Modeling of Transdermal Drug Delivery in Randomly Rough Skin

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Introduction & Background

As a pathway for drug delivery, skin is a natural target for biomedical research. Transdermal drug delivery is influenced by the geometry of contact between the bandage and the tissue. The topology of skin has been studied extensively across different age ranges, conditions, and sun exposure in the medical and cosmetic industry. Skin roughness is affected by numerous factors, but wrinkles and other common skin conditions have a big impact. Skin roughness was found to be greater in the high age ranges compared to younger people in different anatomical regions on the body including the forearm, cheek, and eye rim [1].

There are three different windows of the drug based on the drug concentration at a given point in time. The three windows are the subtherapeutic window, therapeutic window, and toxic window [2]. In the subtherapeutic window, the drug has no effect on the patient as the drug concentration is too low. In the therapeutic window, the drug can now take effect but if the drug concentration becomes too high then the toxic window is reached.

In this research, I investigated the impact of the surface roughness of human skin on the concentration profile. This has tremendous importance because it is possible that with the wrong dosage the concentration may reach a toxic level.

Methods

A randomly rough surface was simulated using an algorithm deployed on commercial computer hardware. An initial set of discrete topographic points was convolved with a Gaussian filter to attain correlation using the discrete Fast Fourier Transform algorithm. The convolution theorem for two signals is $x(t) \cdot y(t) = \mathcal{F}^{-1}\{\mathcal{F}\{x(t)\} \cdot \mathcal{F}\{y(t)\}\}$, as described by Garcia and Stoll [3]. Normalizing prefactors such as the size of the sample, overall number of locations/points, and correlation lengths were multiplied by the convolution to obtain the final heights (Figure 1).

The discrete points defining the random, rough surface were then converted into an element mesh in preparation for simulation of the mass transport utilizing the finite element method (FEM) (Figure 2). FEM is a popular method used to numerically solve partial differential equations for mathematical and engineering models of physical phenomena that cannot be solved analytically because the geometry is too complex. A numerical approximation of the solution can be numerically on a discrete grid or mesh.

Fick's 2nd Law, the differential equation that governs diffusive transport of chemical species, is

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

where $C(x, y, z, t)$ is the concentration of the species and D is the diffusivity parameter related to the mobility of the species. Fick's 2nd Law was solved numerically at the points of the mesh, and C was determined from $t = 0$ to $t = 72$ hr using realistic boundary conditions. This included a Dirichlet boundary $C(x, y, 0, t) = 0$ because it is assumed that the drug is instantaneously absorbed into the blood. A Neumann boundary was set on the x and y boundaries to ensure there was zero flux across the boundary. A Robin boundary that related the concentration function to the concentration in the patch via a partition parameter K. K (taken with values ranging from 0.15 to 0.60) represents the solubility of the drug in the skin, and the diffusivity ($D = 1.08 \times 10^{-6}$ cm^2/hr) describes how fast a substance is diffusing from one region to another through each cross section per unit of time.

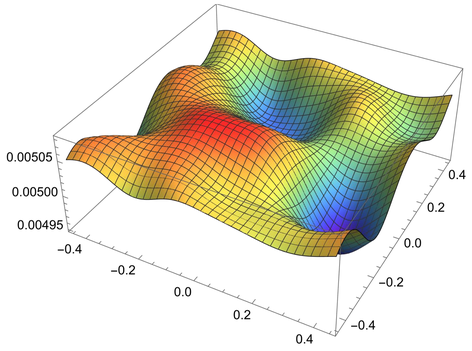

Figure 1. Example of randomly rough surface generated using the algorithm.

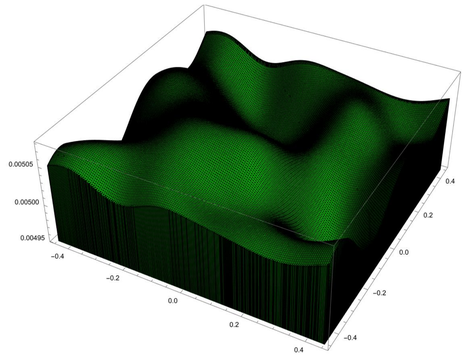

Figure 2. The surface from Figure 1, converted into an element mesh.

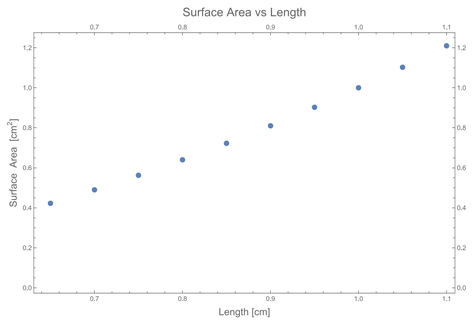

Figure 3. The overall surface area of the surface, as a function of sample edge length.

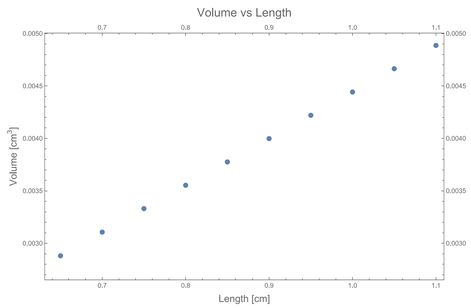

Figure 4. The overall volume of the surface, as a function of sample edge length.

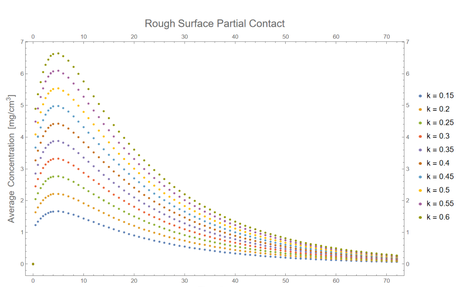

Figure 5. Average concentration as a function of time for various K values.

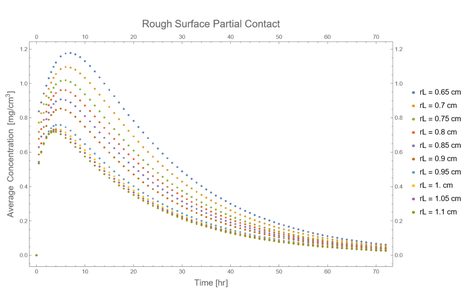

Figure 6. Average concentration as a function of time for various sample edge lengths.

Results

The behavior of the concentration with respect to time shows an absorption phase where the concertation increases to a peak and then the sink condition $C(x, y, 0, t) = 0$ takes over and the concentration of the drug decreases as part of the elimination phase. This type of behavior of concentration with respect to time matches the literature [4]. The higher the K value the higher the peak concentration of the drug (Figure 5). This is as expected as the higher K value represents a greater solubility/absorption of the drug in the skin. The drug concentration is higher in the rough surface due to more surface area and in the case of partial contact it is similar to the flat surface as only part of the surface is in contact with the bandage. As the length of the sample, L, increased, the surface area increased parabolically (Figure 3) and the volume increased linearly (Figure 4). Larger L gave a lower peak of C_{avg} (Figure 6). The higher surface area allows the diffusion of the drug to be more spread out, have a shorter absorption phase, and lower total dosage of exposure to the drug.

Conclusion

Simulations using Fick's 2nd Law applied to a realistic interface between a medicated patch and a region of skin, produced discrete solutions $C(x, y, z, t)$ for the concentration of the drug throughout the simulated space. From this solution, spatially averaged $C_{avg}(t)$ profiles for the levels of the drug in the tissue were obtained. The parameters K (solubility), D (diffusion), and surface area can be tuned to match different drugs/biological circumstances, and these modifications will produce different profiles. These profiles can be evaluated for therapeutic efficacy or toxicity, as well as drug loading required in the patch.

References

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