Intelligent Design of Microneedle Structure for Drug Delivery System

by

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LIST OF ABBREVIATIONS

ABC	Artificial Bee Colony
ACO	Ant Colony Optimization
AI	Artificial Intelligence
ANSYS	Analysis System
BioMEMS	Biological-MEMS
CAD	Computer Aided Design
CaSyn-MEMS	Case-based Synthesis of MEMS
CBR	Case-based Reasoning
CDP	Constraint-domination principle
CFD	Computational Fluid Dynamic
CPS	Coherent Porous Silicon
CS	Cuckoo Search
DRIE	Deep Reactive-ion Etching
EA	Evolutionary Algorithm
FPS	Fitness Proportionate Selection
GA	Genetic Algorithm
GDA	Great Deluge Criteria
GSO	Genetic Swarm Optimization
HPSOGA	Hybrid PSO-GA
ICP	Inductively Coupled Plasma
LIGA	*Lithographie, Galvanoformung, Abformung* (Lithography, Electroplating and Molding)
MEMS	Micro Electro Mechanical System
MOEA	Multi-objective Evolutionary Algorithm
MOGA	Multi-objective Genetic Algorithm
NN	Neural Network
PGA	Poly Glycolic Acid
PLA	Poly Lactic Acid

PLGA	Poly *Lactideco Glycolide* Acid
PSO	Particle Swarm Optimization
SA	Simulated Annealing
SR	Stochastic Ranking
TDD	Transdermal Drug Delivery
TS	Tabu Search
VPGA	Variable Population-size Genetic Algorithm

LIST OF SYMBOLS

E	Strain
σ	Stress
∇P	The pressure drop across the microneedle lumen
σ_y	Yield strength of material
μ	Viscosity of fluid at temperature of 25ºC
A	Cross-sectional area of microneedle tip
c	Distance from vertical axis to the outer edge of the section
c_1	Determine the relative influence of the cognitive component
c_2	Determine the relative influence of the social component
D_b	Base diameter
D_i	Inner diameter
D_o	Outer diameter
D_t	Tip diameter
E	Young's Modulus of material
$F1$	Fitness value for total deformation (μm)
$F2$	Fitness value for strain energy (pJ)
$F3$	Fitness value for equivalent stress (MPa)
$F4$	Fitness value for flow rate (μL/s)
$F_{Bending}$	Bending force
$F_{Buckling}$	Buckling force
$F_{Compress}$	Compressive force
F_m	Fitness value for the specification *m*
$F_{maverage}$	Average value of specification m at first iteration
$F_{Resistance}$	Resistive force
F_{tot}	Normalized overall fitness function
I	Moment of inertia
$iter_{id}$	Current iteration
$iter_{max}$	Maximum iteration number
L	Length of microneedle

P_{gd}	gbest of the group
P_{id}	pbest of particle i
P_{pierce}	Require pressure for microneedle to penetrate into skin
Q	Flow rate fluid flow through microchannel
r_1, r_2	Random numbers
T_b	Base thickness
T_w	Wall thickness
U	Strain energy
V	Volume
V_i	New velocity of particles
V_{id}	Current velocity of particles
w	Inertia factor
W_b	Base width
W_m	Weight for specification m
w_{max}	Initial weight
w_{min}	Final weight
x	General deformation of a body
X	Reference position of material points in the body
X_i	New position of particles
X_{id}	Current position of particles

Reka Bentuk Pintar Struktur Jarum Mikro untuk Sistem Penyaluran Ubat

ABSTRAK

Penyaluran ubat melalui kulit (TDD) adalah satu sistem yang digunakan untuk mengangkut ubat-ubatan atau komposisi biologi ke dalam tubuh manusia, berkelebihan untuk menghilangkan kesakitan dan ketidakselesaan yang disebabkan oleh suntikan di dalam salur darah. Jarum mikro merupakan satu contoh peralatan TDD yang melibatkan pelbagai parameter dan keperluan set reka bentuk yang rumit. Reka bentuk dan analisis struktur jarum mikro untuk sistem penyaluran ubat telah menjadi satu isu penting di kalangan pengkaji terutamanya dalam bidang biologi MEMS (BioMEMS). Oleh kerana jarum mikro yang berasaskan MEMS berkembang dengan rumit, terdapat satu keperluan yang besar bagi mengurangkan masa yang diambil oleh pereka bentuk MEMS untuk menganalisa reka bentuk mereka sebelum diteruskan kepada proses fabrikasi. Kajian ini mencadangkan penggunaan kaedah Kepintaran Tiruan (AI) sebagai alat pengoptimum yang sistematik untuk mengurangkan masa yang diambil bagi mereka bentuk satu struktur jarum mikro. Pengoptimuman struktur jarum mikro dilakukan dengan menggunakan dua teknik AI iaitu Pengoptimum Zarah Berkumpulan (PSO) dan Algoritma Genetik (GA). Satu penyelidikan tentang kacukan algoritma pengoptimum dijalankan dengan menggabungkan PSO dan GA untuk meningkatkan kecekapannya berkerja. Kaedah gabungan ini dipanggil kacukan PSO-GA (HPSOGA). Reka bentuk struktur jarum mikro yang rumit melibatkankan lapan pembolehubah iaitu bentuk jarum mikro, bahan yang digunakan, saiz susunan, tapak jarum mikro, diameter saluran, tinggi jarum mikro, tinggi saluran dan tinggi bekas penyimpanan ubat. Terdapat tiga pembolehubah yang dimalarkan; tekanan ke atas hujung jarum mikro iaitu 3.18 MPa, saiz tapak susunan jarum mikro iaitu 5000 µm x 5000 µm x 50 µm dan tekanan statik pada 10 kPa pada masukan jarum mikro. Fokus utama kajian ini menekankan beberapa sasaran spesifikasi seperti memaksimakan pengaliran bendalir dalam saluran dan meminimakan kadar perubahan, tenaga ketegangan dan jumlah tekanan. Alatan MEMS CAD yang digunakan untuk menganalisa dan mensimulasi struktur jarum mikro ialah ANSYS V11.0 manakala pembangunan pengoptimum dilakukan dalam MATLAB. Reka bentuk jarum mikro yang menggunakan teknik HPSOGA memberikan nilai maksimum untuk pengaliran bendalir iaitu 6.732 µL/s dan juga nilai minimum untuk kadar perubahan, tenaga ketegangan dan jumlah tekanan iaitu masing-masing 0.010 µm, 1.101 pJ dan 10.092 MPa. Teknik HPSOGA dibandingkan dengan teknik PSO dan GA yang biasa. Keputusan menunjukkan bahawa HPSOGA dapat mengoptimum reka bentuk jarum mikro dan berjaya mencapai spesifikasi yang dikehendaki dengan pencapaian yang lebih baik. Teknik HPSOGA yang dicadangkan menyediakan satu laluan mudah untuk mencari reka bentuk struktur jarum mikro yang lebih baik dan dapat digunakan untuk mengoptimumkan reka bentuk MEMS yang rumit serta melibatkan kepelbagaian parameter dan pembolehubah.

Intelligent Design of Microneedle Structure for Drug Delivery System

ABSTRACT

Transdermal drug delivery (TDD) is an attractive system to transport drugs or biological compounds into human body, for its apparent benefit of eliminating pain and inconvenient intravenous injections. Microneedle is one example of TDD devices that involves various parameters and complex set of design requirements. Design and analysis of microneedle structure for drug delivery system has been an important issue among researchers especially in biological micro-electro-mechanical system (BioMEMS) field. As MEMS-based microneedles develop in complexity, there is a greater need to reduce the time taken for a MEMS designer to analyze their design before proceed to fabrication process. This study proposed the used of artificial intelligence (AI) methods as a systematic optimization tool to reduce the amount of time taken for designing a microneedle structure. An optimization of microneedle structure is demonstrated by using two techniques of AI which are particle swarm optimization (PSO) and genetic algorithm (GA). A hybrid optimization algorithm has been investigated by combining the PSO with GA to improve computation competency. This combination method is called hybrid PSO-GA (HPSOGA). There are eight design variables of microneedle structure to be optimized in this research. The complex design of microneedle structure considers the shape of microneedle, material used, size of the array, the base of microneedle, the lumen base, the height of microneedle, the height of the lumen, and the height of the drug container or reservoir. There are three constant variables; the pressure applied at the tip of microneedle which is 3.18 MPa, the size of the microneedle array base which is set to 5000 µm x 5000 µm x 50 µm and static pressures of 10 kPa at the inlet of the microneedle. The main focus of this study is that the microneedle is supposed to meet numbers of significant specifications such as minimizing the total deformation, strain energy, equivalent stress of the microneedle and maximizing the flow rate of the fluid that flow through its channel. The MEMS CAD tools used to analyze and simulate the microneedle structure in this research is ANSYS V11.0 while the developments of optimizer part are conducted in MATLAB environment. The microneedle design with HPSOGA technique gives the maximum value of flow rate which is 6.732 µL/s and also the minimum value of total deformation, strain energy and equivalent stress which are 0.010 µm, 1.101 pJ and 10.092 MPa respectively. The HPSOGA technique is compared with standard PSO and GA technique. The results show that HPSOGA is able to optimize the design parameters of microneedle and capable to achieve the required specifications with better performance. The proposed HPSOGA optimization in this research provides an easier platform to direct the search towards a better microneedle structural design and can be used to optimize complex MEMS designs that often involve multiple parameters and design variables.

CHAPTER 1

INTRODUCTION

1.1 Introduction

Microneedle is a painless medical device for the purpose of drug transportation to patients. This tiny device has been used to extract blood from patient's body for bio-sampling purpose. The work presents here is about the design and optimization of microneedle structure for drug delivery system. This chapter summarizes the main content of this thesis. It first covers the background overview of microneedle. Next, this chapter describes the problem statement involves in this research. Then, the main research objectives and the scope of research are discussed in detail. Finally, the organization of this thesis is briefly explained.

1.2 Overview of Microneedle

Drug delivery and blood transportation are the frequent and normal applications that have been used in hospitals. Receiving injection for vaccines and medication are medical treatments that most people are familiar with. Commonly, patients with diabetes and kidney failure use the hypodermic needles for blood transport process. Sometimes the process of drug delivery and blood extraction or insertion is repeated many times in a day. This process is a painful experience and many patients will delay or ignore their necessary medical treatment in order to avoid the unpleasant visit to the hospital. Hypodermic needle can cause pain, swelling and infection after repeated insertion. The use of microneedle overcomes these limitations due to small needle size and biocompatible material used for fabrication process (Tayyaba, Ashraf & Afzulpurkar, 2010).

Nowadays, microneedles are mainly used for biological fluidic extraction and drug delivery on skin. Microneedle has the ability to increase the delivery of drugs dramatically, as the structure has the advantage in increasing the permeability of the skin (Mukerjeee, Issseroff, Collins & Smith, 2003). In the past few years, many researchers had begun to investigate and come out with various experimental procedures in order to test the transdermal drug delivery method by using microfabricated needles. As the size is very small, the ability of these microneedles to deliver drugs through the top layer of skin, or epidermis has been proven. In fact, the microneedle can eliminate the pain caused by the injection because it will not go too deep into the dermis layer of skin to touch the nerve endings.

The sizes of microneedles are generally hundreds of microns long, 1 to 50 microns wide at the tip, and around 50 to 300 microns at the base. They can be made-up as one single needles or multi-needle arrays (Prausnitz, Bronaugh & Maibach, 2005). For the purpose of drug delivery, the suitable length of microneedle is 100 to 300 μm, but the appropriate length of microneedle for blood extraction purpose is 1100 to 1600 μm (Ashraf et al., 2010). According to Toon (1998), microneedle can be divided into two main groups based on their common design. One is in-plane needles which the microchannel is parallel to the substrate level surface. The second one is out-of-plane needle. The microchannels of out-of-plane needles are perpendicular to the substrate surface. Out-of-plane design allows multiple needles being fabricated in two-dimensional arrays (Mukerjeee et al., 2003).

Different shapes of microneedle have been developed in micro-electro-mechanical system (MEMS) technology using a variety of different materials. It has been reported that microneedles have been fabricated in metals, silicon, silicon dioxide, polymers, glass and other materials. There are two main categories of microneedles, which are solid microneedles and hollow microneedles. Hollow microneedles allow a better control of drug administration in terms of amount and time compared to solid microneedles. For both types, to guarantee an adequate of drug delivery, microneedles are arranged in the form of arrays. A study by Al-Qallaf & Das (2008) demonstrates the importance of this array design. There is also a study that shows the importance of microneedles design in terms of skin penetration as demonstrated by Davidson, Al-Qallaf & Das (2008). Figure 1.1 shows variety types of microneedle developed from single crystal silicon and nickel iron (NiFe) electroplating that have been fabricated all over the world.

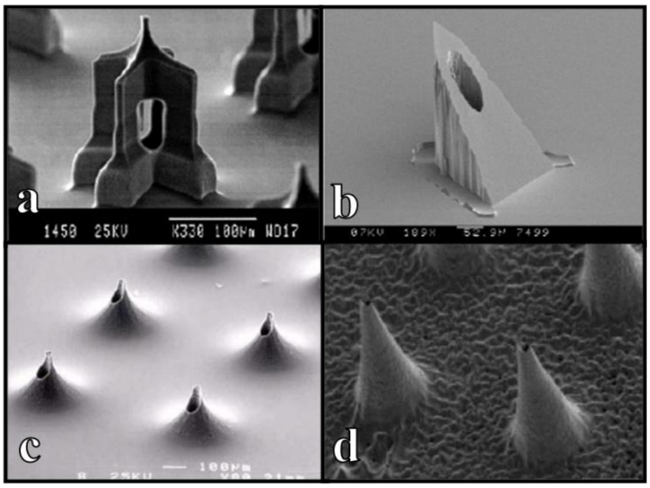

Figure 1.1: Microneedles developed from single crystal silicon reported by: a) (Griss & Stemme, 2003); b) (Gardeniers et al., 2003); c) (Stoeber & Liepmann, 2005); and NiFe electroplating: d) (McAllister et al., 1999).

A number of necessities are needed in microneedle features in order to construct a painless microneedle. First and foremost, the microneedle is supposed to be strong and sharp enough to pierce the epidermis layer without failure. Secondly, to minimize the contact between microneedle and nerves, the length of the needle needs to be controlled by the base of the needle. Besides that, due to the fact that the skin is elastic and there is random blood vessels distribution in skin, it is important for the microneedle design to have a high aspect ratio and arrayed structures. Finally yet importantly, each needle of the array should have small-penetrated area to reduce pain and skin damage (Moon & Lee, 2003). Microneedle can be integrated with micropump, biosensor, microelectronic devices and microfluidic chips. These devices are being rapidly developed by researchers around the world to fulfill the demand of biomedical field.

1.3 Problem Statement

As MEMS devices especially microneedles develop in complexity, there is a greater need in reducing the amount of time taken for MEMS designers to analyze their design before they proceed into the fabrication process. Most of the time taken by a MEMS designer is spent in the initial conceptual stages of design by using the efficient computer-aided design (CAD) tools. At the moment, there are variety of MEMS CAD programs that offer MEMS designers pre-configured cell libraries with reusable apparatus such as Cadence, IntelliSuite and ANSYS (Cobb & Agogino, 2010). However, there is issue for the designer on how and when these components should be used. In other words, these simulation tools are not efficient during the simulation process of design as they require detailed modeling data and take up hours or even days to analyze one design. This situation, if not being handled properly can become a serious problem to MEMS industry.

Microneedle structure design is one example of the MEMS design that involves various parameters and complex set of design requirements. To the best of author's knowledge, most of the previous works focused only on the design of the microneedle itself and/or the fabrication process for the microneedle. Work on how to reduce the amount of time taken to complete one microneedle design is virtually nonexistent. There is a need for simulation and design tools that can provide faster concept generation during the initial stages of the design process. The simulation process of microneedle or other complex MEMS design might become simple and easy if we have a systematic optimization tool. The use of artificial intelligence (AI) approach has been effectively employed to deal with reliability optimization problems. Therefore, this research investigates the most appropriate method to optimize the microneedle structure in a lesser time.

1.4 Research Objectives

In this research, the main objective is to design and optimize the microneedle structure by a given design variables. Other than that, several more objectives must be achieved. The objectives are listed below:

i. To maximize the flow rate of the fluid flow through microneedle channel and to minimize the total deformation, strain energy and equivalent stress of microneedle according to specified requirement by using two artificial intelligence (AI) techniques which are particle swarm optimization (PSO) and genetic algorithm (GA).

ii. To improve the effectiveness of the microneedle optimizer by combining PSO technique with GA technique, known as a hybrid PSO-GA method (HPSOGA).

iii. To compare the PSO, GA and HPSOGA in terms of the performance of microneedle structure.

1.5 Research Scope

The research starts by studying and understanding about the structure and different layers of human skin. The information on the thickness and the sensitivity of human skin is very important to determine the design variables of microneedle. The optimization study for maximization of flow rate and minimization of total deformation, strain energy and equivalent stress of microneedle are the main focus in this research. The MEMS CAD tool, ANSYS is used to analyze and simulate the microneedle structure in this research. The approach of AI techniques which are PSO and GA are proposed to optimize the design of microneedle structure. In order to improve computation competency, hybrid optimization algorithms are investigated by combining the PSO with GA. The developments of algorithm part in this research are conducted in MATLAB environment.

1.6 Thesis Organization

This research thesis is divided into five sections, which are Chapter 1 - Introduction, Chapter 2 - Literature review, Chapter 3 - Methodology, Chapter 4 - Result and Discussion and Chapter 5 - Conclusion. The contents of each chapter are shown as follow:

i. **Chapter 1** presents the overview of microneedle, problem statement, research objectives, research scope and the organization of thesis.

ii. **Chapter 2** explains the previous studies that are related to the research. It covers a review on the material that is required for designing the microneedles, the parameters that are suitable for the design, the shape of the microneedle, the fabrication process flow, types of microneedle and review on human skin. This chapter also explains the usage of artificial intelligence (AI) as the optimization tools in engineering field especially MEMS and biomedical area. The process of particle swarm optimization (PSO) and genetic algorithm (GA) are also discussed in detail.

iii. **Chapter 3** discusses the methodology of the research that covers the most preferred method and procedure used in carrying out the project. Besides that, a brief description on a systematic approach, tools and techniques applied in order to achieve the given research objectives.

iv. **Chapter 4** illustrates the optimization results of microneedle structure by using various optimization methods. Important findings are presented in a comprehensive manner and the research objectives are reviewed to ensure the goals set are satisfied. The results obtained are discussed in detail.