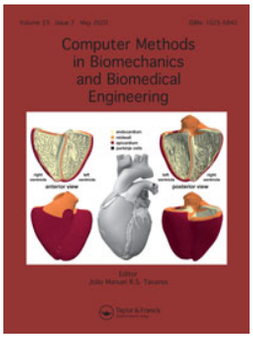

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Optimizing neotissue growth inside perfusion bioreactors with respect to culture and labor cost: a multi-objective optimization study using evolutionary algorithms

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ABSTRACT

Tissue engineering is a fast progressing domain where solutions are provided for organ failure or tissue damage. In this domain, computer models can facilitate the design of optimal production process conditions leading to robust and economically viable products. In this study, we use a previously published computationally efficient model, describing the neotissue growth (cells + their extracellular matrix) inside 3D scaffolds in a perfusion bioreactor. In order to find the most cost-effective medium refreshment strategy for the bioreactor culture, a multi-objective optimization strategy was developed aimed at maximizing the neotissue growth while minimizing the total cost of the experiment. Four evolutionary optimization algorithms (NSGAII, MOPSO, MOEA/D and GDEIII) were applied to the problem and the Pareto frontier was computed in all methods. All algorithms led to a similar outcome, albeit with different convergence speeds. The simulation results indicated that, given the actual cost of the labor compared to the medium cost, the most cost-efficient way of refreshing the medium was obtained by minimizing the refreshment frequency and maximizing the refreshment amount.

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Multi-objective optimization; evolutionary algorithms; bone tissue engineering; 3D scaffold; labor cost

Introduction

Despite the elaborate ongoing research efforts, the tissue engineering (TE) field still faces many challenges, several of those related to the translation of TE products from the laboratory to the patient (Srijaya et al. 2014; Steeves 2015). One of the main challenges in TE applications is the economic costs associated with the process of creating living implants (Salter et al. 2011). Another major challenge is the translation of the complex biological systems into robust manufacturing processes.

Computer modeling is an enabling technology that can contribute to tackling the challenges faced in the TE community (Geris et al. 2016). One such example is computational models of bioreactor processes that can be used to define optimal operating conditions, e.g. in terms of nutrient concentration and medium refreshment rate (Guyot 2015; Guyot et al. 2015; Hossain et al. 2015; Mehrian et al. 2018). In previous work by the authors, a mechanistic computational model was developed describing the neotissue growth in perfusion bioreactors, taking into account influences of geometry, flow-induced shear stress, oxygen, glucose, lactate and pH (Guyot 2015). A reduced version of this model was developed to decrease the computational costs associated to the model and to allow for rigorous optimization procedures to be executed without running into computational challenges (Mehrian et al. 2018; Olofsson et al. 2019).

Evolutionary algorithms are a class of non-gradient metaheuristic methods that have gained popularity for optimization in a vast array of problems. Examples of evolutionary algorithms include, but are not limited to, genetic algorithms (GA), particle swarm optimization (PSO) and differential evolution (DE) (Eberhart and Shi 1998; Panduro et al. 2009). Evolutionary algorithms are suitable for non-costly (in terms of time per function evaluation) objective functions because they browse the entire input space, starting from a random initial population without considering the time for each function evaluation. In many optimization studies, conflicting objectives have to be reconciled in a multi-objective optimization (MOO)

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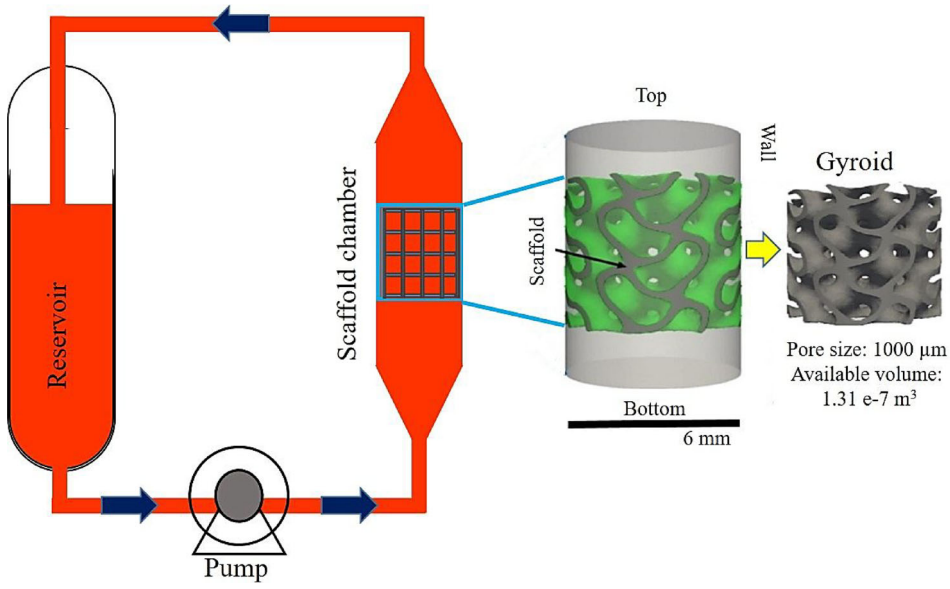

Figure 1. Schematic representation of the perfusion bioreactor and the scaffold used in this study. The green volume inside the Gyroid scaffold (center) represents the neotissue (cells and their extracellular matrix).

problem (Hwang and Masud 1979). In the literature, there are numerous examples in biopharmaceutical manufacturing domain where MOO is used to find a trade-off between the yield and the cost of a process or where MOO is used to find a trade-off between effectiveness of therapy and drug-induced side-effects. Dedieu et al. (2003) and Kim and Smith (2004) used a multi objective genetic algorithm (MOGA) approach for designing environmental friendly and economically affordable processes for waste solvent (acetic acid) recycling from aqueous waste mixtures with the aim of maximizing the total profit and minimizing the potential environmental impacts. In the study by Petrovski and McCall (2001), the authors used a PSO technique for the MOO of cancer chemotherapy with the aim to maximize the damage to the tumor cells while restricting the side effects of the drug. In the study by Heris and Khaloozadeh (2011), a non-dominated sorting genetic algorithm II (NSGA II) was used to find the optimal strategy for HIV therapy with the aim to minimize the drug usage and maximize the quality of the treatment.

In this study, we work with a previously published model (Mehrian et al. 2018) to optimize neotissue growth inside a 3D scaffold in a perfusion bioreactor set-up using evolutionary algorithms. The objective is to optimize the bioreactor culture strategy, in terms of the frequency of medium refreshment and fraction of medium to be refreshed at each refreshment step, maximizing neotissue growth while minimizing the cost of labor and medium consumed during the culture period. We will first apply GA, PSO and DE in a single objective optimization procedure, focusing only on maximizing the biological output (scaffold filling). This is followed by a MOO taking into account also the cost of labor and the culture medium, comparing the performance of four different evolutionary algorithms. This study shows how well-known optimization algorithms and computer modeling can help to reconcile conflicting objectives in the manufacturing process of TE constructs.

Methods

Summary of the neotissue growth model

The neotissue growth model describes the production of extracellular matrix by cells seeded onto a 3D scaffold cultured in a perfusion bioreactor set-up as depicted in Figure 1. As the neotissue starts growing in the scaffold over time, cells consume more nutrient (e.g. glucose and oxygen in the model) and produce lactate (a waste product). The model that describes this process, as detailed in the work by Mehrian et al. (2018), is a system of four ordinary differential equations that describe the evolution over time of a homogenized neotissue volume, curvature and shear stress (the latter two both in function of the homogenized neotissue volume) as well as the levels of oxygen, glucose and lactate (pH) in the scaffold. Model and implementation details are provided in the Supplementary Material. The simulation results were corroborated by comparison with results obtained from a first-principles based 3D mechanistic model

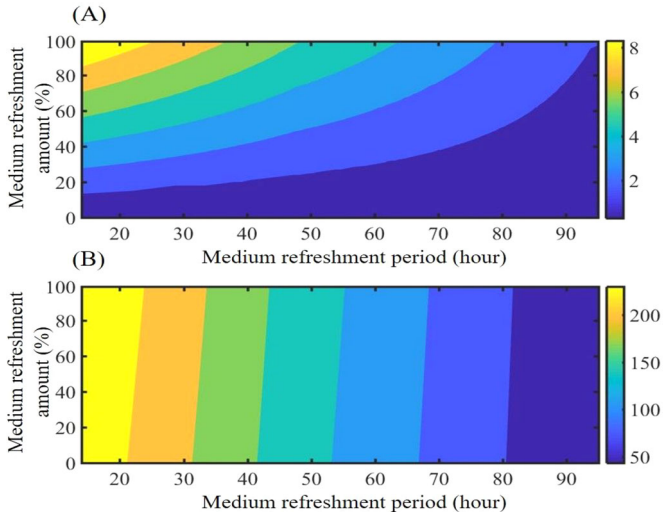

Figure 2. Culture costs over a 21 days culture period. (A) Cost of culture medium in function of the medium refreshment time (hour) and amount (%). (B) Costs of labor and culture medium using different combinations of medium refreshment time (hour) and amount (%). Colors represent the cost in euro (€).

(Guyot 2015) as well as with experimental results (Sonnaert et al. 2017).

Objective functions

The first step in running an optimization study is the definition of the objective function, detailing the overall aim(s) of the optimization process, in function of the design variable(s), being the parameter(s) that can be altered to arrive at an optimal solution.

In this study, the two design variables are refreshment period (p) that ranges from 12 h to 96 h and refreshment amount (a), varying between 0% and 100%.

The first objective function in our study is the neotissue filling percentage inside the scaffold that we try to maximize during the culture period. The second objective function is the total cost of culture, including the cost of the medium and the labor costs. Equation (1) expresses the calculation of the costs of the culture medium and the labor

$$C = M\left(1 + \frac{24d}{p}.a\right) + L\left(1 + \frac{24d}{p}\right). \quad (1)$$

In this equation, C is the total cost of the experiment, d is the total amount of days of the experiment, p is the refreshment period and a is the fraction of medium being refreshed each time ($0 \leq a \leq 1$). The first term is related to the costs of the medium. The medium composition used in the experiments on which our model is based is as follows: Dulbecco's modified Eagle's medium with high-glucose medium (Invitrogen) containing 10% fetal bovine serum (BioWhittaker), 1% sodium pyruvate (Invitrogen) and 1% antibiotic–antimycotic (100 units/mL penicillin, 100 mg/mL streptomycin and 0.25 mg/mL amphotericin B; Invitrogen). Taking current commercial prizes, the cost of the aforementioned medium composition is 26.11 €/L. The bioreactor system contains 13 mL of culture medium in total, of which 10 mL is located in the reservoir and 3 mL in the circuit (Sonnaert et al. 2017).

In Equation (1), $M = 0.2611$ € as we use 10 mL of the medium for a complete medium refreshment. The second term in Equation (1) is related to the labor costs. One medium exchange step takes an experienced lab technician about 15 min, which translates into 6.8 € per medium exchange ($L = 6.8$). As the only parameter affecting the labor cost is the frequency of refreshments (p), parameter a is eliminated in the second term in Equation (1). Figure 2A shows the cost of the culture medium only ($L = 0$), in function of the design variables. Figure 2B depicts the total experimental cost of a 21-day experiment as proposed in Equation (1).

As it is depicted, increasing the medium refreshment period results in a cheaper outcome (dark blue region in Figure 2B), as it decreases the labor cost and the labor cost is dominating the total cost in this study ($L > M$). Figure 2A shows only the medium cost, shifting the expensive region toward the top-left corner with high medium refreshment amounts and a low medium refreshment period.

Optimization techniques

As mentioned earlier, we will focus on the use of multiple optimization algorithms. In the following, we

briefly introduce the different types of optimization techniques used in this study for single and MOO. In MOO, the goal is to reach a compromise between conflicting objectives. Two common ways to deal with MOO are the 'weighted sum approach' and the 'Pareto front'. In the first approach, a single aggregated objective function is created using a weighted sum of the functions $f_s(x) = \sum_{i=1}^{m} \lambda_i f_i(x)$ (Zadeh 1963) with λ_i being the weights and f_i being the functions. This method is easy to apply but the choice of weights introduces a new challenge to the problem. The second approach is computing the Pareto-frontier (Horn 1997). Pareto optimality is a state in which it is impossible to improve the value of one objective function without worsening the value of the other. Alternatively stated, we are looking for the border between infeasible and suboptimal in our problem. In order to apply these techniques to the problem at hand and obtain the Pareto front, we used the Platypus package in python (Hadka 2015).

Single objective optimization

GA and other related evolutionary strategies such as PSO belong to the class of non-gradient methods which was first introduced by Holland (1975) and has been growing in popularity over the past years. The basic idea in GA is inspired from biology and based on the mechanisms of natural selection. Each parameter in GA, (x_i), represents a gene (real number or string of bits). The corresponding genes for all parameters, $x_1, \ldots, x_n$, form a chromosome (called individual). Each individual is a candidate for the solution of the problem. To initialize the GA algorithm, we start from multiple guess points forming the initial population. All the individuals will be evaluated using the objective function. In the next step, the best individuals (yielding maximum output) are selected for mating by combining genes from parents to produce children (offspring) through natural operator (cross over) evolving to a new, better fitting population. Finally, the newly created population (children) is added to the population where some mutations are randomly performed. This procedure continues until the population has converged or a predefined maximum number of generations has been reached.

PSO is a more recent approach inspired by the choreography of a bird flock. PSO was first introduced by Kennedy (1995) and has been found to be successful in a wide variety of optimization tasks (Kennedy 2006). PSO solves a problem by creating a random population of candidates called 'particles'. Each particle moves in the search space based on its position and velocity, following a mathematical formula. The movement of the particles is influenced by their local best-known positions, i.e. the position of that specific particle leading to the lowest/highest objective function value, as well as the global best-known position found by any of the particles in the total population. The velocity of each particle updates according to its distance from the best-known positions. Same as in GA, this process is repeated until the population converges or the algorithm reaches the maximum number of iterations.

DE is an evolutionary algorithm, which uses the difference of solution vectors to create new candidate solution. DE was originally introduced in 1997 (Storn and Price 1997). In this method, new candidate solutions (called agents) are created by combining existing solutions according to a simple formula. Then, solutions with the best fitness will be kept for the next generation. Same as previously introduced evolutionary methods, the optimization problem is treated as a black box without needing the gradient of the objective function.

Multi-objective optimization

For the MOO problem tackled in this study, an extended version of the aforementioned algorithms is used, being SMPSO, NSGAII and GDEIII. Speed-constrained multi-objective PSO (SMPSO) is a more advanced method compared to the basic PSO. In this method, the maximum velocity of particles in the search for new solutions is limited which has been shown to enhance the search capability of the technique and to improve the overall performance (Nebro et al. 2009). Nondominated sorting genetic algorithm II (NSGA-II) is an extension of the GA for multiple objective function optimization. One of the advantages of NSGAII compared to its predecessors is the reduced computational complexity (Deb et al. 2002). Generalized Differential Evolution (GDEIII) is an extension of the DE method for MOO problems. GDEIII results in better distributed solutions compared to earlier GDE versions (Kukkonen and Lampinen 2005).

A fourth MOO is added, being the multi-objective Evolutionary Algorithm Based on Decomposition (MOEA/D) that was first introduced in 2007 by Zhang and Li (Zhang and Li 2007). In this method, the decomposed objective functions (subproblems) are solved simultaneously by evolving a population of solutions. Each subproblem is optimized only using the information from its neighbor subproblems which

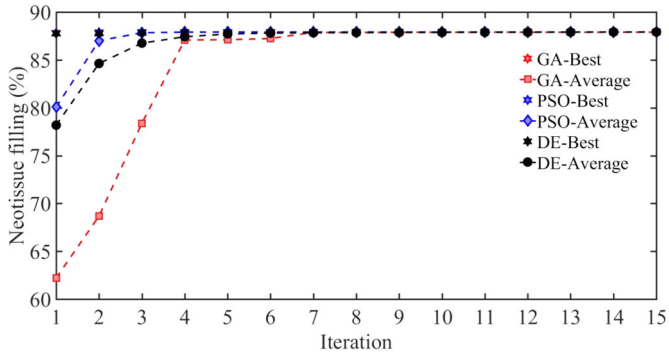

Figure 3. The best (star) and average (dashed lines) filling percentage in each iteration using PSO (blue), GA (red) and DE (black). The best solution in each iteration (star) for all three techniques completely overlaps each other.

makes the MOEA/D method more efficient in terms of computational complexity in each generation compared to some other methods such as non-dominated sorting genetic algorithm (NSGA).

Results and discussion

Single objective optimization: neotissue filling percentage

For finding the best refreshment amount and refreshment period of the medium in the bioreactor, the GA, PSO and DE methods were used. The initial population was set to 10 individuals and the optimization procedure stopped after 15 iterations as convergence was reached in all methods after a few iterations. Figure 3 shows the best and average filling percentage in each iteration over 15 iterations.

For each iteration, the best value (shown by star) and the average value of the whole population are shown (dashed line). As it is depicted, PSO and DE converged toward the best value (dashed blue and black lines) in each iteration faster than GA. The convergence rate of PSO was slightly better than DE. The high speed of convergence in PSO compared to GA has also been shown in the literature (Hassan et al. 2005; Li et al. 2010). All three algorithms converged to the maximum filling percentage, which is around 88%, after seven iterations. The optimal solution (refreshment time and amount) proposed by all three methods indicated that increasing the refreshment frequency and amount will result in the highest filling percentage. This is in line with previous studies (Mehrian et al. 2018; Olofsson et al. 2019), where we have shown using Bayesian optimization that an optimum region for refreshing the medium exists by keeping the refreshment period less than 40 h and the refreshment amount more than 70 percent (top-left region in Figure 2A), resulting in more than 85% filling.

Multi-objective optimization

For balancing the conflicting objectives of maximal neotissue formation and minimal cost, we compared the results of the four algorithms introduced earlier: MOEA/D, NSGAII, SMPSO and GDEIII. Each algorithm was run for 50, 100 and 1000 generations with the population size of 50. In order to be able to compare and evaluate the obtained Pareto front from each algorithm, we needed to first determine a global Pareto front (Van Veldhuizen and Lamont 1999). In this study, the global Pareto front was obtained by running the objective function 10^6 times. Figure 4 shows the results of the MOO using different approaches.

As it is depicted, the best result (closest to the global Pareto shown in the dashed black line) is obtained using 1000 generations (green line). One of the main features of a good Pareto front is that the proposed solutions cover the whole feature space as is the case for the black and green lines where they contain very cheap to very expansive solutions. For example, the generated Pareto front using 50 iterations (blue line) in SMPSO method (Figure 4C) does not include very cheap solutions where the neotissue filling is less than 60%. Furthermore, it could not find solutions in the top-left corner which is the most desirable area in our problem where the best trade-off between our conflicting objectives could be found. The results using 100 iterations (red line) in all of the four approaches are better than the blue generated lines as the algorithm had more time to evolve toward the best feasible solutions. The red lines (100 iterations) generated by the SMPSO (C) and GDEIII (D) methods are better compared to the other two methods as their performance is very close to the green (1000 iterations) and black line (global Pareto). The fastest converging method is the GDEIII method (Figure 4D), where the generated Pareto using only 50 iterations (blue line) is very similar to the global Pareto (black line).

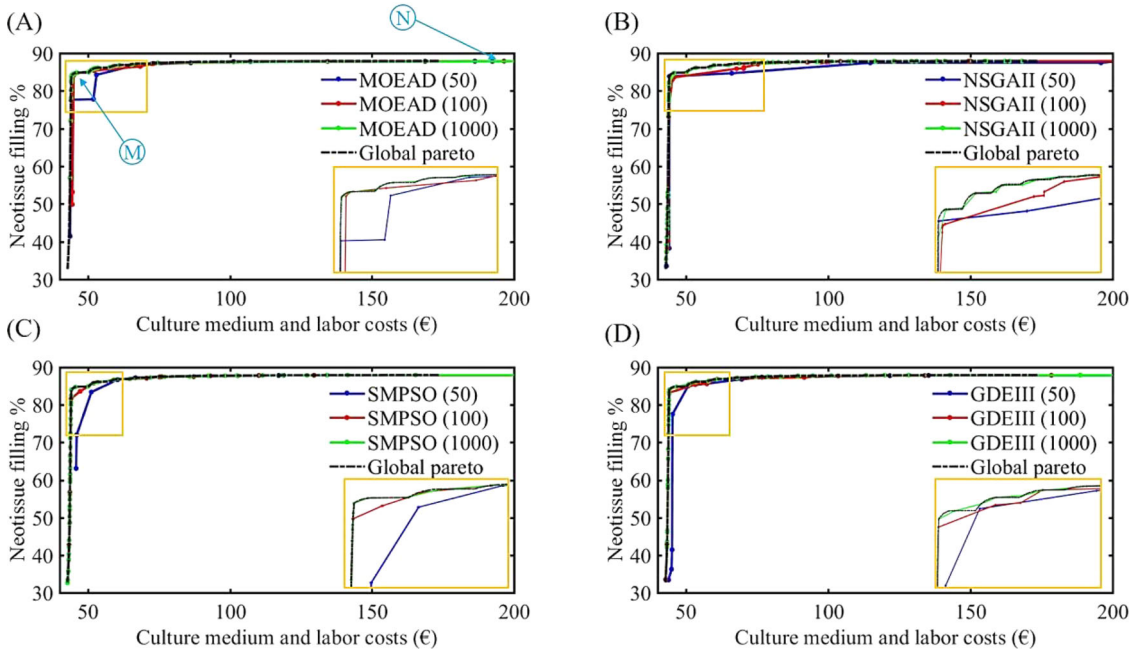

Figure 4. The Pareto front obtained from (A) MOEA/D, (B) NSGAII, (C) SMPSO, (D) GDEIII algorithms using 50 generations (blue line), 100 generations (red line), 1000 generations (green line) and the global Pareto front (black line). The green and black lines are fully overlapping. Point M shows the knee region which is the best answer to the problem. Point N shows a very expensive solution to the problem.

In the Pareto front, there are multiple optimum spots, each of them corresponding to a different refreshment time and amount. The user/decision maker has to decide, based on certain preferences and objectives, which individual solution is preferred to the others. In the absence of a decision maker, there exist special regions on the obtained Pareto front known as the 'knee regions' where the maximal trade-off between different objectives occurs. According to the obtained Pareto fronts, the best answer to the problem could be the turning point in Figure 4 (knee-region, point M) which results in 84.5% filling at a cost of 46 euros, and corresponds to refreshing the medium every 90 h by 99%. Going further to the right on the Pareto front will make very little improvement to the neotissue filling percentage while it dramatically increases the costs. For example, 88% filling (Figure 4A, point N) could be reached by refreshing the medium every 18 h by 88%, resulting in a cost of 196 euro, which is economically unjustifiable in comparison to point M.

Figure 5A shows the corresponding refreshment time and amount for each of the four Pareto fronts using 1000 generations and the global Pareto front. In order to investigate the effect of medium costs on the generation of optimal points, labor cost is neglected ($L = 0$) in Figure 5B.

In order to reduce the labor cost, which is the dominant cost among the two cost sources, most of the non-dominated points leading to the best result are selected by maximizing the refreshment time, which leads to less frequent medium exchange by the operator (Figure 5A). The optimum point in our problem resulting in 84.5% filling is shown by point M in Figure 5A. Moving toward the left of the optimum point will slightly increase the filling percentage (maximum increase 3.5%) and at the same time increases the total cost of the experiment. Whereas moving toward bottom from the optimum point in Figure 5A will decrease the filling percentage and at the same time decreases the total cost of the experiment. In Figure 5B, as the labor cost is not considered, increasing the frequency of the refreshment does not make the experiment more expensive. Therefore, many points are chosen on the horizontal axis, corresponding to very little refreshment amounts, whereas in Figure 5A, no points are situated on this axis.

Choosing the proposed refreshment strategy by the Pareto front (every 90 h by 99%) could result in inhomogeneous neotissue growth inside the scaffold. As the cells start growing inside the scaffold, they consume more nutrients (glucose in the model) and produce more lactate, which makes it necessary to refresh the medium more often. Especially during the final days of the culture, refreshing the medium every 90 h could be harmful to the cells as neotissue growth is at its peak resulting in a rapid decrease of the pH due to the cells' increasing lactate production.

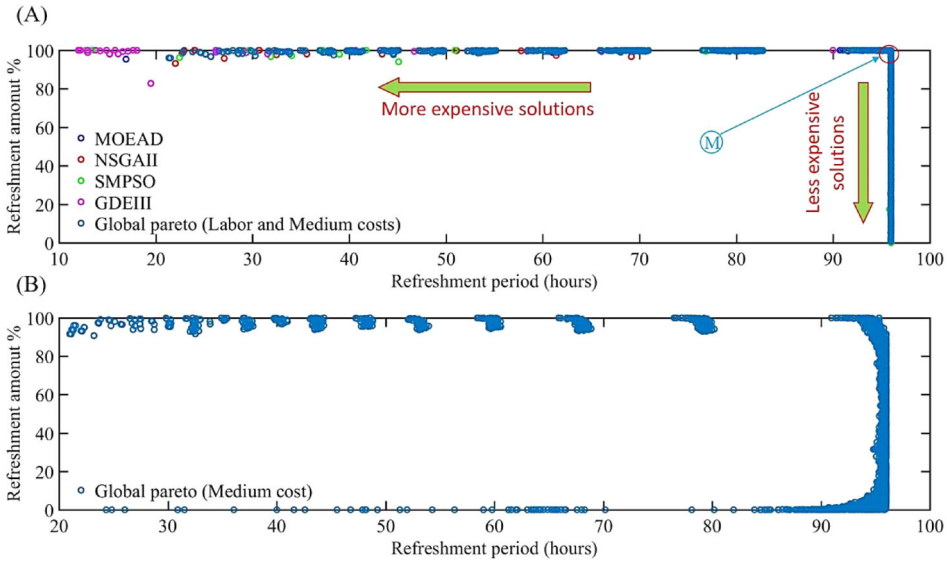

Figure 5. (A) Corresponding refreshment time and amount for each of the four optimization methods using 1000 generations and the global Pareto front. (B) Corresponding refreshment time and amount of the global Pareto front considering only the cost of culture medium.

Therefore, the proposed refreshment strategy needs to be investigated in laboratory experiments to verify the model predictions and if needed, we have to sacrifice the cost and choose a refreshment strategy with more frequent refreshments which would reduce the risk of harming the cells during the culture period. Another way of tackling this issue is to add a constraint for the pH value in the optimization procedure and therefore, refresh the medium when the pH value in the medium goes below a certain threshold.

To date, in the field of TE, most of *in vitro* bioreactor cultures settings have been (and are being) determined based on trial and error without considering the costs of the experiment. The availability of computational models is an advantage for determining the most cost-effective refreshment strategy before conducting laboratory experiments. In this study, we have used evolutionary algorithms for finding the best trade-off between culture costs and neotissue growth in a perfusion bioreactor. Note that currently, the medium refreshment strategy in our laboratory is based on historic developments with a medium change every 48 or 72 h by 100%. These settings result in a cost of 81.2 € and 56.4 €, respectively, yielding a more expensive refreshment strategy than the one proposed in this study. In addition to the proposed optimal point (point M), a few other possible scenarios for new experiments could be chosen from the obtained Pareto front. For instance, when the long intervals between medium refreshment are not possible due to the presence of other substances in the medium with a short half-life, other points with a higher medium change frequency need to be tested. One such point could be to refresh the medium every 68 h by 100% which leads to 86% filling at a cost of 59 €.

In Equation (1), the total price of the experiment is dominated by the labor cost. For example, in the proposed optimum strategy for refreshing the medium by Pareto front (every 90 h by 99%), only 3.5% (1.7 €) of the total price during 21 days of culture is related to the culture medium and the rest belongs to labor costs (44.3 €). Therefore, there is a clear need to go toward automation in bioreactor settings and eliminate as much as possible the labor cost in the experiments. Efforts for moving toward automation are under way. For instance, in the study by Kami et al. (2013), the authors present the first time use of the AutoCulture® system which can automatically replace the culture medium, centrifuge cells, split cells and take photographs for morphological assessment.

The optimization results both for single and MOO in all four methods showed no significant difference in finding the Pareto front. However, the performance of different metaheuristics could vary depending on the problem and the settings they are being used. In a recent study, Piotrowski et al. (2017) compared the performance of 33 metaheuristic methods on 22 real-world studies in vastly different domains. It was shown that the performance of all these methods were highly dependent on the number of function calls that the algorithm demands during the optimization procedure as in many modern metaheuristics,

the number of function calls may vary even within one generation. It was shown that the performance of all these metaheuristic methods constantly improves or deteriorates with the increase in the allowed number of function calls. They demonstrated, amongst others, that out of all the tested metaheuristic methods, PSO performs better when the number of function evaluations is low whereas GA and DE perform better when the computational budget is not limited (Piotrowski et al. 2017). Another important point to consider in applying metaheuristics is that they suffer from finding a balance between exploration, where we are not certain about the objective function values, and exploitation, i.e. choosing values for sampling where the objective function is expected to be high for maximization and low/small for minimization (Črepinšek et al. 2013). Therefore, we can expect that more exploitative algorithms such as PSO win the competition when the number of function evaluations is limited as it was the case in our study for single objective optimization (Figure 3). Other explorative algorithms such as GA and DE perform better with the availability of more function evaluations (Piotrowski et al. 2017).

Recent advances in TE and regenerative medicine have led to remarkable achievements and tissue engineered constructs are finding their way to the clinical use. However, in order to have a successful transition from laboratory into clinics, for any pharmaceutical product, it is crucial to reduce the cost of goods in the process while at the same time minimizing the variability in each of the elements involved in the process (Suresh and Basu 2008). This could be achieved by a careful selection of the materials used in the experiments and by automating different culture procedures. There are different sources of uncertainty in the cell culture process which needs to be experimentally minimized (removed). These variations are mainly attributed to four factors: raw materials (including consumables), operational inputs (measurements, methods, personnel, equipment), environmental factors (e.g. change in room temperature within normal range) and biological variability inherent to living cells (Shimoni et al. 2017). Optimization of the process with respect to conflicting objectives, such as the work presented in this article, would bring us one step closer to the application of tissue engineered products in a robust and reliable manner. Moreover, in order to have a robust and reproducible therapeutic product, the variability in each of these elements should be at its lowest limits.

Conclusion

In this work, a single objective optimization using GA, PSO and DE was performed on a previously developed model describing neotissue growth inside 3D scaffolds. The optimal solution found by all of the algorithms resulted in the same filling percentage indicating that increasing the refreshment frequency and amount will result in the highest neotissue filling, although the speed of convergence was different for each algorithm. Adding cost of the medium culture and labor into the optimization problem, required a formal multi-objective approach to reconcile the conflicting requirements of maximizing neotissue growth and minimizing the associated experimental costs. Hereto, we applied four different evolutionary algorithms and the obtained Pareto front from these methods were compared. No significant differences in terms of the speed of convergence and performance were observed between the Pareto fronts obtained from different algorithms, especially when the number of generations was set to 1000. The most optimum refreshment strategy in all the algorithms was the same. Depending on user/decision maker preferences, also other refreshment strategies could be selected on the Pareto front. In summary, this study proposes an optimal strategy for medium refreshment minimizing the medium and labor costs.

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Disclosure statement

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