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Automated optimal design of wells for electromagnetic cell stimulation

Abstract. *In the paper, a device for in vitro electromagnetic stimulation of cells at low frequency (75 Hz) is considered. In particular, shape and position of a well-plate are identified in order to obtain a homogeneous stimulation and to maximize the space allotted to cell culture. To this end, the BiMO and μ-BiMO optimization algorithms, which have shown good performances in multi-objective optimization of electromagnetic devices, are applied.*

Streszczenie. *W artykule opisano urządzenie do elektromagnetycznej stymulacji komórek metodą in vitro z wykorzystaniem sygnału o niskiej częstotliwości (75 Hz). W szczególności rozważane były kształt i położenie płytki do hodowli komórkowej w celu uzyskania jednorodnej stymulacji i maksymalizacji przestrzeni obejmującej hodowlę komórkową. W tym celu zastosowano algorytmy optymalizacji BiMO i μ-BiMO, które umożliwiły optymalizację wielokryterialną urządzeń elektromagnetycznych. (**Zautomatyzowany optymalny projekt urządzenia do elektromagnetycznej stymulacji komórek**).*

Keywords: cell stimulation, force distribution, shape synthesis, multi-objective optimization.
Słowa kluczowe: stymulacja komórek, rozkład sił, synteza kształtu, optymalizacja wielokryterialna

Introduction

In the last decades, the electromagnetic stimulation *in vitro* and *in vivo* has become a promising research field because it allows to modulate the behaviour of cells and tissues. In particular, when the cells are exposed to a time-varying magnetic field, an electric field is induced and thus a current density arises, because the cell culture medium is conductive. The interaction between the induced current density and the time-varying magnetic field gives rise to mechanical stress acting on the cells [1]. In this paper, new kind of wells for obtaining a homogeneous stress and stimulation of a considerable large amount of cells are designed [2]. This design problem is formulated as a multi-objective one and its solution is found by means of the Biogeography-Inspired Multi-objective Optimization algorithms, BiMO [3,4] and the μ-BiMO algorithms [5]. These methods have shown to be successful for various applications [6-10]. In particular, when the forward problem requires a high computational time e.g. when Finite Element FE simulations are used, the μ-BiMO algorithm gave good results. In general, the aim of this study has been to design different optimally-shaped wells for electromagnetic stimulation of cells [11-15].

The forward problem

The electromagnetic stimulation of cells is done by means of the so-called “electromagnetic bioreactor” (Fig. 1), which is a device based on two solenoids connected in series and powered by a pulse generator (Igea, Carpi, Italy) at 75 Hz [11].

In order to simulate the electric E and magnetic B fields in the bioreactor, a 3D time-dependent finite-element model was implemented in MagNet, a commercial code by Mentor-Infolytica.

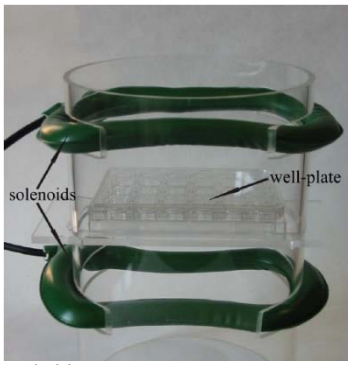


Fig.1. Electromagnetic bioreactor

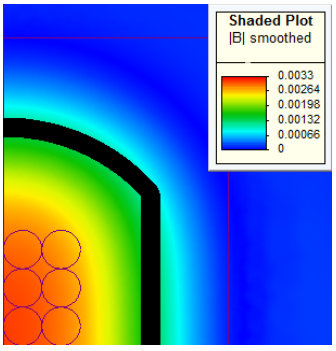


Fig.2. Magnetic induction field [T] distribution in the middle of the bioreactor

In the conductive regions, the electromagnetic problem is solved in terms of the phasors of the electric vector potential T and the scalar magnetic potential Ω according to:

(1) $$\overline{\nabla}^2 T - \mu\sigma\frac{\partial T}{\partial t} = -\overline{\nabla}\times J$$

(2) $$\nabla^2\Omega - \mu\sigma\frac{\partial\Omega}{\partial t} = 0$$

such that

(3) $$\overline{\nabla}\times T = J$$

and

(4) $$\overline{\nabla}\cdot T = \mu\sigma\frac{\partial\Omega}{\partial t}$$

where $J = J_0 + \sigma E$ is the source current density, with J_0 impressed current density and E electric field, μ is the magnetic permeability and σ the electric conductivity.

Hence the magnetic field H and the induced electric field E are calculated as follows:

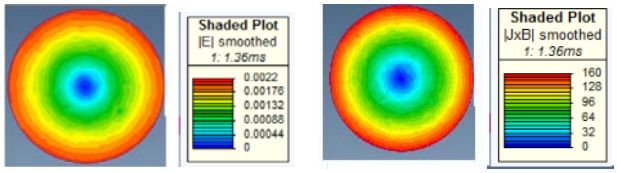
(5) $$H = T - \overline{\nabla}\Omega$$

(6) $$E = \sigma^{-1}(\overline{\nabla}\times T - J_0).$$

Once electric and magnetic fields are known, the mechanical stresses acting on the cells in the well can be calculated by means of the line integral of the divergence of the Maxwell's stress tensor, which reads:

(7) $$\overline{\nabla}\cdot\overline{\overline{T}} = \rho E - \frac{\varepsilon_0}{2}E^2\overline{\nabla}\varepsilon_r + J\times B + -\frac{\mu_0}{2}H^2\overline{\nabla}\mu_r + \mu\varepsilon\frac{\partial}{\partial t}(E\times H)$$

where ρ the volume charge density. The second and the fourth term at the right-hand side of eq (7) are related to electrostriction and magnetostriction effects, respectively. Because of the homogeneity of the fluid, it is possible to neglect them. Moreover, another remark can be put forward: let the term $J\times B$ be written as $\sigma\mu(E\times H)$ and let's note that in time harmonics regime condition the term $\mu\varepsilon\frac{\partial}{\partial t}(E\times H)$ is proportional to $\mu\varepsilon\omega(E\times H)$; because in low-frequency approximation one has εω<<σ, the last term of eq (7) can be neglected with respect to the third one.



a) b)

Fig.3. Induced electric field [V/m] (a) and $J\times B$ term [Nm^{-3}] (b), related to tangential and radial forces, respectively, acting on the well positioned at the center of the bioreactor.

After these remarks, only two terms can be considered in eq (7): ρE and $J\times B$; the term ρE gives rise to forces F_t tangentially directed with respect to the lateral surface of the well; in turn, the term $J\times B$ gives rise to radially directed forces F_r. It can be noted that the magnetic field distribution inside the bioreactor is non-uniform as shown in Fig. 2. Also, the induced electric filed is non-uniform (Fig. 3a). Therefore, non-uniform mechanical stresses F_t and F_r are originated in the wells (Fig. 3). For the sake of simplicity, considering a well placed at the center point of the bioreactor, the electric field distribution is symmetric according to annulus-shaped regions (Fig. 3): the thinner the annulus, the more homogeneous the stimulation. On the other hand, it is not practical to design very thin annulus-shaped wells, because it is usually necessary to stimulate a large quantity of cells.

The inverse problem

In order to design new wells for a homogeneous stimulation and allowing the stimulation of a large quantity of cells, the inverse problem can be stated as follows: find position and radii of the annulus-shaped well in such a way that the electromagnetic stresses are homogeneously distributed in the physiological fluid and, simultaneously, the space allotted to the well is maximized.

According to the shape synthesis problem, two design criteria are considered:

(8) f_1: R_{out}-R_{in},

to be maximized

(9) $$f_2 = \frac{E_{t,max} - E_{t,min}}{E_{t,ref}} + \frac{|J\times B_{max}| - |J\times B_{min}|}{|J\times B_{ref}|},$$

to be minimized.

The terms $E_{t,ref}$ and $J\times B_{ref}$ are the maximum values of force densities referred to the well set at the center of the bioreactor (Fig. 3) [2].

The optimization methods

For solving this problem, the μ-BiMO, an optimization algorithm found to be cost-effective, is applied. The μ-BiMO is a modification of the BiMO algorithm, which, in turn, is an extension of the BBO. The BBO algorithm is based on the process of natural immigration and emigration of species between small islands in the search for more friendly habitats, which is observed in nature. Each solution considered is treated as a habitat or island (design vector or individual in genetic algorithms) composed of suitability index variables (SIV, design variables), and each habitat exhibits a quality given by the habitat suitability index (HSI, objective function). The ecosystem, which is the whole set of islands or habitats, is progressively modified by means of two stochastic operators, i.e. migration and mutation: migration improves the HSI of poor habitats by sharing features from good habitats (exploitation step); in turn, mutation modifies some randomly selected SIV of a few habitats in view of a better search in the design space (exploration step). An appropriate balance between migration and mutation tunes the algorithm.

BBO algorithm has been widely used in the last decade as single-objective algorithm for different applications; in turn, in the last two years, it was extended to multi-objective optimisation problems (BiMO algorithm) [3,4], thanks to the concept of generalized fitness.

In this new version of BiMO, the role of small rocks in the migration of individuals is considered. As in reality the small rocks help immigrants to colonize islands that otherwise would not be reached, with the concomitant loss of the individuals who would never reach the ground, in the proposed method the rocks have the function not to waste habitats that otherwise would never characterize an ecosystem.

In particular, during the migration procedure it could happen that good habitats are replaced. To recover this, the discarded habitats are stored in a vector (rock vector) that tracks the habitats.

In BiMO, when the number of islands is very small, during the processes of immigration and emigration, the generation of duplicates is a frequent event. Instead of generating new habitats randomly, they are taken from the best habitats belonging to the rock vector.

The number of islands used for solving this design problem with μ-BiMO is equal to 5 and the stopping criterion is the maximum iteration number, set to 200. In turn, for BBO 20 islands have been used and the optimization has been stopped after 20 iterations.

Results

The results obtained are shown in Fig. 4. For the sake of a comparison, the results obtained by means of the well-known NSGA-II algorithm are reported [2].

For μ-BiMO, starting from 5 initial points, two non-dominated solutions are obtained. They are the two end-points of the approximated Pareto front.

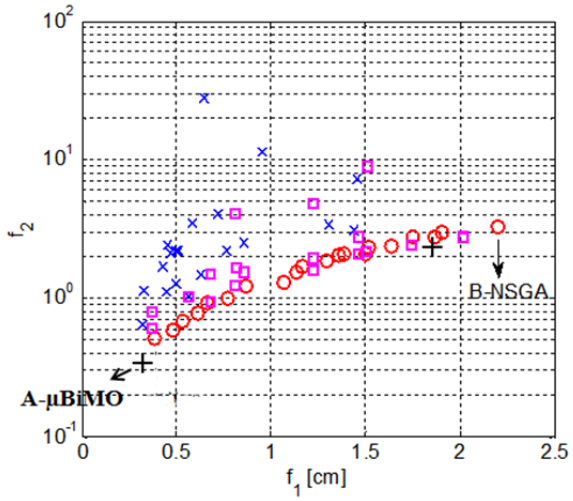


Fig.4. Results: starting points – cross, results NSGA-II – circle, results BiMO – square, results μBiMO – plus.

In Table I the two end-points of the approximated Pareto front are described in terms of design variables and objective functions.

Table I - Design variable [cm] and objective function values for two points highlighted in Fig. 4.

point	x	y	z	R_{out}	R_{in}	f_1	f_2
A-μBiMO	4.48	6.28	4.47	0.64	0.32	0.32	0.35
B-NSGA	2.88	2.63	3.39	2.5	0.3	2.2	3.29

In Figs. 5 and 6 the geometry and force density distribution of the two end-points of the approximated Pareto front found in Fig. 4 are shown.

The well represented by the A-μ-BiMO point shows a homogenous force distribution but allows the stimulation of a small amount of cells. On the other hand, the device of the B-NSGA point is larger, hence more cells can be stimulated with respect to the A-μ-BiMO device, while the stimulation is less homogenous with respect to the one of A-μ-BiMO device.

In Fig. 7 the end-points of the approximated Pareto front obtained by means of the μ-BiMO are represented at different iterations.

It can be notice that the results obtained with 80 iterations are very close to those obtained with 200 iterations. This demonstrates that the μ-BiMO algorithm is able to approximate the end-points of the Pareto front with 80 iterations and 5 islands i.e. 400 objective function calls.

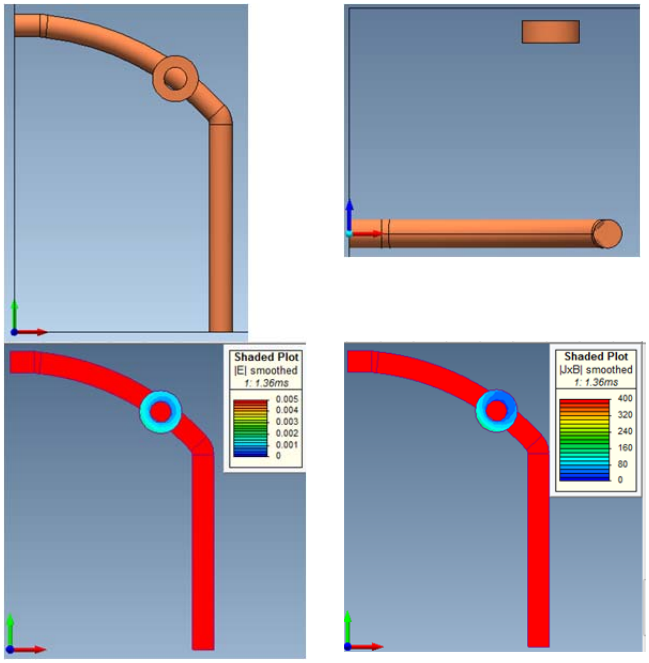


Fig.5. Optimal geometries and force density distribution of points A-μ-BiMO in Fig. 4.

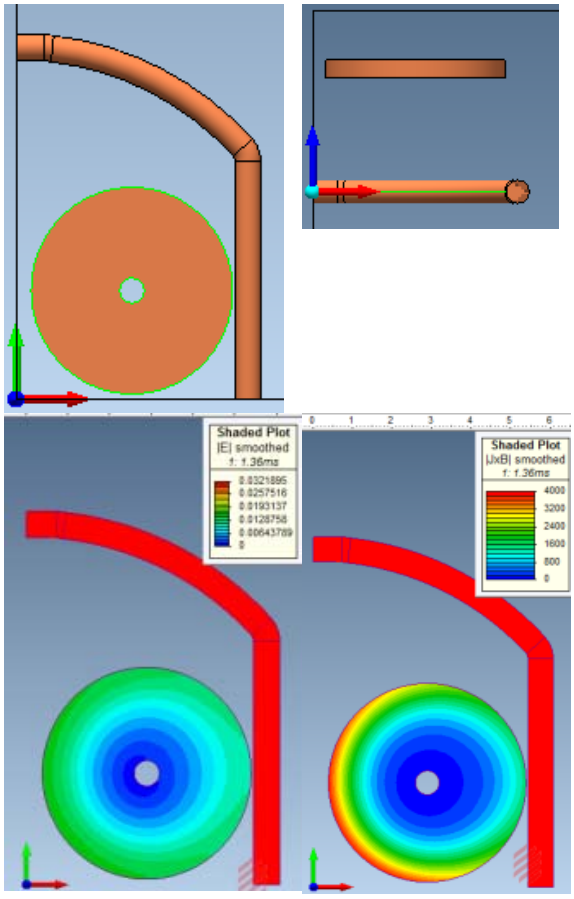


Fig.6. Optimal geometries and force density distribution of point B-NSGA in Fig. 4.

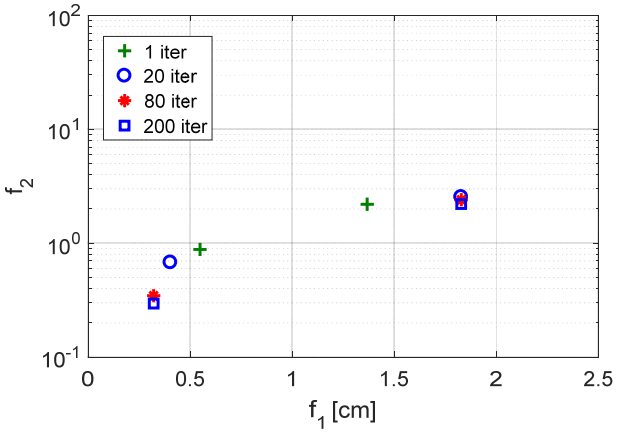


Fig.7. End-points of the approximated Pareto front, μBiMO method.

Conclusion

Different optimally-shaped wells for electromagnetic stimulation of cells have been designed. In particular, BiMO and μ-BiMO methods are applied, with reference to NSGA-II. All methods found non-dominated solutions. Among the latter, two end-points of the approximated Pareto front have been analyzed and discussed with respect to the application.

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