Title	Iontophoretic drug delivery models
Author(s)	Pang, GKH; Qiao, D
Citation	The 1st Middle East Conference on Biomedical Engineering (MECBME 2011), Sharjah, UAE, 21-24 February 2011. In Proceedings of the 1st MECBME, 2011, p. 331-334
Issued Date	2011
URL	http://hdl.handle.net/10722/135855
Rights	Middle East Conference on Biomedical Engineering Proceedings. Copyright © IEEE.

Iontophoretic Drug Delivery Models

G.K.H. Pang
Department of Electrical and Electronic Engg.
The University of Hong Kong
Pokfulam Road, Hong Kong
gpang@eee.hku.hk

DaPeng Qiao
Department of Electrical and Electronic Engg.
The University of Hong Kong
Pokfulam Road, Hong Kong
dpqiao@eee.hku.hk

***Abstract*—Iontophoresis relies on active transportation of the charged medication agent within an electric field and delivers medication transdermally. It uses electric current to ionize drug molecules and propel them through the skin. It is a kind of transdermal drug delivery method, and hence the method has to handle the variability in skin characteristics of a patient. In this paper, a preliminary study based on the different models of the skin impedance is carried out. The purpose is to examine several skin models for iontophoretic drug delivery. This paper carries out a simulation study based on three different skin impedance models.**

Keywords Non-invasive drug delivery, electrically-assisted delivery, skin impedance, iontophoresis.

I. INTRODUCTION

Drug delivery to a patient can be carried out in many different ways. The traditional ways include oral intake and hypodermal injection. Nowadays, a transdermal drug delivery method would release the medicament directly into the patient's body via the skin. There are various ways for transdermal drug delivery and they have been developed based on various principles. The developed methods could be based on diffusion, absorption, thermal energy, radio frequency energy, ultrasound, electrostatic force (electrophoresis) or electric field (iontophoresis). These are non-invasive methods, and recent developments also include transdermal skin patch that is placed on the skin to deliver a specific dose of medication through the skin, and then into the blood stream of the patient. The main advantage of a transdermal drug delivery is that it provides a controlled release of the medicament without serious pain to the patient.

All transdermal drug delivery methods have to deal with the complicated properties of the patient' skin, which is a very effective barrier, and its characteristics can vary a lot from one person to another. It is a natural barrier to foreign chemicals and biological agents. Methods that are based on the use of microneedles [1,2,3] have also been developed. These microneedles would physically puncture the skin but for less than 1mm and deliver the drug without piercing blood vessels or damaging nerves, that are typically around 1mm under the skin surface. The mechanical stability and the puncture behaviour of microneedles have been investigated experimentally [3].

It is known that a saturation phenomenon occurs in iontophoretic drug delivery, which means when a limiting transport number is achieved, increasing the current has no further effect in iontophoretic transport [4]. This "plateau" phenomenon is due to the special characteristics of the skin. In [4], ionic mass transport through a homogeneous membrane was analyzed under a mathematical model for describing drug transport through skin. Experimental departures from his theory is observed, which is probably due to deviations from ideal behavior of the skin. Hence, there is a need to develop physical models for skin which can reflect the skin behavior more accurately.

Iontophoresis provides a mechanism to enhance the penetration of hydrophilic and charged molecules across the skin. In [5], the underlying mechanisms that drive iontophoresis is described and the impact of drug concentration, applied current and pH on iontophoretic delivery efficiency is discussed. *In vitro* sumatriptan transdermal absorption through human skin is characterised in [6], and the effect of chemical enhancers and iontophoresis applied both individually and in combination are investigated. In this paper, several electrical models for skin impedance are investigated and simulations have been carried out for a comparative study of the parameters for drug delivery through iontophoresis [7, 8].

II. METHOD AND ANALYSIS

A. Introduction

Research has found that skin impedance can be modeled by typical RC (resistor-capacitor) circuits, without the need of any inductive component [9 ,10, 11, 12]. Hence, it is generally agreed that the skin impedance is made up of some amount of resistance and some form of capacitance. Different models of RC circuits can be developed to simulate current responses in actual skin.

B. Model A

The template is used to format your paper and style the text. All margins, column widths, line spaces, and text fonts are prescribed; please do not alter them. You may note peculiarities. For example, the head margin in this template measures proportionately more than is customary. This measurement and others are deliberate, using specifications that anticipate your paper as one part of the entire proceedings, and not as an independent document. Please do not revise any of the current designations.

978-1-4244-7000-6/11/$26.00 ©2011 IEEE

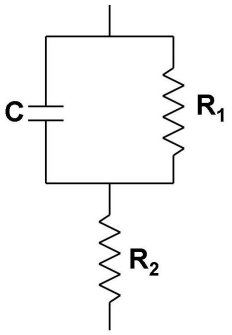

Figure 1 *Skin Impedance Model A*

C. Model B

Another model can also be found in [11] by Tregear which is consisted of multiple parallel RC circuits in series. This is designed to model the varying capacitance and resistance of the epidermal skin layers at different depths of the skin. This model is shown in Figure 2 below. As mentioned in [8], this model represents the decreasing values of capacitance and resistance as individual layers of the stratum corneum are removed in experiments. The experimental result was important as it allows for the development of a more precise model of the skin impedance. Also, it has shown that the stratum corneum accounts for the major portion of the skin impedance in the skin.

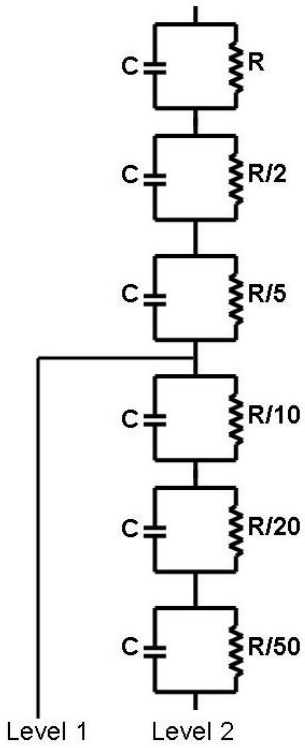

Figure 2 *Skin Impedance Model B*

D. Model C

Lykken [12] has proposed another model of skin impedance as shown in Figure 3. The model consists of several parallel paths, and each path is made up of several RC circuits, with each circuit representing a different layer of the skin. Figure 3 provides a more distributed nature when modeling the skin impedance, and can potentially provide a more accurate model.

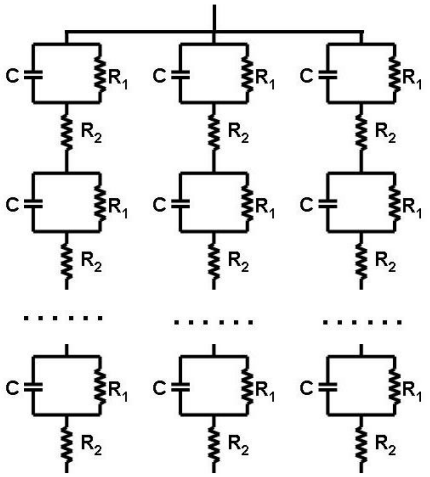

Figure 3 *Skin Impedance Model C*

III. Result and Simulations

In this section, simulations based on the three skin impedance models discussed in the previous section are presented. In these simulations, a voltage is applied at time 0.1 second and it varies linearly to 5V at time 0.5 second.

A. Simulation based on Model A

Several simulations have been carried out to examine the characteristics of the responses that may be obtained based on different parameter values. For the purpose of simulation, R1 and R2 have been assigned a value of 100kΩ cm2 and three different values of the capacitor have been used. Below are the results from the simulation:

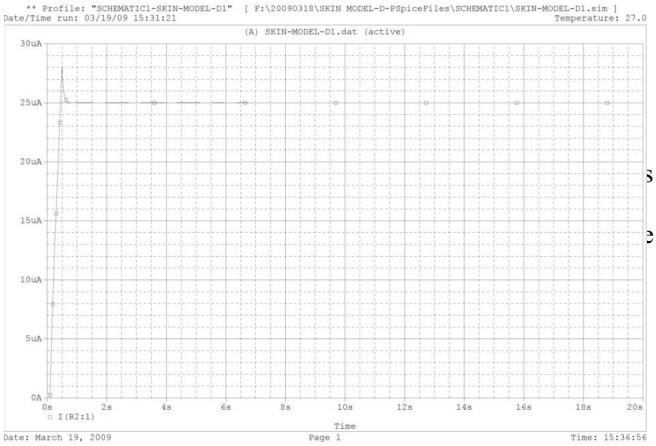

Figure 4 *Model A with capacitor value 1μF cm2*

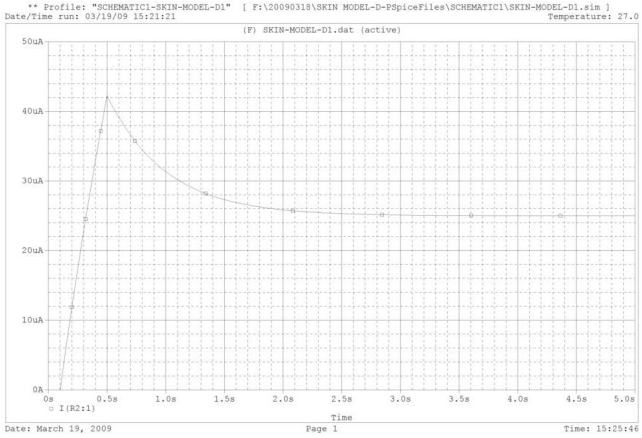

Figure 5 *Model A with capacitor value 10 μF cm2*

It can be seen from the simulation that as the voltage is increased from 0.1 second to 0.5 second, the current passes through the capacitor C of Model A. At 0.5 second, the applied voltage has already reached the final value, and the current passes through R1 and R2. For the two simulations, the final steady-state current depends on the value of the two resistors. As shown in Figures 4 and 5, the value of the capacitor can have considerable effect on the shape of the response.

B. Simulation based on Model B

In the first simulation of Model B, we will examine the response from Level 1. The capacitance value is 0.1μF cm2.

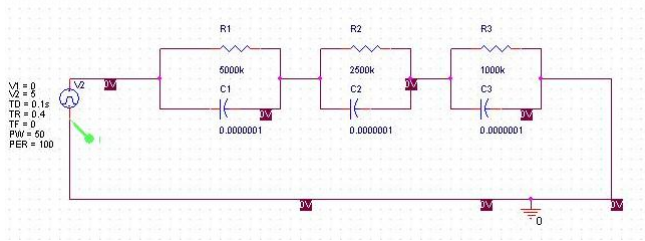

Figure 6 *Level 1 of Model B*

Figure 7 gives the current for Model B having only three sections (Level 1). This would model after three epidermal skin layers at different depths of the skin. Figure 8 gives the current for Model B having six sections (Level 2). More sections (or skin layers) can be included for further study, but in this paper, we show the simulations of only Level 1 and 2. As shown in Figures 7 and 9, the current can have very different response at different point of the circuit model. In both cases, the current would settle down to its steady-state level very quickly after the voltage has been steady at 0.5 second.

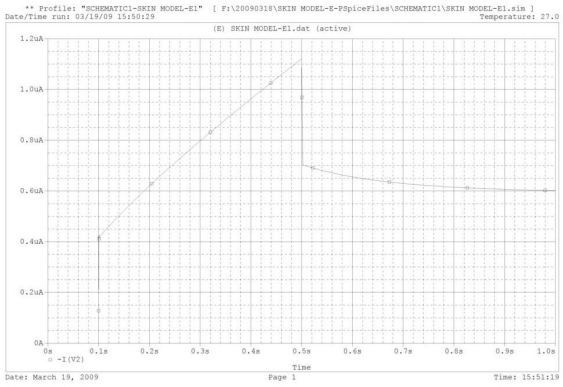

Figure 7 *Model B Level 1with capacitor value 0.1μF cm2*

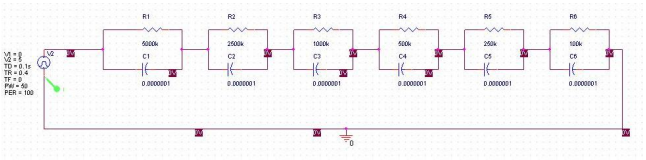

Figure 8 *Level 2 of Model B*

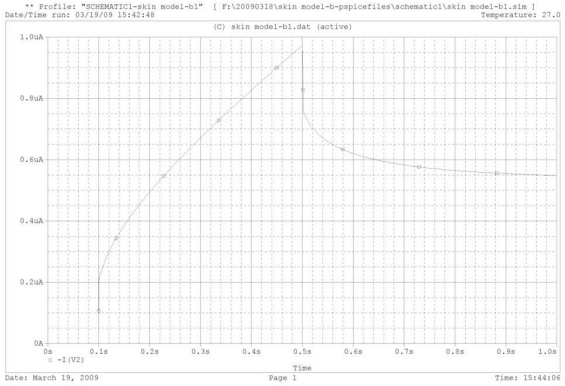

Figure 9 *Model B Level 2 with capacitor value 0.1μF cm2*

C. Simulation based on Model C

In Figure 10, Model C with three parallel paths is shown. Each path is consisted of three sub-sections.

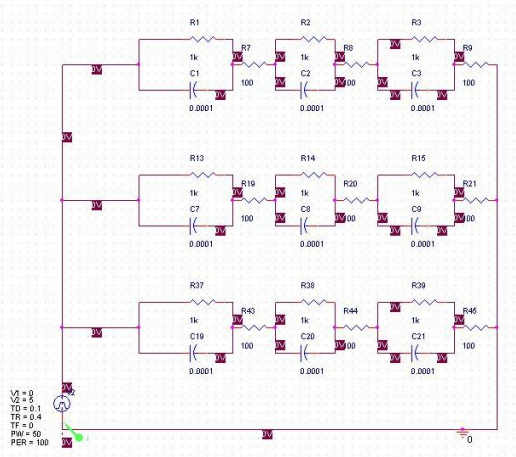

Figure 10 *Model C with three parallel paths*

Figure 11 is similar in shape but differ in its vertical scale. The vertical scales can be aligned with a careful choice of the resistor values.

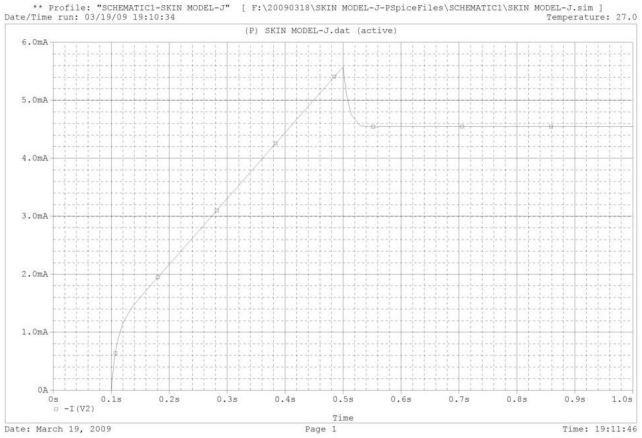

Fig. 11 Simulation result of Model C with three parallel paths, each with three sub-sections, with capacitor value 100μF cm2, R1 = 1000 Ω cm2 R2 = 100 Ω cm2

IV. CONCLUSIONS

The method of iontophoresis delivers medication transdermally using electric current to ionize drug molecules and propel them through the skin. In a patch form, an electrical potential can be established by two adjacent electrodes for driving charged drug compounds through the skin. Hence, a study of the electrical properties of the skin is of paramount importance. This paper aims to examine the skin impedance that is modeled in three different ways. Although there are many parameters and variations for each model, this paper serves to provide an initial comparison for the three skin impedance models. In addition, simulations of the three models have been carried out, and the results are presented.

The three-element circuit of Model A is a very simple model of the skin impedance. Considering the different characteristics to the different layer of the epidermis, the model seems not too accurate in its representation. The Model B by Tregear captures the effects of capacitance for the different layers of the epidermis. However, it is not clear how many stages should best represent the skin impedance for a certain depth of the epidermis. The model C by Lykken has added another resistance in between the different stage, which is used to represent deep tissue resistance. This would provide a more complete model to the skin impedance. Yet, the great variability of the parameters in the model exists and experimentally study is needed for a more complete understanding of the impedance characteristics of the skin.

REFERENCES

[1] Stoebar, B. and Liepmann, D. "Array of hollow out-of-plane microneedles for drug delivery", Journal of MEMS, Vol. 14, No. 3, pp. 474-479, 2005.

[2] Ji, J., Tay, F.E.H., Miao, J. and Iliescu, C. "Microfabricated microneedles with porous tip for drug delivery", Journal of Micromech. Microeng., Vol. 16, pp. 958-964, 2006.

[3] Lam, D.C.C., Lee, Y.H., Shek, K.T. and Pang, G. "Puncture Depth and the Mechanical Stability of Microneedles", International Joint Conference on Biomedical Engineering Systems and Technologies, Biodevices 2008, Funchal, Portugal, 2008.

[4] Kasting, G.B. and Keister, J.C. "Application of electrodiffusion theory for a homogeneous membrane to iontophoretic transport through skin", J. Control. Release 8, pp. 195–210., 1989.

[5] Kalia, Y.N., et al., "Iontophoretic drug delivery", Advanced Drug Delivery Review, 56(5): p. 619- 58, 2004.

[6] Femenía-Font, A. et al. "Combination strategies for enhancing transdermal absorption of sumatriptan through skin", Int J of Pharmaceutics, 323: p. 125-130, 2006.

[7] Coston, A.F. and Li, J.K-J. "Iontophoresis: Modeling, Methodology, and Evaluation. Cardiovasc", Engineering, Vol. 1, pp. 127-136, 2001.

[8] Coston, A.F. and Li, J.K-J. "Transdermal drug delivery: a comparative analysis of skin impedance models and parameters", Proc. IEEE Engg. in Medicine and Biology, Vol. 3, pp. 2982-2985,2003.

[9] Lawler, J.C., Davis, M. J. and Griffith, E. C. "Electrical Characteristics of the Skin: The Impedance of the Surface Sheath and Deep Tissues", Journal Invest. Dermatol. 34, pp. 301-308, 1960.

[10] Edelberg, R. "Electrical properties of Skin", In: Biophysical Properties of the Skin. Elden, H. R. (ed.). New York: John Wiley & Sons, Inc., 1971.

[11] Tregear, R.T. Physical Functions of the Skin. New York: Academic Press, 1966.

[12] Lykken, D.T. "Square-Wave Analysis of Skin Impedance", Psychophysiology, 7 (2), pp. 262-27, 1970.