

even a cell, if all (or some) of the mRNA's obtained from the same gene, but edited differently, can be translated.

If the concentrations of editing operators can vary according to environmental contexts, different resulting phenotypes may be selected accordingly, and thus evolve a system which is able to respond to environmental changes without changes in the major part of its genetic information -- one genotype, different contexts, different phenotypes. Notice, however that what is inheritable, and subjected to variation, is the original non-edited genotype, which is ultimately selected and transmitted to the offspring of the organism (Rocha, 1995; 1997). This type of phenotypic plasticity may be precisely, for instance, what the Trypanosome parasites have achieved: control over gene expression during different parts of their complex life cycles.

The role of RNA editing in the development of more complex organisms has also been shown to be important. Lomeli et al. (1994) discovered that the extent of RNA editing affecting a type of receptor channel responsible for the mediation of excitatory postsynaptic currents in the central nervous system, increases in rat brain development. As a consequence, the kinetic aspects of these channels differ according to the time of their creation in the brain's developmental process. Another example is that the development of rats without a gene (ADAR1) known to be involved in RNA editing, terminates midterm (Wang et al., 2000). This showed that RNA Editing is more prevalent and important than previously thought. RNA editing processes have also been identified in mammalian brains (Simpson and Emerson, 1996). More recently, Hoopengardner et al. (2003) found that RNA editing plays a central role in nervous system function. Indeed, many edited sites alter conserved and functionally important amino acids, some of which may play a role in nervous system disorders such as epilepsy and Parkinson Disease.

2. Introducing Editing in Genetic Algorithms

Genetic Algorithms (GA) (Holland, 1975) have been used as computational models of natural evolutionary systems and as adaptive algorithms for solving optimization problems. GA operate on an evolving population of artificial organisms, or agents. Each agent is comprised of a genotype (encoding a solution to some problem) and a phenotype (the solution itself). Evolution occurs by iterated stochastic variation of genotypes, and subsequent selection of the best phenotypes in an environment – that is, according to how well the respective solution solves a problem (or fitness function). Table 1 depicts the process of a simple genetic algorithm.

The essence of GA lies on the separation of the description of a solution (the Genotype) from the solution itself (the Phenotype): variation is applied solely to the descriptions, while the respective solutions are evaluated,

and the whole selected according to this evaluation. Nonetheless, one important difference between evolutionary computation and biological organisms lies precisely on the relation between Genotype and Phenotype. In GA, typically, the relation between the two is linear and direct: one genotype produces a unique phenotype. In contrast, in biological organisms there exists a multitude of processes, taking place between the transcription of genes and their expression and subsequent development into a phenotype, responsible for the establishment of an uncertain, contextually regulated relation, between Genotype and Phenotype.

Table 1. Mechanism of a simple GA

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| <ol style="list-style-type: none"> 1. Randomly generate an initial population of l n-bit agents, each defined by a genotype string of symbols from $\{0, 1\}$. 2. Evaluate each agent's (phenotype) fitness. 3. Repeat until l offspring agents have been created. <ol style="list-style-type: none"> a. select a pair of parent agents for mating; b. apply crossover operator to genotype string; c. apply mutation operator to genotype string. 4. Replace the current population with the new population. 5. Go to Step 2 until terminating condition. |
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In other words, the same genotype does not always produce the same phenotype; rather, many phenotypes can be produced from one genotype depending on states of the environment. One of the biological processes responsible for such phenotypic plasticity is RNA Editing.

In analogy with the process of RNA Editing, Rocha (1995; 1997) proposed an expanded GA with stochastic edition of genotypes (chromosomes), prior to translation into phenotypes. Here we present novel experiments to show how this GA with Genotype Editing can be successfully used to model the environmentally-regulated control of gene expression achieved by RNA Editing in real organisms.

Genotype Editing (Rocha, 1995; Huang and Rocha, 2003, 2004) is implemented by a set of editors with different editing functions, such as insertion or deletion of symbols in the original genotypes. Before genotypes can be translated into the space of phenotype solutions, they must "pass" through successive layers of editors, present in different concentrations. In each generation, each genotype encounters an editor in its layer with probability (given by the concentrations). If an editor matches some subsequence of the genotype when they encounter each other, the editor's function is applied and the genotype is edited. The detailed implementation of the simplest GA with Edition (GAE) is described in the following:

The GAE model consists of a family of r m -bit strings, denoted as (E_1, E_2, \dots, E_r) , which is used as the set of editors for the genotypes of the agents in a GA population.

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The length of the editor strings is assumed much smaller than that of the genotypes: $m \ll n$, usually an order of magnitude. An editor E_j is said to match a substring, of size m , of a genotype string, S , at position k if $e_i = s_{k+i}$, $i=1,2,\dots,m$, $1 \leq k \leq n-m$, where e_i and s_i denote the i -th bit value of E_j and S , respectively. For each editor E_j , there exists an associated editing function F_j that specifies how a particular editor edits genotypes: when the editor matches a portion of a genotype string, a number of bits are inserted into or deleted from the genotype string.

For instance, if the editing function of editor E_j is to add one randomly generated allele at s_{k+m+1} when E_j matches S at position k , then all alleles of S from position $k+m+1$ to $n-1$ are shifted one position to the right (the allele at position n is removed). Analogously, if the editing function of editor E_j is to delete an allele, this editor will instead delete the allele at s_{k+m+1} when E_j matches S at position k . All the alleles after position $k+m+1$ are shifted in the inverse direction (one randomly generated allele is then assigned at position n).

Finally, let the concentration of the editor family be defined by (v_1, v_2, \dots, v_r) . This means that the concentration of editor E_j is denoted by v_j : the probability that S encounters E_j . With these settings, the algorithm for the GA with genotype editing is essentially the same as the regular GA, except that step 2 in Table 1 is now redefined as:

“For each agent in the GA population, apply each editor E_j with probability v_j (i.e., concentration). If E_j matches the agent’s genotype string S , then edit S with editing function F_j and evaluate the resulting agent’s fitness.”

It is important to notice that the “post-transcriptional” edition of genotypes is not a process akin to mutation, because editions are not inheritable. Just like in biological systems, it is the unedited genotype that is reproduced. One can also note that Genotype Editing is not a process akin to the Baldwin effect as studied by, e.g., Hinton and Nowlan (Hinton and Nowlan, 1987). The phenotypes of our agents with genotype edition do not change (or learn) ontogenetically. In Hinton and Nowlan’s experiments, the environment is defined by a very difficult (“needle in a haystack”) fitness function, which can be made more amenable to evolutionary search by endowing the phenotypes to “learn” ontogenetically. Eventually, they observed, this learning allows genetic variation to discover, and genetically encode fit individuals. In contrast, genotype edition does not grant agents more “ontogenetic learning time”, it simply changes inherited genetic information ontogenetically but the phenotype, once produced, is fixed. Also, as we show below, it is advantageous in environments very amenable to evolution, such as Royal Road functions (the opposite of “needle in a haystack”) (Huang and Rocha, 2003, 2004).

It is also important to retain that just like an mRNA molecule may be edited in different degrees according to the concentrations of editing operators it encounters, in the

GAE the same genotype string may be edited differently because editor concentration is a stochastic parameter that specifies the probability of a given editor encountering a chromosome. Thus, if a genotype string is repeated in the population, it may actually produce different solutions (or phenotypes). This is akin to what happens with RNA editing in biological organisms where, at the same time, several different proteins coded by the same gene may coexist.

In (Huang and Rocha, 2003, 2004), we have conducted a systematic study of the GAE in several static environments to investigate if there are any evolutionary advantages of genotype editing, even without control of environmental changes. We demonstrated that genotype editing can improve the GA’s search performance by suppressing the effects of hitchhiking. We have also showed that editing frequency plays a critical role in the evolutionary advantage provided by the editors -- only a moderate degree of editing processes facilitates the exploration of the search space. Therefore, one needs to choose proper editor parameters to avoid over or under-editions in order to develop more robust GAs. Here, we extend our study of the GAE to dynamic problems by linking concentrations of editors to environmental states (or contexts) – thus allowing editor concentrations to serve as a control switch for environmental changes.

3. Evolution in Dynamic Environments

How rapid is evolutionary change, and what determines the rates, patterns, and causes of change, or lack thereof? Answers to these questions can tell us much about the evolutionary process. The study of evolutionary rate in the context of GA usually involves defining performance measures that embody the idea of rate of adaptation, so that its change over time can be monitored for investigation.

In this paper, two evolutionary measures, the maximum fitness and the population fitness at each generation, are employed.¹ To understand how Genotype Editing works in the GAE model, we employ a testbed, the small Royal Road S1 (Huang and Rocha, 2003) due to its simplicity for tracing evolutionary advancement.

Table 2 illustrates the schematic of the small Royal Road function S1. This function involves a set of schemata $S = (s_1, \dots, s_8)$ and the fitness of a bit (genotype) string x is defined as

$$F(x) = \sum_{s_i \in S} c_i \sigma_{s_i}(x),$$

where each c_i is a value assigned to the schema s_i as defined in the table; $\sigma_{s_i}(x)$ is defined as 1 if x is an instance of s_i and 0 otherwise. In this function, the fitness of the global optimum string (40 1’s) is $10 \cdot 8 = 80$.

¹ The maximum fitness is the fitness of the best individual in the current population; the population fitness here is defined as the value obtained by averaging the fitness of all the individuals in the current population.

1. **L1L0**. Landscapes oscillate without genotype edition. The population evolves solely according to the traditional GA.
2. **L1C1L0C1**. Landscapes oscillate with genotype edition, but edition is always implemented with family C1.
3. **L1C0L0C0**. Same as above but with family C0.
4. **L1C1L0C0**. Landscapes oscillate with edition, but the family of editors changes with the environment: family C1 operates when landscape L1 is in place, and C0 operates with L0.

The dramatic oscillation of environments is very hard for scenario 1 that uses only the traditional GA (L1L0). The first time the environment changes, the population is forced to evolve new solutions for L0 from a population already evolved for L1 and, before it is able to produce good individuals in L0, the environment changes again. Subsequent oscillations produce the same result, and the population never reaches a good solution.

In scenario 2, when editor family C1 is used on both environments (L1C1L0C1) we observe that the population behaves very well on landscape L1 but poorly on L0. This is an improvement over L1L0, but worse than the other two scenarios.

The results for scenario 4 (L1C1L0C0) show that the association of editor concentrations to environmental contexts (i.e., the association of L1 with C1, and L0 with C0) is indeed beneficial, as the population of agents is capable of evolving very good solutions in both environments.

However, we also notice that in scenario 3 (L1C0L0C0), which uses solely editor family C0, the population is capable of producing very good individuals on both oscillating environments. This means that family C0 is good at editing genotypes in both landscapes. The results obtained for scenarios 3 and 4 thus show that genotype editing can lead to evolutionary advantages in two distinct ways to cope with dynamic environments: (1) by employing editors which can produce genotypes encoding good solutions in both landscapes (scenario 3: L1C0L0C0), or (2) by changing the concentrations of editors when the environment changes (scenario 4: L1C1L0C0).

We do notice, however, that scenario 4 provides a quicker response immediately after the environment changes from L0 to L1. In figure 3, we can see that when this change occurs at generations 200 and 400, the averaged maximum fitness of L1C0L0C0 (scenario 3) suffers a larger setback than that of L1C1L0C0 (scenario 4). In scenario 3, the population needs to completely re-adapt to the new environment, whereas in scenario 4 the population contains some individuals that are very fit in L1, but, after edition, are somewhat fit in L0. Thus, whereas the average maximum fitness (for 50 runs of each scenario) at generations 200 and 400 is very close to 0 for scenario 3, it is about 15 for scenario 4. These values are

clearly significant given the 95-percentile confidence intervals computed and depicted in the figure.

Furthermore, a microscopic inspection shows that in the case of scenario 4, at generation 199, the chromosome of one individual of fitness 60 is defined by substring {0,1,0,1,0} at the position of schema S7. When the landscape oscillates from L0 to L1 at generation 200, this individual undergoes some edition which results in these alleles being altered to {1,1,1,1,1}. This individual thus acquires a fitness amount of 10 from building block S7. This situation is relatively typical in scenario 4; yet in scenario 3, since more individuals converged to genotype strings of all 0's at generation 199, it is more difficult for the agents to acquire corresponding building blocks at generation 200 simply by genotype edition. All this means that under scenario 4, the GAE evolves genotypes which produce fair solutions in both landscapes, but which are edited differently accordingly: genuine phenotypic plasticity. Therefore, the same genotypes may exist in both landscapes, whereas in the case of scenario 3 the constant editor family, C0 seems to facilitate the evolution of new good genotypes after the landscape changes.

4. Conclusion and Future Work

This paper presents our computational methodology using Genetic Algorithms with Genotype Editing for investigating the role of RNA editing in dynamic environments. Based on several genetic editing characteristics that are gleaned from the RNA editing system, we show that the incorporation of editing mechanisms indeed provides a means for artificial agents with genotypes to gain greater phenotypic plasticity, and /or a mechanism to generate novel fit individuals when a population is faced with dramatic environmental changes. By linking changes in the environment with internal parameters such as concentrations of editors, the artificial agents can use genotype edition to their advantage, as gene expression can become contextually regulated, such ability thus gives organisms an adaptive advantage. In a nutshell, the results obtained have provided the following insights:

There are two strategies for artificial agents with genotype edition to produce phenotypic plasticity to cope with environmental changes: (1) by using different families of editors for different environmental demands, or (2) by employing a single family of editors that allows the evolutionary process to cope well with a changing environment.

We have thus far studied the association of editor families with different concentrations to environmental changes. The work here presented details simulations with two specific editor families. Based on such anecdotal evidence, our results simply show that Genotype Editing may provide evolutionary advantages in oscillating environments. In future work, we intend to allow the family of editors and the genotypes of agents to co-evolve, so that the artificial agents can discover proper editor

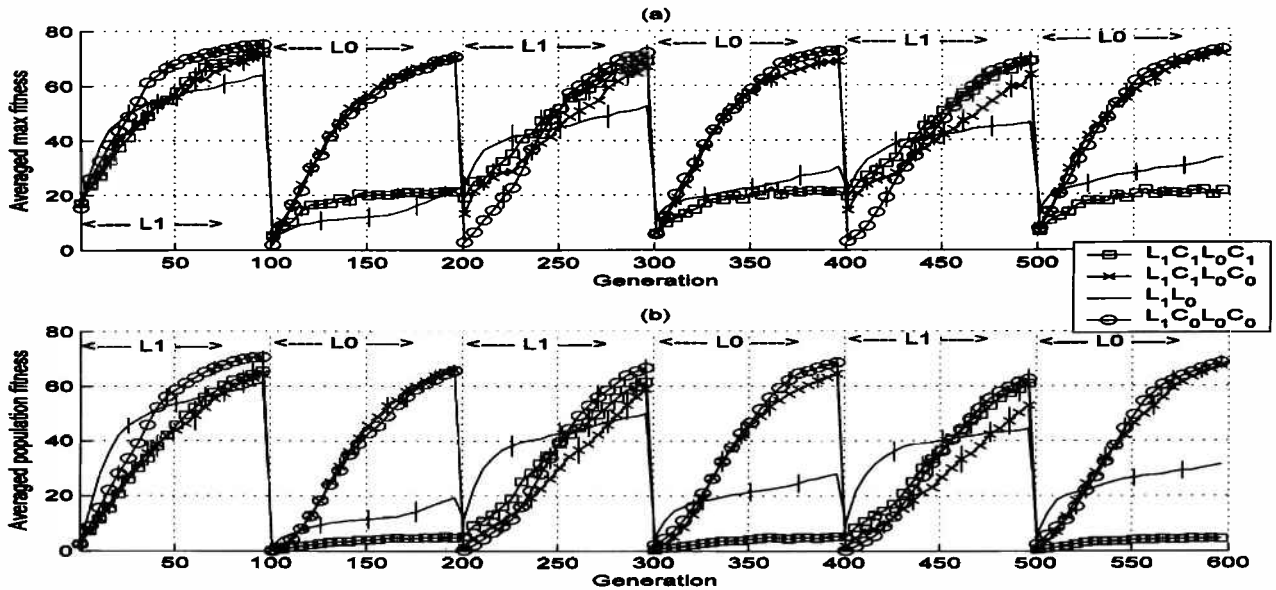


Figure 3. Evolutionary measures on dynamic landscapes

concentrations to adapt to changing environments. Since there are several internal editor parameters involved in an editing system, such as the size of the editor family, editor length and editor functions, in addition to the investigation of editor concentrations, our future work is also going to study the effects of associating other parameters with external environments. Since the length of oscillation period is expected to be another critical parameter that will affect how well the GAE's population adapts to changing environments, we will also study the effects of oscillation periods. With a systematic study on these editor parameters, our hope is to gain a deeper understanding of the role of RNA Editing in nature and also to design robust evolutionary computation algorithms for complex, dynamic real-world tasks, as we have done in Huang and Rocha, (2003; 2004) for non-changing environments.

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