

Approximations for the optimization problem for medical microneedle systems

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Microneedle systems are used for transdermal (hypodermic) medicine injections at the treatment of different diseases. The efficiency of using such systems depends significantly on the size and parameters of microneedles. The problem of determining such dependencies and optimal parameters is considered as the problem of optimizing the interaction of microneedle systems with an elastic surface. Minimization problems for integral functional, whose solutions are approximations for solutions to the interaction problem, are obtained by the homogenization theory methods. Such problems are formulated in the form of classical problems with obstacles .

Keywords: Approximation; microneedle systems; optimization; minimization problems; homogenization

Introduction. Numerous publications confirm the high efficiency of the microneedle system applications for transdermal (subcutaneous) medicine injections at the treatment of various diseases [1, 2, 3]. Moreover, microneedle systems provide a new method of drug delivery. There are few such methods and these have long been known as pills, potions and injections. Such microneedle systems are used for injection of vaccines, proteins and insulin. For example, the press reported testing a vaccine in the form of microneedle patches to prevent coronavirus infections, which is relevant in the context of the current pandemic.

The ease of use of microneedle systems in practice substantially depends on the size and number of microneedles that make up the system. Moreover, systems with sufficiently thick microneedles can cause injuries to the skin during injection, which leads to the problem of determining the optimal parameters of microneedles. This problem will be considered here on the basis of a model of the elastic interaction of the microneedle system with the surface (which corresponds to the area of the skin) and the calculation of the parameters will be performed by approximating the solutions of minimization problems for integral functionals.

For the first time, such limit transitions for minimization problems with constraints and obstacles were calculated in [4, 5, 6]. The homogenization theory for general variational inequalities were considered and developed for the corresponding problems in [7, 8, 9]. Specific asymptotic approximations for the problems of elastic interaction of a microneedle system with a surface were calculated in [10, 11]. The

case minimization problem considered herein more accurately models the microneedle systems made in the form of a patch.

1. A model for elastic interaction of a microneedle system with a surface

In order to represent a model of a real microneedle system, consider, for example, a square $A=[0,a]^2$ on a plane with sides of a length. Specifying a positive integer N , we split the square A into N^2 smaller squares α_{ij}^ε for $i, j=1, \dots, N$ with sides of $\varepsilon = a/N$ length and select the same sets $\beta_{ij}^\varepsilon \subset \alpha_{ij}^\varepsilon$ for $i, j=1, \dots, N$ in every square, for example, circles of the same radius r_ε in the center of every square α_{ij}^ε .

Let us fix a real number $b > 0$ and a square $\Omega = (-b, a+b)^2$ with sides of $a+2b$ length. Specifying a positive number l , we define the function

$$\Psi_\varepsilon^l(x) = \begin{cases} l & \text{for } x \in \bigcup_{ij} \beta_{ij}^\varepsilon, \\ 0 & \text{for } x \in \Omega \setminus \bigcup_{ij} \beta_{ij}^\varepsilon. \end{cases} \quad (1)$$

Consider the following functional with the natural domain of definition

$$F_\varepsilon^l(u) = \int_\Omega |\nabla u|^2 dx \quad \text{for } u \in \{v \in H_0^1(\Omega) : v \geq \Psi_\varepsilon^l\}, \quad (2)$$

where $\Psi_\varepsilon^l(x)$ is the simplest model of the microneedle system from (1). Minimum of functional $F_\varepsilon^l(u)$ defines the optimal configuration of the surface (corresponding to a skin area if injections are considered) above the domain Ω under the action of the simplest system of microneedles $\Psi_\varepsilon^l(x)$ from (1).

It is known [12] that the minimum $u_\varepsilon^l(x)$ of functional (2) exists and is defined uniquely for fixed ε and l . Assume initially that the sets β_{ij}^ε for $i, j=1, \dots, N$ are given as circles of the same radius $r_\varepsilon < \varepsilon/2$, located in the center of suitable squares.

The following statement holds for a minimum of functional (2).

Theorem. For sufficiently small ε the minimum $u_\varepsilon^l(x)$ of the functional $F_\varepsilon^l(u)$, defined in (3), is approximated by the function u_0^l in the space $H_0^1(\Omega)$, where

- 1) $u_0^l = 0$, if $\varepsilon^2(-\ln r_\varepsilon) \rightarrow \infty$ as $\varepsilon \rightarrow 0$;
- 2) u_0^l is unique minimum of the functional

$$F_l(u) = \int_\Omega |\nabla u|^2 dx + \frac{2\pi}{r_A} \int (l-u)^2 dx \quad \text{for } u \in \{v \in H_0^1(\Omega) : v \geq 0\},$$

if $\varepsilon^2(-\ln r_\varepsilon) \rightarrow r$ as $\varepsilon \rightarrow 0$;

- 3) $\|u_0^l\|_{H_0^1(\Omega)} = \infty$, if $\varepsilon^2(-\ln r_\varepsilon) \rightarrow 0$ as $\varepsilon \rightarrow 0$.

The last case of this theorem is quite illustrated in Fig. 1. This situation is natural, since the minimum of problem (2) is strongly oscillating, characterizing very large energy of elastic resistance of the surface above the square Ω under the assumption of the absence of transversal displacements.

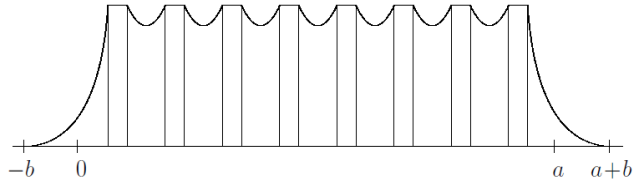


Fig. 1. The model of using a system of not very thin microneedles

The first case of this theorem is quite right represented in Fig. 2. This situation is also natural, since the minimum of problem (2) is zero, which characterizes a very small energy of elastic surface resistance over the square Ω under the assumption that for very thin microneedles there are no transverse displacements. This surface configuration should ideally be realized when using microneedle systems for drug delivery in the treatment of diseases in modern medicine.

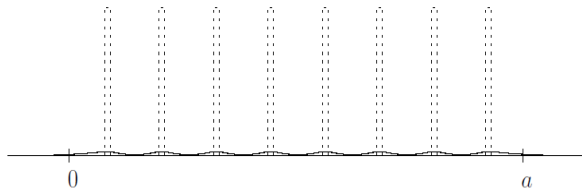


Fig. 2. The model of using a system of very thin microneedles

The fulfillment of these cases is not in doubt, since the latter is used in real medicine, and the first case can be visualized theoretically, for example, when we select as the sets β_{ij}^ε for $i, j = 1, \dots, N$ a circle of $r_\varepsilon = \varepsilon / 2$ radius. This visualization is shown in Fig. 1. Thus, there must be a case averaging the considered cases. The surface configuration for this case must be characterized by the averaged surface between the surfaces shown in Figures 1 and 2. This situation corresponds to case 2 of Theorem 1. The averaged surface can be calculated explicitly, for example, in the case when homogeneous Dirichlet boundary conditions in (1) are replaced by periodic boundary conditions in one of the coordinate directions. These calculations are given in [11]. In general, numerical methods can be used to calculate this surface.

Integral functional $F_l(u)$ from Theorem 1 is usually called *homogenized*, since the minimum of this functional approximates the minimum of the considered functional of problem (2) for sufficiently small ε or, which is equivalent by definition, for a sufficiently large number of microneedles in the system under consideration.

2. Independence of homogenized configurations from microneedle bases

It can be verified directly that the statements of Theorem 1 do not change for finite-proportional variation of the microneedle radius r_ε of the considered system. Indeed,

for the sets $\beta_{ij}^{1\varepsilon} \subset \beta_{ij}^{2\varepsilon} \subset \alpha_{ij}^\varepsilon$ for $i, j = 1, \dots, N$ defined as circles of the same radius $c_1 r_\varepsilon$ and $c_2 r_\varepsilon$ located in the center of suitable squares α_{ij}^ε for $i, j = 1, \dots, N$ conditions of the theorem hold or do not hold simultaneously for fixed constants c_1 and c_2 such that $c_1 \leq c_2 \leq 1$.

Moreover, it follows from results of book [12] and the theorem that statements of Theorem 1 are fulfilled simultaneously for the sets holding the inclusions $\beta_{ij}^{1\varepsilon} \subset \beta_{ij}^\varepsilon \subset \beta_{ij}^{2\varepsilon} \subset \alpha_{ij}^\varepsilon$ for $i, j = 1, \dots, N$ if the sets $\beta_{ij}^{1\varepsilon}$ and $\beta_{ij}^{2\varepsilon}$ for $i, j = 1, \dots, N$ defined as circles of the same radius $c_1 r_\varepsilon$ and $c_2 r_\varepsilon$ located in the center suitable squares. In other words, the fulfillment of statements of Theorem 1 does not depend on the shape $\beta_{ij}^\varepsilon \subset \alpha_{ij}^\varepsilon$ for $i, j = 1, \dots, N$ of needle base in the simplest system of microneedles, if it is possible to clamp this base between two circles $\beta_{ij}^{1\varepsilon}$ and $\beta_{ij}^{2\varepsilon}$ for $i, j = 1, \dots, N$ defined as circles of the same radius $c_1 r_\varepsilon$ and $c_2 r_\varepsilon$ located in the center of suitable squares for fixed constants c_1 and c_2 such that $c_1 \leq c_2 \leq 1$.

Indeed, it follows from [12] that for minimums $u_{1\varepsilon}^l$, u_ε^l , and $u_{2\varepsilon}^l$ corresponding to such shapes of microneedles bases in definition (1), which are used in the problem of minimization (2), the inequalities

$$u_{1\varepsilon}^l \leq u_\varepsilon^l \leq u_{2\varepsilon}^l$$

hold. Assuming the fulfillment of one of the conditions of the theorem and passing to the limit for $\varepsilon \rightarrow 0$, we conclude that these inequalities transform into equalities, which proves the above formulated independence of the theorem statements of the shape microneedle base. The ascertained independence of the given statements of the needle base shapes is caused, first of all, by microthickness of needles, located periodically and forming the considered systems. The given statements clarify also that systems with circular cylindrical microneedles have the most optimal parameters since they have optimal contact surface and the best transmission capacity.

Conclusion. Thus a new variational method of modeling and computation of the parameters of transdermal (hypodermic) injection of medicines on the use of a microneedle system is presented in the report. By the homogenization theory methods, we studied the problems of minimization for integral functionals with oscillating obstacles, which model the considered systems of microneedles. Such problems describe elastic resistance of surfaces on interaction with microneedle systems.

Invariance of the adduced statements from the shape of microneedle system base is proved. Such invariance is caused first of all by microthickness of needles located central-symmetrically and forming the considered microneedle systems. The given statements also show that systems with circular cylindrical microneedles are the most optimal since such needles have the optimal square of contact and the best transmission capacity for medicine injections at the treatment of various diseases.

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Апроксимації для задач оптимізації медичних систем мікроголок

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Системи мікроголок використовуються для трансдермальних (підшкірних) ін'єкцій ліків при лікуванні різних захворювань. Ефективність використання таких систем залежить істотно від розміру та параметрів мікроголок. Задача визначення таких залежностей і оптимальних параметрів розглянута як задача оптимізації взаємодії систем мікроголок з пружною поверхнею. Задачі мінімізації інтегральних функціоналів, розв'язки яких є апроксимаціями для розв'язків задачі взаємодії, отримані методами теорії осереднення. Такі задачі формулюються у вигляді класичних задач з перешкодами.

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