Mathematical Model Developments for Thermochemical Ablation

Samuel Oedi[1], David Fuentes[2], Greg Morrison[1], Drew Mitchell[2], Evan Gates[2], Michael Spors[2], Niloofar Karbasian[2], Nina M. Muñoz[2], Chunxiao Guo[2], Jossana Damasco[2], Erik Cressman[2]

[1]University of Houston – Department of Physics, [2]University of Texas MD Anderson Cancer Center

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Introduction

Thermochemical ablation (TCA) is a novel, conceptual platform of minimally invasive therapy of hepatocellular carcinoma (HCC), which is the most common type of liver cancer. In TCA, an acid and a base are mixed immediately prior to injection. As a result, heat is released as exothermal reaction occurs and hot salt solution enters the targeted tissue.[1] Understanding the impact heat and salt have on treated tissue is important. Therefore, to develop the mathematical model of TCA, several key components must be understood. The first component is an equation of state that describes how the density of injected solutions change with temperature and concentration. The second component is a cell damage model that estimates the viability of cells treated with TCA. The last component is the development of a porous media flow phantom that will be used to validate the mathematical models. In these experiments, we show that 1) the selected equation of state can reasonably describe temperature- and concentration-induced changes in density; 2) a modified Arrhenius model can predict cell viability after the treatment; and 3) we determined the porosity of different foams, which is a necessary step to develop a liver mimicking phantom that will provide a reproducible, controlled environment to validate the model predictions.

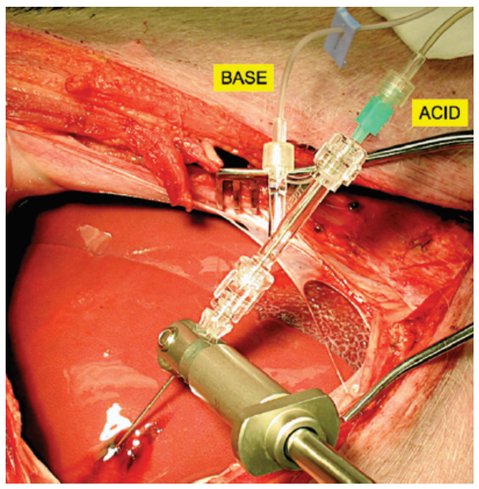

Fig. 1 Illustration of a TCA injection into a targeted tissue (porcine model).[1]

Equation of State

Governing equations for our formulation enforce mass, momentum and energy balance, and are derived from mixture theory.[2] To describe the density of the ablative solutions during the injection, the model proposed by Laliberté and Cooper (Eq. 1-3) was selected. This model has a relatively simple form and parameters for HCl, NaOH, and NaCl that were already determined experimentally. The density measurements of HCl, NaOH, and NaCl solutions tabulated in Perry's Chemical Engineers' Handbook[3] were used to validate this model.

The data were also extrapolated up to 200°C using Matlab's "interp1" from data between 0°C and 100°C.

Here is the Laliberté and Cooper model[4]

$$\rho_m = \left(w_{H_2O}\bar{v}_{H_2O} + \sum_i w_i \bar{v}_i\right)^{-1} \quad (1)$$

$$\bar{v}_i = \frac{w_i + c_2 + c_3 u}{(c_0 w_i + c_1)\exp(0.000001(u + c_4)^2)} \quad (2)$$

$$\bar{v}_{H_2O} = \frac{1 + au}{bu^5 + cu^4 + du^3 + eu^2 + fu + g} \quad (3)$$

Here, u is temperature, w is mass fraction and $\bar{v}$ is specific volume.

Figure 2 shows that the model can capture the trend of the densities of aqueous HCl, NaOH, and NaCl between 0°C and 200°C ($0.81 < R^2 < 1.0$).

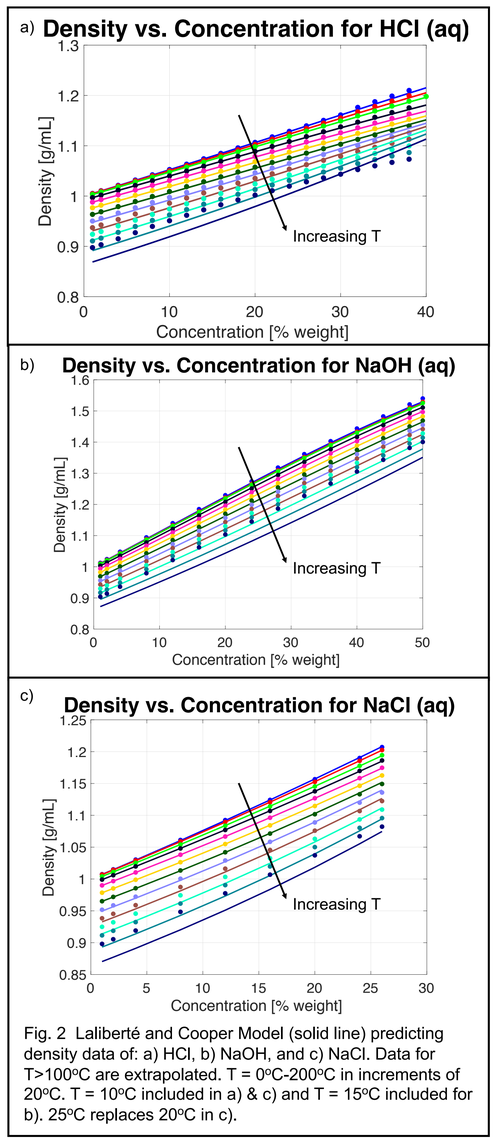

Fig. 2 Laliberté and Cooper Model (solid line) predicting density data of: a) HCl, b) NaOH, and c) NaCl. Data for T>100°C are extrapolated. T = 0°C-200°C in increments of 20°C. T = 10°C included in a) & c) and T = 15°C included for b). 25°C replaces 20°C in c).

Cell Damage

The Arrhenius rate equation (Eq. 4) describes a first-order irreversible reaction, in this case, from viable to nonviable. The equation was modified to account for salt concentration (C_i in M) in addition to temperature (T in K). Then, it was used as dose model for estimating cell viability (V), shown in (Eq. 5). The modification of the activation energy term, such that $E_a(C_i) = E_a^0 + E_a^1 C_i$ [J/mol], was considered as a first approximation.

The data used to verify the model simulate the interplay of hyperthermal and hyperosmotic stresses. These are the Arrhenius model equations: [5],[6]

$$\Omega = A\int_0^\tau \exp\left[\frac{-E_a}{R*T}\right]dt, \quad (4)$$

where R = 8.314 J/(mol K)

$$\ln A = [3.8 * 10^{-4} * E_a] - 9.36 \quad (5)$$

$$V = \exp(-\Omega) \quad (6)$$

Figure 3 shows that the damage model can accurately predict ($R^2 \geq 0.96$) the viability of two human HCC cell types, Hep3B and SNU449.

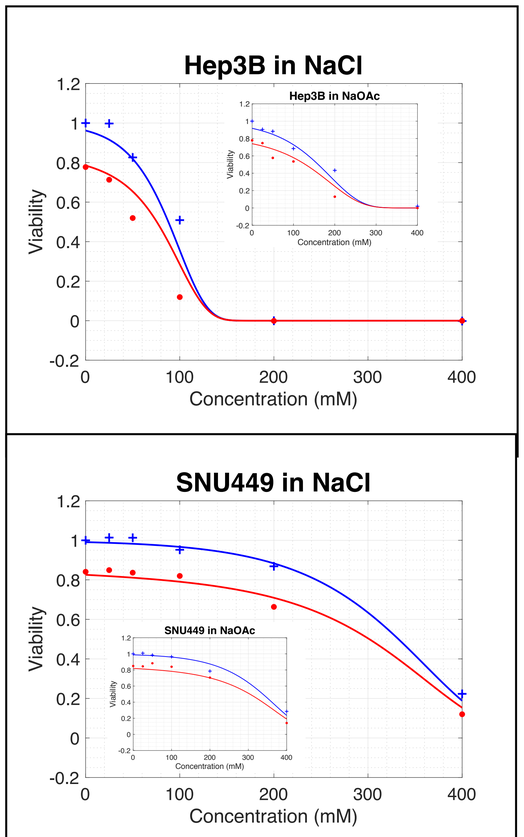

Fig. 3 Arrhenius Model (solid line) predicting viability (data points) of Hep3B and SNU449 cells, in NaCl and NaOAc, at 37°C-blue and 43°C-red. $R^2 \geq 0.96$.

Table 1. Arrhenius parameters Ea (J/mol) for model fitting.

	Hep3b Parameters		SNU449 Parameters	
Salt	Ea^0	Ea^1	Ea^0	Ea^1
NaCl	7.E+05	-4.E+03	8.E+05	-2.E+03
NaOAc	6.E+05	-2.E+03	8.E+05	-1.E+03

Foam Phantom

Acquisition of datasets of salt distribution and temperature are required to design and evaluate mathematical models of TCA injections. The development of a liver mimicking phantom begin with combining open-cell foams and gelatin. The porous foam was selected as the basis of the phantom because liver is porous. The gelatin was added to simulate the resistance when injecting into liver tissue.

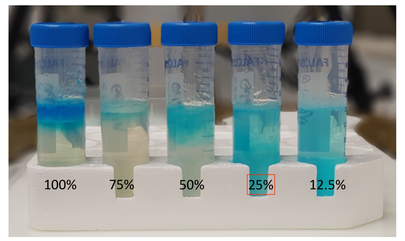

Fig. 4 Different gelatin concentrations in water. High gelatin concentration samples are unsuitable for injection because water could not flow through.

To calculate porosity, ϕ, of the foam, liquid intrusion method was used[7]:

$$\phi = \frac{V_{void}}{V_{total}} = \frac{V_{water}}{V_{water} + V_{foam}} \quad (7)$$

Table 2. Porosity calculations for various 1" cube foams.

Manufacturer: Foam Factory Inc.

Foam	V_{foam} [mL]	m_{dry} [g]	m_{wet} [g]	V_{water} [mL]	Porosity
Super Lux	15.7	0.480	16.3	15.8	0.501
Lux Reg	15.7	0.445	15.5	15.1	0.491
HD36 Reg	15.4	0.490	15.4	14.9	0.492
Super Max	15.0	0.650	14.9	14.2	0.486

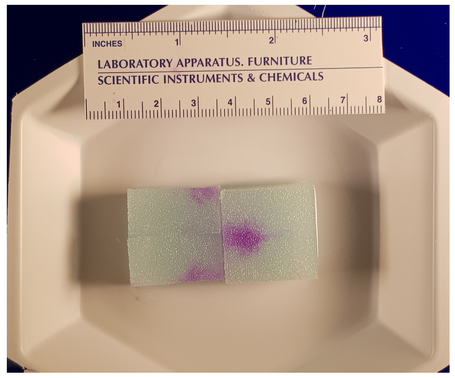

Fig. 5 Cross section of Lux Reg foam soaked in 15% gelatin water, and set overnight. Colored water (0.1 mL) injected into the foam.

Conclusion

The Laliberté and Cooper equation can be used to describe density at temperatures and concentrations relevant to TCA. The modified Arrhenius model should be tested on HCC cells that are more sensitive to heat to further confirm its accuracy. The practice of modifying Arrhenius model can also be used to develop more sophisticated models, such as two-transition-state model of cell survival curves.[6] An early procedure to develop liver mimicking phantom was completed to assess the range of porosity available from commercially available materials.

Acknowledgement

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