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# Structural optimization of PNIPAM-derived thermoresponsive polymers: a computational approach employing artificial neural networks and genetic algorithms

## Otimização estrutural de polímeros termorresponsivos derivados de PNIPAM: uma abordagem computacional empregando redes neurais artificiais e algoritmos genéticos

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## ABSTRACT

In this study, artificial neural networks (ANNs) and genetic algorithms (GAs) are employed together to design optimized polymeric structures with superior cloud points. The database from a previous study of polymer synthesis with thermoresponsive polymers was used to create ANN-based models, which enabled the formulation and solution of the inverse problem using the GA. The regressors, with an average RMSE of less than 0.7 ºC, were used in the polymer evolution process over 20 generations. Mutation and selection operations led to the creation of 10 novel hybrid macromolecules with an average cloud point of 80 ºC. Furthermore, the special roles of some chemical groups are recognized and favor the structural mapping of PNIPAM-based materials. The computational approach presented here demonstrates that it is a promising tool in the development of new materials.

**Keywords**: Poly(*N*-isopropylacrylamide); Artificial neural networks; Genetic algorithms; Smart polymers

## RESUMO

Neste estudo, redes neurais artificiais (ANN) e algoritmos genéticos (GA) são empregados em conjunto para projetar estruturas poliméricas otimizadas com superior ponto de névoa. O banco de dados proveniente de um estudo prévio de síntese de polímeros com caráter termorresponsivo foi utilizado para criar modelos baseados em ANN, a partir do qual possibilitaram a formulação e solução

do problema inverso, empregando o GA. Os regressores, com RMSE médio inferior a 0,7 ºC, foram utilizados no processo de evolução dos polímeros ao longo de 20 gerações. Operações de mutação e seleção levaram à criação de 10 macromoléculas híbridas e inéditas com ponto de névoa médio de 80 ºC. Ainda, os papéis especiais de alguns grupos químicos são reconhecidos e favorecem o mapeamento estrutural dos materiais a base de PNIPAM. A abordagem computacional aqui apresentada demonstra ser uma ferramenta promissora no desenvolvimento de novos materiais.

**Palavras-chave**: Poli(*N*-isopropilacrilamida); Redes neurais artificiais; Algoritmos genéticos; Polímeros inteligentes

## 1 INTRODUCTION

Smart materials exhibit a responsive or adaptive characteristic in response to external stimuli. They are structures or systems of great interest for materials science and technology, where their applications permeate the most diverse areas, such as regenerative medicine (Sponchioni et al., 2019; Suamte et al., 2023), the pharmaceutical industry (Sana et al., 2022), the textile industry (Dai et al., 2023; Marešová et al., 2018), the food industry (Lu et al., 2016), development of biosensors (Wang et al., 2019) and environmental and energy development (Dai & Li, 2023; Da Silveira et al., 2017; Ding et al., 2023; Gadore and Ahmaruzzaman, 2021). As highlighted by Aguilar and Román (2014), polymers emerge as promising building blocks for synthetic smart materials owing to their inherent responsiveness to various stimuli, such as temperature, pH, and mechanical stress, or even the presence of molecules like carbon dioxide ($CO_2$), making them suitable for integration into diverse systems.

Thermoresponsive polymers react to temperature changes with a significant phase transition, which influences the solvation process. There are two main types: those with a lower critical solution temperature (LCST) and those with an upper critical solution temperature (UCST). Below the LCST, the solution is clear, with polymer chains in the extended conformation, solvated by the solvent. As the temperature surpasses the LCST, the solution turns cloudy. This phenomenon, known as the cloud point, indicates a shift in preference toward *polymer-polymer* interactions, leading to the collapse of polymer chains and their subsequent aggregation into a distinct phase (Da

Silveira et al., 2017). This transition is reversible in aqueous solutions, depending on the hydrophilic-hydrophobic balance of the macromolecule, and has been extensively investigated in the literature, with special interest in poly(*N*-isopropylacrylamide) (PNIPAM) and its derivatives. These structures, with their unique characteristic of undergoing an LCST phase transition close to human body temperature, hold diverse applications in the pharmaceutical and biomedical fields (Aguilar & Román, 2014).

Nevertheless, the cloud point temperature represents a limiting factor for the viability of using some polymers in the industry. This is particularly evident in oil and gas production, where deposition temperature can restrain its activity. For instance, if a polymeric inhibitor undergoes an LCST-driven phase transition, its effectiveness will be compromised. Usually, the deposition temperature is between 5 and 15 °C above the cloud point temperature; however, in certain environments, this value can be higher (Da Silveira et al., 2017; Park et al., 2017; 2019; Sheng et al., 2017).

Optimizing the chemical structure of synthetic polymers to achieve specific properties remains a major challenge in materials science, demanding significant resources for traditional approaches like combinatorial synthesis. Fortunately, computational methods offer a promising alternative, enabling the rational design of novel structures with tailored properties (Da Silveira et al., 2023; Santos et al., 2023a; 2023b). These optimization problems can be solved using meta-heuristic methods, capable of exploring the space of possible solutions (Silva Neto et al., 2016). Among them, bioinspired methods such as Genetic Algorithms (GAs) and Artificial Neural Networks (ANNs) have a strong appeal in the inverse design of polymer structures or systems, being applied in the optimization of composite materials (Zhang and Friedrich, 2003); enhanced oil recovery (Sun and Ertekin, 2019; Jiang et al., 2014) and polymer synthesis (Kim et al., 2021; Kumar et al., 2019). Furthermore, these methods find valuable use in developing Quantitative Structure-Property Relationship (QSPR) models, which consist of mapping the structure-property relationship of materials (Liu et al., 2019; 2021).

This work leverages the synergy of Artificial Neural Networks (ANNs) and Genetic Algorithms (GAs) for the optimized design of thermoresponsive polymers. Artificial Neural Networks are an efficient strategy for modeling and solving problems of a nonlinear and multivariate nature. By simulating the human brain, and reproducing the dynamics observed in biological neural networks, ANNs can learn complex relationships without requiring knowledge of the environment to be represented (Jiang et al., 2014; Silva Neto et al., 2016). On the other hand, the Genetic Algorithm, which is established on the principles of evolution through natural selection, is a suitable approach for global optimization and has proven to be efficient in systems of greater complexity (Silva Neto et al., 2016). After the ANN learning phase, the GA maps the material space, generating new materials with the required properties by solving the optimization problem. Although this approach is well-disseminated in the literature, its application to polymeric systems is still in its initial phase (Kim et al., 2021).

Building upon a library of thermoresponsive PNIPAM-based polymers obtained through high-throughput synthesis protocol (Da Silveira et al., 2017), this study implements a combined ANN-GA model. This approach demonstrates its potential to accelerate the discovery of advanced PNIPAM-based materials with desired functionalities.

## 2 METHODOLOGY

### 2.1 Experimental Data

The chemical structures evaluated in this work were obtained through a post-synthetic modification reaction (Da Silveira et al., 2015; 2017). The polymer synthesized in-house, poly(*N*-isopropylacrylamide-co-acrylic-acid) (PNIPAM-co-AA), was modified at 1.5; 3; 6; 7.5; 12; 15; and 20 mol% with the individual insertion of 11 segments from the following primary amines: cyclopropylamine (cycloprop); cyclobutylamine (cyclobut); cyclopentylamine (cyclopent); cycloheptylamine (cyclohept); cyclooctylamine

(cyclooct); propylamine (C3); butylamine (C4); tert-butylamine (C4t); pentylamine (C5); heptylamine (C7); and octylamine (C8).

A total of 34 macromolecules were evaluated at different concentrations, 0.5 and 1 wt%. The system allows the observation of the behavior of the solutions as a function of temperature, in the range of 25 to 90 °C (± 2 °C). The cloud point was determined visually, being the moment when the solution becomes turbid, easily identified by the color change of the sample holder, with a transition from red to pink and, finally, completely white. The heating rate was fixed at 0.2 °C/min. Further details are provided in the previous work (Da Silveira et al., 2017).

## 2.2 Data Processing

The set of thermoresponsive polymers (Da Silveira et al., 2017) was organized in a matrix based on polymer composition, defined as the average number of times each repeating unit is found in the final macromolecule (Da Silveira et al., 2023). These repeating units are the fundamental building blocks of the polymer chain. Table 1 presents this information, where the extent of chemical modification is denoted by the number of blocks (repeating unit), characterizing the polymer composition.

Table 1 – Summary of input parameters

| Parameters | Data range | |
|---|---|---|
| Polymer composition (*block*) | 0 | 32 |
| Concentration (wt%) | 0.5 | 1 |
| Cloud point (°C) | 26.5 | 83 |

Source: Authors (2024)

Each of the 59 data points captured in the study involves the analysis of 13 distinct input parameters influencing the cloud point property. These parameters include *CARB. ACID block (carboxylic acid group)*; the *modified block* (representing the structure derived from each of the 11 primary amines used for the polymer modification step); and the concentration of the polymer solution.

### 2.3 Direct Model Formulation via Artificial Neural Networks (ANNs)

This study utilized an Artificial Neural Network (ANN) approach for direct problem modeling. The data, without prior treatment, was divided into two sets: training/testing (90%) and validation (10%). The performance of the models was evaluated using two main metrics: the coefficient of determination ($R^2$) and the Root Mean Square Error (RMSE). RMSE evaluates model accuracy by calculating the mean of the squared errors between observed (real) and predicted values. On the other hand, $R^2$ is a dimensionless statistical measure between 0 and 1 that offers a comprehensive view of the generalized statistical model's fit to the dataset, considering all $n$ observations.

The Multilayer Perceptron (MLP) method was used to build the ANN. Two algorithms are used for training: feedforward, which consists of forwarding the input data to the neurons arranged in the hidden layers (HL), processing it, and resulting in output; and backpropagation, which performs the backpropagation of the error calculated between the prediction and the target value, adjusting weights iteratively through partial derivatives and an optimization algorithm. ReLU (Rectified Linear Unit) functions served as the activation function, enabling non-linear relationships between HLs. Error calculation employed Mean Square Error (MSE), summing the squares of differences, while the Adam (Adaptive Moment Estimation) algorithm performed optimization. These functions are crucial for weight adjustments during backpropagation.

Leveraging the *Keras* library within *TensorFlow* (v. 2.12.0), two distinct neural architectures were created using MLP: 3HLs and 4HLs, respectively, each with 30 neurons per layer. These ANNs were implemented alongside the k-fold cross-validation (K-Fold) method and trained/tested using 90% of the dataset divided into 10 partitions. K-Fold allows data partitioning for generating diverse training configurations within the same dataset, ensuring the neural network trains on different data during each training iteration (Silva et al., 2016). This step is

crucial to prevent overfitting and ensure models generalize well. Following cross-validation, a final model for the tested configuration was trained using the entire training dataset.

Due to the limited experimental data available, constant data distribution patterns and weight fixation were not applied, resulting in increased variability among the trained models. After 50 simulations, one trained model from each ANN was selected, using the $R^2$ and RMSE of the training and validation as a reference, with the requirement that $R^2$ exceeded 0.8 and RMSE was less than 2 $^oC$, simultaneously. Further tests assessed the trained models using 20 random data partitions to calculate and evaluate the mean RMSE.

### 2.4 Inverse Model Formulation via Genetic Algorithm (GA)

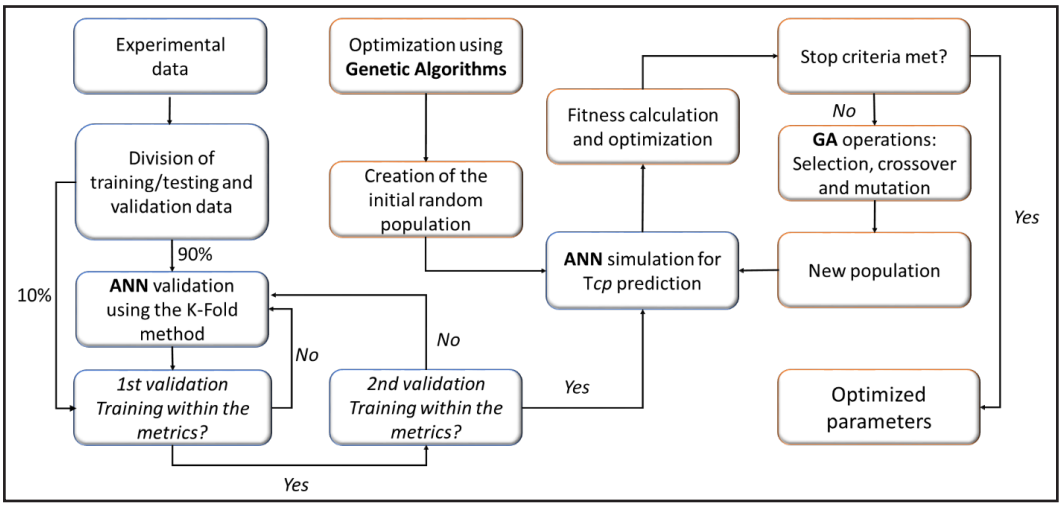
The genetic algorithm facilitates the coordination of the various essential steps of a complex optimization process for designing thermoresponsive macromolecules. From generating the initial population to selecting the most promising candidates, each step aims to improve the search for optimal solutions. Initially, a random population of 100 individuals was generated. These individuals were created by applying a dedicated function, each of them being characterized by variations in the values of the blocks (repeating units), referring to the composition of the polymeric structure. Crucially, the sum of these values must reach 32 due to the chemical modification limitations (Da Silveira et al., 2017), resulting in structures with up to 12 repeating units. The cloud point temperature is simulated for a fixed concentration (1 wt%) to assess the structure-property relationship.

The next step involves mutation, where the positions of individuals within the population are randomly permuted with a 0.6 probability. This stage introduces the required diversity by altering gene combinations, which provides the search for a wider solution space. This enhances overall optimization by preventing premature convergence to suboptimal solutions.

The previously trained and optimized artificial neural network (ANN), representing the problem's direct model, is integrated to reinforce the selection process. This model effectively predicts fitness scores based on both macromolecule composition and concentration. By incorporating this prediction, the genetic algorithm prioritizes individuals with higher predicted fitness, leading to an effective selection of fitter individuals for the next generation, ultimately contributing to improved results in inverse modeling.

The selection operation compares the performance of each individual in the initial population with its counterpart in the mutated population. This process identifies individuals with the highest fitness scores, which are then selected for reproduction in the next generation. This ensures the preservation and transmission of the most promising genetic characteristics, leading to further improvement in the following generations.

Figure 1 – Implemented model flowchart (ANN-GA) for the structural optimization of PNIPAM-based polymers




Source: Authors

The process of generation, mutation, evaluation, and selection was repeated over a defined number of 20 iterations. Each iteration represents a cycle of improvement, allowing the population to gradually evolve toward the optimal configuration. By

iteratively selecting and reproducing individuals with higher predicted fitness, the algorithm converges toward solutions that best match the desired cloud point behavior. Finally, upon reaching the defined iteration limit, the algorithm terminates, resulting in a population composed of highly adapted individuals with high fitness levels, representing potential candidates for the optimized macromolecules. Figure 1 presents the flowchart of the combined ANNAG model implemented for the optimization of PNIPAM-based macromolecules, previously generated by chemical modification (Da Silveira et al., 2017).

## 3 RESULTS AND DISCUSSION

The present work proposes a computational approach for optimizing the composition of PNIPAM-derived macromolecules. This method combines artificial neural networks (ANNs) and genetic algorithms (GAs) to maximize their cloud point temperature, a critical property related to their industry application. Poly(*N*-isopropylacrylamide) and its derivatives present a transition phase temperature with an intense response to chemical composition variation, which was investigated in this study.

Experimental data demonstrates that increasing the hydrophobic character of the chain, referring to the modified block, leads to higher cloud point values. Interestingly, the presence of reaction byproducts like isourea and *N*-hydroxysuccinimide can further enhance the polymer's solubility through a phenomenon called the hydrotropic effect, as discussed by Da Silveira et al. (2017). This behavior is also highlighted by the computational model presented here, demonstrating an increased solubility potential, even in the presence of intense hydrophobic segments, such as C7 and C8, in unprecedented compositions. It is worth noting that the sole presence of the reaction byproducts in solution in the PNIPAM-co-AA precursor polymer (before the modification reactions) is not sufficient to impact the transition temperature values (Da Silveira et al., 2017). However, these same molecules have a great effect in the

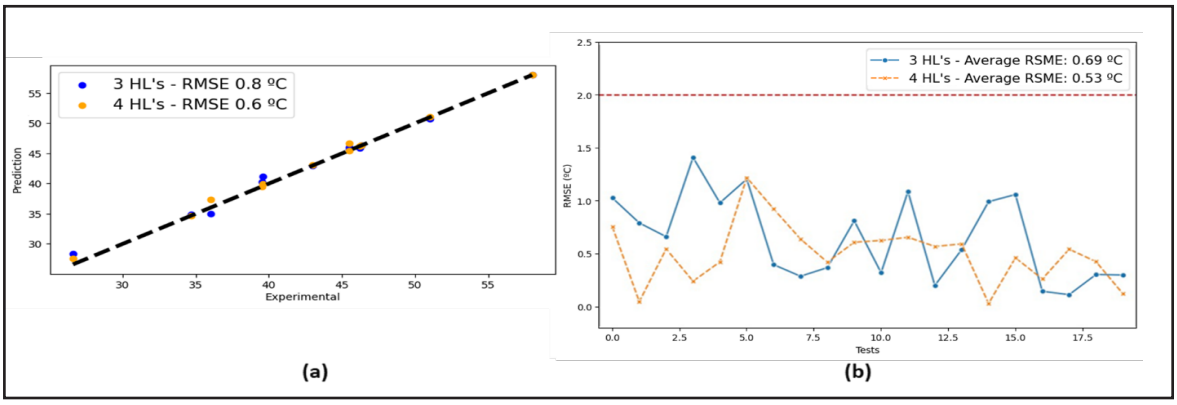
presence of polymeric structures with the insertion of a more significant hydrophobic portion (here evaluated up to 20 mol%). The difference between the collapsed and solvated states of the polymer results from the action of hydrotrope species in an aqueous solution. The hydrophobic interaction (polymer-polymer) is inhibited, resulting in increased solubilization of the macromolecule and, consequently, in a higher phase transition temperature.

Artificial neural network (ANN) algorithms excel at mapping inputs and outputs, leading to improved prediction power, especially for highly complex nonlinear systems like PNIPAM copolymers, with numerous influential factors. This study employs the multilayer perceptron (MLP) network for modeling the phase transition temperature property. After exploring models with varying numbers of hidden layers, those with 3 and 4 HLs were selected due to the superior generalization power, based on defined selection criteria focusing on models with $R^2$ exceeding 0.8 and RMSE below 2 ºC.

After training, 10% of the original experimental data set aside for validation was used to evaluate the selected models. Figure 2(a) shows the correlation between the experimental results and the predicted values. The data points representing the predictions from the models with 3 and 4 hidden layers (3HLs and 4HLs, respectively) are plotted against the experimental values. The proximity of the data points to the dashed line stresses the accuracy of the models.

The trained ANN models demonstrate excellent predictive ability for cloud point temperature prediction. The first validation confirms their accuracy, particularly the 4 HLs model with an RMSE of 0.6 °C, while 3 HLs have an RMSE of 0.8 ºC. In the next step, after addressing limitations, the models underwent further evaluation using 20 different data splits. The models' RMSE was assessed, and the results are presented in figure 2(b). None of the tests exceeded the defined threshold (RMSE 2 °C), and the average RMSE was less than 0.7 °C, demonstrating the adequate training of the regressors.

Figure 2 – (a) First validation for the 3HL´s e 4HL´s. (b) Second validation for the 3HL´s e 4HL´s, networks, where the dashed red line represents the pre-established limit for the RMSE (2 ºC)

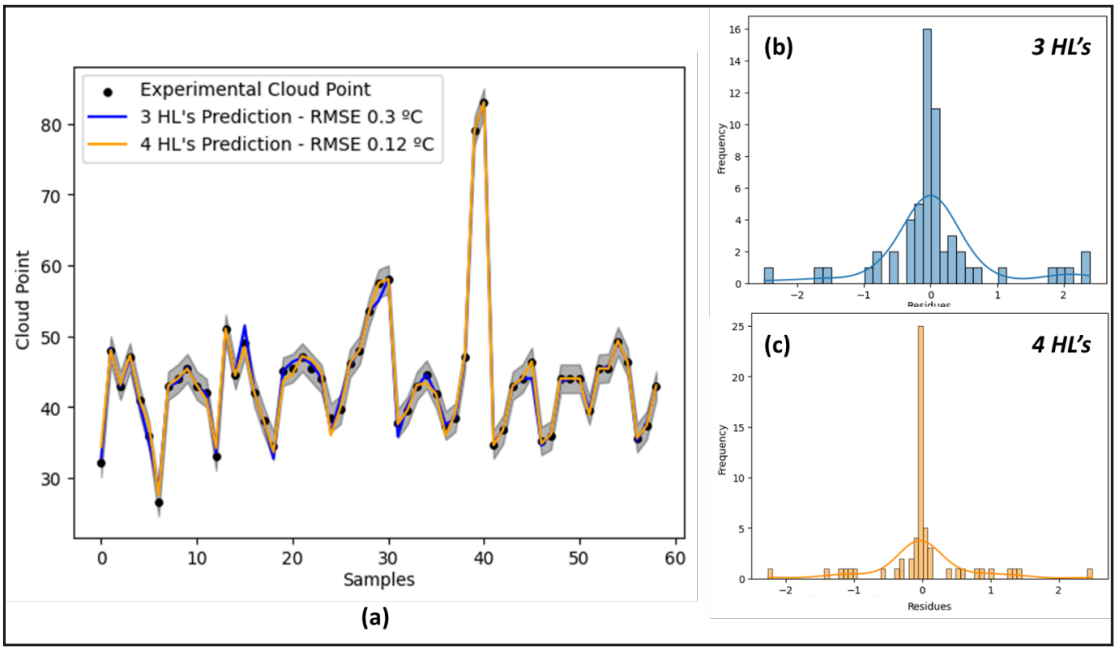



Source: Authors (2024)

After the validation process, an in-depth analysis was conducted to assess the overall difference between the experimental data and the predictions from the trained networks. This analysis generated a prediction response for the entire dataset. Figure 3(a) shows the prediction response of both models alongside the experimental data, represented as small black circles. In figure 3(a), the margin of error surrounding the real data is represented by the shaded area, with a range of ± 2 ºC corresponding to the experimental uncertainty. This again emphasizes the good agreement between the predictions and the experimental data. Figures 3(b) and 3(c) present the difference between the real and predicted values through residual plots. These plots show that over 90% of the data points fall within the stipulated margin of error.

The trained models were submitted to optimization using genetic algorithm (GA). Randomly, 100 individuals were generated. In each generation, mutated variants of these individuals are created. If these variations generate fitter structures, they replace the individuals in the initial population. The population size remains constant during this analysis, and no new independent individuals were created.

Figure 3 – (a) Global comparison of the experimental data with the data predicted by the models. The shadow refers to the uncertainty of the experimental method. (b) Residual data from the network with 3 HL's. (c) Residual data from the network with 4 HL's




Source: Authors (2024)

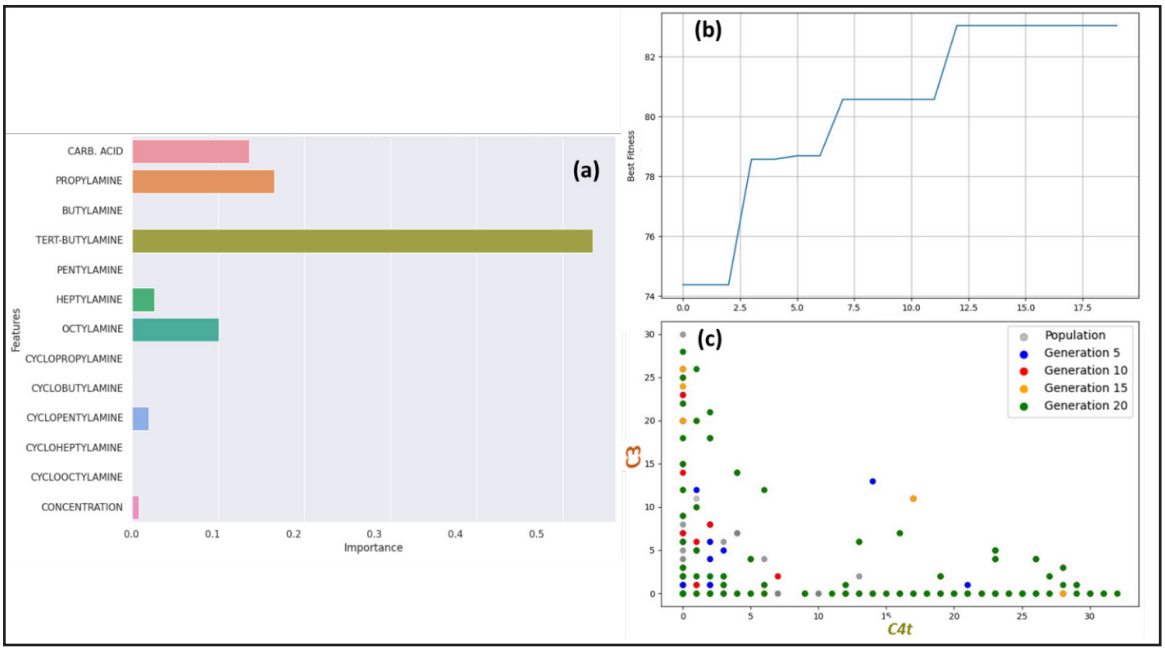
Due to pre-established constraints, mainly related to experimental limitations, a set of 10 polymer compositions was selected. These new macromolecules have optimized compositions, with cloud points in the range of 78.68 °C – 81.49 °C. Due to the low heterogeneity of the input experimental data, a trend is observed with the strong preference for the C4t block to obtain high cloud point temperatures. To investigate this trend further, additional machine learning algorithms were evaluated (Random Forest, Extra Trees, AdaBoostRegressor, and XGBoost) from algorithms we have expertise in (Da Silveira et al., 2023; Santos et al., 2023b). The level of importance of the input parameters (specific building blocks) was then analyzed. Very little difference was observed between the models; therefore, the average result of this analysis is presented in figure 4(a).

The new macromolecules identified by GA follow the same compositional pattern highlighted by the additional models evaluated in this work, as presented in figure 4(a).

As the main parameter, the C4t block stands out, as well as the carboxylic acid, which is a group known to enhance solubility. Furthermore, the more hydrophobic groups C3, C7, and C8 present relevant importance for the set of polymers evaluated, likely due to their stronger hydrophobic interactions. However, these results require further experimental evaluation.

Figure 4(b) shows the improvement in the fitness score of the polymer population over the generations of the genetic algorithm, providing an overview of the GA's convergence to better solutions over time. The compositional space explored by the polymers over 20 generations is visualized in figure 4(c) using the two most important building blocks, C4t and C3. Each point represents a polymer from a specific generation, highlighting the diversity in their final compositions. The aim is to show how the polymer population is adapting its chemical composition concerning these groups and, over time, demonstrate how the GA optimizes the composition towards the desired properties.

Figure 4 – (a) Average importance level of the parameters studied. (b) Fitness evolution as a function of generations. (c) Distribution of individuals across generations




Source: Authors (2024)

The experimental data demonstrated already an increasing cloud point trend as a function of chemical modification (mol%) for modified blocks C3, C4, C4t, cycloprop, cyclobut, cyclopent, and cyclohept. For polymers with the same modified block, the percentage of hydrophobic groups (mol%) plays a larger role than the individual monomer's hydrophobicity. Interestingly, it is observed that only C4t, C3, and cycloprop blocks maintain this increasing cloud point trend beyond 15 mol% modification, reaching the 20 mol% limit imposed by synthesis, as earlier discussed by Silveira et. al (2017). In contrast, this computational optimization identified 10 novel hybrid compositions exhibiting the same cloud point profile as the initial PNIPAM-C4t structure. These new polymers showcase a synergistic effect when combining the C4t block with the most hydrophobic segments studied (C3, C7, and C8). While experimental validation for these hypothetical structures is still pending, the evaluation metrics of both direct and inverse models suggest they are optimal candidates for achieving high cloud points.

Future research exploring a broader range of polymer compositions with greater chemical diversity could significantly improve the capabilities of this model. The combined ANN-GA approach, presented in this study, has immense potential to achieve desired polymer properties. Its applicability to diverse material systems positions it as a strong general strategy for materials discovery.

## 4 CONCLUSIONS

This work has successfully demonstrated a combined ANN-GA approach for optimizing the structure of smart polymers based on poly(*N*-isopropylacrylamide). By exploring a set of 12 monomers, this method identified 10 unprecedented hybrid structures with cloud points exceeding 80 °C, a significant improvement compared to existing materials. The trained model, with excellent accuracy (RMSE<0.8°C), minimizes the need for extensive experimental trials. Furthermore, this approach facilitates future investigations exploring a more heterogeneous polymer library for advanced materials development.

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