The Diffusion of Gadolinium Contrast Agent through Patellar Cartilage

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Introduction

Articular cartilage is a load bearing, friction-reducing tissue that covers, seals, and protects the bones of synovial joints. Cartilage is a biphasic matrix: the solid components of which is composed of type II collagen and associated proteoglycans. The liquid phase of the matrix is mainly water, mixed with solutes such as ions and growth factors. [10] Seeded within this matrix are chondrocytes, which regulate the remodeling and growth of this tissue. [5] The orientation of chondrocytes and the collagen matrix changes as a function of depth. Traditionally, the depth dependent architecture of cartilage is divided up into three zones: the superficial zone, the middle zone, and the deep zone.[4] The superficial zone, or the top 25% of the cartilage located closest to the joint cavity, features collagen and chondrocytes arranged in layers running parallel to the surface of the cartilage. The middle zone, the 50% lying below the superficial layer, features collagen and chondrocytes arranged in a random fashion. The deep zone, the final 25% that lies on top of the bone, features collagen and chondrocytes arrange in columnar structures. This change in orientation causes a decrease in diffusivity of many solutes as a function of cartilage depth.

Osteoarthritis, or OA, is one of the most common disorders experienced by the human population. Hallmarks of OA include the degradation of cartilage, inflammation of the joint space, and increased susceptibility to injury. OA results in two major types of damage to the cartilage matrix, full tissue degradation in which collagen and proteoglycan content is decreased throughout the entire thickness of the cartilage, and focal defects in which a specific region of the cartilage is lost.

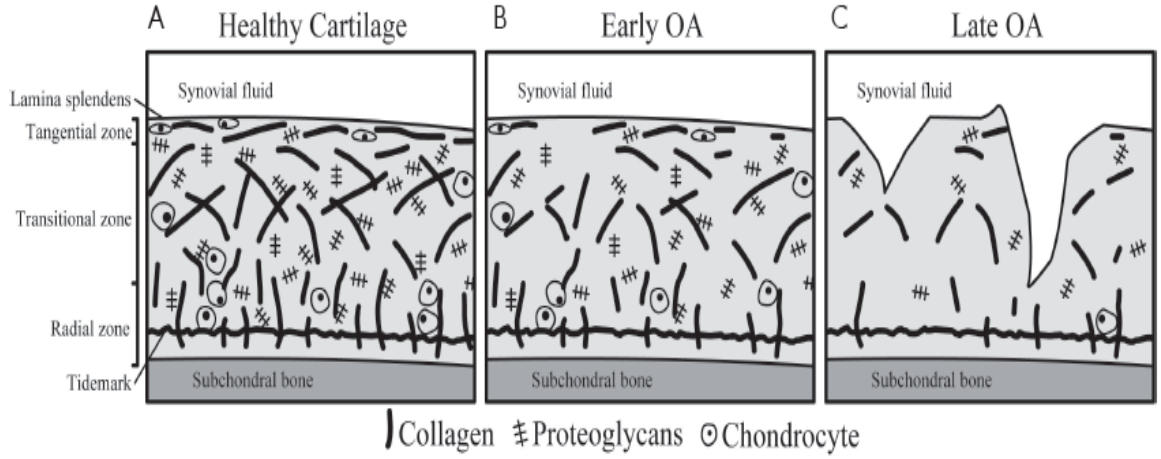

Figure 1 Progression of Osteoarthritis

Both of these injuries lead to increased permeability of the cartilage, allowing the inflammatory agents, and the other components of the synovial fluid to enter the cartilage matrix.[4] The degradation and wear of cartilage in particular causes increased levels of pain and limited mobility for those who suffer from OA. Currently, cell and artificial matrix based treatments are the clinical gold standard for treating the degradation of cartilage. Osteochondral allografting has also proven effective for the treatment of focal defects.[11]

Due to the avascular nature of cartilage and the complex architecture of the tissue, repair and regeneration occur at a very slow rate.[8] Essentially, all damage incurred by cartilage over the course of a lifetime is permanent. Current treatments for articular cartilage defects are most effective when utilized early in the degradation process.[7] The most effective, non-invasive way to diagnose articular cartilage degradation and the progression of OA in the clinic is to take a contrast agent aided MRI scan of the joint in concern. The most common contrast agent used to diagnose the progression of OA is the element gadolinium (Gd).[2] Gd is injected intravenously to the patient and diffuses through the tissues in the joint over the course of several hours prior to the scan. The magnetic properties of Gd allow it to reduce the relaxation time of tissues in its proximity, creating a larger local signal for the MRI scanner to detect.[12]

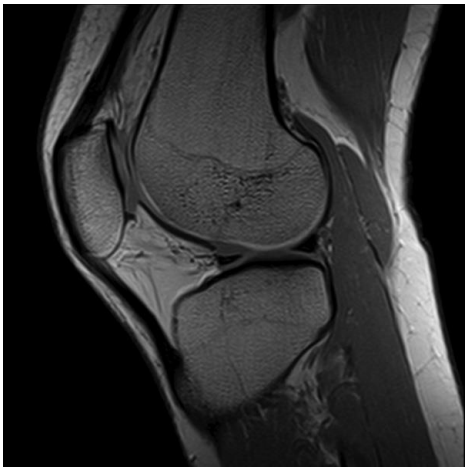

Figure 2 Normal MRI Scan

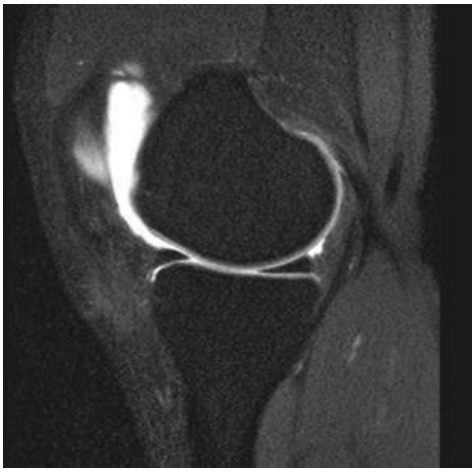

Figure 2 MRI with Gadolinium Contrast Agent

Due to the deterioration of the cartilage matrix caused by OA, the diffusion profile of Gd through cartilage will change in a healthy versus a diseased state. Thus, a mathematical model of the diffusion of the Gd through cartilage has potential to be clinically relevant in predicting the progression of OA as a function of diffusion.

Problem Statement

The goal of this project was to see if the group could create a mathematical model of the changes in diffusivity of gadolinium through patellar cartilage in both a healthy and diseased (osteoarthritic) state. The patella was chosen due to its relatively spherical architecture.

Analytical Solution

We begin with the diffusion equation in three dimensional Cartesian coordinates.

$$\frac{\partial U}{\partial t} = D\left(\frac{\partial^2 U}{\partial x^2} + \frac{\partial^2 U}{\partial y^2} + \frac{\partial^2 U}{\partial z^2}\right)$$

However, since we are modeling the patellar cartilage as a sphere, it makes more sense to work in spherical coordinates which we can do with the following coordinate transformation.

$$x = r\,cos(\theta)\sin(\phi)$$
$$y = rsin(\theta)\sin(\phi)$$
$$z = r\cos(\theta)$$

The diffusion equation in spherical coordinates:

$$\frac{\partial U}{\partial t} = D\left(\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial U}{\partial r}\right) + \frac{1}{r^2\sin^2\phi}\frac{\partial^2 U}{\partial \theta^2} + \frac{1}{r^2\sin^2\phi}\left(\sin(\phi)\frac{\partial U}{\partial \phi}\right)\right)$$

We assume diffusion only happens along the radial axis, and that the diffusion is symmetric with respect to θ, ϕ, which lets us simplify the equation.

$$\frac{\partial U}{\partial t} = D\left(\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial U}{\partial r}\right)\right)$$

Boundary Conditions:

1. The concentration of Gadolinium must be finite at $r = 0$
2. The concentration of Gadolinium at the outside of the sphere, $r = L$ is equal to the concentration of Gadolinium of the synovial fluid, a constant c_0

Initial Conditions:

1. We assume that there is initially no Gadolinium in the patellar cartilage, $U(r, 0) = 0$

We can solve this using the "poison tooth" extraction method. Let us decompose the solution in a particular and a homogeneous solution:

$$c(r, t) = c_p(r, t) + c_h(r, t)$$

Let the particular solution be the steady state solution where $\frac{\partial c}{\partial t} \to 0$ and $c_p(r)$ becomes a function of r only.

The PDE becomes an ODE in the particular solution:

$$\frac{d}{dr}\left(r^2\frac{dc_p}{dr}\right) = 0$$

$$r^2 \frac{dc_p}{dr} = C_1$$
$$dc_p = \frac{C_1}{r^2} dr$$
$$c_p(r) = C_2 - \frac{C_1}{r}$$

Apply the boundary conditions:

1. C_p must remain bounded as $r \to 0$, thus $C_1 = 0$
2. Fixed concentration at the outer boundary, thus $c_p(L) = C_2 = C_0$

Our particular solution is simply the concentration of contrast agent at the boundary

$$c_p(r) = C_0$$

Now we solve the homogeneous problem:

$$\frac{1}{D}\frac{\partial c_h}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial c_h}{\partial r}\right)$$

Homogeneous BCs:

1. c_h remains bounded at $r = 0$
2. $c_h(R_1, t) = 0$

We can use separation of variables:

$$c_h(r, t) = R(r)T(t)$$

Substituting into the original equation:

$$\frac{1}{D}R(r)T'(t) = \frac{1}{r^2}\frac{\partial}{\partial r}[r^2 R'(r)T(t)]$$
$$\frac{1}{D}R(r)T'(t) = \frac{1}{r^2}\left(2rR'(r)T(t) + r^2 R''(r)T(t)\right)$$
$$\frac{1}{D}R(r)T'(t) = \frac{2}{r}R'(r)T(t) + R''(r)T(t)$$
$$\frac{T'(t)}{DT(t)} = \frac{\frac{2}{r}R'(r) + R''(r)}{R(r)} = -\lambda$$

ODE in time:

$$\frac{dT}{dt} = -\lambda DT$$

ODE in space:

$$\frac{d^2R}{dr^2} + \frac{2}{r}\frac{dR}{dr} + \lambda R = 0$$

Solution in time:

$$T(t) = Ae^{-\lambda Dt}$$

Now let's solve the equation in space:

$$\frac{d^2R}{dr^2} + \frac{2}{r}\frac{dR}{dr} + \lambda R = 0$$

Consider the case when $\lambda = 0$:

$$R(r) = \frac{B_1}{r} + B_2$$

Boundary Conditions:

1. $R(0)$ is bounded at $r = 0 \quad \rightarrow \quad B_1 = 0$
2. $R(L) = B_2 = 0 \quad \rightarrow B_2 = 0$

Thus, the solution is trivial

Consider the case when $\lambda < 0$. We will guess that $R(r)$ be of the form:

$$R(r) = \frac{e^{sr}}{r}$$

Substituting into the original equation:

$$\frac{2}{r^3}e^{sr} - \frac{2s}{r^2}e^{sr} + \frac{s^2}{r}e^{sr} + \frac{2}{r}\left(-\frac{1}{r^2}e^{sr} + \frac{s}{r}e^{sr}\right) + \frac{\lambda e^{sr}}{r} = 0$$

Canceling out terms:

$$\frac{s^2}{r}e^{sr} + \frac{\lambda e^{sr}}{r} = 0$$

$$s^2 = -\lambda$$

$$s = \pm\sqrt{-\lambda}$$

General Solution in space:

$$R(r) = \frac{B_1 e^{r\sqrt{-\lambda}}}{r} + \frac{B_2 e^{-r\sqrt{-\lambda}}}{r}$$

Now let us consider the case where $\lambda < 0$:

Apply our boundary conditions:

1. At $r = 0$:
   $R(r) = \frac{B_1 + B_2}{r}$

Thus, $B_1 = B_2 = 0$ and the solution is trivial

Now let us consider the case when $\lambda > 0$:

$$R(r) = \frac{B_1 e^{ir\sqrt{\lambda}}}{r} + \frac{B_2 e^{-ir\sqrt{\lambda}}}{r}$$
$$R(r) = \frac{B_1}{r}\cos(\sqrt{\lambda}\, r) + \frac{B_2}{r}\sin(\sqrt{\lambda}\, r)$$

1. In order for $R(r)$ to be bounded at zero, B_1 must be zero because $\cos(0) = 1$
2. Applying the outer B.C. $R(L) = 0$

$$\frac{B_2}{r}\sin(\sqrt{\lambda}\, r) = 0$$
$$\lambda = \left(\frac{n\pi}{L}\right)^2$$

General solution:

$$c(r,t) = C_0 + \sum_{n=1}^{\infty} \frac{A_n}{r}\sin\left(\frac{n\pi}{L}r\right) e^{-D\left(\frac{n\pi}{L}\right)^2 t}$$

Solve for our initial condition:

$$c(r,0) = 0$$
$$c(r,0) = C_0 + \sum_{n=1}^{\infty} \frac{A_n}{r}\sin\left(\frac{n\pi}{L}r\right) = 0$$

Multiply both sides by $r^2 \frac{\sin\left(\frac{k\pi}{L}r\right)}{r}$ and integrate. The reason we use these new basis functions is because we are now working in spherical coordinates.

$$\sum_{n=1}^{\infty} A_n \int_0^{R_1} \mathrm{r}^2 * \frac{1}{\mathrm{r}^2}\sin\left(\frac{n\pi}{L}r\right)\sin\left(\frac{k\pi}{L}r\right) dr = -C_0 \int_0^{R_1} r\sin\left(\frac{k\pi}{L}r\right) dr$$

Due to orthogonality, all terms on the left hand side of the equation drop out except when $n = k$.

$$A_k = -\frac{C_0 L}{2}\int_0^{R_1} r\sin\left(\frac{k\pi}{L}r\right) dr$$
$$A_k = \frac{2C_0 L\cos(\pi k)}{\pi k}$$

Final Analytical Solution:

$$c(r,t) = C_0 + \sum_{n=1}^{\infty} \frac{2C_0 L\cos(\pi k)}{\pi k r}\sin\left(\frac{n\pi}{L}r\right) e^{-D\left(\frac{n\pi}{L}\right)^2 t}$$

Results

Matlab was used along with the parameters in Table [1] to model the changes in diffusivity of Gadolinium through Patellar cartilage.

Parameter	Description	Value
c_0	Concentration of contrast agent in sinovial fluid	$6 * 10^{-5} \frac{mol}{mm^2}$ [2]
$D_{overall}$	Average healthy patient	$1.78 * 10^{-4} \frac{mm^2}{s}$ [5]
$D_{superficial}$ (healthy)	Diffusivity in superficial patellar region for healthy patients	$2.23 * 10^{-4} \frac{mm^2}{s}$ [3]
D_{deep}(healthy)	Diffusivity in deep patellar region for healthy patients	$1.58 * 10^{-4} \frac{mm^2}{s}$ [3]
$D_{superficial}$ (OA)	Diffusivity in superficial patellar region for arthritic patients	$2.58 * 10^{-4} \frac{mm^2}{s}$ [3]
D_{deep} (OA)	Diffusivity in deep patellar region for healthy patients	$2 * 10^{-4} \frac{mm^2}{s}$ [3]
L	Radius of patella	5 mm[1] [5]
Length of superficial region		0.75 mm [3]

Table 1 Parameters for Diffusion Model

First, the analytical solution was verified by comparing it to the numerical pdep Matlab function.

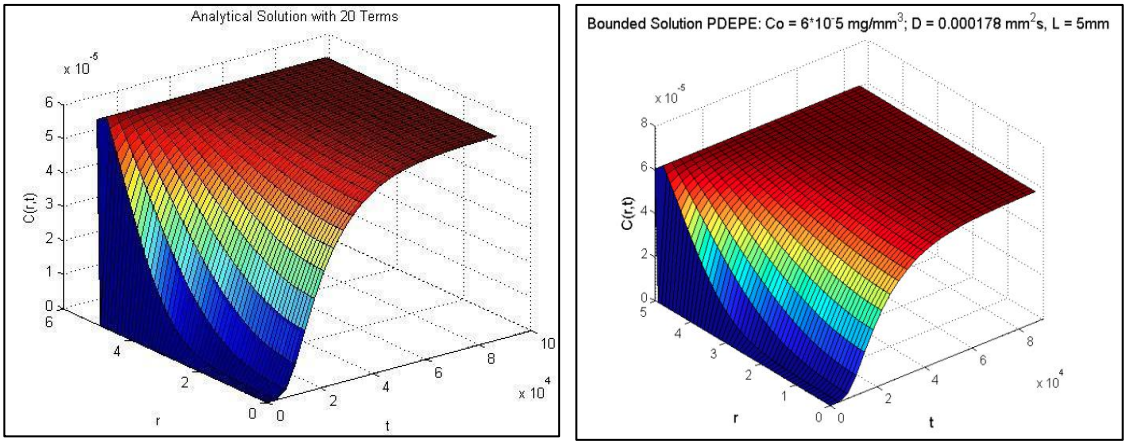

Figure 4: Analytical (left) and numerical (right) surface plot of the diffusion of Gadolinium through the patellar cartilage

Since *Figure 4* indicated that both solutions had a similar diffusion profile, the numerical model could now be used to compare changes in diffusivity of Gadolinium through Patellar cartilage in a healthy and diseased state. Additionally, to make the

model more realistic, the different diffusivities of the deep layer and superficial layers of the cartilage were incorporated into the solution.

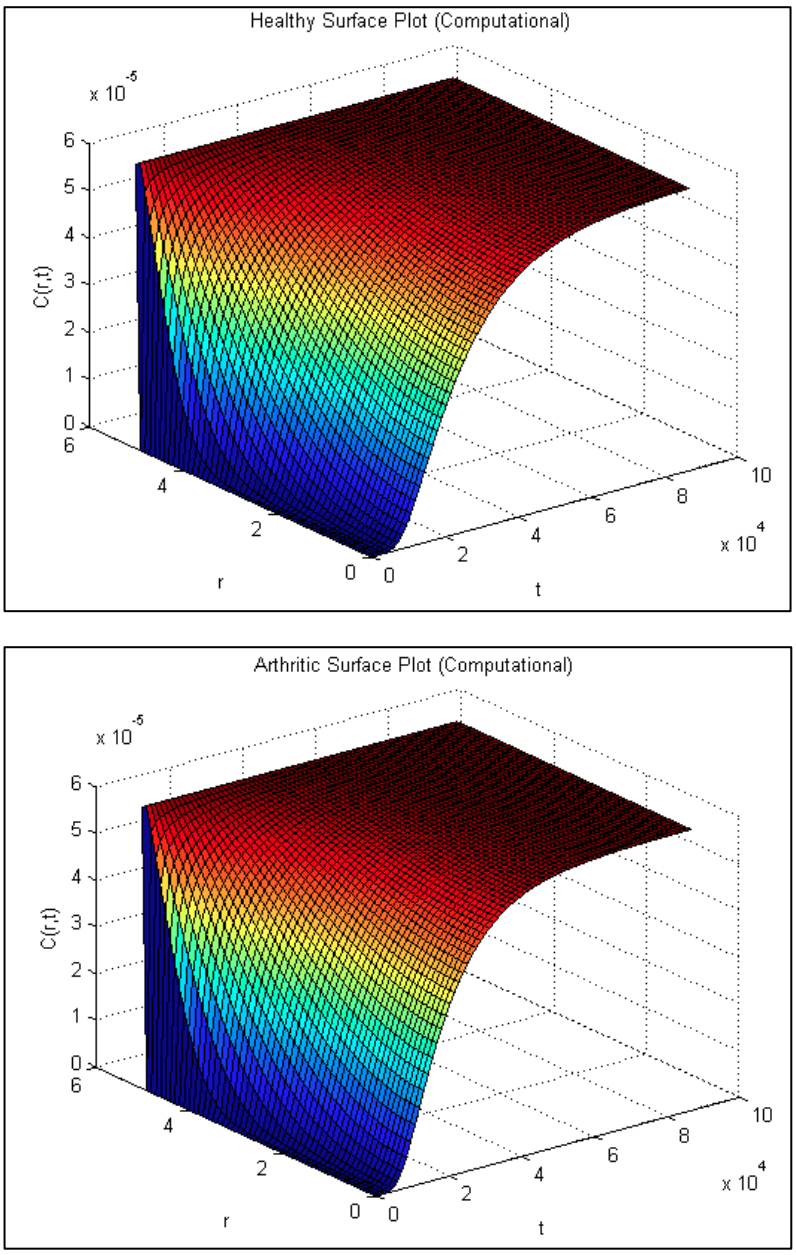

Figure 5: Computational Model of the diffusion of Gadolinium through Healthy (top) and Arthritic Patellar Cartilage (bottom).

Figure 5 shows minute differences between the surface plots of the healthy and arthritic models. To get a closer look at the differences the diffusion at three different time points (2hours, 10 hours, and 24 hours) was plotted in Figure 6. Results of this graph indicated that at each time point diffusion was faster in the arthritic case.

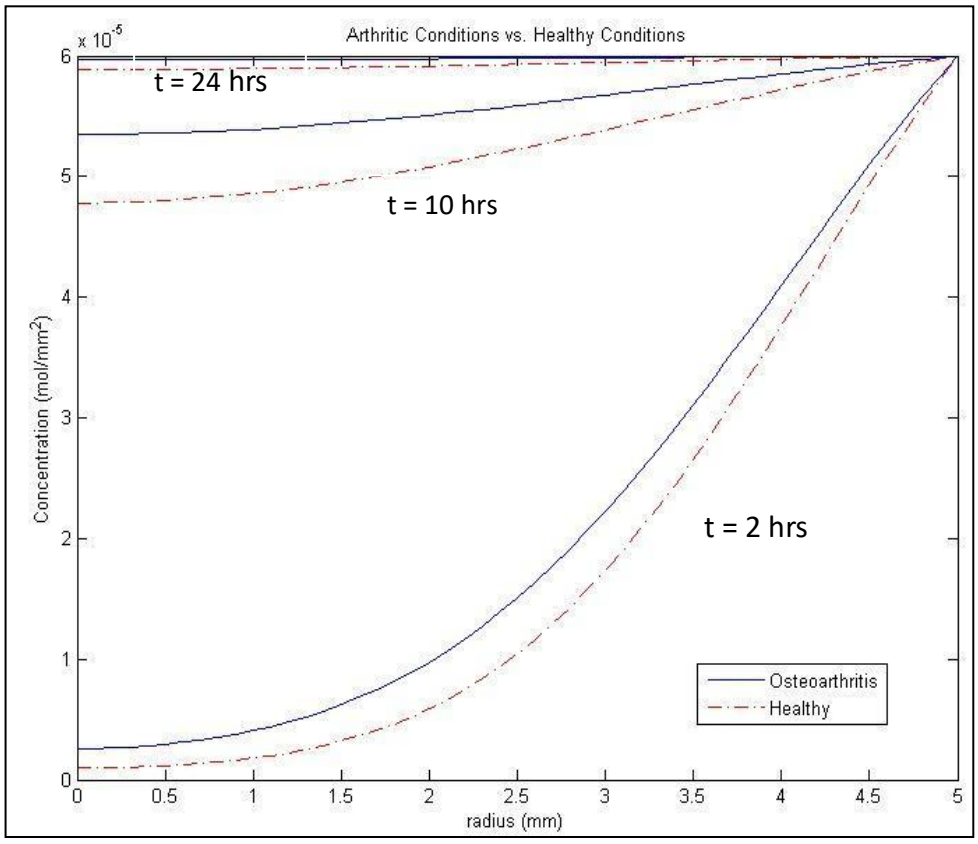

Figure 6: Comparison of the Diffusion of Gadolinium through Patellar Cartilage in Healthy and Arthritic Tissue at 2hours, 10 hours and 24 hours.

Conclusion & Discussion

The mathematical model showed that osteoarthritis affected the diffusivity of the Gadolinium in the patellar cartilage. When compared the analytical solution and the mathematical model both agree with each other. Both models showed the rate of diffusion increased due to osteoarthritis, which correlates with reality. Upon completion of our model our group was able to predict the time dependent concentration profile of Gadolinium in Healthy and Osteoarthritis affected cartilage

Moving forward there are many things that could be taken into account to improve our model. The greatest of these is the geometry of the patellar cartilage; it is important to note that the patellar cartilage is not a sphere and includes a region of bone in its center. Our model simplifies the geometry and ignores the bone portion of the patella, as it isn't of interest in our problem. However, taking into account the unique geometry of the patella would allow the model to better model patient specific diffusion of Gadolinium.

In the real world, doctors that want to look at a specific layer of cartilage in there patient could use our model. It allow them to predict how much time is necessary for the Gadolinium to diffuse into the layer of interest. This would be useful in monitoring the progression of osteoarthritis in a very useful way. For example, if our model predicts that Gadolinium should diffusion to a certain depth of the cartilage in a set amount of time. Yet it diffuses deeper than expected with the allotted time, then this will let the Doctor know that the cartilage has degraded faster than anticipated. This would be huge in preventative medicine, as it will allow doctors to monitor the progression of osteoarthritis in there patient. Ideally the model will take into account the patient specific geometry of the patellar cartilage by taking a MRI scan of the patient and using the first geometry seen as a reference for subsequent MRIs.

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MatLab Code

Analytical Solution

```
function analytical_solution_full_cartilage
% Number of Terms
ns = 20;

% Diffusion constant
global D
D = 0.000178;

% Concentration of gadolinium in the sinovial fluid
global c0
c0 = 6*10^-5; % Initial concentration of Ga

% Radius of the patellar cartilage
global L
L = 5; % Outer radius is 5 mm

% domain
dx = 0.5; % step size in x dimension
dt = 1000;  % step size in t dimension
xmesh = 0:dx:5; % domain in x; L/2 = 1
tmesh = 0:dt:(3600*24);  % domain in t (24 hours)
nx = length(xmesh); % number of points in x dimension
nt = length(tmesh); % number of points in t dimension


% solution on bounded domain using separation of variables
sol_sep = zeros(nt, nx);
sol_sep = sol_sep + c0;
for n = 1:1:ns
    k = n*pi/L; % R = 5 mm
    for i = 1:length(tmesh)
       for j = 1:length(xmesh)
          sol_sep(i,j) = sol_sep(i,j) +
2*c0*cos(n*pi)*L/(pi*n*xmesh(j)) * exp(-D*(k^2)*tmesh(i)) *
sin(k*xmesh(j));
       end
    end
end

% Plot analytical solution
figure(1)
surf(tmesh,xmesh,sol_sep')
title(['Separation of variables on bounded domain (first ',
num2str(ns), ' terms in series)'])
xlabel('t')
ylabel('r')
zlabel('C(r,t)')
```

PDEPE Full Cartilage

```
function PDEPEFullCartilage
%%%
%%%

% diffusion constant
global D
D = 0.000178;

% domain
dx = 0.1; % step size in x dimension
dt = 1200;  % step size in t dimension
xmesh = 0:dx:5; % domain in x
tmesh = 0:dt:(3600*24);  % domain in t

sol_pdepeOA = pdepe(2,@pdefunOA,@ic,@bc,xmesh,tmesh);
sol_pdepeHE = pdepe(2,@pdefunHE,@ic,@bc,xmesh,tmesh);

figure
surf(tmesh,xmesh,sol_pdepeHE')
% plot(xmesh,sol_pdepeOA(floor(2*3600/500),:))
% hold on
% plot(xmesh,sol_pdepeHE(floor(2*3600/500),:),'r-.')
% hold on
% plot(xmesh,sol_pdepeOA(floor(10*3600/500),:))
% hold on
% plot(xmesh,sol_pdepeOA(floor(20*3600/500),:))
% hold on
% plot(xmesh,sol_pdepeHE(floor(10*3600/500),:),'r-.')
% hold on
% plot(xmesh,sol_pdepeHE(floor(20*3600/500),:),'r-.')
title('Healthy Surface Plot (Computational)')
xlabel('t')
ylabel('r')
zlabel('C(r,t)')
axis([0 10*10^4 0 6 0 6*10^-5])
% legend('Osteoarthritis','Healthy');

% function definitions for pdepe:
% ------------------------------------------------------
----

function [c, f, s] = pdefunOA(xmesh, t, u, DuDx)
% PDE coefficients functions
a = 4.25;
Df = zeros(length(xmesh));
for i = 1:length(xmesh)
   if xmesh(i) >= a
       Df(i) = 1.45*D;
   elseif xmesh(i) <= a
       Df(i) = 1.12*D;
   end
```

```
end
c = 1./Df;
c = diag(c);
f = DuDx; % diffusion
s = 0; % homogeneous, no driving term
end
% ------------------------------------------------------------
----

function [c, f, s] = pdefunHE(xmesh, t, u, DuDx)
% PDE coefficients functions
a = 4.25;
Df = zeros(length(xmesh));
for i = 1:length(xmesh)
   if xmesh(i) >= a
       Df(i) = 1.2*D;
   elseif xmesh(i) <= a
       Df(i) = 0.89*D;
   end

end
c = 1./Df;
c = diag(c);
f = DuDx; % diffusion
s = 0; % homogeneous, no driving term

end

function u0 = ic(xmesh)
% Initial conditions function
u0 = 0;
end
% ------------------------------------------------------------
----

function [pl, ql, pr, qr] = bc(xl, ul, xr, ur, t)
% Boundary conditions function

pl = ul; % zero value left boundary condition
ql = 0;  % no flux left boundary condition
pr = ur-(6*10^-5); % zero value right boundary condition
qr = 0;  % no flux right boundary condition
end

end
```