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Comparing Evolutionary Programs and Evolutionary Pattern Search Algorithms: A Drug Docking Application

William E. Hart
Applied Mathematics Dept
P.O. Box 5800, MS 1110
Albuquerque, NM 87185-1110
wehart@cs.sandia.gov
(505) 844-2217

ABSTRACT

Evolutionary programs (EPs) and evolutionary pattern search algorithms (EPSAs) are two general classes of evolutionary methods for optimizing on continuous domains. The relative performance of these methods has been evaluated on standard global optimization test functions, and these results suggest that EPSAs more robustly converge to near-optimal solutions than EPs. In this paper we evaluate the relative performance of EPSAs and EPs on a real-world application: flexible ligand binding in the Autodock docking software. We compare the performance of these methods on a suite of docking test problems. Our results confirm that EPSAs and EPs have comparable performance, and they suggest that EPSAs may be more robust on larger, more complex problems.

1 Introduction

Evolutionary programs (EPs) and evolutionary pattern search algorithms (EPSAs) are two classes of evolutionary algorithms (EAs) that have been specifically developed for solving problems of the form

$$\min_{x\in\mathbb{R}^n} f(x).$$

In particular, both of these classes of EAs include mechanisms for controlling the step length of the mutation operator. EPs employ a self-adaptive mechanism that dynamically adapts the step length along with the search parameters, using an indirect feedback from the evolutionary search to guide the selection of step lengths. EPSAs employ an explicit control mechanism of the step length parameter that uses statistics about the prior success of previous mutation steps about the best point in the population.

EPSAs are distinguished from EPs, however, by the convergence theory that guarantees that they weakly converge to a stationary point with probability one [6, 5, 8]. In particular, this is the only convergence theory for EAs that ensures stationary-point converge for nonconvex functions. This provides strong evidence that the step length control used by EPSAs will be robust. Further, termination rules have been developed for EPSAs that have been seen to robustly terminate near a stationary point [7].

We have recently evaluated the relative performance of EPs and EPSAs on a test suite of standard global optimization problems [9]. These results confirmed that EPs and EPSAs perform a global search of the initial search domain. They also suggest that EPSAs will frequently converge to better solutions than EPs, even when EPs are allowed to run beyond the point when an EPSA terminates its search.

In this paper we consider the relative performance of EPs and EPSAs on a real-world application: molecular docking. Computational methods for molecular docking are valuable tools for structure-based drug discovery. Autodock [4, 13] uses a physically detailed model that allows for a fixed receptor site and flexible ligand that is docked into the receptor. Autodock employs a rapid grid-based method for energy evaluation and precalculates ligand-protein pairwise interaction energies so that they may be used as a look-up table during the conformational search. Autodock has been successfully applied to a variety of applications [3] using a simulated annealing search method.

More recently, evolutionary algorithms (EAs) have been incorporated into Autodock and applied to standard test problems [10, 14, 12]. In this work, the EAs consistently perform better than simulated annealing. The molecular docking problem solved by Autodock is a challenging global optimization problem, and the EAs appear to perform a better global search across the range of positional, orientational and conformational parameters for flexible ligands.

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Two forms of EAs have been used with Autodock: a genetic algorithm [2] and a hybrid EA that uses local search. The hybrid EAs apply local search in each iteration to refine points. Rosin et al. [14] and Morris et al. [12] show that this local refinement can significantly improve the performance of the EA. However, the genetic algorithm used in these studies does not adaptively modified the mutation operator's step length, so these results do not completely justify the use of an EA hybrid.

In this paper we apply a standard formulation of EP with the formulation of an EPSA recommended by Hart and Hunter [9] to the standard Autodock test cases. Our results confirm that EPSAs and EPs have comparable performance, and they suggest that EPSAs may be more robust on larger, more complex problems. We compare these results to the performance of the hybrid EAs described by Hart et al. [10], and note that the hybrid EAs have much better performance for this application.

2 Autodock

Autodock docks small flexible substrate molecules to large rigid macromolecules like proteins [13]. A candidate docking gives specific positions and orientations for the protein and a small molecule. Autodock uses an approximate physical model to compute the energy of a candidate docking, and uses a heuristic search to minimize this energy. This method makes most sense when there is a single docked configuration that is at a much lower energy than other configurations, so that we expect this low-energy configuration to be the consistent result of physical interaction between the two molecules. If the prediction of this configuration is to be accurate, the energy function must have its global minimum at or near this physical configuration.

Heuristic search operates on the configuration of the small molecule, assuming (without loss of generality) a fixed position for the protein. The small molecule can take any position around the protein, and can have any orientation. Global orientation is expressed as a quaternion, which can be thought of as a vector giving an axis of rotation, along with an angle of rotation about this axis. The small molecule may also have several internal rotatable bonds so that its shape is somewhat flexible. The representation of a candidate docking consists of 3 coordinates giving the position of the small molecule, followed by the 4 components of the quaternion specifying the overall orientation of the small molecule, followed by one angle for each of the rotatable bonds.

The docking potential used in Autodock 3.0 is an empirical free energy potential. This energy potential is composed of five terms (see Morris et al. [12] for further details). The first three are pairwise interatomic potentials that account for short-range electrostatic repulsive forces and long-range weak van der Waals attractive forces. The standard Lennard-Jones 12-6 potential is used for the van der Waals forces, and a 12-10 potential is used for hydrogen bonds. The next term measures the unfavorable entropy of a ligand binding due to the restriction of conformational degrees of freedom, using a measure that is proportional to the number of sp^3 bonds in the ligand. The last term uses a desolvation measure adapted from Stouten et al. [18] which works well with the precalculated grid formulation used by Autodock.

To account for internal energy in a flexible small molecule with internal rotatable bonds, we calculate the same energy contributions summed over all pairs of atoms within the small molecule. This sum is added to the total energy evaluation. This penalizes conformations of the small molecule that are energetically unfavorable independent of their interaction with the macromolecule.

To save time when computing energy of interaction with the macromolecule, 3-D potential grids are computed for each atom type before optimization begins. Interaction energy is computed as described above at each point in the grid. Then, when calculating total energy during optimization, the energy contribution of an atom is obtained via trilinear interpolation of its position within the grid specific to its atom type, based on the values at the nearest 8 points in the grid. Calculation of the energy due to pairwise interactions within the small molecule does not make use of these grids.

Computation of the grids for energy evaluation requires knowledge of the (assumed fixed) 3-D positions of each atom in the protein; these positions are usually obtained by X-ray crystallography. We also require the structure of the small molecule, along with the locations of internal rotatable bonds. Small molecules tend to be chemically simple, so that we can determine their structure (at least up to the degrees of freedom represented by the rotatable bonds) from their chemical composition alone. Partial charges are required to calculate electrostatic interaction potentials, but these partial charges can be computed from the structure with molecular modelling software such as MOPAC. So, it is possible to use Autodock to test many candidate small molecules against a single target protein, after obtaining the structure of this protein experimentally. This makes Autodock an important computational tool in the initial stages of drug design.

3 Background

3.1 Evolutionary Programs

Evolutionary programs (EPs) are a standard paradigm for applying evolutionary methods to continuous optimization problems [1]. EPs are similar to evolutionary strategies [16] in many respects. These EAs generally do not rely on recombination to perform a global search of the search domain. Mutation is typically performed by adding normally distributed random variables to each dimension of an individual, and the standard deviation of these normal deviates is usually modified by a self-adaptive mechanism. This mechanism can be viewed as a separate encoding of the mutation standard deviation along with the search parameters.

Figure 1 shows pseudo-code for a canonical EP that uses self-adaptation. $N(0,1)$ is a normally distributed variable with standard deviation 1, and $N(0,\sigma)$ is a vector of normally distributed random variables with standard deviation σ_i. The function **selection** selects individuals from the previous population (possibly creating a multiset) that are used to perform additional search, and the function **compose** forms the next population using the newly generated points and the previous population. This code uses a log-normal update to σ_i, which Saravanan, Fogel and Nelson [15] confirm is generally preferable to the additive update that has been proposed for EPs. This update uses the constants $\tau = \left(\sqrt{2\sqrt{n}}\right)^{-1}$ and $\tau' = \left(\sqrt{2n}\right)^{-1}$ [15]. The stopping rules used for EPs typically rely on measures of the rate of improvement or population statistics that evaluate whether the population has converged to a single point [1].

3.2 Evolutionary Pattern Search Algorithms (EPSA)

Figure 2 shows pseudo-code for a class of simple EPSAs. These methods share many of the common features of standard EAs like EP and ES. Mild conditions are placed upon the **selection** and **compose** functions to ensure that (a) the best point in the population has a nonzero chance of being selected in each generation and (b) the best point in the population is always kept in subsequent populations. The **crossover** function is also restricted to generate a point such that crossover$(x,y) \in \{x_1,y_1\} \times \{x_2,y_2\} \times \ldots \times \{x_n,y_n\}$, which is consistent with most standard crossover operators (e.g. two-point crossover). The call to uint(j) uniformly generates an integer from 1 to j. The expansion of steps is controled by an expansion factor, **exp-factor**, which is greater than or equal to one.

EPSAs differ from self-adaptive EAs like the EP in Figure 1 in that the step length parameter is controlled explicitly. Further, EPSAs use a single step length parameter for all dimensions, while EPs have separate step length parameters for each dimension. The EPSA step length parameter may be expanded if an improving step is generated from a mutation step off of the current best point. Also, the step length may be contracted if all mutation steps about the current best point have worse fitness than the current best point.

This method of explicitly controlling the step length for mutation enables a stationary point convergence theory for EPSAs. This convergence theory guarantees that for a continuously differentiable function the sequence of best solutions in each generation, $\{x_k^*\}$, has the property that

$$P\left(\liminf_{k\to\infty} \| \nabla f(x_k^*)\| = 0\right) = 1,$$

where $\nabla f(x)$ is the gradient of f at x [6, 5]. Although this is a local convergence theory, experience with direct search methods suggests that EPSAs can be successfully applied to a wide range of optimization problems (e.g. see [11]). Our previous empirical evaluation of EPSAs [9, 7] indicates that they can perform a nonlocal optimization of the search domain.

The convergence theory requires that the set of mutation offsets in an EPSA, S, form a positive basis of the search domain. The *positive span* of a set of vectors $\{a_1,\ldots,a_r\}$ is the cone $\{a \in \mathrm{R}^n \mid a = c_1a_1 + \ldots + c_ra_r, c_i \geq 0 \quad \forall i\}$. The set $\{a_1,\ldots,a_r\}$ is *positive independent* if none of the a_i's is a positive combination of the others. A *positive basis* is a positive independent set whose positive span is R^n. A positive basis has at least $n+1$ vectors and at most $2n$ vectors. Figure 3 illustrates two sets of mutation offsets. Figure 3a depicts the *standard mutation offsets.* This set of offsets uses $S = S_{\text{std}} = \{e_1,-e_1,\ldots,e_n,-e_n\}$. Hence, the mutation steps are parallel to coordinate axes. S_{std} contains $2n$ mutation offsets, so it forms a maximal positive basis. Figure 3b depicts a set of mutation offsets that form a minimal positive basis. The $n+1$ mutation offsets are defined by vectors from the centroid of a regular simplex to each of its corners. This set of mutation offsets consists of axes that are separated by an angle of 120 degrees. The regular simplex is an equilateral triangle in two dimensions, a tetrahedron in three dimensions, and so on. In n dimensions *regular simplex mutation offsets* can be derived using the method defined by Spendley, Hext, and Himsworth [17].

4 Experimental Comparison

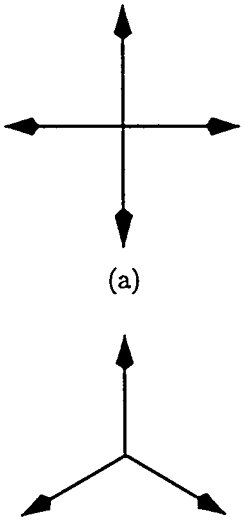
4.1 Methods

We used the EPSA that was recommended by our preliminary experiments with standard global optimization test problems [9]. This EPSA uses the regular simplex mutation offsets and no expansion of the step length is allowed. To make a direct comparison between EPSA and EP, no crossover was used with the EPSA. For both EP and EPSA tests, we used a population size of 50. The mutation operator is always applied in both EAs.

The docking problems have different ranges in each dimension, but we normalized the search by rescaling each dimension to the range [0.0, 1.0]. In this range, the initial step length for EPSAs was set to 0.1. We set up the EP step length parameters to correspond to the step lengths for the EPSA. Specifically, we selected the initial vectors σ_j^0 so that the expected distance of mutation was approximately equal to 0.1 by setting $\bar{\sigma} = 0.1/\sqrt{n}$ (see Hart and Hunter [9] for further details).

```
Given initial step length vectors $\{\sigma_1^0,\dots,\sigma_N^0\}$
Select an initial population $X_0 = \{x_1^0,\dots,x_N^0\}$, $x_i^0 \in \mathrm{R}^n$
Determine the fitness of each individual
$x_0^* = \arg\min\{f(x_1^0),\dots,f(x_N^0)\}$ and $y_0^* = f(x_0^*)$
Repeat $t = 1, 2, \dots$
    $\hat{X} = \text{selection}(X_t)$
    For $i = 1 : N$
        $\nu = N(0,1)$
        For $j = 1 : n$
            $\sigma_i^{t+1}(j) = \sigma_i^t(j) * \exp(\tau'\nu + \tau N(0,1))$
            $\hat{x}_i(j) = \hat{x}_i(j) + N(0, \sigma_i^{t+1}(j))$
    $X_{t+1} = \text{compose}(X_t, \hat{X})$
    $x_t^* = \arg\min\{f(x_{t-1}^*), f(x_1^t),\dots,f(x_N^t)\}$ and $y_t^* = f(x_t^*)$
Until some stopping criterion is satisfied
```

Figure 1 A canonical EP or ES using self-adaptation.



(a)

(b)

Figure 3 Illustrations of sets of mutation offsets: (a) standard mutation offsets and (b) regular simplex mutation offsets.

The EPSA was terminated when the mutation step length fell below a threshold of 10^{-8}. Because of the stochastic nature of step length updates in the EP, we simply bounded the σ_i values below by $10^{-8}/\sqrt{n}$, which keeps the step length above 10^{-8}. This makes the comparison between the EPSA and the EP fair by not allowing the EP to shrink its step length below the step length of the EPSA. The EP was terminated after 1.5 million function evaluations (which enables a comparison with previous work [14, 12]), and performance comparisons between the EPSA and the EP were made based upon the termination point for the EPSA.

4.2 Experiments

A test suite of six cases was used in all of the experiments. Each test case consists of a macromolecule and a small substrate molecule. The salient features of the six test cases are summarized in Table 1. The different test cases were selected to test various aspects of the energy function [13]. In each experiment, 30 trials were done with different random seeds.

The number of torsion angles is an important feature of these test cases because it determines the dimensionality of the search space. The representation used in each experiment consisted of a triple of Cartesian coordinates, a four dimensional quaternion, and the torsion angles. Thus, the dimensionality of the search space is 7+(number of torsion angles). The range of the coordinates defines a cube that is 23 angstroms long in each dimension. The quarternion parameters lie within $[-1,1]^3 \times [0,2\pi]$, and each torsion angle lies within $[-\pi,\pi]$; the points in the initial population have each parameter generated randomly in its range.

5 Results

Figures 4 shows boxplots of the relative rank of the final docking energies for EPSA and EP. Boxplots are a convenient method of summarizing data that provide a visual indication of the spread and skewness of the data. The dark bar in the boxplots show range between the first and third quartile; one quarter of the data is below the first quartile, and three quarters of the data is below the third quartile. The white line inside the dark bar represents the median. The whiskers at the top and bottom of each boxplot indicate the spread of the data up to 1.5 times the range of the first and third quartile.

For each test case, the trials for the hybrid EAs are ranked, and the boxplots show the distribution of ranks within each test case. For EP, we include both the final results after 1.5 million function evaluations, as well as

```
Given $\Delta_0$
Given $S = \{s_1, \ldots, s_k\}$, where $s_i \in \mathbf{Z}^n$ and $S$ forms a positive basis.
Let $\nu = \{0\}^k$
Select an initial population $X_0 = \{x_1^0, \ldots, x_N^0\}$, $x_i^0 \in \mathbf{Q}^n$
$x_0^* = \arg\min\{f(x_1^0), \ldots, f(x_N^0)\}$ and $y_0^* = f(x_0^*)$
Repeat $t = 0, 1, \ldots$
    $\overline{X} = \text{selection}(X_t)$
    For $i = 1 : N$
        If ($\text{unif}() < \chi$) then
            $\hat{x}_i = \text{crossover}(\overline{x}_{\text{uint}(N)}, \overline{x}_{\text{uint}(N)})$
        Else
            $\hat{x}_i = \overline{x}_{\text{uint}(N)}$
    For $i = 1 : N$
        If ($\text{unif}() < \mu$) then
            $j = \text{uint}(k)$
            If $(\hat{x}_i == x_{t-1}^*)$ $\nu_j = 1$
            $\hat{x}_i = \hat{x}_i + \Delta t \cdot s_j$
    $X_{t+1} = \text{compose}(X_t, \hat{X})$
    $x_t^* = \arg\min\{f(x_{t-1}^*), f(x_1^t), \ldots, f(x_N^t)\}$ and $y_t^* = f(x_t^*)$
    If $(f(x_t^*) < f(x_{t-1}^*))$
        $\nu = \{0\}^k$
        If ($\exists s \in S$ s.t. $x_t^* = x_{t-1}^* + s$) $\Delta_t = \Delta_{t-1} * \exp - \text{factor}$
    ElseIf $(|\nu| == k)$
        $\nu = \{0\}^k$
        $\Delta_t = \Delta_{t-1}/2$
    Else
        $\Delta_t = \Delta_{t-1}$
Until $(\Delta_t < \Delta_{lb})$
```

Figure 2 **A simple EPSA using multinomial mutation.**

the results at the median number of function evaluations for the EPSA. Thus we can make direct comparisons between the EP and EPSA as well as consider whether running the EP longer would ultimately find better solutions.

Neither the EP nor the EPSA appears to have a strict advantage in performance. However, there is a distinction between the performance on the test cases 2cpp and 3ptb and the other four test cases. The EP does somewhat better on 2cpp and 3ptb and the EPSA does somewhat better on the other test cases. The difference between these is that 2cpp and 3ptb are the smallest problems, and they have no torsion angles in the ligand. This suggest that the EPSA is more effective for larger, more complicated problems.

6 Discussion

These results provide the first validation of the utility of EPSAs on real-world applications. The EPSA and EP used in our experiments had comparable performance. Further, the comparison between the EPSA and EP recommends the EPSA for its robustness in larger, more complex problems. We did not evaluate the gradient final point that the EPSA terminated with because the docking potential in Autodock is not everywhere differentiable. However, a more careful analysis is needed to evaluate whether or not the point found by the EPSA is locally optimal.

Although our experiments accounted for initial step lengths, there remain a number of important differences between the basic design of the EPSA and EP used in our experiments. Specifically, the EP and EPSA used different mechanisms for selecting individuals and composing the next generation of points. These differences may have a substantial impact on the performance of these EAs, but a complete experimental comparison is beyond the scope of this work. We also did not compare the performance of the EPSAs with crossover. Our prior work with EPSAs [7, 9] strongly indicates that adding crossover will help the EPSAs find better solutions at the expense of a longer time to converge.

Table 2 compares the performance of the EPSA and EP against the hybrid EA used by Hart et al. [10]. It is clear that the hybrid EA finds better results than the EAs in all cases. This confirms that the local search used in these hybrid EAs is a critical part of their success, and

Ligand/Protein Complex	PDB Shorthand	Number of Torsions	Number of Dimensions
β-Trypsin/Benzamidine	3ptb	0	7
Cytochrome P-450cam/Camphor	2cpp	0	7
McPC-603/Phosphocholine	2mcp	4	11
Streptavidin/Biotin	1stp	5	12
HIV-1 protease/XK263	1hvr	10	17
Influenza Hemagglutinin/sialic acid	4hmg	11	18

Table 1 Summary of test cases.

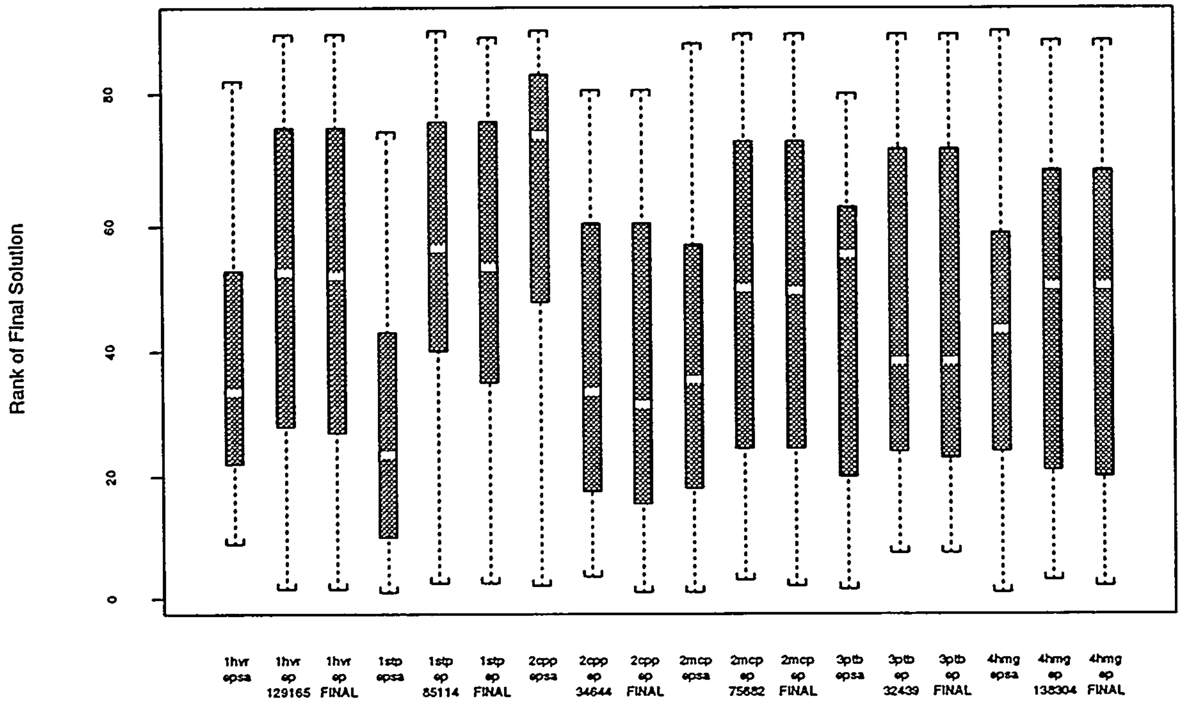


Figure 4 Relative ranks of final docking potentials. EP results include (a) results truncated to the median number of function evaluations and (b) results after 1.5 million function evaluations.

not simply that the local search performs the localized step length adaptation that are not performed by the EA.

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	Hybrid EA		EPSA		EP	
	Minimum	Mean	Minimum	Mean	Minimum	Mean
1hvr	-21.42	-21.40	-19.12	-2.94	-21.22	28.99
1stp	-10.17	-10.15	-9.75	-5.86	-8.52	-4.58
2cpp	-7.36	-7.36	-7.36	-5.80	-7.36	-7.28
2mcp	-5.55	-5.52	-5.37	-3.15	-4.86	-2.70
3ptb	-8.19	-8.16	-8.19	-7.71	-8.15	-6.98
4hmg	-7.91	-7.85	-7.38	-2.74	-7.36	-2.86

Table 2 Best and mean final energies for the EPSA, EP and hybrid EA reported by Hart et al. [10].

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