

# A Computational Model for the Facilitated Transport of Metronidazole by Iontophoresis

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BEE 4530

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## I. Executive Summary

Burns are one of the most common and devastating forms of trauma. Thermal injuries often result in a state of immuno-suppression that predisposes burn patients to complications such as infection. As a result penicillin or other broad spectrum antibiotics are often taken as preventatives. Oral or intravenous administration can result in a deleterious, sudden, and systemic “burst” of drug in the body. Recently, trans-dermal delivery of antibiotics has become popular for use in such scenarios. The dosage can be carefully controlled and administered continuously as opposed to one large burst. However, delivery of the drug at therapeutic levels is often hindered when using ionized (charged) drugs. Furthermore, passive diffusion is not sufficient to allow the drug to adequately penetrate the skin. We propose here the development and optimization of an iontophoretic trans-dermal patch to deliver metronidazole (MN) for use in post burn scenarios.

The iontophoretic patch makes use of electric charges to propel the drug through the skin faster than passive diffusion could alone. Unlike in normal transdermal patches where you can only control the diffusivity of the drug in the patch, iontophoretic patches allow you to control the potential difference across the electrodes. Using our model, we sought to optimize the voltage in the patch that would make transdermal delivery of metronidazole possible at a therapeutic level in burn victims. Many voltage sequences were experimented with, and two phasic voltage profiles (one using higher voltage and one with lower voltage) were produced in an attempt to achieve better MN distribution within the damaged epidermis layer. We found that application of a complex, sequential voltage profile for 24 hours resulted in the most optimized concentration profile. The mass of drug in the patch moved as a block into the epidermis during voltage application and diffused normally thereafter. The mass of the drug spread throughout much of the skin layer without significant penetration into the dermis. Our findings are significant in that they demonstrate that the application of an applied voltage can greatly improve the efficacy of localized drug delivery as compared with diffusion alone.

## II. Introduction

Burns represent one of the most prevalent injury types in the United States, with approximately 450,000 such injuries requiring professional medical attention each year (American Burn Association 2010). This does not include the many superficial 1st degree burns for which medical attention is not sought and treatment is administered by the patient using over the counter bandages and ointments. The latter are most often associated with burn injuries originating in the home, which represent approximately 68% of reported burns.

Burn injuries can develop from a wide variety of sources, and are indiscriminate with regard to the demographic of the patient. In addition, burns have a wide range of severities, from superficial irritation to deep tissue damage. In order to categorize burn injuries, they are typically classified into four different burn types, or “degrees,” based on the depth and severity of the burn. First degree burns involve damage that is restricted to the epidermis. Patients present minimal swelling and erythema accompanied by minor discomfort. These burns are typically treated as outpatient procedures or by the patients themselves. Second degree burns can be divided into two major categories: superficial partial-thickness and deep partial-thickness. The former involves damage to the epidermis and the superficial portion of the dermis. Often associated with scalding injuries, these burns are characterized by blister formation. These burns are also treated as outpatient procedures, and require a healing time between one to three weeks. Deep partial-thickness burns involve the epidermis and most of the dermis. These burns may not blister due to damage to the vasculature. In addition, they may require more time to heal (3-4 weeks) and may require wound excision/grafting. Third degree burns are full thickness burns which include damage to the epidermis, the entirety of the dermis, and extend into the subcutaneous tissue. These burns often require specialized attention from a burn surgeon and require skin grafting to correct. Finally, fourth degree burns are full-thickness burn that extends to the muscle and/or bone. These require hospital admission and intensive care treatment (The Mayo Clinic 2012).

The two least severe burn types, 1<sup>st</sup> degree and superficial 2<sup>nd</sup> degree, are of particular interest in that they both have the potential to be treated as outpatient procedures. For the former, commonly referred to as “minor burns,” it is often the case that a simple at-home treatment is sufficient. This involves submerging the affected areas in cool water for ten to fifteen minutes, followed by loosely wrapping the wound with sterile gauze. This treatment strategy, however, is limited in that it is only appropriate and effective for 1<sup>st</sup> degree burns that cover a small area of the skin surface: it proves ineffective and can lead to complications in larger or more severe burns. For these burns, one of the major causes for concern with respect to complications is the development of wound-site infections. Essentially, opportunistic or nosocomial microbial pathogens are able to colonize the wound site as a result of burn-related immunosuppression in the affected regions. This can compromise the healing process, increase the healing time, and possibly require more invasive treatment strategies. Untreated, these infections can cause necrosis of the surrounding tissue, requiring debridement of the wound site. In order to prevent these infections from occurring or combatting them in their early stages IV antibiotics are administered. Such a treatment route is problematic, however, as it will require hospitalization for administration.

One alternative to the aforementioned treatment options is to engineer wound dressings which provide additional healing benefits over traditional gauze without requiring in-hospital treatment beyond bandage application. Such dressings draw from a wide variety of materials and techniques. Some examples include (but are not limited to) hydrocolloid dressings, silicon-coated nylon dressings, Ag/I bearing antimicrobial dressings, and biofibre dressings. Hydrocolloid dressings contain bio-derived components such as gelatin or pectin in an adhesive polymer that form gels when applied. This gel encourages wound debridement via autolytic activities. Silicon-coated nylon dressings provide a flexible mesh which allows for drainage of exudate generated at the wound surface, which can decrease the risk of infection. Ag/I bearing antimicrobial dressings severely reduce the risk of bacterial infection by diffusing silver or iodine at the wound surface. Finally, bio-fibre dressings use calcium alginate (derived from seaweed) maintains an optimal healing environment at the wound surface while simultaneously abrogating bacterial infections (Wasiak, Cleland and Campbell 2008).

Unfortunately, none of the dressings described above has the potential to effectively introduce antibiotics and larger antimicrobial drugs to the wound site. Simple diffusion is insufficient to transport molecules of this size through the tissue with any noticeable degree of penetration, much less reaching concentrations that are sufficient to abrogate bacterial infection proliferation. As such, other techniques must be sought if such drugs are to be delivered using a dressing motif.

One possible avenue of therapy that has recently been explored is iontophoresis. Iontophoresis is a transport phenomenon by which an applied voltage is used to enhance the rate of permeation through a diffusion barrier. By this mechanism one is able to increase the flux of a target molecule through a barrier, which is sometimes referred to as the flux enhancement ratio. This technique was rapidly adopted by biomedical researchers, who were interested in the potential for drug delivery through the skin but had been stymied by the size/charge restrictions on delivery that skin presents. Within this setting, iontophoresis was redefined as, “the permeation of ionized drug molecules across biological membranes under the influence of electrical current” (Dhonte, et al. 2011).

A substantial amount of research has been conducted to determine the viability of iontophoresis as a potential avenue for drug delivery. Glass et al, considered by some to be the pioneers of transdermal iontophoretic drug delivery demonstrated that this technique was effective in delivering drugs in Rhesus monkeys (Glass, Stephen and Jacobsen 1979). Wearley et al sought to deliver verapamil using iontophoresis and were subsequently able to conclude that delivery of systemically-toxic drugs through the skin offered better safety potential than conventional delivery mechanisms (Wearley, Liu and Chien 1989). Prasad et al demonstrated that iontophoresis could enhance the delivery of methotrexate in a hydrogel patch motif, simultaneously demonstrating that the observed transport phenomena were influenced by properties of the hydrogel patch, duration of electrical current application, and condition of the skin (Prasad, Koul and Khar 2005). Mutalik et al were able to show in a series of studies that a matrix patch system coupled with iontophoresis was more effective in the delivery of the drug Glipizide than an oral formulation (Mutalik, Upuda and Kumar 2006).

While the drugs that were investigated in the studies mentioned above represent a wide range of therapeutic interests, we determined that moderate (second degree) burns represented an attractive target for iontophoretic drug delivery, since the transport phenomenon is effective over

the range of damaged tissue. Work conducted as far back as 1965 by Rapperport et al has confirmed this target. They used iontophoresis to deliver penicillin to both rat and human subjects directly at the site of burn injury, and found a 200 fold increase in drug permeation with respect to conventional delivery strategies (Rapperport, et al. 1965).

In this study we attempt to model the feasibility of using a new drug delivery system to treat burned tissues and prevent infection by bacterial and fungal pathogens: transdermal delivery of metronidazole utilizing iontophoretic driven flow. This represents a novel application of our drug of interest, which is often used as a therapeutic against anaerobic bacterial infections. The relatively low molecular weight (171.6 Daltons) and negative net charge of metronidazole make it an attractive candidate for iontophoretic delivery (Sipahigil, et al. 2011). Furthermore by utilizing the transdermal approach, our team hopes to bypass many of the harmful side effects presented by oral delivery of the medication. In addition, by applying the patch directly to the site of injury we accomplish rapid, targeted delivery and minimize the amount of drug necessary for treatment. Ultimately if our proposed design is successful, our model may prove useful in the development of additional transdermal delivery systems.

### III. Model Design and Development Criterion

The following provides an exhaustive summary of the conditions and assumptions that are included in the final model.

#### A. *Problem Statement*

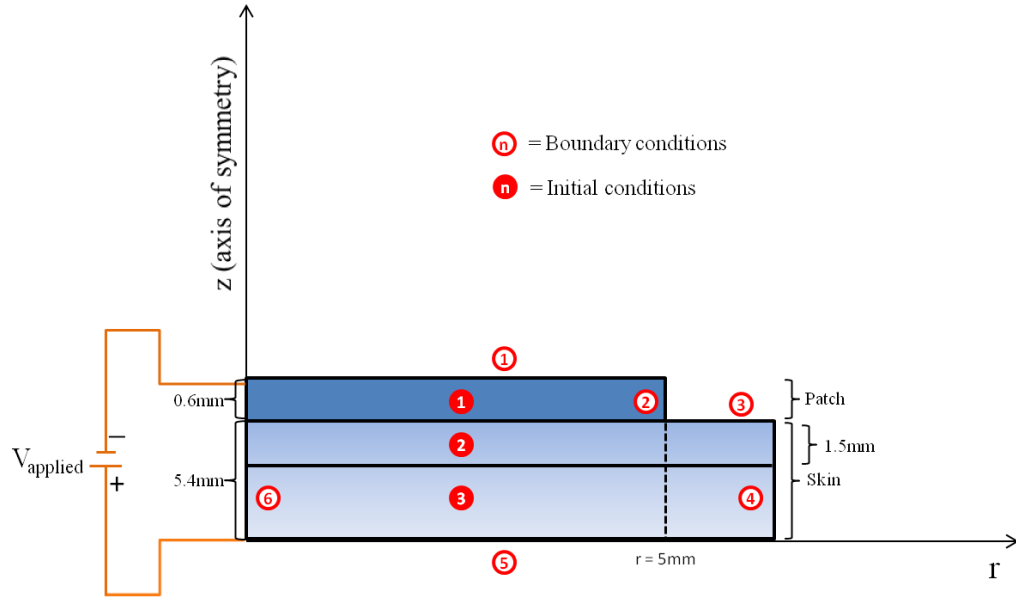
We propose the development and optimization of a computational model which accurately describes the drug transport phenomena observed in the application of an iontophoretic trans-dermal patch to deliver Metronidazole for use in post-burn scenarios.

#### B. *Design Objectives*

- Develop a COMSOL computational model for iontophoretic transport of Metronidazole from a patch into burnt skin/tissue that accurately reflects how this phenomena actually occurs *in vivo*
- Optimize voltage and initial concentration in patch needed to achieve therapeutic concentration at steady state

#### C. *Schematic*

Based on our knowledge of the process of patch-based iontophoretic drug delivery as it is currently implemented both in the scientific literature and commercially (for drugs other than Metronidazole), we have developed a schematic that describes this transport phenomena. It should be noted that for the purpose of simplification, we have determined that the scenario we model here is 2D axisymmetric. While many commercial applications have more rectangular patch geometries, we have determined that the primary direction of transport that we are concerned with is in the Z direction (into the skin) and therefore this simplification is justified.



**Figure 1: Schematic for the patch-based iontophoretic delivery of Metronidazole into burn-damaged skin. The numbered circles in the diagram correspond to the boundary conditions (hollow circles) and the initial conditions (filled circles) that are included below.**

**Boundary Conditions:**

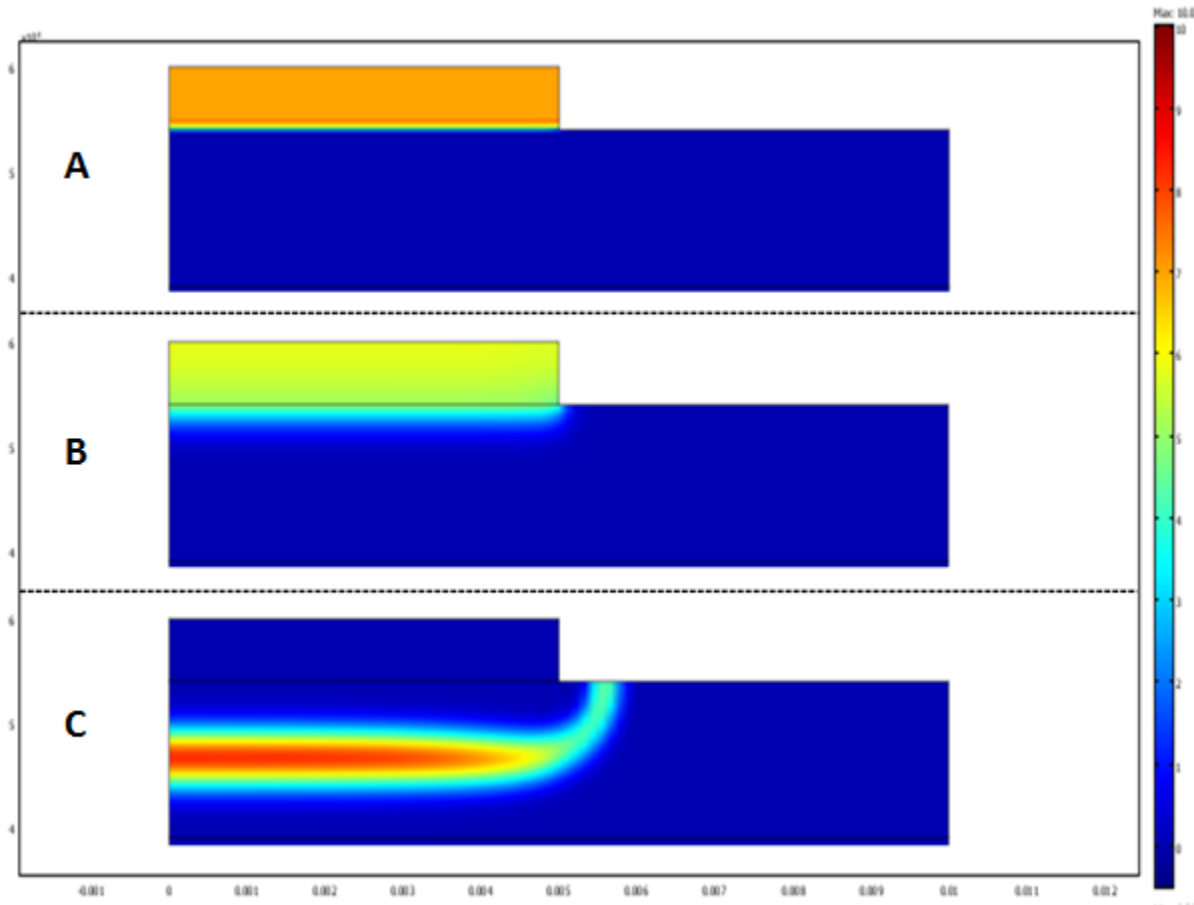
1.  $-D \frac{dc}{dz} \Big|_{z=0.006m} = 0$
2.  $-D \frac{dc}{dr} \Big|_{r=0.005m} = 0$
3.  $-D \frac{dc}{dz} \Big|_{z=0.0054m} = 0$
4.  $-D \frac{dc}{dr} \Big|_{r=\infty} = 0$
5.  $c_{z=-\infty} = 0$
6.  $-D \frac{dc}{dr} \Big|_{r=0m} = 0$

**Initial Conditions:**

1.  $c_{t=0} = c_0$
2.  $c_{t=0} = 0$
3.  $c_{t=0} = 0$

## IV. Results and Discussion

Using the coupled model of Conductive Media DC and Nernst-Planck modules to mimic the effect of iontophoresis, the characteristics of metronidazole (MN) migration into damaged skin are studied. The goal of this study was to establish a more therapeutically effective MN concentration profile in the damaged skin that cannot be achieved with diffusion alone. Two specific aims of this study were: 1) accelerate the rate of MN transport to skin and 2) establish a therapeutically effective and safe profile using varied voltages. The concentration of MN in the patch is set to  $7\text{mols/m}^3$  as shown in Figure 2A.

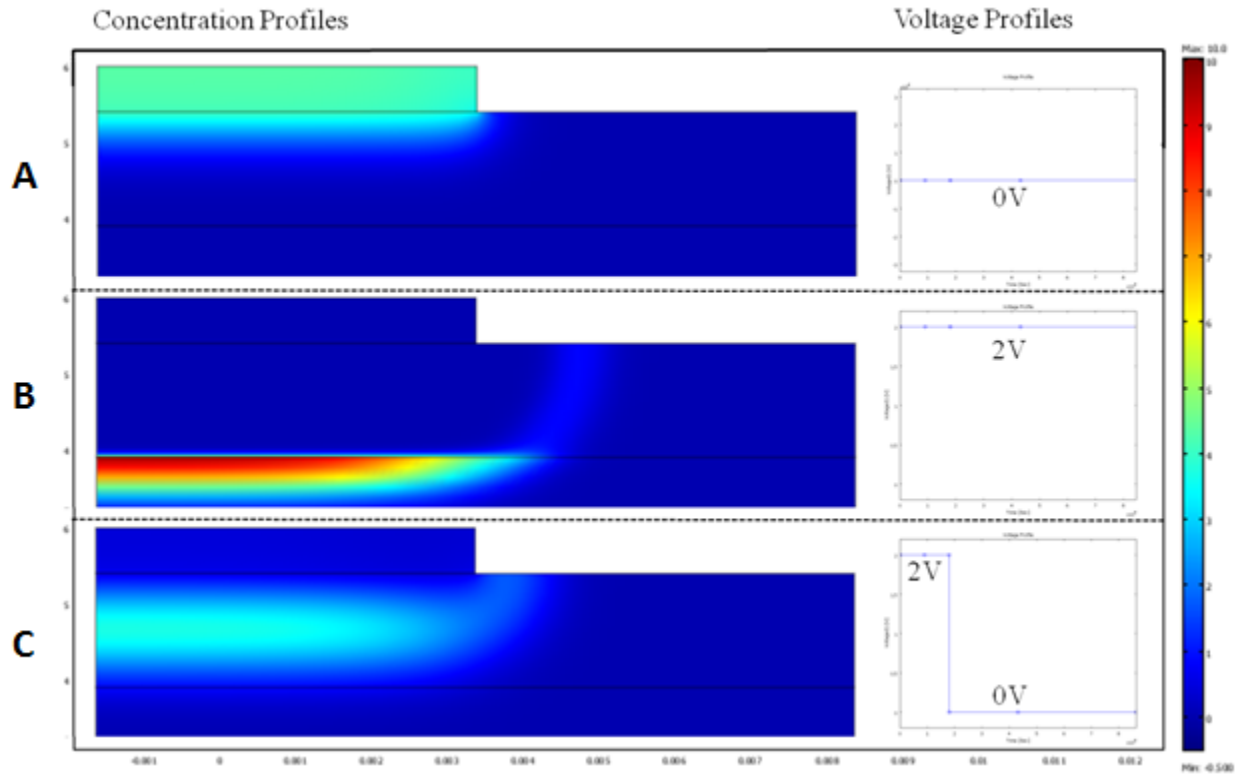


**Figure 2:** (A) The initial concentration profile of MN.  $C_{\text{initial}} = 7\text{mols/m}^3$ ,  $t = 0$  sec. (B) The concentration profile of the drug after 5 hours of diffusion. The concentration of MN after 5 hours (18000 sec) of diffusion (0V) is displayed in color scale. (C) The concentration profile of the drug after 5 hours of iontophoresis. The concentration of MN after 5 hours (18000 sec) of iontophoresis using 2V is displayed in color scale. Red indicates high concentration and blue indicates low concentration.

When a voltage of 2V was applied for 5 hours, all of the MN in the patch was transported into the skin (Fig. 2C). This is significantly faster than the diffusion-based transport where the majority of the MN remained in the patch after 5 hours (Fig. 2B). During iontophoretic transport, the voltage-induced driving force pushes the drugs into the skin against the resistive

force of the tissue to compress the drugs, forming a thin, compact block of MN with a maximum concentration higher than that of the original patch. These results suggest that while iontophoresis is an effective way to accelerate the process of MN transport, it does not effectively promote drug spread and establish a desired profile.

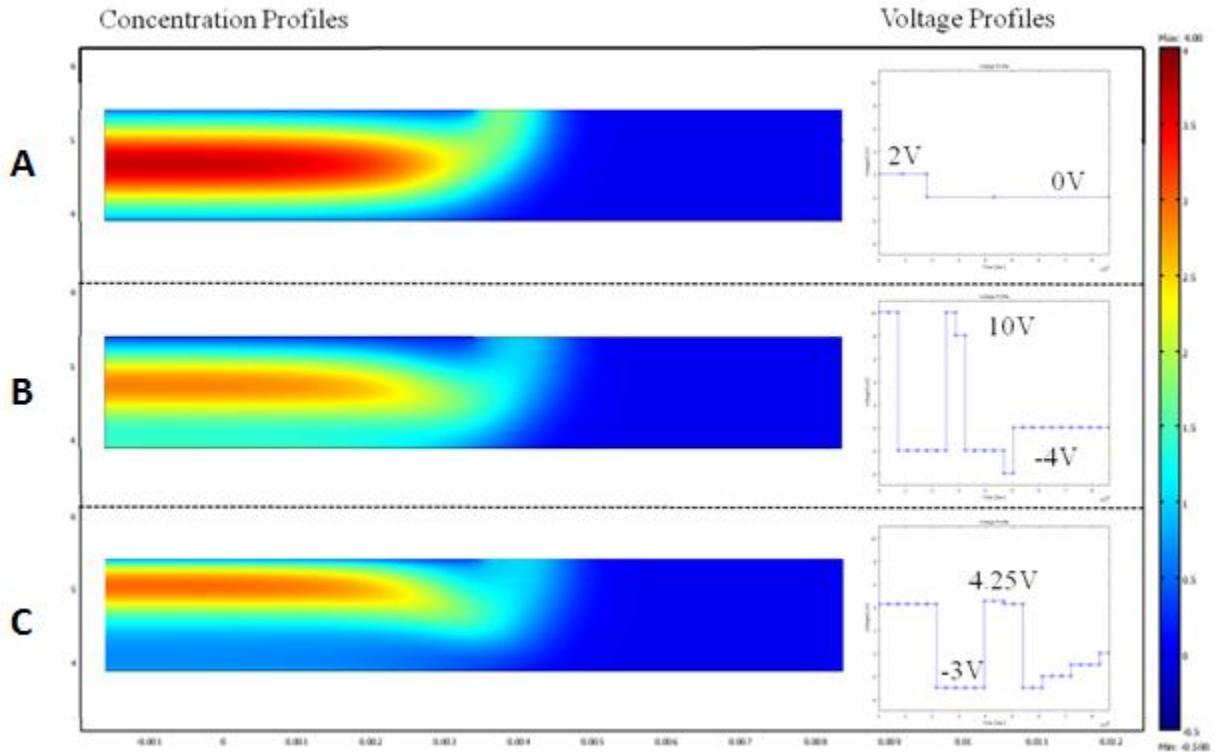
In an attempt to rapidly establish a therapeutically effect MN profile in the damaged skin, the combination of iontophoretic and diffusive transports are used. A simple on-and-off system (Fig. 3C) is used to establish a system where the drug is first transported into the tissue with iontophoresis and then diffuses without applied voltage. Figure 3C shows the result after 5 hours of 2V iontophoresis and 19 hours of passive diffusion (a total of 24 hours). As can be seen from the figure, the drug diffuses nicely throughout the top epidermis layer (damaged layer) and remains entirely in the top epidermis layer. The effectiveness of combined transport is apparent when the above profile is compared to the concentration profile of only diffusive or only iontophoretic transport (Fig. 3A, 3B). While the lack of iontophoresis caused the drugs to remain in the patch, prolonged iontophoresis caused the drugs to form undesired high-concentration blocks elsewhere in the tissue.



**Figure 3:** (A) The concentration profile after 24 hours of diffusion. (B) The concentration profile after 24 hours of iontophoresis. (C) The concentration profile of MN after 5 hours of 2V iontophoresis and 19 hours of simple diffusion is displayed in color scale.

The increased transport rate due to iontophoresis and the extended drug spread due to diffusion has demonstrated the potential of combined transport as a possible drug delivery method to a desired skin layer. However, the limited and uneven drug distribution in the epidermis layer makes the simple on-and-off system a problematic design. To meet therapeutic

needs, the drugs must not only spread, but also achieve a more uniform distribution within the epidermis layer. In other words, in order to be considered practical clinically, the regional concentration discrepancies must be reduced so that the majority of the regions are exposed to a drug concentration that is both effective and safe. This problem suggest that the simple on-and-off voltage driven delivery system is not sufficient and further control over the drug delivery is needed through a phasic voltage driven delivery system.



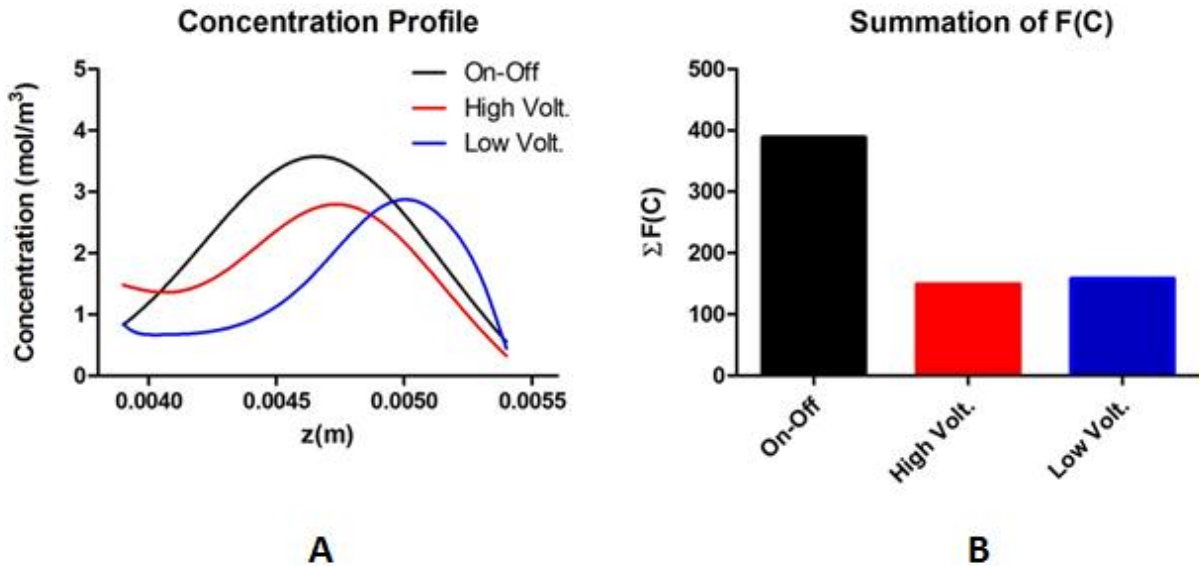
**Figure 4:** (A) The concentration profile of MN after 5 hours of 2V iontophoresis and 19 hours of simple diffusion is displayed in color scale. This profile is identical to Fig. 3C. However, the color scale is changed for a more direct comparison with (B) and (C). (B) The high voltage profile. The voltage sequence over 24 hours is depicted on the right hand side of the figure.  $V_{max} = 10V$  and  $V_{min} = -4V$ . (C) The low voltage profile. The voltage sequence over 24 hours is depicted on the right hand side of the figure.  $V_{max} = 4.5V$  and  $V_{min} = -3V$ .

Many voltage sequences were experimented with, and two fluctuating voltage profiles (one using higher voltage and one with lower voltage) were produced in an attempt to achieve better MN distribution within the damaged epidermis layer (Fig. 4). Using the two phasic voltage profile, two MN concentration profiles were produced as shown in figures 4B and 4C. When compared to the concentration profile produced by the simple on-and-off system (shown in Fig. 4A in comparable scale), the concentration profiles of the phasic systems have a much lower maximum concentration, indicating a more uniform distribution within the epidermis layer. This trend can also be seen by comparing the cross-sectional concentration plots of the three profiles (Fig. 5A).

To quantitatively analyze the MN concentration profile, an objective function (shown below) is used to assess the effectiveness and safety of the profiles produced. Studies have shown the effective concentration of MN to be approximately  $0.5\text{mol/m}^3$  and the toxic concentration to be approximately  $3\text{mol/m}^3$ .  $1\text{mol/m}^3$  and  $2.5\text{mol/m}^3$  are, therefore, chosen to be the lower and the upper bound for the allowable concentration.

$$F(C) = \begin{cases} 2C - 2.5 & C > 2.5 \\ 0 & 1 \leq C \leq 2.5 \\ 1 - C & C < 1 \end{cases}$$

A harsher penalty was applied to toxic concentrations because it is better to be ineffective than to be toxic and cause additional complications. The penalties at all sample points are summed up for each profile and the results are shown in figure 5B. The results indicate that while many regions in the epidermis layer were above or below the allowable concentration range using the simple on-and-off system, the distribution of ineffective or toxic concentrations was significantly reduced when phasic systems were used. This suggests that the proper alternation of voltage during iontophoretic transport can lead to increased MN dispersion within the tissue. The  $F(C)$  summation of the high-voltage system and the low-voltage system showed no significant difference, indicating that MN dispersion is more dependent on the sequence of voltage alteration than the voltage magnitude. The low-voltage system, therefore, should be used to prevent further voltage induced burns.



**Figure 5: (A) The cross-sectional concentration profiles at  $r = 0.0025\text{m}$  for high-voltage, low-voltage, simple on-and-off. (B) The summation of  $F(C)$  from all sample points for each voltage profile is displayed. A high sum corresponds to a high number of undesired concentrations (number of sample points = 200).**

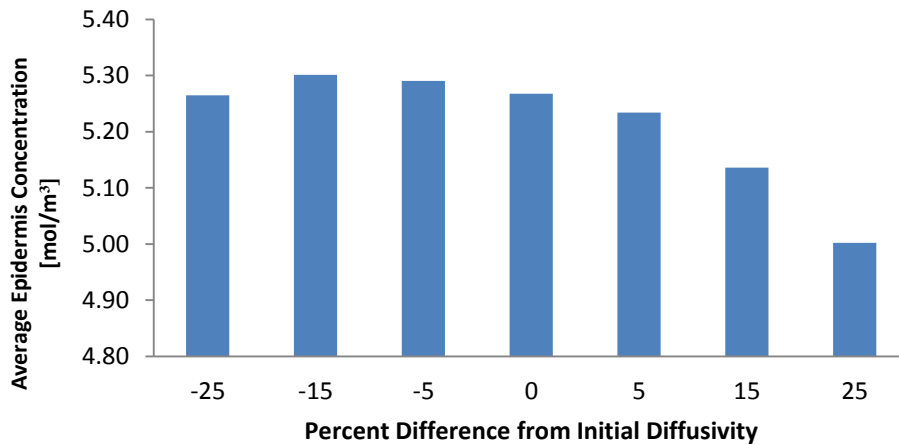
The results obtained using this model has demonstrated that the phasic iontophoresis combined with simple diffusion is an effective method to rapidly distribute MN in the damaged epidermis layer. The ability to improve both the transport rate and the distribution profile makes phasic iontophoresis a preferred method for delivery of any drug.

## V. Sensitivity Analysis

Next we analyzed the sensitivity of our model to various key parameters for which values were derived from the literature. In order to determine sensitivity the simple on/off scheme was used. We focused our analysis on three key parameters: diffusivity, conductivity, and voltage as they may affect average concentration of drug in the epidermis layer. The methodologies employed and the results of the sensitivity analysis for each of the four parameters listed above are included below.

### A. Diffusivity

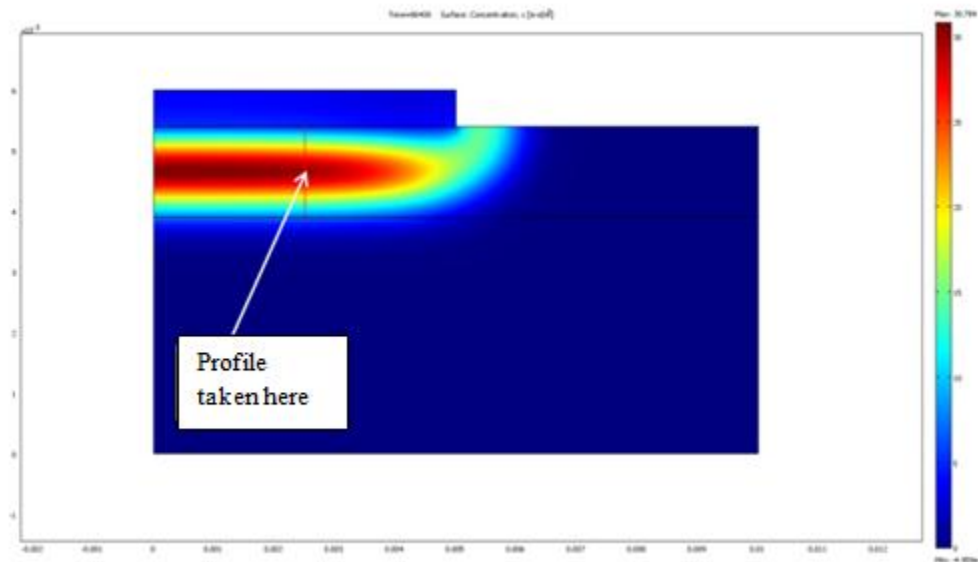
We investigated the effect on the model of varying the diffusion coefficient. While we used  $1.2 \times 10^{-12} \text{ m}^2/\text{s}$  as the diffusivity in our model, the diffusion coefficient has been reported as being between  $1.2 \times 10^{-12} \pm 1.0 \times 10^{-13} \text{ m}^2/\text{s}$  in the literature. Additionally, burnt or damaged skin may have a diffusivity that falls outside of this range. Since we would like to be able to apply our burn treatment to a wide array of burn situations, we need to assess the change in delivery dynamic when the diffusion coefficient is altered. We elected to vary this parameter up to 25% in each direction (between  $9 \times 10^{-12}$  and  $1.5 \times 10^{-11} \text{ m}^2/\text{s}$ ) and determine the average metronidazole concentration in the damaged skin layer (epidermis) (see figure 6).



**Figure 6: Sensitivity of average concentration of drug within the epidermis to diffusivity. The decrease in observed average epidermal concentration as diffusivity increases is due to drug lost to the dermis.**

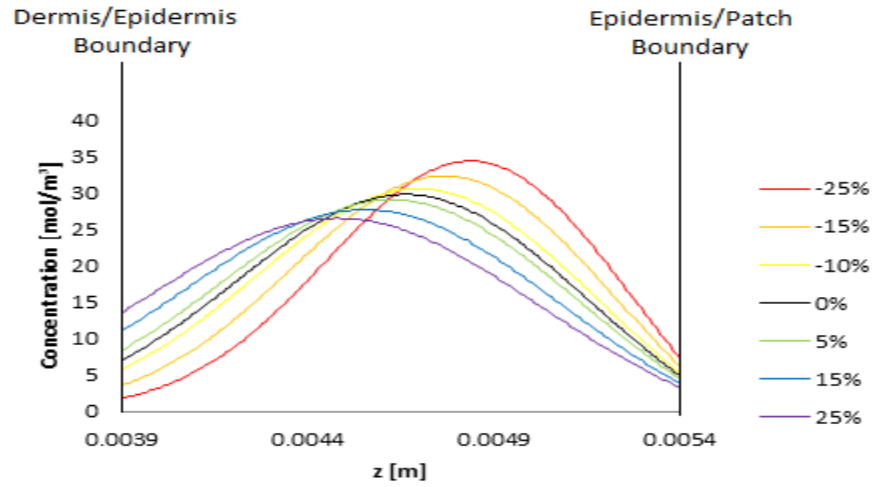
Upon further investigation, we noticed that the average concentration in the tissue of interest was not affected significantly by modulation of the diffusivity over the range mentioned above (A variance of only 5% is observed between decreasing the parameter's initial value by 25% and increasing it by 25%). The limited effects of diffusivity on average concentration are a result of drug largely remaining within the region of interest for all reasonable diffusivity values tested. We noticed however that diffusivity played a greater role in the overall distribution of drug within the region rather than total amount or concentration of drug delivered to the region. Since a greater distribution of drug is beneficial for treatment, we further investigated the

concentration distributions obtained for each diffusivity value. The decrease in average concentration as we increased diffusivity may seem counterintuitive, but it is simply due to the efflux of drug from the epidermis into the dermis (average concentration is only measured in the epidermis).



**Figure 7: Concentration profiles were taken at a representative cross-section of the epidermis over the line shown ( $r = 0.0025\text{m}$ ), in order to observe relative change in drug distribution within the epidermis.**

The variation that was visually observed appeared to be most significant with respect to the width of the delivered drug “band”. As such, we chose to plot the concentration values along the line  $r=0.0025\text{m}$  in the burnt skin subdomain ( $0.0039\text{m} < z < 0.0054\text{m}$ ) (Figure 7). We repeated this process for several diffusivity values within the range established above, and plotted the results on the same axes such that the effect of diffusivity on the distribution of drug in the burnt skin could be observed (Figure 8). From this plot we see two important things: first that lower diffusion coefficients result in drug being delivered closer to the patch side of the epidermis and second, lower diffusion coefficients result in a narrower band of drug delivered. Therefore, while diffusivity plays a limited role in the total amount of drug delivered to the epidermis, it does play a pivotal role in the distribution of drug in this region.



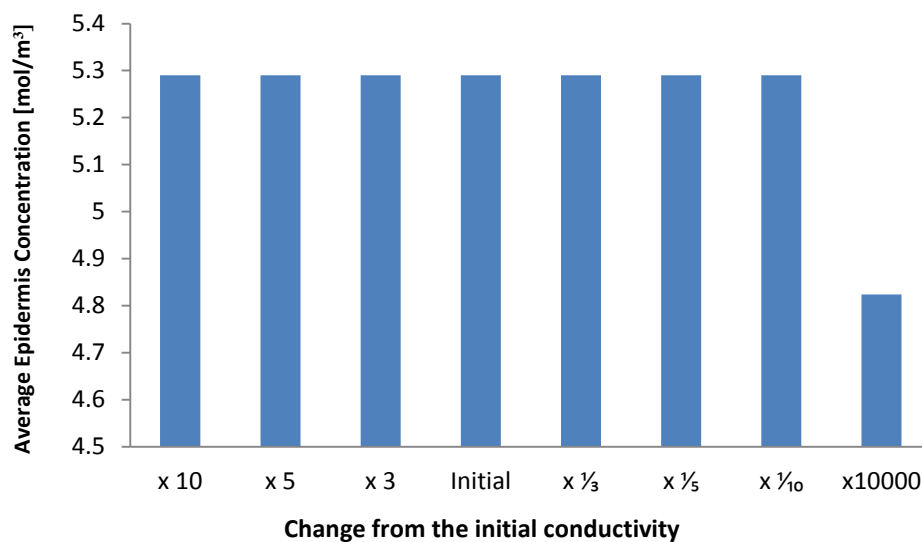
**Figure 8:** Concentration profiles along the line highlighted in Figure 7. Each line represents the profile associated with the indicated difference from the diffusivity chosen from the literature.

### **B. Electrical Conductivity**

While 0.0000125S/m is used for epidermis conductivity, this value can vary within a factor of five depending on the skin condition. For burnt skin, this variation can be even greater. To assess the model's conductive sensitivity, the epidermis conductivity is increased or decreased by factors of three, five, and ten. The numerical results are shown in Table 1 and Figure 9.

**Table 1:** Average concentration of metronidazole in epidermis layer with different conductivities

Conductivity [S/m]	Initial (1.25x10 <sup>-5</sup> )	x10 (1.25x10 <sup>-3</sup> )	x5 (6.25x10 <sup>-5</sup> )	x3 (3.75x10 <sup>-5</sup> )	x3 <sup>-1</sup> (4.17x10 <sup>-6</sup> )	x5 <sup>-1</sup> (2.5x10 <sup>-6</sup> )	x10 <sup>-1</sup> (1.25x10 <sup>-6</sup> )	x10000 (0.125)
Average Conc [mol/m <sup>3</sup> ]	5.29	5.29	5.29	5.29	5.29	5.29	4.82	5.29

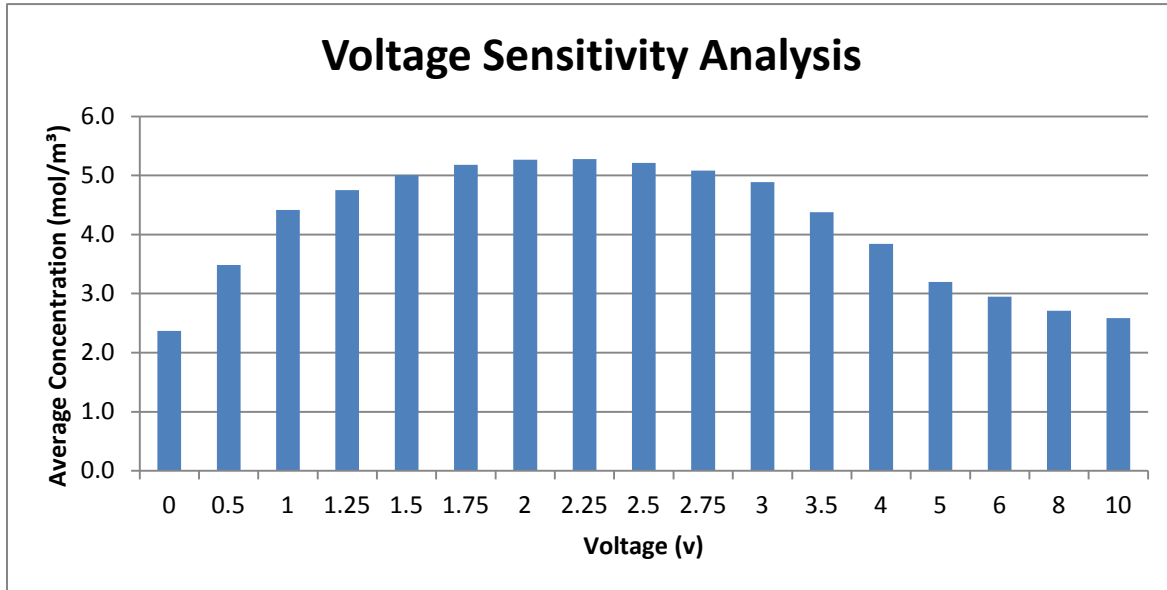


**Figure 9: Average concentration of metronidazole in epidermis layer. The conductivity is altered by factors of 3, 5, and 10. The 10000 fold increase is used as positive control.**

From the analysis, we can see that the change in epidermis conductivity does not significantly alter the results. The average concentration remains unchanged when epidermis conductivity is increased or decreased by factors of three, five, and ten. To confirm that this observation is due to an extremely low sensitivity (rather than the malfunction of DC-conductance module), the conductivity of the tissue is increased by 10000 fold – beyond its physiological value – as a positive control. When the epidermis conductivity is increased dramatically, the rate of drug transfer *via* iontophoresis is reduced, resulting in lower average metronidazole concentration in the epidermal tissue after 24 hours.

### C. Voltage

One of the key goals of our model was to determine the optimum voltage; therefore, determination of our model's sensitivity to voltage is critical in determining our solution. We determined our model's sensitivity to a range of voltages: 0v (diffusion only)-10v (Figure 10).



**Figure 10: Sensitivity of average concentration of drug within the epidermis to the voltage parameter. The decrease in observed average epidermal concentration as voltage increases is due to drug lost to the dermis.**

From the figure it is evident that at low voltages much less drug is delivered to the epidermis since the drug is transported by diffusion only. Interestingly however, at voltages greater than 2.25v, the average concentration of drug begins to decrease. This result is a consequence of drug being transported too far and leaving the region of interest (the epidermis) and entering the dermis. Our models high degree of sensitivity to voltage allowed us to modulate average concentration to deliver optimum therapeutic dosages.

## VI. Model Verification

The delivery of metronidazole (MN) using phasic iontophoresis is a novel treatment strategy for the treatment of burn injuries. As such there is no precedent established in the literature and subsequently no experimental results for use in validating our model specifically. Drug delivery via intradermal iontophoresis is by no mean a novel concept, however, and there is a wealth of experimental results that have been published which assess the delivery of other drugs through the skin by this transport mechanism. It is therefore plausible that we could find published results for a different drug which, by its similarity in physical characteristics to our own can be used to experimentally validate the results generated by our model.

Previous work has demonstrated that the delivery rate of azidothymidine (AZT) through the mouse skin can be increased substantially by the application of a constant electric potential (Oh, et al. 1998). In order to facilitate the comparison of the results, we made several changes to the boundary and initial conditions of our model which we are confident will not significantly compromise the validity of using this comparison as an accuracy check. The alterations that were made are itemized below:

The initial drug concentration was changed to reflect the constant molar concentration that was experimentally interrogated by Oh et al (20mg/mL, which is equal to  $74.838\text{mol/m}^3$ ). Therefore we modified the initial drug concentration of  $58.9624\text{mol/m}^3$  in the patch subdomain (subdomain 3) to a constant drug concentration of  $74.838\text{mol/m}^3$  at the patch-skin interface.

The phasic voltage is changed to constant voltages of 1V, 3V, and 5V, corresponding to 0.1mA, 0.3mA, and 0.5mA used in Oh's study. The phasic voltages are calculated assuming a skin resistance of 10,000ohms (which can vary between 1,000 to 500,000ohms).

Finally, the drug diffusivity is changed from diffusivity of MN in human skin ( $1.2 \times 10^{-12} \text{m}^2/\text{s}$ ) to diffusivity of AZT in human skin ( $0.8 \times 10^{-12} \text{m}^2/\text{s}$ ). Due to the lack of published value, the diffusivity of AZT in human skin is calculated based on the diffusivity of MN in human skin assuming a linear relationship between diffusivity and molecular weight. MN has a higher diffusivity because it has a lower molecular weight compared to AZT (171.5g/mol and 267.24g/mol, respectively).

The figures included below show the total amount of drug delivered as a function of time for a series of constant applied currents (as corresponding to voltage). The conservation of form that is observed between the experimental results (Figure 11[Left]) and our model using the modified parameters (Figure 11[Right]) indicate that the transport phenomena observed in our model is physiologically reasonable. It should be noted that the total amount of AZT transported in our model is considerably higher than what is observed experimentally for AZT. We posit that this is likely a result (at least in part) of the difference between the skin properties. While our model computed the transfer of AZT in human skin, the experiment measured the transfer of AZT in mouse skin. Some of these disparities are diffusivity differences which can impact the rate of transport and resistivity differences which can affect the effective potential generated by each current. Another interesting point to note is that while the delivery rates (slopes) decreased

over time in our model, Oh et al.'s experimental results maintains a fairly constant delivery rate. This suggests that there may be some sort of tissue reaction or blood transportation that can effectively reduce the local drug concentration *in vivo*. Since our model assumes no tissue reaction or blood transportation during the delivery process, the drug will build up in the local tissue over time, hindering the further transfer. It is difficult to incorporate tissue reactions into a computational model since different drugs are likely to induce different tissue responses which can only be determined experimentally. Blood transportation, on the other hand, is difficult to model in burnt tissues since the degree of vascularization vary greatly in damaged tissues. As such we are unable to include such effects in our model. As a result, we conclude that while modifications may be needed to correctly portray certain details, the model does produce a relatively accurate tendency that is physiologically reasonable.

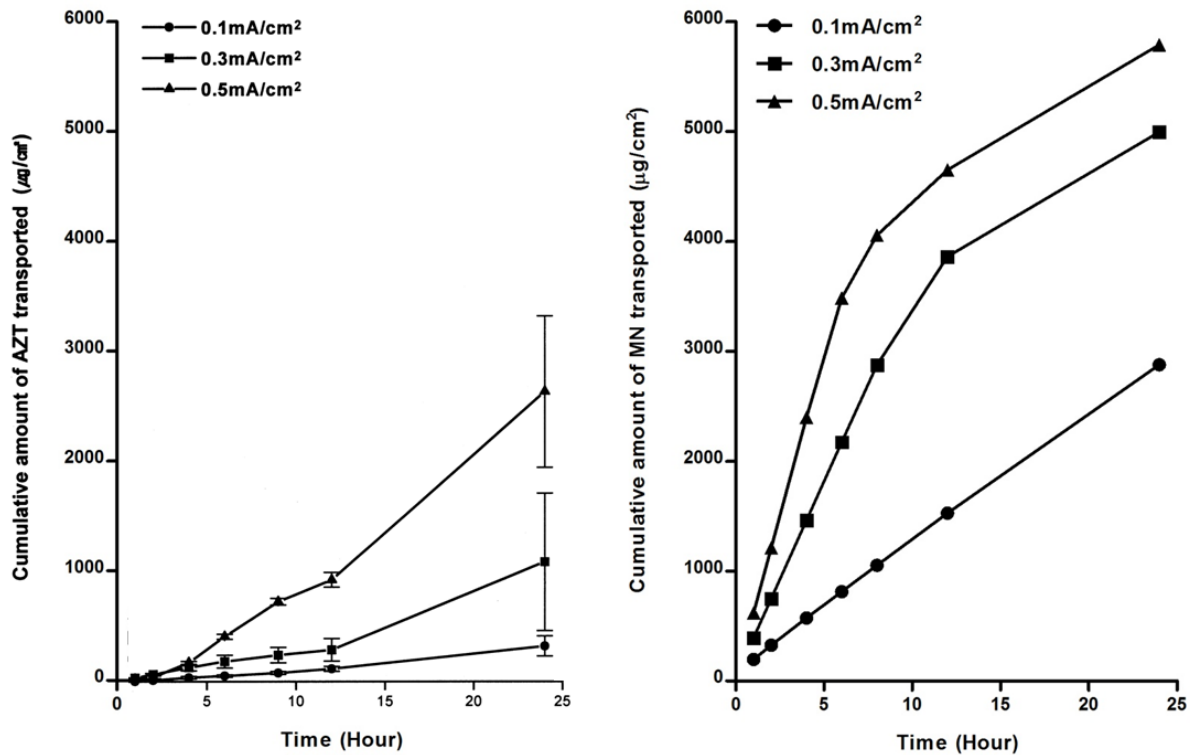


Figure 11: [Left] The total amount of AZT transported over time measured during experiments. Surface concentration =  $74.838\text{mol}/\text{m}^3$ .  $n=4-6$ . (Oh et al). [Right] The total amount of AZT transported over time modeled by COMSOL. Surface concentration =  $74.838\text{mol}/\text{m}^3$ .

## VII. Conclusion & Design Recommendations

Using our model, we sought to determine the voltage in the patch that would optimize the delivery of metronidazole such that a therapeutic level is achieved in burned epidermis tissue. Many voltage sequences were investigated, and two phasic voltage profiles (one using higher voltage and one with lower voltage) were developed in an attempt to achieve better MN distribution within the damaged tissue. Both of the phasic voltage profiles achieved better results than the simple on/off profile as evaluated by our objective function. We found that application of the high phasic voltage sequence resulted in the most optimized concentration profile. However, the lower phasic voltage pattern represented a more clinically relevant voltage profile, as the application of the higher voltage sequence could precipitate further tissue damage. Therefore we recommend using the low phasic voltage profile in the design criteria. Our findings are significant in that they demonstrate that a phasic applied voltage can greatly improve the efficacy of localized drug delivery even at low voltage. While our study focused on superficial tissues, it has not escaped our attention that this is a potential method for drug delivery to the deeper tissues. Furthermore, although our model was used to increase drug delivery rates and intra-tissue drug distribution, even more complex delivery patterns can be achieved via phasic iontophoresis using appropriate voltage sequences. This ability to manually control the movement of drugs using phasic iontophoresis can promote further advancement in personalized medicine where unique delivery dynamics will be adopted for patients of unique conditions.

## VIII. Appendix A: Mathematical Statement of the Problem

### A. Governing Equations

We determined from the literature that the following equations govern the transport phenomena that we model here:

Equation 1: Nernst-Planck without Electroneutrality

$$\delta_{ts} \frac{\delta c}{\delta t} + \nabla \cdot (-D \nabla c - z u_m F c \nabla V) = R - u \cdot \nabla c$$

In Equation 1, the following variables are used:

$\delta_{ts}$	time scaling coefficient
D	diffusion coefficient
c	drug concentration
z	charge number
$u_m$	mobility
F	Faraday constant
V	potential
R	reaction rate
u	r- velocity

Equation 2: Voltage Equation

$$-\nabla \cdot (\sigma \nabla V - J^e) = Q_j$$

In Equation 2, the following variables are used:

$\sigma$	electric conductivity
V	potential
$J^e$	external current density
$Q_j$	current source

## B. Input Parameters

The following parameters for our model were determined based on the literature:

**Table 2: Summary of input parameters used in COMSOL model**

Variables & constants	Numerical values & units	Citation
<i>Nernst-Planck without Electroneutrality</i>		
$\delta_{ts}$ (time scaling coefficient)	1	
$D_{patch}$	$1 \times 10^{-11} \text{ [m}^2/\text{s]}$	(Oosten, Notten and Mikx 1986)
$D_{epidermis}$	$1.2 \times 10^{-12} \text{ [m}^2/\text{s]}$	(Oosten, Notten and Mikx 1986)
$D_{dermis}$	$1.2 \times 10^{-12} \text{ [m}^2/\text{s]}$	(Oosten, Notten and Mikx 1986)
$C_{patch}$	$7 \text{ [mol/m}^3\text{]}$	(Miklavcic, Pavselj and Hart 2006)
$C_{effective}$	$1 \text{ [mol/m}^3\text{]}$	(Miklavcic, Pavselj and Hart 2006)
$C_{toxic}$	$2.5 \text{ [mol/m}^3\text{]}$	(Miklavcic, Pavselj and Hart 2006)
$z$ (charge number)	1	–
$u_m$ (mobility)	$D \times 2577.34 \text{ [s} \cdot \text{mol/kg]}$	–
$F$ (Faraday constant)	$96485 \text{ [C/mol]}$	–
$V$ (potential)	Varies [V]	–
$R$ (reaction rate)	–	–
$u$ (r- velocity)	–	–
<i>Voltage Equation</i>		
$\sigma_{epidermis-patch}$	$0.0000125 \text{ [S/m]}$	(Miklavcic, Pavselj and Hart 2006)
$\sigma_{dermis}$	$0.227 \text{ [S/m]}$	(Miklavcic, Pavselj and Hart 2006)
$V$ (potential)	Varied [V]	–
$J^e$ (external current density)	–	–
$Q_j$ (current source)	–	–

## Justification for input parameters

While the input parameters we use for the model directly determine the results we get, it is important to note that the purpose of the model is to be able to test what would happen given any parameters we choose. Most of the values we required for this model had not been experimentally determined under the exact conditions utilized in our model and required some approximation.

## Metronidazole Concentrations

The first things we needed to determine were the therapeutic and toxic concentrations of the drug in the body since these values dictate the boundaries of the effective range of drug in the body. Based on values from the literature, we determined that the minimum inhibitory concentration of MN was about 1 mol/m<sup>3</sup>, and the toxic level was about 2.5 mol/m<sup>3</sup> (Oosten et al. 1986). Other than these values, we only needed to decide the initial concentration of drug in the patch. This is completely up to the designer.

## Diffusivities

The diffusivity of the drug was needed not only in both the layers of skin in the model, but in the patch as well. No literature was found regarding the difference in diffusivity of metronidazole in different skin layers, so we were forced to use the same D for both the epidermis and dermis. This is fairly inconsequential because we are optimizing concentration in the epidermis, so once the drug leaves this region, how it diffuses is of little importance. The diffusivity in the skin that we use comes from a study performed by Sipahigil et al., 2011. They first ran a diffusion experiment with metronidazole in human skin using a Franz diffusion cell. Following the experiment, they modeled the apparent diffusivity with the following equation:

$$D_{app} = [(slope)^2 \cdot \pi] / 4C^2$$

In this equation, C is the initial concentration of metronidazole and *slope* is the slope of the regression line on a graph of amount of drug released per unit area versus square root of time. They determined a value of 1.2E-12 m<sup>2</sup>/s, and we decided that this value was adequate. For the diffusivity of metronidazole in the patch, we had more flexibility since the patch could be designed to meet our needs as long as it was physically possible. The value we decided on was 1E-11 m<sup>2</sup>/s.

## Conductivity of skin

Electrical properties, such as conductivity, of biological materials depend on many factors and are usually not constant given variation in other physical properties. They can change depending on orientation relative to an applied field, frequency of an applied field, distance from an applied field or even the time spent in an applied field (Miklavčič et al. 2006). The value we chose for the conductivity of skin came from an experimental value reported in the Wiley Encyclopedia of Biomedical Engineering. The value was 0.0000125 S/m and reflected the conductivity of outer layers of skin such as the epidermis. Despite the number of ways in which conductivity could be a non-constant parameter, we modeled it as such because of the following reasons:

1. The relative orientation of the patch and the skin beneath it should not change during the therapy assuming the adhesive remains intact.
2. There is no frequency of the applied field since we use a direct current.
3. The depth of skin modeled is not large enough to create a significant difference in conductivity.
4. The longer skin is left in the presence of an electric field, the greater the possible effect of electroporation on the diffusivity of metronidazole in the skin. For simplicity, we did not account for this effect in our model, and the sensitivity analysis of diffusivity justifies this decision.

## Voltage

Previous studies in iontophoresis as well as actual products that utilize the phenomenon use voltages in the single digits. For our model, we assumed that we could manipulate the voltage in this range to optimize concentration the epidermis. The voltage used in the primary model is 2V.

## Time

Based on actual products that use patches such as the nicotine patch or the birth control patch, it seems that they are typically worn for 24 hours or less. Given this limit, we assumed that we had control over the run time for our model. The effectiveness of wearing the patch longer than recommended would be insignificant in terms of our model because diffusion into the skin is limited by the concentration in the patch, not just by time.

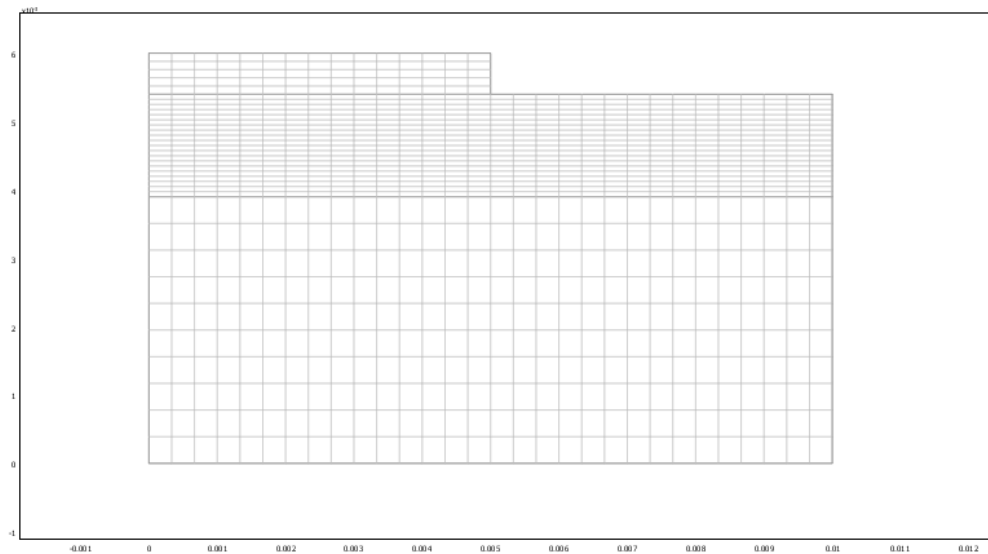
## IX. Appendix B: Solution Strategy

### A. Mesh Development and Refinement

Once we had established a working schematic with applicable boundary conditions, initial conditions, and input parameters we proceeded to develop a working mesh using COMSOL 3.5a with Nernst-Planck without Electroneutrality" and "Conductive media DC" modules. This section details the development of the mesh for our model, as well as the subsequent mesh convergence analysis.

We have performed our mesh convergence using difference mesh sizes (different number of elements). Since we are interested in the delivery of the drug from the patch to the top skin-layer, more mesh elements are used at the patch-skin interface.

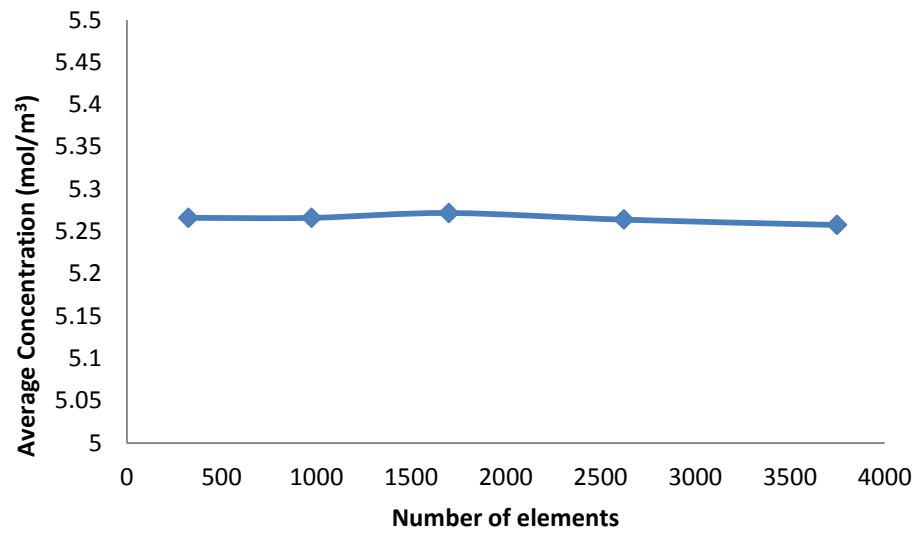
The results are shown below (Table 3 & Fig. 13). The results show that the average epidermis concentration begins to converge as early as 325 elements and produces a reliable output at 975 elements. We will therefore use around 975 elements in order to optimize the calculation time while maintaining a good level of accuracy (Fig. 12). Also, as can be seen in Figure 14, while the 325-element mesh produces converged results, the graphical quality is low due to pixilation. Therefore, 975-element mesh will be used to reduce the unwanted pixilation. Given the number of elements, we elected to use the direct (UMFPACK) solver and automatic time stepping using BDF method.



**Figure 12: Mesh used in our computational model. Our Mesh is “lagrange-Quadratic”, with a relative tolerance level of 0.01 and absolute tolerance level of 0.001**

**Table 2: Mesh convergence – Number of element v. Average concentration**

# of elements	325	975	1700	2625	3750
Avg Conc.	5.462150939	5.34315397	5.30801893	5.312156955	5.312625931



**Figure 13: Average concentration in epidermal tissue using different mesh**

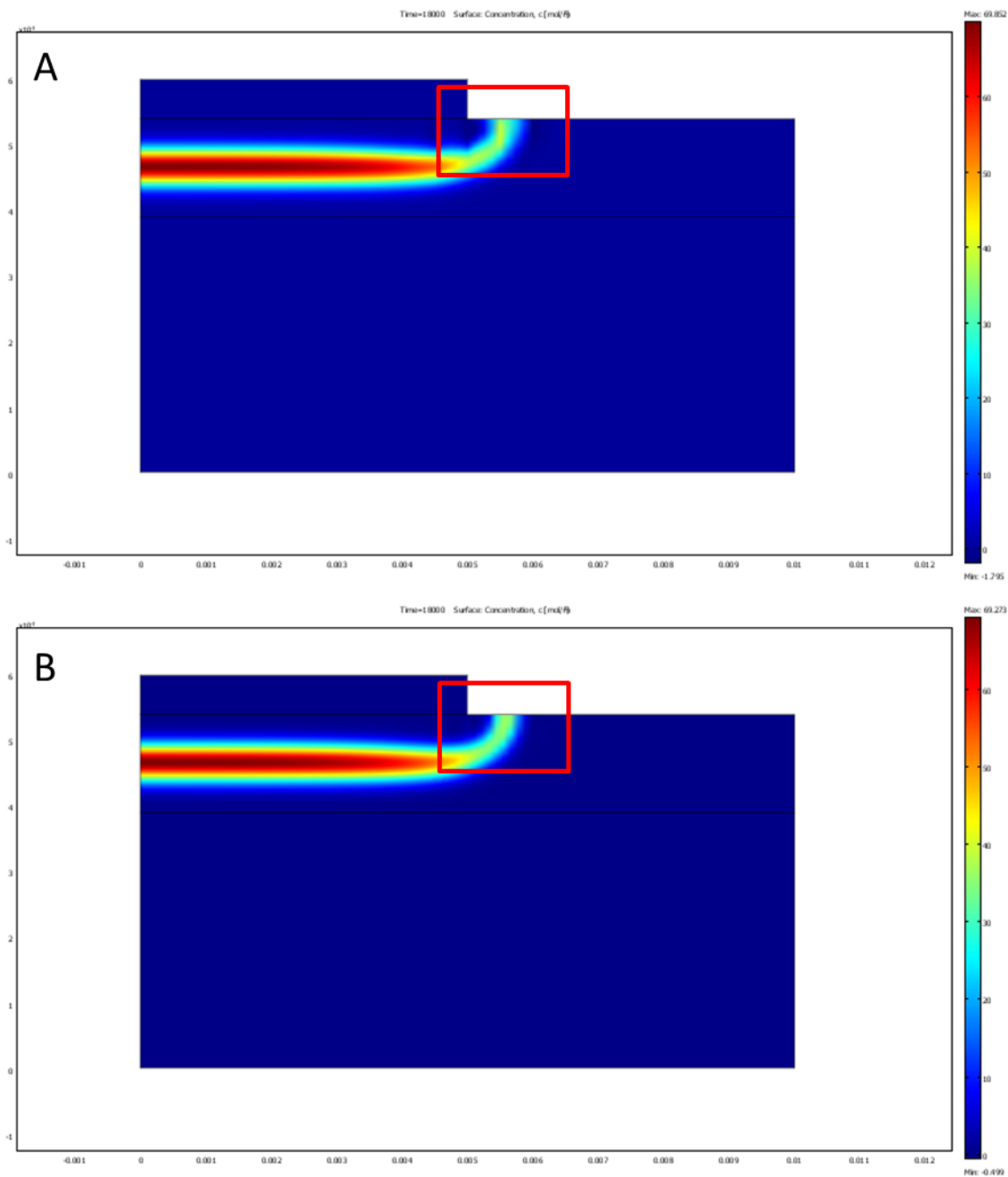


Figure 14: Pixelation difference between 325-element mesh and 975-element mech. Pixelation difference is more prevalent in the boxed region. (A) Result after 5 hours of 2V iontophoresis using 325-element mesh. (B) Result after 5 hours of 2V iontophoresis using 975-element mesh.

## **X. Appendix C: Additional Visuals**

**None**

## XI. Appendix D: References

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