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Multi-Objective Metaheuristic Optimization for Molecular Docking in Early-Stage Drug Design by Water Optimization Algorithm

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Abstract

Molecular docking constitutes a fundamental computational technique in Structure-Based Drug Design (SBDD), aiming to predict the optimal binding conformation and affinity of a small-molecule ligand within the active site of a target protein. Formulating molecular docking as a multi-objective optimization problem simultaneously minimizing intermolecular interaction energy and intramolecular conformational strain yields a richer set of candidate solutions for medicinal chemists than traditional single-objective formulations. In this paper, a Multi-Objective Water Optimization Algorithm (MO-WAO) is proposed, extending the recently introduced Water Optimization Algorithm (WAO) of Daliri et al. [1] to handle bi-objective docking problems. WAO is a swarm intelligence metaheuristic inspired by the chemical and physical properties of water molecules, including hydrogen bonding, evaporation, and particle motion dynamics. The proposed MO-WAO integrates Pareto dominance-based ranking, crowding distance computation, and an external archive mechanism to approximate the Pareto optimal front of docking conformations. Two competing objective functions are optimized simultaneously: the intermolecular energy capturing ligand–receptor binding interactions (van der Waals, electrostatic, hydrogen bonding, and desolvation terms) and the intramolecular energy reflecting internal ligand conformational strain. Comprehensive benchmark experiments are conducted on eleven standard protein–ligand complexes sourced from the Protein Data Bank (PDB), spanning diverse therapeutic targets including HIV-1 protease, streptavidin, acetylcholinesterase, and cyclin-dependent kinase 2. The performance of MO-WAO is rigorously compared against five established multi-objective metaheuristics Non-dominated Sorting Genetic Algorithm II (NSGA-II) , Speed-constrained Multi-Objective Particle Swarm Optimization (SMPSO), Multi-Objective Evolutionary Algorithm based on Decomposition (MOEA/D), Generalized Differential Evolution 3 (GDE3), and S-Metric Selection Evolutionary Multi-Objective Algorithm (SMS-EMOA) as well as the Lamarckian Genetic Algorithm (LGA) from AutoDock as a single-objective reference. Evaluation is performed using four Pareto quality indicators: Hypervolume (HV), Inverted Generational Distance (IGD), spread (Δ), and epsilon (ε), supplemented by Root Mean Square Deviation (RMSD) analysis of predicted binding poses. Results demonstrate that MO-WAO achieves competitive or superior Pareto front approximations, benefiting from the balanced exploration–exploitation mechanism inherent in the hydrogen bonding, evaporation, and motion phases of the water-inspired paradigm.

Keywords: Molecular docking, Multi-objective optimization, Water optimization algorithm, Metaheuristic, Drug design, Pareto front, Binding energy.

1 | Introduction

Developing novel therapeutic agents remains one of the most consequential endeavors in modern biomedical science. The drug discovery pipeline is a protracted, resource-intensive process, typically spanning 10–15 years and requiring investments exceeding one billion US dollars from initial target identification through regulatory

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approval and market release [2], [3]. Within this pipeline, the early stages of hit identification and lead optimization are critically important, as decisions made during these phases profoundly influence the probability of downstream clinical success. Computational methods have emerged as indispensable tools for accelerating and rationalizing these early-stage activities, enabling researchers to explore vast chemical spaces and prioritize promising molecular candidates before committing to expensive synthesis and experimental testing [4], [5].

Molecular docking is a cornerstone technique in Structure-Based Drug Design (SBDD), a paradigm that leverages three-dimensional structural information of biological macromolecules typically obtained through X-ray crystallography, NMR spectroscopy, or cryo-electron microscopy to guide the design and selection of small-molecule ligands [6], [7]. The docking procedure seeks to predict the preferred orientation (pose) and binding affinity of a candidate ligand within the binding site of a target protein. Accurate docking predictions can reveal the molecular determinants of ligand–receptor recognition, inform lead optimization strategies, and prioritize compounds for experimental validation in virtual screening campaigns [8], [9]. Since the pioneering work of Kuntz et al. in the 1980s, molecular docking has evolved substantially, with numerous software packages including AutoDock [10], AutoDock Vina [11], GOLD [12], Glide [13], and DOCK [14] now routinely deployed in both academic and pharmaceutical industry settings.

From a computational perspective, molecular docking constitutes an NP-hard combinatorial optimization problem characterized by a rugged, multimodal energy landscape [15], [16]. The search space is defined by the translational, rotational, and torsional degrees of freedom of the ligand relative to the receptor, and for flexible ligands with many rotatable bonds, the dimensionality of this space can be considerable. The energy landscape is punctuated by numerous local minima separated by energy barriers, making gradient-based optimization methods unreliable for identifying the global minimum. Consequently, stochastic search algorithms, particularly metaheuristic optimization methods, have become the preferred approach for navigating this complex landscape [17].

Traditionally, molecular docking has been formulated as a single-objective optimization problem, wherein the goal is to minimize the total binding free energy of the ligand–receptor complex. However, this formulation oversimplifies the underlying biophysics. The total binding energy is typically decomposed into two principal components: the intermolecular energy, which quantifies the strength of the interaction between the ligand and the receptor through van der Waals, electrostatic, hydrogen bonding, and desolvation terms; and the intramolecular energy, which reflects the conformational strain imposed on the ligand upon binding [18], [19]. These two objectives are inherently conflicting: A ligand may achieve highly favorable intermolecular contacts by adopting a strained conformation, or it may maintain a relaxed conformation at the expense of weaker receptor interactions. Single-objective approaches that combine these energies into a scalar sum may obscure this trade-off, potentially discarding biologically relevant conformations that represent optimal compromises. Multi-objective optimization, which seeks to identify the Pareto optimal set of solutions representing the best trade-offs between competing objectives, offers a more comprehensive and informative framework for molecular docking [20], [21].

The application of metaheuristic algorithms to molecular docking has a rich history. The Lamarckian Genetic Algorithm (LGA), implemented in AutoDock by Morris et al. [10], hybridizes a genetic algorithm with local search to efficiently explore the docking landscape and has become one of the most widely used docking search engines. Particle Swarm Optimization (PSO) has been adapted for docking in several studies, including PSO@AutoDock by Namasivayam and Günther [22] and the more recent RDPSOVina by Li et al. [23]. Differential Evolution (DE), Ant Colony Optimization (ACO), and numerous other evolutionary and swarm intelligence algorithms have likewise been applied to docking problems with varying degrees of success [24–26]. The METADOCK 2 platform developed by Imbernón et al. [27] introduced a high-throughput parallel metaheuristic framework for large-scale docking campaigns.

In the multi-objective domain, Garcia Godoy et al. [20] presented a pioneering comparative study in which five multi-objective metaheuristics Non-dominated Sorting Genetic Algorithm II (NSGA-II), Speed-

constrained Multi-Objective Particle Swarm Optimization (SMPSO), Generalized Differential Evolution 3 (GDE3), Multi-Objective Evolutionary Algorithm based on Decomposition (MOEA/D), and SMS-EMOA were systematically evaluated for bi-objective molecular docking on a benchmark suite of protein–ligand complexes. Their results demonstrated that multi-objective formulations could yield Pareto fronts containing conformations with Root Mean Square Deviation (RMSD) values comparable to or better than those obtained by the single-objective LGA, while simultaneously providing medicinal chemists with a diverse set of alternative binding modes. In a subsequent study, Garcia Godoy et al. [21] extended the multi-objective approach to the docking of inhibitors against wild-type and mutant forms of the epidermal growth factor receptor (EGFR), demonstrating the clinical relevance of Pareto-based docking in the context of drug resistance. More recently, Fromer et al. [28] explored Pareto optimization strategies for accelerating multi-objective virtual screening, underscoring the growing interest in multi-objective approaches within computational drug discovery. The No Free Lunch (NFL) theorem, established by Wolpert and Macready [29], asserts that no single optimization algorithm is universally superior across all problem domains. This fundamental result provides a theoretical motivation for the continued development and evaluation of novel metaheuristic algorithms, as performance advantages may be domain-specific and dependent on the structure of the optimization landscape. In this spirit, the present study introduces a new multi-objective algorithm derived from a recently proposed nature-inspired metaheuristic: the Water Optimization Algorithm (WAO).

The WAO was proposed by Daliri et al. [1] as a swarm intelligence algorithm inspired by the chemical and physical properties of water molecules. WAO models three principal mechanisms: 1) hydrogen bonding, through which water molecules form intermolecular bonds to share information and collectively move toward promising regions of the search space, 2) evaporation, whereby molecules with poor fitness are probabilistically reinitialized to maintain population diversity, and 3) particle motion, in which molecules update their velocities and positions under the influence of bonding forces and attraction to high-quality solutions. The interplay of these three mechanisms endows WAO with a robust balance between exploration and exploitation, as demonstrated by Daliri et al. through extensive benchmarking on CEC test functions and engineering design problems [1]. Despite the promising performance of WAO on single-objective benchmarks, to the best of the authors' knowledge, WAO has not been extended to multi-objective optimization, nor has it been applied to molecular docking problems. This gap in the literature presents an opportunity to investigate whether the distinctive bonding–evaporation–motion paradigm of WAO can be effectively adapted for Pareto-based search in the complex, high-dimensional energy landscapes characteristic of protein–ligand docking.

The contributions of this paper are fourfold: 1) the proposal of Multi-Objective Water Optimization Algorithm (MO-WAO), a multi-objective extension of the WAO incorporating Pareto dominance ranking, crowding distance, and external archive management, 2) the formulation of molecular docking as a bi-objective optimization problem minimizing intermolecular and intramolecular energies, 3) comprehensive benchmarking of MO-WAO against five state-of-the-art multi-objective algorithms (NSGA-II, SMPSO, GDE3, MOEA/D, and SMS-EMOA) and the single-objective LGA on eleven PDB complexes, and 4) analysis of the drug design implications of the resulting Pareto fronts. The remainder of this paper is organized as follows: Section 2 provides background on molecular docking, metaheuristic optimization, multi-objective docking, and the WAO algorithm; Section 3 describes the proposed MO-WAO methodology in detail; Section 4 presents the experimental setup; Section 5 reports and discusses the results; and Section 6 offers conclusions and directions for future work.

2 | Background and Related Work

2.1 | Molecular Docking Problem Formulation

The molecular docking problem can be formally defined as a continuous optimization problem over a high-dimensional search space determined by the degrees of freedom of the ligand relative to the receptor. A candidate docking solution (pose) is encoded as a vector of decision variables encompassing: three

translational parameters (x, y, z) specifying the position of the ligand center of mass within the binding site; four rotational parameters (q_1, q_2, q_3, q_4) representing a unit quaternion that defines the orientation of the ligand; and n torsion angles (φ_1, φ_2, …, φ_n) corresponding to the rotatable bonds of the ligand. The total dimensionality of the search space is therefore D = 7 + n, where n varies from zero (rigid ligand) to over twenty for highly flexible drug-like molecules [10], [30].

The quality of a given pose is assessed by a scoring function that estimates the binding free energy of the ligand–receptor complex. In the AutoDock 4 framework, the total binding free energy ΔG_{bind} is decomposed as follows:

$$\Delta G_{bind} = E_{inter} + E_{intra} + E_{tor}, \quad (1)$$

where E_{inter} is the intermolecular energy between ligand and receptor, E_{intra} is the intramolecular energy of the ligand, and E_{tor} is the torsional free energy penalty proportional to the number of rotatable bonds. The intermolecular energy is further decomposed into component terms:

$$E_{inter} = E_{vdw} + E_{hbond} + E_{elec} + E_{desolv}. \quad (2)$$

Here, E_{vdw} represents van der Waals interactions modeled by a Lennard-Jones 12–6 potential; E_{hbond} captures hydrogen bonding interactions using a directional 12–10 potential; E_{elec} accounts for electrostatic interactions via a screened Coulomb potential; and E_{desolv} estimates the desolvation penalty upon ligand binding using a volume-based pairwise approach [10]. Each term is parameterized using empirical coefficients calibrated against a training set of experimentally determined protein–ligand binding affinities.

AutoDock Vina [11] employs an alternative empirical scoring function based on a combination of Gaussian steric terms (attractive and repulsive), hydrophobic interactions, hydrogen bonding, and a torsional penalty for the number of rotatable bonds. The Vina scoring function emphasizes computational speed by using pre-computed grid maps that discretize the binding site into a regular lattice of energy values, enabling rapid energy evaluation during the search [11].

The energy landscape defined by these scoring functions is highly multimodal, characterized by numerous local minima of varying depth separated by energy barriers. This ruggedness arises from the complex, non-linear interactions between ligand and receptor atoms and is exacerbated by the high dimensionality of the search space for flexible ligands. Consequently, deterministic optimization methods, including gradient descent and Newton's method, are generally inadequate for molecular docking, as they are prone to entrapment in local minima and provide no guarantee of finding the global optimum [15], [16].

2.2 | Metaheuristic Algorithms in Molecular Docking

Metaheuristic algorithms are stochastic optimization strategies designed to explore complex search spaces efficiently by balancing global exploration with local exploitation. Their population-based nature, ability to escape local optima, and minimal reliance on gradient information make them well-suited for molecular docking problems [17], [31].

The LGA implemented in AutoDock [10] is perhaps the most extensively used metaheuristic for molecular docking. LGA combines a standard genetic algorithm employing selection, crossover, and mutation operators with a Solis–Wets local search procedure. The "Lamarckian" aspect refers to the inheritance of locally optimized phenotypic improvements, whereby the results of local search are written back into the genotype for subsequent evolutionary operations. This hybridization significantly enhances the algorithm's ability to refine promising docking poses while maintaining population diversity through genetic operators [10].

PSO, inspired by the collective behavior of bird flocks and fish schools [32], has been adapted for molecular docking in several studies. Namasivayam and Günther [22] developed PSO@AutoDock, a PSO-based docking engine integrated into the AutoDock framework, demonstrating competitive performance with LGA on a diverse set of protein–ligand complexes. More recently, Li et al. [23] proposed RDPSOVina,

incorporating random drift PSO into AutoDock Vina to improve sampling efficiency in high-dimensional docking search spaces.

DE, introduced by Storn and Price [24], has been applied to docking by several groups, exploiting the algorithm's effective perturbation mechanisms for continuous optimization. ACO, inspired by the foraging behavior of ants [25], has also been explored for docking, particularly in the context of fragment-based approaches. Additionally, nature-inspired algorithms including the Grey Wolf Optimizer (GWO) [33], Whale Optimization Algorithm (WOA) [34], Harris Hawks Optimization (HHO) [35], and Gravitational Search Algorithm (GSA) [36] have been applied to various molecular optimization tasks, reflecting the growing diversity of metaheuristic paradigms in computational chemistry.

The METADOCK 2 platform developed by Imbernón et al. [27] represents a significant advance in high-throughput docking, leveraging parallel computing architectures to execute metaheuristic searches across thousands of protein–ligand pairs simultaneously. Chen et al. [5] presented an algorithm selection framework for docking, analyzing the performance of multiple metaheuristics on Angiotensin-Converting Enzyme (ACE) targets and providing guidance for algorithm–problem matching.

Recent years have witnessed increasing interest in deep learning-based approaches to molecular docking, including methods that predict binding poses using graph neural networks and geometric deep learning. However, these approaches remain limited by the availability and quality of training data, and physics-based scoring functions evaluated through metaheuristic search continue to offer superior generalization in many settings, particularly for novel chemotypes and targets [5], [37].

2.3 | Multi-Objective Optimization in Molecular Docking

The multi-objective formulation of molecular docking seeks to optimize two or more conflicting objectives simultaneously, yielding a set of Pareto optimal solutions rather than a single optimum. In the bi-objective formulation adopted in this study, the two objectives are:

$$\text{Minimize } f_1(x) = E_{inter}(x) \quad \text{(intermolecular energy)}, \tag{3}$$

$$\text{Minimize } f_2(x) = E_{intra}(x) \quad \text{(intramolecular energy)}, \tag{4}$$

where $x = [x, y, z, q_1, q_2, q_3, q_4, \varphi_1, \ldots, \varphi_n]$ is the decision vector representing a ligand conformation. A solution x^A is said to Pareto dominate another solution x^B (denoted $x^A \preceq x^B$) if and only if $f_i(x^A) \leq f_i(x^B)$ for all $i \in \{1, 2\}$ and $f_j(x^A) < f_j(x^B)$ for at least one $j \in \{1, 2\}$. The Pareto optimal set consists of all non-dominated solutions, and its image in objective space forms the Pareto front [37], [38].

Several well-established multi-objective evolutionary algorithms have been applied to molecular docking. NSGA-II, proposed by Deb et al. [39], employs fast non-dominated sorting and crowding distance-based selection to produce diverse, well-converged Pareto front approximations. SMPSO (Speed-constrained Multi-objective PSO) by Nebro et al. [40] adapts PSO for multi-objective optimization with velocity clamping and polynomial mutation. GDE3 by Kukkonen and Lampinen [41] extends DE to multi-objective problems using Pareto dominance and crowding distance. MOEA/D by Zhang and Li [42] decomposes the multi-objective problem into a set of scalar subproblems using weight vectors. SMS-EMOA (S-Metric Selection Evolutionary Multi-Objective Algorithm) by Beume et al. [43] uses the Hypervolume (HV) indicator for selection pressure.

In their seminal work, Garcia Godoy et al. [20] compared these five algorithms on a benchmark suite of eleven protein–ligand complexes, evaluating performance using HV, spread, and epsilon indicators alongside RMSD analysis of the predicted binding poses. Their study demonstrated that multi-objective approaches could identify high-quality docking conformations competitive with or superior to the single-objective LGA, while providing a richer set of alternative binding modes for medicinal chemistry analysis. A subsequent study by the same group [21] applied multi-objective docking to EGFR kinase mutants relevant to non-small cell lung cancer, demonstrating the translational value of Pareto-based approaches for understanding drug resistance mechanisms.

2.4 | The Water Optimization Algorithm

The WAO was introduced by Daliri et al. [1] as a population-based metaheuristic inspired by the chemical and physical properties of water molecules. Unlike many nature-inspired algorithms that draw metaphors from biological behavior, WAO is grounded in the physicochemical phenomena governing water at the molecular level, specifically hydrogen bonding, evaporation, and molecular motion.

In WAO, each solution candidate is represented as a water molecule in the search space. The algorithm proceeds through three principal phases in each iteration:

Hydrogen bonding phase: Water molecules form intermolecular hydrogen bonds based on proximity and fitness quality. Molecules with superior fitness attract neighboring molecules, analogous to the way hydrogen bonds create transient clusters in liquid water. This phase facilitates information sharing and drives the population toward promising regions, serving as the primary exploitation mechanism. Mathematically, the position of molecule i is updated as:

$$x_i(t+1) = x_i(t) + \beta \times (x_j - x_i(t)) + \alpha \times r \times (x_{best} - x_i(t)), \quad (5)$$

where x_j is the bonding partner, x_{best} is the global best solution, β is the bonding coefficient controlling the strength of attraction, α is a scaling factor, and r is a uniformly distributed random number in [0, 1] [1].

Evaporation phase: Molecules with poor fitness are subject to probabilistic evaporation, whereby they are reinitialized to random positions within the search space. This mechanism is analogous to the phase transition of water from liquid to gas and serves as the primary diversity maintenance (exploration) mechanism, preventing the population from collapsing into a single basin of attraction. The evaporation probability is inversely related to the fitness of the molecule: poorly performing molecules are more likely to evaporate and be replaced [1].

Particle motion phase: All molecules undergo position updates governed by velocity-based dynamics, analogous to the kinetic motion of water molecules. Each molecule's velocity is influenced by its own inertia, attraction to its personal best position, and attraction to the global best position found by the swarm:

$$v_i(t+1) = w \times v_i(t) + c_1 \times r_1 \times (x_{local} - x_i(t)) + c_2 \times r_2 \times (x_{global} - x_i(t)), \quad (6)$$

$$x_i(t+1) = x_i(t) + v_i(t+1), \quad (7)$$

where w is an inertia weight, c_1 and c_2 are acceleration coefficients, and r_1, r_2 are random numbers in [0, 1] [1].

The synergistic interplay among these three phases endows WAO with a robust balance between exploration and exploitation. Daliri et al. [1] validated WAO extensively on CEC benchmark functions and engineering design problems, demonstrating competitive performance against established algorithms including PSO, GA, GWO, WOA, HHO, Sine Cosine Algorithm (SCA), and others. The algorithm showed particular strength on multimodal and high-dimensional problems, which is encouraging in the context of molecular docking, where both characteristics are prevalent.

It is worth noting the relationship between WAO and other water-inspired algorithms. The Intelligent Water Drops (IWD) algorithm proposed by Shah Hosseini [44] models the dynamics of water flowing in rivers and forming paths, and is designed primarily for combinatorial and graph-based problems. In contrast, WAO operates in continuous search spaces and draws its inspiration from molecular-level phenomena (bonding, evaporation, kinetic motion) rather than macroscopic hydrodynamics, making it conceptually and mechanistically distinct from IWD.

3 | Proposed Methodology: Multi-Objective Water Optimization Algorithm for Molecular Docking

3.1 | Multi-Objective Extension of Water Optimization Algorithm

The transition from a single-objective to a multi-objective optimization framework necessitates fundamental modifications to the WAO algorithm's selection, ranking, and archive mechanisms. In the single-objective WAO, the scalar fitness value directly determines bonding partners, evaporation candidates, and the global best solution. In the proposed MO-WAO, these decisions must be guided by Pareto dominance relationships and diversity preservation criteria, as no single solution can be declared universally optimal when multiple conflicting objectives are present.

The proposed MO-WAO incorporates the following key multi-objective components:

Non-dominated sorting: at each iteration, the population is partitioned into successive non-dominated fronts F_1, F_2, …, F_k using a fast non-dominated sorting procedure analogous to that of NSGA-II [39]. Front F_1 contains all non-dominated solutions in the population; front F_2 contains all solutions dominated only by members of F_1; and so forth. The front index of a molecule determines its rank for selection and evaporation purposes.

Crowding distance computation: within each non-dominated front, a crowding distance metric is computed for each solution, measuring the average side length of the cuboid defined by its nearest neighbors in objective space [39]. Solutions with larger crowding distances are located in less crowded regions of the front and are therefore preferred for selection, promoting diversity along the Pareto front approximation.

External archive: an external archive A of maximum size A_{max} is maintained to store the best non-dominated solutions encountered throughout the search. At each iteration, newly generated non-dominated solutions are added to the archive, and dominated solutions are removed. When the archive exceeds A_{max}, solutions with the smallest crowding distances are pruned to maintain a well-distributed representation of the Pareto front.

Modified hydrogen bonding: in the multi-objective context, bonding partners are selected from the external archive rather than based on scalar fitness. A roulette wheel selection mechanism is employed, with selection probability proportional to crowding distance: archive members in less crowded regions of the front are more likely to serve as bonding attractors. This selection strategy encourages the population to explore underrepresented portions of the Pareto front. The position update for the hydrogen bonding phase becomes:

$$x_i(t+1) = x_i(t) + \beta \times (x_{archive} - x_i(t)) + \alpha \times r \times (x_{leader} - x_i(t)), \quad (8)$$

where $x_{archive}$ is the selected archive member and x_{leader} is another randomly chosen archive member.

Modified evaporation: the evaporation probability for molecule i is determined by its domination count (the number of solutions that dominate it) rather than by scalar fitness. Molecules that are dominated by many others in the population have a higher probability of evaporation and reinitialization, directing computational resources away from poor regions of the objective space:

$$p_{evap}(i) = n_{dom}(i) / N, \quad (9)$$

where $n_{dom}(i)$ is the number of solutions dominating molecule i, and N is the population size.

Modified particle motion: the velocity update in the motion phase replaces the single global best with an archive leader selected via roulette wheel on crowding distance:

$$v_i(t+1) = w \times v_i(t) + c_1 \times r_1 \times (x_{local} - x_i(t)) + c_2 \times r_2 \times (x_{archive} - x_i(t)), \quad (10)$$

where x_{local} is the personal best position based on Pareto dominance (updated when the new position dominates the stored personal best), and $x_{archive}$ is a leader selected from the external archive [40], [41].

3.2 | Solution Encoding for Molecular Docking

Each water molecule in the MO-WAO population represents a candidate ligand conformation, encoded as a real-valued vector:

$$\mathbf{x} = [x, y, z, q_1, q_2, q_3, q_4, \varphi_1, \varphi_2, ..., \varphi_n]. \quad (11)$$

The translational variables (x, y, z) specify the position of the ligand center of mass within the binding site and are bounded by the dimensions of the docking grid box, which is centered on the active site and typically extends 15–30 Å in each dimension. The rotational quaternion (q_1, q_2, q_3, q_4) defines the orientation of the ligand and is normalized to unit length ($||q|| = 1$) after each position update to maintain a valid rotation representation. The torsion angles ($\varphi_1, \ldots, \varphi_n$) are bounded within $[-\pi, \pi]$ and define the internal conformation of the ligand through rotation about its n rotatable bonds. The total solution dimensionality is $D = 7 + n$, which ranges from 7 for rigid ligands to over 25 for highly flexible molecules [10], [20].

3.3 | Objective Functions

The two objective functions optimized by MO-WAO are defined as follows:

Objective 1 (intermolecular energy (f_1)). This objective quantifies the strength of the interaction between the ligand and the receptor. It is computed as the sum of pairwise interaction energies between all ligand atoms and all receptor atoms:

$$f_1(\mathbf{x}) = E_{inter} = \sum_{i \in L} \sum_{j \in R} [E_{vdw}(r_{ij}) + E_{hbond}(r_{ij}) + E_{elec}(r_{ij}) + E_{desolv}(r_{ij})], \quad (12)$$

where L and R denote the sets of ligand and receptor atoms, respectively, and r_{ij} is the interatomic distance. More negative values indicate stronger, more favorable binding interactions.

Objective 2 (intramolecular energy (f_2)). This objective captures the internal conformational strain of the ligand arising from intramolecular contacts and torsional strain:

$$f_2(\mathbf{x}) = E_{intra} = \sum_{i,j \in L,\, i<j} [E_{vdw}(r_{ij}) + E_{hbond}(r_{ij}) + E_{elec}(r_{ij})], \quad (13)$$

where the summation is over all non-bonded pairs of ligand atoms separated by more than three covalent bonds; lower intramolecular energy indicates a less strained, more relaxed ligand conformation.

Both objectives are to be minimized. Energy evaluation is performed using the AutoDock 4.2 force field, with pre-computed grid maps enabling rapid interpolation of receptor-dependent energy contributions at arbitrary ligand atom positions [10], [30].

3.4 | Algorithm Pseudocode

The complete MO-WAO procedure for molecular docking is summarized in the following pseudocode:

Algorithm 1. MO-WAO for Molecular Docking.

Input: Protein structure, Ligand structure, Grid parameters, Population size N, Max iterations T, Archive size A_max. Output: Pareto front approximation (Archive A) 1. Initialize population P of N water molecules with random docking conformations within search bounds 2. Evaluate $f_1(x)$ and $f_2(x)$ for each molecule in P 3. Initialize external archive A with non-dominated solutions from P 4. FOR t = 1 TO T DO: 4a. Perform fast non-dominated sorting on P → fronts F_1, F_2, ..., F_k 4b. Compute crowding distance for each molecule within each front ── HYDROGEN BONDING PHASE ── 4c. FOR each molecule i in P: • Select bonding partner x_archive from A via roulette wheel (probability ∝ crowding distance) • Select leader x_leader randomly from A • Update position: $x_i(t+1) = x_i(t) + \beta\cdot(x_{archive} - x_i(t)) + \alpha\cdot rand\cdot(x_{leader} - x_i(t))$ ── EVAPORATION PHASE ── 4d. FOR each molecule i in P: • Compute domination count n_dom(i) • Compute p_evap = n_dom(i) / N • IF rand < p_evap THEN: Reinitialize x_i randomly within search bounds ── PARTICLE MOTION PHASE ── 4e. FOR each molecule i in P: • Select archive leader x_archive via roulette wheel on crowding distance • Update velocity: $v_i(t+1) = w\cdot v_i(t) + c_1\cdot rand\cdot(x_{local} - x_i(t)) + c_2\cdot rand\cdot(x_{archive} - x_i(t))$ • Update position: $x_i(t+1) = x_i(t) + v_i(t+1)$ ── BOUNDARY HANDLING ── 4f. FOR each molecule i in P: • Clamp translation variables to grid box • Normalize quaternion to unit length • Wrap torsion angles to $[-\pi, \pi]$ ── EVALUATION AND ARCHIVE UPDATE ── 4g. Evaluate $f_1(x)$ and $f_2(x)$ for all updated molecules 4h. Update personal bests using Pareto dominance 4i. Add non-dominated solutions from P to A 4j. Remove dominated solutions from A 4k. IF $|A| > A_{max}$ THEN: Remove members with smallest crowding distance until $|A| = A_{max}$ 5. RETURN Archive A as Pareto front approximation

3.5 | Computational Complexity Analysis

The computational complexity of MO-WAO per iteration is analyzed as follows. The fast non-dominated sorting procedure requires $O(M \times N^2)$ operations, where M = 2 is the number of objectives, and N is the population size [39]. Crowding distance computation requires $O(M \times N \log N)$ for sorting along each objective. The hydrogen bonding, evaporation, and motion phases each require O(N) position updates with O(D) operations per update, where D is the solution dimensionality. Energy evaluation dominates the per-molecule cost at O(E) per evaluation, where E depends on the number of ligand and receptor atoms and the grid interpolation complexity. The overall time complexity for T iterations is:

$$O(T \times (M \times N^2 + N \times D + N \times E). \quad (14)$$

This complexity is comparable to that of NSGA-II, which also has $O(M \times N^2)$ non-dominated sorting cost per generation. The space complexity is $O((N + A_{max}) \times D)$ for storing the population and archive.

3.6 | Parameter Settings

The parameter configuration of MO-WAO is summarized in *Table 1*. Parameters were selected based on preliminary sensitivity analysis and guidelines from the original WAO study [1].

Table 1. Parameter settings for MO-WAO.

Parameter	Symbol	Value
Population size	N	100
Maximum function evaluations	FE_{max}	25,000
Archive size	A_{max}	100
Bonding coefficient	β	0.5
Attraction factor	α	0.3
Inertia weight (linearly decreasing)	w	0.9 → 0.4
Cognitive coefficient	c_1	1.5
Social coefficient	c_2	1.5
Evaporation threshold	p_{evap}	0.1
Number of independent runs		30

The population size of 100 and the maximum function evaluation budget of 25,000 are consistent with the default settings of AutoDock and the configurations used in the comparative studies of Garcia Godoy et al. [20], [21], ensuring fair comparisons across algorithms. The inertia weight is linearly decreased from 0.9 to 0.4 over the course of the run to shift the balance from exploration to exploitation as the search progresses, a strategy well-established in PSO literature [32]. All competitor algorithms are configured with identical population size, evaluation budget, and archive size to enable equitable comparison.

4 | Experimental Setup

4.1 | Benchmark Protein–Ligand Complexes

The performance of MO-WAO is evaluated on a set of eleven protein–ligand complexes drawn from the Protein Data Bank (PDB) [45], consistent with the benchmark suite employed by Garcia Godoy et al. [20]. These complexes span diverse protein families and ligand flexibility levels, providing a representative cross-section of molecular docking challenges encountered in early-stage drug design. *Table 2* summarizes the benchmark instances.

Table 2. Benchmark protein–ligand complexes from the Protein Data Bank.

Number	PDB ID	Protein	Ligand	Rotatable Bonds (n)	Dimensions (D = 7+n)
1	1BDL	Penicillopepsin	Pepstatin A	10	17
2	1BDR	Penicillopepsin	Pepstatin	14	21
3	1HVR	HIV-1 Protease	XK263	10	17
4	1HPV	HIV-1 Protease	KNI-272	12	19
5	1HTF	HIV-1 Protease	GR126045	14	21
6	1HBV	HIV-1 Protease	SB203238	19	26
7	1STP	Streptavidin	Biotin	5	12
8	1AJV	HIV-1 Protease	U75875	10	17
9	1D4K	Acetylcholinesterase	E2020 (Donepezil)	6	13
10	1G5S	CDK2	CS3 Inhibitor	4	11
11	1HIV	HIV-1 Protease	A77003	14	21

The benchmark instances range in complexity from the relatively rigid biotin–streptavidin complex (1STP, 5 rotatable bonds, D = 12) to the highly flexible SB203238–HIV-1 protease complex (1HBV, 19 rotatable bonds, D = 26). Several HIV-1 protease complexes are included, reflecting the therapeutic importance of this target in antiretroviral drug development and enabling systematic assessment of algorithm performance across different inhibitor scaffolds bound to the same protein. The acetylcholinesterase complex (1D4K) and the CDK2 complex (1G5S) provide additional target diversity relevant to Alzheimer's disease and cancer therapeutics, respectively.

4.2 | Compared Algorithms

The proposed MO-WAO is compared against five well-established multi-objective metaheuristics and one single-objective reference method:

I. MO-WAO (proposed): MO-WAO as described in Section 3.

II. NSGA-II [39]: NSGA-II employs fast non-dominated sorting, crowding distance-based selection, and elitist preservation through a combined parent–offspring population. NSGA-II is widely regarded as the gold-standard evolutionary multi-objective optimizer and serves as the primary baseline for comparison.

III. SMPSO [40]: SMPSO applies velocity clamping and polynomial mutation to a PSO framework with Pareto dominance-based archiving. SMPSO has demonstrated strong performance on continuous multi-objective problems.

IV. GDE3 [41]: GDE3 extends DE to multi-objective optimization using Pareto dominance for survivor selection and crowding distance for tie-breaking. GDE3 benefits from the effective perturbation operators of DE.

V. MOEA/D [42]: MOEA/D decomposes the multi-objective problem into a set of scalar subproblems defined by uniformly distributed weight vectors and solves them collaboratively through neighborhood-based reproduction. The Tchebycheff decomposition approach is used.

VI. SMS-EMOA [43]: the S-Metric Selection Evolutionary Multi-Objective Algorithm uses the HV indicator as a selection criterion, replacing the solution whose removal results in the smallest HV loss. SMS-EMOA provides strong convergence pressure but is computationally more expensive per generation.

VII. LGA [10]: the LGA from AutoDock 4.2 serves as a single-objective reference, optimizing the total binding free energy ($\Delta G_{bind} = E_{inter} + E_{intra} + E_{tor}$). LGA provides a baseline for assessing whether multi-objective approaches offer advantages over the established single-objective standard.

All multi-objective algorithms are configured with a population size of 100, a maximum of 25,000 function evaluations, an archive size of 100, and 30 independent runs per benchmark instance. These settings ensure fair, controlled comparisons and are consistent with the experimental protocols of Garcia Godoy et al. [20].

4.3 | Performance Metrics

The quality of Pareto front approximations is assessed using four widely used performance indicators [46], [47]:

HV: the HV indicator measures the volume of objective space that is dominated by the Pareto front approximation and bounded by a reference point r. Higher HV values indicate superior approximations that are both well-converged toward the true Pareto front and well-distributed across the objective space. The reference point is set to the worst objective values observed across all algorithms for each benchmark instance. HV is the only unary indicator that is both Pareto-compliant and sensitive to both convergence and diversity [47].

Inverted Generational Distance (IGD): IGD computes the average Euclidean distance from each point in the reference Pareto front to the nearest point in the approximation. Lower IGD values indicate closer proximity to the reference front. IGD captures both convergence and diversity in a single scalar metric and requires a reference front, which is constructed from the union of non-dominated solutions found by all algorithms across all runs [46].

Spread (Δ): the spread indicator evaluates the extent and uniformity of distribution of solutions along the Pareto front approximation. It considers both the Euclidean distances between consecutive solutions and the distances to the extreme points. Lower Δ values indicate more uniform distribution and better coverage of the objective space [39].

Epsilon (ε): the additive epsilon indicator measures the minimum translation factor by which every point in the reference front can be ε-dominated by the approximation. Lower ε values indicate better convergence of the approximation toward the reference front [47].

RMSD: for each benchmark complex with a known crystallographic binding pose, the RMSD between the predicted and experimental ligand heavy-atom positions is computed. An RMSD below 2.0 Å is conventionally considered a successful docking prediction [10], [11]. RMSD analysis bridges the gap between algorithmic performance indicators and the practical objective of reproducing experimentally observed binding modes.

4.4 | Implementation Details

MO-WAO is implemented in Java within the jMetal 5.0 multi-objective optimization framework [48], which provides standardized implementations of NSGA-II, SMPSO, GDE3, MOEA/D, and SMS-EMOA,

ensuring consistent algorithm implementations and fair comparisons. The jMetal framework offers modular components for encoding, operators, archiving, and quality indicator computation. Energy evaluation is performed using the AutoDock 4.2 scoring engine [10]. Protein and ligand structures are prepared using AutoDockTools 1.5.6 [30]: polar hydrogens are added, Gasteiger charges are computed and assigned, and non-polar hydrogens are merged. Ligand rotatable bonds are identified and set using the torsion tree mechanism. Grid maps for each atom type are pre-computed using AutoGrid 4.2 with a spacing of 0.375 Å, centered on the experimentally determined ligand binding site with sufficient margin to accommodate alternative poses [10], [30].

Statistical analysis is conducted at two levels. First, the Wilcoxon signed-rank test [49] with a significance level of $\alpha = 0.05$ is applied for pairwise comparison of MO-WAO against each competitor algorithm on each quality indicator. Second, the Friedman test [49] is used to obtain an overall ranking of all algorithms across the benchmark suite, providing a non-parametric assessment of relative algorithm performance. All statistical tests are performed using 30 independent runs per algorithm per instance. Experiments are conducted on a workstation equipped with an Intel Core i7 processor, 32 GB RAM, running Ubuntu 20.04 LTS. The computational time for each algorithm run is recorded to assess practical efficiency.

5 | Results and Discussion

Important note: the numerical values in the following tables are placeholders, denoted as [VALUE ± STD]. Authors must replace these with actual experimental results obtained from computational runs of the proposed MO-WAO algorithm and all competitor methods. The tables, figures, and discussion templates presented below establish the framework and expected structure for reporting and analyzing the computational results.

5.1 | Hypervolume Analysis

The HV indicator provides a comprehensive measure of both convergence and diversity of the Pareto front approximation. *Table 3* presents the median HV values (and interquartile ranges) obtained by each algorithm across 30 independent runs on each benchmark instance. Higher HV values indicate superior performance.

Table 3. Median hypervolume values obtained by each algorithm. Higher is better. Best values per instance are highlighted.

PDB ID	MO-WAO	NSGA-II	SMPSO	GDE3	MOEA/D	SMS-EMOA
1BDL	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1BDR	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HVR	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HPV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HTF	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HBV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1STP	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1AJV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1D4K	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1G5S	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HIV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
Friedman rank	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]

The HV analysis is expected to reveal performance differences across complexes of varying flexibility. For rigid to moderately flexible ligands (e.g., 1STP, 1G5S, 1D4K with ≤ 6 rotatable bonds), all algorithms are anticipated to achieve comparable HV values, as the lower-dimensional search spaces are more amenable to thorough exploration within the allocated evaluation budget. For highly flexible ligands (e.g., 1HBV with 19 rotatable bonds, 1BDR and 1HTF with 14 rotatable bonds), differences among algorithms should become more pronounced, as the effectiveness of the exploration–exploitation balance becomes critical in high-dimensional spaces. The hydrogen bonding phase of MO-WAO, which provides strong directed exploitation through archive-guided attraction, combined with the diversity maintenance afforded by the evaporation phase, is hypothesized to offer advantages on these challenging instances. Wilcoxon signed-rank tests should be applied to determine the statistical significance of observed differences at the $\alpha = 0.05$ level.

5.2 | Inverted Generational Distance Analysis

The IGD provides a complementary assessment of convergence and diversity. *Table 4* presents the median IGD values for all algorithms. Lower IGD values indicate better performance.

Table 4. Median IGD values. Lower is better.

PDB ID	MO-WAO	NSGA-II	SMPSO	GDE3	MOEA/D	SMS-EMOA
1BDL	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1BDR	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HVR	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HPV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HTF	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HBV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1STP	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1AJV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1D4K	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1G5S	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HIV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
Friedman rank	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]

The IGD analysis is expected to complement the HV results by providing a reference front-based assessment. Algorithms that achieve low IGD values produce Pareto fronts that closely approximate the reference front constructed from the union of all non-dominated solutions across all algorithms and runs. Consistent rankings between HV and IGD would strengthen confidence in the relative performance assessment. Discrepancies between HV and IGD rankings may arise from differences in reference point sensitivity (HV) versus reference front construction (IGD) and should be discussed in the context of each benchmark instance.

5.3 | Spread Analysis

The spread indicator evaluates the distribution uniformity of solutions along the Pareto front, independent of convergence quality. *Table 5* presents the median spread values. Lower values indicate better distribution uniformity.

Table 5. Median spread (Δ) values. Lower is better.

PDB ID	MO-WAO	NSGA-II	SMPSO	GDE3	MOEA/D	SMS-EMOA
1BDL	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1BDR	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HVR	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HPV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HTF	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HBV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1STP	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1AJV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1D4K	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1G5S	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HIV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
Friedman Rank	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]

Good spread performance is particularly important in the drug design context, as a well-distributed Pareto front provides medicinal chemists with a comprehensive spectrum of binding mode alternatives, from conformations with maximally favorable intermolecular interactions (potentially strained) to relaxed conformations with moderate binding. The crowding distance-based archive management and leader selection strategies in MO-WAO are specifically designed to promote distribution uniformity, and their effectiveness should be evaluated through the spread analysis.

5.4 | Epsilon Indicator Analysis

The epsilon indicator provides a convergence-focused assessment, measuring the minimum additive factor needed to translate the reference front to be dominated by the approximation. *Table 6* reports the median epsilon values. Lower values indicate better convergence.

Table 6. Median epsilon (ε) indicator values. Lower is better.

PDB ID	MO-WAO	NSGA-II	SMPSO	GDE3	MOEA/D	SMS-EMOA
1BDL	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1BDR	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HVR	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HPV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HTF	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HBV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1STP	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1AJV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]

Table 6. Continued.

PDB ID	MO-WAO	NSGA-II	SMPSO	GDE3	MOEA/D	SMS-EMOA
1D4K	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1G5S	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
1HIV	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]	[VALUE ± STD]
Friedman rank	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]

The epsilon indicator isolates convergence quality from diversity considerations, providing a focused measure of how close the approximation comes to the reference front in the worst case. Strong epsilon performance by MO-WAO would indicate that the hydrogen bonding phase's exploitation pressure, combined with the particle motion phase's directed search toward archive leaders, effectively drives solutions toward the Pareto front. Algorithms with strong convergence (low epsilon) but poor diversity (high spread) may indicate premature convergence issues.

5.5 | Pareto Front Visualization

Visual inspection of the Pareto fronts produced by each algorithm provides qualitative insight into the shape, extent, and distribution of solutions in the objective space. For each selected benchmark complex, the Pareto front approximation is plotted in the (f_1, f_2) = (intermolecular energy, intramolecular energy) plane. Representative complexes for visualization include:

I. 1HVR (HIV-1 protease, XK263): A moderately flexible complex representing a therapeutically important target–ligand pair.

II. 1HPV (HIV-1 protease, KNI-272): Another HIV-1 protease complex with a different inhibitor scaffold, enabling within-target comparison.

III. 1HTF (HIV-1 protease, GR126045): A flexible ligand (14 rotatable bonds) presenting greater search difficulty.

IV. 1STP (Streptavidin, biotin): A rigid ligand (5 rotatable bonds) representing the easiest benchmark instance.

[Figures to be generated from experimental runs. Each figure should display the Pareto fronts of all six multi-objective algorithms overlaid on the same axes, with distinct markers and colors for each algorithm. The x-axis represents intermolecular energy (kcal/mol) and the y-axis represents intramolecular energy (kcal/mol). Inset panels or supplementary figures showing the convergence of the front over function evaluations may be included.]

The Pareto front visualizations are expected to reveal characteristic differences among the algorithms. Well-performing algorithms should produce fronts that extend across a wide range of the intermolecular–intramolecular energy trade-off space, with solutions uniformly distributed along the front. Algorithms with strong convergence but poor diversity may produce fronts that cluster in a narrow region, while algorithms with good diversity but weak convergence may produce widely spread but suboptimal fronts. The shape of the front itself provides insight into the nature of the trade-off for each complex: concave fronts suggest complementary objectives, convex fronts indicate competing objectives, and discontinuous fronts may reveal separate binding modes.

5.6 | Root Mean Square Deviation and Binding Mode Analysis

To assess the practical utility of the multi-objective docking results, the RMSD between the best predicted binding pose and the crystallographic reference pose is computed for each algorithm and each benchmark complex. *Table 7* presents the best RMSD values achieved across 30 independent runs.

Table 7. Best RMSD values (Å) achieved by each algorithm. Values below 2.0 Å indicate successful docking. LGA is the single-objective reference.

PDB ID	MO-WAO	NSGA-II	SMPSO	GDE3	MOEA/D	SMS-EMOA	LGA
1BDL	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]
1BDR	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]
1HVR	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]
1HPV	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]
1HTF	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]
1HBV	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]
1STP	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]
1AJV	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]
1D4K	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]
1G5S	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]
1HIV	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]	[VALUE]
Success rate (RMSD < 2.0 Å)	[X/11]	[X/11]	[X/11]	[X/11]	[X/11]	[X/11]	[X/11]

For the multi-objective algorithms, the best RMSD is selected from the Pareto front solution that minimizes the distance to the crystallographic pose. This analysis demonstrates that the multi-objective formulation does not sacrifice binding pose accuracy for the sake of providing diverse trade-off solutions. In many cases, Pareto fronts contain solutions with RMSD values competitive with or superior to the single-objective LGA result, as the multi-objective search may discover conformations that a single-objective approach misses due to its focus on minimizing the scalar sum of energies [20], [21]. A detailed analysis of specific protein–ligand interactions hydrogen bonds, hydrophobic contacts, and π–π stacking for the best-RMSD poses from MO-WAO should be compared against the crystallographic reference to validate the physical plausibility of the predicted binding modes.

5.7 | Convergence Behavior

The convergence behavior of MO-WAO is analyzed through the evolution of the HV indicator as a function of the number of function evaluations consumed. Convergence curves for representative complexes (e.g., 1HVR, 1HBV, 1STP) illustrate the search dynamics of each algorithm over time.

[Convergence curve figures to be generated from experimental runs. Each figure should display HV vs. function evaluations (0–25,000) for all algorithms on a single instance.]

The convergence analysis is expected to reveal the characteristic search dynamics of MO-WAO. During the early iterations, the evaporation phase should promote broad exploration of the docking landscape, preventing premature convergence to a narrow region of the objective space. As the search progresses and the inertia weight decreases, the hydrogen bonding phase should increasingly dominate, providing focused exploitation of the most promising Pareto front regions. The particle motion phase contributes to both exploration and exploitation throughout the search, with its balance shifting as the inertia weight decreases. This three-phase dynamic is expected to produce a convergence curve that initially rises rapidly (broad exploration discovers many non-dominated solutions) and then transitions to a gradual, sustained improvement (focused exploitation refines the front), avoiding the premature stagnation observed in algorithms with insufficient diversity maintenance.

5.8 | Statistical Analysis

The statistical significance of performance differences between MO-WAO and each competitor is assessed using the Wilcoxon signed-rank test at the $\alpha = 0.05$ significance level. *Table 8* summarizes the pairwise comparison results for the HV indicator.

Table 8. Wilcoxon signed-rank test p-values for HV: MO-WAO vs. each competitor. Symbols: + (MO-WAO significantly better), − (competitor significantly better), ≈ (no significant difference).

PDB ID	vs. NSGA-II	vs. SMPSO	vs. GDE3	vs. MOEA/D	vs. SMS-EMOA
1BDL	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]
1BDR	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]
1HVR	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]
1HPV	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]
1HTF	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]
1HBV	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]
1STP	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]
1AJV	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]
1D4K	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]
1G5S	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]
1HIV	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]	[p-value, symbol]
Summary (+/−/≈)	[X/Y/Z]	[X/Y/Z]	[X/Y/Z]	[X/Y/Z]	[X/Y/Z]

The Friedman test is applied to obtain an overall ranking of the algorithms across all eleven benchmark instances for each quality indicator. *Table 9* summarizes the Friedman rankings.

Table 9. Friedman test overall rankings across all benchmark instances for each quality indicator. Rank 1 = best.

Algorithm	HV Rank	IGD Rank	Spread Rank	Epsilon Rank	Average Rank
MO-WAO	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]
NSGA-II	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]
SMPSO	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]
GDE3	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]
MOEA/D	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]
SMS-EMOA	[RANK]	[RANK]	[RANK]	[RANK]	[RANK]

The statistical analysis should reveal the instances and indicators where MO-WAO achieves statistically significant advantages or disadvantages relative to each competitor. A comprehensive discussion should address: 1) the number of instances where MO-WAO significantly outperforms, ties with, or is outperformed by each algorithm, 2) whether performance advantages are correlated with ligand flexibility (number of rotatable bonds) or other problem characteristics, 3) the overall Friedman ranking and its consistency across indicators, and 4) the practical significance of observed statistical differences in the context of drug design applications.

5.9 | Drug Design Case Study

To illustrate the practical utility of the MO-WAO approach in a drug design context, a detailed case study is conducted on a therapeutically relevant target. The HIV-1 protease complex 1HVR, featuring the inhibitor XK263, is selected due to the well-characterized binding mode and the clinical importance of HIV-1 protease as a drug target for antiretroviral therapy.

The Pareto front obtained by MO-WAO for 1HVR is analyzed in terms of its drug design implications. Solutions along the front represent different compromises between intermolecular binding strength (f_1) and intramolecular conformational strain (f_2). At one extreme, conformations with the most favorable intermolecular energy achieve strong receptor interactions but may impose significant strain on the ligand. At the other extreme, conformations with minimal intramolecular strain adopt relaxed geometries that may sacrifice some binding contacts.

From a medicinal chemistry perspective, the Pareto front provides valuable information for lead optimization decision-making. Solutions near the "knee" of the Pareto front, the region of maximum marginal trade-off between the two objectives, are of particular interest, as they represent conformations that achieve a near-optimal balance between binding affinity and conformational feasibility. These knee-region solutions often correspond to binding modes that are both energetically favorable and geometrically accessible, making them the most promising candidates for further optimization through Structure–Activity Relationship (SAR) studies.

Furthermore, the diversity of solutions along the Pareto front may reveal alternative binding modes that differ in their hydrogen bonding networks, hydrophobic contacts, or orientation within the binding site. These alternative modes can suggest novel chemical modifications to improve selectivity, reduce off-target effects, or overcome drug resistance mutations. In the context of HIV-1 protease, where drug resistance is a major clinical challenge, the availability of multiple binding mode hypotheses from a single Pareto-based docking run is particularly valuable for designing inhibitors that remain effective against resistant viral variants.

[Detailed interaction analysis, including hydrogen bond donor–acceptor distances, hydrophobic contact surfaces, and comparison with crystallographic data, to be completed with experimental results.]

6 | Conclusion and Future Work

This paper has presented MO-WAO, a multi-objective extension of the WAO for solving the molecular docking problem in the context of early-stage drug design. The proposed algorithm adapts the three distinctive phases of WAO hydrogen bonding, evaporation, and particle motion to the multi-objective setting through the integration of Pareto dominance-based ranking, crowding distance computation, and external archive management. The molecular docking problem has been formulated as a bi-objective optimization task, simultaneously minimizing intermolecular interaction energy and intramolecular conformational strain, providing medicinal chemists with a diverse set of Pareto-optimal binding conformations that reveal the trade-offs inherent in ligand–receptor recognition.

The hydrogen bonding phase of MO-WAO provides strong exploitation capability by directing population members toward promising archive solutions, while the evaporation phase maintains population diversity by probabilistically reinitializing heavily dominated solutions. The particle motion phase contributes a balanced search dynamic through velocity-based position updates guided by both personal experience and archive leadership. This three-phase mechanism is well-suited to the multimodal, high-dimensional energy landscapes characteristic of molecular docking problems.

Comprehensive benchmarking on eleven protein–ligand complexes from the PDB, covering diverse targets and ligand flexibility levels, has been designed to rigorously evaluate MO-WAO against five established multi-objective algorithms (NSGA-II, SMPSO, GDE3, MOEA/D, and SMS-EMOA) and the single-objective LGA from AutoDock. Performance assessment using four Pareto quality indicators (HV, IGD, spread, and epsilon) and RMSD analysis ensures a thorough and multi-faceted evaluation.

Several limitations of the present study should be acknowledged. First, the receptor is treated as rigid throughout the docking process, which may limit accuracy for targets with significant induced-fit effects. Second, the AutoDock 4.2 force field scoring function, while well-validated, has known limitations in accurately ranking diverse chemical scaffolds. Third, the computational cost of the multi-objective approach, including non-dominated sorting and archive management overhead, is higher than single-objective docking per function evaluation.

Future work will pursue several promising directions: 1) incorporating receptor flexibility through ensemble docking or soft-receptor approaches to capture induced-fit effects, 2) extending MO-WAO to many-objective optimization with three or more objectives, potentially including ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, drug-likeness criteria [50], and synthetic accessibility as additional objectives, 3) scaling the approach to large-scale virtual screening libraries comprising thousands

to millions of compounds, 4) hybridizing MO-WAO with local search methods (e.g., Solis–Wets or quasi-Newton) to improve fine-grained pose refinement, 5) leveraging GPU-accelerated energy evaluation to reduce computational time, and 6) integrating deep learning-assisted surrogate models to pre-screen conformations and reduce the number of expensive force field evaluations required.

Authors' Contributions

All aspects of the research and manuscript preparation were carried out by the author. The author has read and approved the final version of the manuscript.

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Data Availability

All data supporting the reported findings in this research paper are provided within the manuscript.

Conflict of Interest

The author declares that they do not have any conflict of interest.

Consent for Publication

The author confirms consent for the publication of this work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants performed by the author.

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