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MICRONEEDLE STRUCTURE DESIGN AND OPTIMIZATION USING GENETIC ALGORITHM

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Abstract

This paper presents a Genetic Algorithm (GA) based microneedle design and analysis. GA is an evolutionary optimization technique that mimics the natural biological evolution. The 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. The GA is executed in conjunction with ANSYS simulation system to assess the design specifications. The GA uses three operators which are reproduction, crossover and mutation to manipulate the genetic composition of the population. In this research, the microneedle is designed to meet a number of significant specifications such as nodal displacement, strain energy, equivalent stress and flow rate of the fluid / drug that flow through its channel / lumen. A comparison study is conducted to investigate the design of microneedle structure with and without the implementation of GA model. The results showed that GA is able to optimize the design parameters of microneedle and is capable to achieve the required specifications with better performance.

Keywords: Microneedle, MEMS, Optimization, Genetic Algorithm, Design and specifications.

1. Introduction

Micro-Electro-Mechanical System (MEMS), is a combination of mechanical elements, sensors, actuators, and electronics on a common silicon substrate (or

Nomenclatures

F_1	Fitness value of total deformation of microneedle
F_2	Fitness value of strain energy of microneedle
F_3	Fitness value of equivalent stress of microneedle
F_4	Fitness value of flow rate of fluid flow through lumen
F_m	Fitness value for the specification m
$F_{maverage}$	Average value of specification m at Generation 1
FR	Flow rate of fluid flow through lumen, μL/s
F_{tot}	Normalized overall fitness function
W_m	Weight for specification m

Abbreviations

bio-MEMS	Biological MEMS
CBR	Case-Based Reasoning
GA	Genetic Algorithm
MEMS	Micro-Electro-Mechanical System
MOGA	Multi-Objective Genetic Algorithm
NiFe	Nickel iron
TDD	Transdermal drug delivery

other substrates) through microfabrication technology [1]. MEMS have been used in various applications such as medical, automotive, aerospace, integrated circuit design and etc. Nowadays, biological MEMS (bio-MEMS) have been the research attention in the design of medical instruments.

The biological applications of MEMS (bio-MEMS) and microfluidics are inextricably related for the reason that the majority of devices in systems for biological and medical analysis work with samples in liquid form. Microfluidic systems deal with the fluid flow in very small amounts, typically a few microlitres (μL) in a miniaturized system [2]. Outside of biological analysis, microfluidic has applications in chemical analysis, drug synthesis, drug delivery, and point-of-use synthesis of harmful chemicals.

One micro fabricated invention that shows great promise for medical dealings around the human race is the microneedle. These devices are typically designed with two purposes which are drug delivery to the patient and blood extraction from the patient for biosampling [3].Transdermal drug delivery (TDD) is refers to the movement of pharmaceutical compound across the skin to reach the systematic circulation for subsequent distribution in the human body [4]. Drug delivery devices using MEMS technology are progressively being developed for biomedical applications. The main advantage of the MEMS based drug delivery system is the ease of mass fabrication of small feature sizes at low cost and making such systems desirable for commercial applications [5].

Various studies have been conducted on new drug delivery methods using emerging micro and nanotechnologies. The main focus of MEMS for drug delivery has been towards the development of microneedles for minimally invasive TDD applications [6]. MEMS technology brings new means for biomedical field. One application of interest to the biomedical industry is the development of microneedles.

From literature, different shapes of microneedles have been developed in MEMS technology using a variety of different materials, sizes, and fabrication processes. The shape of the microneedle is very critical and important during design and fabrication. Different designs of microneedles have been proposed and fabricated such as cylindrical, canonical, pyramidal, candle, spike, spear, square, pentagonal, hexagonal, octagonal and rocket shape [4, 6]. In order to design painless microneedles, the design of microneedles needs to satisfy a number of requirements such as nodal displacement, strain energy density, equivalent stress and flow rate of drugs. Therefore, design parameter optimization is important to achieve the output specifications of the microneedles.

Evolutionary computation has become an important area of research in the 21st century. It covers almost all fields such as engineering, science, education, medicine, business, accounting, finance, marketing, economics, stock market and law [7-13].

Genetic Algorithm (GA) is an evolutionary optimization technique that mimics the natural biological evolution. In computer science, GA is well-known for its capability to search for approximate solutions to the optimum [14] based on the concepts of biological inheritance, mutation, selection and crossover.

The used of GA in optimizing and solving hard problems that require intelligence from human perspective is very famous in many fields including MEMS field. For instance, H. Bang et al. [15] present a novel method of optimizing particle-suspended microfluidic channels using GA whereas Zhou et al. [16] were the first to demonstrate that a Multi-Objective Genetic Algorithm (MOGA) can synthesize MEMS resonators and produce new design structures. Previous work by Cobb et al. [17] has shown that the integration of a Case-Based Reasoning (CBR) knowledge base with a MOGA can increase the number of optimal solutions generated for a given MEMS design problem.

In addition, Zhang et al. [18, 19] implemented a hierarchical MEMS synthesis and optimization architecture, using a component-based genotype representation and two levels of optimization: global GA and local gradient-based refinement. Meanwhile, similar to the work proposed by Zhang [19], Wang et al. [20] conduct a MEMS synthesis by utilizing bond graphs and genetic programming with a tree-like structure of building blocks to incorporate knowledge into the evolutionary process. In related research, Muhkerjee et al. [21] conducted work on MEMS synthesis for accelerometers using parametric optimization of a pre-defined MEMS topology. They expanded the design exploration within a multidimensional grid in order to find the global optimal solution.

In this research, a GA-ANSYS design model is developed to assist the structural design of microneedles. ANSYS is used to simulate the output specifications of microneedles whereas GA is applied to optimize the design parameters based on the simulated results from ANSYS.

2. Microneedle Design

The success of transdermal drug delivery has been severely limited by the inability of most drugs to enter the skin at therapeutically useful rates. Recently, the use of micron-scale needles in increasing skin permeability has been proposed

and shown to dramatically increase transdermal delivery, especially for macromolecules [3, 4, 6].

Using the tools of the microelectronics industry, microneedle has been fabricated with a range of sizes, shapes and materials such as metals, silicon, silicon dioxide, polymers, glass and other materials [22]. Figure 1 shows variety types of microneedle developed from single crystal silicon reported by: a) Griss and Stemme, 2003 [23]; b) Gardeniers et al., 2003 [24]; c) Stoeber and Liepmann, 2005 [25]; and nickel iron (NiFe) electroplating reported by d) McAllister et al., 1999 [26].

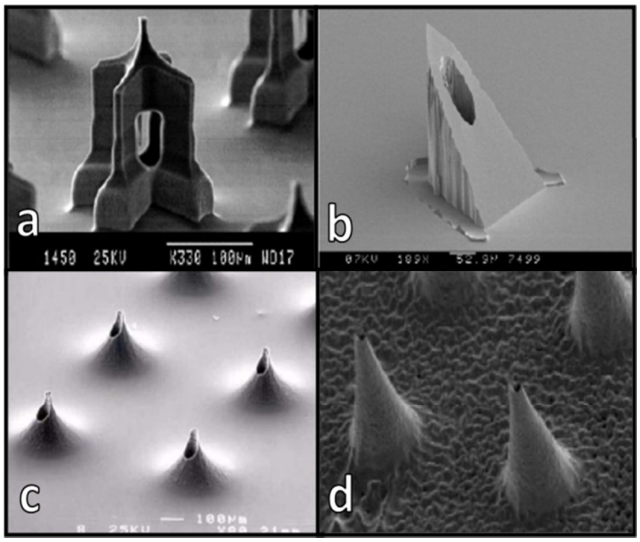

Fig. 1. Microneedles Developed from (a, b, c) Single Crystal Silicon; and (d) Nickel Iron Electroplating [23-26].

Microneedle is a very useful drug delivery device. This device provides an interface between the drug reservoir and the patient's body for releasing or extracting the fluid. The length of microneedle should be long enough that it penetrates the epidermis and short enough not to reach the dermis, in order to avoid pain. A minimum length of around 100 μm is necessary to penetrate the stratum corneum of the skin [27, 28]. The suitable length of microneedle for drug delivery is 100 μm to 300 μm, but for blood extraction the appropriate length of microneedle is 1100 μm to 1600 μm [29]. This study is concentrating on the microneedle for drug delivery purpose.

Microneedle can be integrated with micropump, biosensor, microelectronic devices and microfluidic chips. Microneedles are promising microfabricated devices for minimally invasive drug delivery applications. In order to be minimally invasive, the needles are designed to be as small as possible. Needles are also designed to be extremely sharp, with submicron tip radii. This allows the needles to be effectively inserted into the skin. Microneedle offers an attractive way for advanced drug delivery systems by mechanically penetrating the skin and injecting drug just under the stratum corneum where it is rapidly absorbed by the capillary bed into the bloodstream [30, 31].

In general, a microneedle must be able to penetrate into the skin layer at least 40 µm so that it can be used effectively as a drug delivery. However, a microneedle must not penetrate far beyond the thickness of the epidermis layer. This is because the layer below the epidermis which is the dermis layer contains blood vessels and nerve pain endings [3]. Therefore, one will feel hurt if the needle penetrates to the dermis layer.

3. Determination of Microneedle Design Variables

Table 1 shows the design variables/parameters that are considered for the structural optimization of microneedle in this research. There are eight design variables to be manipulated and optimized. The variables involved are the shape of microneedle, the material used, the array of the needles, microneedle base, lumen base, height of microneedle, height of lumen and height of the drug container/reservoir. These variables are manipulated to achieve the required microneedle specification as shown in Table 2. Figure 2 shows four types of microneedle's shape involved in this study which are: a) canonical; b) pyramidal; c) hexagonal; and d) octagonal. The dimension of microneedle viewed in cross-section is depicted in Fig. 3 while the isometric view of microneedle design is shown in Fig. 4.

Table 1. Design Variables of Microneedle Structure.

Design Variable	Range	No. of Range
Shape	Canonical, Square base, Hexagonal base, Octagonal base	4
Material	Silicon, Polymeric, Stainless steel	3
Array	4x4, 6x6, 8x8, 10x10, 12x12	5
Microneedle Base	60 µm, 65 µm, 70µm, 75 µm, 80 µm, 85 µm, 90 µm, 95 µm, 100 µm, 105 µm, 110 µm	11
Lumen Base	14µm, 16µm, 18µm, 20µm, 22µm, 24µm, 26µm, 28µm, 30µm, 32µm, 34µm	11
Microneedle Height	150µm, 175µm, 200µm,225µm, 250µm, 275µm, 300µm	7
Lumen Height	150µm, 175µm, 200µm,225µm, 250µm, 275µm, 300µm	7
Drug Container Height	1000µm, 1200µm, 1400µm, 1600µm	4

Table 2. The Required Specification for the Microneedle Structure Optimization.

Parameters	Range Min	Range Max	Optimization	Weight
Total Deformation (µm)	-	-	Minimize	3
Strain Energy (pJ)	-	-	Minimize	1
Equivalent Stress (MPa)	-	-	Minimize	6
Flow Rate (µL/s)	5	-	Maximize	10

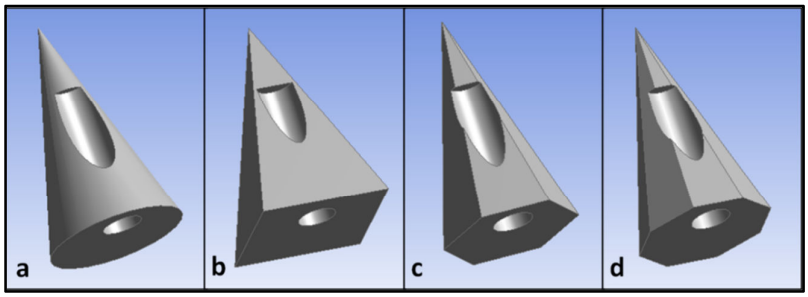

Fig. 2. Four Types of Microneedle's Shape: a) Canonical; b) Pyramidal; c) Hexagonal; and d) Octagonal.

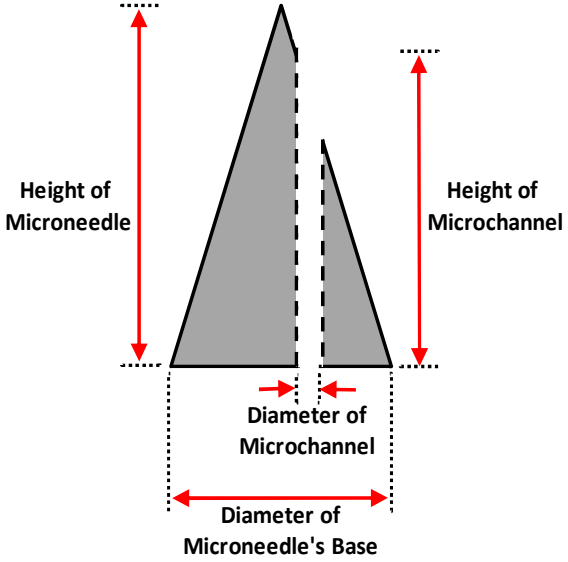

Fig. 3. Dimensions of Microneedle View in Cross-section.

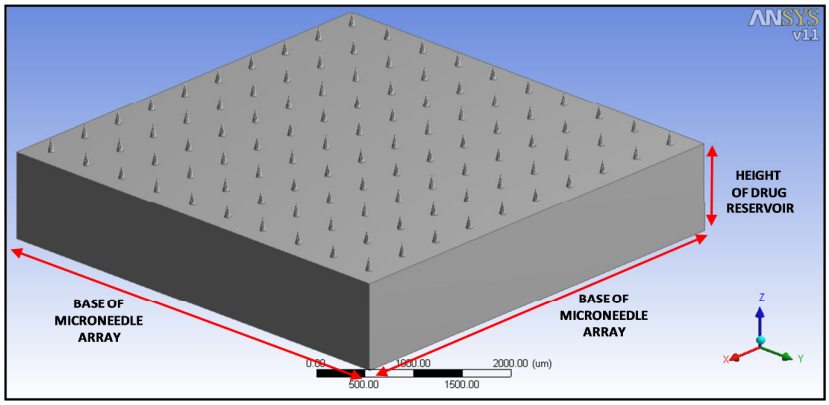

Fig. 4. Isometric View of Microneedle's Design in this Research.

The optimization study for maximization of flow rate and minimization of total deformation, strain energy and equivalent stress of microneedle are the main objectives in this research. Simulations using ANSYS were used to solve for the total deformation, strain energy density, equivalent stress and flow rate of microneedle. This study considered that a microneedle would fail or undergo a fracture when simulation results predict the stress is greater than or equal to the yield strength of the microneedle material [32]. Hence, it is very important to come out with a minimum value of the total deformation, strain energy density and equivalent stress. Meanwhile, it is better for a microfluidic device to have a higher flow rate so that the time taken to deliver drug to the body can be reduced. As a result, a maximum flow rate is desired in this study.

The reason of putting the weight ratio in Table 2 is to indicate the importance level of each of the parameter specification. In this case, the most important parameter that needs to be achieved is the flow rate of the fluid flow. Therefore, the weight ratio is being set to 10. Optimization weight for each specification in Table 2 is assigned according to the expected design requirement.

Despite the eight design variables to be optimized, there are two constant variables in this study. The constant variables are the pressure applied at the tip of microneedle and the size of the microneedle array base. In this study, the pressure is set to 3.18 MPa because according to [3, 33-34], human skin offers resistance of 3.18 MPa during microneedle penetration. Hence, to overcome this skin resistance, the microneedle must withstand the load more than 3.18 MPa. As for the size of the microneedle array base, it is set to 5000 μm × 5000 μm × 50 μm.

4. Research Methodology: GA-ANSYS

This research proposes the execution of GA in conjunction with ANSYS simulation system for the optimization of microneedle structural design. A GA-ANSYS model is developed in MATLAB environment and the flow of GA-ANSYS operation is depicted in Fig. 5. This algorithm explores the search space of microneedle design parameters through the genetic mechanism of reproduction, crossover and mutation.

The GA-ANSYS operation starts with an initialization of chromosome population in which each chromosome in the population represents a candidate solution for the setting of microneedle design parameters. In each chromosome, there are genes. Through the analogous of biological evolution, each gene in the chromosome indicates a specific design parameter. For instance, gene 1 represents the shape of microneedle, gene 2 represents the material used, gene 3 represents the shape of microneedle, gene 4 represents the microneedle base, gene 5 represents the lumen base, gene 6 represents the height of microneedle, gene 7 represents the height of lumen and gene 8 represents the height of the drug container.

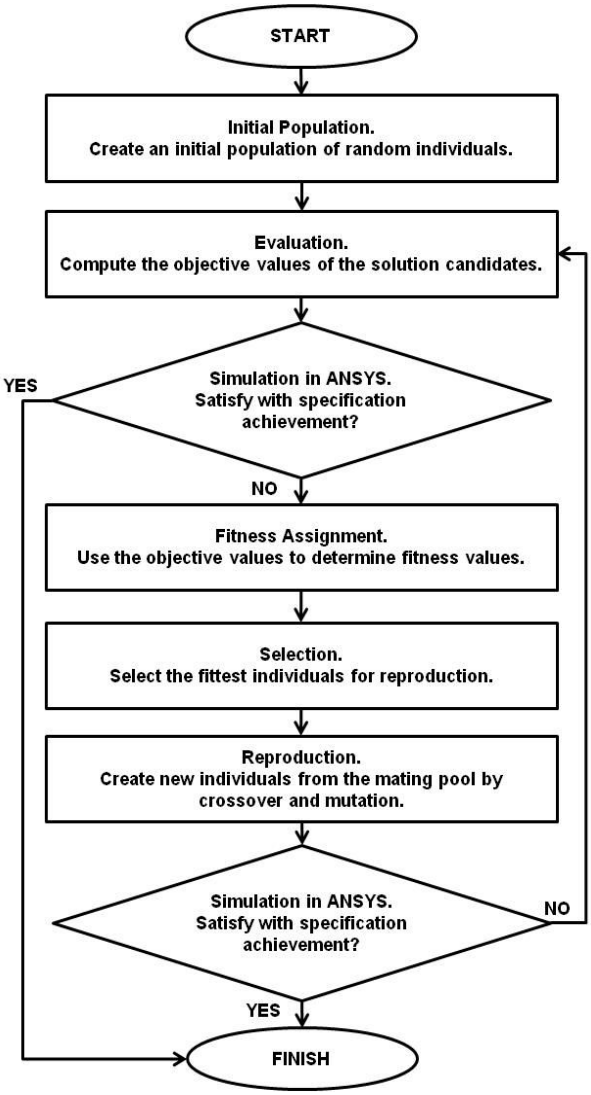

Fig. 5. GA-ANSYS Flow of Operation in this Study.

The generated chromosomes or candidate solutions are fed to the ANSYS simulator to simulate the output specifications of the microneedle such as total deformation, strain energy, equivalent stress and flow rate. These outputs are then evaluated through the formulated fitness assignment function to measure the proximity towards the targeted specifications in Table 2. Therefore, the closer the achievement towards targeted output specifications, the better is the fitness for the chromosome.

After fitness evaluation, chromosomes will be selected for crossover and mutation based on their fitness. The better the fitness, the higher is the probability for the chromosome to be selected for reproduction of offspring to the next GA generation.

Chromosomes that are selected for reproduction will be forwarded to two genetic operators: crossover and mutation. Both crossover and mutation are genetic operators used to increase the solution diversity. Crossover recombines genetic information from two selected parent chromosomes. In this study, the setting of some design variables in the selected chromosomes is swapped to produce offspring solutions that inherit some genetic information from the parents. As for mutation, the process involves random alteration of gene value in a particular chromosome [35, 36]. Both genetic operators are conducted according to the predefined crossover and mutation probability. The newly generated offspring from crossover and mutation will then be fed to the ANSYS simulation system for microneedle output performance evaluation. The mechanisms of ANSYS simulation, fitness assignment, selection, and reproduction are repeated until all the specifications are satisfied.

5. Experimental Setup

In this work, single-point crossover and mutation operations are used at the beginning of the GA generation. Then, these points are modified according to the suitable condition. A real-value encoded GA is used in this research to represent the parameter setting of the microneedle. The GA parameters used in this research are shown in Table 3.

Table 3. Parameters of the GA Setup.

Generation	0	1	2	3	4	5
Population Size	30	30	30	30	30	30
Generation Gap	0.9	0.9	0.9	0.9	0.9	0.9
Maximum Generation	100	100	100	100	100	100
Crossover Probability	0.8	0.7	0.7	0.1	0.3	0.2
Mutation Probability	0.2	0.3	0.3	0.9	0.7	0.8
No. of Crossover	1	2	2	1	1	2
No. of Mutation	1	2	2	3	3	2

The effectiveness of a GA is related to the ability of defining a "good" fitness function [37]. Therefore, it is important to have an appropriate formulation of fitness function. The main objective of this research is to optimize the overall microneedle design performance in terms of the value of total deformation, strain energy density, equivalent stress and the flow rate for fluid flow. From Table 2, all specifications are to be minimized except for flow rate. There are four specifications fitness in this study, F_1, F_2, F_3, and F_4. F_1 is the fitness value for total deformation (μm), F_2 is the fitness value of strain energy (pJ), F_3 is the fitness value of equivalent stress (MPa), and F_4 the fitness value of flow rate (μL/s). Equation 1 shows the formulation for flow rate's fitness value. Since the flow rate is to be maximized and the minimum requirement for flow rate is 5 μL/s, the formulation of specification fitness for flow rate is based on the achievement of minimum constraints. A penalty value of 100 is given when the

constraint requirement is not satisfied. The reference value of the targeted flow rate used in this study is 7 µL/s.

$$F4 = \begin{cases} 100 + (5 - FR), if\ FR < 5 \\ 7 - FR\ , if\ FR > 5 \end{cases} \quad (1)$$

Since different specification consists of different unit of measurement, bias might exist when overall fitness is calculated in a weighted sum equation. As a result, a normalized approach is employed to divide the fitness for each specification with the average specification fitness. Equation 2 shows the normalized overall fitness function:

$$F_{tot} = \sum_{m=1}^{z} W_m \frac{Fm}{Fm_{average}}, \quad (2)$$

where:

W_m = Weight for specification m;
F_m = Fitness value for the specification m;
$F_{maverage}$ = Average value of specification m at Generation 1.

6. Result and Discussion

Based on the proposed GA approach, the optimized variables of the best individual are given in Table 4 which shows the five best results that have been obtained in MATLAB and ANSYS software. These variables have been chosen based on the lowest fitness value. In this study, the lower the value of F_{tot}, the better the candidate solution is. The GA have suggests a set of values for the design variables in Table 4 and the respective design performance in terms of total deformation, strain energy, equivalent stress and flow rate in Table 5. From the results, it is observed that the design setting is approaching the required specification for the microneedle structure optimization. Figures 6-8 respectively show the results of total deformation, strain energy and equivalent stress from ANSYS.

Table 4. Optimized Design Variables for Microneedle Structure using GA (Five Best Individuals).

Design Variable	GA Suggested Value				
	1	2	3	4	5
Shape	Square	Octagonal	Square	Octagonal	Octagonal
Material	Stainless steel	Silicon	Stainless steel	Stainless steel	Silicon
Array	8x8	8x8	8x8	8x8	12x12
Microneedle Base (µm)	90	90	85	90	70
Lumen Base (µm)	26	26	24	26	18
Microneedle Height (µm)	150	175	175	175	175
Lumen Height (µm)	100	125	125	125	125
Drug Container Height (µm)	1200	1400	1600	1600	1000

Table 5. Specification Achievement after Optimization (Five Best Individuals).

Parameter	GA Suggested Value				
	1	**2**	**3**	**4**	**5**
Total Deformation (μm)	0.0075	0.0382	0.0185	0.0324	0.0611
Strain Energy (pJ)	1.1720	2.5961	1.9633	1.9165	3.2681
Equivalent Stress (MPa)	11.3580	23.6040	23.7480	24.5550	35.4480
Flow Rate (μL/s)	5.2112	5.6287	5.1272	6.0174	5.1301

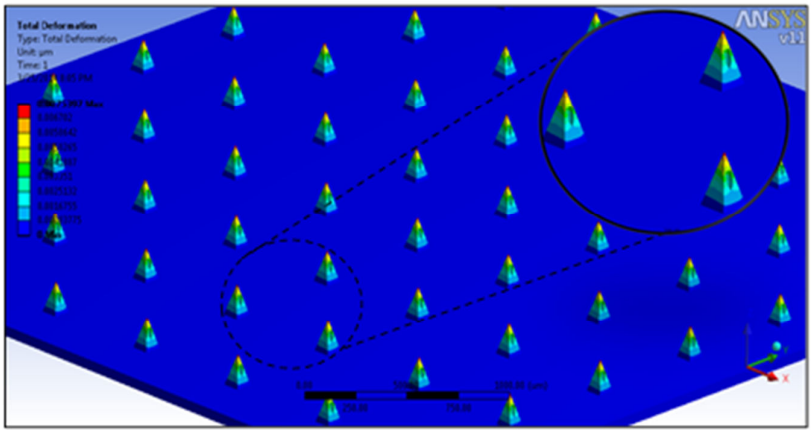

Fig. 6. Total Deformation for Best Microneedle's Design.

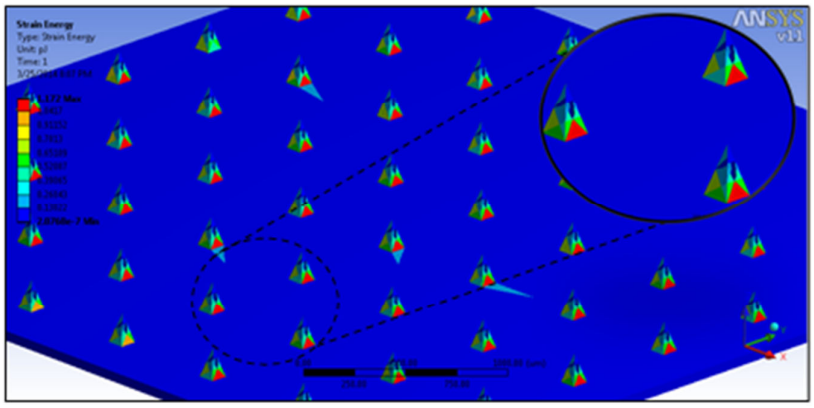

Fig. 7. Strain Energy for Best Microneedle's Design.

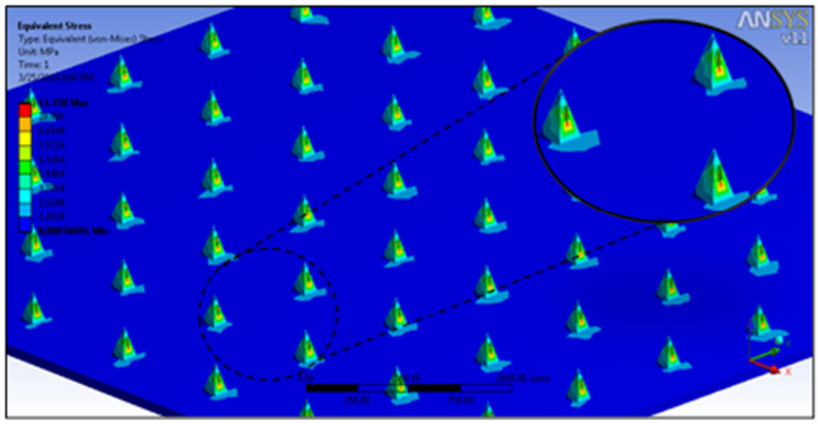

Fig. 8. Equivalent Stress for Best Microneedle's Design.

Table 6 shows the improvement of result obtained in this study by the implementation of GA and the results without GA obtained from [38]. In [38], only three design variables (microneedle shape, microneedle height and the pressure applied to the microneedle) were considered for the output design specification on total deformation, strain energy, and equivalent stress. However, in this research, eight design variables of microneedle are optimized for four design output specifications as listed in Table 4, and Table 5. From Table 6, it is observed that the GA-based microneedle design achieve a better results in all design specifications as compared to the previous study. The specifications to be minimized such as total deformation, strain energy density and equivalent stress are smaller than the result in [38]. Besides, the maximization of flow rate has also been considered in the current study as compared to the previous. Five best proposed candidate solutions of GA are depicted in Table 4. The results are all better than the previous research in terms of output performance. Even though the increase of flow rate to 6.0174 µL/s might lead to the increase of other design output specification, the overall design performance are still better than the previous research in [38]. Thus, the GA-based structural optimization of microneedle is proven to outperform the conventional design without GA.

Table 6. Result Obtained in this Study and Previous Study [38].

Parameter	Microneedle Design with GA	Microneedle Design without GA [38]
Total Deformation (µm)	0.0075	1.01
Strain Energy Density (pJ)	1.1720	8.8089
Equivalent Stress (MPa)	11.3580	93.423
Flow Rate (µL/s)	5.2112	-

In the previous study [38], the analysis of microneedle structure has been conducted based on simulation experience without the assistance of any optimizer. The identification for the best microneedle structural setting is time consuming and there is no directional search for a better setting. However, the

proposal of GA-ANSYS optimization in this research provides an easier platform to direct the search towards a better microneedle structural design.

7. Conclusion

MEMS designs that involve multiple variables are often difficult to be optimized. The presented optimization algorithms in this paper can be used for a design of microneedle structure or for improving an existing microneedle system. It can also be used for micropump, microchannel, microreservoir, microvalve and other mechanical system in MEMS. The presented optimization study shows the integration of GA in ANSYS simulation. Eight design variables and four output specifications are optimized. Improvements have been shown in terms of total deformation, strain energy density, equivalent stress, and flow rate.

GAs are not guaranteed to achieve the total optimum, but they are generally good at finding a satisfactory solution during a suitable amount of time. They are generally designed to solve optimization problems. However, when cooperating with other methods, that is usually called 'hybrid', it can also deal with problems and constraints. Future work will focus on the hybridization of GA technique in the optimization of more complex microneedle design.

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