Thermal Biophysics Lectures

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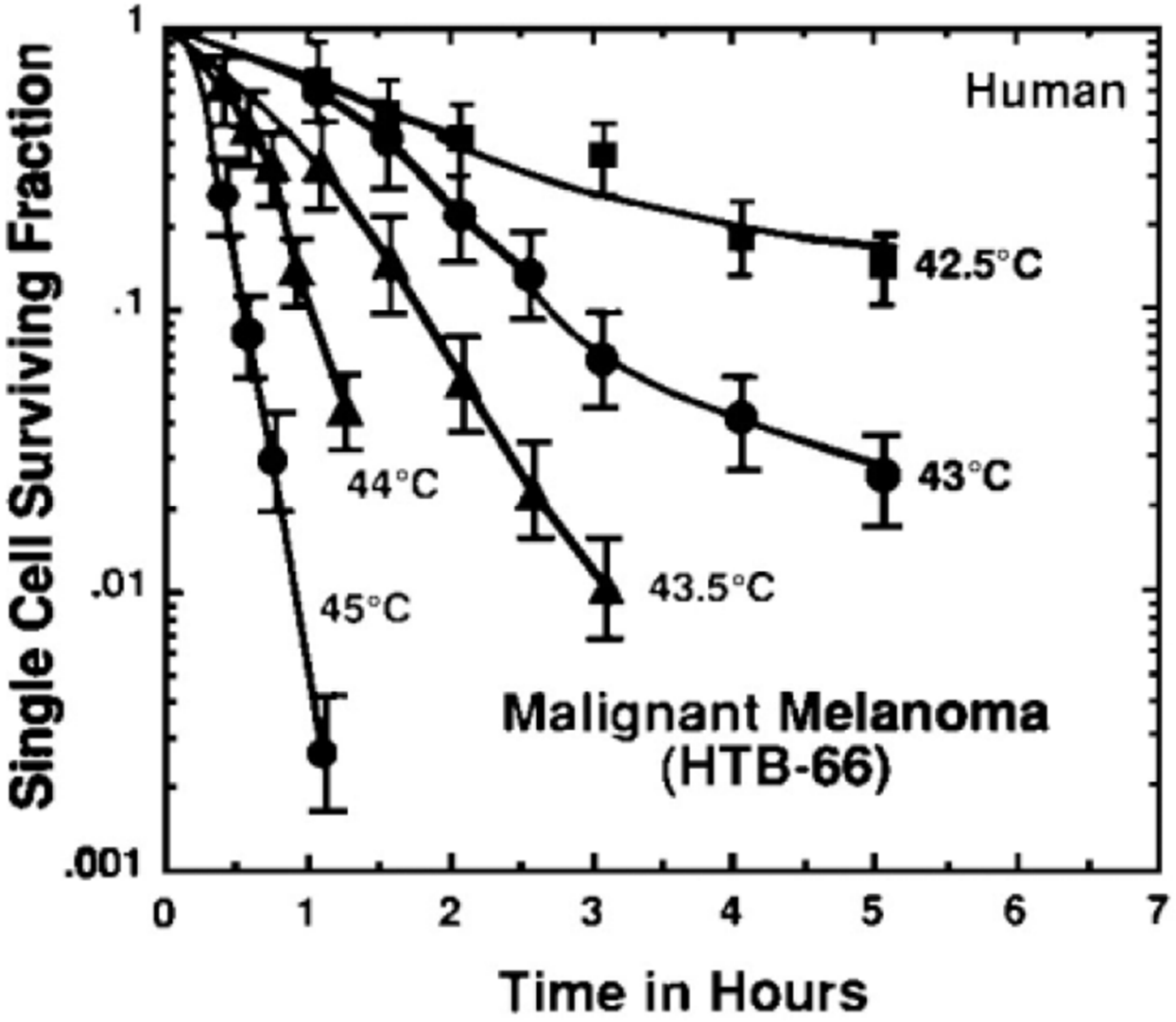
Big Picture

- **Lecture 1: Biology/Rationale/Nomenclature**
- Lecture 2: Blood Flow/Modelling
- Lecture 3: Energy Delivery
- Lecture 4: Thermometry/Treatment monitoring

Review

- Key physical/biological concepts in thermal therapy
- Hyperthermia/High temperature thermal therapy
- Cell-survival curves
- Cell death at mild & high temperatures
- Thermotolerance & heat shock proteins

Cell Survival



Dewhirst, Int J Hyperthermia, 2003

Question

BIOLOGICAL EFFECTS OF HEAT

Question

HEAT SHOCK PROTEINS

Lecture 3

BLOOD FLOW & MODELLING THERMAL THERAPY

Question

BLOOD FLOW IN THERMAL THERAPY

Blood Flow & Thermal therapy

- Most important physiological parameter governing spatial temperature distribution for hyperthermic temperatures
- Spatially variable
- Influence depends on vessel size, distribution, direction of blood flow
- Temperature dependent
- Differential response in tumours & normal tissue

Blood Flow & Heating

- Extensive body of literature by C.W. Song
- Mostly pertains to hyperthermia

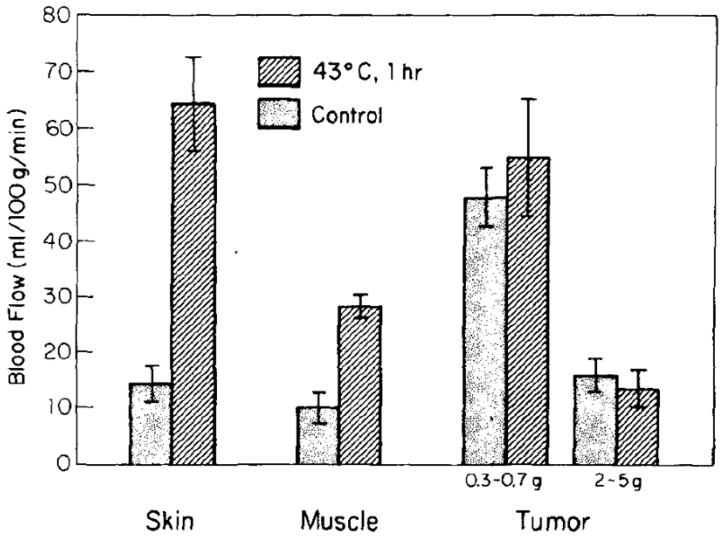


FIGURE 4. The bars show the average blood flow in skin, muscle, and tumors with or without heating at 43°C for 1 hr. The skin and muscle are those adjacent to tumor. The tumor blood flow is the average of that in 0.3–0.7 g and 2–5 g tumors shown in FIGURES 1 and 2. Errors are ±1 standard error.

TABLE 1

VASCULAR CHANGE BY HYPERTHERMIA (43°C FOR 1 HR)*

	Vascular Volume (ml/100 g)		Vascular Permeability (ml/100 g per hr)		Blood Flow (ml/100 g per min)	
Tissue	Control	Heated	Control	Heated	Control	Heated
Skin						
Normal	0.59 ± 0.06	1.43 ± 0.17	1.57 ± 0.14	4.61 ± 0.81	7.82 ± 0.76	29.13 ± 3.39
Near Tumor					14.39 ± 3.37	64.61 ± 8.38
Muscle						
Normal	0.44 ± 0.03	0.65 ± 0.05	0.52 ± 0.04	1.20 ± 0.16	4.97 ± 0.55	14.61 ± 1.75
Near Tumor					10.26 ± 2.71	28.45 ± 2.12
Tumor						
0.3–0.7 g	0.87 ± 0.10	0.92 ± 0.11	10.05 ± 0.94	10.21 ± 0.83	48.08 ± 5.39	55.55 ± 10.41
2–5 g	0.79 ± 0.11	0.77 ± 0.09	8.34 ± 0.96	8.59 ± 0.78	15.66 ± 3.01	14.02 ± 3.37

*The values are means of more than 10 determinations ± standard error. The weights are wet weight. The vascular volume and vascular permeability are not determined for skin and muscle adjacent to tumor.

- Tumours (Walker 256 carcinoma) implanted on thigh leg of rat
- legs heated in water bath at 43°C for 1 hour
- Vascular volume and permeability measured using ^{51}CR labelled RBC's and ^{125}I labelled albumin
- Blood flow measured using radioactive microspheres

Song et al, NYAS, 1980

Normal Tissues

- Typically measured using radioactive microspheres

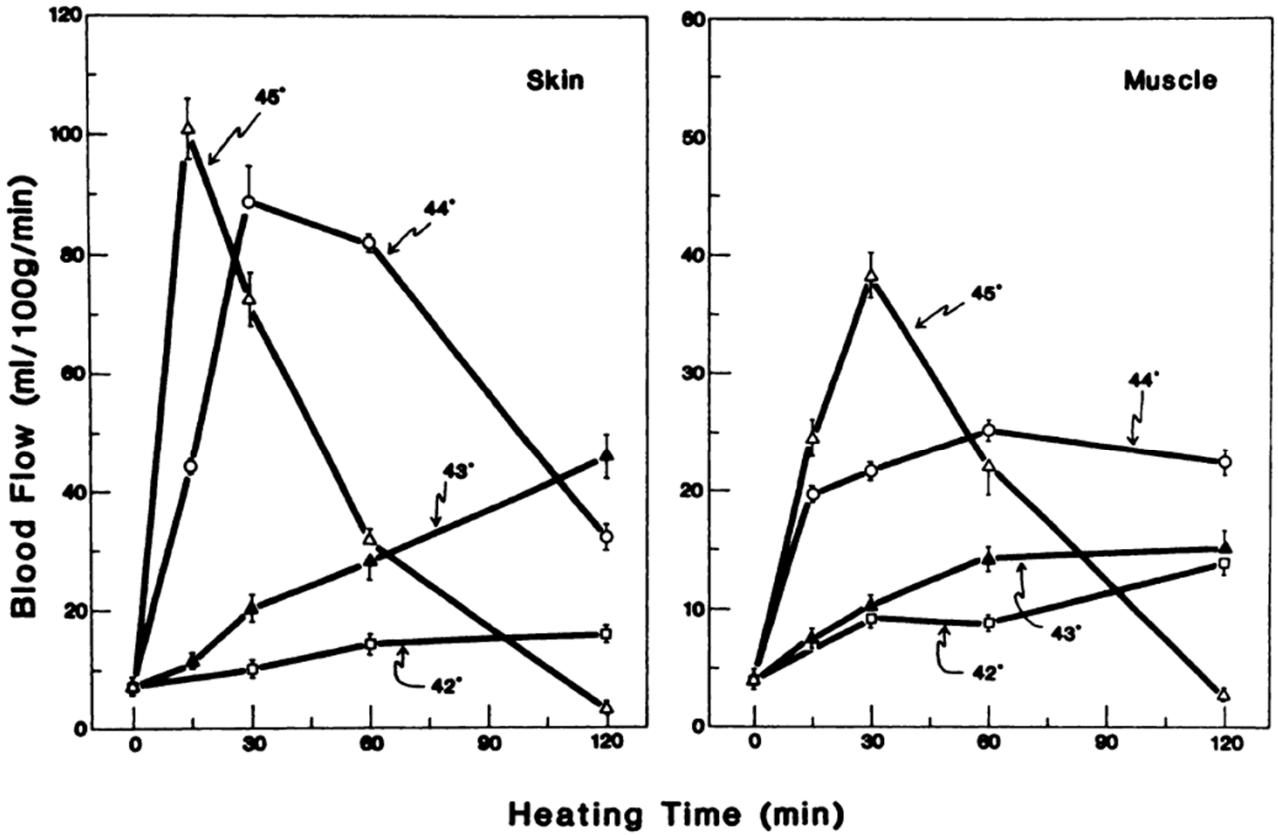


Chart 1. Changes in blood flow in the skin and muscle of normal leg of SD rat during heating at various temperatures for 120 min. *Points*, average of 8 to 12 measurements; *bars*, S.E. (49).

Song, Cancer Res, 1984

Tumours

- Different response from normal tissues
- Reduced ability to compensate for temperature elevation by increasing blood flow
- Initially proposed as the mechanism whereby tumours would be more sensitive to heating in vivo

Table 1

Heat dose for vascular stasis in tumors

Tumor	Animal	Temperature	Time	Reference
Walker carcinoma 256	Rat	>43.0°	1 hr	Song *et al.* (46)
Walker carcinoma 256	Rat	>43.0°	1 hr	Gullino *et al.* (19)
Yoshida sarcoma	Rat	42.0°	1 hr	Dickson and Calderwood (6)
BA-1112 rhabdomyosarcoma	Rat	42.5°	40 min	Emami *et al.* (9)
BA-1112 rhabdomyosarcoma	Rat	40.0°	1 hr	Endrich *et al.* (11)
BA-1112 rhabdomyosarcoma	Rat	42.5°	2.5 hr	Reinhold *et al.* (36)
DS carcinoma	Rat	42.0°	30 min	Vaupel *et al.* (60)
13762A carcinoma	Rat	43.5°	1 hr	Rappaport and Song (35)
SCK carcinoma	Mouse	40.5°	30 min	Song *et al.* (47)
RIF-1 tumor	Mouse	42.5°	1 hr	Song *et al.*[a]
Mammary carcinoma	Mouse	42.0°	40 min	Bicher *et al.* (3)
Ependymoblastoma	Mouse	42.0°	1 hr	Sutton (57)
SAFA tumor	Mouse	42.5°	1 hr	Stewart and Begg (52)
CAMT	Mouse	42.5°	1 hr	Stewart and Begg (52)
CANT	Mouse	42.5°	1 hr	Stewart and Begg (52)
SAF	Mouse	42.5°	1 hr	Stewart and Begg (52)
Squamous carcinoma	Hamster	43.0°	30 min	Eddy (8)
VX2 carcinoma	Rabbit	42.5°	40 min	Dudar and Jain (7)

[a] Presented at the Fourth International Symposium on Hyperthermic Oncology, July 2–6, 1984, Aarhus, Denmark.

Song, Cancer Res, 1984

High Temperatures?

EFFECTS OF PHYSICAL PARAMETERS ON HIGH TEMPERATURE ULTRASOUND HYPERTHERMIA

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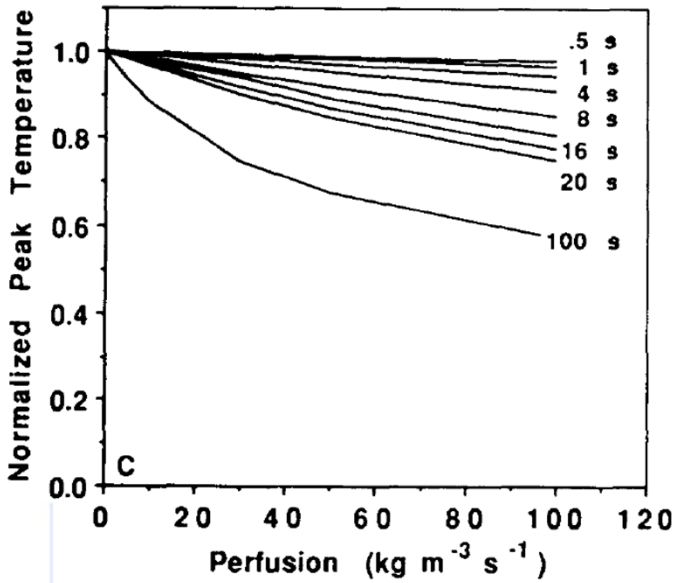
(*Received* 8 *June* 1989; *in final form* 23 *November* 1989)

Abstract—The purpose of this research was to investigate the feasibility of inducing perfusion independent, predictable therapeutic thermal dose using high power ultrasonic pulses. Computer simulations were used to



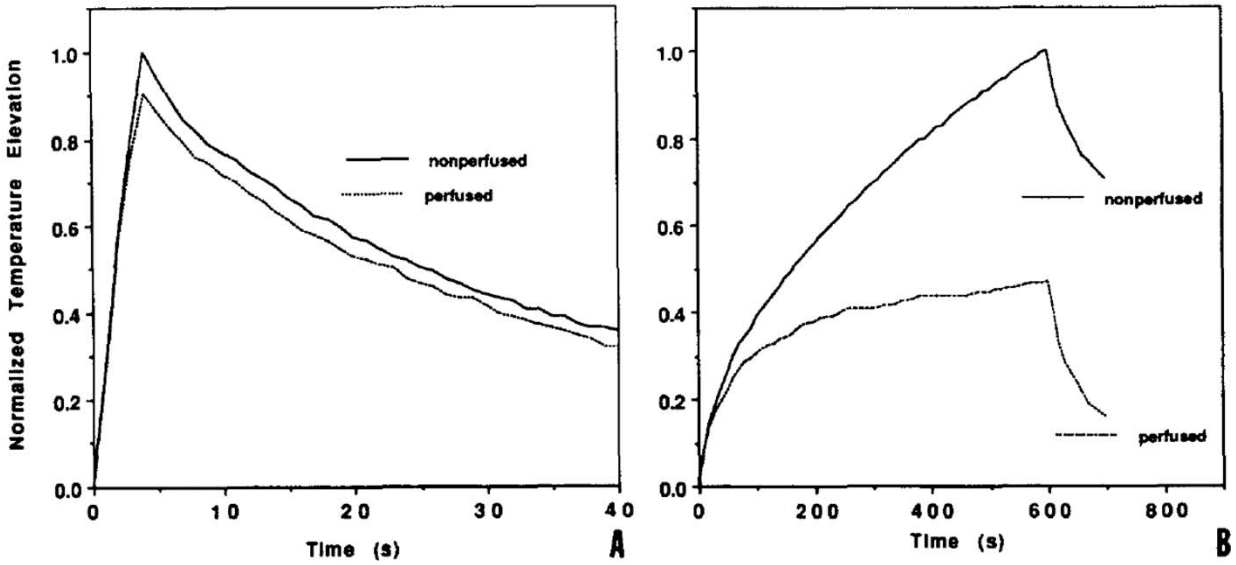


Fig. 13. Example from *in vivo* dog thigh study of perfusion effects on pulse length. (A) Four-second pulses given in perfused and nonperfused tissue. (B) Ten-minute pulses in the same location. In these experiments the same transducers were used as in Fig. 12.

UMB, 1990

Question

- Given that most of the subtle biological and physiological processes associated with hyperthermic temperatures disappear above 46-48°C, why bother studying them?

Lecture 3

MODELLING THERMAL THERAPY

Modelling Thermal Therapy

- Understand influence of physical parameters on heating
- Design heating strategies & device configurations
- Study delivery of heat to target and surrounding tissues
- Bioheat Transfer Equation one of the most widely used models

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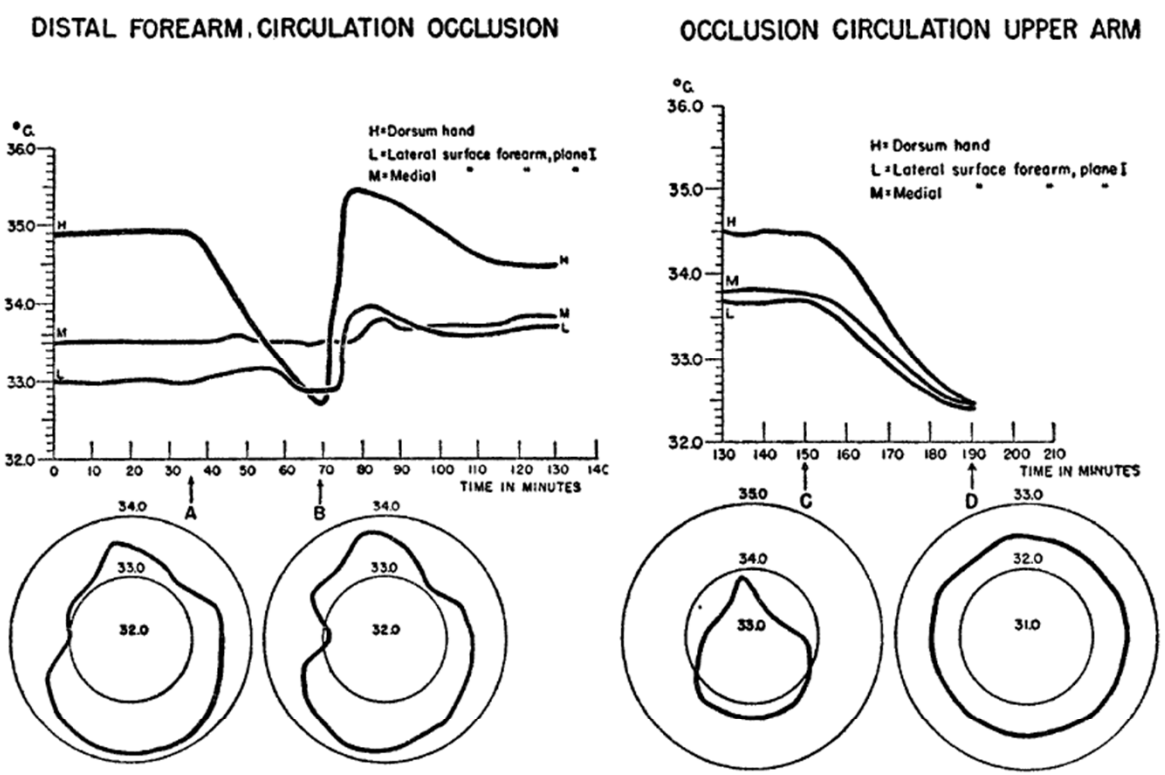
PHYSIOLOGY

VOLUME 1 *AUGUST 1948* NUMBER 2

Analysis of Tissue and Arterial Blood Temperatures in the Resting Human Forearm

HARRY H. PENNES, *From the Department of Neurology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute, New York.*

- Studied the temperature distributions in the resting forearm
- Experiments performed on male subjects from the ward population of the Neurological Institute
- Needles inserted into the forearm with thermocouples to record T(t) without anasthesia, and maintained for hours
- Radiometer measurements of surface temperature made
- Effects of blood flow occlusion studied



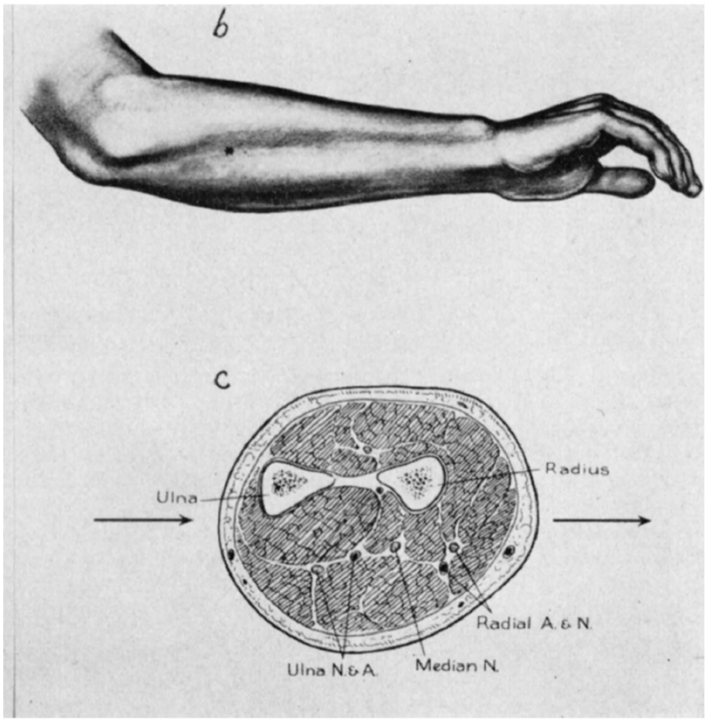
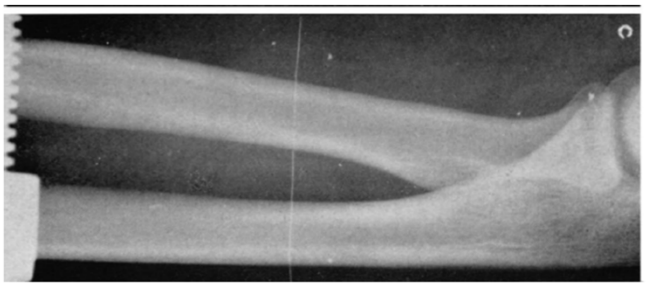
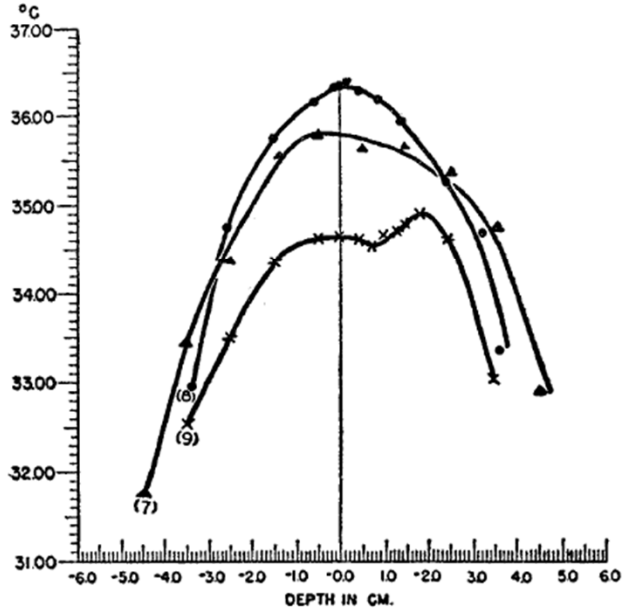


Fig. 13. COMPARISON OF EFFECTS of occlusion of circulation at distal forearm and at upper arm, in same subject, on skin temperature of the proximal forearm and hand. Note only minor changes in surface temperature distribution between *A* and *B* at conclusion of period of occlusion at distal forearm. Virtual isothermal state at *D* at conclusion of period of occlusion upper arm.





Eq. 4 $$h_b = V \cdot s\,(\theta_a - \theta)$$

The general differential equation of heat conduction is in cylindrical coordinates:

Eq. 5 $$cp\,\frac{\partial\theta}{\partial t} = -K\left[\frac{\partial^2\theta}{\partial r^2} + \frac{1}{r}\frac{\partial\theta}{\partial r} + \frac{1}{r^2}\frac{\partial^2\theta}{\partial\phi^2} + \frac{\partial^2\theta}{\partial Z^2}\right] + h_m + h_b$$

Eq. 6 $$-K\left[\frac{d^2\theta}{dr^2} + \frac{1}{r}\frac{d\theta}{dr}\right] = h_m + h_b \qquad \frac{\partial\theta}{\partial\phi},\ \frac{\partial^2\theta}{\partial Z^2} = 0$$

$$\theta = \left[\theta_s - \frac{(h_m + h_b)}{4K}R^2\right] - \frac{(h_m + h_b)}{4K}r^2$$

Solution for h_m, h_b uniform

Surface temperature

Eq. 8 $$\frac{d^2\theta}{dr^2} + \frac{1}{r}\frac{d\theta}{dr} + a\theta = b$$

which is a Bessel's equation of zero order in which

$$a = \frac{V \cdot s}{K} \qquad b = V \cdot s\,\frac{\theta_a - h_m}{K}$$

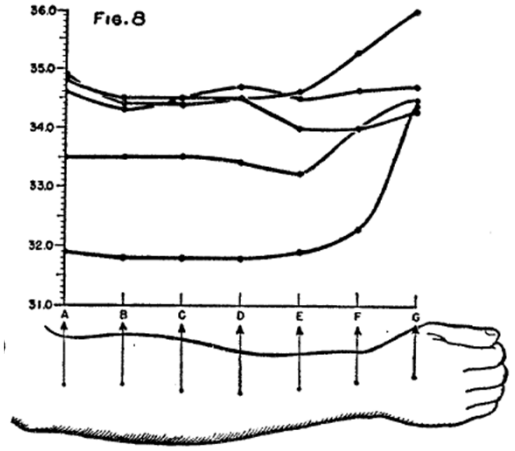
Eq. 9 $$\theta = \frac{\left(\theta_s - \frac{b}{a}\right)}{J_0(i\sqrt{a}\,R)}\,J_0(i\sqrt{a}\,r) + \frac{b}{a}$$

Solution for h_m constant
H_b function of θ

0th order Bessel Function (1st kind)

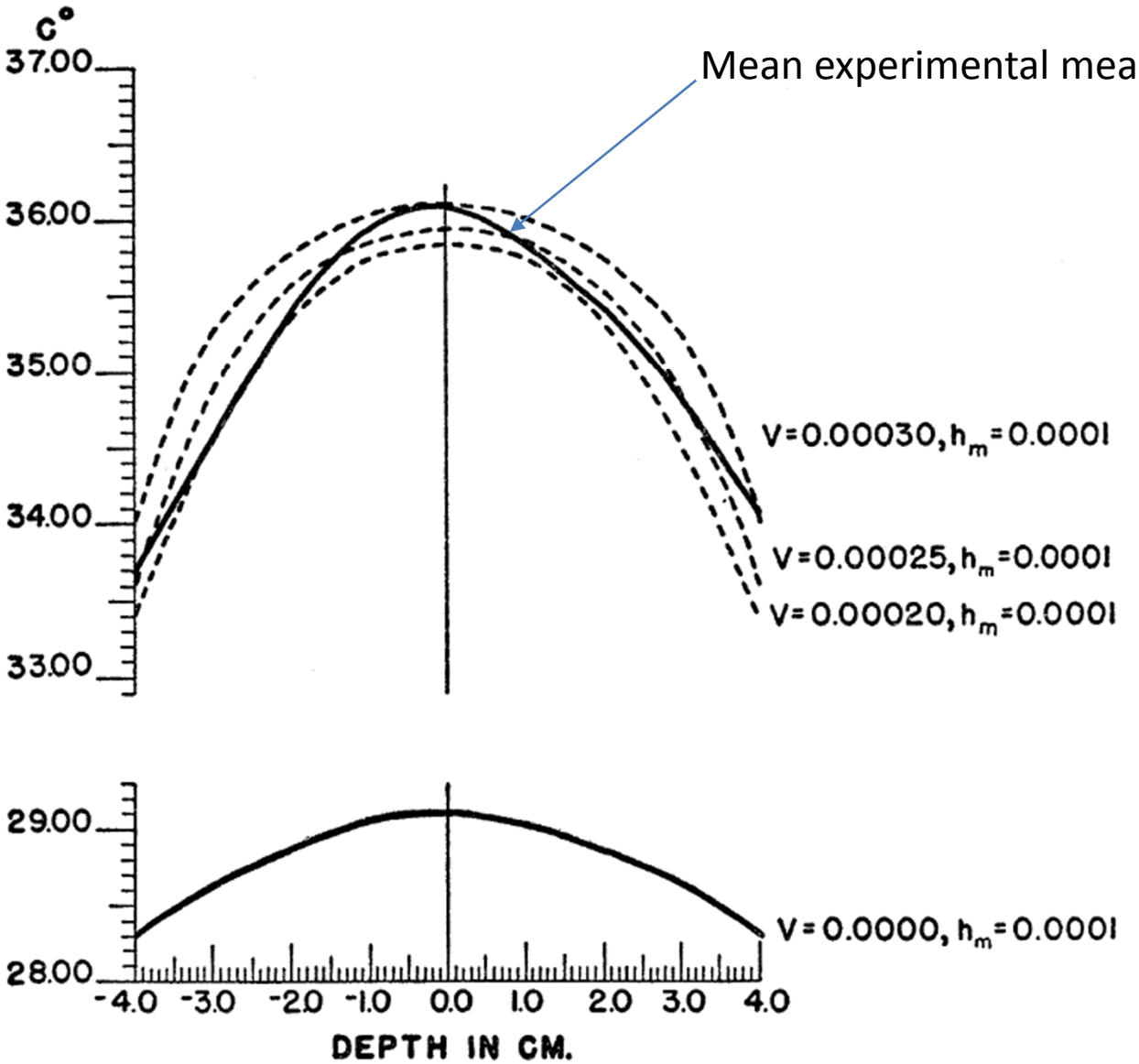
Eq. 10 $$-K\frac{d\theta}{dr} = E(\theta_s - \theta_E)$$

Eq. 11 $$\theta_s = \frac{\frac{b}{K\sqrt{a}}\left[-iJ_1\,(i\sqrt{a}\,R)\right] + 1.21EJ_0(i\sqrt{a}\,R)\theta_E}{K\sqrt{a}\left[-iJ_1\,(i\sqrt{a}\,R)\right] + 1.21EJ_0(i\sqrt{a}\,R)}$$



θ = tissue temperature, °C.
θ_a = arterial blood temperature, °C.
θ_v = venous blood temperature, °C.
r = normal to cylindrical isothermal surface (radial distance from axis), cm.
R = radius of cylinder, cm.
K = specific thermal conductivity tissue in grams cal. per cm.² per sec. per °C. per cm.

E = Newton cooling constant in grams cal. per cm.² per sec. per °C.
h_m = rate of tissue heat production in grams cal. per cm.³ per sec.
h_b = rate of heat transfer from blood to tissue in grams cal. per cm.³ per sec.
V = Volume flow of blood through tissue in grams per cm.³ per sec.
s = specific heat blood in grams cal. per gram per °C.



Mean experimental measurements from 9 subjects

$$\theta = \frac{\left(\theta_s - \frac{b}{a}\right) J_o(i\sqrt{a}\, r)}{J_o(i\sqrt{a}\, R)} + \frac{b}{a}$$

$$\theta = \left[\theta_s - \frac{(h_m + h_b)}{4K} R^2\right] - \frac{(h_m + h_b)}{4K} r^2$$

Fig. 16. MEAN EXPERIMENTAL and theoretical curves.

The Pennes Model (Bio-heat transfer equation):

❖ describes heat transfer in tissue

$$\rho c \frac{\partial T}{\partial t} = \nabla k \bullet \nabla T + \underbrace{(\rho c)_b \omega_b (T_a - T)}_{\text{contribution of flowing blood}} + q_m$$

k – thermal conductivity

T – temperature

ρ – tissue density

c – heat capacity

b - blood

ω – blood perfusion

a – arterial

q_m – metabolic volumetric heat

Arkin H, Xu LX and Holmes KR, Recent developments in modeling heat transfer in blood perfused tissues. *IEEE Trans Biomed Eng* **41**(2)**:** 97-107, 1994.

BHTE

Assumptions:

- energy exchange between blood vessels and the surrounding tissue occurs mainly across the wall of capillaries
- Capillary blood and tissue are at equilibrium
- Blood enters an imaginary pool (capillary bed) at the temperature of major supply vessels (Ta) and immediately thermally equilibrates with the surrounding tissue, blood then exits the pool and enters the venous circulation at tissue temperature (T)

Drawbacks:

- non directional blood flow and does not take into account the countercurrent heat exchange between an artery and adjacent vein
- there is no distinction between large and small vessels
- tissues and vessels are not treated as separate entities – note: There are thermal variations in large blood vessels
- Largest set back is that BHT, like many other variations, are modeled after normal tissues and the lack of knowledge regarding tumuor vasculature makes it difficult to model blood flow and thermal distributions within tumour tissues.

Mechanisms of Heat Exchange (Croft 1989)

Heat Conduction

-Transfer of heat through a medium through molecular interactions

-Heat flow proportional to the temperature difference & area

$$Q_x = -kA\frac{\partial T}{\partial x}$$

Q: rate of heat flow (J/s), A: Area normal to direction of heat flow (m^2), dT/dx: temperature gradient along x (K/m), k: thermal conductivity (W/mK)

Heat Convection

-Transfer of heat through motion of molecules (liquids/gases or solid/fluid interface)

-Heat flow proportional to temperature difference between solid and fluid and contact area

$$Q_x = hA(T_s - T_f)$$

Q: rate of heat flow (J/s), A: contact area (m^2), h: heat transfer coefficient (W/m^2K)

Radiation

- transmission of energy through EM waves $Q = E\sigma T^4$

Heat Generation

-Units of W; depends on source of energy being used.

Croft 1989, Heat Transfer Calculations using finite difference equations

Heat Transfer Equation

-Q_inc: net increase in internal energy in a volume element in time dt

-Q_flow : total heat absorbed in a volume element (difference between heat flowing in and out) in time dt

$$\partial Q_{xnet} = k(\partial x \partial y \partial z)\frac{\partial^2 T}{\partial x^2}\cdot \partial t$$

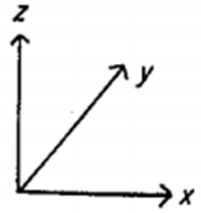
$$\partial Q_{flow} = k(\partial x \partial y \partial z)\left[\frac{\partial^2 T}{\partial x^2}+\frac{\partial^2 T}{\partial y^2}+\frac{\partial^2 T}{\partial z^2}\right]\cdot \partial t$$

$$\partial Q_{gen} = H\cdot(\partial x \partial y \partial z)\cdot \partial t$$

$$\partial Q_{inc} = \rho\cdot(\partial x \partial y \partial z)\cdot c_p \cdot \frac{\partial T}{\partial t}\partial t$$

$$\partial Q_{inc} = \partial Q_{flow} + \partial Q_{gen}$$

$$\rho c_p \frac{\partial T}{\partial t} = k\nabla^2 T + H \quad [W/m^3]$$



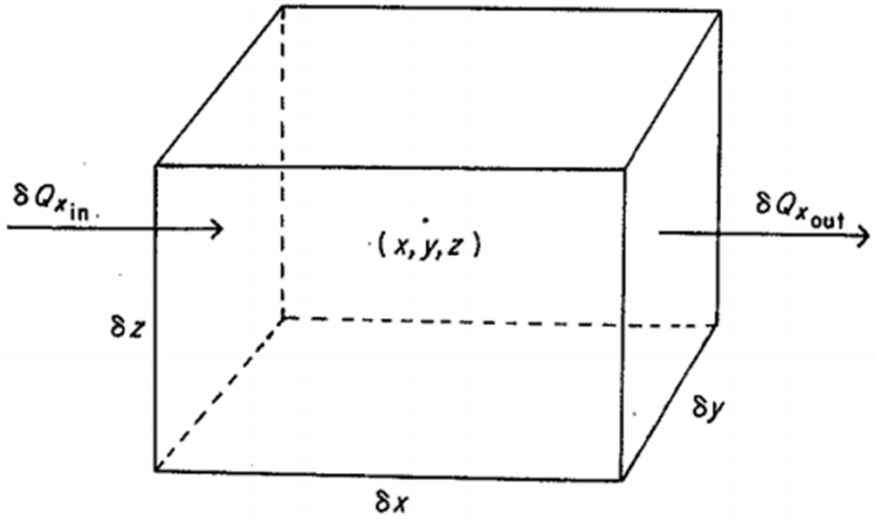


FIG. 2.3. Heat conduction through a differential element.

Croft 1989, Heat Transfer Calculations using finite difference equations

Finite Differences

-Q_inc: net increase in internal energy in a volume element in time dt

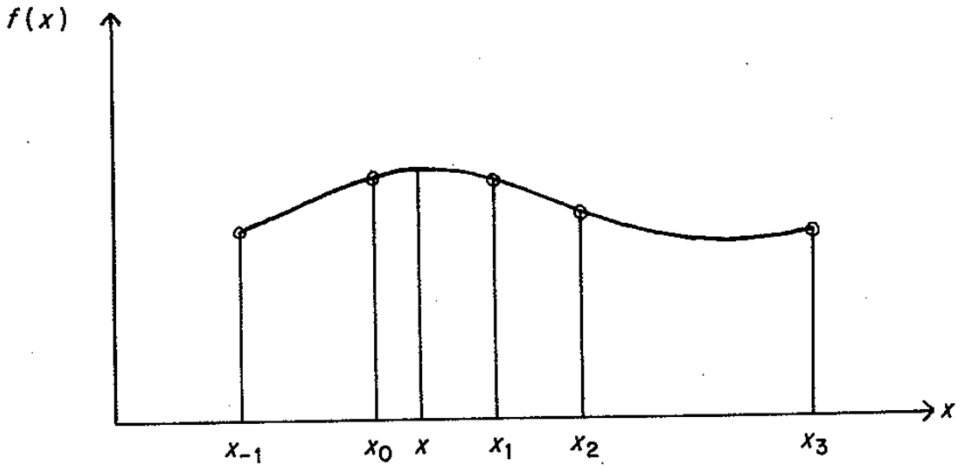
-Q_flow : total heat absorbed in a volume element (difference between heat flowing in and out) in time dt

$$\left.\frac{\partial T}{\partial x}\right|_{x=x_0} = \frac{T_{1/2} - T_{-1/2}}{\Delta x}$$

$$\frac{\partial^2 T}{\partial x^2} = \frac{\partial}{\partial x}\left[\left.\frac{\partial T}{\partial x}\right|_{x=x_0}\right]$$

$$= \frac{\left.\frac{\partial T}{\partial x}\right|_{x=x_{1/2}} - \left.\frac{\partial T}{\partial x}\right|_{x=x_{-1/2}}}{\Delta x}$$

$$= \frac{T_1 - 2T_0 + T_{-1}}{\Delta x^2}$$



Croft 1989, Heat Transfer Calculations using finite difference equations

Finite Differences for Transient Problem

$$\rho c_p \frac{\partial T}{\partial t} = k\nabla^2 T + H$$

$$\frac{1}{\alpha}\frac{\partial T}{\partial t} = \nabla^2 T + H \qquad \alpha = \frac{k}{\rho c}$$

Explicit formulation (Forward difference in time)

$$\frac{1}{\alpha}\left(\frac{T_P^{'} - T_P}{\Delta t}\right) = \frac{T_0 - 2T_P + T_I}{\Delta^2} + \frac{T_E - 2T_P + T_W}{\Delta^2} + \frac{T_N - 2T_P + T_S}{\Delta^2}$$

$$\frac{1}{F_0}T_P^{'} = \left(T_O + T_I + T_E + T_W + T_N + T_S\right) - \left(6 - \frac{1}{F}\right)T_P$$

$$F_o = \frac{\alpha \Delta t}{\Delta^2}$$

For most tissues, Δt = 1s, and Δ = 1 mm achieves convergence (1/Fo < 6)

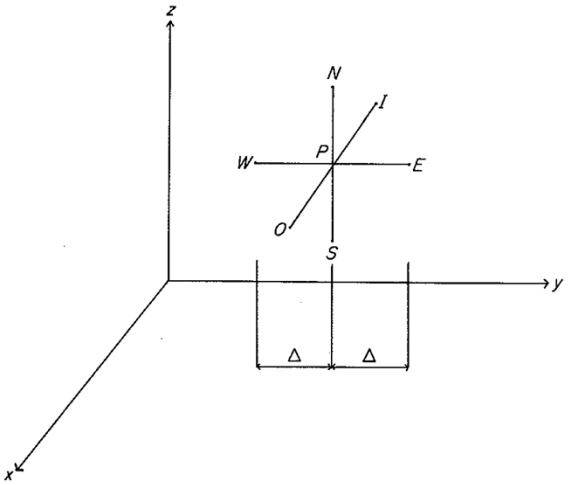


FIG. 3.4. Typical point *P* with its six neighbours in a 3-D cartesian coordinate region with uniform grid spacing.

Implicit formulation

$$\frac{1}{\alpha}\left(\frac{T_P^{t+1} - T_P}{\Delta t}\right) = \frac{T_O^{'} - 2T_P^{'} + T_I^{'}}{\Delta^2} + \frac{T_E^{'} - 2T_P^{'} + T_W^{'}}{\Delta^2} + \frac{T_N^{'} - 2T_P^{'} + T_S^{'}}{\Delta^2}$$

$$-\frac{1}{F_0}T_P = \left(T_O^{'} + T_I^{'} + T_E^{'} + T_W^{'} + T_N^{'} + T_S^{'}\right) - \left(6 + \frac{1}{F_0}\right)T_P^{'}$$

Croft 1989, Heat Transfer Calculations using finite difference equations

Finite Differences for Transient Problem

$$\rho c_p \frac{\partial T}{\partial t} = k\nabla^2 T + H$$

$$\frac{1}{\alpha}\frac{\partial T}{\partial t} = \nabla^2 T + H \qquad \alpha = \frac{k}{\rho c}$$

Generalized formulation

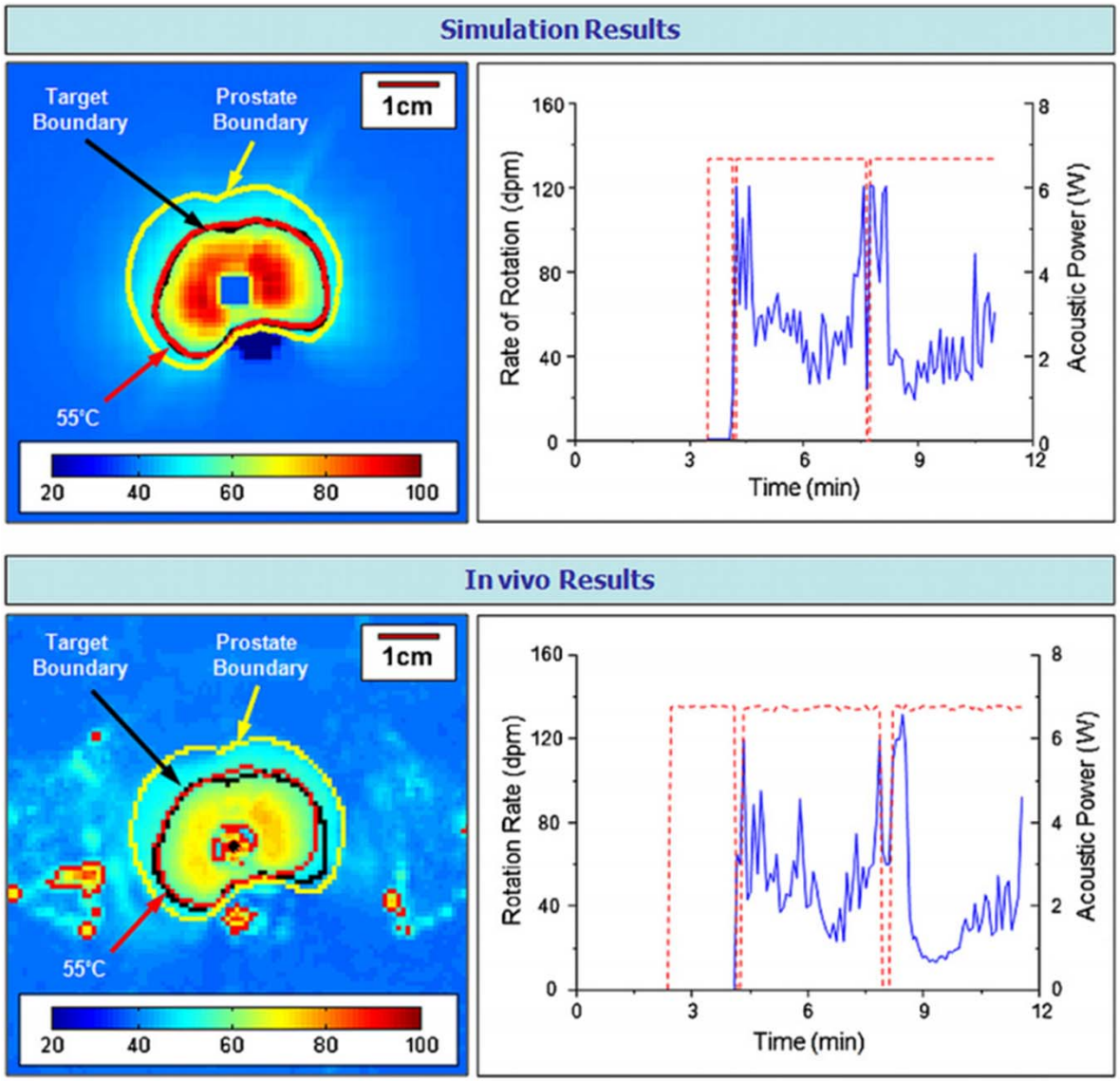
$$\lambda\left(T_O^{'} + T_I^{'} + T_E^{'} + T_W^{'} + T_N^{'} + T_S^{'}\right) - \left(6\lambda + \frac{1}{F_0}\right)T_P^{'}$$

$$= -(1-\lambda)(T_O + T_I + T_E + T_W + T_N + T_S) + \left(6(1-\lambda) - \frac{1}{F_0}\right)T_P$$

λ=0, Explicit Formulation
λ=1, Implicit Formulation
λ=0.5, Crank-Nicolson mid-difference formulation

Croft 1989, Heat Transfer Calculations using finite difference equations

Comparison

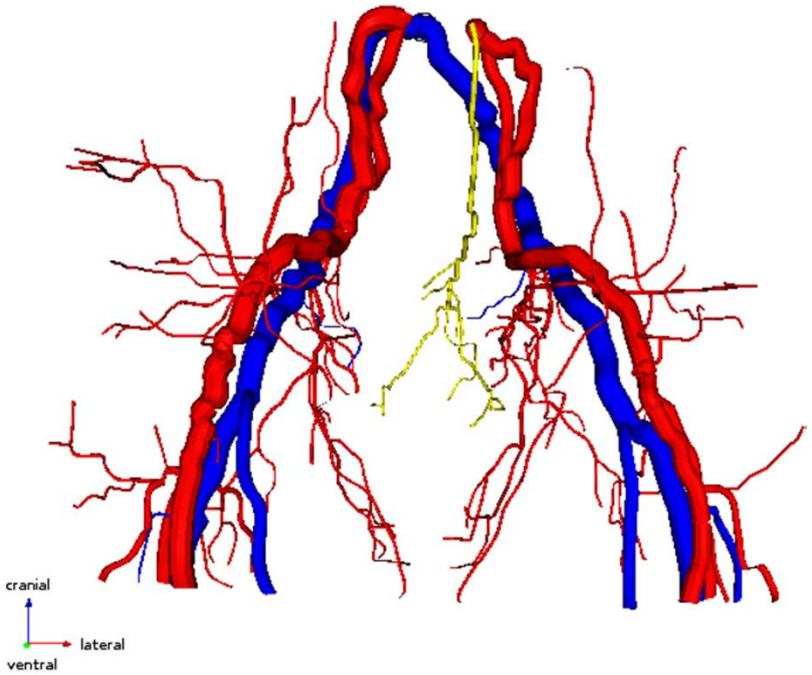

Simulation Results
Target Boundary
Prostate Boundary
1cm
55°C
20
40
60
80
100
Rate of Rotation (dpm)
Acoustic Power (W)
Time (min)
In vivo Results
Target Boundary
Prostate Boundary
1cm
55°C
20
40
60
80
100
Rotation Rate (dpm)
Acoustic Power (W)
Time (min)

Current Efforts

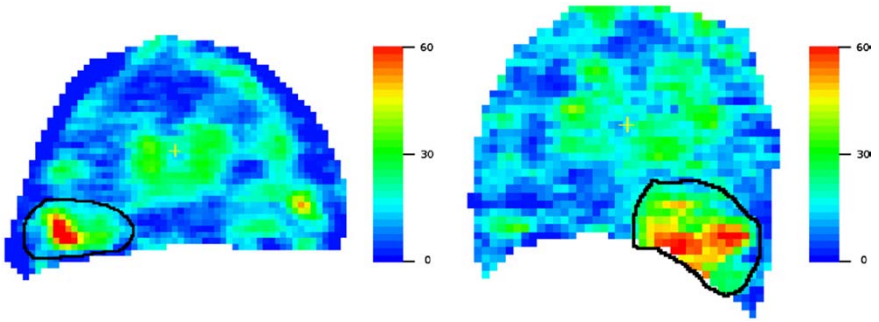
- Patient-specific modeling for improved safety and precision of treatment, device selection
- Similar to radiation therapy
- Based on imaging data & thermal modelling

Examples

Phys Med Biol. 2006 Feb 21;51(4):809-25.
Towards patient specific thermal modelling of the prostate.
Van den Berg CA, Van de Kamer JB, De Leeuw AA, Jeukens CR, Raaymakers BW, van Vulpen M, Lagendijk JJ.

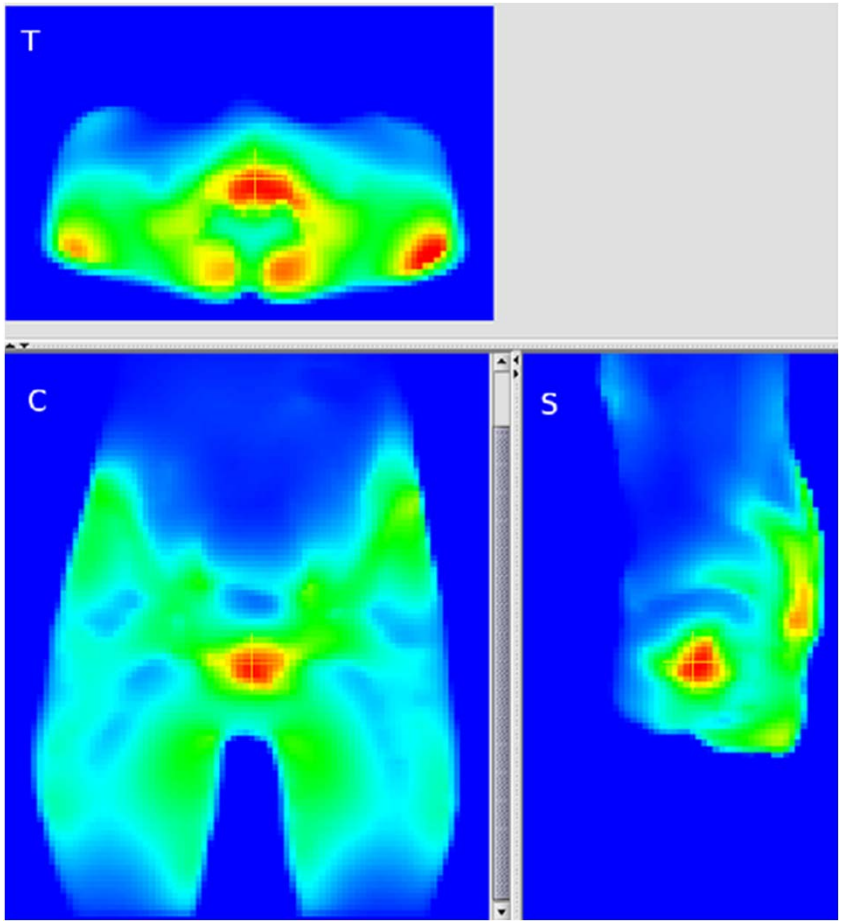


Pelvic vasculature obtained from dynamic CT information

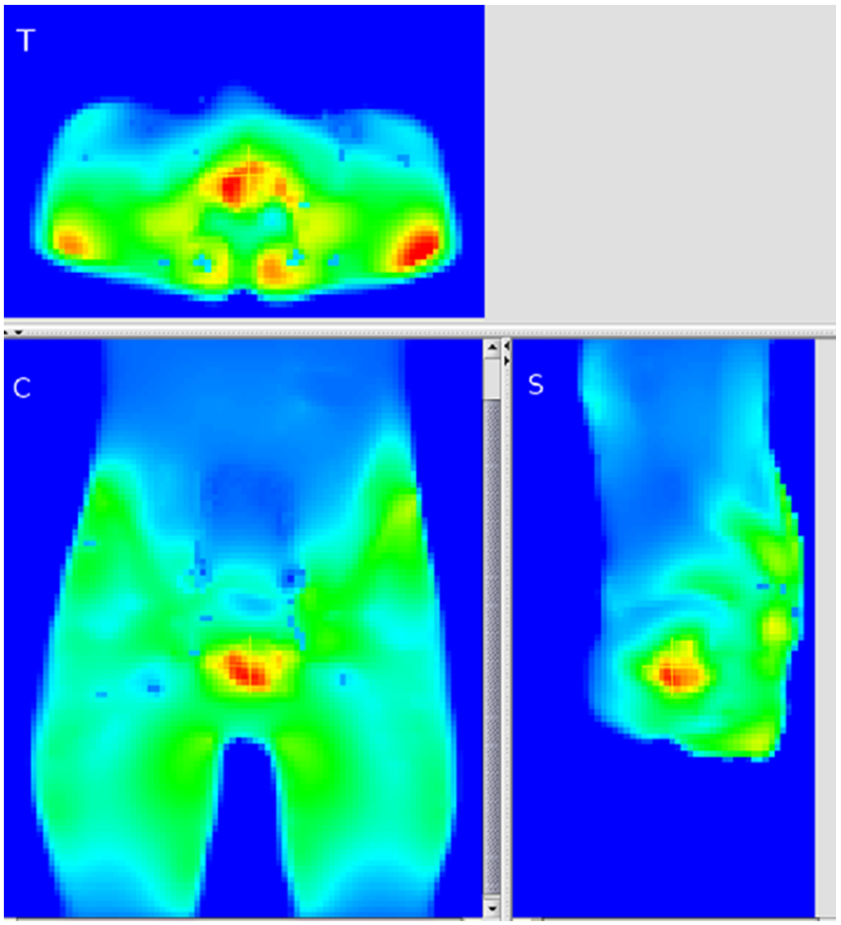


Prostate perfusion maps obtained with Dynamic CT information and kinetic modeling

Examples



BHTE



Discrete Vessel Model