

# Automated Design of Hyper-Heuristics Components to Solve the PSP Problem with HP model

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**Abstract**—The Protein Structure Prediction (PSP) problem is one of the modern most challenging problems from science. Hence, many heuristics strategies have been applied in order to find protein structures that minimize its free energy. However, these strategies have difficulties on finding the optimal solutions to the longer sequences of amino-acids, due to the complexity of the problem and the huge amount of local optima. The hyper-heuristics framework are usually useful in this kind of context since they try to combine different heuristics strengths into a single framework. However, there is lack of works addressing the automated design of hyper-heuristics components. This paper proposes GEHyPSP an approach which aims to the generation, through grammatical evolution, of selection mechanisms and acceptance criteria for a hyper-heuristic framework applied to PSP problem.

## I. INTRODUCTION

Proteins execute an essential role in nature, they are responsible of many important functions of the living cells. Proteins can be seen as amino-acids structures that guarantee the correct operation of many process from the biological entities. These structures are product of the so-called protein folding process where an unfolded chain of amino-acids is transformed into its final/native structure.

The protein structure prediction (PSP) has a broad range of medical and biotechnology applications. For instance: synthesis of new proteins and folds [29], structure based synthesis of new drugs [8], refinement of theoretical models obtained by comparative modeling [21], [16], and obtaining experimental structures from incomplete nuclear magnetic resonance data [25].

The task of determining the native structures of proteins is challenging even for the modern super computers. The difficulty raises up due to the huge search space to test all possible conformation that a sequence of amino-acids can adopt. There are many models to represent proteins structures and can be used to simulate the folding process. Extremely detailed models exist however these representations are computationally very expensive. Hence, many authors [6], [12], [18], [28], [24], [7], [11] have used simplified models to represent the protein structures. A very common model for this purpose is the Hydrophobic-Polar (HP) model presented by Lau and Dill [17]. This model abstract the amino-acids into just two types: hydrophobic (H) or polar (P). Two-dimensional (2D) and three-dimensional (3D) grids can be used to represent

the conformations that a protein can adopt. Each conformation in the grid has an associated energy [28].

A wide range of heuristics strategies were proposed to search conformations of minimum energy in the HP model. Among the approaches that have been applied are genetic algorithms [28], ant colony optimization [26], [27], estimation distribution algorithms [24], and others [9]. Even though there are different strategies already proposed for the PSP, all face difficulties to reach the optimal conformations when the length of amino-acids sequences increases.

This fact motivates the study here presented. It is in this kind of context that hyper-heuristics are usually a good option. In general the hyper-heuristics frameworks propose a strategy to select, from a pool, the heuristic which is more appropriate for a given stage of the search. Also the hyper-heuristics frameworks define a move acceptance criterion, which is responsible to decide on whether accept or reject worse solutions generated by the heuristics. These strategies are high level heuristics from a hyper-heuristic framework.

Usually the high level heuristics are human-designed approaches although a recent study [23] proposes the automate design of those components. This study presented promising results and so inspired the idea of automating the design of high level heuristics for a hyper-heuristic framework to solve the PSP problem. Since the PSP with the HP-2D model presents a very complex landscape, automating the design of hyper-heuristic framework could save time, money and human effort. Another motivation of the present study is that the hyper-heuristics frameworks have been applied to other domains problems and achieving good results as example in the bin packing, personnel scheduling, flowshop, TSP, MAXSAT and VRP problems [23].

Burke et al. [5] recently defined hyper-heuristics as "an automated methodology for selecting or generating heuristics to solve hard computational search problems". Over the years, these methodologies have succeeded while solving a wide range of real world problems. However, there is not an in-depth investigation of the suitability of this approach to solve the PSP problem.

We introduce GEHyPSP: an automated mechanism for generation of high level heuristics for a hyper-heuristic framework to solve the PSP problem. The high level heuristic includes two main components: a selection mechanism and an acceptance

criterion. Both components are generated using grammatical evolution (GE) [22], which is a kind of genetic programming (GP) [13]. A set of experiments was designed to evaluate the approach using eleven PSP instances. The results are compared with the previous works of the literature [28], [14], [26], [27], [12].

This paper is organized as follows: in the next section we briefly introduce the Protein Structure Prediction problem and a review of the related works is also presented. Section III presents a background of hyper-heuristics, GP and the GE algorithm. Thereafter, in Section IV, the GEHyPSP is introduced. In Section V, the experimental benchmark and numerical results of the conducted experiments are presented. Finally, in Section VI, the conclusions of the research are given, and further work is discussed.

## II. PROTEIN STRUCTURE PREDICTION

Proteins are macromolecules composed by an alphabet of twenty different amino-acids, also referred to as residues. An amino-acid is formed by a peptide backbone and a distinctive side chain group. The peptide bond is defined by an amino group and a carboxyl group connected to an alpha carbon to which a hydrogen and side chain group are attached.

The protein sequence folds, under particular conditions, into a unique native 3-D structure. Each possible protein conformation/structure has an associated energy value. The thermodynamic hypothesis states that the native structure of a protein is the one for which the free energy achieves the global minimum. Based on this hypothesis, many methods [6], [12], [14], [18], [28] that search for the protein native structure define an approximation of the protein energy and use optimization algorithms that look for the protein fold that minimizes the energy. These approaches mainly differ in the type of energy approximation employed and in the characteristics of the protein modeling.

### A. The HP Model

Lau and Dill [17] created a model called *Hydrophobic-Hydrophilic Model* (HP Model), to represent the proteins using simplifications. The model can be used either to represent proteins in a 2D space or 3D space.

The HP model considers only two types of residues: hydrophobic (H) and hydrophilic or polar (P) residues. A protein is considered a sequence of these two types of residues, which are located in regular lattice models and must form a self-avoided walk (SAW). If a structure is not SAW it means that it contains collisions between the amino-acids and this structure is invalid. Given a pair of residues, they are considered neighbors if they are adjacent either in the chain (connected neighbors) or in the lattice but not connected in the chain (topological neighbors). In the HP context the amino-acid sequences are used as instances for the problem.

For the HP model, an energy function that measures the amount of topological neighbor residues is defined as  $\epsilon_{HH} = -1$  and  $\epsilon_{HP} = \epsilon_{PP} = 0$ . The HP problem consists of finding the solution that minimizes the total energy. In the

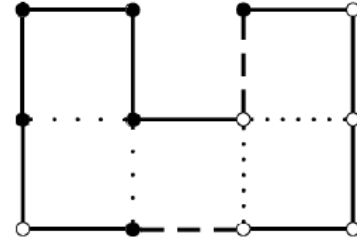


Fig. 1. One possible configuration of sequence *PPPHPHPPH* in the HP model. The white circles represents the P amino-acids and the black circles describes the H amino-acids. There is two *H-H* (represented by a dotted line with wide spaces), one *H-P* (represented by a dashed line) and two *P-P* (represented by dotted lines) contacts.

linear representation of the sequence, hydrophobic residues are represented with the letter H and polar ones, with P. In the graphical representation, hydrophobic proteins are represented by black beads and polar proteins, by white beads. Figure 1 presents a possible graphical conformation for the sequence *PPPHPHPPH* in a 2D space. The energy associated with this conformation is  $-2$ .

We briefly review some of the previous studies on simplified PSP, relevant for our work research.

A study presented by [14] introduces the MMA (Multimeme algorithm) which consisted in an EA combined with a group of local search methods. For each individual in the population, the MMA, selects the local search method that is more suitable with the individual. Used first to find solutions for the functional model protein, the strategy was later improved with fuzzy-logic-based local searches, leading the algorithm to achieve improved results in the PSP problem.

In [12], Hsu et al. presents the pruned-enriched Rosenbluth method (PERM), also known as chain growth algorithm, that is based on growing the sequence conformation by adding particle by particle, aiming to increase good configurations and eliminating bad ones.

The ant colony optimization (ACO), in [26], [27], was applied to the PSP problem using the HP-2D model. This strategy, uses artificial ants to build conformations for a given HP instance (sequence of amino-acids). A local search method is then applied to further improve the solutions and also maintain the quality of the solutions.

The study of Santana et al. [24] applies EDAs as an efficient evolutionary algorithm that learns and exploits the search space in the form of probabilistic dependencies. They introduced new ideas for the application of EDAs to 2D and 3D simplified protein folding problem. The obtained results showed that EDAs can achieve superior solutions compared with other well-known population based optimization algorithms.

The present paper proposes the use of a grammatical evolution GE to generate high level heuristics for a hyper heuristic framework that will be applied to the PSP problem.

### III. BACKGROUND

This section will present the background context in order to provide the readers with the necessary information, for a good comprehension of the concepts and techniques used in this paper.

#### A. Hyper-Heuristics

Mainly, a generic hyper-heuristic framework is composed of two main components known as high-level and low-level heuristics. Figure III-A shows a general scheme of hyper-heuristic frameworks. The high and low levels are separated by a domain barrier which means that the low-level component is problem dependent while the high-level component does not require any knowledge of the problem domain. Ideally it is possible to apply a hyper-heuristic framework to a different problem domain by replacing the low level component, and no changes should be required at the high level. It is responsibility of the high-level component to manage the selection or generation of which heuristic should be applied at each decision point. The low-level component corresponds to a pool of heuristics or heuristic components [23].

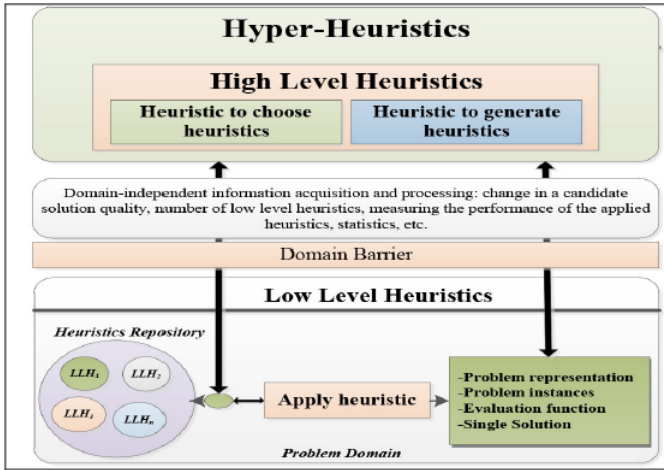


Fig. 2. General scheme of a hyper-heuristic framework.

Based on the nature of the search space, hyper-heuristics can be classified [5] as either selecting or generating heuristics for the underlying problem. Next we analyze both kinds of high-level heuristics.

- **Selecting Heuristics:** The majority of hyper-heuristic frameworks define high level heuristics to select low level heuristics [3]. In general, these frameworks define a selection mechanism and also an acceptance criterion. These strategies use information from the statistical history of low level heuristics applications. For instance, a greedy selection considers only the number of improvements that a low level heuristic obtained. In contrast, the choice function [3] is a reward-based strategy, which considers both the number of improvements and the elapsed time since the last application.

- **Generating Heuristics:** In this case, the hyper-heuristic framework starts with a set subcomponents from the low level heuristics and has the goal of building new low level heuristics with it. GP is reported as a good strategy to combine and generate new heuristics for the SAT, scheduling, and bin-packing problems [23].

A study presented by Sabar et al. [23], proposes an on-line approach to generate selection mechanisms and acceptance criteria (high level heuristics) to a hyper-heuristic framework, using GEP [9] (gene expression programming, a variant of GP). The experiments presented by Sabar et al. [23], using the 6 problem domains provided by the HyFlex hyper-heuristic framework [20], showed impressive results in comparison with other human-designed hyper-heuristic strategies from the state-of-art. The encouraging result inspired the present study which has the objective of generating selection mechanisms and acceptance criteria, through a grammatical evolution process in a off-line manner, for a hyper-heuristic framework to solve the PSP problem using the simplified HP-2D model.

#### B. Genetic Programming (GP)

It is a sub-field from the program synthesis which uses ideas from the evolution theory to produce programs [13].

Grammatical Evolution (GE) is a relatively new technique from the evolutionary computing, introduced by Ryan et al. [22] and it is a type of GP where programs are evolved using a genetic algorithm. The chromosome encode production rules of the grammar. GE uses a mapping mechanism between the genotype (coded individuals by integer vectors) and phenotype (generated programs to solve a problem). The BNF notation is used to represent a grammar from a language in form of production rules. A BNF grammar consists in a set of terminals, which are items that are allowed to the language, for instance:  $+$ ,  $-$ ,  $*$ ,  $/$ , etc and non-terminals, which can be expanded into one or more terminals. The Grammar can be expressed as a tuple  $N, T, P$ , where  $N$  is a set of non-terminals presented in the Grammar 1 as  $\langle expr \rangle$ ,  $\langle op \rangle$ ,  $\langle pre - op \rangle$  and  $\langle var \rangle$ ,  $T$  a set of terminals and is presented in the Grammar 1 as  $+$ ,  $-$ ,  $/$ ,  $*$ ,  $Sin$ ,  $Cos$  and  $Tan$ . Finally,  $P$  is the set of production rules that maps the elements  $N$  to  $T$  and is presented in Table I.

TABLE I  
EXAMPLE OF POSSIBLE PRODUCTION RULES AND THE NUMBER OF CHOICES ALLOWED

Production Rules	Number of choices
$\langle expr \rangle$	4
$\langle op \rangle$	4
$\langle pre - op \rangle$	3
$\langle var \rangle$	1

Ryan et al. [22] proposed the use of GA to control which choices should be made, in this sense allowing the GA to select which production rules should be utilized. Algorithm 1 presents the pseudocode of a grammatical evolution program. Lines 3 to 6 represent the initialization of the algorithm: a randomly generated population is created and then mapped to

$\langle expr \rangle$	$::= \langle expr \rangle \langle op \rangle \langle expr \rangle$	(0)
	$(\langle expr \rangle \langle op \rangle \langle expr \rangle)$	(1)
	$\langle pre-op \rangle (\langle expr \rangle)$	(2)
	$\langle var \rangle$	(3)
$\langle op \rangle$	$::= +$	(0)
	$-$	(1)
	$/$	(2)
	$*$	(3)
$\langle pre-op \rangle$	$::= \text{Sin}$	(0)
	$\text{Cos}$	(1)
	$\text{Tan}$	(2)
$\langle var \rangle$	$::= X$	(0)

Grammar 1. Sample grammar to demonstrate how to decode integer vectors in computer programs

programs using the GF (Grammar File). Those programs are evaluated and a fitness value is assigned for each individual in the population. Line 7 indicates the start of the main loop of the algorithm and the evolution process occurs within this loop. Line 8 invokes the parent selection that will be used in the crossover in Line 9 which will generate an offspring (integer vectors). The offspring is then used as input to prune and duplication operators in Lines 10, 11. The mutation operator is applied to the offspring in Line 12. The mapping between the integer vectors to programs is accomplished in Line 13. Next the execution and fitness assignment to the individuals from the population are implemented in Line 14 and 15. The population replacement with the fittest individuals is done in Line 16. Finally, line 18 return the program with the best fitness found.

For the sake of comprehension the chromosome mapping process will be illustrated using Grammar 1. Algorithm 2 presents the general template of the generated programs. The expression  $\langle expr \rangle$  shown in line 2 is replaced by mathematical expressions coded by the chromosomes (integer vectors). Now suppose the following integer vector:

[220, 203, 17, 6, 108, 215, 104, 30]

This vector will be used to decode the chromosome (genotype) into a piece of code (phenotype) using the Grammar 1. Table I summarizes the number of choices associated within each production rule from Grammar 1.

There are 4 options of production rules that can be selected for the expression  $\langle expr \rangle$ . In order to select which option, the first value from the vector should be used. The value is 220 and its remainder divided by 4 (four options that can be selected for the expression  $\langle expr \rangle$ ) results in 0, which means that the first option should be selected  $\langle expr \rangle \langle op \rangle \langle expr \rangle$ . Note that the first expression is also  $\langle expr \rangle$  and following the same logic we should expand using the next value from the integer

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**Algorithm 1:** Pseudo code from the Grammatical Evolution

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```

1 Input: GF – Grammar File
2 begin
3   population  $\leftarrow$  Create population;
4   programs  $\leftarrow$  Maps the population to programs using GF;
5   Execute the program;
6   Assign fitness value to the solutions of population according with
   the output obtained by the respective decoded program;
7   while Stop condition not reached do
8     parents  $\leftarrow$  Select individuals for crossover;
9     offspring  $\leftarrow$  Crossover(parents);
10    Apply the Prune operator to the offspring;
11    Apply the Duplicate operator to the offspring;
12    Apply the Mutation operator to the offspring;
13    programs  $\leftarrow$  Maps offspring to programs using GF;
14    Execute programs;
15    Assign fitness value to solutions offspring according with
    the output obtained by the respective decoded program;
16    population  $\leftarrow$  Replacement;
17  end
18  return Best program from the population;
19 end

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**Algorithm 2:** General template for the generated algorithms

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```

1 float symb(float x)
2 a =  $\langle expr \rangle$ ;
3 return a;

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vector and apply its remainder by the division of the number of options. The remainder of  $203 \% 4 = 3$ , which indicates that we should select the fourth option:  $\langle var \rangle$  which is a terminal. The  $\langle var \rangle$  has just one option associated with it and is the value  $X$ . Placing this selection in the original expression we have  $X \langle op \rangle \langle expr \rangle$ .

Next it is necessary to decode the non-terminal expression  $\langle op \rangle$ . The next value from the integer vector is 17 and again we have 4 options ( $+$  |  $-$  |  $/$  |  $*$ ). The result is equal to 1, and indicates to select the:  $-$ . Re-writing the expression we got:  $X - \langle expr \rangle$ . This process should continue until all the non-terminals have been expanded to terminals. In this example the resulting expression (phenotype) is:  $X - \sin(X)$ . Note that not all of the genes were necessary to obtain the phenotype. In these cases, the genes that were not used are discarded. Moreover, the opposite case can occur: if a chromosome does not contain the necessary number of genes to map to a program. In this scenario the strategy is re-utilize the genes starting from the first one.

#### IV. GEHyPSP

This section presents GEHyPSP: an off-line grammatical evolution application for generating high level heuristics of hyper-heuristics framework to the Protein Structure Prediction problem. Our approach is based on the study by Sabar et al. [23]

The high level heuristics are composed by a selection mechanism and an acceptance criterion. These high level heuristics use information related with the history of low level heuristics applications. Data about the improvements obtained by the low level heuristics, number of times since the last application of a low level heuristic and the fitness difference between the current solution and the generated one are examples of information used by selection mechanisms and acceptance criteria. Furthermore, two terminal sets (one for the selection mechanisms and another for the acceptance criteria) were defined according with the information that can be extracted during the search progress. The selection terminals are:

- *RC (Reward Credit)*: The reward that a given heuristic should receive based on its performance. The improvement is calculated, for the  $i_{th}$  heuristic, using  $M(i) = (|f1 - f2|/f1) * 100$  if  $f2 < f1$ , where  $f1$  is the current fitness and  $f2$  is the fitness of the solution generated by the  $i_{th}$  heuristic.
- $C_{best}$ : Number of times that the  $i_{th}$  heuristic updated the best known solution. This terminal is useful to systematically improve the current local minimum.
- $C_{current}$ : Number of times that the  $i_{th}$  heuristic updated the current solution. This terminal is useful to keep the search near to the current solution.
- $C_{accept}$ : Number of times that the generated solution by the  $i_{th}$  heuristic was accepted by the acceptance criterion. This terminal favors heuristics that can escape from local minimum.
- $C_{ava}$ : The average of previous improvements made by the  $i_{th}$  heuristic during the search progress. This terminal favors heuristics that made big improvements on average.
- $C_r$ : Number of times that the  $i_{th}$  heuristic was selected to be applied.

A specific terminal set for generating acceptance criteria was also defined.

- Delta: The difference between the quality of the current solution and the generated solution.
- PF: The quality of the previous solution.
- CF: The quality of the current solution.
- CI: Current iteration.
- TI: Total number of iterations.

Using these statistics as terminals and a function set containing the following arithmetic operations: addition, subtraction, multiplication and division, a grammar was designed to support the generation of the high level heuristics. The designed grammar to generate selection mechanisms and acceptance criteria is shown in the Grammar 2.

For the initialization of the terminal set data: all heuristics were executed once and the data was calculated for each terminal. Every consecutive iteration will update the terminal set data and this information will be used during the search progress.

$$\begin{aligned}
 \langle hh\text{-}selection \rangle &::= \langle selection\text{-}mechanism \rangle \\
 &\quad \langle acceptance\text{-}criterion \rangle \\
 \langle selection\text{-}mechanism \rangle &::= \langle selection\text{-}terminal \rangle \\
 &\quad | \langle selection\text{-}mechanism \rangle \langle math\text{-}function \rangle \\
 &\quad \langle selection\text{-}mechanism \rangle \\
 &\quad | (\langle selection\text{-}mechanism \rangle \langle math\text{-}function \rangle \\
 &\quad \langle selection\text{-}mechanism \rangle) \\
 \langle selection\text{-}terminal \rangle &::= RC \mid C_{best} \mid C_{current} \mid C_{accept} \mid \\
 &\quad C_{ava} \mid C_r \\
 \langle math\text{-}function \rangle &::= + \mid - \mid * \mid \% \\
 \langle acceptance\text{-}criterion \rangle &::= \langle acceptance\text{-}terminal \rangle \\
 &\quad | \langle acceptance\text{-}criterion \rangle \langle math\text{-}function \rangle \\
 &\quad \langle acceptance\text{-}criterion \rangle \\
 &\quad | (\langle acceptance\text{-}criterion \rangle \langle math\text{-}function \rangle \\
 &\quad \langle acceptance\text{-}criterion \rangle) \\
 \langle acceptance\text{-}terminal \rangle &::= PF \mid CF \mid CI \mid TI
 \end{aligned}$$

Grammar 2. Designed grammar to generate high level heuristics

#### A. Fitness Function

In order to evaluate the generated individuals during the search progress, a fitness function was designed. The fitness function consisted on running the generated high level heuristics, within a hyper-heuristic framework, against three random selected instances from a set of eleven instances. Each run will be executed for one minute and will return the best HP solution found. The fitness value associated with the returned solution is then normalized between 0 and 1. The fitness of an individual, of the GE, it is the sum of the three outcomes from each execution of the three randomly selected instances. Hence, the best possible fitness value is 3 and the worst is 0. The motivation behind executing the high level heuristic (individual) against three HP instances is that executing with only one might not be sufficient to train a high level heuristic to obtain good results for various instances of the HP model.

#### B. Stopping Criterion

To stop the GE process, a maximum number of evaluations was setup to 60000. This value was defined based on previous work [22] where the grammatical evolution general process was introduced for the first time.

#### C. Low Level Heuristics

1) *Representation of the problem*: There are many ways of representing a protein conformation within the HP-2d model. According to Krasnogor et al. [15] the relative representation has a better potential to achieve superior results. The relative representation defines that each gene of the chromosome represents a direction in the grid. Each gene will encode a conformation that a protein could adopt. The directions in the grid for each amino-acid are represented always based on the previous one. There are 3 possible directions within the HP-2d model: forward (F), left (L) and right (R). Hence, the following



integer codification was used  $F \rightarrow 0$ ,  $L \rightarrow 1$  and  $R \rightarrow 2$ . Thereby, the allowed alphabet can be represented as  $\{0, 1, 2\}$ .

2) *Low Level Heuristics Set*: The low level heuristics set was selected from previous studies [1], [7], [6], [10] that explore the PSP. It consists of the following operators:

- *Two Points Crossover* (2X): This operator selects, randomly, two crossing points splitting the individuals in 3 pieces. The genes between the selected positions are exchanged between the parents in order to generate the offspring. [1].
- *Multiple Points Crossover* (MPX): Similar with 2X although with  $c$  points of crossing. We use  $c = \text{int}(n*0.1)$ , ..., where  $n$  is the sequence length. The MPX is useful to promote a wide structural diversity [23].
- *Segment Mutation* (SMUT): It changes a random number (5 to 7) of consecutive genes to distinct values. This heuristic introduces large changes in the protein conformation, and it has a great probability of creating collisions (cases in which the protein conformation are not self avoiding).
- *Exhaustive Search Mutation* (EMUT): This heuristic selects a random gene and modifies it to other possible value. All possible values are tried and the one whom achieved the higher improvement will be kept. This operator demands four fitness evaluations instead of just one. However, this heuristic has great potential of improving the input solution.
- *Local Move Operator* (LM): This heuristic exchanges directions between two consecutive random selected genes. This heuristic introduces small local changes that can reduce the distance between pairs of H-H.
- *Loop Move Operator* (LPM): Similar with LM, this heuristic exchanges directions between two genes that are five genes of distance between each other.
- *Opposite Mutation* (OM): This heuristic exchanges multiple between two genes  $(i, j)$  to the respective opposite. In the HP-2d this means that genes that code L are changed to R or vice and versa. The F has no opposite so, the operator is not applied.

3) *Backtrack Repair*: The low level heuristics have a great potential of creating solutions with collisions [1]. Those solutions are submitted to repair attempt using a backtrack strategy. The solutions that can be repaired are kept and the others are penalized.

4) *Memory Mechanism*: Sabar et al. [23] suggested that the use of a memory of solutions to the PSP would be more effective than relying on a single solution and may restrict the ability of dealing with large and heavily constrained search spaces. Also, Blum et al. [2] mention that single solution based methods are widely known to not cope with large search spaces and heavily constrained problems.

## V. EXPERIMENTS

In this section, we will present and discuss the conducted experiments in order to evaluate GEHyPSP. Three groups of experiments were designed/executed. The first group was only

TABLE II  
INSTANCES AND THE RESPECTIVE SIZE OF EACH ONE

Inst	1	2	3	4	5	6	7	8	9	10	11
Size	20	24	25	36	48	50	60	64	85	100	100

concerned on generating selection mechanisms. The second group was designed only to generate acceptance criteria. The third group was developed to generate both selection and acceptance mechanisms. All experiments were executed 30 times because of the stochastic behavior of the GEHyPSP.

The results obtained by the groups were first compared **within each other**. The results were compared with the results obtained by the previous studies [6], [18], [24], [7]. Also a final comparison was made with a state-of-art hyper-heuristic will be presented. The proposed strategy was compared with the Generic Intelligent Hyper-heuristic (GIHH) presented by Misir et al [19].

In the first group of experiments (GEHyPSP-1) only selection mechanisms are generated. The acceptance criterion was fixed with a "better or equal" acceptance [4]. The goal of this group is to evaluate the ability of our approach to generate selection mechanisms using a fixed acceptance criterion.

The second group of experiments, GEHyPSP-2, consisted on generating only acceptance criteria. The selection mechanism was fixed using the best selection mechanism found in the first group. Consequently, this group of experiments depends on the output from the first group. The goal of this experiment was to evaluate the generation of acceptance criteria separately from the selection mechanism using a fixed one.

The third group of experiments GEHyPSP-3 was designed to generate both selection mechanisms and acceptance criteria. The goal of this group was to evaluate the ability of generating selection mechanisms along with acceptance criteria. Differently from GEHyPSP-2, this group of experiment does not depend on any output from previous experiments since it generates both mechanisms without fixing any component.

For each group of experiments eleven instances (amino-acid sequences from the HP model) were selected from the previous studies with the PSP problem [6], [18], [24], [7]. The sizes (number of residues) of the HP instances used in the experiments are presented in Table II. For the sake of space, the sequences are not reproduced here. They can be obtained from [24]. Also, for each group of experiments the training phase consisted on executing the GE process with three randomly selected instances from the eleven available instances. In the validation phase the best generated selection mechanisms and acceptance criteria were executed together against all eleven instances.

### A. Results from GEHyPSP-1

The best individual found in the GEHyPSP-1 was the following selection mechanism:  $RC * C_{current} * C_{ava} - Cr$  and it was executed 30 times with a time limit of 10 minutes against the eleven instances. Table III presents the average,

TABLE III  
RESULTS FROM THE BEST INDIVIDUAL FOUND IN GEHyPSP-1

Inst	1	2	3	4	5	6	7	8	9	10	11
Avg	8.1	7.6	6.7	11.9	17.4	16	30	28.3	40.1	35.6	35.9
St Dv	0.3	0.5	0.5	0.7	1	1.4	1.7	2	2.7	2.1	2.9
Min	8	7	5	11	15	13	25	23	34	32	27
Max	<b>9</b>	<b>9</b>	<b>8</b>	<b>14</b>	<b>23</b>	<b>21</b>	33	<b>42</b>	46	40	41
O(x*)	<b>9</b>	<b>9</b>	<b>8</b>	<b>14</b>	<b>23</b>	<b>21</b>	<b>36</b>	<b>42</b>	<b>53</b>	<b>48</b>	<b>50</b>

TABLE IV  
RESULTS FROM THE BEST INDIVIDUAL FOUND IN GEHyPSP-2

Inst	1	2	3	4	5	6	7	8	9	10	11
Avg	8	7.6	6.7	10.1	14.8	14.7	27	25.7	38.3	32.8	30.
St Dv	0.6	0.4	0.6	0.7	1.5	1.4	2.0	2.5	3.3	3.7	3.4
Min	7	7	5	8	12	12	23	22	31	26	24
Max	<b>9</b>	8	<b>8</b>	11	17	18	31	31	44	40	37
O(x*)	9	9	8	14	23	21	36	42	53	48	50

standard deviation, minimum and maximum of 30 executions of the best individual found in the GEHyPSP-1 experiment. The last row denoted with O(x\*) is the best known value for each sequence. It is possible to note analyzing the last two rows that only for the smaller instances the generated selection mechanism achieved good results. For the sequences 8, 9, 10 and 11 the results obtained are very far from the best known results.

#### B. Results from GEHyPSP-2

The best individual found in the GEHyPSP-2 was the following acceptance criterion:  $((TI/Delta)/((Delta * ((TI/Delta)/CI) * Delta/Delta * TI) - CI))$  and combined with the best individual from the GEHyPSP-1 the hyper-heuristic framework was executed 30 times for each one of the eleven instances with a time limit of 10 minutes. Table IV presents the results for the best generated acceptance criterion in GEHyPSP-2 and also using the best selection mechanism generated in GEHyPSP-1. Again, looking to the two last rows it is possible to notice that the hyper-heuristic framework, using the best generated selection mechanisms and acceptance criterion, was not able to reach the best known results for the larger sequences. And comparing Tables III and IV it is possible to visualize that there is a slight difference between the results, favoring the generated selection mechanism using the "better or equal" acceptance criterion.

#### C. Results from GEHyPSP-3

The best individual generated by the experiment GEHyPSP-3 was both a selection mechanism and an acceptance criterion. And they are presented below:

Selection Mechanism:  $(((((Caccept/RC) * Cr/Caccept)/RC * Cr)/Caccept/RC) * Cr)/Caccept$   
Acceptance Criterion:  $(((((CI/PF) * Delta/CI)/PF * Delta)/CI/PF) * Delta)/CI$

Table V presents the results, of the best individual generated by the experiment GEHyPSP-3, of 30 executions with a time limit of 10 minutes. Once again the values presented did not achieve good results when analyzing the most difficult instances. Furthermore, when comparing Table V with Tables III and IV it is possible to see that generating both selection

TABLE V  
RESULTS FROM THE BEST INDIVIDUAL FOUND IN GEHyPSP-3

Inst	1	2	3	4	5	6	7	8	9	10	11
Avg	7.6	7.0	5.7	9.7	13.8	12.7	24	24.2	31.6	27	26.4
St Dv	0.6	0.7	0.8	0.9	1.3	0.9	1.1	1.6	1.7	1.7	2
Min	7	6	4	7	12	11	21	21	29	24	24
Max	<b>-9</b>	-8	<b>-8</b>	-11	-18	-15	-26	-28	-37	-31	-31
O(x*)	9	9	8	14	23	21	36	42	53	48	50

TABLE VI  
BEST RESULTS FOUND BY GEHyPSP, BEST RESULTS FOUND BY GIHH AND THE BEST KNOW RESULTS O(x\*)

Inst	1	2	3	4	5	6	7	8	9	10	11
GEHyPSP	9	9	7	13	19	20	33	32	46	40	41
GIHH (max)	9	9	8	13	22	21	35	37	49	43	45
O(x*)	9	9	8	14	23	21	36	42	53	48	50

mechanisms and acceptance criteria produces worse results than generating them separately.

#### D. Comparison with a state-of-art hyper-heuristic

In order to compare the generated high level heuristics with an already proposed hyper-heuristic strategy a state-of-art human-designed hyper-heuristic framework [19] was selected. This framework produced the best results applied to the 6 domain problems from HyFlex framework [20]. Misir et al. [19] provided us the source code from the GIHH and then it was executed against the PSP problem.

Table VI presents the best results, for each instance, found by the best generated high level heuristic with GEHyPSP, the best results found by the GIHH [19] and finally the best know results (O\_x(\*)). The GEHyPSP and the GIHH were executed 10 minutes. It is possible to note that the GEHyPSP found worse results than the GIHH as the sequences length increase. However, the GIHH is a human-designed hyper-heuristic which demanded several years of research in order to be completed and achieved good results in the six domains problems provided by HyFlex. Despite the good performance obtained by the GIHH in the domains from HyFlex, it is possible to notice that the GIHH was also unable to achieve the best known results in many instances.

#### E. Discussion

In order to better investigate the relationship between the generated selection mechanisms and acceptance criteria another experiment was designed. From the 30 executions of the GEHyPSP-2 ten random individuals were selected to be further analyzed. These individuals were re-executed in debugging mode in order to check its behavior. Note that only the acceptance criterion was different between them because the selection mechanism was fixed, using the best generated in the previous experiment GEHyPSP-1. From 10 individuals 7, were accepting only better or equal solutions just like the fixed acceptance criterion that was used in the GEHyPSP-1. The difference between the individuals and a fixed acceptance criterion was that individuals were slower than the fixed, because it is required to execute arithmetical functions and in the other hand only a simple *if* was evaluated. But with

respect to their behavior they were exactly the same. It was also noticed that 2 individuals, the worst of the group, were always accepting worst solutions just like the "all moves" described by Burke et al. [3]. Finally, one individual was never accepting any solution.

These experiments showed that the GE managed, several times, to find different acceptance criteria with the same behavior of human-designed strategies.

## VI. CONCLUSION

In this work GEHyPSP, an automatic way of generating high level heuristics to a hyper-heuristic framework for the PSP problem, was presented and evaluated. The PSP is a very challenging problem with a high number of local optima and a very complex landscape. Many authors explored the PSP problem with heuristic methods. However, very often the proposed heuristic approaches are unable to find the best known results when executing against longer sequences. Usually, the hyper-heuristic framework fits well in this kind of complex scenario. Hence, the goal of this paper was to generate, using a grammatical evolution strategy, selection mechanisms and acceptance criteria to a hyper-heuristic framework and evaluate its performance and behavior with a set of eleven HP instances. Three groups of experiments were executed, using three randomly selected HP instances, in order to generate the high level heuristics and later the best individuals found in the experiments were executed using all the eleven HP instances.

Three groups of experiments were executed: first generating only selection mechanisms within a fixed acceptance criterion; second generating only acceptance criteria using the best selection mechanism found in the first; finally both high level heuristics were generated in parallel. The results showed that better high level heuristics were found when generating them separately. Unfortunately, when analyzing the behavior of the generated high level heuristics against the eleven instances it was possible to see that they were not able to achieve the best known results for the longer sequences. However, when comparing with a good state-of-art human-designed hyper-heuristic framework (GIHH) [19] the results are slightly close. This fact shows that it is possible to automate the creation of high level heuristics and obtain results close to the state-of-art hyper-heuristics frameworks.

Another finding of this work was the behavior of the best generated acceptance criteria. It was noticed that it behaves just like "a better or equal" human-designed move acceptance strategy. Also some of the generated acceptance criteria were always accepting worst solution and this fact impacted in the individual fitness. This fact demonstrates that GEHyPSP was able to generate acceptance criteria with the same behavior of simple human-designed move acceptance strategies. However, in order to obtain better results it might be necessary to improve GEHyPSP to generate more complex selection mechanisms and acceptance criteria to couple with the landscape complexity of the PSP problem.

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