# Mathematical Modeling of Heat Distribution during Cryosurgery

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# Introduction

Cryosurgery, also referred to as cryoablation, is a surgical technique where undesirable or diseased tissue is frozen down using extremely low temperatures. In practice since the 1940s, Cryosurgery began as early surgeons were interested in the anesthetic properties of low temperatures. It was eventually discovered that most tissues will begin undergoing necrosis between -15°C to -40°C, and undesirable tissues were frozen from the exterior. It was not until the 1960s that the invention of surgical probes internally perfused with liquid nitrogen allowed for the insertion of such probes into the target tissue to freeze them from within. Several advantages of cryosurgery include the low invasiveness of the procedure, minimal blood flow, localizing of the site of surgery and reducing the recovery time and hospitalization time for the patient. In some instances, local anesthesia can be used in place of general anesthesia, which will result in less surgical complications. This means that in general the procedure will reduce costs for the patient. [1]

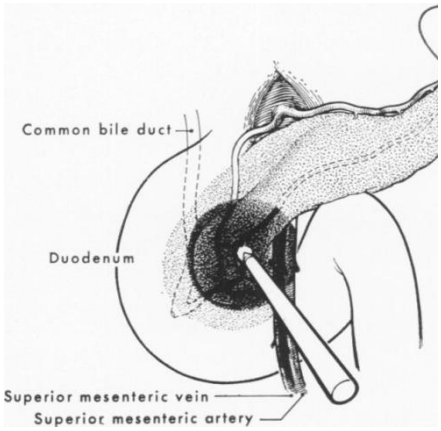



Fig 1. A Schematic of how cryosurgery is performed on a pancreatic lesion.[2]

While the procedure can be easily performed, it is difficult to monitor the temperature of the tissue in real time, since it would require the insertion of temperature probes which increases the invasiveness of the surgery. Thus, many researchers have turned to mathematical modeling to better understand the temperature profile of the tissue. Here, we modified the bioheat equation to obtain,

$$C\,\frac{\partial u}{\partial t} = k\left(\frac{\partial^2 u}{\partial r^2} + \frac{2}{r}\cdot\frac{\partial u}{\partial r}\right) + Q_m$$

where u is the temperature in the tissue, r is the radius of a sphere away from the probe, k is the thermal conductivity of tissue, C is the specific heat of tissue and $Q_m$ is the metabolic heat generation.

# Problem Formulation

## Establishment of geometry, boundary and initial conditions.

In this study, we simulated a spherical mass of tissue that is isotropic in its thermal properties. In the middle of the tissue nests an ideal probe that occupies an infinitesimally small volume perfused by liquid nitrogen, thereby keeping the center of the sphere at -196°C. Our subsequent boundary condition is at a region infinitely far away from the probe, where the temperature should be that of body temperature, kept constant at 37°C. Before the start of the surgery, the temperature of the tissue should be constant at 37°C.

However, in the freezing process, the cells will undergo a phase change at the freezing point, where they will be losing latent heat of freezing and temperature change in these cells should, theoretically, be 0. However, it has been observed clinically that the freezing state takes place across the temperature range -1°C > u > -8°C. Another point for consideration is that tissues have different thermal properties in their frozen/freezing/unfrozen states, which will be listed in the table of constants in the bioheat equation section below. Hence, our analysis will be broken down into three different temperature ranges, 37°C > u > -1°C when cells are unfrozen, -1°C > u > -8°C when cells are freezing and -8°C > u > -196°C when cells are frozen. This yields us three separate equations with different boundary conditions. Knowing the total amount of latent heat required, we took an average latent heat and combined it with the specific heat capacity constant so as to simplify the problem. We believe this range of temperature is as such since different tissues will contain a different composition of matrix components, organelles and solutes in it which will depress the freezing point.

## Bioheat Equation

The temperature profile in the tissue can be described with Penne's bioheat equation, which is a second ordered differential equation that goes by the form:

$$C\frac{\partial u(\mathbf{X},t)}{\partial t} = \nabla \cdot k\nabla[u(X,t)] + C_b\omega_b T_a - \omega_b C_b u(X,t) + Q_m$$

Where C, $C_b$ are the heat capacity of biological tissue and blood, X contains the Cartesian Coordinates x, y and z; k is the thermal conductivity of tissue, $\omega_b$ is the perfusion of blood, Ta is the arterial temperature, u is the tissue temperature and $Q_m$ is the metabolic heat generation. The values are presented in the table of constants below.

Typical thermophysical properties of soft biological tissues [2,16,20]

| | Unit | Value |
|---|---|---|
| Heat capacity of the frozen tissue | $MJ/m^3$ °C | 1.8 |
| Heat capacity of the unfrozen tissue | $MJ/m^3$ °C | 3.6 |
| Heat capacity of the blood | $MJ/m^3$ °C | 3.6 |
| Thermal conductivity of the unfrozen tissue | W/m °C | 0.5 |
| Thermal conductivity of the frozen tissue | W/m °C | 2 |
| Latent heat | $MJ/m^3$ | 250 |
| Body core temperature | °C | 37 |
| Lower phase transition temperature | °C | −8 |
| Upper phase transition temperature | °C | −1 |
| Blood perfusion of normal tissue | ml/s/ml | 0.0005 |
| Blood perfusion of tumor tissue | ml/s/ml | 0.002 |
| Metabolic rate of normal tissue | $W/m^3$ | 4200 |
| Metabolic rate of tumor tissue | $W/m^3$ | 42,000 |

Fig 2. A table of constants for values used in the bio heat equation for all three temperature ranges

This equation can be further simplified in our instance if we consider that in rapidly freezing tissues, we will first cause vasoconstriction in the capillaries before freezing all the blood in the capillaries. In the absence of perfusion, the already small $\omega_b$ term goes to zero. Also, cells will not be able to generate any metabolic heat when frozen, and $Q_m$ is nonexistent in temperatures below 0. Putting these together, before the cells are freezing we have a nonhomogenous differential equation and cells in the frozen and freezing states can be described with a homogenous differential equation instead.

Upon inspection, it becomes apparent that the diffusion in the system is radial in spherical coordinates and independent of the other spherical coordinates, φ and θ. By converting Penne's bioheat equation into spherical coordinates, we obtain the equation first mentioned in our introduction,

$$C\,\frac{\partial u}{\partial t} = k\left(\frac{\partial^2 u}{\partial r^2} + \frac{2}{r}\cdot\frac{\partial u}{\partial r}\right) + Q_m$$

Which we will solve analytically to obtain our temperature profile. It is worth mentioning here that in converting from a Cartesian coordinate system, we generate an additional "$\frac{2}{r}\cdot\frac{\partial u}{\partial r}$" term describing the dependence of change in temperature with time on the spatial variation of temperature in both the first and second order, which hints at a solution utilizing spherical Bessel's functions.

## Analytical Solution

Starting with our modified bioheat equation,

$$c\times\frac{\partial u}{\partial t} = k\times\left(\frac{\partial^2 u}{\partial r} + \frac{2}{r}\times\frac{\partial u}{\partial r}\right) + Q_m \ldots(1)$$

And our boundary and initial conditions,

$u(0,t) = T_1$ and $u(b,t) = T_b$. (2 and 3)

$$\tilde{c} = \begin{cases} c_u & u > -1^{\circ}C \\ \frac{Q_1}{7} + \frac{c_f + c_u}{2} & -8^{\circ}C < u < -1^{\circ}C \\ c_u & u < -8^{\circ}C \end{cases} \quad (4), \qquad \tilde{k} = \begin{cases} k_u & u > -1^{\circ}C \\ \frac{k_f + k_u}{2} & -8^{\circ}C < u < -1^{\circ}C \\ k_u & u < -8^{\circ}C \end{cases} \quad (5)$$

$$\tilde{Q}_m = \begin{cases} 0.042 & u > -1^{\circ}C \\ 0 & -8^{\circ}C < u < -1^{\circ}C \\ 0 & u < -8^{\circ}C \end{cases} \quad (6) \qquad u(r,0) = T_1 = \begin{cases} 37 & u > -1^{\circ}C \\ -1 & -8^{\circ}C < u < -1^{\circ}C \\ -8 & u < -8^{\circ}C \end{cases} \quad (7)$$

Where (2) and (3) are our boundary conditions, (7) is our initial condition and (4) through (6) are our constants.
To solve the non-homogeneous equation with non-homogeneous boundary conditions, we first find a particular solution and then add it to the solution of the homogeneous equation.

$$u(r,t) = u_s(r) + u_h(r,t) \quad (8)$$

The particular solution is found by finding the steady state solution- $u_s(r)$ which is u at infinite time. Therefore,

$$c \times \frac{\partial u}{\partial t} = 0 = k \times (\frac{\partial^2 u}{\partial r} + \frac{2}{r} \times \frac{\partial u}{\partial r}) + Q_m \quad (9)$$

Solving the steady state equation and applying the boundary conditions, we get,

$$u(r) = -\frac{Q_m r^2}{6k} + (\frac{(T_1 - T_2)}{b} + \frac{Q_m b}{6k})r + T_2 \quad (10)$$

Subsequently, the homogeneous solution:

$$u(r,t) - u_s(r) = u_h(r,t) \quad (11)$$

The boundary conditions of $u_h(r,t)$ are

$$u_h(0,t) = 0$$
$$u_h(b,t) = 0$$

The differential equation is

$$\frac{\partial u_h}{\partial t} = \frac{k}{c} \times (\frac{\partial^2 u_h}{\partial r} + \frac{2}{r} \times \frac{\partial u_h}{\partial r}) \quad (12)$$

Using separation of variables, we get

$u_h(r,t) = p(r) \times g(t)$ - which when substituted in (12) gives us

$$\frac{c}{k} \times \frac{g'(t)}{g(t)} = \frac{1}{p(r)} (p''(r) + \frac{2}{r} p'(r)) = -\lambda^2 \quad (13)$$

Solving for g, we get: $g(t) = C_1 \times e^{-\lambda^2 \frac{k}{c} t}$. (14)

To solve for p(r)

$$p''(r) + \frac{2}{r} p'(r) = -\lambda^2 p(r) \ldots . (15)$$

To solve this equation, use the substitution:

$$p(r) = \frac{q(r)}{\sqrt{r}}.$$

The equation becomes $r^2 q''(r) + r q'(r) + q(r)(\lambda^2 \times r^2 - \frac{1}{4}) = 0$ (16) which is of the form

$r^2 q''(r) + r q'(r) + q(r)(\lambda^2 \times r^2 - (m + \frac{1}{2})^2) = 0$. This is the rescaled Bessel function of half integer order (m+1/2). The solution to this is:

$q(r) = J_{\frac{1}{2}}(\lambda r)$ and hence $p(r) = \frac{J_{\frac{1}{2}}(\lambda r)}{\sqrt{r}}$ .... (17).

The Spherical Bessel function of order m is defined as

$$S_m(x) = \sqrt{\frac{\pi}{2x}} J_{m+\frac{1}{2}}(x)$$

.

Therefore, $p(r) = \sqrt{\frac{2\lambda}{\pi}} \times S0(\lambda r)$. On applying the boundary condition at r=b, we get $\lambda = \frac{n\pi}{b}$ .

The overall equation becomes,

$$u(r,t) = -\frac{Q_m r^2}{6k} + (\frac{(T_1 - T_2)}{b} + \frac{Q_m b}{6k})r + T_2 + L \times \sum_{n=1}^{\infty} (\frac{1}{r\pi}\sqrt{\frac{2b}{n}} \times \sin(\frac{n\pi r}{b}) \times e^{-(\frac{n\pi}{b})^2 \frac{k}{c}t}$$

where L is a constant.

To find L, apply the initial condition u(r,0)=37 °C.

$$u(r,t) = -\frac{Q_m r^2}{6k} + (\frac{(T_1 - T_2)}{b} + \frac{Q_m b}{6k})r + T_2 + \frac{(1-\frac{r}{b})(T1 - T2 - \frac{Q_m b}{6k} r)}{\sum_{n=1}^{\infty} (\frac{1}{r\pi}\sqrt{\frac{2b}{n}} \times \sin(\frac{n\pi r}{b})} \times \sum_{n=1}^{\infty} (\frac{1}{r\pi}\sqrt{\frac{2b}{n}} \times \sin(\frac{n\pi r}{b}) \times e^{-(\frac{n\pi}{b})^2 \frac{k}{c}t}$$

Which simplifies to our analytical solution

$$u(r,t) = -\frac{Q_m r^2}{6k} + (\frac{(T_1 - T_2)}{b} + \frac{Q_m b}{6k})r + T_2 + \sum_{n=1}^{\infty} (1-\frac{r}{b})(T_1 - T_2 - \frac{Q_m b}{6k} r) \times e^{-(\frac{n\pi}{b})^2 \frac{k}{c}t}$$

The analytical solution was then plotted using MATLAB. However, we were unable to stitch the three different graphs together, and hence, will be presenting them separately in three separate plots. While these plots will not be able to tell us the temperature profile of tissue from 37°C to freezing at -196°C through our proposed 3-phase temperature change, we can see how the varying constants and conditions during each phase will change the temperature profile gradient. Pieced together, we can roughly see how the temperature progression will be changed. This comparison can be then drawn to our numerical solution, where we managed to stitch the solutions together.

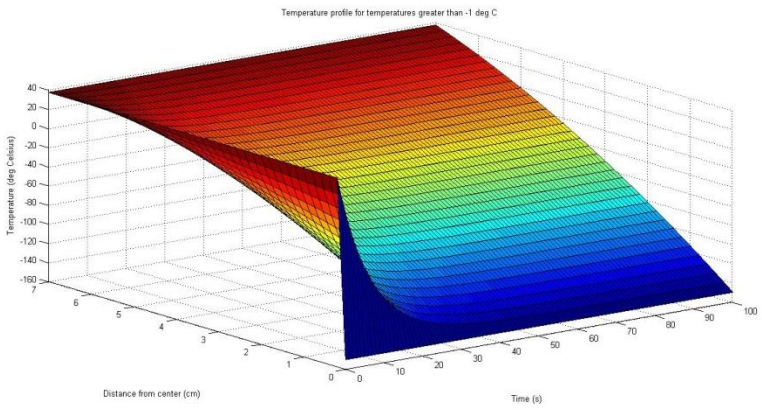
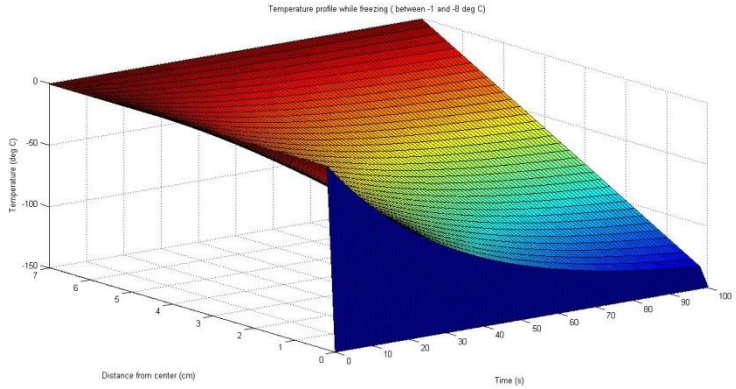



Fig 3a. Temperature profile for the tissue above freezing point.

The temperature closest to the probe, x drops quickly and drastically. At steady state, temperature is a curve. This is only valid for u > -1°C

Fig 3b. Temperature profile for the tissue during freezing.

The temperature profile here drops much slower due to latent heat. This is



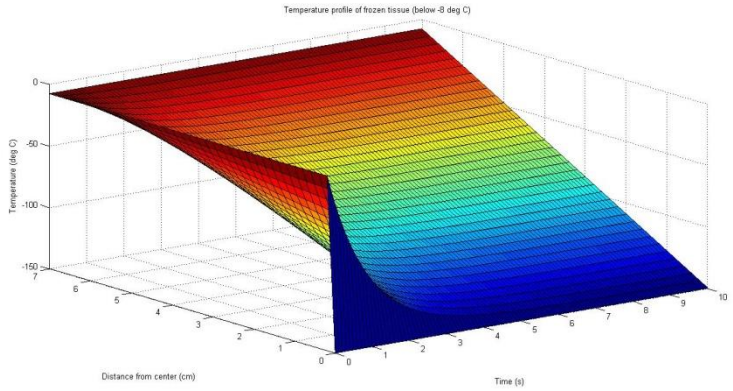




Fig 3c. Temperature profile for the tissue after freezing.

The temperature profile here returns to dropping much faster. This is valid for a temperature range of -8°C > u.

## MATLAB codes

### For temperatures greater than -1 deg C.

```
k1=0.005;
c1=3.6;
Qm1=0.042;
b=7;
tmesh=0:5:1000;
nt=length(tmesh);
rmesh=0:0.2:b;
nr=length(rmesh);
u=zeros(nr, nt);
u(:,1)=37;
u(1,:)=-150;
for r=2:nr
   a=-Qm1*((r-1)*0.2)^2/(6*k1)+(187/b +Qm1*b/(6*k1))*(r-1)*0.2-150;
   for t=2:nt
      k1=0.005;
      c1=3.6;
      sum=0;
      for i=1:20
         p=i*pi;
         m=((sqrt(2*b/i))*sin(p*(r-1)*0.2/b))/((pi*(r-1)*0.2));
```

```
        sum=sum+m;
    end
    L=(1-((r-1)*0.2/b))*(187-Qm1*b*(r-1)*0.2/(6*k1))/sum;
    u(r,t)=u(r,t)+L*sum*exp(((p/b)^2)*(-k1/c1)*(t-1)*5)+a;
  end
end
u(1,:)=-150;
surf  (tmesh, rmesh, u);
```

## For temperatures between -1 and -8 deg C

```
k2=0.0125;
c2=(250/7)+2.7;
Qm2=0;
tmesh=0:1:100;
nt=length(tmesh);
b=7;
rmesh=0:0.2:b;
nr=length(rmesh);
u=zeros(nr, nt);
u(:,1)=-1;
u(1,:)=-150;
for r=2:nr
  a=-Qm2*((r-1)*0.2)^2/(6*k2)+(149/b +Qm2*b/(6*k2))*(r-1)*0.2-150;
  for t=2:nt
```

```
      sum=0;
      for i=1:20
         p=i*pi;
         m=((sqrt(2*b/i))*sin(p*(r-1)*0.2/b))/((pi*(r-1)*0.2));
         sum=sum+m;
      end
      L=(1-((r-1)*0.2/b))*(149-Qm2*b*(r-1)*0.2/(6*k2))/sum;
      u(r,t)=u(r,t)+L*sum*exp(((p/b)^2)*(-k2/c2)*(t-1)*1)+a;
   end
end
surf  (tmesh, rmesh, u);
```

## For temperatures below -8deg C

```
k3=0.02;
c3=1.8;
Qm3=0;
tmesh=0:0.1:10;
nt=length(tmesh);
b=7;
rmesh=0:0.2:b;
nr=length(rmesh);
u=zeros(nr, nt);
u(:,1)=-8;
u(1,:)=-150;
```

```
for r=2:nr
   a=-Qm3*((r-1)*0.2)^2/(6*k3)+(142/b +Qm3*b/(6*k3))*(r-1)*0.2-150;
   for t=2:nt
      sum=0;
      for i=1:20
         p=i*pi;
         m=((sqrt(2*b/i))*sin(p*(r-1)*0.2/b))/((pi*(r-1)*0.2));
         sum=sum+m;
      end
      L=(1-((r-1)*0.2/b))*(142-Qm3*b*(r-1)*0.2/(6*k3))/sum;
      u(r,t)=u(r,t)+L*sum*exp(((p/b)^2)*(-k3/c3)*(t-1)*0.1)+a;
   end
end
surf  (tmesh, rmesh, u);
```

## Numerical Solution

Using MATLAB, we generated an algorithm that would take the forward finite difference for our second ordered differential equation, which we present below.

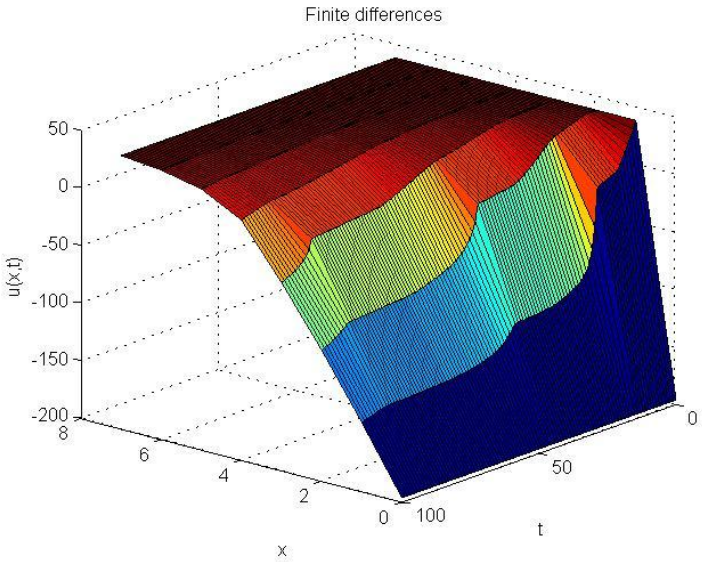



Fig 4. Using the method of finite differences, we stitched the three conditions together to present this solution where we can see that in a time-span of 100 seconds, we are able to freeze down a spherical radius of 4 cm (orange section). We also see a slightly less steep gradient around u = 0 from the graph because of latent heat.

## Conclusion

We can see from our solutions that the method of cryoablation is fast and efficient way of removing a harmful or undesirable piece of tissue. An exposure of a few minutes is enough to free down a sphere of 8 cm diameter. As expected, the latent heat is an obvious enough term to result in a slowdown of heat transfer as the gradient becomes less steep in both our analytical and the numerical. Here we have also ignored perfusion, which other groups have actually shown to play only a small role in the heat generation. Furthermore in our study where most of the cells can be frozen down quickly, the blood would have simply frozen over and ceased to be a significant contributor to the heat generation in our tissue.

We notice that the temperature at the boundary does not decrease. This is possibly because of the boundary condition we have set at r=7cm. Since the temperature there is fixed, the regions around it remain at a higher temperature close to 37deg C as there is an influx of heat into the sphere from the boundary. This assumption is crude but had to be made to simplify the problem. This is also why we have a linear variation of temperature with radius at steady state.

There have been several groups working on injectable fluids that would increase the rate at which the tissue cools because of a dilution of fluids with a lower specific heat capacity that displaces the interstitial fluid. This results in a general lower specific heat capacity that improves the efficacy of cryosurgery.

## References

1. Myers RS, Hammond WG, Ketcham AS. **Ann Surg. 1970** Cryosurgical necrosis of the head of the pancreas Mar;171(3):413-8

2. Deng ZS, Liu J. **Cryobiology 50** Numerical simulation of selective freezing of target biological tissues following injection of solutions with specific thermal properties (2005) 183–192

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