skin
10^9
10^10
10^11
10^12
Frequency, Hz

Bioelectromagnetics 19:42

Heating of Tissues by Microwaves: A Model Analysis

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Pennes' Bioheat Equation (1948)

Heat conduction

Blood flow

$$k\nabla^2 T - \rho_b \rho_t C_b m_b T + \rho_t SAR = C_t \, \rho_t \frac{\partial T}{\partial t}$$

T = tissue temperature
k = thermal conductivity of tissue (0.4 W/m °C)
SAR = microwave power deposition rate (W/kg)
C_b = heat capacity of blood (4000 W sec/kg°C)
C_t = heat capacity of tissue (4000 W sec/kg°C)
D_b = density of blood (1000 kg/m^3)
D_t = density of tissue (1000 kg/m^3)
m_b = volumetric perfusion rate of blood
(40 mL/100 g of tissue per min)

Limiting solutions to BHTE

Early transient period (heat storage term dominates)

$$\left.\frac{dT}{dt}\right)_0 = SAR / C_t$$

Steady state (convection term dominates)

$$T_{ss} = \frac{SAR}{\rho m_b C} + \frac{k\nabla^2 T}{\rho_b \rho_t C_b m_b}$$

↑ Usually smaller term

Two Time Scales in Bioheat Equation

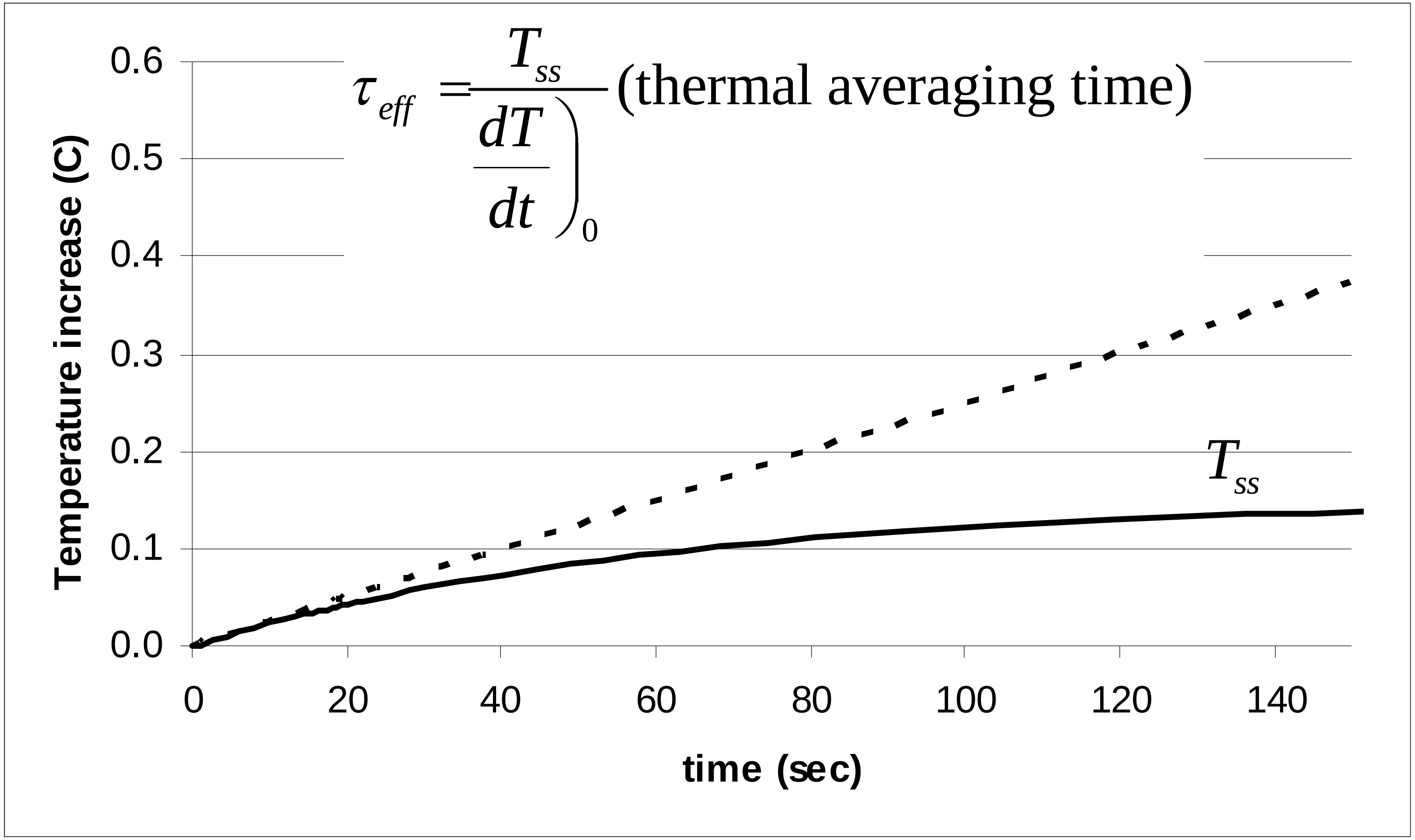
$$\tau_1 = \frac{1}{m_b \rho} \approx \ 60 \text{ sec} \ \ \text{(convection)}$$

$$\tau_2 = \frac{\rho C L^2}{k} \approx 800 \text{ sec (diffusion, for L = 1 cm)}$$

$$\approx 8 \text{ sec (diffusion, for L = 1 mm)}$$

Shorter time constant dominates

m_b = blood flow
ρ= tissue density
k = thermal conductivity of tissue
L = distance scale of heating (SAR)
C = specific heat of tissue



$\tau_{eff} = \frac{T_{ss}}{\left.\frac{dT}{dt}\right)_0}$ (thermal averaging time)
Temperature increase (C)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
T_{ss}
0
20
40
60
80
100
120
140
time (sec)

Green's function for BHTE

Steady-state spherical $$G(R) = \frac{\rho_t}{4\pi k_t R} e^{-R/R_{conv}}$$

$$R_{conv} = \frac{\sqrt{k_t}}{\rho\sqrt{m_b c}} \approx 1-2 \text{ cm}$$

R = distance from center of source

R_{conv} = distance scale for convection

ρ_t= tissue density

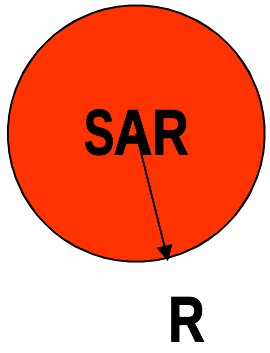
k_t = thermal conductivity of tissue

c = specific heat of tissue

m_b = blood perfusion rate

Thermal Response Time and Steady State Temp. Increase in Heated Tissue Sphere (heat conduction only)

Radius	Thermal relaxation time, sec	Maximum steady-state temperature increase above surrounding medium, °C (SAR 10 W/kg)
1 nm	3.5 ps	$8 \bullet 10^{-15}$
10 nm	0.35 ns	$8 \bullet 10^{-13}$
1 µm	3.5 µs	$8 \bullet 10^{-9}$
1 mm	3.5 s	0.008
1 cm	350 s	0.8



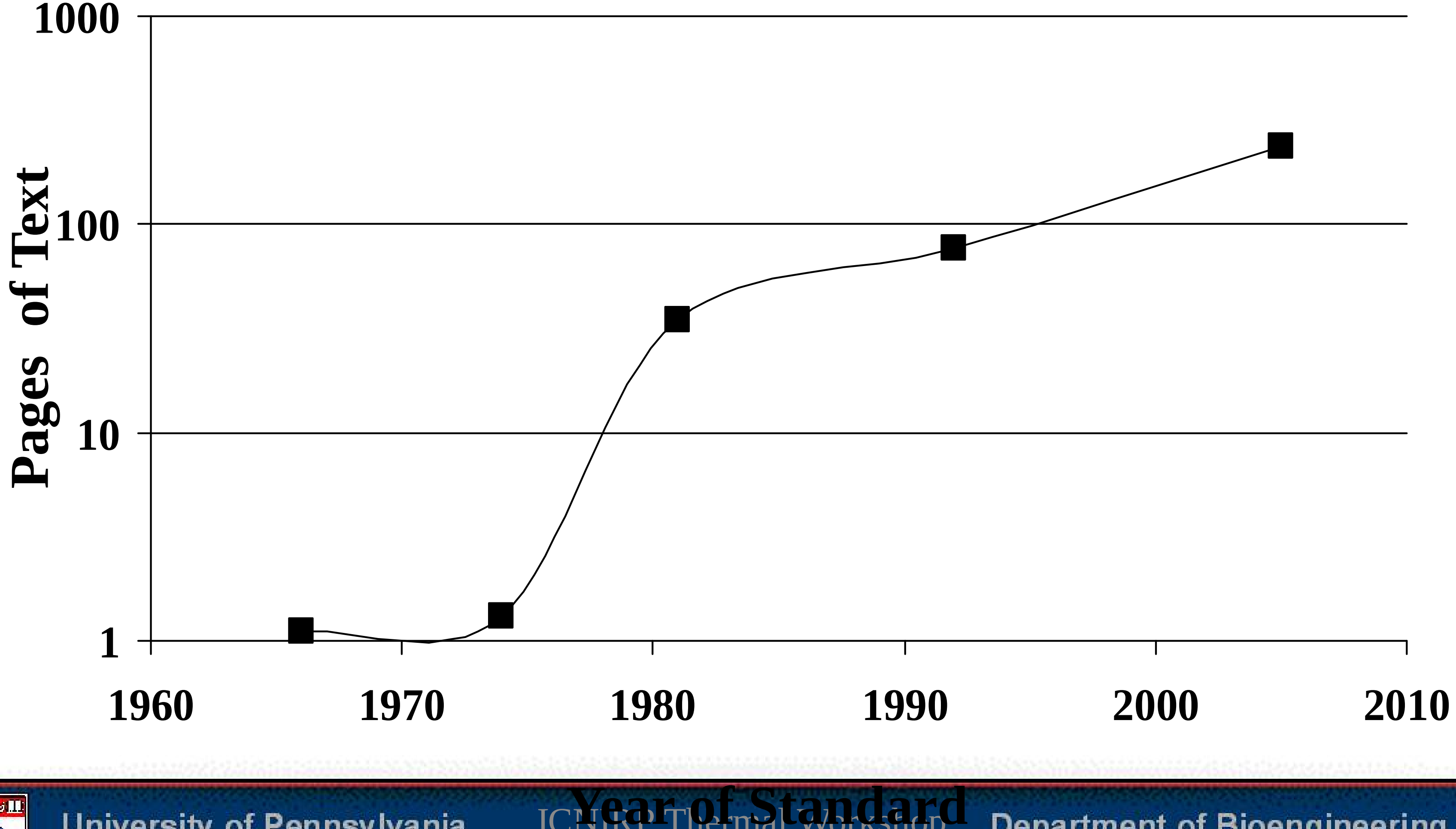
Bottom Line

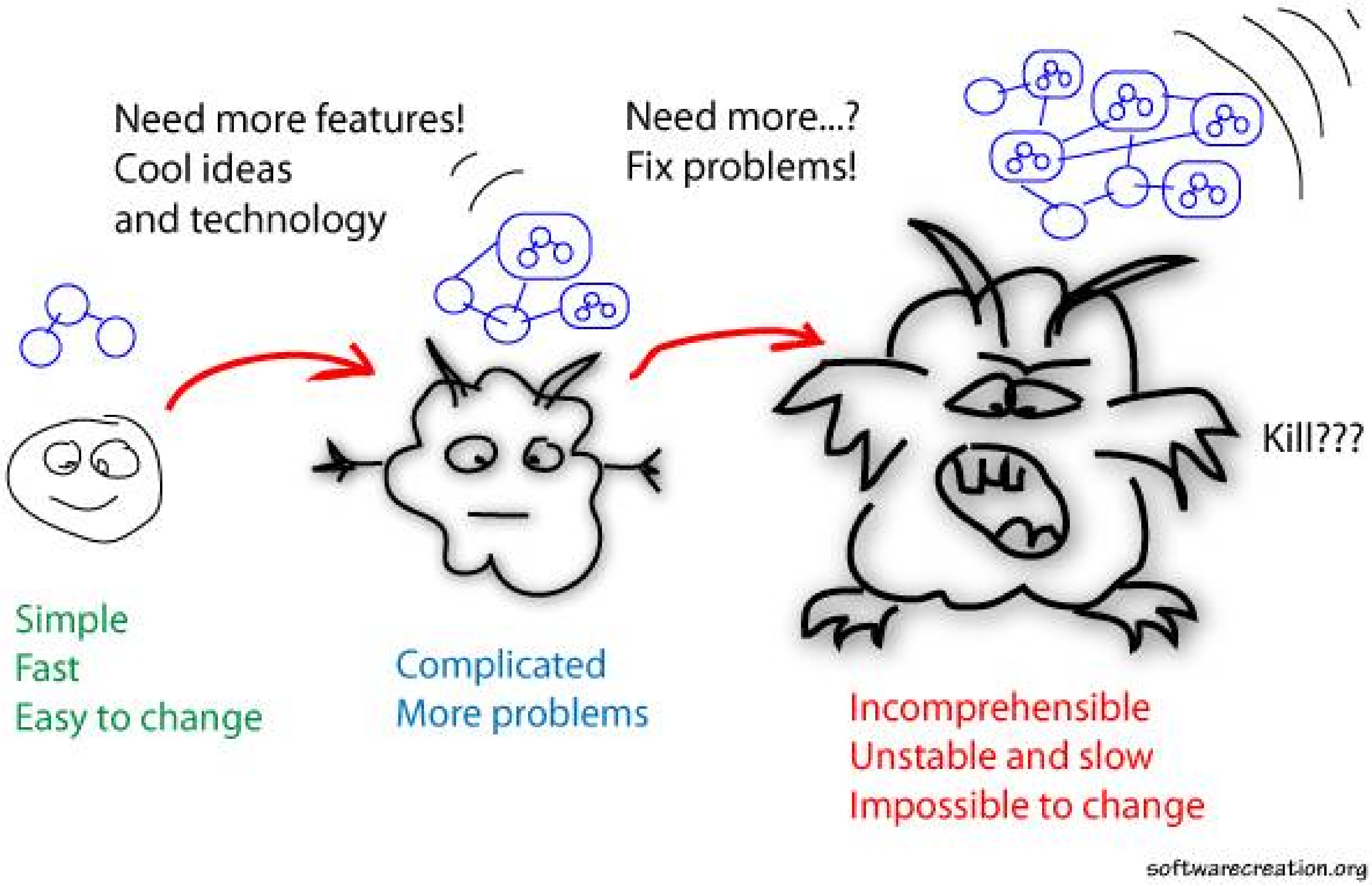
- Averaging distance is ≈ 1-2 cm (steady state heating)

  Thermal conduction is nature's way of averaging thermal exposure
- Useful definition of averaging time: steady state temperature increase/ peak SAR

How much precision is needed and at what cost in complexity?

Does ANSI C95.1 Follow Moore's Law?




Need more features!
Cool ideas
and technology
Need more...?
Fix problems!
Kill???
Simple
Fast
Easy to change
Complicated
More problems
Incomprehensible
Unstable and slow
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