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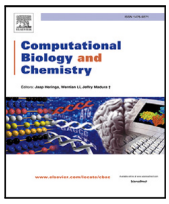

Research Article

# Multi-objective consensus optimization for gene regulatory networks inference: A preference-based approach

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ABSTRACT

Gene regulatory networks (GRNs) model key gene interactions, enabling the understanding of essential biological processes and their relationship with diseases. Inferring GRNs from expression data is fundamental in computational biology. However, existing methods exhibit limitations like domain biases and a lack of biological knowledge integration that affect their performance in in-vivo experimentation, particularly when several conflicting objectives are considered. To address these challenges, we propose a new approach that adopts a preference-guide selection mechanism aimed at helping the partitioner direct the search towards regions of high biological relevance by defining reference points in the objective space. This mechanism is integrated into MO-GENECI, a multi-objective evolutionary algorithm designed to optimize consensus between multiple machine learning techniques through biologically relevant objectives. Driven by research questions, the proposed approach is evaluated on 43 GRNs from benchmarks like DREAM3 and DREAM4, and real-world databases such as TFLink, using AUROC and AUPR metrics. The results demonstrate that the generated consensus networks obtained by using the preference selection outperform the original algorithm in quality and accuracy and reduce computational effort, especially in large networks. PBEvoGen achieved mean AUROC and AUPR values of 0.67 and 0.23 across 43 benchmark networks, improving the already state-of-the-art MO-GENECI by 1.2% and 4.3%, respectively. This combination of expert knowledge and evolutionary algorithms offers a robust, efficient methodology for GRN inference. The source code is hosted in a public repository at GitHub under MIT license: https://github.com/AdrianSeguraOrtiz/PBEvoGen. Moreover, to facilitate its installation and use, the software associated with this implementation has been encapsulated in a Python package available at PyPI: https://pypi.org/project/geneci/2.5.1.

## 1. Introduction

Gene regulatory networks (GRNs) model the interactions between gene products and other transcription factors that control gene expression (Davidson and Levin, 2005). These networks are essential for understanding the molecular mechanisms governing key biological processes and their involvement in diseases (Han et al., 2017; Parikshak et al., 2015), providing a foundation for the development of new therapies (Nazarieh et al., 2016; Wijst et al., 2018).

The inference of GRNs from gene expression data has become an essential activity in computational biology, enabling the discovery of unknown interactions from experimental data (Huynh-Thu et al., 2010; Margolin et al.; Huynh-Thu and Sanguinetti, 2015). However, existing approaches are often biased by domain specialization (Shen et al., 2023) and lack explicit integration of biological aspects and prior domain knowledge (Zhao et al., 2021), focusing on the mathematical validation of models while overlooking the biological coherence and relevance of the interactions.

In the context of evolutionary algorithms, proposals such as MO-GENECI (Segura-Ortiz et al., 2024) have been developed to address these shortcomings by optimizing the consensus of a set of multiple well-known machine learning techniques, while pursuing multiple biologically relevant objectives, including aspects such as degree distribution and the presence of motifs in the inferred networks. Results have shown that the best solutions tend to concentrate on specific regions of the objective space, which can be anticipated based on known properties, such as network size.

Based on this observation, this work proposes an approach that introduces preference-based selection (Wierzbicki, 1979), allowing a

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domain expert to define a reference point in the objective space to guide the evolutionary search. This strategy, previously applied in other fields (Wang et al., 2021; Li et al., 2024), is presented here for the first time in the context of GRN inference, where a new strategy regarding the selection of reference points is included, according to the characteristics of the networks to be inferred. The proposal, called PBEvoGen, is evaluated in this paper in order to address the following research questions:

RQ1: What impact can the use of this methodology have on the biological accuracy of the inferred networks?
RQ2: Are preference zones beneficial and detectable by domain experts?
RQ3: Can integrating this selection process reduce execution costs without compromising network quality?

The proposed approach was evaluated using an academic benchmark composed of 43 networks, obtained from well-known challenges (DREAM3 (Prill et al., 2010), DREAM4 (Meyer and Saez-Rodriguez, 2021), and IRMA (Cantone et al., 2009)), widely used simulators such as SysGenSIM (Pinna et al., 2011), and validated data sources with real-world networks like TFLink (Liska et al., 2022).

Experimental results demonstrate that when the evolutionary algorithm is guided by points located in regions of high biological relevance, the accuracy of the inferred networks (AUPR and AUROC) improves significantly compared to those obtained by the original algorithm, which has already demonstrated its dominance over a large set of inference techniques (Segura-Ortiz et al., 2024). Moreover, midway through execution, it dominates over half of the front obtained by the original algorithm restricted to the preference region.

Taken together, these elements result in the following main contributions to the state of the art:

1. The introduction of a preference-based evolutionary selection mechanism for the first time in the context of gene regulatory network inference.
2. The integration of expert knowledge into the consensus optimization process through biologically guided reference points.
3. A comprehensive validation across 43 benchmark networks demonstrating consistent improvements in accuracy and computational efficiency.

This paper is organized as follows: Section 3 presents a review of the state of the art in the field of study. The methodology and the adopted approach are described in detail in Section 4. Subsequently, the experimental design of the study is detailed in Section 5, followed by a comprehensive analysis and discussion of the obtained results in Section 6. Finally, Section 7 presents the main conclusions and suggests possible directions for future research.

## 2. Background

Evolutionary multi-objective optimization seeks to improve several conflicting objectives simultaneously, yielding an approximation of the Pareto front. In each iteration, four phases are performed: evaluation, selection, crossover, and mutation. PBEvoGen and its baseline MO-GENECI (Segura-Ortiz et al., 2024) base their evolutionary core on the Non-dominated Sorting Genetic Algorithm II (NSGA-II) (Deb et al., 2002). NSGA-II is a widely adopted evolutionary multi-objective algorithm that organizes the population into a hierarchy of dominance-based fronts through a fast non-dominated sorting procedure. It incorporates elitism by retaining the best individuals across generations and employs the crowding-distance metric to estimate local solution density, promoting diversity within each front. Its selection mechanism prioritizes individuals with better dominance rank and, when ranks are equal, those located in sparser regions of the objective space. This combination of convergence pressure and diversity preservation has made NSGA-II a standard baseline in multi-objective optimization and provides MO-GENECI and PBEvoGen with a robust and efficient evolutionary backbone to explore the trade-offs inherent to consensus inference in gene regulatory networks.

In both MO-GENECI and PBEvoGen, individuals are weight vectors representing the contribution of multiple inference techniques to a consensus GRN. The evaluation phase is identical to that in MO-GENECI (detailed in the next section), while the selection phase constitutes the main novelty of PBEvoGen, replacing the binary tournament of MO-GENECI with a preference-based mechanism driven by g-dominance (Molina et al., 2009), which favors individuals closer to expert-defined reference points in the objective space (Wierzbicki).

The variation operators are adapted to the simplex representation. The Simplex Crossover (Tsutsui et al.) combines several parent vectors by uniformly sampling offspring inside the simplex spanned by them, ensuring that all resulting weights remain feasible (non-negative and summing to one). This operator has demonstrated good performance in multimodal functions with moderate epistasis, enhancing exploration without leaving the feasible region. The Simplex Mutation, introduced in MO-GENECI (Segura-Ortiz et al., 2024), maintains feasibility by randomly splitting the vector into two disjoint subsets: one undergoes a negative perturbation proportional to its total weight, and the same amount is redistributed among the second subset. This design preserves normalization and injects controlled diversity according to two parameters, mutation probability and strength, avoiding the drift of weights outside the simplex.

The optimization process produces an approximated Pareto front. To assess accuracy, benchmarks with available gold-standard networks are used. For each non-dominated individual, its consensus network is compared to the reference using two standard metrics: AUROC (Area Under the Receiver Operating Characteristic), which measures the model's ability to distinguish true from false interactions, and AUPR (Area Under the Precision–Recall Curve), more appropriate for imbalanced data such as GRNs, as it emphasizes the trade-off between precision and recall.

To statistically validate performance differences across algorithms, the Friedman test is applied (Demšr, 2006). Given $k$ algorithms evaluated on $N$ datasets, each dataset assigns ranks $r_{ij}$ to algorithm $j$. The Friedman statistic is computed as:

$$\chi_F^2 = \frac{12N}{k(k+1)}\left(\sum_{j=1}^{k} R_j^2\right) - 3N(k+1), \qquad R_j = \sum_{i=1}^{N} r_{ij}$$

Under the null hypothesis that all algorithms perform equally, $\chi_F^2$ follows a chi-square distribution with $k-1$ degrees of freedom. Once the null hypothesis is rejected, post-hoc pairwise comparisons are carried out using Holm's step-down procedure (Eisinga et al., 2017). The unadjusted $p$-values are sorted in ascending order $p_1 \leq p_2 \leq \cdots \leq p_m$, and each hypothesis is tested sequentially according to:

$$p_i \leq \frac{\alpha}{m - i + 1}$$

In this work, Holm's correction is applied by comparing each algorithm with the one obtaining the best Friedman rank, which acts as the control method in the step-down procedure. Together, these statistical tools provide a rigorous and reproducible framework to determine whether performance differences among algorithms are statistically significant across all benchmark networks.

## 3. Related work

The inference of gene regulatory networks (GRNs) from expression data is a central topic in computational biology that has been extensively studied from quite varied and diverse methodological approaches. Among the most prominent approaches are ordinary differential equations (ODEs) (García-Nieto et al., 2019; Hurtado et al., 2021;

Wu et al., 2016), machine learning techniques such as neural networks (Gan et al., 2022; Ghazikhani et al., 2011; Kizaki et al., 2015; Yasuki et al., 2011), and probabilistic graphical models (Watanabe et al., 2012). Additionally, causality-based methods (Finkle et al., 2018), approaches that integrate multiple types of omics data (Zarayeneh et al., 2017), and strategies related to mutual information (Yang and Xu, 2017) have also been explored. This variety of approaches has driven the development of numerous computational techniques for GRN inference. Among the most recognized machine learning-based tools for their accuracy and frequent use in the literature are: ARACNE (Margolin et al.), MRNET (Meyer et al., 2007), CLR (Faith et al., 2007), GENIE3 (Huynh-Thu et al., 2010), and GRNBOOST2 (Moerman et al., 2018).

However, the bias of these tools across different domains of specialization (Shen et al., 2023) and the demonstrated potential of their combined applicability (Marbach et al., 2012) have led to the emergence of algorithmic proposals aimed at integrating these techniques to address these limitations (Fujii et al., 2017; Alawad et al., 2023). This type of ensemble learning strategy is also widely adopted in other biomedical fields, where it has evolved into sophisticated approaches that incorporate deep learning and explainable AI techniques (Bhosale et al., 2024). Nevertheless, in the GRN consensus inference context, some of these approaches are supervised learning methods limited to labeled data (Peignier et al.; Schmitt et al., 2023), and most lack the incorporation of biological domain aspects in their implementations (Aluru et al., 2022). For this reason, recent contributions such as MO-GENECI (Segura-Ortiz et al., 2024) stand out due to their unsupervised nature and the inclusion of objectives related to the biological domain of the problem. Nevertheless, even within this promising line of unsupervised consensus-based optimization, the exploitation of prior knowledge of specific GRNs characteristics remains limited, leaving room for improvement in guiding the search process toward biologically relevant solutions.

Closely related to the purpose of this proposal, it is important to note that the inclusion of expert knowledge in this specific area has already been explored in other ways. In Segura-Ortiz et al., the introduction of an additional memetic phase to the initial proposal (Segura-Ortiz et al., 2023) is suggested, where the specification of the existence or absence of certain interactions influences the refinement process of individuals. However, the algorithm employs a single, rather simplistic objective, resulting in inferior outcomes compared to the baseline algorithm of this proposal, which is further slowed down by the inclusion of this additional phase.

For this reason, PBEvoGen adopts a comprehensive consensus-based algorithm for the inference of GRNs, and introduces for the first time in this context a preference-based selection process aimed at enabling the human expert to manually set preference by means of reference points of biological interest, hence injecting domain expert knowledge. In this way, the proposed approach directly addresses the two major shortcomings identified in previous work: the lack of expert knowledge integration and the absence of biologically guided selection during the optimization process.

## 4. Proposed architecture and expert interaction

PBEvoGen is based on the multi-objective evolutionary algorithm developed in Segura-Ortiz et al. (2024), which is originally designed for the optimization of consensus networks in GRN inference. Both algorithms share the same evolutionary structure and operators, differing only in the selection phase: in MO-GENECI, selection was performed through a standard binary tournament, whereas in PBEvoGen it is replaced by a preference-based mechanism guided by the g-dominance concept. Consequently, the pseudocode of MO-GENECI (Algorithm 1 in Segura-Ortiz et al., 2024) is identical to Algorithm 1 except for lines 5–7, which implement this new selection step. The incorporation of preference-based selection is illustrated in the conceptual diagram of Fig. 1, while PBEvoGen implementation, based on NSGA-II, is outlined in the pseudocode of Algorithm 1. This implementation is specifically tailored to the problem through a weight vector representation, customized crossover and mutation operators, and fitness functions specifically designed to address the challenges of the biological context.

**Algorithm 1** PBEvoGen Algorithm.

**Input** Num of generations $T$, Population size $P$, Crossover operator $x_{simplex}$, Mutation operator $m_{simplex}$, Reference point $R$
**Output** Pareto-optimal front $PF$

1: $P \leftarrow$ generate_random_population($P$)
2: $E \leftarrow$ evaluate_population($P, F$)
3: $t \leftarrow 1$
4: **while** $t < T$ **do**
5: $g\_dominance \leftarrow$ compute_g_dominance($E, R$)
6: $ranks \leftarrow$ rank_population($E, g\_dominance$)
7: $selected \leftarrow$ select_population($P, ranks$)
8: $offspring \leftarrow$ crossover($selected, x_{simplex}$)
9: $offspring \leftarrow$ mutate($offspring, m_{simplex}$)
10: $P \leftarrow$ replace_population($P, offspring$)
11: $E \leftarrow$ evaluate_population($P, F$)
12: $t \leftarrow t + 1$
13: $PF \leftarrow$ get_pareto_front($E$)
14: **return** $PF$

The main flow of the algorithm begins with the generation of an initial random population (line 1 in Algorithm 1), represented as weight vectors that sum up to 1. Each individual represents a weighted voting system for the selection of inference techniques, among multiple of them, hence allowing the transformation of their weights into a consensus network. Concretely, a number of 26 inference techniques taken from the current state of the art are used: ARACNE (Margolin et al.), BC3NET (de Matos Simoes and Emmert-Streib, 2012), C3NET (Altay and Emmert-Streib, 2010), CLR (Faith et al., 2007), GENIE3_RF (Huynh-Thu et al., 2010), GRNBOOST2 (Moerman et al., 2018), GENIE3_ET (Huynh-Thu et al., 2010), MRNET (Meyer et al., 2007), MRNETB (Meyer et al.), PCIT (Reverter and Chan, 2008), TIGRESS (Haury et al., 2012), KBOOST (Iglesias-Martinez et al., 2021), MEOMI (Lei et al., 2023), JUMP3 (Huynh-Thu and Sanguinetti, 2015), NARROMI (Zhang et al., 2013), CMI2NI (Zhang et al., 2014), RSNET (Jiang and Zhang, 2022), PCACMI (Zhang et al., 2012), LOCPCACMI (Chen et al., 2019), PLSNET (Guo et al., 2016), PIDC (Chan et al., 2017), PUC (Chan et al., 2017), GRNVBEM (Sanchez-Castillo et al., 2017), LEAP (Specht and Li, 2017), NONLINEARODES (Ma et al., 2020) and INFERELATOR (Bonneau et al., 2006). Therefore, this solution coding allows the algorithm to act as an ensemble capable of generating consensus genetic regulatory networks, oriented to reinforce those topologies that are more frequent and robust.

The set of 26 inference techniques used in this study corresponds to those originally employed in MO-GENECI, ensuring a controlled and unbiased comparison. Being aware of the potential impact of ensemble composition, PBEvoGen inherits from MO-GENECI the flexibility to freely define the ensemble configuration, allowing users to include or exclude inference techniques or incorporate additional networks generated by other algorithms according to their preferences. Although ensemble composition can influence performance, this effect is largely mitigated by the algorithm's evolutionary weighting mechanism, which can assign negligible or null weights to techniques that do not contribute positively to the optimization objectives. When selecting the inference techniques to be combined, caution should be taken not to rely solely on their accuracy over a limited set of networks, since domain specialization effects have been widely reported (Shen et al., 2023). Moreover, previous studies have shown that the complementarity among techniques can sometimes be more beneficial for consensus performance than their individual accuracy (Marbach et al., 2012).

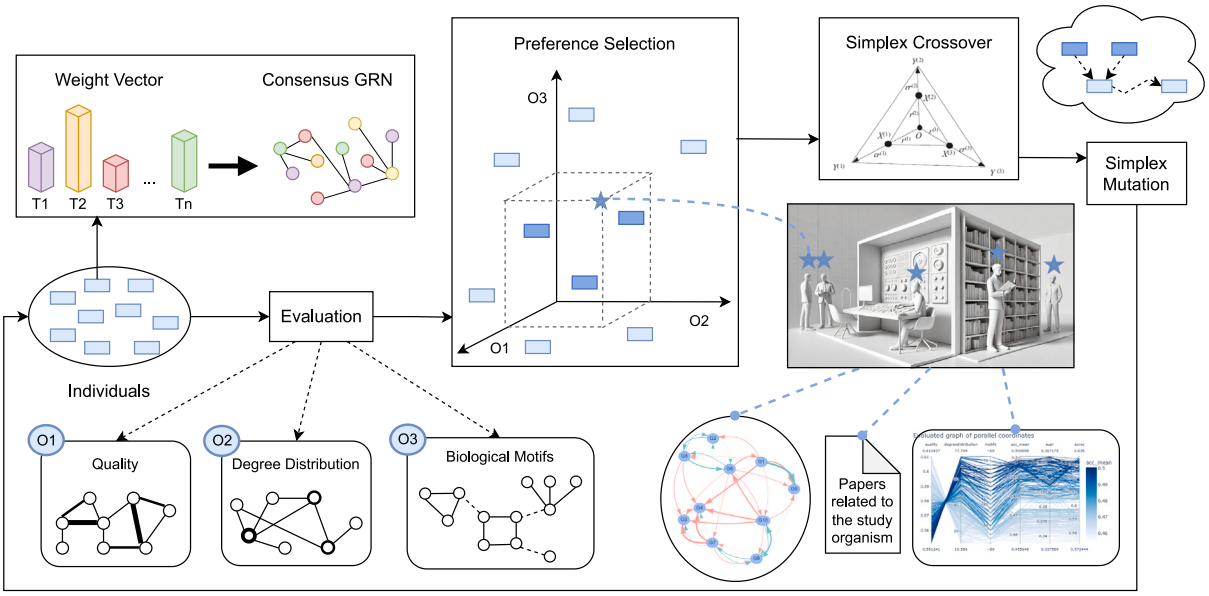



**Fig. 1.** Conceptual diagram of the proposed multi-objective evolutionary algorithm. Individuals, represented as weight vectors, are converted into their respective consensus regulatory networks for subsequent evaluation. Three objectives are considered: Quality, Degree Distribution, and Motifs. Once the performance of each individual is obtained for these objectives, selection is carried out based on the reference point established by the domain expert. The expert draws from various sources and personal experience to guide the population of individuals toward a region of interest in the problem. Afterward, the selected individuals undergo crossover and mutation to form a new generation of individuals.

Based on this representation, individuals are evaluated (lines 2 and 11 in Algorithm 1) using three conflicting objectives originally defined in Segura-Ortiz et al. (2024), whose pseudocodes are provided as Algorithms 3–5 in that reference:

1. **Quality**: This objective favors networks where a subset of interactions exhibits high confidence levels derived from a consistent weight distribution across techniques. Interactions that do not show agreement between techniques are penalized, encouraging more reliable networks. Formally, each interaction is assigned a quality value: $q_i = \frac{c_i+(1-d_i)}{2}$ where $c_i$ is the consensus confidence and $d_i$ is obtained from the spread of those scores around their median (Segura-Ortiz et al., 2023). The objective value for an individual is $f_1(x) = 1 - \overline{q_i}$ over interactions exceeding the mean. This criterion yields smooth improvements during optimization, as incremental adjustments in the weight vector gradually increase concordance between techniques (Algorithm 3 in Segura-Ortiz et al., 2024).
2. **Degree Distribution**: This objective aims for networks with degree distributions that follow a power-law, a typical characteristic of biological networks. For the network generated by each individual, the undirected weighted degree of each gene is computed as the sum of the confidence values of all incident edges. After adding 1 to avoid zeros, the resulting degree vector is evaluated through a Pareto (power-law) goodness-of-fit test based on log-spacings. The statistic returned is $f_2(x) = Z_0 \geq 0$, where lower values indicate a degree distribution more consistent with scale-free behavior. This criterion favors structures where most nodes have few connections, but a few act as highly connected hubs. Because this objective is continuous and nonlinear (Algorithm 4 in Segura-Ortiz et al., 2024), its optimization tends to produce gradual structural adjustments that reinforce heterogeneity.
3. **Motifs**: This objective promotes networks that display structural patterns characteristic of regulatory networks, such as bifurcations, feedback loops, and regulatory pathways (Algorithm 5 in Segura-Ortiz et al., 2024). The detection of these motifs reinforces the biological functionality of the generated networks. Each motif ($m$) has a frequency ($n_m$) and a predefined weight ($w_m$); the function is expressed as $f_3(x) = -\sum_m w_m n_m$. Because motif counts are discrete, the optimization of this objective shows a stepwise pattern: improvements occur abruptly when new structural configurations emerge in the network.

The original selection process, based on binary tournament selection, has been replaced in this proposal by a preference-based selection mechanism (lines 5 to 7 in Algorithm 1). Concretely, we have adopted the reference-point method (Wierzbicki), which constitutes a simple way to delimit an interest region of the objective space by indicating a user-defined point. We have used the scheme existing in jMetal (Durillo and Nebro, 2011), based on the g-dominance concept (Molina et al., 2009).

At the beginning of each iteration, `compute_g_dominance`$(E, R)$ (line 5 in Algorithm 1) determines, for each solution $x$ with objectives $f(x) = (f_1(x), f_2(x), f_3(x))$ and a reference point $R = (r_1, r_2, r_3)$, a binary preference flag that encodes whether the solution lies inside or outside the preference region:

$$s_R(x) = \begin{cases} 1, & \text{if } \forall i: \ f_i(x) \leq r_i \text{ or } \forall i: \ f_i(x) \geq r_i, \\ 0, & \text{otherwise.} \end{cases}$$

The resulting dominance relation is

$$x \prec_g y \ \Leftrightarrow \ \big(s_R(x) > s_R(y)\big) \text{ or } \big(s_R(x) = s_R(y) \ \wedge \ x \prec y\big),$$

where $x \prec y$ denotes standard Pareto dominance. In practice, this mechanism is integrated within the ranking phase to guide the non-dominated sorting toward regions preferred by the expert.

Next, `rank_population`$(E, g\_dominance)$ (line 6 in Algorithm 1) performs the non-dominated sorting of NSGA-II using the g-dominance-based comparison described above. Each individual is assigned to a Pareto front $F_1, F_2, \ldots$, with those satisfying the preference flag ($s_R(x) = 1$) naturally prioritized in lower-rank fronts. This ensures that the resulting hierarchy already reflects expert preferences before diversity preservation is applied.

The procedure `select_population`$(P, ranks)$ (line 7 in Algorithm 1) builds the mating pool through a binary tournament guided by two criteria: first, the Pareto rank (already influenced by g-dominance),

and second, the crowding distance to maintain population diversity. Thus, the effect of the preference-based mechanism propagates implicitly through the ranking hierarchy rather than being directly applied during tournament selection.

The functions `crossover`$(selected, x_{simplex})$ and `mutate` $(offspring, m_{simplex})$ (lines 8 and 9 in Algorithm 1) apply the operators described in Section 2. The crossover recombines parent vectors within their simplex to generate feasible offspring, while the mutation redistributes a small fraction of each offspring's weights among components, preserving $\sum_i x_i = 1$ and $x_i \geq 0$ for all $i$.

After variation, `replace_population`$(P, offspring)$ (line 10 in Algorithm 1) merges the current population with the offspring and retains the best $|P|$ individuals according to their Pareto rank and crowding distance, following the elitist replacement policy typical of NSGA-II.

At the end of each iteration, `evaluate_population`$(P, F)$ (line 11 in Algorithm 1) computes the three objective values defined previously for all individuals in the population $P$, generating a new evaluation matrix $E$. Each individual is decoded into its corresponding consensus network, and its objectives $(f_1, f_2, f_3)$ are independently calculated to provide the information required for the next iteration.

Finally, `get_pareto_front`$(E)$ (line 13 in Algorithm 1) extracts the first non-dominated front, which constitutes the current approximation of the Pareto-optimal set. This front represents the trade-offs achieved between quality, topological realism, and structural complexity in the inferred networks.

Thanks to the architecture finally built, the inclusion of domain knowledge in GRN consensus inference is no longer limited to the algorithm's objectives, but is now complemented by even more precise guidelines in the selection phase. This expert-guided selection phase also avoids the limitations associated with overfitting to supervised quantitative metrics such as AUROC or AUPR, by adding an additional level of guidance that, unlike other consensus strategies, is not oriented toward numerical maximization of accuracy.

The specialization of the objectives in this algorithm within the context of biological networks makes the search space more understandable for domain experts, who can anticipate certain topological features or the presence of expected regulatory motifs. These predictions can be based on literature reviews of the organism under study, analyses of networks from similar organisms, results from experiments on simulated datasets, or knowledge of previously validated interactions. All this information can now be utilized during the algorithm's execution, guiding the search towards solutions with greater biological relevance instead of being limited to the final selection on the approximated Pareto front.

## 5. Experimentation

The experimentation in this study utilizes a set of 43 problem instances comprising gene regulatory networks with sizes of up to 370 genes. This set includes 15 networks from the DREAM3 challenge (Prill et al., 2010), 10 networks from the DREAM4 challenge (Meyer and Saez-Rodriguez, 2021), 12 synthetic networks generated from scratch by the SysGenSIM simulator (Pinna et al., 2011) with both scale-free and EIPO modular distributions (Guelzim et al., 2002) ranging in size from 20 to 50 nodes, 2 instances of the yeast network from IRMA (Cantone et al., 2009), and 4 additional real networks collected by TFLink (Liska et al., 2022), whose expression data were generated again using the SysGenSIM simulator. Although this benchmark is a subset of the one used in MO-GENECI (Segura-Ortiz et al., 2023), it already provides a diverse and realistic evaluation environment. DREAM3 incorporates continuous differential equations with Gaussian noise, whereas DREAM4 relies on stochastic differential equations with noise proportional to expression levels under wild-type, knock-out, and knock-down conditions. The IRMA yeast network includes switch-on and switch-off experiments captured through quantitative RT-PCR, and the synthetic SysGenSIM networks encompass both scale-free and EIPO-modular topologies, incorporating knock-out, knock-down, and over-expression perturbations. Finally, the TFLink networks combine curated transcription-factor interactions from four model organisms, for which SysGenSIM simulated mixed perturbations. This diversity primarily impacts the behavior of the individual inference techniques rather than the consensus process itself; however, it is necessary to conduct rigorous experimentation.

For each of these 43 instances, the phase-organized workflow shown in Fig. 2 was executed, maintaining the same parameter values that were properly justified in Segura-Ortiz et al. (2024). First, each gene expression dataset was subjected to 15 independent runs of MO-GENECI (without preference articulation mechanisms) to subsequently extract an initial reference front (Fig. 2(a)). The resulting Pareto approximation front, already filtered to include only non-dominated solutions, was evaluated using the AUROC and AUPR accuracy metrics, which compare the consensus networks of the individuals with the corresponding gold standard of each instance (Fig. 2(b)).

The selection of the reference point by a domain expert was, in this case, approximated by choosing points in the objective space close to high-accuracy solutions. To make this approximation more rigorous, different points were considered for each metric. This approach allows for the observation of whether setting reference points in regions of high AUPR leads to specific improvements in that metric, while setting them in regions of high AUROC results in improvements exclusively for the latter metric.

The objective is to demonstrate that the preference-based selection introduced in this work influences the algorithm's evolution, not only by guiding individuals towards the reference point in the objective space (spatial improvement), but also by indirectly enhancing the inference accuracy or, equivalently, the biological relevance of the solutions associated with the selected region (accuracy improvement).

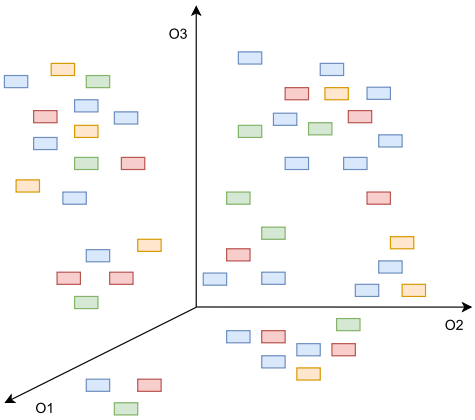
To expand the experimental study, several configurations were considered for each metric used as a reference. For both AUPR and AUROC, reference points were established by calculating the maximum coordinates of the top 5, 10, and 20 best solutions from the filtered reference approximation front.

In total, six reference points were tested for each instance. Fifteen independent runs with preference-based selection were performed for each reference point (Fig. 2(c)). Finally, the filtered front associated with each point was extracted and evaluated again using the AUROC and AUPR metrics (Fig. 2(d)), enabling a rigorous algorithmic comparison between the different configurations and the original algorithm.

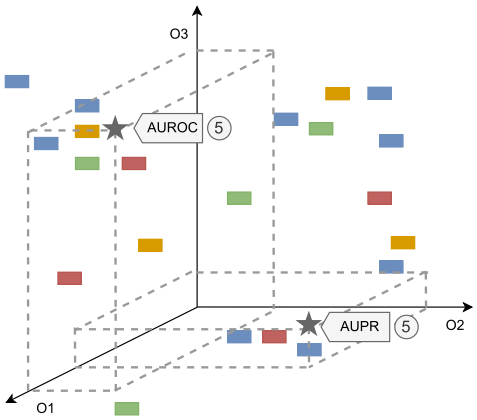
The algorithmic comparison focuses primarily on MO-GENECI because this approach has already been shown (Segura-Ortiz et al., 2024) to statistically significantly outperform a broad set of well-established techniques in gene regulatory network inference. Therefore, if PBEvoGen achieves better results than MO-GENECI, comparing it to these other 26 techniques becomes redundant, as its dominance would be implicitly established.

This comparison is performed using a Friedman statistical ranking with Holm's non-parametric tests for each metric (Eisinga et al., 2017). Once the best configuration for AUPR and the best for AUROC are identified, and both spatial and accuracy improvements are demonstrated, an additional experimental phase (Phase 5) is conducted to validate the performance improvement offered by this proposal.

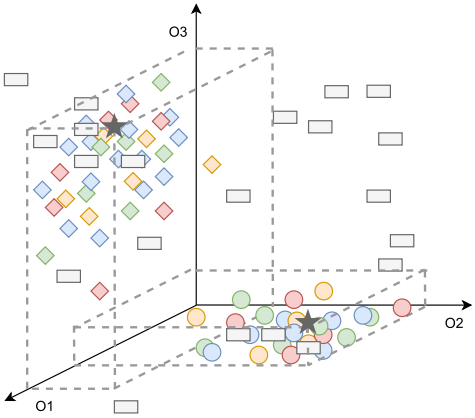
This phase consists of five additional runs for each winning configuration associated with each metric and for each of the largest networks in the benchmark ($\geq 100$ genes). A custom observer is employed, which takes the filtered reference front (obtained by MO-GENECI, which does not uses preference-based selection mechanism) as input, restricts it to the search region defined by the reference point, and calculates in each generation the percentage of solutions from the original front that are dominated by the current population. This approach allows identifying the point at which the execution of the proposed method



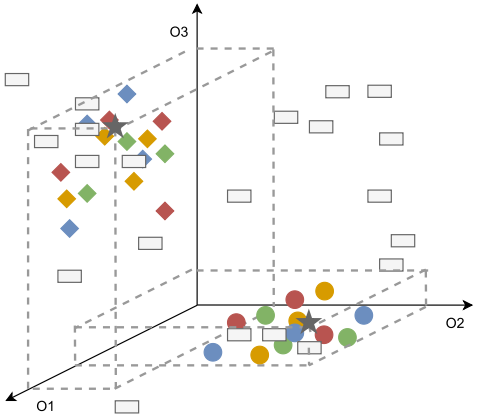

(a) Phase 1: 15 independent runs of MO-GENECI. Each rectangle represents an individual, and each color is used to represent a different independent run.




(b) Phase 2: Filtering of non-dominated individuals from the previous phase, validation using accuracy metrics (AUROC and AUPR), and establishment of reference points. For visual simplification, only the reference points corresponding to the top 5 individuals for each metric have been represented.




(c) Phase 3: 15 independent runs of the modified algorithm with preference-based selection for each reference point established in the previous phase. Individuals from the original algorithm are colored in gray, while the new individuals are represented by circles (AUPR) and diamonds (AUROC) in different colors, corresponding to the various independent runs.




(d) Phase 4: Filtering of non-dominated individuals from the previous phase and validation using accuracy metrics (AUROC and AUPR) to enable subsequent comparison of the different populations.

**Fig. 2.** Phases carried out during the experimentation of this study.

could be terminated, while maintaining the same optimization level as the original one, providing an estimate of how much execution time could be reduced for large networks.

It should be noted that the use of multiple independent runs in this study aims solely to ensure statistical robustness due to the stochastic nature of the algorithm. In practical use cases, the tool is designed to be executed once with the reference point defined by the domain expert, which substantially reduces the computational cost in routine analyses.

It is important to recall that the objective of PBEvoGen is to optimize the consensus among multiple network inference techniques rather than to act as a single inference method. Therefore, direct comparison with individual deep learning or hybrid models, which perform network reconstruction from scratch, would not be methodologically appropriate. In this study, to rigorously evaluate the consensus optimization capability of the proposed approach, MO-GENECI was selected as the most relevant baseline, and all experimental conditions — including the 26 underlying inference techniques — were maintained to ensure a fair and controlled comparison environment.

## 6. Results and discussion

Following the execution of the experimentation described in the previous section, the results obtained are presented from different perspectives and through several representations to justify and demonstrate each of the three improvements pursued in this work: solution quality improvement, spatial improvement, and performance improvement.

### 6.1. Solution quality improvement

The completion of the fourth phase of experimentation across the entire benchmark (see Fig. 2(d)) leads to the calculation of the Friedman statistical ranking with Holm's non-parametric tests for each metric, aiming to compare the original version of the algorithm with the different configurations of the proposed approach in this work.

The results of this ranking for the AUPR and AUROC metrics are presented in Tables 1 and 2, respectively. As observed, in both cases, the original algorithm ranks last, below all configurations of the proposed approach. This underperformance is accompanied by clear statistical

**Table 1**
Friedman mean rank with Holm's adjusted $p$ values (0.05) for AUPR.

| AUPR | | |
|---|---|---|
| Technique | $Friedman's Rank$ | $Holm's Adj - p$ |
| **PBEvoGen AUPR-10** | **2.0465** | – |
| PBEvoGen AUPR-5 | 2.3023 | 0.3582 |
| PBEvoGen AUPR-20 | 2.7442 | 0.0244 |
| MO-GENECI | 2.9070 | 0.0060 |

**Table 2**
Friedman mean rank with Holm's adjusted $p$ values (0.05) for AUROC.

| AUROC | | |
|---|---|---|
| Technique | $Friedman's Rank$ | $Holm's Adj - p$ |
| **PBEvoGen AUROC-10** | **2.2791** | – |
| PBEvoGen AUROC-20 | 2.3372 | 1.0080 |
| PBEvoGen AUROC-5 | 2.4651 | 1.0080 |
| MO-GENECI | 2.9186 | 0.0649 |

significance for the AUPR metric, while for AUROC, the $p$-value is close to the commonly used threshold of 0.05. These results not only demonstrate a superiority in accuracy over MO-GENECI but also over the 26 inference techniques that the original proposal had already proven to outperform.

**Answer to RQ1**

The first experimental results confirm that the proposed methodology enhances result quality, aligning with the rationale behind the accurate positioning of reference points in the 3D objective space, specifically improving the metric used for point selection.

Regarding the different configurations, it can be seen that the one considering the top 10 individuals (from the perspective of the respective metric) achieves the first position in both rankings. This outcome is consistent and reinforces the hypothesis that an intermediate distance is appropriate when establishing reference points. Specifically, a point that is too close ends up discarding other high-quality solutions, whereas a point that is too distant excessively broadens the significant search area, allowing non-relevant solutions.

Identifying the top 10 individuals as the winning configuration enables a more focused analysis in the following sections to address the two remaining improvements to be demonstrated.

It is worth noting that the effectiveness of preference-based selection depends on the quality of the expert-defined reference points. When these points are established based on sound biological knowledge, the algorithm benefits from a guided search that enhances both accuracy and interpretability. Conversely, poorly chosen references may lead to suboptimal convergence, a situation analogous to the selection of inappropriate trade-off solutions in standard multi-objective optimization. Nevertheless, this controlled involvement of expert knowledge should be regarded as a strength, as it enables a more meaningful exploration of biologically relevant regions of the search space.

### 6.2. Spatial improvement

Once the solution quality improvement has been demonstrated, it is necessary to verify whether this increase in quality is due to the proper functioning of the preference-based selection process. Fig. 3 displays objective space generated by individuals of the population of MO-GENECI and those of the two winning configurations of PBEvoGen (one for each metric) for several GRN benchmarking instances. Several observations can be drawn from the three-dimensional plots:

- The color gradient present in the original population across all cases demonstrates that both, the biological context and the original algorithm are well-suited for implementing the preference-based selection explored in this study. The fact that spatially close solutions exhibit similar quality metric levels makes restricting the search to specific regions an interpretable strategy for domain experts.
- The spatial positioning of the solutions guided by a reference point respects the boundaries defined by its coordinates, confirming the correct functioning of the selection process. Moreover, individuals generated by PBEvoGen tend to cluster more tightly around the reference point, forming denser and more coherent regions in the objective space. This reduced dispersion indicates a clearer convergence pattern, evidencing the guiding effect of the preference-based mechanism. In contrast, the original algorithm shows a wider spread of individuals with lower density in high-quality areas, reflecting a less efficient exploratory behavior.
- The individuals generated by the algorithm with preference-based selection outperform those of the original algorithm, achieving a higher level of optimization when executed with the same number of evaluations. Additionally, AUPR- and AUROC-guided configurations occupy adjacent yet distinct regions within the search space, suggesting that the articulation of preferences can adapt to different expert-driven goals without compromising the population diversity.

**Answers to RQ2**

The graphical representations in this section clearly illustrate a correlation between the quality of the networks and the individuals' locations in the search space. This correlation indicates that the search constraints in specific areas are aligned with neighborhoods where individuals share similar qualities related to inference accuracy, extending beyond just the objectives. Additionally, due to the biological profile of the algorithm's objectives, selecting reference points becomes a task that domain experts can easily understand.

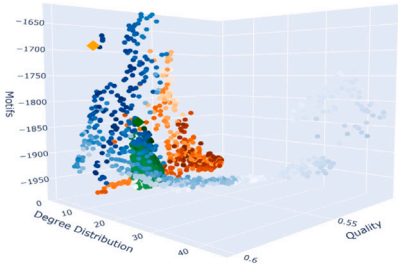
Additionally, for the *Saccharomyces cerevisiae* network from the TFLink database, which is the largest network in the benchmark with 370 genes, two additional violin plots have been included to represent the AUROC and AUPR values for the individuals in each population. These plots further reinforce the findings from the previous section: the solutions of the algorithm with preference-based selection are influenced not only spatially by the reference point but also by its meaning, biological relevance, and quality of solutions. The narrower distributions observed in both violin plots confirm a lower variability among individuals, highlighting the robustness and consistency of the obtained solutions. This aspect is crucial for making the injection of expert knowledge truly effective.

### 6.3. Performance improvement

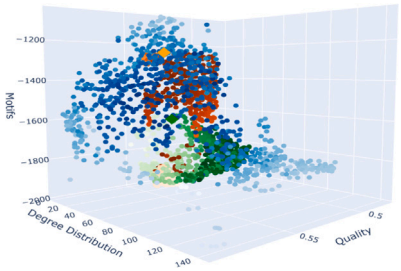
In the previous section, it was observed that the solutions obtained by PBEvoGen outperform those of MO-GENECI. However, identifying the point during execution when this occurs in large networks would allow for estimating the potential computational savings if the same level of optimization is to be maintained.

In the previous study (Segura-Ortiz et al., 2024), it is noted that execution for large networks can extend to nearly three days. Therefore, if the region of interest within the search space is known, it would be valuable to verify whether the proposed approach in this work could reduce execution time due to its ability to lower the algorithm's exploration effort.

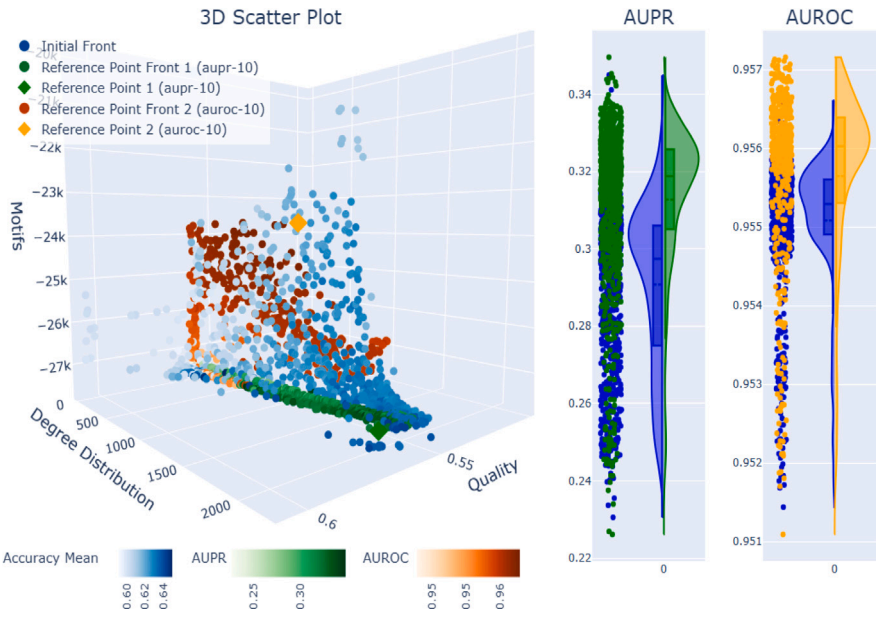
In Fig. 4, it can be observed that in both cases, more than 50% of the networks dominate nearly the entire original front by the midpoint of




(a) Representation of the three populations for the second 100-node network of the *Ecoli* organism in the DREAM3 challenge.




(b) Representation of the three populations for the fifth 100-node network of the DREAM4 challenge.




(c) Representation of the three populations for the *Saccharomyces cerevisiae* network from the TFLink database. In addition to what is presented in Fig. 3(a) and Fig. 3(b), this case includes the legend of the three-dimensional plot and two additional violin plots corresponding to the AUPR and AUROC metrics.

**Fig. 3.** Graphical representation for different gene regulatory networks of the three most relevant populations in the study. Specifically, the population of non-dominated solutions from the 15 independent runs of: (1) the original algorithm, colored based on the average of the AUPR and AUROC metrics; (2) the algorithm with preference-based selection guided by the point corresponding to the top 10 individuals with the best AUPR (green diamond), colored based on AUPR values; and (3) the algorithm with preference-based selection guided by the point corresponding to the top 10 individuals with the best AUROC (orange diamond), colored based on AUROC values.

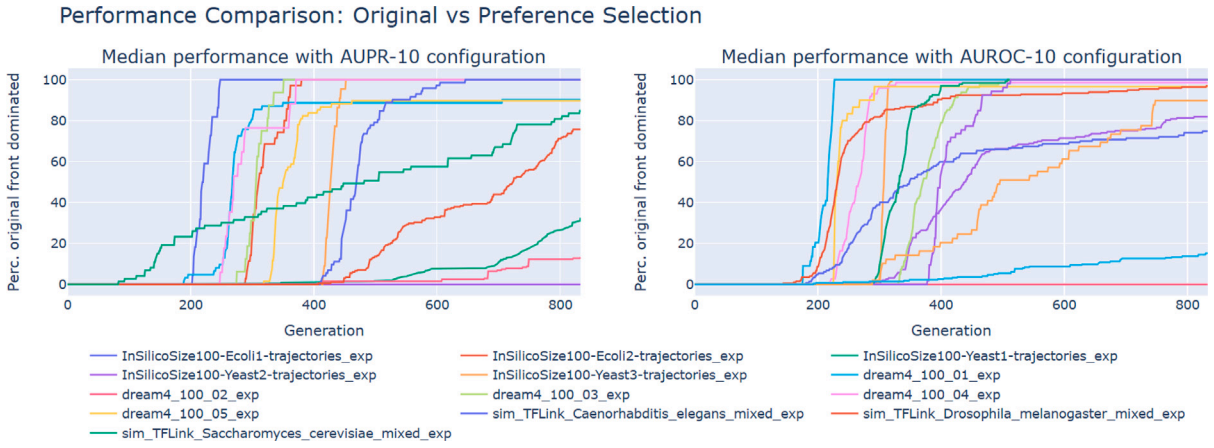



**Fig. 4.** Median of the 5 independent runs of the percentage of dominated solutions from the original front (trimmed by the reference point) in each generation for large networks (≥ 100 nodes) using the winning configurations (one for each metric).

the evolutionary process. This demonstrates that the preference-based selection mechanism increases the algorithm's efficiency by focusing the search effort on the most promising and biologically meaningful regions of the objective space, improving performance with the same computational cost per generation. This equivalence in computational cost is justified, as both algorithms share the same architecture and execution pipeline, differing only in the selection phase (lines 5–7 in Algorithm 1), which, as explained in Section 4, does not introduce any significant computational complexity. As a result, with only half the evaluations, a similar level of optimization to that of the original algorithm is achieved, allowing for a highly significant reduction in execution time for these cases. This is a remarkable result when, as mentioned above, implementation times are in the order of days.

The sharp and almost simultaneous increase of most curves from 0% to 100% reveals that, even though PBEvoGen restricts the search to the bounded region defined by the reference point, it maintains a homogeneous and balanced exploration within that area. In other words, the new individuals dominate the trimmed portion of the original front in a uniform way rather than progressively across subregions, demonstrating that the guided evolution preserves local diversity while advancing coherently across the restricted space.

**Answers to RQ3**

By adopting the preference-based approach, computational costs for large networks can be reduced by up to half of the original computation times while still achieving solution fronts with similar accuracy.

Although large-scale GRN inference remains computationally demanding, the proposed preference-based selection mitigates this limitation by restricting exploration to biologically relevant regions, thereby reducing execution time without compromising accuracy.

## 7. Conclusion

This work presents the adoption of a preference-based selection approach to address the consensus of a numerous set of gene regulatory network inference techniques. The search space, defined by three conflicting biologically-driven objectives, enables domain experts to assign reference points to guide the algorithm's evolution based on their knowledge.

The results have shown that the solutions generated by the proposed method are influenced not only by the spatial coordinates of the reference points but also inherit their biological relevance and accuracy. This provides a deeper understanding beyond the algorithm's primary objective space. Consequently, this approach offers reliability for application to real-world networks, where selecting a reference point based on specific biological traits indirectly related to the search space can guide the inference toward networks that reflect these characteristics.

Additionally, it has been demonstrated that the algorithm effectively transforms the constrained exploration effort into greater exploitation within the area defined by the reference points. This not only improves the optimization level of the solutions but also, in real-world scenarios with larger networks, significantly reduces execution time compared to the original algorithm when aiming to achieve similar objective optimization.

Finally, future work will explore the implementation of a dynamic reference point assignment, allowing domain human experts to observe the real-time evolution of the approximated Pareto front and request the translation of certain individuals to obtain their consensus networks. This would enable experts to make informed decisions during the execution process based on the network content. In addition, future studies will investigate the integration of new inference techniques, including those based on deep learning and hybrid paradigms, to further enhance consensus accuracy without altering the underlying methodology. Another promising direction involves the development of a machine-learning-based support tool that can learn from previous optimization results to recommend appropriate reference points for subsequent executions.

## CRediT authorship contribution statement

**Adrián Segura-Ortiz:** Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Antonio J. Nebro:** Writing – review & editing, Validation, Supervision, Conceptualization. **José García-Nieto:** Writing – review & editing, Validation, Supervision, Conceptualization. **José F. Aldana-Montes:** Supervision, Project administration, Funding acquisition.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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