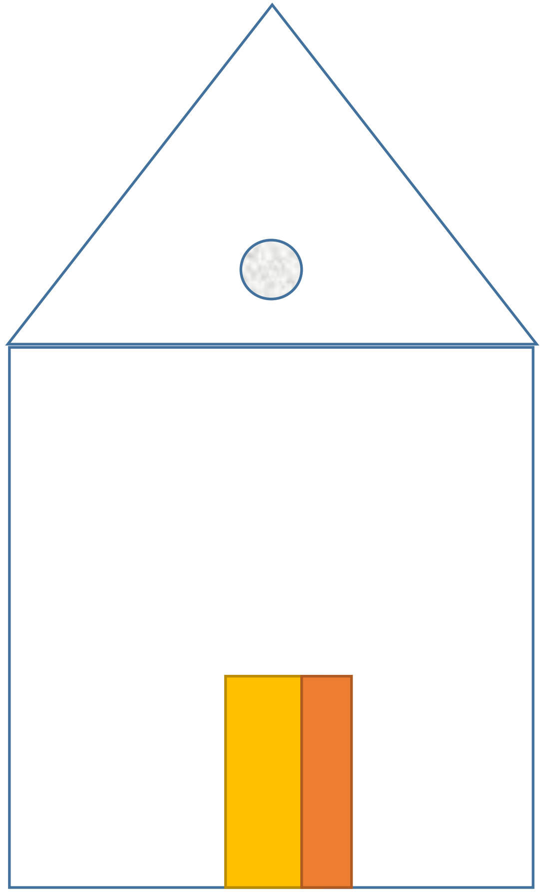
Simple Game

Draw a house on a paper

90% of people have drawn a house like



Question:

How many of your houses are like this?

10% people raised their hands

Another Game

Rapid Fire Round: Quiz

What does it represent?

$$A = lb$$

Answer (100%): Rectangle

What does it represent?

$$W = mg$$

Answer (90%):

Weight = mass times gravity

What does it represent?

$$F = ma$$

Answer (90%):

Newton's Second Law

What does it represent?

$$y = mx$$

Answer (100%):

Equation of Straight Line

What does it represent?

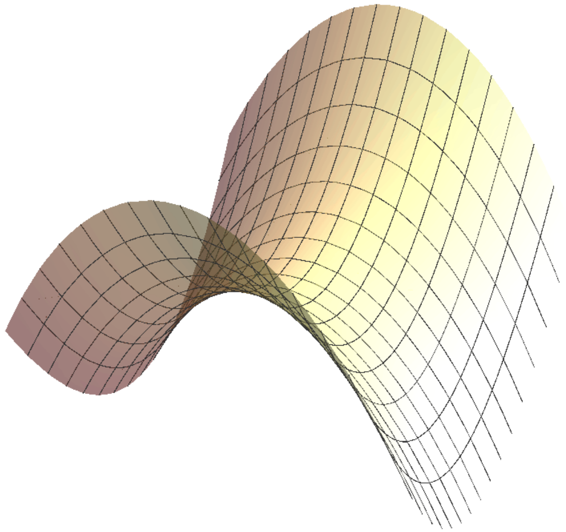
$$z = xy$$

Answer (100%):

Complete Silence

What does it represent?

$$z = xy$$



hyperbolic paraboloid

What does it represent?

$$A = \pi r^2$$

Answer (100%):

Area of a Circle

What does it represent?

$$E = mc^2$$

Answer (100%):

Einstein Equation

What does it represent?

$$y = ax^2$$

Answer (80%):

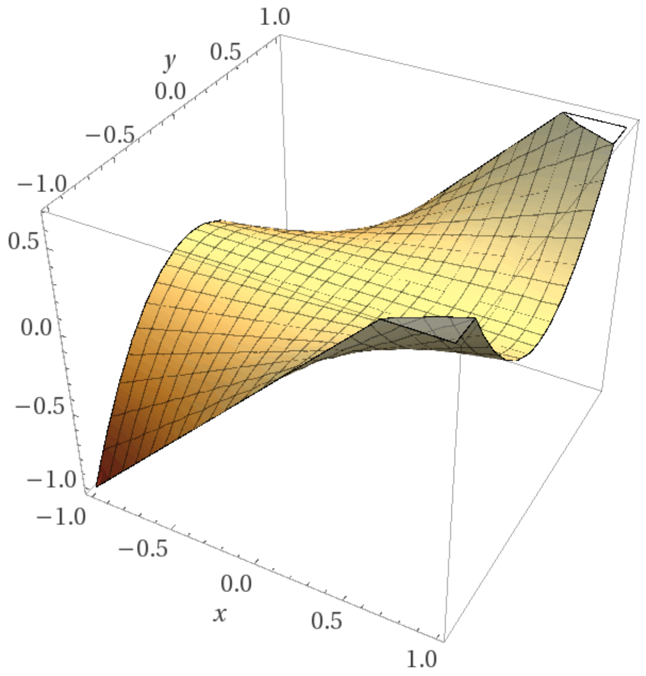
Parabola

What does it represent?

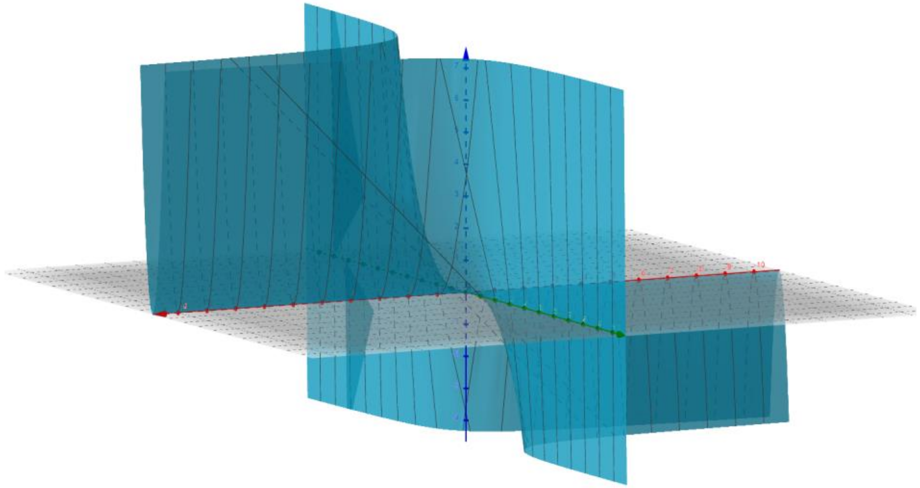
$$z = xy^2$$

Answer (100%):

Complete Silence



$$z = xy^2$$

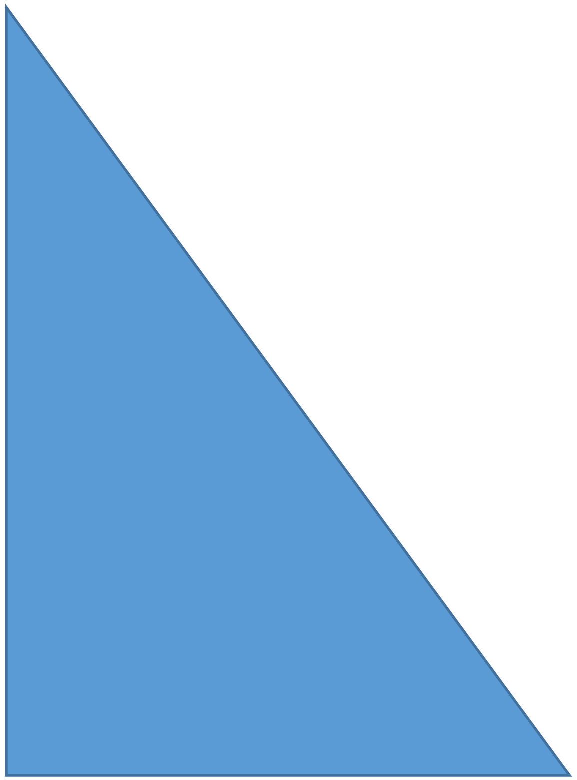


What does it represent?

$$a^2 + b^2 = c^2$$

Answer (100%):

Pythagoras Theorem



What does it represent?

$$x^2 + y^2 = r^2$$

Answer (70%):

Equation of Circle

What does it represent?

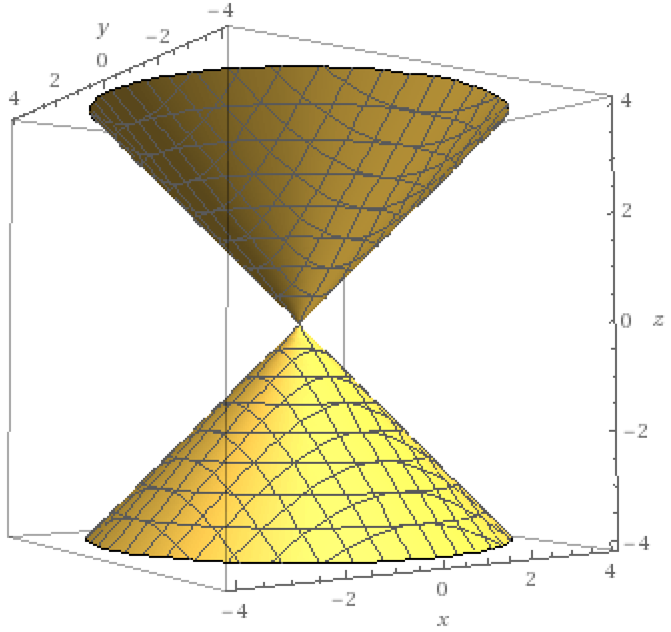
$$x^2 + y^2 = z^2$$

Answer (90%):

Some 3D equation

What does it represent?

$$x^2 + y^2 = z^2$$



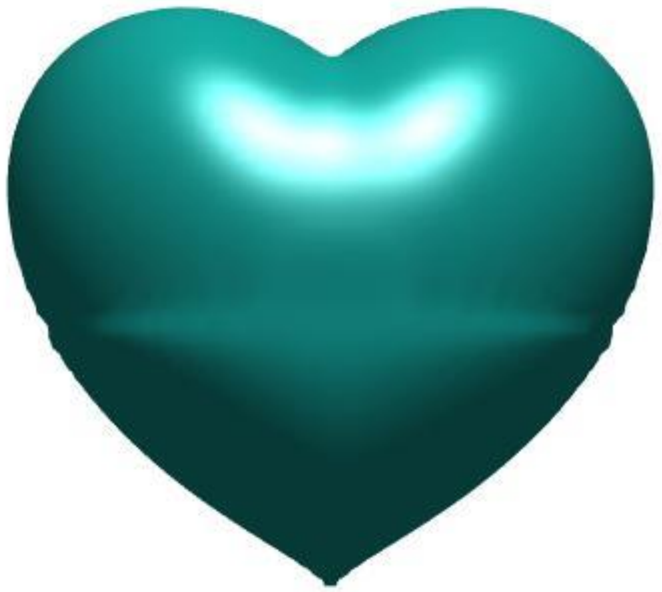
What does it represent?

$$\left(x^2+\frac{9}{4}y^2+z^2-1\right)^3-x^2z^3-\frac{9}{80}y^2z^3=0$$

Answer (90%):

Pin drop silence

$$\left(x^2 + \frac{9}{4}y^2 + z^2 - 1\right)^3 - x^2z^3 - \frac{9}{80}y^2z^3 = 0$$



$$y = mx$$

$$A = lb$$

$$F = ma$$

$$W = mg$$

$$z = xy$$

$$y = ax^2$$

$$A = \pi r^2$$

$$E = mc^2$$

$$z = xy^2$$

$$x^2 + y^2 = z^2$$

$$x^2 + y^2 = r^2$$

$$a^2 + b^2 = c^2$$

Mathematics is the art of giving the same name to different things.

--Henri Poincare

$$f(x, y, z) = 0$$

$y = mx$ $A = lb$ $y = ax^2$ $A = \pi r^2$ $z = xy$ $z = xy^2$ $x^2 + y^2 = z^2$

$F = ma$ $W = mg$ $E = mc^2$ $\left(x^2 + \frac{9}{4}y^2 + z^2 - 1\right)^3 - x^2z^3 - \frac{9}{80}y^2z^3 = 0$ $a^2 + b^2 = c^2$ $x^2 + y^2 = r^2$

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Mathematical Modelling of Differential Equations and its Applications in Biomedical Industry

Panchatcharam Mariappan

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Department of Mathematics and Statistics, IIT Tirupati

Mathematical Modelling

Panchatcharam Mariappan

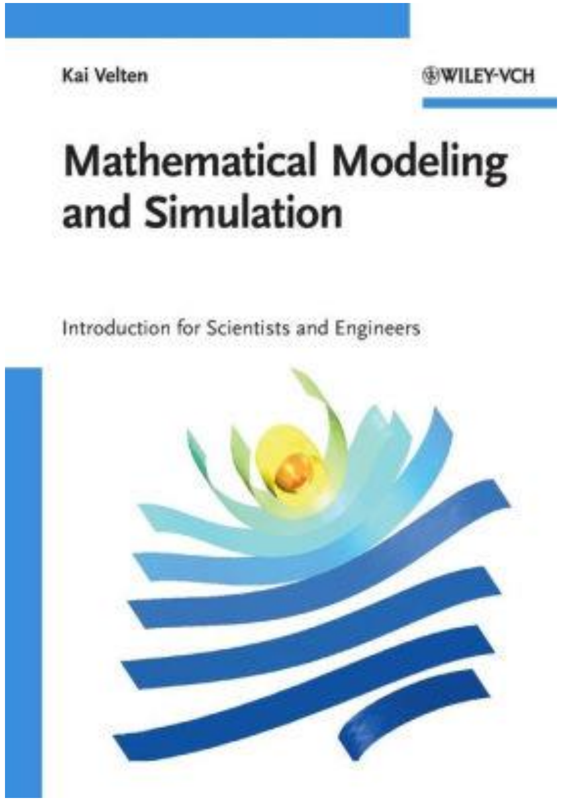
Associate Professor

Department of Mathematics and Statistics, IIT Tirupati

Modeling

Reference

Kai Velten, *Mathematical Modeling and Simulation, Introduction for Scientists and Engineers*, Wiley-VCH Verlag GmbH & Co. KGaA, 2009



A few Examples

- ✓ **Car/Bike not starting**
- ✓ **Headache**

Complexity

- **How complex a car is!**
- **How complex our body/brain is!**

Scientists and Engineers: Break up the complexity of a system and use simplified descriptions of that system

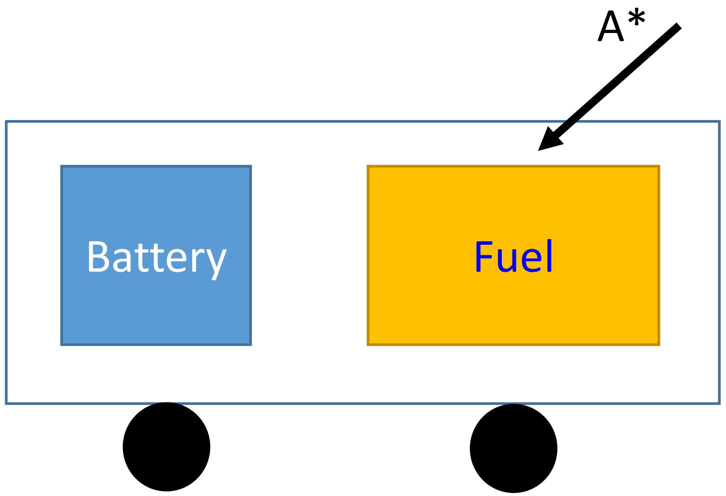
Model

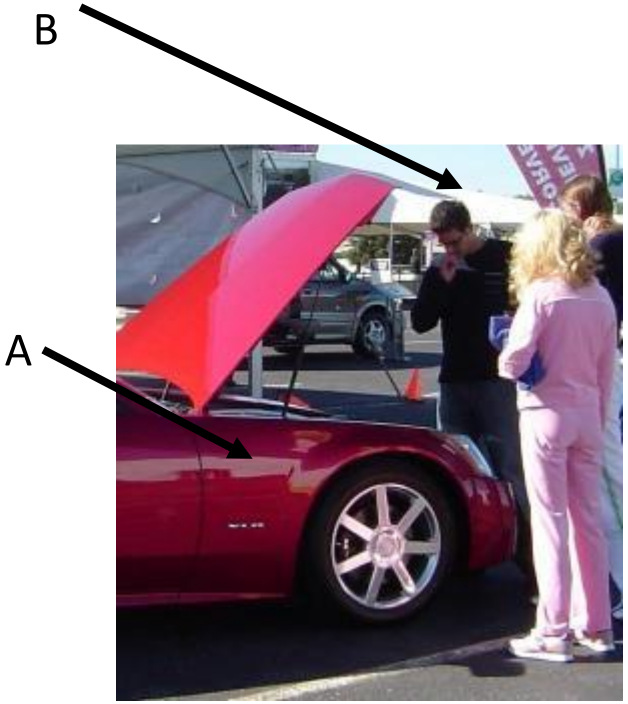
To an observer B, an object A$*$ is a *model* of an object A to the extent that B can use A$*$ to answer questions that interest him about A.

Model

To an observer B, an object A∗ is a *model* of an object A to the extent that B can use A∗ to answer questions that interest him about A.

B: Driver
A: Car
A*: Fuel Tank/Battery





Model

- The best model is the simplest model that still serves its purpose, that is, which is still complex enough to help us understand a system and to solve problems.

Teleological Nature

- Aim and Purposes
- **Main Purpose of Modeling and Simulation: governed by its purpose of problem solving**

- Definitions
  - Problem definition to be solved
  - A question to be answered
  - System definition for which answer is required
- System Analysis
  - Identification of parts of the system related to question
- Modeling
  - Development of a model of the system based on the results of the systems analysis step

A *system* is an object or a collection of objects whose properties we want to study.

- Simulation
  - Application of the model to the problem
  - Derivation of a strategy to solve the problem
  - Answer the question
- Validation
  - Does strategy derived in the simulation step solve the problem or answer the question for the real system

Simulation is the application of a model with the objective to derive strategies that help to solve a problem or answer a question pertaining to a system.

Model

System: Car

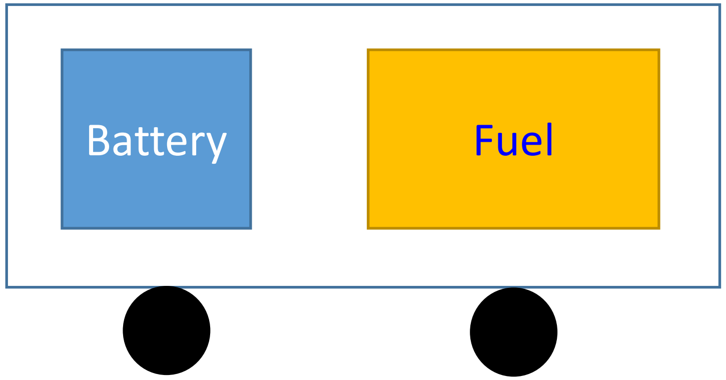
System Analysis: Identifying battery and fuel levels

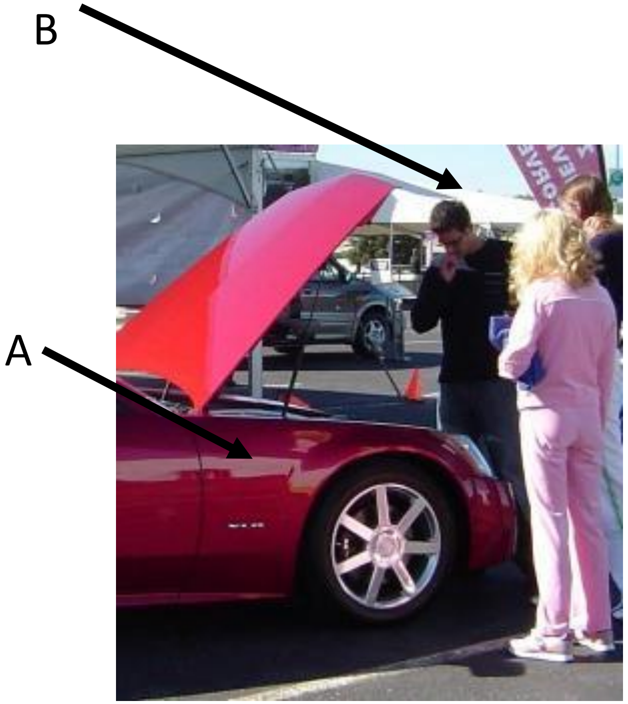
Modeling: Model consists of battery and fuel

Simulation: Check battery and fuel level

Validation: Apply this concept to real car

Validated: If refilling the tank or battery, starts the car





Steps Involved

System Analysis:

- **Use literature, get benefit from others' experiences.**
- **Discussions, meetings and consultations from various disciplines.**
- **New data to understand the system and improve the model, and experimental program**

Modeling and Simulation:

- **Appropriate software to solve the mathematical model**
- **Standard software or customized software or your own software**

Validation: Compare with existing experimental data, from literature or your own experiments, and fit data quantitatively and qualitatively.

Note: Quantitative and qualitative fit may fail the validation step, if it can't be used to solve the problem

Conceptual Model and Physical Model

Optimize the fuel consumption

Conceptual Model:

Car drawn on a paper.

No physical reality

All life is problem solving. Conceptual model is an important tool to solve our everyday problems.

Physical Model:

Simplified version of the engine

Few parts of the engine connected to the fuel injection process

Relating our idea to the real part of the physical world

Mathematical Modeling

Mathematics:
A Natural Language Modeling

Input – Output system

Input Parameters:

- Identify list of input parameters involved in the system

Output Parameters

- List of output parameters

- Relations between input-output
- Technology

$$y = f(x)$$
$$(y_1, y_2, \dots, y_m) = f(x_1, x_2, x_3, \dots, x_n)$$

Numerical Data

- Collection of data from experiments, input, output, described naturally in mathematical terms

$$y = f(x)$$
$$(y_1, y_2, \dots, y_m) = f(x_1, x_2, x_3, \dots, x_n)$$

Initial Study:

- The system is a black box
- Uncertainty
- Hypothesis: Experimenter wants to investigate
- Question-And-Answer Game

Mathematical Model

A mathematical model is a triplet (S, Q, M) where S is a system, Q is a question relating to S, and M is a set of mathematical statements $M = \{\Sigma_1, \Sigma_2, \ldots, \Sigma_n\}$ which can be used to answer Q.

Basic Group of Variables

- Decision variables - quantity that the **decision**-maker controls
- Input variables
- Output variables
- State variables
- Exo/Endogenous variables - in/dependent variable
- Random variables

State Variables

Let (S, Q, M) be a mathematical model. Mathematical quantities $s_1, s_2, \ldots, s_n$ which describe the state of the system S in terms of M and which are required to answer Q are called the *state variables* of (S, Q, M).

State Variables

Let $s_1, s_2, \ldots, s_n$ be the state variables of a mathematical model (S, Q, M). Let $p_1, p_2, \ldots, p_m$ be mathematical quantities (numbers, variables, functions) which describe properties of the system S in terms of M, and which are needed to compute the state variables. Then $Sr = \{p_1, p_2, \ldots, p_m\}$ is the *reduced system* and $p_1, p_2, \ldots, p_m$ are the *system parameters* of (S, Q, M).

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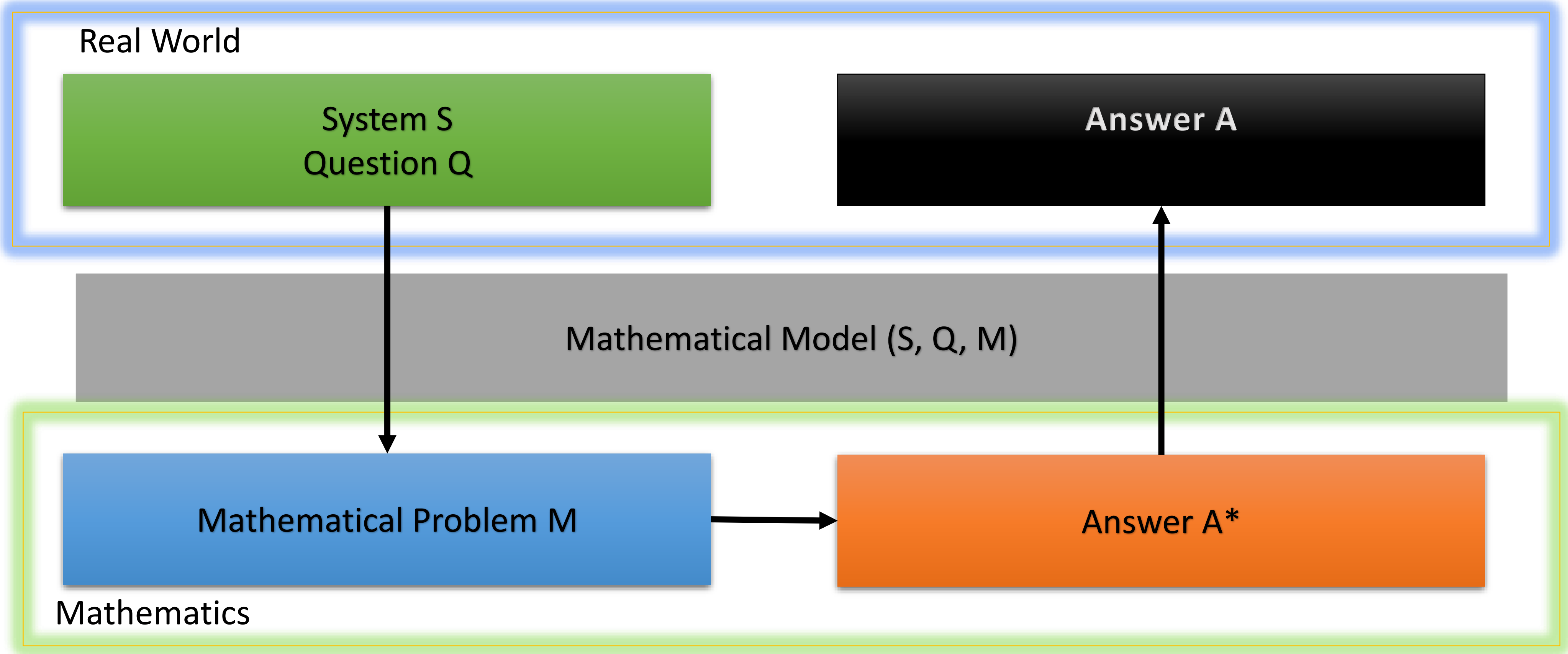
Connecting Real world to Mathematical Model



Mathematical concepts

Mathematical Model (S, Q, M)

S
Physical-Conceptual
Natural-Technical
Stochastic-Deterministic
Continuous-Discrete
Dimension
Fields of Application

Q
Phenomenological-Mechanistic
Stationary-Unstationary
Lumped-Distributed
Direct-Inverse
Research-Management
Speculation-Design
Scale

M
Linear-Nonlinear
Analytical-Numerical
Autonomous-Nonautonomous
Continuous-Discrete
Difference Equations
Differential Equations
Integral Equations
Algebraic Equations

Mathematical concepts

no a priori information available

all necessary information is available

Black Box	Grey Box	White Box
Social Systems	Chemical Systems Biological Systems	Mechanical Systems

Don’t

1. Don’t Believe that the model is reality
2. Don’t extrapolate the region of fit
3. Don’t distort reality to fit the model
4. Don’t retain a discredited model
5. Don’t fall in love with your model

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Bioheat Equation

for Cancer Treatment

Panchatcharam Mariappan

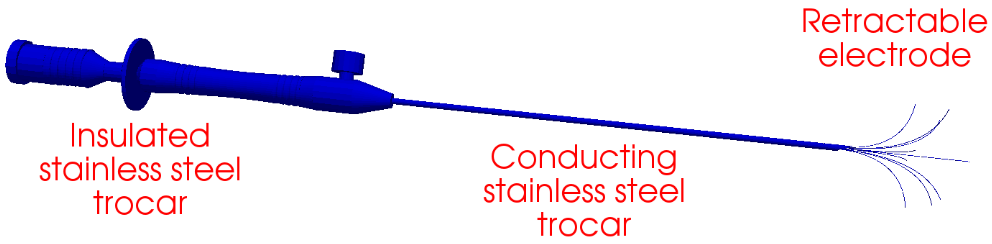
Associate Professor

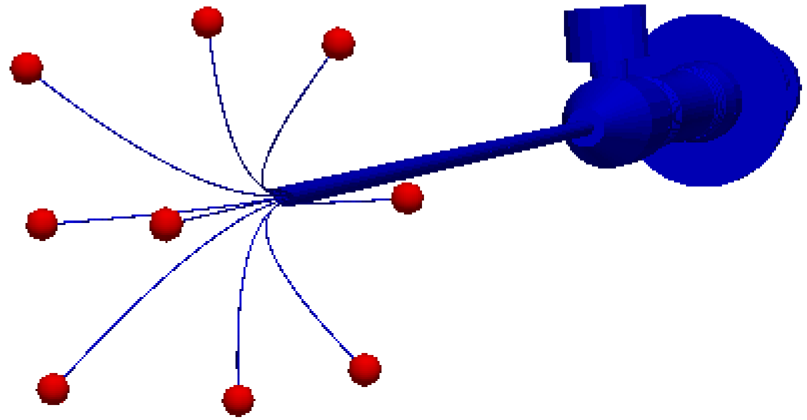
Department of Mathematics and Statistics, IIT Tirupati

MICT-RFA

- MICT: Recommended by IRs
  - Minimal Invasive Cancer Treatment
  - Under treatment:
    - Recurrence of Tumour
  - Over Treatment:
    - Kills unnecessary cells → Death
- RFA is most common
  - Requires more experienced IRs
- RFA Procedure
  - Locoregional treatment
  - Use RFA needle (umbrella shaped) to induce heat energy

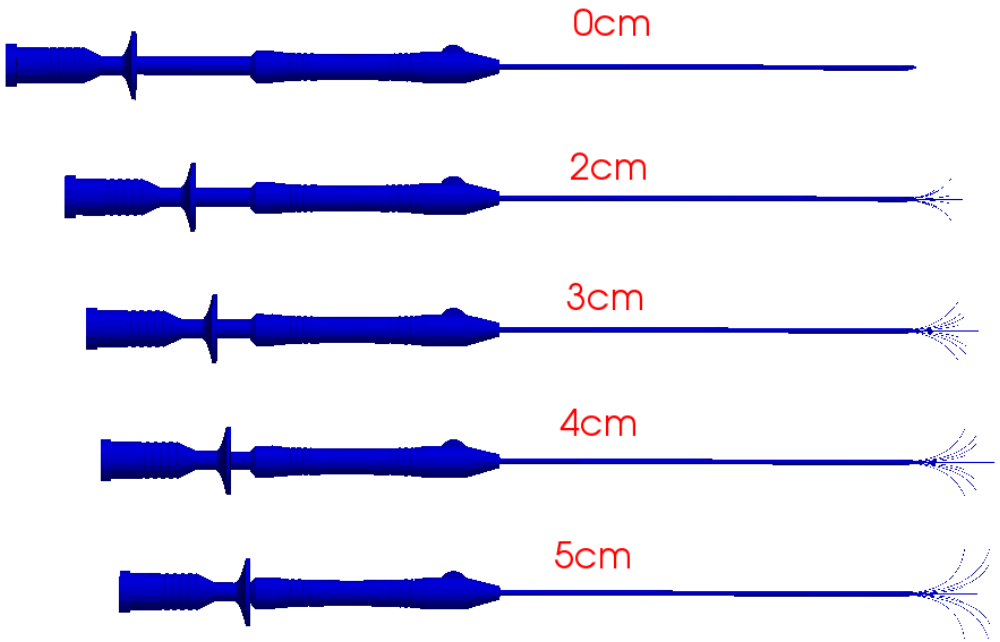
Needles

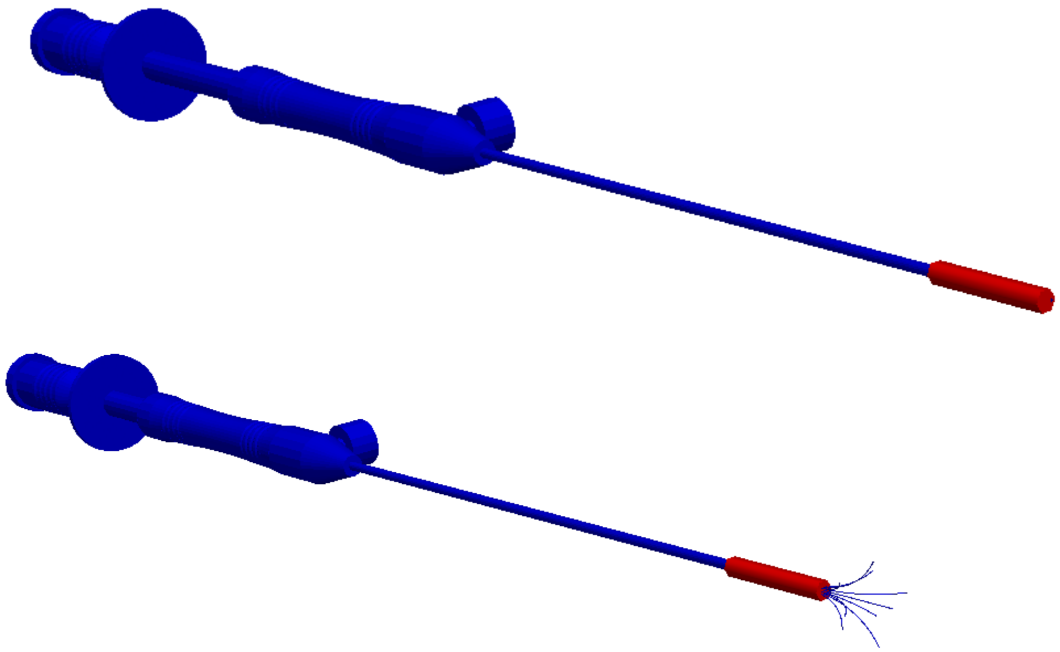

Retractable electrode
Insulated stainless steel trocar
Conducting stainless steel trocar




Insulated Stainless steel Trocar
Conducting Stainless Steel Trocar
Retractable Electrode

Needles





System:

- Entire Body, Clinical Environment of RFA Treatment

Questions:

1. Can we create a simple model for RFA Treatment?
   a) Can we create liver, vessel, tumour model?
   b) Can we produce the same power produced by the needle virtually?
   c) Can we implement the same protocol followed by doctors?
2. Can we predict the temperature profile before the treatment?
3. Can we predict the cell deaths?

Mathematical Statements for:

1. Heat transfer from RFA needle to the liver
2. Power generation or Heat Source from needle
3. Temperature controlled power supply
4. Cell death due to temperature

Input-Output System

Input

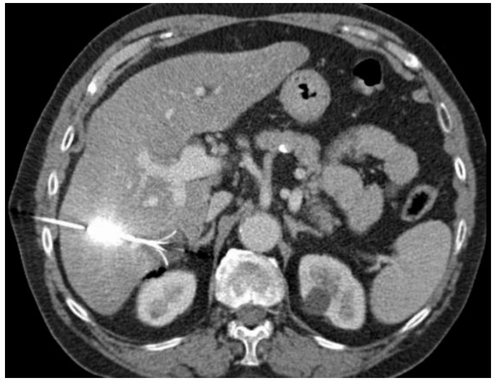
- CT Scan Images
- Blood Perfusion
- Body Temperature
- Protocol
- Needle location on image
- Power output from machine

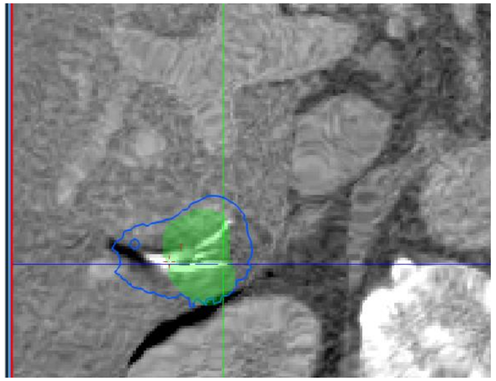
Output

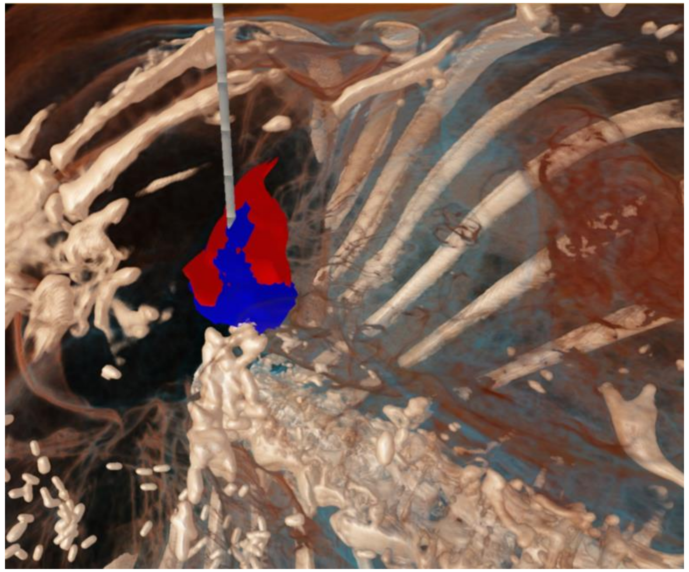
- Liver Geometry, Tumour Geometry
- Vessel Geometry, Needle Geometry
- Temperature around tumour cells
- Cell States around tumour cells

RFA Guardian

- Planning and Simulation Software Tool
  - Helpful for less experienced IRs
  - Visualize the treated ablation zone
- Existing Planning software tool
  - Too slow to predict the ablation zone
  - Limited Patient-Specific Parameters: Perfusion
  - Can run on distributed computing
  - Not suitable at clinical environment setup







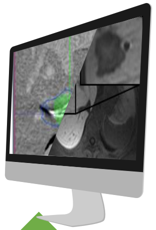
Cancer Treatments

Common Liver Cancers

HCCs

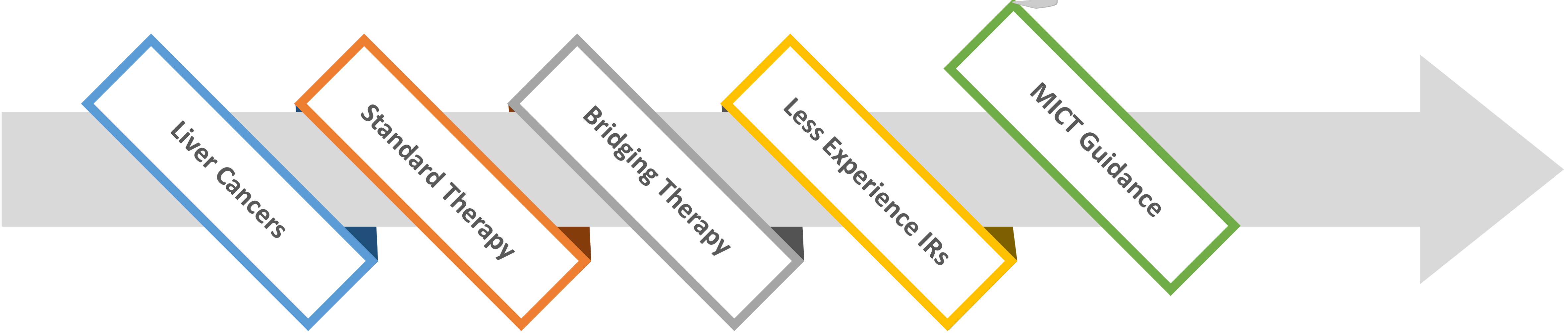
Bridging Therapy

RFA, MWA
IRE, Cryo
FUS, Laser



MICT Guidance

Help IRs
Change of parameters



Standard Therapy

- Surgical Treatments: 75-90% unsuitable[1]
- Transplantation

Less Experienced IRs

Under treatment: Recurrence
Over Treatment: Death

1. Bruix J, Sherman M (2011) Management of hepatocellular carcinoma: an update. Hepatology 53(3):1020–1022

Image Sources: https://angiodynamics.com
https://http://www.mermaidmedical.dk/

Patient-, Device-Specific Parameters

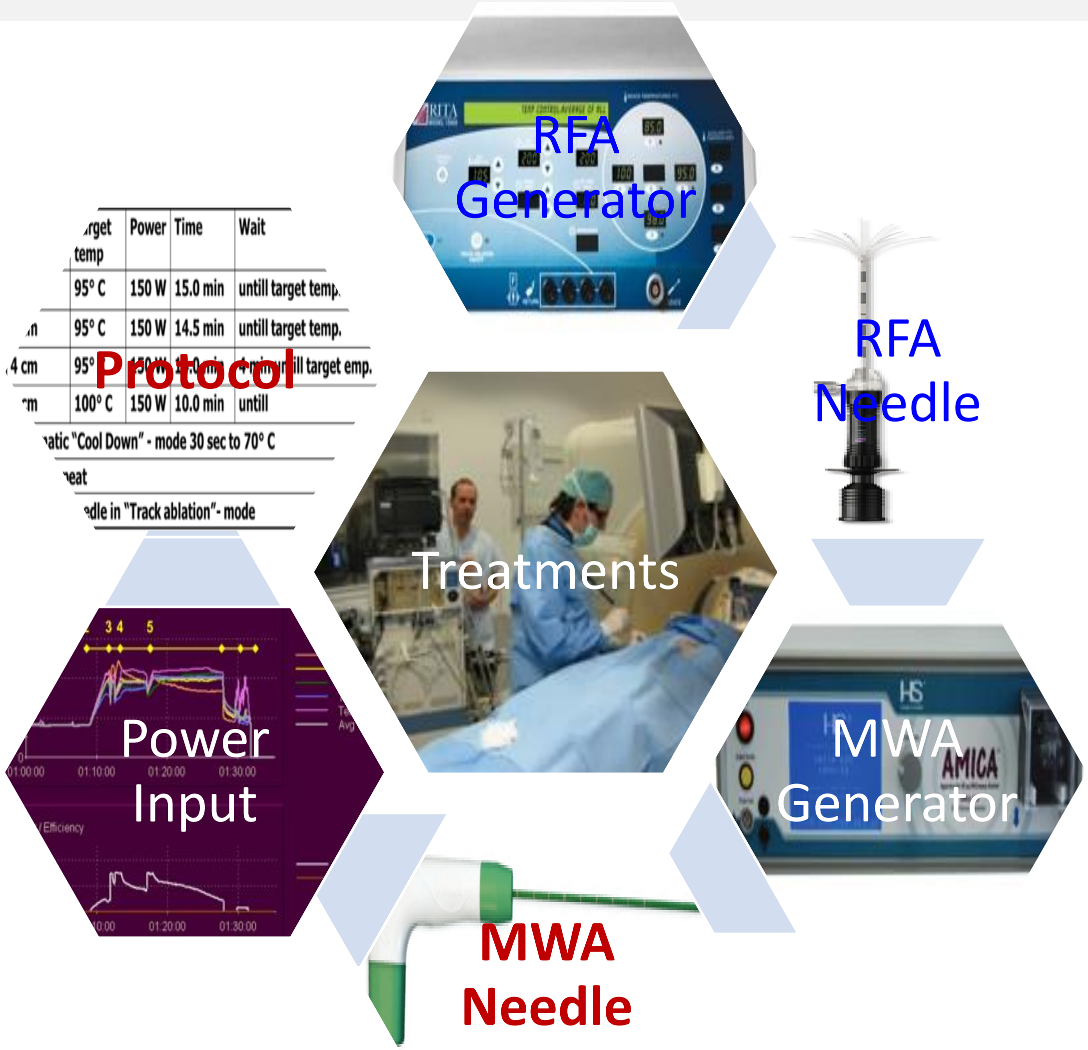
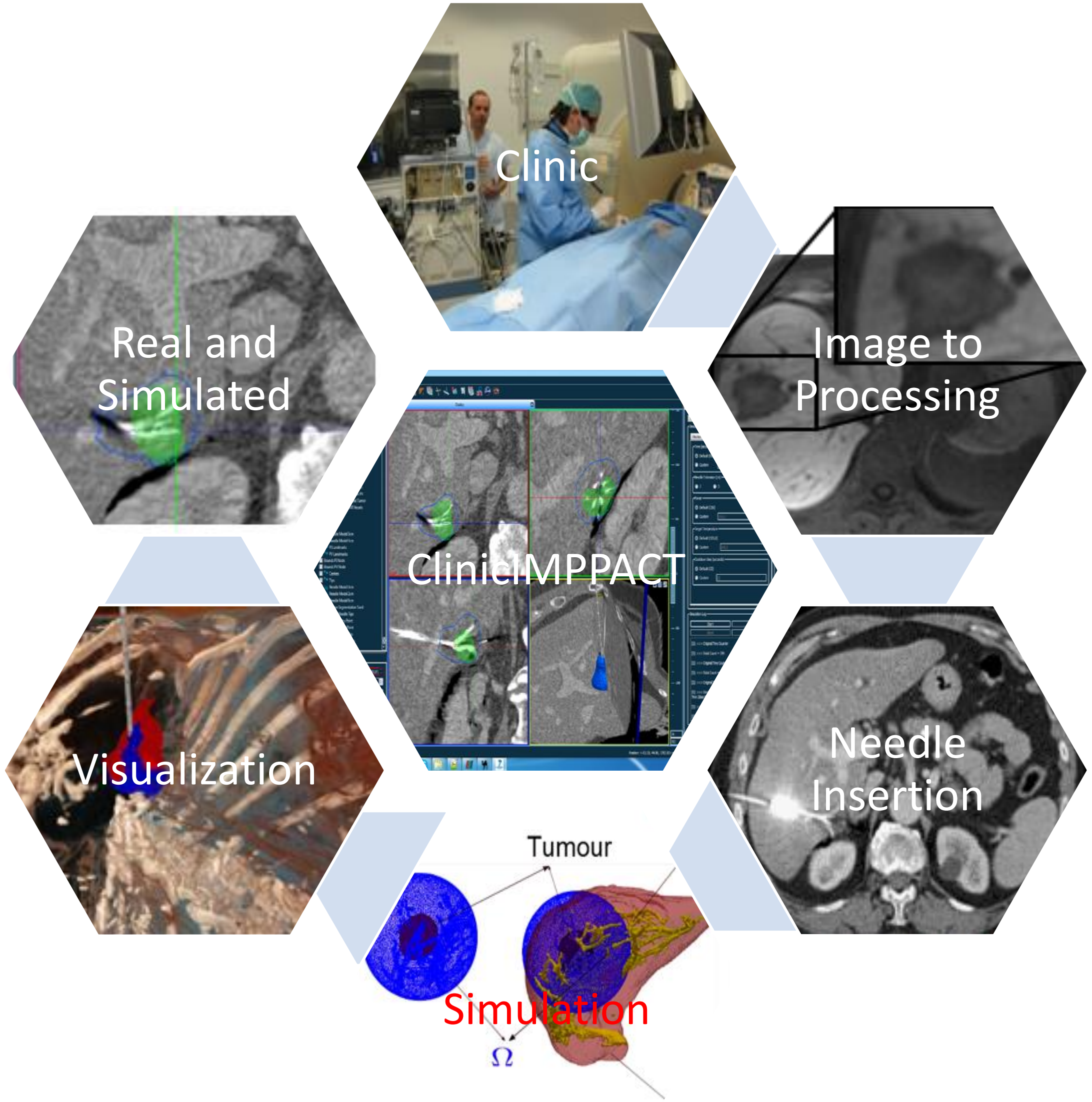


Image Sources: https://angiodynamics.com
https://http://www.mermaidmedical.dk/

Objective

- Developed a software tool such that
  - Useful for the RFA treatment of liver cancer
  - Runs on a Single-PC
  - Usable at clinical environment
  - Predicts the lesion on the day of the treatment within few seconds
  - Accepts Patient-Specific parameters
  - Accepts Device-Specific parameters
  - Cost-efficient



ClinicIMPPACT Project

Clinical Intervention Modelling, Planning and Proof for Ablation Cancer Treatment

EU Commission

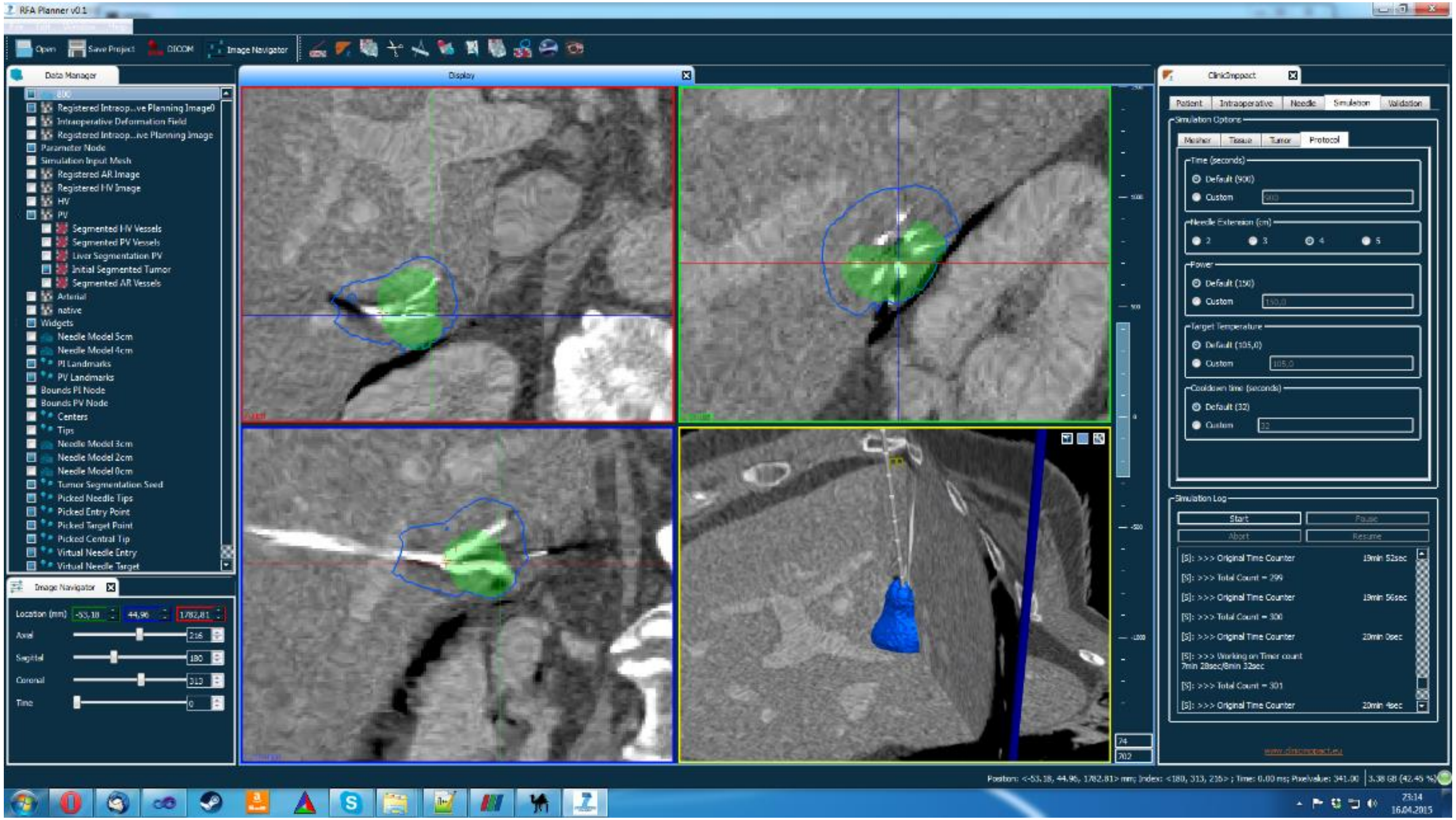
Fraunhofer FIT

- Universitätsklinikum Leipzig / Universität Leipzig Medizinische Fakultät
- Medizinische Universität Graz — TU Graz, Graz University of Technology
- Radboud Universiteit
- Varsinais-Suomen Sairaanhoitopiiri — Aalto University
- numa

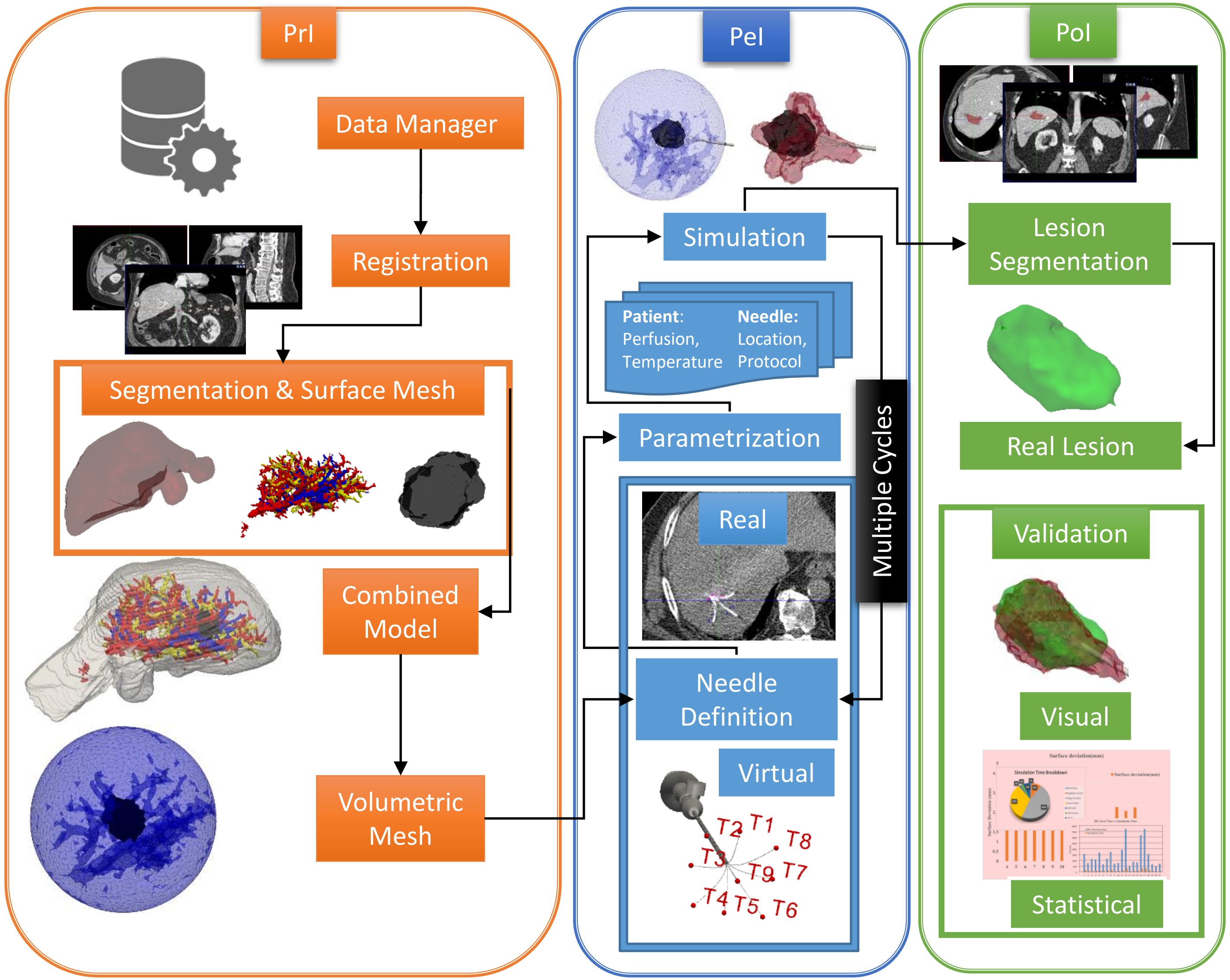
Rs.~41 Crores

http://www.clinicimppact.eu

RFA Guardian



Workflow


PrI
Data Manager
Registration
Segmentation & Surface Mesh
Combined Model
Volumetric Mesh
PeI
Simulation
Patient: Perfusion, Temperature
Needle: Location, Protocol
Parametrization
Multiple Cycles
Real
Needle Definition
Virtual
T2 T1 T8
T3 T9 T7
T4 T5 T6
PoI
Lesion Segmentation
Real Lesion
Validation
Visual
Statistical

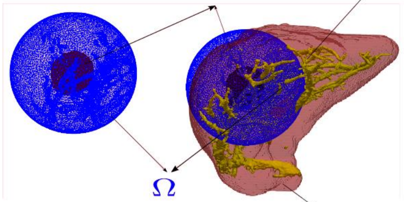
Governing Equations

Bioheat Equation[1]

$$\rho C \frac{\partial T}{\partial t} = k\Delta T + \omega_b \rho_b C_b (T_a - T) + Q_r \ on\ \Omega$$

$$h_c T + k\frac{\partial T}{\partial \vec{n}} = h_c T_\infty \text{ on vessels boundary}$$

$$T = T_0 \text{ on } \partial\Omega$$



Cell Death Model[2]

$$\frac{dA}{dt} = -k_f e^{\frac{T}{T_k}} (1 - A)A + k_b(1 - A - D)$$

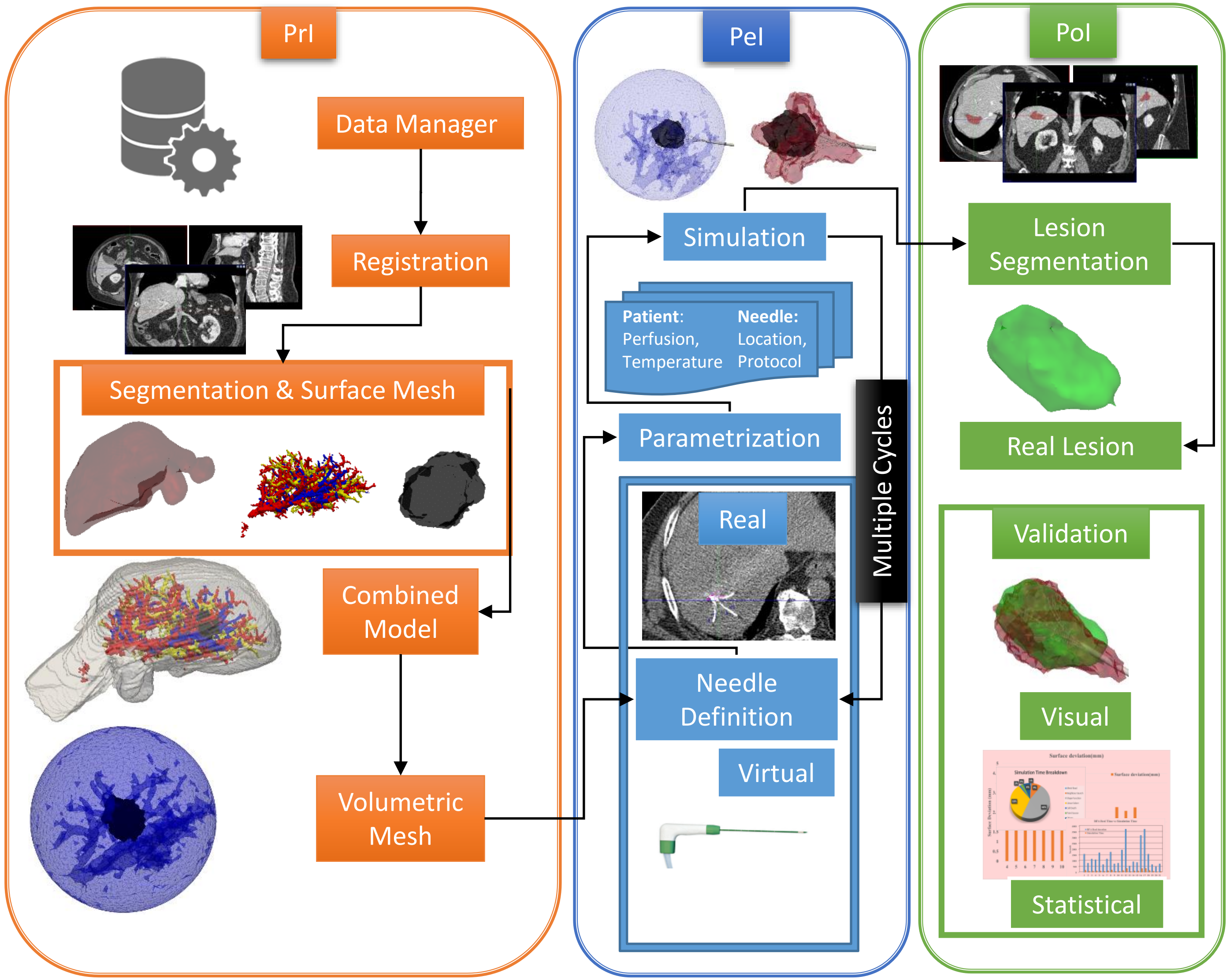
$$\frac{dD}{dt} = k_f e^{\frac{T}{T_k}} (1 - A)\,(1 - A - D)$$

$$A(0) = 0.99, D(0) = 0.0$$

1. H. H. Pennes, Analysis of tissue and arterial blood temperature in the resting human forearm, J. Appl. Physio. 85(1):93-102, 1948
2. O'Neill DP, Peng T et al (2011) A three-state mathematical model of hyperthermic cell death. Ann Biomed Eng 39(1):570-579

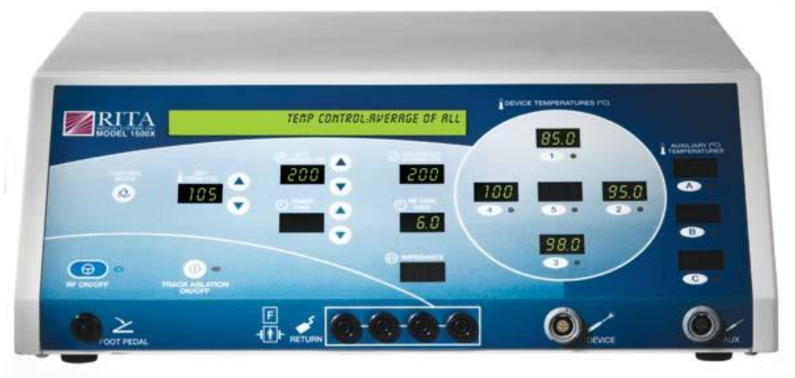
Clinical Model

Clinical Workflow



Device-Specific Parameters

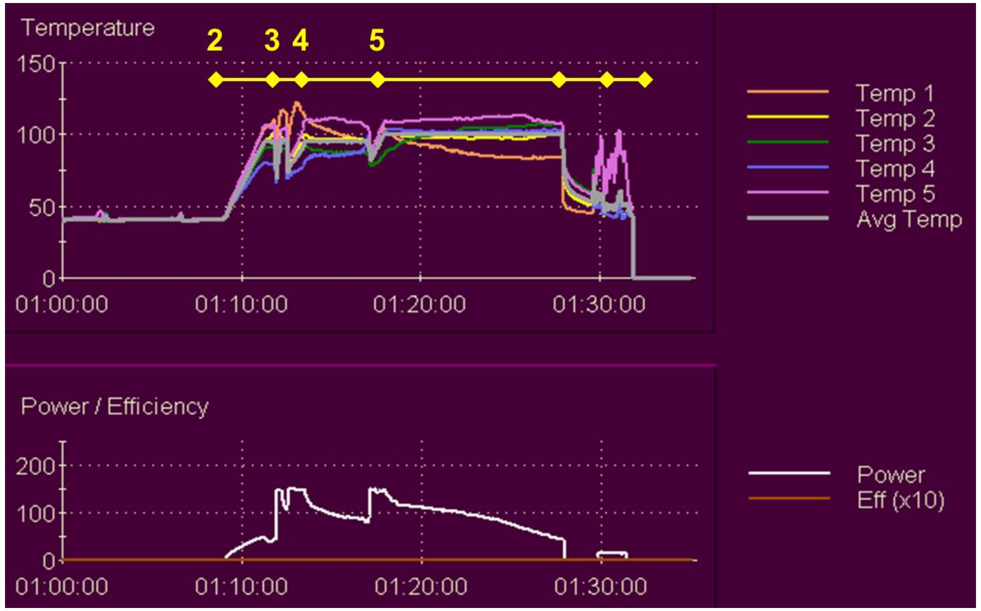
- Power Input
- Needle Geometry
- Temperature Controlled Algorithm
- Treatment Protocol
- Cooling Procedure

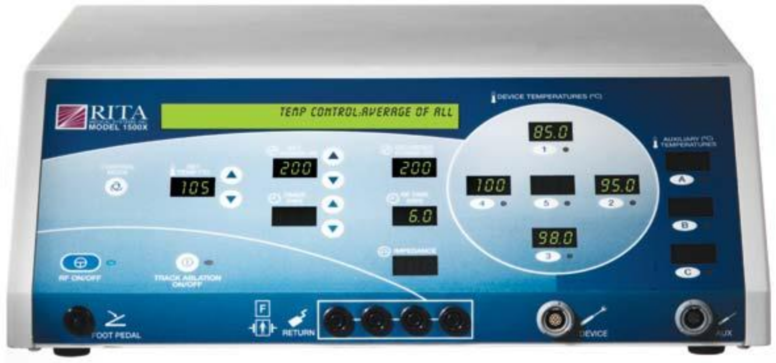


Device-Specific Parameters

RITA Starburst Needle and RF Generator

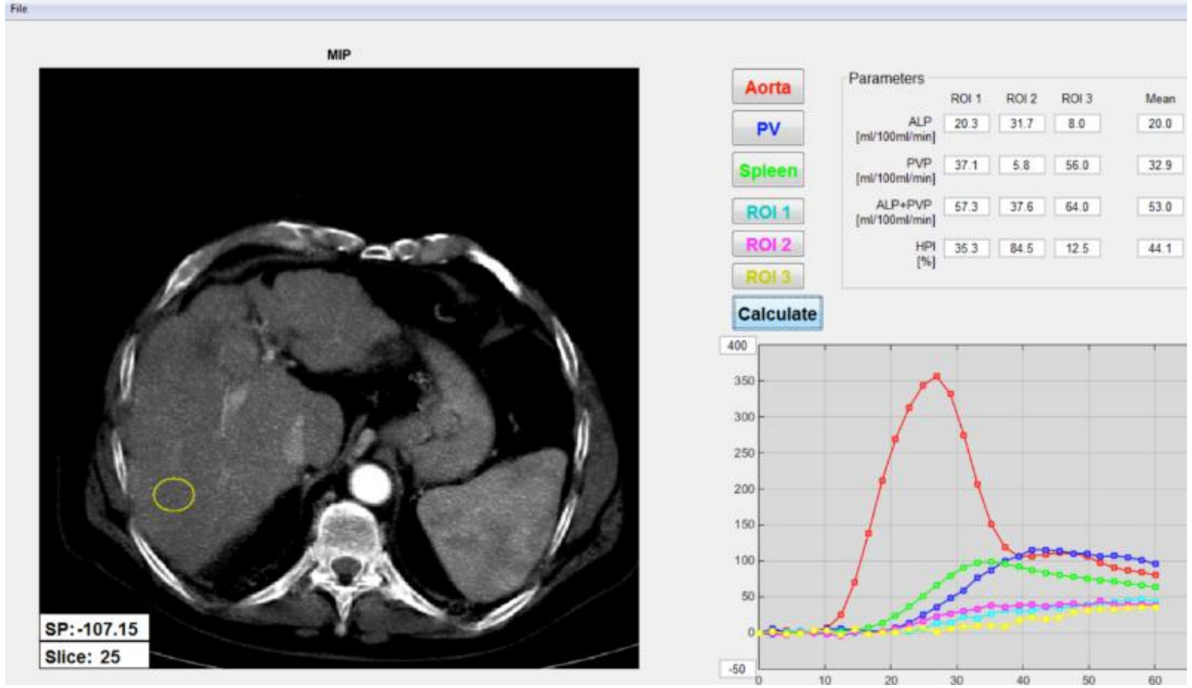
Needle length	Target temp	Power	Time	Wait
2 cm	95° C	150 W	15.0 min	untill target temp.
3 cm	95° C	150 W	14.5 min	untill target temp.
4 cm	95° C	150 W	14.0 min	4 min untill target emp.
5 cm	100° C	150 W	10.0 min	untill
Automatic "Cool Down" - mode 30 sec to 70° C				
If nec. repeat				
Withdraw needle in "Track ablation"- mode				





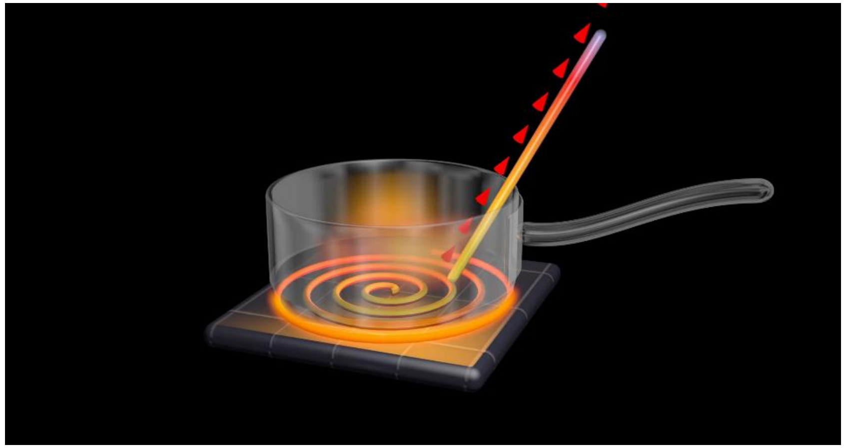
Patient-Specific Parameters

- Blood Perfusion
  - Tissue
  - Tumour
  - TACE
- Specific heat capacity
- Thermal conductivity
- Many more...



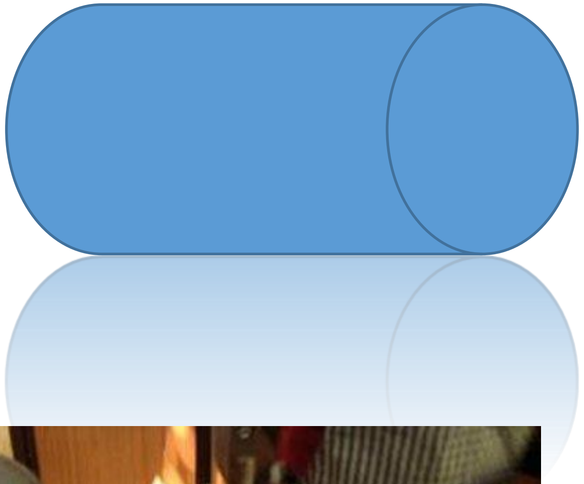
Mathematical Model

- A discipline of thermal engineering
- Conversion, exchange of heat between physical systems

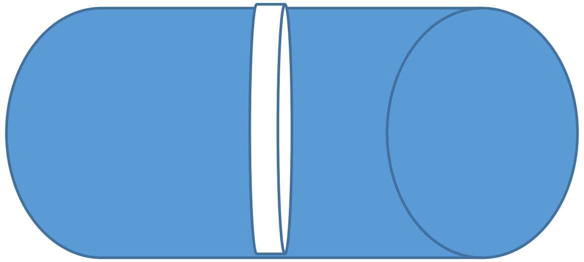


Heat Equation

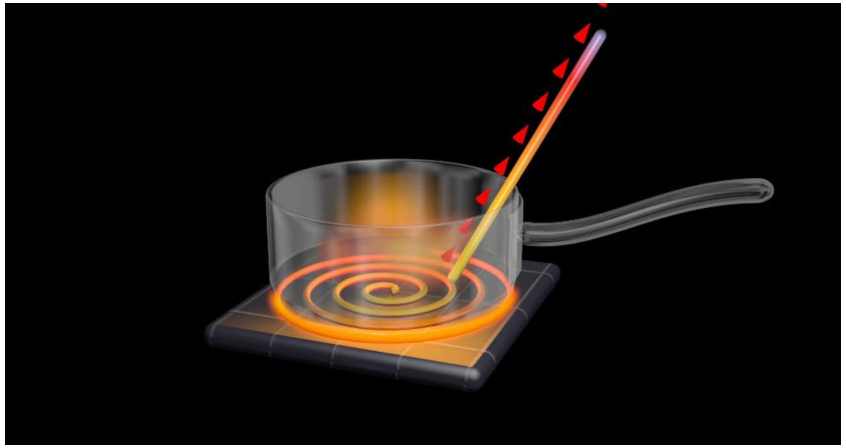
- Heat flow in a solid rod with circular cross section A
- Perfectly insulated rod. No heat escapes radially
- Heat flow only along the axis of symmetry of the rod
- Initial temperature = room temperature



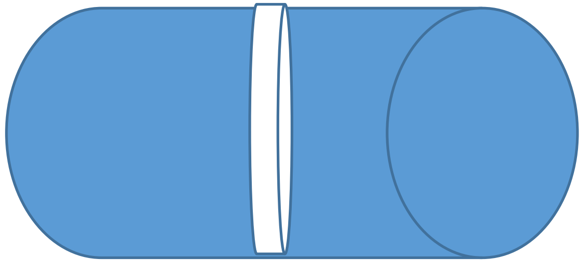
Heat Equation

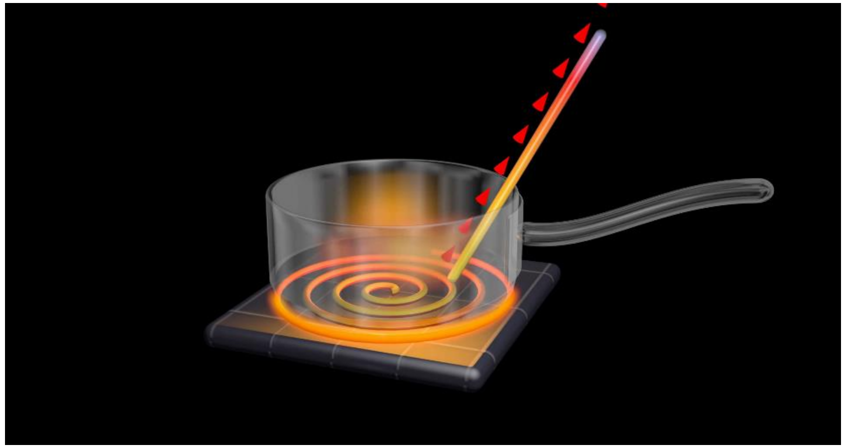


- At one end temperature raised suddenly
- Heat flow from hot to cold
- Let δx denote thickness of a section through the rod located at the point x
- Some of the heat absorbed by the rod
- Heat flow at $x \neq$ Heat flow at $x + \delta x$
- Conservation Energy



Rate of change of heat content = net rate of heat conducted in and out of section

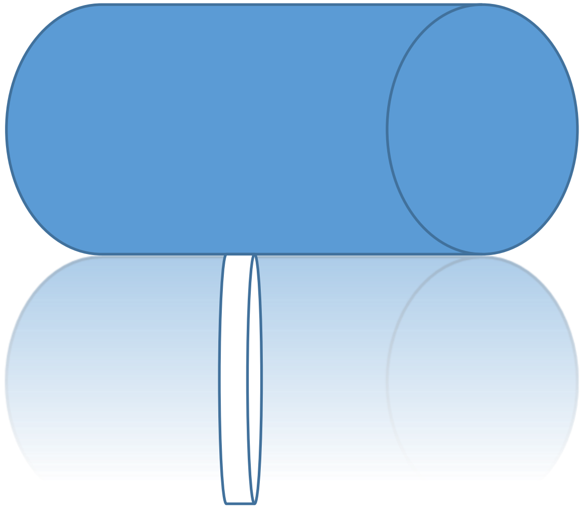




- Assume no heat production inside the rod or heat loss from the surface of the rod.

Rate of change of heat content = net rate of heat conducted in and out of section

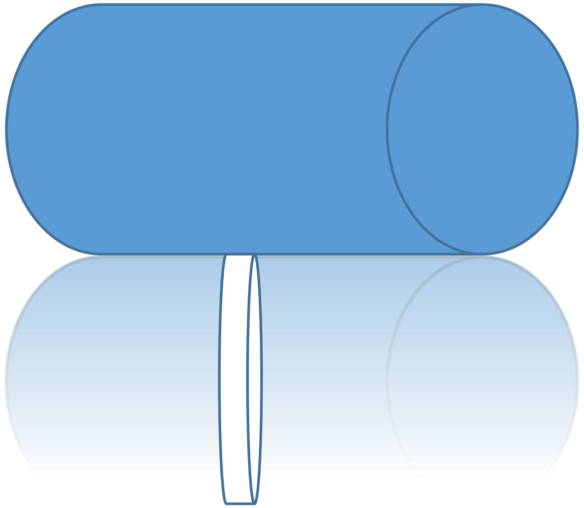
Rate of change of heat content = net rate of heat conducted in and out of section



- $T(x,t)$ denotes the temperature of the rod at position x, at time t.
- Some of the heat energy is absorbed by the rod.
- Changes in temperature at time $t+\delta t$
- Temperature difference: $T(x,t+\delta t)-T(x,t)$

Derivation: Heat Equation

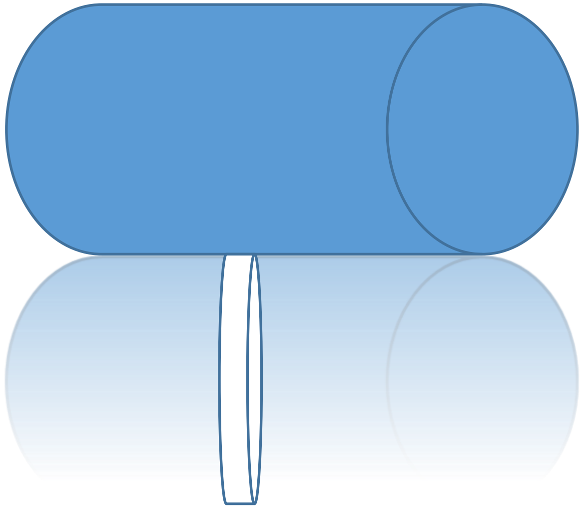
- Temperature difference: $T(x, t + \delta t) - T(x, t)$
- Amount of heat required to change the temperature of the entire mass of the cross section??
- Proportional to mass of section??
- Mass = density x volume
- Volume = $A \times \delta x$
- **Rate of change of heat content =** $c\rho A\delta x \frac{\partial T(\xi,t)}{\partial t}$



Rate of change of heat content = net rate of heat conducted in and out of section

Derivation: Heat Equation

- **Rate of change of heat content** = $c\rho A\delta x \frac{\partial T(\xi,t)}{\partial t}$
- $\xi \in (x, x + \delta x)$
- c proportionality factor or specific heat constant, depends on metal



Rate of change of heat content = net rate of heat conducted in and out of section

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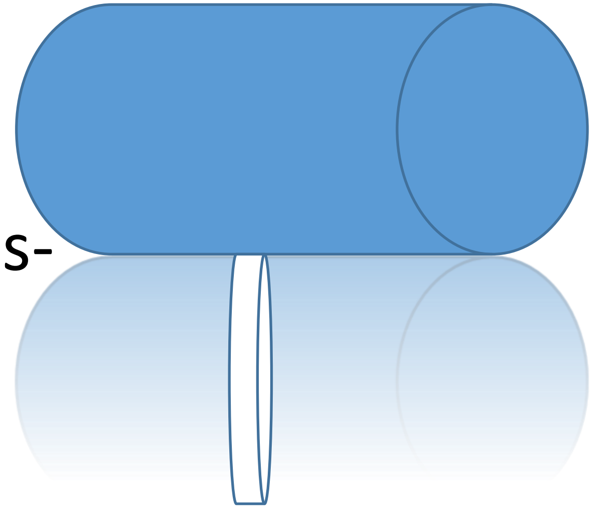


- Heat flux $J(x,t)$: The rate of heat passing through a cross-section, per unit area, per unit time

Fourier's Law

More is the area exposed → More will be the heat transferred

Fourier's Law

More is the area exposed → More will be the heat transferred

$$J \propto A$$

Fourier's Law

More is the temperature difference → More will be the heat transfer.

Fourier's Law

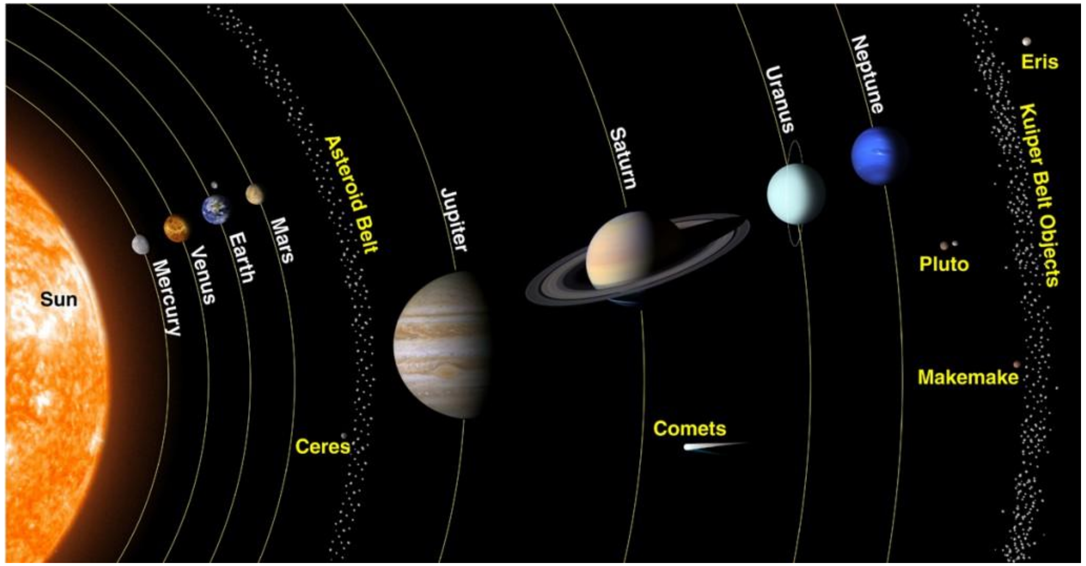
More is the temperature difference → More will be the heat transfer.

$$J \propto dT$$

Fourier's Law

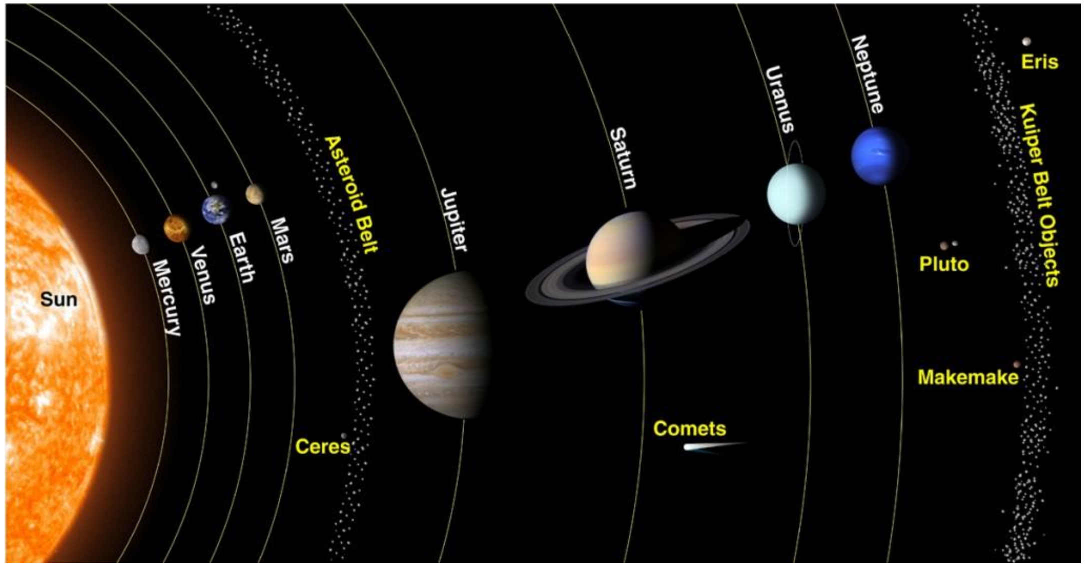
Farther is the heat source – Lesser is the heat transferred

Rank	Planet	Mean Temperature (C)
1	Venus	464
2	Mercury	167
3	Earth	15
4	Mars	-65
5	Jupiter	-110
6	Saturn	-140
7	Uranus	-195
8	Neptune	-200
9	Pluto	-225



Farther is the heat source – Lesser is the heat transferred

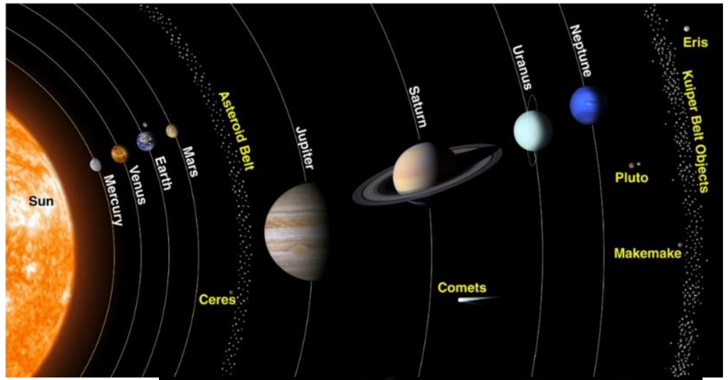
$$J \propto \frac{1}{dx}$$



Fourier's Law

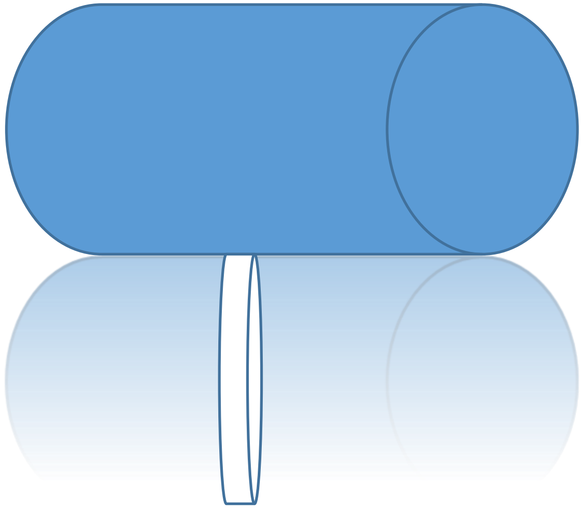
$$J \propto A \frac{dT}{dx}$$

$$J = -kA \frac{dT}{dx}$$



Derivation: Heat Equation

- **Rate of change of heat content** = $c\rho A\delta x \frac{\partial T(\xi,t)}{\partial t}$
- **Net rate of heat conducted in and out of cross section**
- $J(x+\delta x,t) - J(x,t) = kA\frac{dT(x+\delta x,t)}{dx} - kA\frac{dT(x,t)}{dx}$
- $c\rho A\delta x \frac{\partial T(\xi,t)}{\partial t} = kA\frac{dT(x+\delta x,t)}{dx} - kA\frac{dT(x,t)}{dx}$
- $c\rho A\delta x \frac{\partial T(\xi,t)}{\partial t} = kA\left[\frac{dT(x+\delta x,t)}{dx} - \frac{dT(x,t)}{dx}\right]$
- $c\rho \frac{\partial T(\xi,t)}{\partial t} = k\frac{\left(\frac{dT(x+\delta x,t)}{dx} - \frac{dT(x,t)}{dx}\right)}{\delta x}$
- $c\rho \frac{\partial T(x,t)}{\partial t} = k\frac{\partial^2 T}{\partial x^2}$



Heat Equation

$$c\rho\frac{\partial T(x,t)}{\partial t} = k\frac{\partial^2 T}{\partial x^2}$$

$$c\rho\frac{\partial T(x,t)}{\partial t} = k\left(\frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} + \frac{\partial^2 T}{\partial z^2}\right)$$

$$c\rho\frac{\partial T(x,t)}{\partial t} = k\nabla^2 T$$

Bioheat Equation

$$c\rho \frac{\partial T(x,t)}{\partial t} = k\nabla^2 T$$

$$c\rho \frac{\partial T(x,t)}{\partial t} = k\Delta T + \mathrm{Q}_{\mathrm{ext}} + \mathrm{Q}_{sink}$$

Mathematical Model

$$\rho C \frac{\partial T}{\partial t} = k \Delta T + \omega_b \rho_b C_b (T_a - T) + Q_{ext}$$

Temperature

Blood Density

Density

Heat Source Term

Thermal conductivity

Blood Perfusion

Arterial Temperature

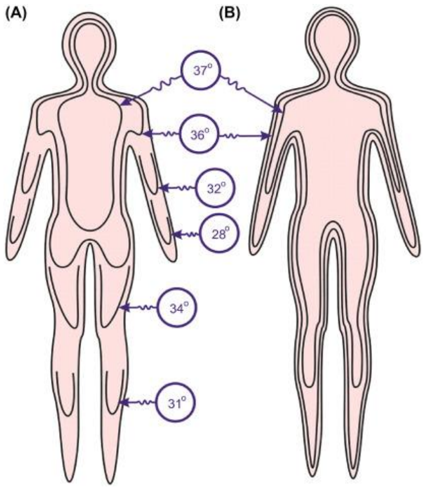
Specific heat of tissue/blood

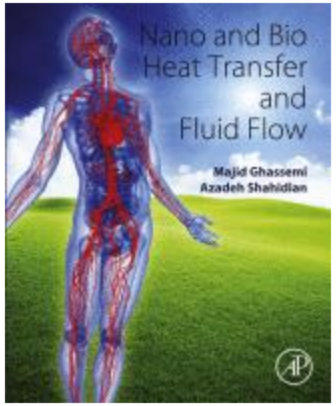
Bioheat Equation: Exercises

- https://www.sciencedirect.com/topics/engineering/bioheat-transfer

$$\rho C \frac{\partial T}{\partial t} = k\Delta T + Q_{perf} + Q_m + Q_{others}$$

"Since the body does not operate with 100% efficiency, only a fraction of the metabolic rate is applied to work and the remainder shows up as heat. The mechanical efficiency associated with metabolic energy utilization is zero for most activities except when the person is performing external mechanical work, such as in walking upstairs, lifting something to a higher level, or cycling on an exercise machine. When external work is dissipated into heat in the human body, the mechanical efficiency is negative. An example of negative mechanical efficiency is walking downstairs. Storage of energy takes place whenever there is an imbalance of production and dissipation mechanisms. In many instances, such as astronauts in space suits or military personnel in chemical defense garments, energy storage is forced due to the lack of appropriate heat exchange with the environment."

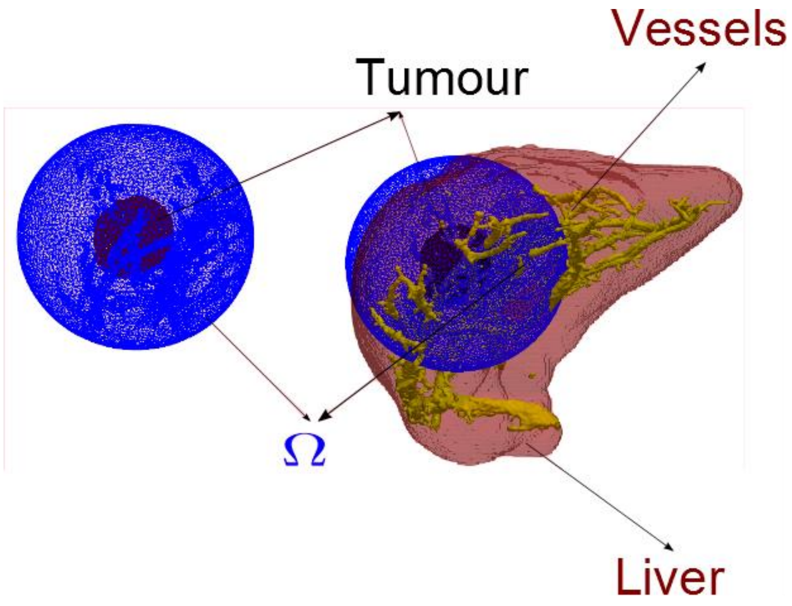




Majid Ghassemi and Azadeh Shahidian, Nano and Bio Heat Transfer and Fluid Flow, 2017, Chapter 3.

Domain of our Problem

- What is the domain of the problem?
- Is the system closed?
- Is the problem well posed?
- Do we need initial conditions?
- Do we need boundary conditions?

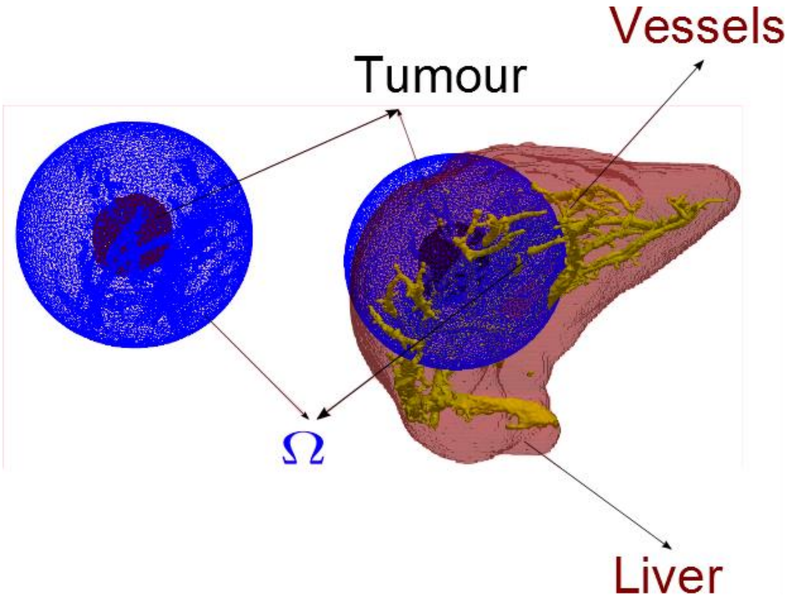


Bioheat Equation[1]

$$\rho C \frac{\partial T}{\partial t} = k\Delta T + \omega_b \rho_b C_b (T_a - T) + Q_r \ on \ \Omega$$

$$h_c T + k \frac{\partial T}{\partial \vec{n}} = h_c T_\infty \text{ on vessels boundary}$$

$$T = T_0 \text{ on } \partial\Omega$$



1. H. H. Pennes, Analysis of tissue and arterial blood temperature in the resting human forearm, J. Appl. Physio. 85(1):93-102, 1948

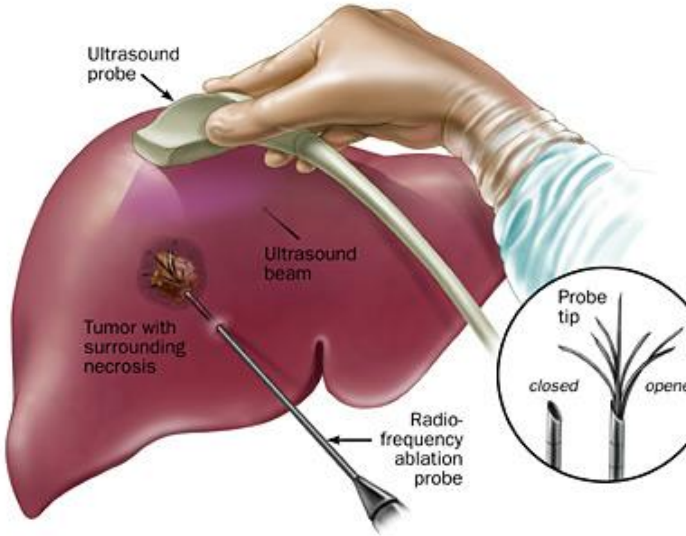
Cell Death Model[1]

Cell Death Model

$$\frac{dA}{dt} = -k_f e^{\frac{T}{T_k}}(1-A)A + k_b(1-A-D)$$

$$\frac{dD}{dt} = k_f e^{\frac{T}{T_k}}(1-A)\,(1-A-D)$$

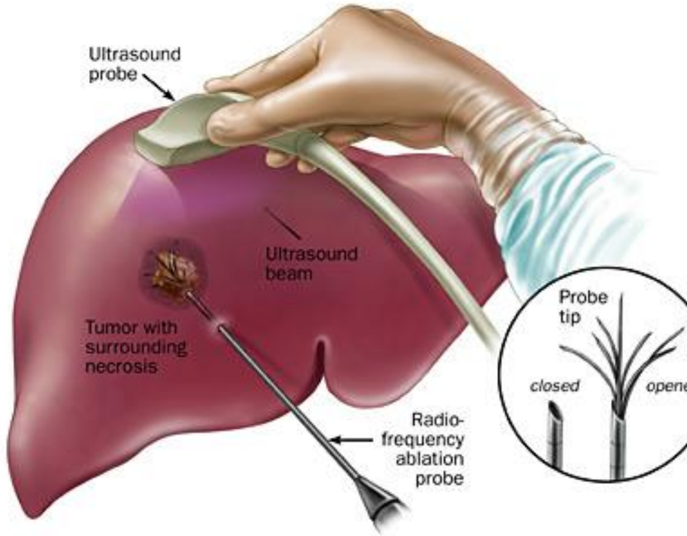
$$\mathrm{A}(0) = 0.99, D(0) = 0.0$$



1. O'Neill DP, Peng T et al (2011) A three-state mathematical model of hyperthermic cell death. Ann Biomed Eng 39(1):570-579

Cell Death Model[1]

Cell Death Model



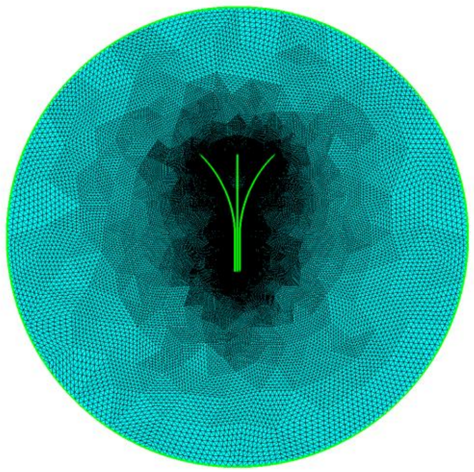
1. O'Neill DP, Peng T et al (2011) A three-state mathematical model of hyperthermic cell death. Ann Biomed Eng 39(1):570-579

Joule Heat Model

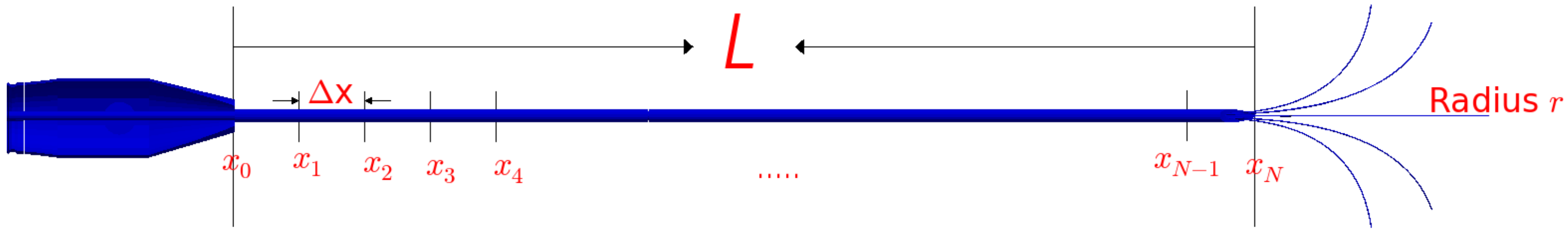
$$\sigma \Delta \phi = 0 \quad on \quad \Omega$$

$$\phi = \begin{cases} \phi_r & on \quad Needle\ Tips \\ \phi_c & on \quad Circular\ boundary \end{cases}$$

$$\frac{\partial \phi}{\partial \vec{n}} = 0 \quad on \quad Needle\ Shaft$$



$$Q_r = \sigma |\nabla \phi|^2$$



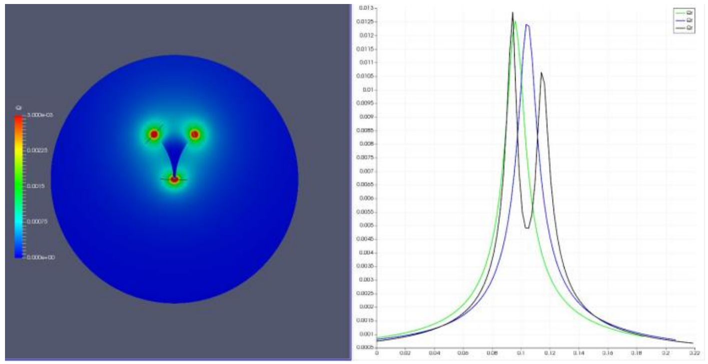
Point Source Model

Gaussian:

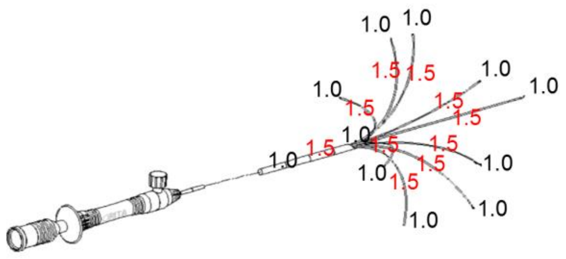
$$P(\vec{x}) = \frac{\sum_{tip} \alpha_{tip} \exp\left(-\frac{\left\|\vec{x} - \vec{x}_{tip}\right\|^2}{2\sigma^2}\right)}{\sum_{tip} \alpha_{tip} \left(\sigma\sqrt{2\pi}\right)^3}$$

Heat Source:

$$Q_r = \sum P(\vec{x}) * power$$



Power Adjustment: PID Controller



End of Lecture