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Optimization of Scaffolds in Alginate for Biofabrication by Genetic Algorithms

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Abstract

With an increasing in the rate of transplants due to damaged or affected tissues or organs by accidents or diseases and also by the aging of the population in many countries as Brazil, have motivated the research of some novel and alternative ways focused on restoring and replacing tissues. Biofabrication by means of Rapid Prototyping techniques can help in the fashioning and final production of scaffolds devoted to support and stimulate the growth of new tissues. For soft tissues, a biomaterial known as Alginate has been studied and used as raw-material for scaffolds fabrication. A scaffold must guarantee good strength and stiffness at the same time the material degrades gradually. In this work, a single mathematical model experimentally obtained that describes an interesting mechanical behavior of the degradation of alginated-scaffolds is developed. The optimization process scheme using Genetic Algorithms to maximize the elastic modulus and therefore to aid the design of scaffolds in alginate is proposed. The optimization is very welcome to tissue engineering and Biofabrication.

Keywords: Genetic Algorithms (GAs), Scaffolds, Biofabrication, Tissue Engineering, Alginate.

1. Introduction

A Brazil’s recent picture of the 2008 waiting list for transplants, according to the Ministry of Health, reveals that there are more than 68,000 candidates waiting the availability of organs to therefore undergo a transplant. Based on those data, alternative methods of tissue and organ recovering have been studied and many developments have been proposed and applied successfully in the Tissue Engineering. Tissue Engineering as an interdisciplinary field combines the use of living cells with either natural or synthetic extra-cellular structures (scaffolds) to develop body parts or devices that will enable the restoration, maintenance or enhancement of living tissue and organs (Rezende et al., 2007a). Usually, the scaffolds have high porosity (macro-porosity), appropriate surface morphology (micro-porosity), large surface area, suitable pore size and highly connected pore structure. They must also be biocompatible and biodegradable. A variety of biodegradable and biocompatible hydrogels, as the alginate, have been used for Tissue Engineering. The alginate is one of the most popular materials due to its relatively low cost, natural origin and easy handling besides other physical properties advantages. Biofabrication is a new class of Rapid Prototyping that represents a group of non-conventional techniques with great potential to produce scaffolds with customised external shape and predefined internal morphology (Leong et al., 2003). These techniques also allow controlling both pore size and distribution. A scaffold must own very dynamical and adaptive characteristics in order to be implanted and to take its main roles which are to carry the stem live cells inside it, to back the growth of these cells and besides this to biodegradate appropriately since the minimum material should remain after the tissue is reconstructed. In this sense, it is fundamental to be aware of the mechanical and chemical properties since the scaffold must guarantee good strength and stiffness at the same time the material degrades gradually. To know how the mechanical behavior of the scaffold will be, some time later, is the keyword. And the understanding about the match between biodegradation and young modulus is mandatory. The present and future of biomedical materials development requires this degree of control prediction in the design, synthesis, and function of next-generation materials. A prediction job is possible and it has already been used so that the scaffold state can be forecasted before its fabrication and, as a good alternative, to know how and how much alginate should be used. Other future analyses can be around the best geometry to be adopted during rapid prototyping technique actuation. This paper presents a single mathematical model experimentally obtained that describes an interesting mechanical behavior of the degradation of alginated-scaffolds. The deal of this work is the optimization of scaffolds in alginate making use of Genetic Algorithms (GAs). GAs represent a class of stochastic optimization procedures based on natural systems according to Darwin's observations. GAs have been successfully applied to a range of problems and have characteristics of easiness of implementation and capability of escaping local optimal solution. The objective of GA is to find out the best values of alginate amount for scaffold fabrication that maximize the elastic modulus.

2. Optimization Problem Formulation

The aim of the optimization is to determine optimal features for the fabrication of optimized alginate scaffolds for Tissue Engineering. The optimization objective in this work is to find out optimal values of alginate composition and initial porosity in order to fabricate scaffolds with, at a pre-determined time, a high mechanical behavior (elastic modulus), since those parameters are two of the most important ones and they need to be well combined in order to reach the best value for the elastic modulus. Then, the optimization problem can be written as:

$$\begin{aligned} &\underset{[\alpha,\phi_0]}{\text{Maximize}} && E(\phi_0,\alpha,t) \\ &\text{Subject to:} && 1\% \leq \alpha \leq 8\% \\ & && 30\% \leq \phi_0 \leq 80\% \end{aligned} \tag{1}$$

where E is the elastic modulus (shear effects are not considered), α is the alginate composition and ϕ_0 is the initial porosity.

The variation of the mechanical properties of alginate is due to degradation and porosity changes. The degradation of alginate structures was determined through the analysis of the shrinkage variation along time as shown in Figure 1 (Rezende et al., 2007a):

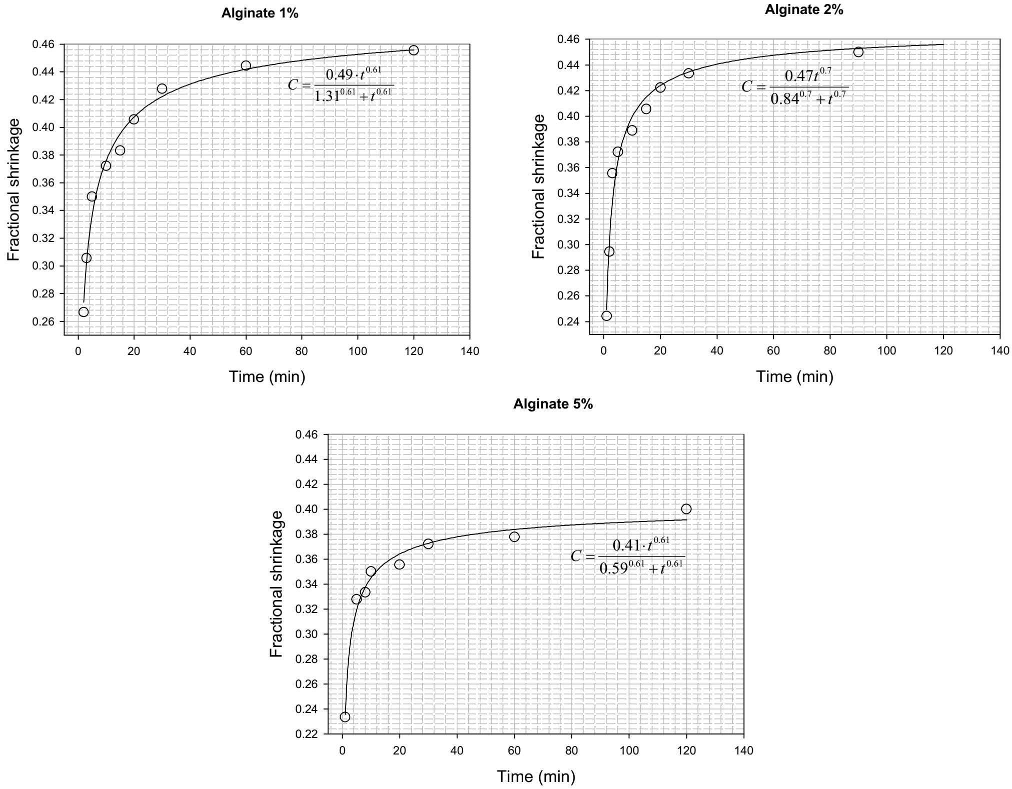

Figure 1 – Fractional shrinkage along time for different alginate compositions (1%, 2%, 5%).

There are various studies modeling tissue scaffolds behaviors in the literature (Nair et al., 2008). In the present case, a sigmoidal model of three parameters represents the shrinkage process that is given by the following equation:

$$C(\alpha, t) = \frac{\varsigma(\alpha) \cdot t^{\vartheta(\alpha)}}{\lambda^{\vartheta(\alpha)} + t^{\vartheta(\alpha)}} \tag{2}$$

where t is the time and $\varsigma, \vartheta, \lambda$ are variables that depend on the alginate composition (α). Porosity at each time is also a function of alginate composition and shrinkage:

$$\phi(\phi_0, \alpha, t) = \phi_0 + \zeta(\phi_0, \alpha) \cdot C(\phi_0, \alpha, t) + \psi(\phi_0, \alpha) \cdot C^2(\phi_0, \alpha, t) \tag{3}$$

where ζ, ψ are constants depending on alginate composition and C is the shrinkage.

The dependence between the elastic modulus and porosity for different alginate compositions is given by the following equation:

$$E(\phi_0, \alpha, t) = E_0(\phi_0, \alpha) + k_1(\phi_0, \alpha) \cdot \phi(\phi_0, \alpha, t) + k_2(\phi_0, \alpha) \cdot \phi(\phi_0, \alpha, t)^2 + k_3(\phi_0, \alpha) \cdot \phi(\phi_0, \alpha, t)^3 \tag{4}$$

with E_0 being the initial elastic modulus, k_1, k_2, k_3 constants dependent on both the alginate composition and the initial porosity and ϕ the final porosity of the scaffold.

The optimization problem presented on Equation 1 is a single constrained optimization problem. In this paper, two cases of constraints are considered: constraints at shrinkage and final porosity: 1) shrinkage higher than 25% and 2) final porosity higher than 80%.

In order to solve the constrained optimization problem, a constraint handling method based on the penalty function approach was used, not requiring any penalty parameter (Rezende et al., 2007b). In this case, the expression of the fitness function for a minimization problem, where infeasible solutions are compared based only on their constraint violation, is given by the Equation 5:

$$F(\mathbf{x}) = \begin{cases} f(\mathbf{x}) & \text{if } \mathrm{g_j}(\mathbf{x}) \geq 0 \;\; \forall \mathrm{j=1,2,...,nc} \\ f_{\max} + \sum_{j=1}^{m} \langle g_j(\mathbf{x}) \rangle & \text{otherwise} \end{cases} \qquad (5)$$

where $f_{\max}$ is the objective function value of the worst feasible solution in the population.

3. Optimization of Scaffolds using GAs

The Genetic Algorithms approach starts with a random population of chromosomes that are a set of solutions for the optimization problem. Traditionally, solutions are represented in binary as strings of 0s and 1s, but other encodings are also possible. In each generation, the fitness of every individual in the population is evaluated, multiple individuals are stochastically selected from the current population (based on their fitness), and modified (recombined and possibly randomly mutated) to form a new population. The new population is then used in the next iteration. Usually, the algorithm terminates when either a maximum number of generations has been produced, or a satisfactory fitness level has been reached for the population.

The Genetic Algorithm used in this research work to solve the scaffolds optimization problem is a Fortran binary code. The employed genetic operators are the tournament selection, the uniform crossover, the creep and the jump mutation. Niching and elitism are also employed. The input parameters, chosen by a trial and error method, are indicated in Table 1.

Table 1 - The GA input parameters.

GA input parameters	Value
Population size per generation	50
Maximum number of generations	30
Crossover probability	0.60
Jump mutation probability	0.077
Creep mutation probability	0.077
Initial random number seed for the GA run	-1000

The following results of the scaffolds optimization using Genetic Algorithms for constrained problem considering two cases of constraints are presented.

3.1. Constraint 1: Shrinkage > 25%

In this case, the objective of the optimization problem is to maximize the elastic modulus subject to a shrinkage higher than 25% and 2) final porosity higher than 80%. The results obtained for this case are shown in Table 2:

Table 2 – Optimization results for the constrained problem (shrinkage > 25%)

Optimization Variables	Initial Alginate composition (%)	7.06
	Initial Porosity (%)	30.00
Objective Function	Elastic modulus (KPa)	17.52
Constraint	Shrinkage (%)	25.22
Output Variable	Final Porosity (%)	70.97

Figure 2 shows the evolution of the objective function along all the generations. Figure 3 presents the obtained profile of the objective function from the best combination of the optimization variables at each generation. The output variables (shrinkage and final porosity) dependent on the best combination are also indicated.

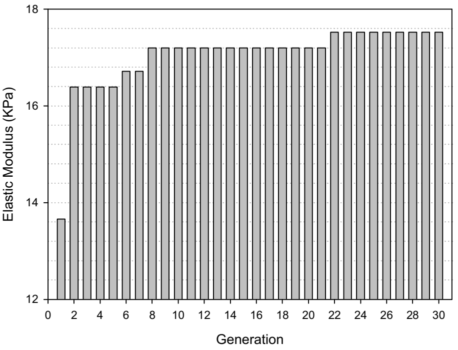

Figure 2 – Evolution of the elastic modulus along all the generations (shrinkage > 25%).

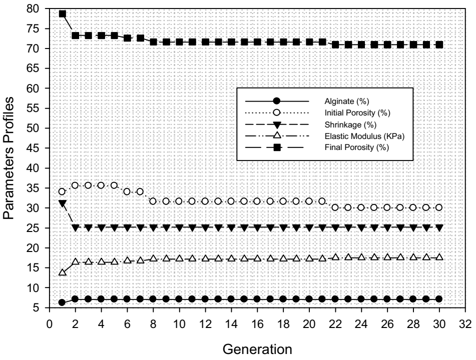

Figure 3 – Profiles of the objective function, shrinkage and final porosity obtained with the best values of the optimization variables at each generation (shrinkage > 25%).

3.2. Constraint 2: Final porosity > 80%

In this case, the objective of the optimization problem is to maximize the elastic modulus subject to a final porosity higher than 80%.

Results obtained for this case are shown in Table 3:

Table 3 – Optimization results for the constrained problem (final porosity > 80%).

Optimization Variables	Initial Alginate composition (%)	5.79
	Initial Porosity (%)	32.38
Objective Function	Elastic modulus (KPa)	12.99
Output Variable	Final Porosity (%)	80.01
Constraint	Shrinkage (%)	33.29

Figure 4 shows the evolution of the objective function along all the generations. Figure 5 presents the obtained profile of the objective function from the best combination of the optimization variables at each generation. The output variables (shrinkage and final porosity) dependent on the best combination are also indicated.

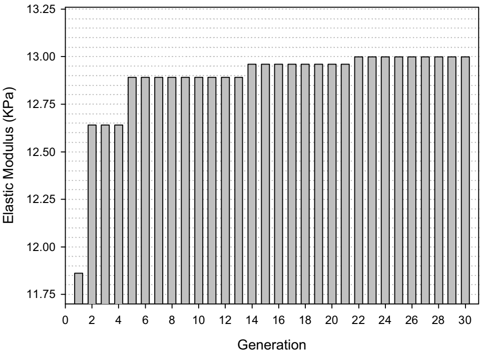

Figure 4 – Evolution of the elastic modulus along all the generations (final porosity > 80%).

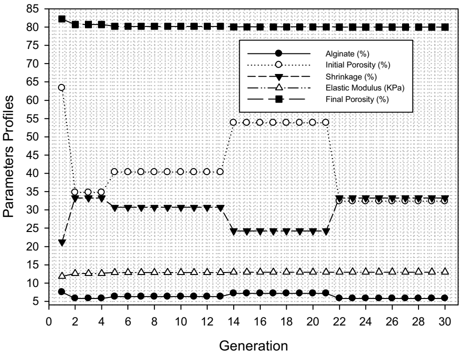

Figure 5 – Profiles of the objective function, shrinkage and final porosity obtained with the best values of the optimization variables at each generation (final porosity > 80%).

Observing the two cases presented, it can be seen that the constraints were respected. In spite of the obtained value of young modulus, the order of this value is compatible with results found in the literature (Khalil, S.E.D., 2005). Throughout this study is incipient and new boundaries and adjustments need to be done. One of the main characteristics of the alginate-scaffold is to degradate along the time where the growing of final porosity indicates this phenomenon. The Initial Alginate composition (α) is the real range that has been used experimentally.

4. Conclusions

This research employs Genetic Algorithms to optimize the mechanical behavior of alginate scaffolds for Biofabrication. The mathematical model was experimentally obtained and the best values for both alginate composition and initial porosity of the scaffold allowing the constrained maximization of the elastic modulus were determined through the optimization by Genetic Algorithms.

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