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An Adaptive Memetic Algorithm With Dynamic Population Management for Designing HIV Multidrug Therapies

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Abstract—In this paper, a mathematical model of human immunodeficiency virus (HIV) is utilized and an optimization problem is proposed, with the final goal of implementing an optimal 900-day structured treatment interruption (STI) protocol. Two type of commonly used drugs in highly active antiretroviral therapy (HAART), reverse transcriptase inhibitors (RTI) and protease inhibitors (PI), are considered. In order to solving the proposed optimization problem an adaptive memetic algorithm with population management (AMAPM) is proposed. The AMAPM uses a distance measure to control the diversity of population in genotype space and thus preventing the stagnation and premature convergence. Moreover, the AMAPM uses diversity parameter in phenotype space to dynamically set the population size and the number of crossovers during the search process. Three crossover operators diversify the population, simultaneously. The progresses of crossover operators are utilized to set the number of each crossover per generation. In order to escaping the local optima and introducing the new search directions toward the global optima, two local searchers assist the evolutionary process. In contrast to traditional memetic algorithms, the activation of these local searchers is not random and depends on both the diversity parameters in genotype space and phenotype space. The capability of AMAPM in finding optimal solutions compared with three popular metaheurestics is introduced.

Keywords—HIV therapy design, memetic algorithms, adaptive algorithms, nonlinear integer programming.

I. Introduction

HUMAN Immunodeficiency Virus infects CD4+ T-cells, which are an important part of the human immune system, and other target cells. The infected cells produce a large number of viruses. Medical treatments for HIV have greatly improved during the last two decades. Highly active antiretroviral therapy (HAART) allows for the effective suppression of HIV-infected individuals and prolongs the time before the onset of Acquired Immune Deficiency Syndrome (AIDS) for years or even decades and increase life expectancy and quality to the patient but antiretroviral therapy cannot eradicate HIV from infected patients because of long-lived infected cells and sites within the body where drugs may not achieve effective levels [1]–[3]. HAART contain two major types of anti-HIV drugs, reverse transcriptase inhibitors (RTI) and protease inhibitors (PI). Reverse transcriptase inhibitors prevent HIV from infecting cells by blocking the integration of the HIV viral code into the host cell genome. Protease inhibitors prevent infected cells from replication of infectious virus particles, and can reduce and maintain viral load below the limit of detection in many patients. Moreover, treatment with either type of drug can also increase the CD4+ T-cell count that are target cells for HIV.

Many of the host-pathogen interaction mechanisms during HIV infection and progression to AIDS are still unknown. Mathematical modeling of HIV infection is of interest to the medical community as no adequate animal models exist in which to test efficacy of drug regimes. These models can test different assumptions and provide new insights into questions that are difficult to answer by clinical or experimental studies. A number of mathematical models have been formulated to describe various aspects of the interaction of HIV with healthy cells, see [4]. The basic model of HIV infection is presented by Perelson et al [5] that contains three state variables healthy CD4+ T-cells, infected CD4+ T-cells and concentration of free virus. Another model is presented in [6] that although maintaining a simple structure, the model offers important theoretical insights into immune control of the virus based on treatment strategies. Furthermore, this model is developed to describe the natural evolution of HIV infection, as qualitatively described in several clinical studies [7].

Some authors have used mathematical model for HIV infection in conjunction with control theory to achieve appropriate goals, by incorporating the effects of therapy on an HIV-infected individuals. For example, these goals my include: maximizing the level of healthy CD4+ T-cells and minimizing the cost of treatment [8]–[12], maximizing immune response and minimizing both the cost of treatment and viral load [13], [14], maximizing both the level of healthy CD4+ T-cells and immune response and minimizing the cost of treatment [15], Maximizing the level of healthy CD4+ T-cells while minimizing both the side effects and drug resistance [16] and maximizing survival time of patient subject to drug cost [17] and etc.

The papers [8], [15], [17], [19]–[21] consider only RTI medication while the papers [22], [23] consider only PIs. In [6], [16], [25]–[27] all effects of a HAART medication are combined to one control variable in the model. In [7], [9]–[14], [24], [28]–[33] dynamical multidrug therapies based on RTIs and PIs are designed.

In the considered control approaches the amount of medications can be either continuous or on-off-type. This treatment is also known as structured treatment interruption (STI). STI has received considerable attentions as it might reduce the risk of HIV mutating to strains which are resistant to current

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medication regimens. STI approach might also reduce possible long-term toxicity of the drugs. A concise summary of clinical STI studies, including protocols and results, is presented in [33].

Some authors have used heuristic methods for designing multidrug therapies for HIV infection. For example in [31], a GA was used to design STI therapies where the cardinality of the combinatorial optimization problem was very modest and the algorithm led to satisfactory results in this case. Nevertheless, for a problems with high dimensional a GA, would probably stagnate or converge to a suboptimal solution. In order to overcome these undesired behaviors and to find the optimal HIV multidrug therapy, computational Intelligence approaches were proposed in [14], [32]. In [14] an adaptive evolution algorithm (AEA) with intelligent mutation local searchers (IMLSs) was proposed for designing STI multidrug therapies for HIV. Moreover, in [32] the same model was used and an Adaptive Multimeme Algorithm (AMmA) was proposed for designing STI antiviral multidrug therapies for HIV. In both of this works the parameters of algorithm and activation of local searchers are based on the phenotypical diversity measure of the population. Motivated by [14], [32], in this paper a mathematical model of HIV dynamics that includes the effect of antiretroviral therapy is considered and a Memetic Algorithm is proposed for designing STI antiviral multidrug therapies for HIV.

The paper is organized as follows: Section II describes a differential model for the pathogenesis of HIV and formulates the problem of designing HIV therapies as an optimization problem. The AMAPM and its components are described in Section III, while Section IV is devoted to numerical results and computational evaluations. Conclusion is presented in SectionV.

II. HIV MODEL AND OPTIMIZATION PROBLEM

In this paper, the pathogenesis of HIV is modeled with a system of ordinary differential equations (ODEs) described in [7]. This model can be viewed as an extension of basic HIV Models of Perelson et al [5].

$$x' = \lambda - dx - rxv \tag{1}$$

$$y' = rxv - ay - \rho yz \tag{2}$$

$$w' = cxyw - qyw - bw \tag{3}$$

$$z' = qyw - hz \tag{4}$$

$$v' = k(1 - \varepsilon_\alpha)y - uv \tag{5}$$

$$r' = r_0(1 - \varepsilon_\beta) \tag{6}$$

Most of the terms in the model have straightforward interpretations as following: The first equation represents the dynamics of the concentration of healthy CD4+ T-cells (x). The healthy CD4+ T-cells are produced from a source, such as the thymus, at a constant rate λ, and die at a rate dx. The cells are infected by the virus at a rate rxv. The second equation describes the dynamics of the concentration of infected CD4+ T-cells (y). The infected CD4+ T-cells result from the infection of healthy CD4+ T-cells and die at a rate ay and killed by cytotaxic T-lymphocyte effectors CTLe (z) at a rate ρyz. The population of CTLs is subdivided into precursors or CTLp (w), and effectors or CTLe (z). Equations (3),(4) describe the dynamics of these compartments. In accordance with experimental findings establishment of a lasting CTL response depends on CD4+ T-cell help, and that HIV impairs T-helper cell function. Thus, proliferation of the CTLp population is given by $cxyw$ and is proportional to both virus load (y) and the number of uninfected T-helper cells (x). CTLp differentiation into effectors occurs at a rate qyw. Finally, CTLe die at a rate hz. Equation (5) describes the dynamics of the free virus particles (v). These free virus particles are produced from infected CD4+ T-cells at a rate ky and are cleared at a rate uv. Model also contains an index of the intrinsic virulence or aggressiveness of the virus (r). This index increases linearly in the case of an untreated HIV-infected individual, with a growth rate that depends on the constant r_0. Finally, equation (6) describes the dynamic of this index. In model variables ϵ_α and ϵ_β denote the efficacies of protease inhibitors (PI) and reverse transcriptase inhibitors (RTI), respectively. The effect of PI drugs is modeled by reducing the proliferation rate of viruses from infected cells, while the effect of RTI drugs is modeled by reducing the infection rate, and in this way, blocking the infection of CD4+ cells by free virus. Hence, in model the RTI drugs have an effect on virulence because their main role is halting cellular infection and prevents virus production by reducing the production rate from infected CD4+ T-cells.

TABLE I
THE PARAMETERS IN THE HIV MODEL

Parameters	Value/Unit	Description
λ	$7\ \frac{cells}{\mu l day}$	Healthy CD4+ production
d	$7 \times 10^{-3}\ \frac{1}{day}$	Healthy CD4+ clearance
a	$0.0999\ \frac{1}{day}$	Infected CD4+ clearance
ρ	$2\ \frac{\mu l}{cells}$	Infected CD4+ kill
c	$5 \times 10^{-6}\ \frac{\mu l^2}{cells^2 day}$	CTLp proliferation
q	$6 \times 10^{-4}\ \frac{\mu l}{cells day}$	CTLe differentiation
b	$0.017\ \frac{l}{day}$	CTLp clearance
h	$0.03\ \frac{l}{day}$	CTLe clearance
k	$300\ \frac{copies \mu l}{cells day}$	Viruse production
u	$0.5\ \frac{1}{day}$	Viruse clearance
r_0	$10^{-8}\ \frac{\mu l}{copies day^2}$	Virulence growth

The model has several parameters that must be assigned for numerical simulations. The descriptions, numerical values and units of the parameters are summarized in Table I. These descriptions and values were taken from [24]. We note that equations (1)-(6) with these parameters, model dynamics of fast progressive patients (FPP).

We consider the structured treatment interruption. This means that, at any given time, a maximum dose of a medicine is administered to a patient or that medicine is not given. For the schedule to be practical the decision to take medication is made for one day intervals. Thus, the RTI medicine can be represented by a binary string α telling whether the RTI medication is taken on ith day ($\alpha_i = 1$) or not ($\alpha_i = 0$),

$i = 0, ..., T$, where T is the duration of the considered schedule in days. In the same way the PI medication can be defined using a vector β. With this form of representation the number of the possible drug administration schedules is 2^{2T}. This type of representation was used in [14], [31]. Another way of medicine representation is the period representation which was used in [32] for STI antiviral medication. In this form of representation, we assume that the maximum number of on and off RTI medication periods during the considered time interval $[t_0, t_f]$ is denoted by $L + 1$. Then, the RTI medicine schedule is represented as an integer vector $\alpha = (\alpha_1, \alpha_2, ..., \alpha_L)$ where α_{2k-1}, $k = 1, 2, ...$, gives the length of the kth time on the RTI medication period in days and α_{2k}, $k = 1, 2, ...$, gives the length of the kth time off the RTI medication period. Actually, the value of variable α_{L+1} is determined from the other periods; hence, we do not need to store it. In the same way the PI medication can be defined using an integer vector β. The main advantage of this representation compared to binary representation is a vast reduction in dimensionality of the possible drug administration schedules [32], which can result in much faster convergence in the optimization. Here we use this kind of representation. In practice, an RTI medication cannot completely block the integration of the viral code into the target cells and a PI can only partially prevent the replication of viruses by infected cells. This means there exist some maximum efficacies ε_α and ε_β which are less than one for the RTI and PI medications, respectively. We have chosen to use the values $\epsilon_\alpha^{max} = 0.85$ and $\epsilon_\beta^{max} = 0.9$ in the numerical experiments [24]. Such as [32], it is assumed that when the medication has been taken the efficacy of drugs immediately increases to fully efficacious whereas after discontinuation of the therapy 24 hours required for the drug to be cleared from the body and this is modeled as a linear decay to zero efficacy, for both medications. An example of the PI efficacy is shown in Fig. 1.

An effective HIV medication can lead to a low viral load, but it cannot completely clear HIV [3]. Therefore, our aims is to find medication schedules that (possibly) keeps CD4+ cells concentration above its lower bound $\underline{x}$ and the concentration of free virions below its upper bound $\overline{v}$, while minimizing the overall dosage. It is easy to see that the constraint $x(t) \geq \underline{x}, \forall t \in [t_0, t_f]$ is equivalent to $\int_{t_0}^{t_f} |x(t) - \underline{x}| - x(t) + \underline{x}| dt = 0$. The same statement is valid for the bounded constraint on viral load. Therefore, the following objective functional should be minimized:

$$J(\alpha, \beta) = \sum_{i=1}^{4} w_i J_i$$

where the weight coefficients w_i are $w_1 = 50$, $w_2 = 2$, $w_3 = 15000$ and $w_4 = 10000$ and the objective functions J_i are

$$J_1 = \int_{t_0}^{t_f} |x(t) - \underline{x}| - x(t) + \underline{x}| dt, J_2 = \int_{t_0}^{t_f} |v(t) - \overline{v}| + v(t) - \overline{v}| dt$$
$$, J_3 = \int_{t_0}^{t_f} \varepsilon_\alpha^2 dt \quad and \quad J_4 = \int_{t_0}^{t_f} \varepsilon_\beta^2 dt. \qquad (7)$$

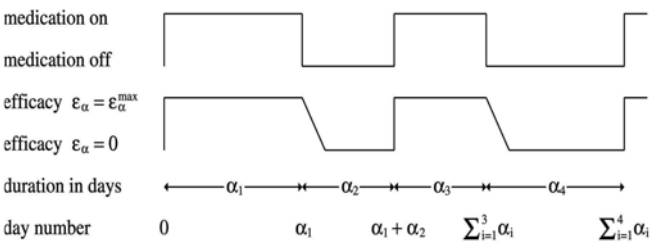

Fig. 1. The beginning of the PI medication schedule and its efficacy.

In (7), v is the number of free viruses, x is the measure of CD4+ T-cells, ε_α is the efficacy of RTI, and ε_β is the efficacy of PI. Thus, J_1 and J_2 measure respectively the amount violations of the bounded constraints on CD4+ T-cells concentration and viral load, over the time interval $[t_0, t_f]$ which are allowed but the amount of such possible violations is penalized in the objective function so that the optimizer tries to avoid (or reduce) them. Moreover, J_3 and J_4 measure the amount of the PI and RTI medications, respectively, over the same time interval. The desired lover bound for the level of CD4+ cells and upper bound for the viral load are set to $\underline{x} = 800 \frac{cells}{mm^3}$ and $\overline{v} = 500 \frac{copies}{ml}$, respectively. The optimization of the HIV multidrug therapy over the time interval $[t_0, t_f]$ is defined by a constrained nonlinear integer programming problem:

$$J(\theta) = \sum_{i=1}^{4} w_i J_i(\theta) \qquad (8)$$

Subject to the constraints:

$$\sum_{i=1}^{L} \theta_i \leq t_f - t_0, \sum_{i=L+1}^{2L} \theta_i \leq t_f - t_0, \qquad (9)$$

and the states (1)-(6) where $\theta = (\alpha, \beta)$. Our numerical studies in the following are based on a 900 day period, and therapy is started two months after the infection occurrence. Furthermore the maximum number, of on and off medication periods is set to 192, that is, $L = 191$ and hence, the last periods are off medication. This numerical problem is difficult in itself from a numerical point of view; therefore, we resort to heuristic approaches.

III. THE ADAPTIVE MEMETIC ALGORITHM WITH DYNAMIC POPULATION MANAGEMENT

This section gives a description of the designed adaptive memetic algorithm with population management (AMAPM) to solve the problem (8), (9). The main components of the proposed algorithm are as follow:

Distance measure: The proposed algorithm uses the population management, which controls the diversity of population of high-quality solutions [34]. For this end a distance measure d that determines for each pair of solutions their relative distance (or similarity) in the solution space is required. Then, by extension, the distance of a solution c to population P is:

$$d_P(c) = \min_{s \in P} d(c, s).$$

Although difficult to prove, it seems natural to conjecture that a distance measure that more accurately reflects the distance between two solutions is preferable to one that does not. For problems of which the solutions are most naturally represented as a binary string, the Hamming distance seems to be the only distance measure to use. For problems represented as real-valued vectors, Euclidean, Manhattan, or Chebychev distance metrics can be used. Several distance measures for problems represented as integer vectors have presented in [35]. The A-distance measure [36], equal to the sum of all absolute differences between the positions of all items in strings c and s , is used in our implementation as follows:

$$d(c,s) = \sum_{i=1}^{2L} |c_i - s_i|.$$

Initialization: Initially, a population P of solutions can be built randomly or using initial heuristics such as those presented in [32]. We construct the initial population to have a sufficient dispersal of initial solutions and a better exploration of the solution space. Distance measure d is used to diversify solutions in P, e.g., s is added to P only if $d_P(s) \geq 100$.

Parent selection and crossover: At each subsequent generation, the individuals undergo parent selection using binary tournament method [37]: two solutions are randomly drawn in P and the best one is kept as a parent and the same process is repeated to get another parent. Here, the uniform, the arithmetic and the heuristic crossover operators [37] diversify the population. These operators only produce one offspring. The total number of crossovers in each generation is set to $3S_{pop}$ and the number of each crossover is set to S_{pop} at the beginning of the search where, S_{pop} is population size. The progress or success rates of these operators are assessed during the search; then, as the search progresses, is made dynamically. The generated solutions are evaluated before and after the application of each crossover operator. Depending on the success of the operator, we calculate an average growth value which is used to dynamically adjust the number of each crossover. More specifically: the progress of the crossover operator C when applied to solutions x and y is 1 if $C(x,y)$ is better than x and y, 0 if $C(x,y)$ is worse than x and y, and 0.5 otherwise. The average $Progress(C(i))$ of each crossover operator C is calculated by summing all the progresses of C and dividing it by the number of parent pairs to which C was applied. Then, the number of each crossover is adjusted using (10) where η is the number of crossover operators and κ indicates the minimal ratio value permitted for each operator. That is, κ is a parameter that permits to keep each operator even if the progress of the operator is too poor.

$$Number_{C(i)} = 3[\frac{Progress(C(i))}{\sum_{j=1}^{\eta} Progress(C(j))} \times (1 - \eta\kappa) + \kappa] S_{pop}. \quad (10)$$

Population management and survivor selection: For each offspring s, Population management determines the distance $d_P(s)$ of given solution s to the population and compares this value to the population diversity parameter δ. If this distance is not smaller than δ, the solution s is added to population. Child s is discarded if it does not pass the distance test. To avoid missing a new best solution, s is also accepted without performing the distance test if it improves the current best solution. Since the recombination may generates many offspring solutions with worse performance than their parents, an age-based replacement or a generational approach are likely inefficient. Here, the survivor selection method is used and the best S_{pop} individuals among both parent and offspring solutions are selected for the subsequent generation.

Control policy for δ: Several population management strategies have been described in [34]. The diversity parameter δ can be considered as a constant value or it can vary by the algorithm. A high value will increase the diversity of the population while lower values will decrease it but must not be too large, otherwise AMAPM spends too much time in unproductive iterations. In this paper a varying diversity parameter based on a minimum value $\delta_{min} = 5$ and a step $\sigma = 5$ is considered: δ takes the value δ_{min} in the beginning of the algorithm and steadily increases by σ and new genetic materials are introduced in the population and δ is reset to δ_{min} each time the best solution is improved. This strategy can be called adaptive because it uses information about the effectiveness of the search to dynamically control the diversity of the population.

Local Searchers: In order to support the evolutionary process, two local searchers are employed. These local searchers offer new search directions leading to a basin of attraction different from starting point and, thus, prevents an undesired premature convergence.

- Simulated Annealing: The Simulated Annealing (SA) metaheuristic [37] has been chosen since it offers an exploratory perspective in the decision space which can choose a search direction leading to a basin of attraction different from starting point and assists the evolutionary framework in finding better solutions which improve the available genotype while at the same time exploring areas of the decision space not yet explored. It accepts, with a certain probability, solutions with worse performance in order to obtain a global enhancement in a more promising basin of attraction and, thus, prevents an undesired premature convergence. The SA starts operating on the best solution.
- Simple tabu search: The simple tabu search (TS) Algorithm is a deterministic local searcher which starts operating on the best solution w. At each iteration of simple TS at most 100 neighborhoods are generated by incriminating or discriminating one unit to genes of w and the best neighborhood is accepted. Moves are tabu if they involve a gene which has been changed recently. An aspiration criterion allows tabu moves to be accepted if they lead to the best solution found so far. This is the basic tabu search, based only on short term memory, as described in [38].

Simulated annealing is similar to tabu search in that it occasionally allows solutions of inferior cost to be generated. It differs from tabu search in the manner in which it avoids cycling. Instead of checking deterministically the preceding solutions for cycling, it simply randomizes its selection of the

next solution. In doing so, it not only avoids cycling, but also provides some theoretical guarantee of escaping from local minima and eventually finding a global minimum.

Adaptation: In order to design a robust algorithm, the following index is calculated [14]:

$$\xi = \min\{1, \tau|\frac{J_{ave} - J_{best}}{J_{best}}|\}.$$

where J_{best} and J_{avg} are the best, and average of the fitness function values in the S^f_{pop} best individuals of the population, respectively and τ is a normalization factor. The variable S^f_{pop} is defined in the next. The index ξ can be seen as a measurement of the state of the phenotypical convergence of the algorithm. If $\xi \approx 1$ the population has high diversity and therefore the convergence conditions are far; if $\xi \approx 0$ there is a low phenotypical diversity and means that the convergence is approaching.

Coordination of the local searchers: We consider two rules for Activation of local searchers. In proposed algorithm the local searchers activate when:

- The diversity of population is decreasing.
- The AMAPM spends too much time in unproductive iterations.

Setting $\overline{\delta} = \frac{\delta}{\delta_{min}}$, the mentioned rules can be incorporated by considering the conditions $\xi \in [0.01\overline{\delta}, 0.02\overline{\delta}]$ for activation of SA and $\xi \in [0, 0.015\overline{\delta}]$ for activation of simple TS. The condition regarding the lower bound of usability of the SA ($0.01\overline{\delta}$) is due to the consideration that if $\xi \leq 0.01\overline{\delta}$ application of the SA is usually unsatisfactory since it most likely leads to a worsening in performance. Note that, the resulted solution from SA, in our implementation, does not replace the original one but it is simply inserted in the population. This gives a chance at enhancing a solution with good performance without possibly ruining the genotype of the best solution. The SA has two parameters, which are the budget and the initial temperature $Temp_0$. Even though these parameters should be simultaneously set since the success of the local searcher depends on both, the budget has been fixed to be 500 fitness evaluations (in order to have a constant computational cost for the SA) and the initial temperature $Temp_0$ has been adaptively set $Temp_0 = |J_{avg} - J_{best}|$. This means that the probability of accepting a worse solution depends on the state of the convergence. In other words, the algorithm does not accept worse solutions when the convergence has practically occurred [32]. Moreover, the main idea behind the activation condition ($\xi \leq 0.015\overline{\delta}$) of simple TS is due this fact that an early application of simple TS local searcher can be inefficient since a high exploitation of solutions having poor fitness values would not lead to significant improvements of the population and hence more intensive condition is considered for activation of it. The considered budget for simple TS has been fixed to be $2,000$ fitness evaluations. It should be noted that in the range $[0.01\overline{\delta}, 0.015\overline{\delta}]$ both local searchers are applied to the best individual of the population. This range is very critical for the algorithm because the population is tending towards a convergence but still has not reached such a condition. In this case, there is a high risk of premature convergence due to the presence of plateaus and suboptimal basins of attraction or false minima introduced by noise. Thus, the two local searchers are supposed to "compete and cooperate" within the same generation, merging the "global" search power of the SA and the "local" search power of the simple TS.

Create initial population;
Set population diversity parameter δ=δ_{min};
Set the number of each crossover to S_{pop};
Calculate $\xi = \min\{1, \tau|\frac{J_{avg} - J_{best}}{J_{best}}|\}$;
Calculate $\overline{\delta} = \frac{\delta}{\delta_{\min}}$;
***while* (conditions)**
  Parent selection by binary tournament;
  Apply the crossover operators with respect to the number of each crossover and generate $3S_{pop}$ offspring individuals;
  Update the number of each crossover operator;
  ***for* each offspring o do**
    ***if* $J(o) < J_{best}$ or $d_P(o) \geq \delta$**
      $P := P \cup \{o\}$;
    end-if
  end-for
  if $0.01\overline{\delta} \leq \xi \leq 0.02\overline{\delta}$
    Execute the SA on the best individual;
  end-if
  if $\xi \leq 0.015\overline{\delta}$
    Execute the simple TS on the best individual;
  end-if
  Calculate $\xi = \min\{1, \tau|\frac{J_{avg} - J_{best}}{J_{best}}|\}$;
  Calculate $S_{pop} = S^f_{pop} + (1-\xi)S^v_{pop}$;
  Select the S_{pop} best individuals to the subsequent generation;
  Update diversity parameter δ;
  Calculate $\overline{\delta} = \frac{\delta}{\delta_{\min}}$;
end-while

Fig. 2. Adaptive Memetic Algorithm with population management pseudocode.

Dynamic population size in survivor selection: The population is resized at each generation and the S_{pop} individuals having the best performance are selected for the subsequent generation [14], [32]:

$$S_{pop} = S^f_{pop} + (1 - \xi)S^v_{pop},$$

where S^f_{pop} and S^v_{pop} are the fixed minimum and maximum sizes of the variable population, respectively. The coefficient ξ is then used to dynamically set the population size in order to prevent a premature convergence and stagnation. When the population is highly diverse, a small number of solutions need to be exploited. When $\xi \approx 0$, the population of individuals is converging and a larger population size is required to increase the exploration. Fig. 2 shows the pseudocode of the AMAPM.

IV. NUMERICAL RESULSTS AND COMPARISION WITH OTHER OPTIMIZATION METHODS

For the AMAPM, 30 simulation experiments have been executed. Each experiment has been stopped after 70,000 fitness evaluations. At the end of each generation, the best fitness value has been saved. Analogously, 30 experiments have been carried out with a Genetic Algorithm (GA), Evolution Strategy (ES) and the simulated annealing (SA) in order to perform a comparison of the performance between the AMAPM and three classical methods.

TABLE II
PARAMETER SETTING FOR THE AMAPM, THE GA, AND THE ES

PARAMETER	AMAPM	GA	ES
Size of initial population	500	500	500
Population size for subsequent iterations	Dynamic between 30 and 100	160	160
Number of crossovers per generation	Dynamic between 90 and 300	100	100
Mutation probability	0	0.1	1
Fitness evaluations	70,000	70,000	70,000

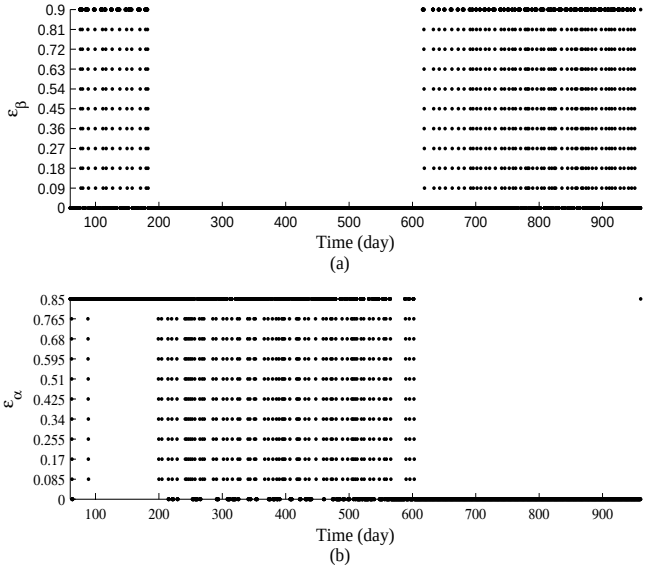

Fig. 3. PI and RTI medication efficacies.

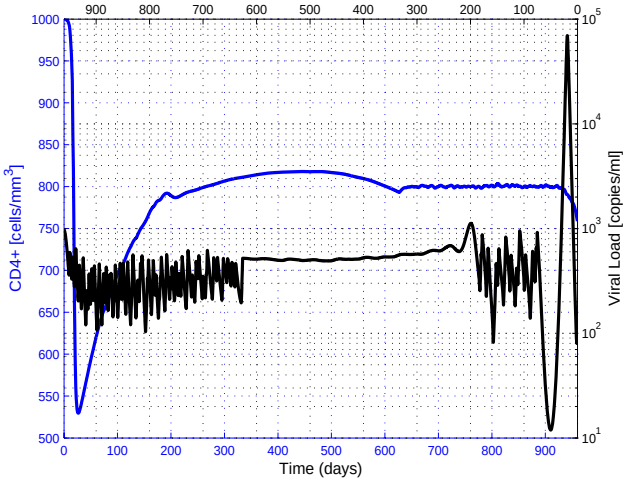

Fig. 4. Dynamic behavior of x and v.

The GA employs a random initial sampling, roulette wheel selection based on the rank of the solutions, binary tournament parent selection, two-point crossover and swap mutation [37].

A σ-self adaptive evolution strategy [37] has been selected. Moreover the uniform crossover and Gaussian mutation (rounding to the nearest integer) has been implemented. As a standard ES, this ES does not contain any parent selection and, thus, it considers all populations to be a population of parents. Finally, a $(\mu + \lambda)$ strategy has been chosen.

The mutation is selected as perturbation operator in simulated annealing algorithm. For the annealing schedule, we set an initial temperature 10^8, and a temperature decreasing factor of 0.95. Each temperature was tried 100 times, and the total number of (different) temperatures tested was 700. Table II shows the parameter settings for the AMAPM, the GA, and the ES.

Figs. 3(a) and 3(b) show the Protease Inhibitor (PI) and Reverse Transcriptase Inhibitor (RTI) efficacies, respectively, for the most effective HIV therapy schedule found by the AMAPM over the 30 experiments carried out. Fig. 4 shows the behavior of the state variables x and v of the model under the best therapy. Fig. 3 shows that the suggested medicine schedules by the AMAPM have some apparent on and off periods. The PI-medication is stopped before 190 days and initializes after 600 days again. Moreover, the RTI-medication is stopped before 610 days. Actually, the suggested mediation by AMAPM requires only 123 days for PI-administration and 351 days for RTI-administration. The rest periods of the medical treatment reduces undesired side effects and the possibility of mutations leading to drug-resistant HIV strains. Fig. 4 shows that the number of uninfected CD4+ T-cells stays very high, around the it's lower bound $\underline{x}$, and the viral load stays very low, around the it's upper bound $\overline{v}$.

Table III gives, for each algorithm under examination, the values of the objective functions J_i , the fitness J^b obtained by the most successful experiment (over the 30 sample runs), the average fitness at the end of the experiments $< J >$, the fitness of the least successful experiment J^w, and the standard deviation σ divided to the related value of $< J >$. Concerning the robustness of the algorithms, the value $\frac{\sigma}{<J>}$ is very small for all algorithms after $70,000$ fitness evaluations. This basically means that the four algorithms offer a good performance in terms of robustness. The results show that, according the average best fitness value $< J >$, the AMAPM outperforms the other methods. Moreover the value of $\frac{\sigma}{<J>}$ is smaller in the case of the AMAPM and therefore the proposed algorithm is probably more robust than the other methods. The comparison between the AMAPM and the GA shows that, although the value of $< J >$ for the AMAPM is less than the obtained value by the GA, this solution does not dominate the one given by the GA. In fact, the solution given by the GA offers slightly better performance in terms of the quantity of PI-medications (J_3) that the patient should take but worse performance than the AMAPM with respect to viral load (J_2)

TABLE III
NUMERICAL RESULTS

METHOD	J_1	J_2	J_3	J_4	J^w	$< J >$	J^b	$\frac{\sigma}{<J>}$
AMAPM	2.2192×10^4	6.5975×10^4	88.1566	281.9552	5.4830×10^6	5.4269×10^6	5.3837×10^6	0.0044
ES	2.2495×10^4	6.2712×10^4	111.8842	343.6849	5.9918×10^6	5.9213×10^6	5.8442×10^6	0.0061
GA	3.5405×10^4	8.5755×10^4	18.2704	400.1296	6.4873×10^6	6.3922×10^6	6.2171×10^6	0.0124
SA	2.2179×10^4	6.8605×10^4	194.1663	171.2373	6.1664×10^6	6.0514×10^6	5.8710×10^6	0.0126

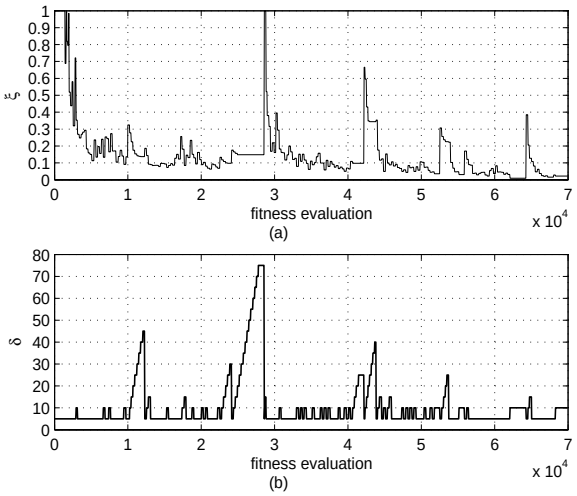

Fig. 5. Behavior of ξ and δ.

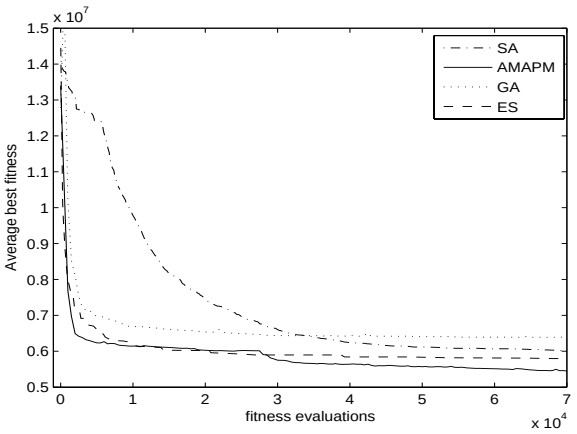

Fig. 6. Comparison of the algorithmic performance of the AMAPM with the GA, the ES, and the SA.

and the level of CD4+ T-Cells (J_1). For the considered STI therapies it is much more important that the therapy keeps the viral load below the threshold value $\overline{v}$ and keeps the CD4+ cells above the threshold value $\underline{x}$ at all times. In this sense the fact that the GA proposes a very smaller quantity of PI-medication than the AMAPM is of minor interest. The comparison between the AMAPM and the SA leads to the similar argument.

In order to better explain the behavior of the AMAPM, the diagram plotting δ and ξ versus fitness evaluations in the most successful experiment are shown in Fig.5. In the range 25,000 to 28,000 fitness evolutions the value of parameter ξ is constant, which means that in this range there are not new genetic materials improving the best individuals of population due to presence of suboptimal basin of attraction. Moreover, in this range the value of parameter δ increases due to unproductive iterations which leads to activation of SA local searcher. An abrupt increase of ξ and decrease of δ correspond to the introduction of a new individual into the population, which has far better performance than the others. More specifically, the peaks around 28,500 fitness evaluations are due to successful searches by the SA. We have the same situation in the range 40,500 to 42,000 fitness evolutions, while the peaks around 52,000, 56,000, and 65,000 fitness evaluations are caused by successful searches by the simple TS. Fig. 6 shows the comparison of the performances. From this figure and Table III, it is qualitatively clear that the AMAPM tending to converge to a solution having a better performance than the other methods. Moreover, it is interesting to consider the relationship of Fig. 5 and Fig. 6. Although Fig. 5 refers to one experiment while Fig. 6 is based on an average, it is clear that, at around 28,500 fitness evaluations, there is slightly steep decrease in the diagram of the algorithmic performance of the AMAPM. This decrease corresponds to high oscillations in the trends of δ and ξ. According to our interpretation, this phenomenon is due to successful runs of the SA local searcher, which led to the generation of solutions with better performance than the rest of the population and, thus, to a temporary increase of the population diversity. In addition, it can be seen that the AMAPM presents a similar algorithmic performance compared to the other algorithms for about 28,500 fitness evaluations and, after a certain point, it clearly starts to slightly outperform the other methods. The numbers of uniform, heuristic and arithmetic crossovers in the most successful experiment are 26,288, 11,953 and 24,042, respectively.

V. CONCLUSION

This paper proposes an Adaptive memetic algorithm with population management (AMAPM) for designing HIV multidrug therapies. The AMAPM is an optimization algorithm consisting of an evolutionary framework using a population management strategy to control the diversity of the population and having dynamic parameters and two different local searchers which are adaptively employed in order to explore the decision space and, in various ways, the available candidate solutions. The optimal solution given by the AMAPM is very satisfactory since it keeps the healthy CD4+ cells population at high level and the viral load at a sufficiently low level during the treatment interval. In addition, the proposed medication contains a relatively low number of medication days and,

therefore, helps to avoid harmful side effects and mutations of HIV to drug-resistant strains. Numerical comparisons show that the AMAPM outperforms three other standard methods for this class of problems.

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