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EXAMPLES AND PRINCIPLES OF MATHEMATICAL MODELLING IN MEDICINE: CRYOABLATION

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1. Clinical Context
Cryoablation

- Cryoablation is a process that uses extreme cold to destroy tissue [1]
- Cooled, thermally conductive fluids are circulated through hollow needles
- System undergoes a number of freeze-thaw cycles
- If tissue reaches -20°C then it is consider treated

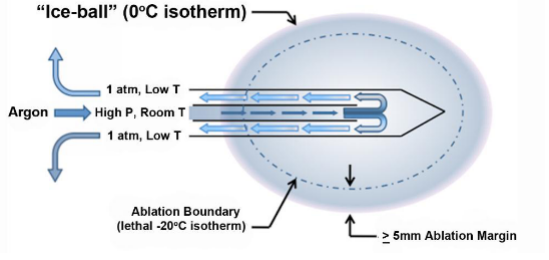

Image taken from [2].

1. Clinical Context
Cryoablation

The volume to be treated will be identified and a safety margin applied. The aim is to position the needle such that the diseased tissue is treated and healthy tissue is spared.

Manufacturers often quote volumes which will be treated in terms of ellipsoids, based on experiments in phantoms or ex vivo tissue. This, however is a simplification which ignores heterogeneity of tissue or biological response.

The prediction of the correct dose requires the accurate modelling of the change of state and the energy require to freeze tissue.

This requires the computation of the enthalpy of the system.

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1. Clinical Context

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Thus, the governing equations must consider enthalpy per unit volume H, i.e., thermal energy, T, and latent heat L, the energy released in the freezing process. As, at the freezing point, the enthalpy jumps by an amount equal to the latent heat.
The heat conduction process is described by a conservation law

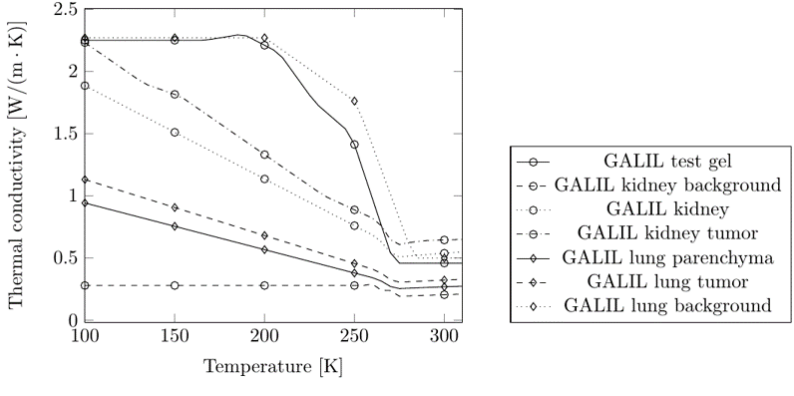
$$\frac{\partial}{\partial t}\left(\rho c_v T + \rho l \Lambda\left(1 + F\right)\right) - \nabla \cdot \left(\kappa_{\text{eff}} \nabla T\right) = 0$$

where ρ is the density, c_v is specific heat capacity, κ_{eff} the effective thermal conductivity, l is the mass-specific latent heat and Λ is the total volume fraction of water within a unit volume of tissue and $F \in [1, 0]$ (unitless) represents the phase of water between frozen and liquid, so that $1 + F$ is the mass fraction of liquid water.

2. Phase Changes

Temperature Dependency

There are significant changes in the material properties within the large temperature range



2. Phase Changes
Cryoablation

Express the governing equation as

$$\frac{\partial}{\partial t}\left(\rho c_v T\right) = \nabla \cdot \left(\kappa_{\text{eff}} \nabla T\right) - l\Lambda \frac{\partial}{\partial t}\left(\rho\left(1 + F\right)\right).$$

Identify voxels in image which contain the actively cooled part of the needle and impose fixed temperature during freezing phase.

Employ an extended predictor-corrector scheme for the evolution of the temperature, the first half step predicts the temperature, without considering the changes in enthalpy, then apply corrections for

- Enthalpy and phase changes
- Changes in specific heat

2. Phase Changes
Cryoablation

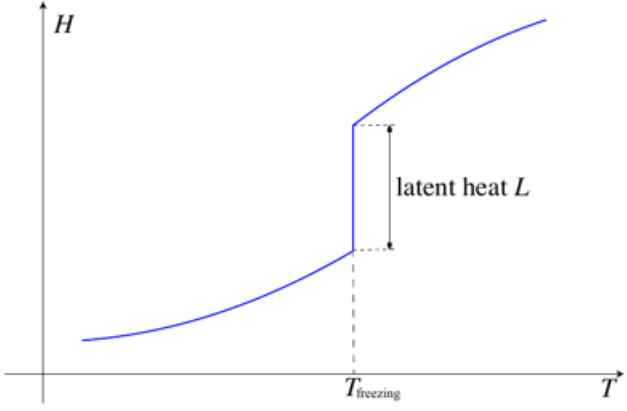


Figure: The enthalpy as a function of temperature is discontinuous, which encapsulates the energy needed to change the state from liquid to sold

The state $F \in [1, 0]$ (unitless) represents the phase of water. A value of –1 indicates a fully frozen unit volume of water, and a value of 0 indicates a fully liquid unit volume of water. Thus, $1 + F$ is the mass fraction of liquid water.

Let F be a piecewise continuous function

$$F(T) = \begin{cases} -1 & \text{if} \quad T \leq T_0 \\ \dfrac{T_1 - T}{T_0 - T_1} & \text{if} \quad T_0 < T < T_1 \\ 0 & \text{if} \quad T \leq T_1 \end{cases}$$

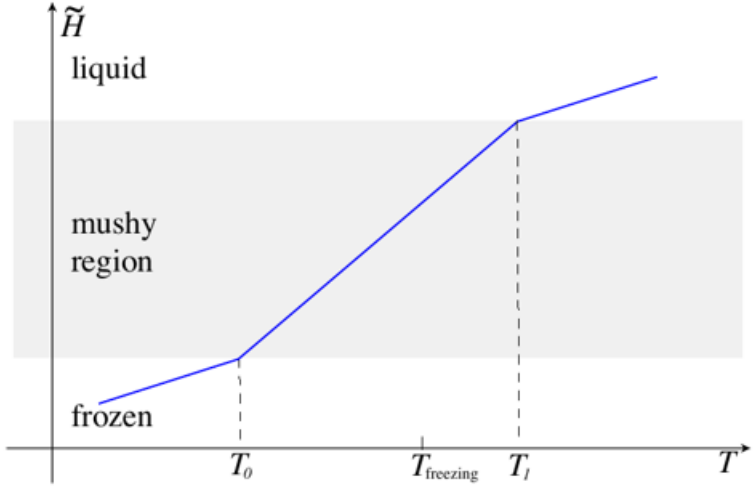
It is invertible: if the temperature is known, so is the ratio of ice to water, and vice versa.

With the “mushy region” approach, the jump in the enthalpy per volume at freezing is converted into an invertible approximation given by

$$H(T) = \begin{cases} \int_0^T \rho(\theta)\, c_v(\theta)\, \mathrm{d}\theta & \text{if} \quad T \leq T_0 \\ \int_0^T \rho(\theta)\, c_v(\theta)\, \mathrm{d}\theta + l\rho(T)\Lambda(1 + F(T)) & \text{if} \quad T_0 < T < T_1 \\ \int_0^T (\rho(\theta)\, c_v(\theta) + l\rho(\theta)\Lambda)\, \mathrm{d}\theta & \text{if} \quad T_1 \leq T \end{cases}$$

2. Phase Changes

Cryoablation



Predictor Step

A simple first-order approximation of the temporal derivative at time $t_i = t_0 + idt$, neglecting enthalpy effects, then yields

$$T^{(i+1/2)} = T^{(i)} + \frac{dt}{\rho^{(i)} c_v^{(i)}} \left(\nabla \cdot \left(\kappa^{(i)} \nabla T^{(i)} \right) \right).$$

It is assumed that the time step is sufficient small such that the material properties are considered to be constant per time step.

Using F, the enthalpy can be approximated as

$$\tilde{H}(T) = \begin{cases} c_v^{(i)} T - I\Lambda & \text{if} \quad T \leq T_0 \\ c_v^{(i)} T + \left(\dfrac{T - T_0}{T_1 - T_0} - 1 \right) I\Lambda & \text{if} \quad T_0 < T < T_1 \\ c_v^{(i)} T & \text{if} \quad T_1 \leq T \end{cases}$$

This approximation $\tilde{H}$ interpolates the slope of the enthalpy H locally around $T^{(i)}$.

This is invertible, so that the temperature can be expressed in terms of the enthalpy.

Corrector for the enthalpy at the predictor time step as

$$H^{(i+1/2)} = c_v^{(i)} T^{(i+1/2)} + \left(\frac{T^{(i)} - T_0}{T_0 - T_1} - 1 \right) l\Lambda.$$

Project the current enthalpy back on the prescribed enthalpy-temperature relation, solving the right hand side of the linearized enthalpy approximation $\tilde{H}^{(i)}$ to get the temperature update at the corrector time step

$$\tilde{T}^{(i+1/2)} = \frac{H^{(i+1/2)}\,(T_1 - T_0) + T_1 l\Lambda}{c_v^{(i)}\,(T_1 - T_0) + T_1 l\Lambda}.$$

Energy Conservation

When c_v is updated it is necessary to modify T to ensure an energy consistent modification on the material based on the enthalpy equation.

Use an (artificial) energy estimate, which

$$\tilde{E}(x) = \frac{1}{2}\left(c_v^{(i+1/2)} - c_v^{(i)}\right)\left(\tilde{T}^{(i+1/2)} - T^{(i)}\right).$$

Thus, introduce a post-processing step after the predictor-corrector steps

$$T^{(i+1)}(x) = \tilde{T}^{(i+1/2)}(x) - \frac{\tilde{E}(x)}{c_v^{(i+1)}(x)}.$$

2. Phase Changes

Computational Steps

1. Compute a predictor $T^{(i+1/2)}$ for the updated temperature through one timestep of the bioheat equation without the enthalpy term

2. If the temperature estimate $T^{(i+1/2)}$ lies
   (a) close to the freezing point, an additional change of the temperature due to the phase change is necessary. In this case, we perform the energy correction step, yielding an updated estimate $\tilde{T}^{(i+1/2)}$.
   (b) outside the mushy region, the energy correction is not applied, thus $\tilde{T}^{(i+1/2)} = T^{(i+1/2)}$.

3. The ratio of ice to liquid is updated according to the corrected temperature value, $F^{(i+1)} = F^{-1}(\tilde{T}^{(i+1/2)})$.

4. The energy conservation step corrects the temperature $\tilde{T}^{(i+1/2)}$ according to the new value of the heat capacity $c_v^{(i+1)}$. This step yields the final temperature update $\tilde{T}^{(i+1)}$.

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3. Validation
Cryoablation

Two types of validation are performed

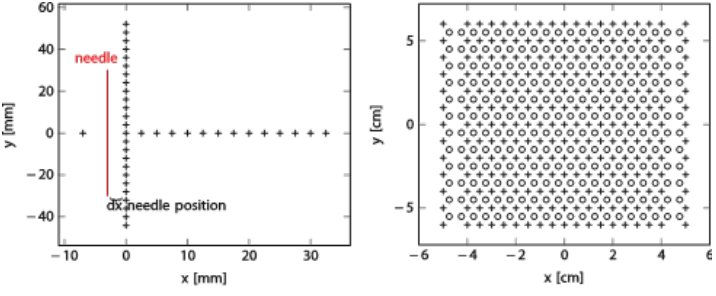
- Expected ice ball dimensions and isotherms are provided by data from phantoms
  - Needles placed in ultrasound gel
  - Multiple needles of same type placed in parallel

- Patient-specific heterogeneous environment:
  - Multiple non-parallel needles
  - Different needle types
  - Biophysical properties of anatomy differ from gel
  - Data from lung and kidney clinical treatments

3. Validation

Validation on Gel Phantom Data: Single Needle

- Show predicting performance by comparing temperature distributions in test gel
- Used thermocouple data of gel experiments [3].



a) Single needle configuration. b) Multiple needle configuration.

Figure: Thermocouple matrices used for measuring the experiments. (a) shows thermocouple positions (+) for single needle assessment. The needle (red) is in-plane with the thermocouples. (b) shows thermocouple positions (+) for experiments with multiple needles. Slots in which the needles can be put are marked with circles (o), the needle is thus orthogonal to the measurement slice. From [1]

3. Validation

Validation on Gel Phantom Data: Single Needle

- Simulate 64 single-needle experiments
- Compare simulated temperature with measured thermo-couple temperature

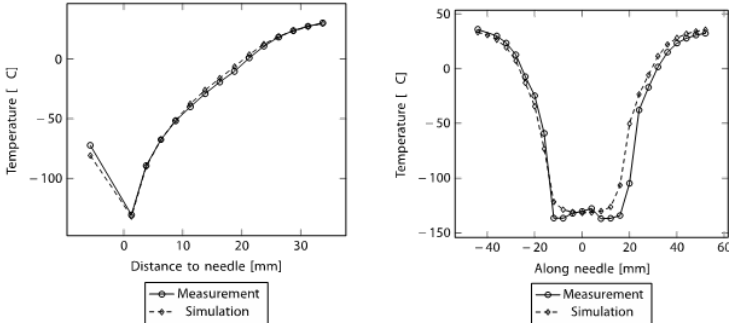


Figure: From [1]

3. Validation

Validation on Gel Phantom Data: Single Needle

Table: Temperature differences over all single needle experiments comparing simulated temperature to measurements.

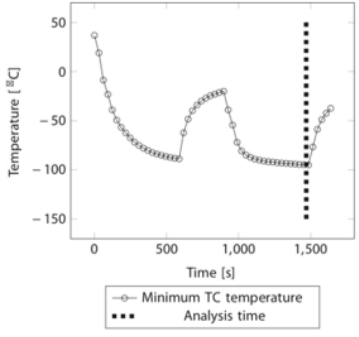
Range [°C]	Avg Diff [°C]	Std Dev
(5, ∞)	1.82	1.67
[-5, 5]	5.11	3.66
(-15, -5)	4.81	4.22
[-25, -15]	4.11	3.69
(-35, -25)	4.90	3.55
[-45, -35]	4.45	3.89
[− ∞, -45)	7.99	7.83

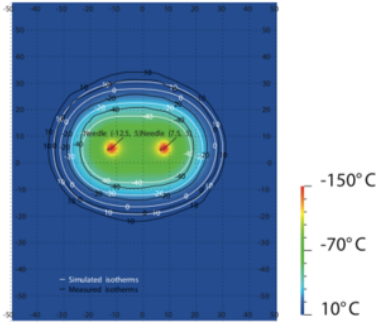
- Within clinically relevant range less than 5°C difference

3. Validation

Validation on Gel Phantom Data: Multiple Needles

- Simulate 12 multi-needle experiments
- Compare simulated temperature with measured thermo-couple temperature





Validation on Gel Phantom Data: Multiple Needles

Table: Temperature differences over all multi needle experiments comparing simulated temperature to measurements.

Temp Range [°C]	Avg Diff [°C]	Std Dev
$(5, \infty]$	1.18	1.31
$[-5, 5]$	6.42	3.93
$(-15, -5)$	6.96	4.36
$[-25, -15]$	5.05	3.47
$(-35, -25)$	6.22	3.42
$[-45, -35]$	5.55	4.24
$[-\infty, -45)$	6.43	4.68

- Within clinically relevant range less than 7°C difference and approximately 2 mm mean distance between isothermal contours

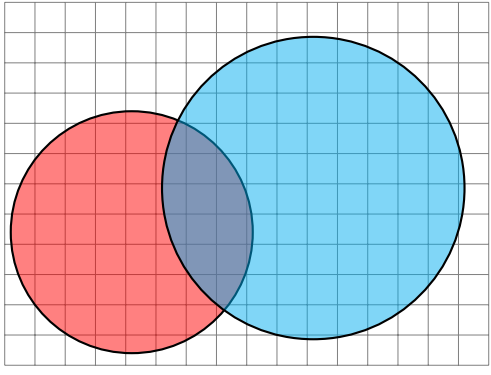
Validation on Gel Phantom Data: Multiple Needles

Table: Overall contour distances for experiments with multiple needles.

Temperature °C	Minimum Surface Distance [mm]	Maximum Surface Distance [mm]	Mean Surface Distance [mm]
-40	0.002	3.29	1.21
-20	0.001	3.28	1.28
0	0.002	3.74	1.52
10	0.755	4.14	2.28

3. Validation

Dice Coefficient



The key is the Dice coefficient, given by

$$\frac{2|X \cap Y|}{|X| + |Y|}$$

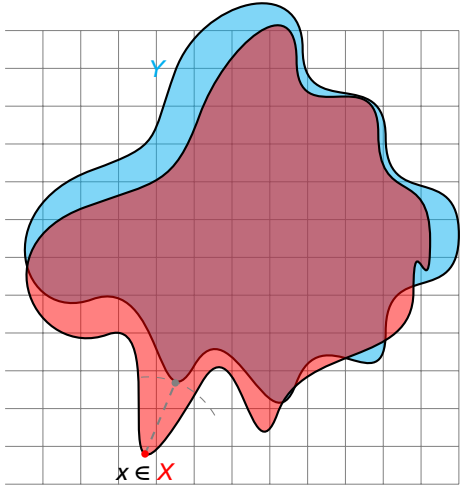
It ranges between $(0, 1)$.

The discretisation of the regions introduces an uncertainty.

And that the smaller the volume, then often worse the score.

3. Validation

Hausdorff Distance



The Hausdorff distance $d_H(X, Y)$ computes on all points, x, of a curve, X, the shortest distance to another curve Y and vice versa, then finds the maximum of these distances

$$d_H(X, Y) = \max\left\{\sup_{x\in X} d(x, Y),\ \sup_{y\in Y} d(y, X)\right\}$$

where $d(a, B) = \inf_{b\in B} d(a, b)$.

3. Validation

Validation on Clinical Model

Table: Parameter values used in the analysis for kidney and lung tissue.

		Kidney			Lung		
Parameter Name	Unit	Min	Max	Default	Min	Max	Default
Density	$kg\ m^{-3}$	1019	1147	1066	255	1050	722
Heat Capacity	$J\ kg^{-1}\ K^{-1}$	3505	3891	3505	3653	4119	3886
Thermal Conductivity	$J\ m^{-1}\ s^{-1}\ K^{-1}$	0.499	0.56	0.55	0.2495	0.4957	0.275
Relative Blood Perfusion Rate	s^{-1}	0.0044	0.0888	0.071	0.00173	0.007	0.0048
Body Temperature	°C	35.5	38.0	37.0	35.5	38.0	37.0
Needle Temperature	°C	-180	-119.15	-143.15	-180	-119.15	-143.15

3. Validation

Validation on Clinical Model

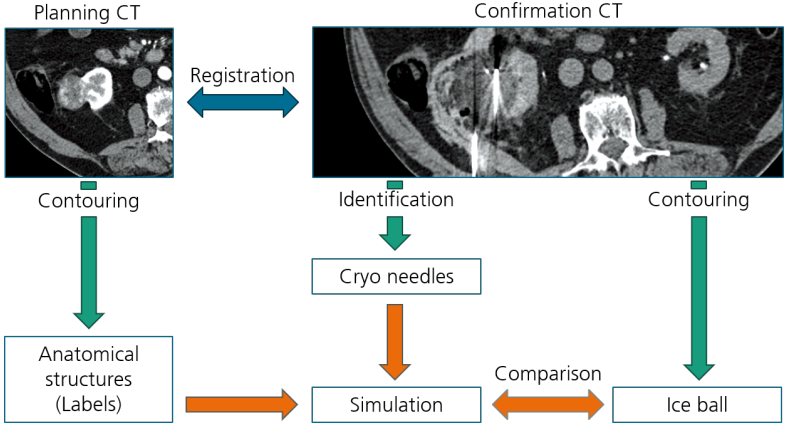


Figure: Steps to perform validation

3. Validation

Validation on Clinical Model

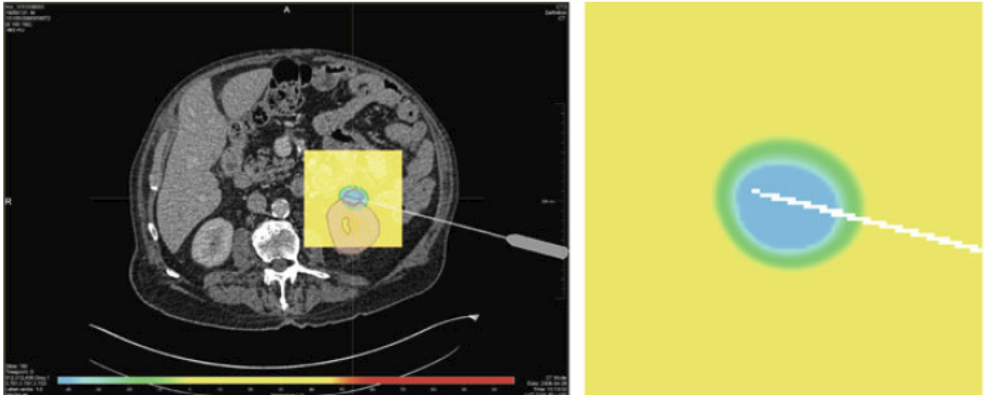
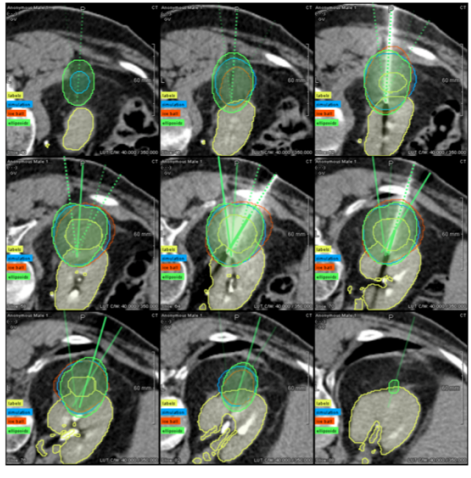


Figure: Left: Overlay of computational domain over segmented image. Right: thermal field [4]

3. Validation

Validation on Clinical Model: Kidney



Example kidney case showing the contoured labels (yellow), the simulation result 0°C isotherm (blue), the contoured ice ball (red), as well as the needles with corresponding ellipsoids (green).

Image data sets are courtesy of Dr. Alex King, University Hospital Southampton

3. Validation

Validation on Clinical Model: Kidney

Table: Averaged measures of the 14 kidney cases (mean values and standard deviation over all cases)

Region(s)	Measure	Mean	Std Dev
Ellipsoid–ice ball	Dice coefficient [0,. . .,1]	0.79	0.06
	Max surface distance [mm]	12.32	3.87
	Mean surface distance [mm]	3.05	0.90
	Relative volume error	0.19	0.13
Simulation–ice ball	Dice coefficient [0,. . .,1]	0.82	0.06
	Max surface distance [mm]	10.57	3.47
	Mean surface distance [mm]	2.59	0.97
	Relative volume error	0.18	0.12
Ellipsoid	Max 3D diameter [mm]	59.42	9.52
	Volume [ml]	67.73	29.30
Ice ball	Max 3D diameter [mm]	62.49	11.79
	Volume [ml]	69.45	36.86
Simulation	Max 3D diameter [mm]	55.03	9.41
	Volume [ml]	65.52	31.79

3. Validation

Validation on Clinical Model: Lung

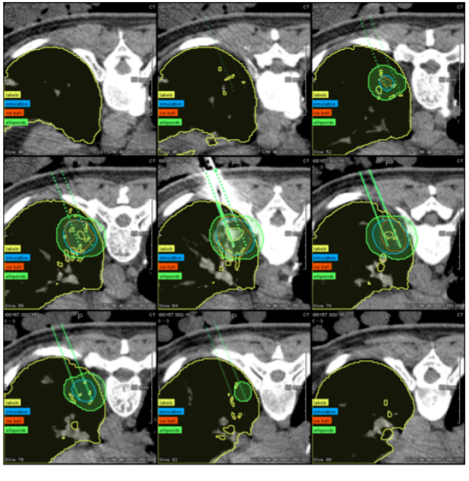


Figure: Slices through CT data showing identified tissues, needles and damaged regions

Validation on Clinical Model: Lung

Table: Averaged measures of the 13 lung cases (mean values and standard deviation over all cases)

Region(s)	Measure	Mean	Std Dev
Ellipsoid–ice ball	Dice coefficient [0,. . .,1]	0.50	0.17
	Max surface distance [mm]	12.24	3.52
	Mean surface distance [mm]	5.22	1.82
	Relative volume error	2.62	2.69
Simulation–ice ball	Dice coefficient [0,. . .,1]	0.63	0.13
	Max surface distance [mm]	10.80	5.81
	Mean surface distance [mm]	3.12	1.15
	Relative volume error	0.70	0.91
Ellipsoid	Max 3D diameter [mm]	41.78	5.68
	Volume [ml]	26.72	5.68
Ice ball	Max 3D diameter [mm]	41.80	10.46
	Volume [ml]	10.57	5.83
Simulation	Max 3D diameter [mm]	32.63	5.17
	Volume [ml]	9.82	3.39

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Results

- Temperature difference in gel experiments:
  - Single needle < 5°C, multi needle < 7°C
  - In range of reported deviations of lethal damage

- In clinical cases:

  - Kidney: Dice: 0.82, mean/max surface distance: 2.59 mm / 10.57 mm
    - In range of safety margin

  - Lung: Dice: 0.63, mean/max surface distance: 3.12 mm / 10.8 mm
    - Further improvement needed

4. Conclusions

Discussion

- Clinical validation is more challenging than thermocouple data from a consistent phantom with well known properties
  - Note differences between time-series at fixed points and volumetric data at end of treatment.
- Model does not distinguish between extra-cellular and intra-cellular components of tissues.
- Effect of freezing on blood flow not modelled. Tissue at low, but not frozen temperatures may be damaged
- Uncertainties in:
  - Needle position – does the needle move in treatment
  - Material properties; dependencies on temperature
  - Tumour properties not well known
  - Segmentation of frozen region

4. Conclusions

Open Problems

- Compare 0°C isothermal contours with segmented ice balls: which temperature would best match the frozen regions?
- Can the function *F* be chosen to yield better results?
- While the fluid is not circulated, i.e. during a thaw cycle, how should the temperature be modelled as?
- Can a Bayesian approach be applied to describe the effect of the uncertainty in the position of the probe as well as the uncertainty in the position of the thermocouple?
- Can multi-scale homogenization approach provide a more accurate model to freezing? But in this case how is the effect of the probe modelled across the length scales?
- Can the occlusion of vessels be modelled and the effect on perfusion on the thermal field be computed? Also how does this relate to the damage to the tissue?

5. Bibliography

[1] Christian Rieder, Michael Schwenke, Torben Pätz, Joachim Georgii, Hanne Ballhausen, Lars Ole Schwen, Sabrina Haase, and Tobias Preusser.
Evaluation of a numerical simulation for cryoablation–comparison with bench data, clinical kidney and lung cases.
Int. J. Hypertherm., 37(1):1268–1278, 2020.

[2] Tsitskari Maria and Christos Georgiades.
Percutaneous cryoablation for renal cell carcinoma.
J Kidney Cancer VHL, 2(3):105, 2015.

[3] Taimur T Shah, Uri Arbel, Sonja Foss, Andrew Zachman, Simon Rodney, Hashim U Ahmed, and Manit Arya.
Modeling cryotherapy ice ball dimensions and isotherms in a novel gel-based model to determine optimal cryo-needle configurations and settings for potential use in clinical practice.
Urol., 91:234–240, 2016.

[4] Joachim Georgii, Torben Pätz, Christian Rieder, Hanne Ballhausen, Michael Schwenke, Lars Ole Schwen, Sabrina Haase, and Tobias Preusser.
Efficient gpu-based numerical simulation of cryoablation of the kidney.
In *Computational Biomechanics for Medicine MICCAI 2019*, pages 171–193. Springer, 2020.

Thankyou for your attention

Any questions?

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