Microneedle Mediated Transdermal Vaccine Delivery

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Introduction

Vaccination remains one of the most effective means of preventative medicine in existence. A wide variety of viral diseases ranging from flu strains to HPV have been severely reduced in prevalence by vaccination practices. Traditionally, these agents are delivered via hypodermic needle or through an aerosolized nasal spray providing an efficient and rapid means of inoculation. However, new and evolving methods geared toward reducing total dosage, reducing hazardous sharp wastes, and improving effectiveness of the elicited immune response continue to emerge. Among these novel vaccination strategies is transdermal administration. Vaccines show improved performance when delivered via transdermal administration due to a large number of specialized "Langerhans" immune cells within the epidermal and dermal layers. Figure 1 outlines the dermal layers and these specialized cells. Transdermal delivery also has the advantage of circumventing first pass metabolism by the gastrointestinal tract and the liver thereby maximizing cellular exposure to the antigen and immune response [1].

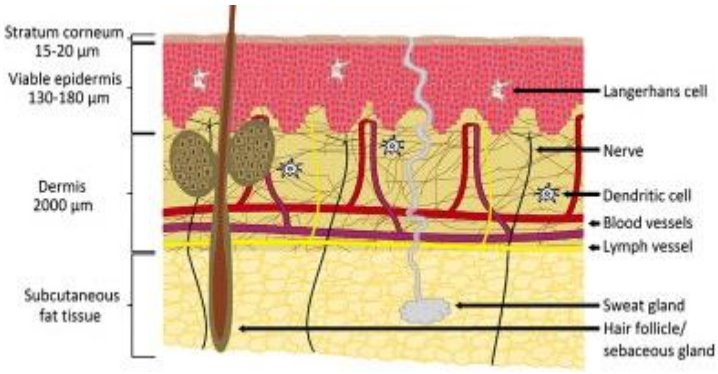

Figure 1: *Diagram of skin. Points of interest include protective stratum corneum (15-20 um) that needs to be bypassed for drug delivery, and the dermal (2000 um) and epidermal (130-180 um) [1] layers that include immune cells.*

A large body of recent work in transdermal drug delivery has focused on microneedles. These devices utilize an array of needles whose length and diameter are on the order of microns. Needles are able to penetrate the stratum corneum and expose epidermal tissue to the drug payload while minimizing pain due to lack of nerve endings. Furthermore, these devices are small, manageable, and sometimes degradable allowing for improved handling administration and medical waste. These traits have made microneedle injection a promising mode for vaccine delivery [2].

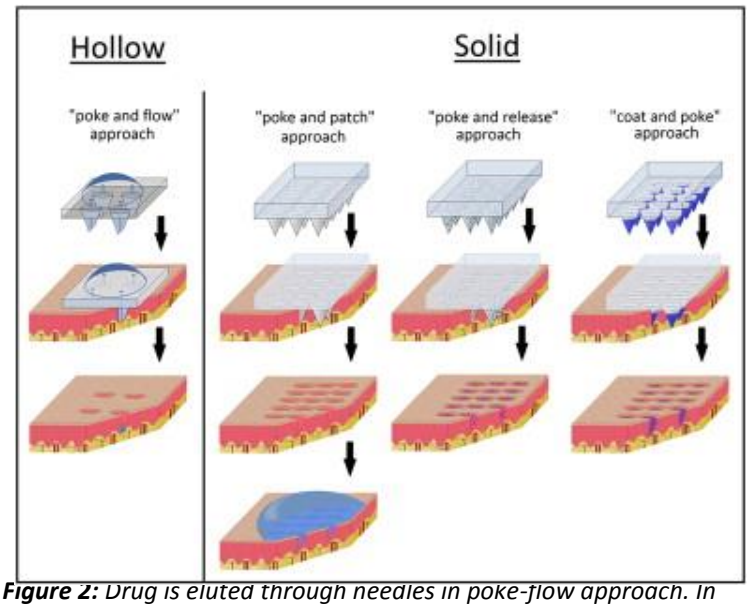

Figure 2: *Drug is eluted through needles in poke-flow approach. In poke-release, the needles are degradable and contain the drug. In coat-poke, the drug is applied on the needles prior to penetration. The poke-patch method uses micro-needles to create pores in the skin; afterwards, a patch is placed on top of the penetration site. [3]*

There are various methods for drug delivery when utilizing microneedles. Needles may be solid or hollow and are in some cases degradable over time. Figure 2 illustrates four common strategies for microneedle drug delivery. Poke and Flow utilizes a hollow needle to inject a small payload of agent into the epidermis where it is then able to diffuse into the

body. Poke and Patch relies on solid needles to create access holes over which a large drug-laden patch is placed allowing diffusion into the skin. Poke and Release and Poke and Coat both involve solid state agent which degrades and diffuses along the boundary of the microneedle. Each method has respective advantages and disadvantages with respect to vaccine delivery that are worthy of consideration [3].

Problem Statement

The aim of this project is to compare and contrast various current methods of transdermal vaccine delivery using microneedle patches. Here we will examine the "Poke and Flow" and "Poke and Patch" methods through a 2D homogeneous diffusion model using both analytical and numerical approaches. Solutions will map the transport of vaccine particles through the epidermis culminating in removal by systemic circulation. From these models efficacy data for each method will be compared and conclusions on their respective benefits will be discussed.

Poke and Flow System

Assumptions:

While the poke and flow model is, by nature, a highly simplified case, there are several assumptions that must be made to ensure an analytical solution can be reached. These assumptions are:

1) Vaccine delivery occurs along a single linear pattern of needles thereby reducing the problem to a function of x,y, and t.

2) The initial dose is delivered at one time (t=0) at discrete points in space represented by $\delta(x, z + z_0)$.

3) The patch length is much smaller than the length of the limb resulting in an unbounded z domain.

4) The Epidermis acts as a homogeneous structure with uniform cell composition, thickness and density.

5) The vaccine is transported away by the dermis very rapidly at X=L, there is no flux outside of the dermis at X=0.

6) The stratum corium is impermeable and there is no flux across it (x=0).

7) The immune response is significantly slower than circulatory removal of vaccine (no internal degradation).

Given these assumptions coupled with the anatomy of the stratum corneum, the following boundary conditions can be generated:

$$C(L_x, z, t) = 0$$
$$\frac{dC}{dx}(0, z, t) = 0$$

Z axis is unbounded (infinite)

As well as the following initial condition:

$$C(x,z,0) = C_0(\delta\left(x,z+\frac{L_z}{2}\right)+\delta(x,z)+\delta\left(x,z-\frac{L_z}{2}\right))$$

Model Parameters:

The poke and flow model relies on several experimentally or clinically derived parameters. The first of these is the initial vaccine antigen concentration denoted as C_0. Data derived from Fluvax, an inactivated flu vaccine, set the antigen dose at $10^{-10}\ \mu g/\mu m^3$ [4]. The second major coefficient is the depth, L_x, of the epidermis over which we wish to observe diffusion. As shown in Figure XX, the epidermis is a relatively thin layer and is estimated here to be 75um across all z (see assumption 4). While the limb itself is unbounded in Z, the specific points of the microneedles require a reference length L_z. Here we hope to model 3 individual microneedles and, by estimating needle density in a recent study of transdermal vaccination, a value of 500um was selected [1]. Finally, the diffusion constant of the epidermis must be estimated for small molecules. This was done experimentally by Römgens et al. who employed Fluorescence recovery after photo bleaching (FRAP) assay for molecules within the skin layers. By observing migration of fluorescent molecules into the bleached region, a value of roughly$9\ \mu m^2/s$ [6]. Given these coefficients we may proceed to an analytical solution for the model.

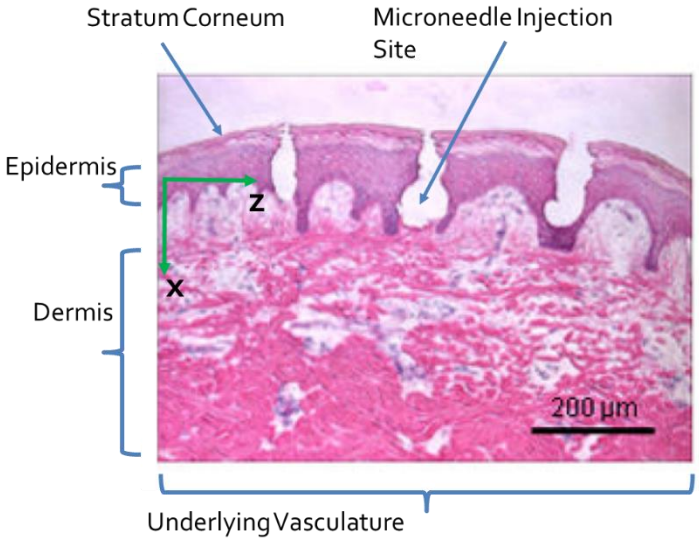

Figure 3: *H&E histology stain of skin with microneedle injection sites. This figure demonstrates the orientation and layers relevant to our 2D model showing X and Z directions as well as the three needle locations [5].*

Analytical Solution:

The diffusion profile of the poke and flow approach was solved analytically, using a Green's function. The two-dimensional diffusion equation is shown, along with our initial condition of three separate microneedle injections modeled by Dirac Delta functions and our homogeneous boundary conditions (zero value at $x = 0$, zero flux at $x = L_x$, and unbounded in *z*). The *x* axis represents the depth into the skin, and the *z* axis represents the length of the limb, which is assumed to be an infinite domain because it is much longer than the thickness of the skin

Two-dimensional diffusion equation:

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

Initial Condition:

$$C(x,z,0) = C_0\left(\delta\left(x, z + \frac{L_z}{2}\right) + \delta(x,z) + \delta\left(x, z - \frac{L_z}{2}\right)\right)$$

Boundary Conditions:

$$\frac{\partial}{\partial x} C(0,z,t) = 0$$

$$C(L_x,z,t) = 0$$

$$C(x,\pm\infty,t) = 0$$

The Green's function for the problem is given by the product of the Green's function in x and the Green's function in z ($G = g_{xk} \cdot g_{zm}$). The full formulation is shown below.

Two-dimensional Green's Function:

$$G(x,z,t;\ x_0,z_0,t_0) = \sum_k \sum_m g_{xk}(x,t;x_0,t_0) \cdot g_{zm}(z,t;\ z_0,t_0)$$

where

$$g_{xk}(x,t;x_0,t_0) = \sum_{k=odd}^{\infty} \frac{2}{L_x} \cos\left(\frac{k\pi x_0}{2L_x}\right) \cdot \cos\left(\frac{k\pi x}{2L_x}\right) e^{-D\left(\frac{k\pi}{2L_x}\right)^2 (t-t_0)}$$

$$g_{zm}(z,t;\ z_0,t_0) = \frac{1}{\sqrt{4\pi D(t-t_0)}} e^{-\frac{(z-z_0)^2}{4D(t-t_0)}}$$

Because this problem has homogeneous boundary conditions and does not contain a generation or consumption term, the solution can be found by integrating the product of the initial condition as a function of x_0 and z_0 and the Green's Function over the x_0 and z_0 domains.

$$C(x,z,t) = \int_0^L \int_{-\infty}^{\infty} C(x_0,z_0,0) \cdot G(x,z,t;\ x_0,z_0,0) dz_0 dx_0$$

The initial condition is a sum of three separate Dirac Delta functions, so the integration above can be separated into the sum of three separate integration terms. The term with $\delta(x,z)$, or an impulse at $(x=0, z=0)$, is shown as an example.

Integral setup for a single microneedle injection:

$$C(x,z,t) = C_0 \sum_{k=odd}^{\infty} \int_0^{L_x} \cos\left(\frac{k\pi}{2L_x}x_0\right) dx_0 \int_{-\infty}^{\infty} e^{-\frac{(z-z_0)^2}{4Dt}} dz_0 \left(\frac{2}{L_x}\right) \cos\left(\frac{k\pi x}{2L_x}\right) \left(\frac{1}{\sqrt{4\pi Dt}}\right) e^{-D\left(\frac{k\pi}{2L_x}\right)^2 t}$$

Solution for a single microneedle injection:

$$C(x,z,t) = \sum_{k=odd}^{\infty} \frac{4C_0}{k\pi} \cos\left(\frac{k\pi x}{2L_x}\right) e^{-D\left(\frac{k\pi}{2L_x}\right)^2 t} e^{-\frac{z^2}{4Dt}}$$

Putting the responses from all three impulses together results in the last decaying exponential being replaced by a sum of three decaying exponentials in the final solution, as shown in the equation below.

Final analytical solution:

$$C(x,z,t) = \sum_{k=odd}^{\infty} \frac{4C_0}{k\pi} \cos\left(\frac{k\pi x}{2L_x}\right) e^{-D\left(\frac{k\pi}{2L_x}\right)^2 t} \left(e^{-\frac{(z+L_z/2)^2}{4Dt}} + e^{-\frac{z^2}{4Dt}} + e^{-\frac{(z-L_z/2)^2}{4Dt}} \right)$$

The model parameters were plugged in, and the concentration as a function of space was computed using the first ten terms of the series expansion and plotted on surface plots in the *x*-*z* plane at various times *t* as shown in Figure 4. As time progresses, the concentration can be seen spreading from the three injection sites as the spikes flatten. Figure Y shows that after 1,000 seconds, the concentration has reached a uniform spread so that the three separate injection sites are no longer distinguishable. Note that the concentration axis has been adjusted to display this behavior.

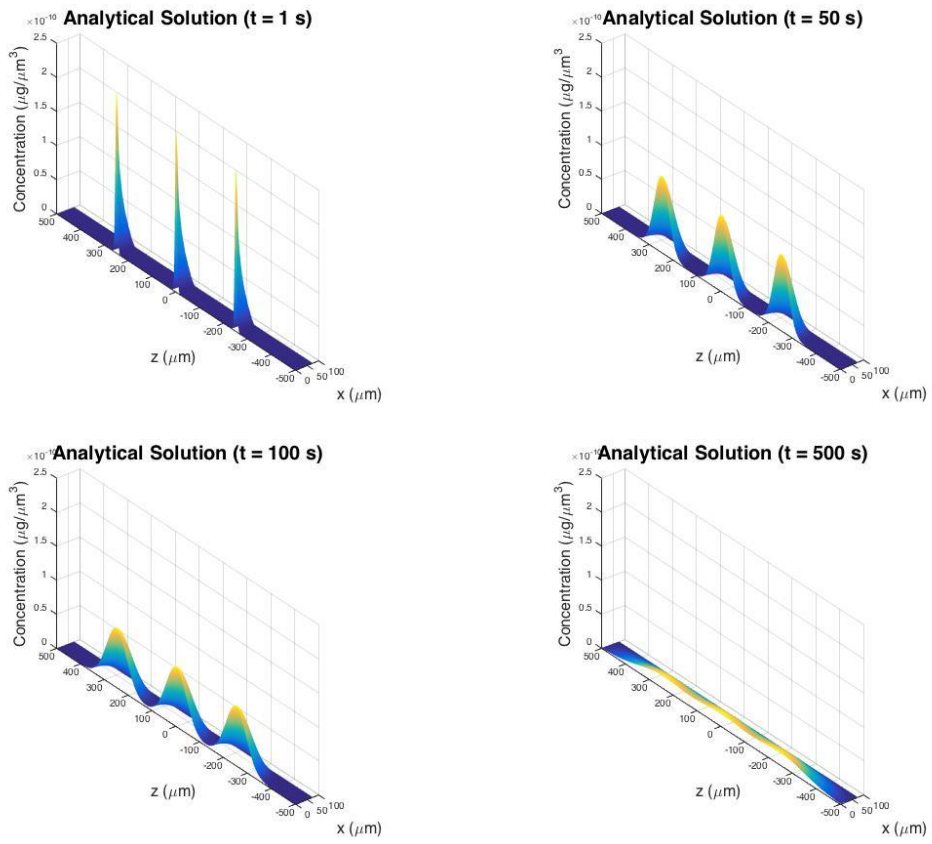

Figure 4*: Concentration in the x-z plane at various times from 1 to 500 seconds.*

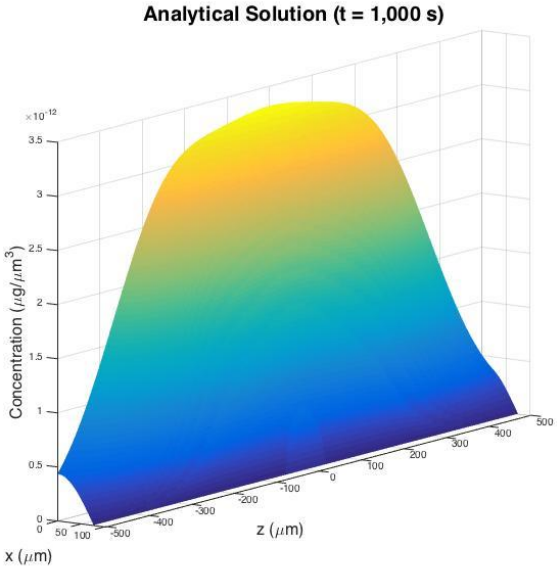

Figure 5: *Concentration in the x-z plane 1,000 seconds post-injection. Note that the concentration axis has been adjusted to show the uniform concentration profile in the z direction, but the maximum concentration is 2 orders of magnitude lower than the maximum concentration depicted by the spikes at t = 1 second.*

Numerical Solution:

The numerical approximation to our problem was found by using finite differences. Finite differences uses discrete substitutions for derivatives to find approximate values of the derivatives at each point on a grid. First, the 2D space was discretized in the x and z directions into a grid with sizes Δx andΔz, respectively. Time was discretized into units Δt large. Next, the discretized approximations of the derivatives could be used. They use points surrounding the point of interest in the spatial dimensions to solve for the next point in time. The approximations are shown below.

$$\frac{\partial C}{\partial t} \rightarrow \frac{C(x,z,t+\Delta t) - C(x,z,t)}{\Delta t}$$

$$\frac{\partial^2 C}{\partial x^2} \rightarrow \frac{C(x-\Delta x,z,t) - 2C(x,z,t) + C(x+\Delta x,z,t)}{\Delta x^2}$$

$$\frac{\partial^2 C}{\partial z^2} \rightarrow \frac{C(x,z-\Delta z,t) - 2C(x,z,t) + C(x,z+\Delta z,t)}{\Delta z^2}$$

These can be substituted into the 2D diffusion equation to yield the following.

$$\frac{C(x,z,t+\Delta t) - C(x,z,t)}{\Delta t} = D\left(\frac{C(x-\Delta x,z,t) - 2C(x,z,t) + C(x+\Delta x,z,t)}{\Delta x^2} + \frac{C(x,z-\Delta z,t) - 2C(x,z,t) + C(x,z+\Delta z,t)}{\Delta z^2}\right)$$

Solving for the point we are interested in calculating, the equation becomes:

$$C(x,z,t+\Delta t) = D\left(\frac{C(x-\Delta x,z,t) - 2C(x,z,t) + C(x+\Delta x,z,t)}{\Delta x^2} + \frac{C(x,z-\Delta z,t) - 2C(x,z,t) + C(x,z+\Delta z,t)}{\Delta z^2}\right)\Delta t + C(x,z,t)$$

We developed a script in MATLAB that would use the finite differences approximation above to solve for the concentration values in 2D over time, given initial concentration values for every point in the discretized grid. To simulate the poke and flow method, every point in the grid was set to zero except the points representing the microneedles, which were set to the concentration C0. These values were then allowed to change according to the values around them. The poke and patch method was simulated with the same initial conditions, but at every time point, the points representing the microneedles were set to C0. This represents the constant concentration of the vaccine at each of these points in the poke and patch method.

The numerical approximation showed nearly the same concentration profile and dynamics as the analytical solution. However, the scaling does not agree well. We believe that this has something to do with the delta function in the analytical solution, because there is no equivalent for this in the discrete domain. Surface plots of the concentration are shown below.

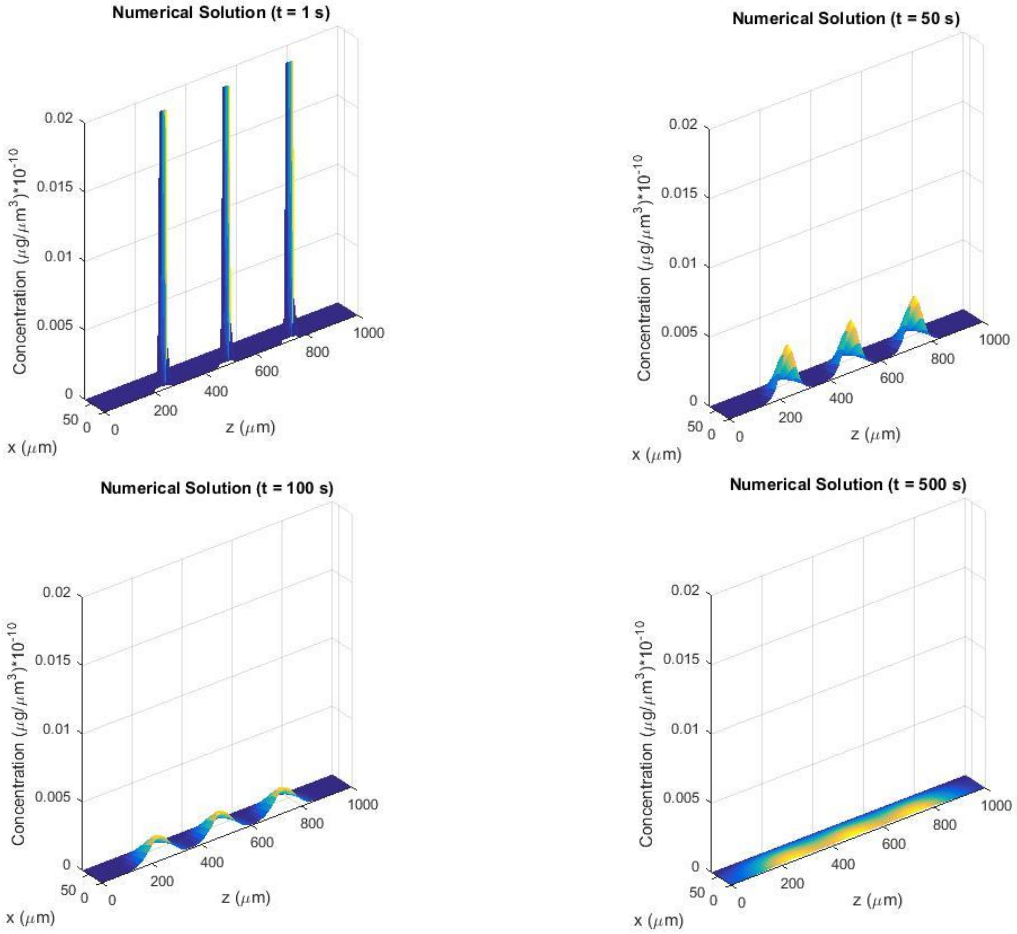

Figure 6: *Numerical solution for the Patch and Flow method. The concentration starts out relatively high and very localized, as is expected from the initial conditions. The peaks spread out and flatten while rounding off at the top. Eventually, a relatively even concentration in the z-direction develops near the microneedles.*

Poke and Patch System

Model Parameters:

The "Poke and Patch" model operates on, unless otherwise stated, the same assumptions, coefficients, boundary conditions, and initial conditions. The notable exception which differentiates this model is the constant reservoir of drug available rather than the instantaneous dose. As shown in Figure 7, this is due to the generation of open punctures in the skin which are covered by a large patch reservoir. This is reflected in the boundary conditions which now reflect this as follows:

$$C(x = 0, z = \left\{-\frac{L}{2_z}, 0, \frac{L}{2_z}\right\}, t) = C_0$$

$$C(L_x, z, t) = 0$$

$$\frac{dC}{dx}\left(0, z \neq \left\{-\frac{L}{2_z}, 0, \frac{L}{2_z}\right\}, t\right) = 0$$

$$\frac{dC}{dz}(x, -L_z, t) = \frac{dC}{dz}(x, L_z, t) = 0$$

In order to evaluate a solution, the initial condition at time=0 is changed to state that the concentration at all points in the model is 0 shown below as:

$$C(x, z, 0) = 0$$

Figure 7: *Poke and Patch method graphical overview. Holes are generated by a solid needle and then covered by a large patch containing a relatively large concentration of drug or antigen [7].*

Numerical Solution:

The poke and patch model starts out identical to the poke and flow method, but the models quickly become different. Instead of widening and flattening the peaks, the peaks stay pinned at the C0 value while the "valleys" in between the peaks become shallower and shallower. The concentration values end up much higher overall, as is expected for a continuous release of vaccine instead of the instantaneous release of vaccine. Surface plots of the poke and patch model are shown below.

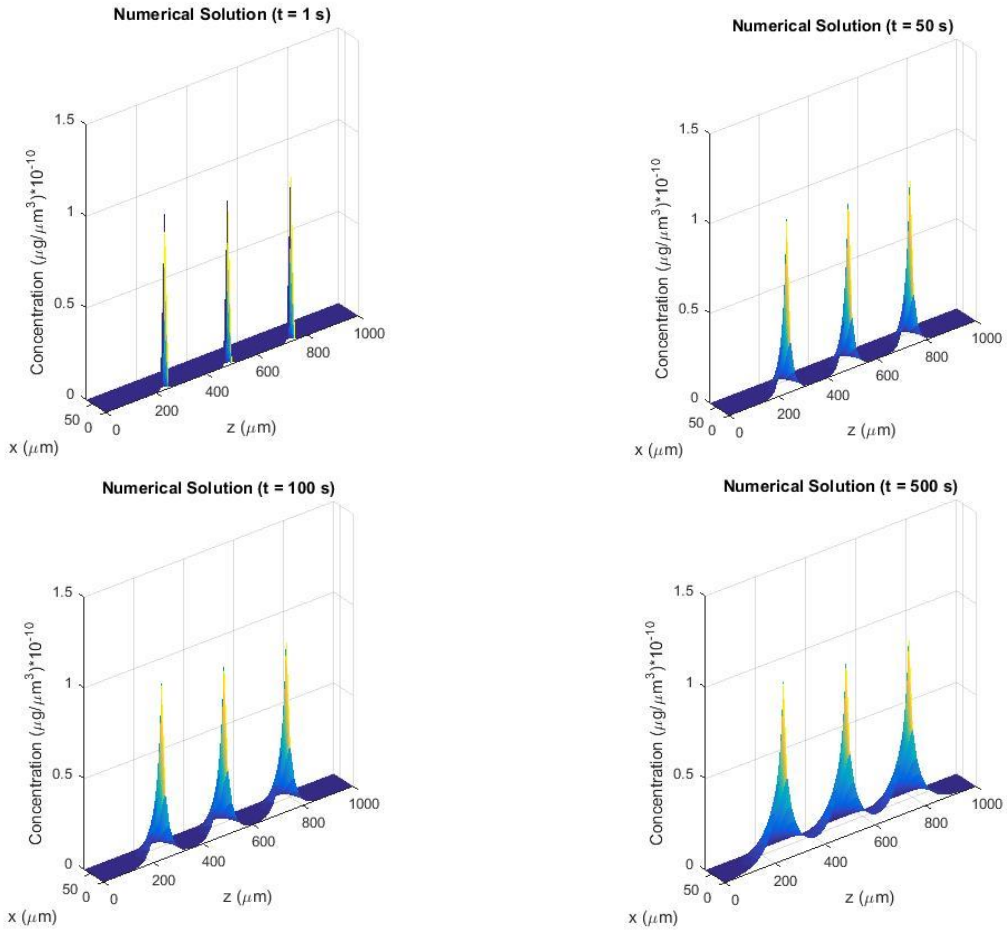

Figure 8: *Numerical solution for the Poke and Patch method. Values begin at a high concentration at the site of needle injection. Over time, valleys between peaks form and steadily increase suggesting increased coverage.*

Discussion and Conclusion

The data modeled here suggests that the Poke and Patch method may produce superior results. At 1,000 seconds post-injection, the minimum concentration of any point in the space enclosed by the three needles is more than an order of magnitude higher in the Poke and Patch model than in the Poke and Flow model. This means that a much greater overall dose can be achieved using the Poke and Patch method. Additionally, Poke and Patch utilizes solid needles which are less prone to failure and are more structurally sound. The inclusion of a patch also makes dose alterations much more manageable as antigen flux can be stopped at any time [2].

Despite the observed advantages for Poke and Patch, there are several inherent limitations within our model that may interfere with results. As stated above, there is a scaling discrepancy with the numerical solution for the Poke and Flow model. While the root cause is unknown, it likely arise from the use of $\delta(x, z)$ functions to describe dose points. Despite interest in the Poke and Release and Poke and

Coat methods, our model is currently unable to resolve the complex boundary of a degrading needle. Thus, for our methods, the injection site is compressed to a single point. For our Poke and Patch solution, the issue of depletion is never fully addressed. In practice, the concentration of drug within the patch would decrease as a function of time though our model assumes the reservoir is so large this is negligible. Finally, it should be noted that the method of action by which vaccines operate is through the immune response. The breakdown of vaccine and corresponding generation of antibodies and antigen presenting cells is not modeled as an inhomogeneous sink term in this model.

Future attempts at microneedle delivery modeling will focus first on the immune response. Obtaining a reliable value for *in-vivo* breakdown of antigen will likely require experimentation though, with this data, the model can be vastly improved in accuracy. Following this improvements to boundary value modeling aimed at incorporating the needle geometry will allow for studies of more advanced methods of transdermal delivery such as Poke and Coat. Finally, expansion to a full 3D geometry of needles would allow for modeling of complex patterns that may optimize dose coverage across the epidermis. These areas of improvement serve as excellent ways to advance the model as well as our understanding of transdermal delivery.

References

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[2] Kim Y-C, Park J-H, Prausnitz MR. Microneedles for drug and vaccine delivery. Advanced drug delivery reviews. 2012;64(14):1547-68.

[3] Prausnitz MR, Langer R. Transdermal drug delivery. *Nature biotechnology*. 2008;26(11):1261-1268. doi:10.1038/nbt.1504.

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[6] Römgens, Anne M., et al. "Diffusion profile of macromolecules within and between human skin layers for (trans) dermal drug delivery." *Journal of the mechanical behavior of biomedical materials* 50 (2015): 215-222.

[7] Ita, Kevin. "Transdermal delivery of drugs with microneedles—Potential and challenges." *Pharmaceutics* 7.3 (2015): 90-105.

Appendix

MATLAB: Poke and Flow

```
function project_analytical

D = 9;          % [um^2/s]
Lx = 75;        % [um]
C0 = 1e-10;     % [ug/um^3]

xmesh = 0:Lx/100:Lx;    % x domain
zmesh = -500:1:500;     % z domain
tmesh = [1, 50, 100, 500, 1000];   % times t to plot solution
nx = length(xmesh);
nz = length(zmesh);
nt = length(tmesh);

u = zeros(nx,nz,nt);    % initialize solution matrix

for x = 1:nx
    xval = xmesh(x);
    for z = 1:nz
        zval = zmesh(z);
        for t = 1:nt
            tval = tmesh(t);
            for k = 1:2:21 % first 10 terms of series expansion
                u(x,z,t) = u(x,z,t) + 4*C0/(k*pi)*cos(k*pi*xval/(2*Lx))*...
                    exp(-D*(k*pi/(2*Lx))^2*tval)*(exp(-zval^2/(4*D*tval))+...
                    exp(-(zval+250)^2/(4*D*tval))+...
                    exp(-(zval-250)^2/(4*D*tval)));
            end
        end
    end
end

u_t0 = u(:,:,1)';   % solution at different "snapshots" in time
u_t1 = u(:,:,2)';
u_t2 = u(:,:,3)';
u_t3 = u(:,:,4)';
u_t4 = u(:,:,5)';

% plot solutions

figure
surf(xmesh,zmesh,u_t0,'edgecolor','none')
zlim([0, 2.5*C0])
pbaspect([75,1000,500])
xlabel('x (\mum)','fontsize',16)
ylabel('z (\mum)','fontsize',16)
zlabel('Concentration (\mug/\mum^3)','fontsize',16)
title('Analytical Solution (t = 1 s)','fontsize',20)
```

```
figure
surf(xmesh,zmesh,u_t1,'edgecolor','none')
zlim([0, 2.5*C0])
pbaspect([75,1000,500])
xlabel('x (\mum)','fontsize',16)
ylabel('z (\mum)','fontsize',16)
zlabel('Concentration (\mug/\mum^3','fontsize',16)
title('Analytical Solution (t = 50 s)','fontsize',20)

figure
surf(xmesh,zmesh,u_t2,'edgecolor','none')
zlim([0, 2.5*C0])
pbaspect([75,1000,500])
xlabel('x (\mum)','fontsize',16)
ylabel('z (\mum)','fontsize',16)
zlabel('Concentration (\mug/\mum^3)','fontsize',16)
title('Analytical Solution (t = 100 s)','fontsize',20)

figure
surf(xmesh,zmesh,u_t3,'edgecolor','none')
zlim([0, 2.5*C0])
pbaspect([75,1000,500])
xlabel('x (\mum)','fontsize',16)
ylabel('z (\mum)','fontsize',16)
zlabel('Concentration (\mug/\mum^3)','fontsize',16)
title('Analytical Solution (t = 500 s)','fontsize',20)

figure
surf(xmesh,zmesh,u_t4,'edgecolor','none')
pbaspect([75,1000,500])
xlabel('x (\mum)','fontsize',16)
ylabel('z (\mum)','fontsize',16)
zlabel('Concentration (\mug/\mum^3)','fontsize',16)
title('Analytical Solution (t = 1000 s)','fontsize',20)

end
```

Published with MATLAB® R2015b

MATLAB: Poke and Flow

```
%%Program for making animation from array C

%Plot first frame
s = surf(z,x,C(:,:,1),'edgecolor','none');

%Set aspect ratio and axis for better viewing
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])

%Label figure
```

```
title('Numerical Solution (Finite Differences)')
xlabel('z (\mum)')
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')

%open video file
vidObj = VideoWriter('AnimationImp.avi');
open(vidObj);

% Step size (30 in this case) determines frame rate
for i = 1:30:length(C(1,1,:));
    %updates data in the plot
    s.ZData = C(:,:,i);
    %captures frame
    F = getframe(gcf);
    %writes to video
    writeVideo(vidObj,F);

end
%close video file
close(vidObj);

%Plots single figure at t = 1,50,100,200,500
figure
s = surf(z,x,C(:,:,10),'edgecolor','none');
title('Numerical Solution (t = 1 s)')
xlabel('z (\mum)')
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])

figure
s = surf(z,x,C(:,:,500),'edgecolor','none');
title('Numerical Solution (t = 50 s)')
xlabel('z (\mum)')
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])

figure
s = surf(z,x,C(:,:,1000),'edgecolor','none');
title('Numerical Solution (t = 100 s)')
xlabel('z (\mum)')
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])

figure
s = surf(z,x,C(:,:,2000),'edgecolor','none');
title('Numerical Solution (t = 200 s)')
xlabel('z (\mum)')
```

```
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])

figure
s = surf(z,x,C(:,:,5000),'edgecolor','none');
title('Numerical Solution (t = 500 s)')
xlabel('z (\mum)')
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])
```

Published with MATLAB® R2015b

MATLAB: Poke and Patch

```
%%Program for making animation from array C

%Plot first frame
s = surf(z,x,C(:,:,1),'edgecolor','none');

%Set aspect ratio and axis for better viewing
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])

%Label figure
title('Numerical Solution (Finite Differences)')
xlabel('z (\mum)')
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')

%open video file
vidObj = VideoWriter('AnimationImp.avi');
open(vidObj);

% Step size (30 in this case) determines frame rate
for i = 1:30:length(C(1,1,:));
    %updates data in the plot
    s.ZData = C(:,:,i);
    %captures frame
    F = getframe(gcf);
    %writes to video
    writeVideo(vidObj,F);

end
%close video file
close(vidObj);
```

```
%Plots single figure at t = 1,50,100,200,500
figure
s = surf(z,x,C(:,:,10),'edgecolor','none');
title('Numerical Solution (t = 1 s)')
xlabel('z (\mum)')
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])

figure
s = surf(z,x,C(:,:,500),'edgecolor','none');
title('Numerical Solution (t = 50 s)')
xlabel('z (\mum)')
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])

figure
s = surf(z,x,C(:,:,1000),'edgecolor','none');
title('Numerical Solution (t = 100 s)')
xlabel('z (\mum)')
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])

figure
s = surf(z,x,C(:,:,2000),'edgecolor','none');
title('Numerical Solution (t = 200 s)')
xlabel('z (\mum)')
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])

figure
s = surf(z,x,C(:,:,5000),'edgecolor','none');
title('Numerical Solution (t = 500 s)')
xlabel('z (\mum)')
ylabel('x (\mum)')
zlabel('Concentration (\mug/\mum^3)*10^-^1^0')
pbaspect([750 75 750])
axis([0 1000 0 75 0 .02])
```

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