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ENGINEERING SCIENCES

Assessment of Drug Flow Rate in Skin Cancer Therapy for Enhancing the Drug Delivery System

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Abstract: The major impact in the clinical field is the harm posed by cancer. One most common type of cancer occurs in the skin. Though the conventionally existing modalities are successful in some cases, there is a need for new sensible methods to detect tumors at their initial stage. In accordance to these reasons and in addition to the incapability of the drugs to cross cellular barriers in skin the conventional administration methods are often compromised. To eradicate these problems the research work aims to develop the electrical analogue of skin involving layers like dermis, subcutaneous tissues, bones and muscular layers. The mathematical model has been developed to determine the electrical network of skin. The response of different skin layers are analyzed through simulation studies. It is observed that the cells present in each layer absorbs some amount of drug and let out the remaining to the neighboring layers. Further to minimize the diffusion rate of the drug a conventional controller has been incorporated and the results are analyzed by the contrast of the absorption and diffusion capacities for different layers of skin.

Key words: absorption rate, diffusion rate, drug delivery, electrical analogue, mathematical modeling, skin cancer.

INTRODUCTION

Cancer is a disease at the cellular level involving heritable disorders in cellular control mechanisms. The reason for this disease largely remains unknown. However various factors have been implicated. Certain undifferentiated cells proliferate uncontrollably and gives rise to tumors. According to microbial hypothesis either a virus or a microbe is a causative agent to induce cancerous growth. Some human cancer may be caused by retro viruses such as adult T cell leukemia. An inhibited immune response from aging, stressor severe systematic infection may promote cancer by preventing the body from destroying and recognizing cancer cells. Tumors are classified based on their origin and histological characters.

SKIN CANCER

Skin cancers may arise due to the ability of abnormal cells to invade or spread across body parts. There are three main types of skin cancer: Basal Cell Cancer (BCC), Squamous Cell Cancer (SCC) and Melanoma. The first two types along with a number of less common skin cancers are known as Non Melanoma Skin Cancer (NMSC). Basal-cell cancer grows slowly and can damage the tissue around it but is less likely to spread to distant areas or result in death. It often appears as a painless raised area of skin that may be shiny with small blood vessel running over it or may be present as a raised area with an ulcer. Squamous-cell cancer is more likely to spread. It usually presents a hard lump with a scaly top but may also form an ulcer. Melanomas are the most aggressive. The symptoms of the melanocytes include a mole that has changed in size, shape, color, has irregular edges, has more than one color, may sometimes be itchy or bleeds. Skin cancer can spread through tissues, lymph system and blood (NIH). Malignant melanomas are dangerous and it is difficult to treat. Certain infectious agent including viruses, bacteria and parasites can cause cancer or increase the risk of cancer. Particularly for skin cancer MCPyV (Merkel Cell Polyomavirus) can cause Merkel cell carcinoma, a rare type of skin cancer which can be passed from one person to another through blood or other body fluids (Marissa 2013).

Treatment Methods

Early diagnosis and treatment of cancer can increase the survival rate from melanoma. There are different methods to treat cancer which includes surgery, radiation therapy, chemotherapy, photodynamic therapy, immunotherapy, targeted therapy, chemical peel and other drug therapy.

Surgery

Simple excision, Mohs micrographic surgery, Shave excision, Laser surgery, Dermabrasion, Curettage and electrodessication are the different surgical procedures which may be used to treat basal cell carcinoma, squamous cell carcinoma of the skin, or actinic keratosis.

Radiation Therapy

High-energy X-rays or other types of radiation are used in radiation therapy to kill cancer cells or stop them from growing. There are two types of radiation therapy internal and external therapy. The radiation therapy is given based on the type of cancer being treated. External radiation therapy is used to treat basal cell carcinoma and squamous cell carcinoma of the skin.

Photodynamic Therapy

Photodynamic therapy (PDT) uses a drug and a certain type of laser light to kill cancer cells. A drug gets activated when exposed to light, which is injected into a vein or put on the surface of skin. The drug is collected more in cancer cells than in normal cells. When laser light is shined onto the skin and the drug becomes active and kills the cancer cells causing less damage to healthy tissue.

Immunotherapy

Immunotherapy is done using the patient's immune system to fight cancer. Substances made by the body or in a laboratory are used to boost, direct, or restore the body's natural defenses against cancer.

Targeted Therapy

Targeted therapy uses drugs or other substances to attack cancer cells. Targeted therapies usually cause less harm to normal cells than chemotherapy or radiation therapy do. Targeted therapy with

a signal transduction inhibitor is used to treat basal cell carcinoma. Signal transduction inhibitors block signals that are passed from one molecule to another inside a cell. Blocking these signals may kill cancer cells.

Chemical Peel

A chemical peel is a procedure used to improve the way certain skin conditions look. A chemical solution is applied on the skin to dissolve the top layers of skin cells. Chemical peels are used to treat actinic keratosis.

Chemotherapy

Chemotherapy procedure involves a suitable drug to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Chemotherapy can be taken by mouth or injected into a vein, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is done directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). Chemotherapy for basal cell carcinoma, squamous cell carcinoma of the skin, and actinic keratosis is usually topical (applied to the skin as a cream or lotion). The way the chemotherapy is given depends on the condition being treated. Topical fluorouracil (5-FU) is used to treat basal cell carcinoma. Though the therapeutic treatment is the main option but still it is not feasible for most of the cases.

To overcome the drawbacks of conventional methods, advanced treatment methods have to be performed. Targeted tumors show more cancer dead cells than chemotherapy. This work aims to control the release of the drug to the cancer cell using a suitable controller (Candas & Radziuk 1994) by calculating the absorption and diffusion rate of the drug by the cells. Hence forth the drug flow rate can be regulated and the issues caused by over dosage can be minimized.

INTRODUCTION TO SKIN

The skin is the largest organ of the body, with total area of about 20 square feet. The skin protects us from microbes and helps to regulate the body temperature and also permits the sensations of touch, heat and cold. It is the outer cover of human beings which protect us from various parameters like light, water, heat, etc. The biological system of the skin consists of three layers such as dermis, tissues, bones and muscles. In humans, skin pigmentation varies among populations and the skin type can range from dry to oily. Skin variety provides a rich and diverse habitat for bacteria which numbers roughly from 19 to 1000 species. Human skins show high color variations from the darkest brown to the lightest pinkish – white hues. This color variation is the highest among any other mammalian species as the result of natural selection. Skin pigmentations in the humans are evolved to regulate the amount of ultraviolet radiation penetrating the skin and to control the biochemical effects.

Layers of the skin

The skin consists of three layers like epidermis, dermis subcutaneous tissue (hypodermis) and some bones and muscular organs. Epidermis, the outer layer of skin creates skin tone and provides waterproof barrier. The dermis is present beneath the epidermis, contains tough connective tissues, hair follicles and sweat glands. The third layer is the subcutaneous tissues made up of fat and beneath all these layers bones and muscles are present.

BIOLOGICAL TO ELECTRICAL ANALOGUE OF SKIN

Conversion of biological system (skin) to electrical system

From the time of the eighties engineers and physician are working together in the field of the development of closed-loop systems for drug delivery (Simanski et al. 2007). The Mathematical modeling has to be achieved (Degasperi et al. 2017) for regulating the flow rate of the drug by means of a controller (Chen & Gross 1979). The modeling is obtained by converting the biological network of skin into its equivalent electrical network. Passive elements like resistance and capacitance (Ionescu et al. 2011) has been considered as the barriers of the skin and the same were used in designing the electrical equivalent network of the biological network. It is observed that the biological system does not convert the electrical energy into magnetic energy. Hence Inductors are not used in the electrical network conversion of skin. The biological system of the skin comprises of dermis, tissues and muscles as shown in figure 2 which is then converted into an equivalent electrical system shown in figure 3.



Figure 1. Layers of skin.



Figure 2. Compartments of the Biological System.

The electrical network of the skin is designed using resistance and capacitance effect (Ionescu et al. 2011) as shown in figure 3.

From the figure 3 the electrical equivalent system for the skin have resistance values of R_a, R_b, R_c and R_d which are assumed to be the external resistance across the cell wall.R₁ and R₂ are the internal resistance of the cell.V₁ acts as the inlet drug and I₁, I₂, I₃ are the drug flow rate across each compartment of dermis, tissues and bone muscles respectively and C₁, C₂ and C₃ are the drug absorbers in the skin.

The transfer function of the electrical system for the first two layers and the current equation is determined using mesh analysis,

$$\begin{bmatrix} \begin{pmatrix} R_{a^{+}}R_{b} + \frac{R_{1}}{1 + R_{1}C_{1}s} & -\begin{pmatrix} \frac{R_{1}}{1 + R_{1}C_{1}s} \end{pmatrix} \\ -\begin{pmatrix} \frac{R_{1}}{1 + R_{1}C_{1}s} \end{pmatrix} & R_{c} + R_{d} + \begin{pmatrix} \frac{R_{1}}{1 + R_{1}C_{1}s} \end{pmatrix} + \begin{pmatrix} \frac{R_{2}}{1 + R_{2}C_{2}s} \end{pmatrix} \end{bmatrix} \begin{bmatrix} I_{1}(s) \\ I_{2}(s) \end{pmatrix} = \begin{pmatrix} V_{1}(s) \\ 0 \end{pmatrix}$$
(1)

On solving the above equation, the transfer function (Gomez et al. 2012) for the first two layers are obtained as follows,

$$\frac{V_{c_2}(s)}{V_1(s)} = \frac{\left(\frac{R_1}{1+R_1C_1s}\right) * \left(\left(\frac{R_1}{1+R_1C_1s}\right) + \left(\frac{R_1}{1+R_1C_1s}\right) \left(R_c + R_d + \left(\frac{R_1}{1+R_1C_1s}\right) + \left(\frac{R_2}{1+R_2C_2s}\right)\right)\right)}{\left(R_{a^+}R_b + \frac{R_1}{1+R_1C_1s}\right) - \left(\left(\frac{R_1}{1+R_1C_1s}\right) + \left(\frac{R_1}{1+R_1C_1s}\right) \left(R_c + R_d + \left(\frac{R_1}{1+R_1C_1s}\right) + \left(\frac{R_2}{1+R_2C_2s}\right)\right)\right)}$$
(2)

Similarly by considering the first three layers, the outlet of the drug absorption rate with respect to the inlet drug is determined by the following equation,

$$\frac{V_{e_{5}}(s)}{V_{1}(s)} = \frac{\left(\left(\frac{R_{1}}{1+R_{1}C_{1}s}\right)\left(\frac{R_{2}}{1+R_{2}C_{2}s}\right)\right)*\left(\left(\frac{R_{1}}{1+R_{1}C_{1}s}\right)+\left(\frac{R_{1}}{1+R_{1}C_{1}s}\right)\left(R_{e}+R_{d}+R_{e}+R_{f}+\left(\frac{R_{1}}{1+R_{1}C_{1}s}\right)+\left(\frac{R_{2}}{1+R_{2}C_{2}s}\right)+\left(\frac{R_{3}}{1+R_{3}C_{3}s}\right)\right)\right)}{\left(\left(\frac{R_{a}+R_{b}}{1+R_{1}C_{1}s}\right)\left(R_{e}+R_{d}+R_{e}+R_{f}+\left(\frac{R_{1}}{1+R_{1}C_{1}s}\right)+\left(\frac{R_{2}}{1+R_{2}C_{2}s}\right)+\left(\frac{R_{3}}{1+R_{3}C_{3}s}\right)\right)\right)}\right)}$$
(3)

Skin Resistance

The resistance of the skin for the people are assumed to be the minimal values by means of experiments and are listed in the below table.

Resistance	Values (Ohm)		
R _a	0.08		
R _b	0.08		
R _c	0.4		
R _d	0.4		
R _e	0.7		
R _f	0.7		
R1	0.4		
R2	0.7		
R3	0.5		





Figure 3. Equivalent Electrical System of skin.

Skin capacitance

The capacitance of the skin for the people are assumed to be the minimal values by means of experiments and are listed in the below table.

By substituting the values of resistance and capacitance in the above equations, the transfer function for first compartment (Dermis) is calculated.

The transfer function of the dermis layer is determined by the equation as follows,

$$\frac{V_{c_1}(s)}{V_1(s)} = R_a + \left(\frac{R_1}{1 + R_1 C_1 s}\right) + R_b$$
(4)

By substituting the values of resistance and capacitance, the transfer function of the dermis layer is obtained as,

$$\frac{V_{c_1}(s)}{V_1(s)} = \frac{2s+7}{s+12.5}$$
(5)

Similarly by substituting the values of the passive elements the transfer functions for the other layers are calculated. The transfer function of the dermis and tissue layer is obtained as,

$$\frac{V_{c_2}(s)}{V_1(s)} = \frac{2.8s^2 + 37.7s + 130.244}{s^2 + 19.642s + 89.275}$$
(6)

Table II. Capacitance of Skin.

Capacitance	Values (Farad)
C ₁	0.2
C ₂	0.2
C ₃	0.2



Figure 4. Equivalent Electrical System of Dermis Layer.

The transfer function for the all the three compartments of the skin membrane is as follows,

$$\frac{V_{c_3}(s)}{V_1(s)} = \frac{0.42 s^3 + 11.219 s^2 + 100.5 s + 299.8}{0.1 s^3 + 2.964 s^2 + 28.569 s + 89.275}$$

(7)

The conversion of biological system to electrical system along with mathematical modeling of each compartment has been formulated.

DRUG DELIVERY CONTROL

Laws relating to interaction of matter

Drug delivery comprises the progress of targeted delivery in which the drug is only lively in the target area (cancerous tissues) and continual release formulation (Debjit et al. 2012) in which the drug is released over a period of time in a forbidden manner. In order to achieve efficient targeted delivery, the various parameters like absorption, diffusion and mass flow rate should be considered.

Absorption

Absorption is the simplest method for enzyme immobilization. It determines the amount of drug absorbed by the cell tissues in the skin layer. The cell absorbs the drug based on its absorption capacity beyond its limit it tends to diffuse the drug. The absorption rate is given by Beer Lambert law.

Beer Lambert Law

Beer's law states that absorbance is proportional to the concentrations of the attenuating species as well as the thickness of the material sample. It relates absorption to concentration and its path length.

Measurement of solute absorbed as it passes into solution is given by,

$$\frac{-dp_x}{p_x} = \frac{ds}{s}$$
(8)

Area of capture must be proportional to number of absorbing particles is given by,

 $ds = a^* dn$

(9)



Figure 5 - Beer Lambert Law.

Where,

ds - Sum of capture area for particles with in the section a - Cross sectional area of capture particle Therefore.

$$\log\left(\frac{\mathbf{p}_0}{\mathbf{p}}\right) = \sum \mathbf{b} \, \mathbf{c} = \mathbf{A} \tag{10}$$

Where

 \mathbf{p}_{0} - Inlet drug (mg)

b - Path length (thickness of the cell (cm))

 $\Sigma = \left(\frac{6.023 \times 10^{23}}{2.3.3 \times 1000}\right) \times bc$

c - Concentration (g/l)

A - Absorbance (no unit)

Diffusion

Diffusion is defined as the performance index and the amount of drug released from the cell when the absorbing capacity of the cell exceeds, it can be identified by the equation below

(11)

$$N_{Da} = \frac{V_{max}}{k_1 [s_b]}$$

(12)

Where,

 N_{Da-} Number of molecules diffused in to the membrane

 $\mathbf{s}_{\mathbf{b}}$ - Concentration of substrate

 \mathbf{k}_1 - Mass transfer co-efficient

The diffusion rate can be identified by the conditions as follow, when $N_{Da} >>1$ diffusion rate is limiting, i.e., mass transfer resistance is high and when $N_{Da} <<1$ mass transfer rate is very low and rate of reaction is equal to diffusion rate when $N_{Da} =1$. The diffusion rate can also be explained by Fick's law.

Fick's Law

When the solute molecules on the left side of a barrier and to right side of the barrier i.e., the solute diffuse to fill the whole container uniformly from high concentration to low concentration area stated by Fick's law, that rate of diffusion of solution through tissue is proportional to concentration gradient of various tissue processing reagents

It is given by,

$$\frac{\mathrm{ds}}{\mathrm{dt}} = \mathrm{DA}\frac{\mathrm{dc}}{\mathrm{dx}} \tag{13}$$

Where,

A= Absorption capacity of cell (mg)

Fick's first law is given by,

$$\mathbf{j} = -\mathbf{D}\frac{\partial \phi}{\partial x} \tag{14}$$

Where, Fick's second law is given by,

$$\mathbf{j} = D \frac{\partial^2 \phi}{\partial x^2} \tag{15}$$

Where,

D - Diffusion co-efficient (
$${
m m}^2$$
 /s)

 ϕ - Concentration of the drug (mol/ $\mathrm{m^3}$)

j - Flux produced (mol/ m^2 s)

Flux is defined as the amount of drug diffuse per unit area per unit time. Where mass flux rate is given by,

$$j(t) = \frac{2C_0 D}{L} \sum_{n=1,3,5,\dots}^{\infty} e^{-(\frac{n\pi}{2L})^2} (Dt)$$
(16)

$$Q = \int_{0}^{t} j(t)dt \tag{17}$$

Where,

j(t) - flux through the boundary of the matrix, x = L, as a function of time

Q - Quantity of released drug per unit area.

 C_0 - initial concentration for dissolved drug per unit volume

- D Diffusion coefficient
- C Concentration for dissolved drug per unit volume

Mass flow rate of the drug

Mass flow rate of the drug is defined as the amount of drug flow into the cell to the amount of drug flow out from the cell. It is given in the expression of hydraulic model as,

Rate of drug accumulation within the cell= Rate of drug entering the surface – Rate of drug leaving the surface + Rate of drug along the sides

Where,

Rate of mass accumulation within the cell = $\frac{\partial}{\partial t}(\rho A\Delta x)$

Rate of mass entering elemental volume across the surface = $\frac{\rho Ax}{r}$

Rate of mass leaving cells = $-\frac{\rho A x}{r}$

 $x + \Delta x$

By substituting and simplifying mass flow rate, the equation obtained is as follows

$$\frac{\partial r}{\partial t} = -V \frac{\partial r}{\partial x} - \frac{r^2}{2} \frac{\partial V}{\partial x}$$
(18)

Where, V- Volume across the surface (m³)

r- radius of the cell (m)

By the above relation the mass flow rate of the drug through the sample cell can be analyzed.

Analysis of Electrical Equivalent System by modeling of each compartment

The relevant electrical system of the skin is analyzed using PSPICE tool. The flow of current in every section indicates the flow rate of drug throughout each section and inlet voltage indicates the inlet drug. The output voltage is assumed to be the amount of drug fascinated by the section (Cobelli & Mari 1985) after travelling across each compartment. By these assumptions the electrical system is analyzed. At this point the drug absorption and the diffusion values were observed through the sample voltage of 1V. The figure 6 shows the flow of current across the passive elements of the skin when the sample of 1V (assumed to be equal to 1mg of drug) is given as input.

The figure 7 shows the output voltage across the capacitive element in each compartments when the sample of 1V (drug) is given as input.

Analysis of absorption rate

When 1V (assumed to be the drug) input is given to the network, the quantity of drug diffused is observed to be 0.04V and the total rate of absorption by all three layers is 0.96V. It is inferred that the absorption rate is maximum in the dermis layer and slowly the absorption starts decreasing in the next two layers.



Figure 6. Current flow in the Network for 1V.

Absorption of the layers	Output Voltage (V)
Inlet drug	1
Dermis	0.65
Dermis & tissue	0.25
Muscles & bones	0.067
Total absorption	0.96
Diffusion	0.033

Table III. Absorption by the layers of the skin.

Diffusion = Inlet Drug – Total Absorption



Figure 7. Output Voltage in the Network for 1V.

RESULTS AND DISCUSSION

A closed loop control system based on the electrical analogue of skin has been developed for computerized drug delivery (Ezra et al. 1995). The quantity of drug absorbed by every layer is denoted in the response plot. Simulation is done with MATLAB for the closed loop system of skin to obtain the absorption ability for every individual layer of skin. This is obtained by manipulating the area under every response curve.

It is observed that the absorption rate for dermis layer is found to be 0.672 V. The absorbing capacity is more while compared to other two layers.

The absorption rate for dermis and tissue layer is found to be 0.953 V. The absorbing capacity for the first two layers is more when compared to first layer alone.

The absorption capacity of each layer increases gradually by means of the amount of cells present in each layer.



Figure 8. SIMULINK Model for Drug Delivery System without Controller.



Figure 9. Response of the Dermis Layer.

Table IV.	Absorption	Rate of	drug l	by the	Layers.
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Compartments	Area (absorption capacity)
Dermis Layer	0.672
Dermis and Tissue Layer	0.953
Total Compartments (Dermis, Tissue and Muscles)	3.325
Total Absorption	4.9



The absorption rate of drug in each layer is obtained by calculating the area under the curve from each plot as it is tabulated as follows

Simulink model for drug delivery system with controller

Controller is used to control the flow of inlet drug to the targeted area in order to reduce the diffusion of drug to the normal cells. Proportional- Integral and Derivative (PID) controller is the most common control algorithm and widely used in all control applications because of its good control methods. In this work the controller is used to analyze the characteristics response obtained for the biological system and to check whether the diffusion rate has been reduced by incorporating the controller.

The absorbing capacity of drug by each layer is analyzed using both PSPICE and MATLAB. By this it is observed that the cells present in each layer absorbs some amount of drug and let out the remaining to the neighboring layers based on its absorbing capacity. The drug let out is considered as the diffusion rate of drug from the targeted cell and it will affect the nearby cells in the targeted area. Thus suitable controller (Goodwin & Sin 1984) has to be designed in order to reduce the diffusion rate of the drug the inlet drug.

CONCLUSIONS

In the proposed work, the appropriate electrical network for the biological system of skin is intended and the mathematical modeling has been determined by substituting the minimal values of the resistance and capacitance for the skin. Simulation studies were done using MATLAB for the obtained model to determine the absorption capacity of drug by individual layers of skin. The response of every skin layer is analyzed using electrical network of skin and a random voltage value is assigned which is assumed to be the inlet rate of drug. The observed results conclude the decay of drug with respect to time by each layer which means the absorption of drug increases with time. It is inferred that the flow rate of drug decreases layer by layer. PID controller is used to analyze the response of the system. The work can be extended by choosing a suitable controller to adjust the quantity of



Figure 12. SIMULINK Model for Drug Delivery System with Controller.



Figure 13. Response of the System with controller.

drug fed at the inlet so as to reduce the diffusion rate. The rate of absorption and diffusion may be examined for different body parameters based on age and various skin types like dry and oily skin.

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Author Contributions

The idea of the work was conceived by Mrunalini Thanaraj and took the lead in writing the manuscript. Mrunalini Thanaraj performed the computations and analyzed the data. Rajasekar Rathanasamy supervised the findings of this work and supported in writing the manuscript. Prakash Maaran helped in verifying the analytical methods and shaping of the manuscript.

