

A Self-Learning Fuzzy Discrete Event System for HIV/AIDS Treatment Regimen Selection

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Abstract—The U.S. Department of Health and Human Services Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) treatment guidelines are modified several times per year to reflect the rapid evolution of the field (e.g., emergence of new antiretroviral drugs). As such, a treatment-decision support system that is capable of self-learning is highly desirable. Based on the fuzzy discrete event system (FDES) theory that we recently created, we have developed a self-learning HIV/AIDS regimen selection system for the initial round of combination antiretroviral therapy, one of the most complex therapies in medicine. The system consisted of a treatment objectives classifier, fuzzy finite state machine models for treatment regimens, and a genetic-algorithm-based optimizer. Supervised learning was achieved through automatically adjusting the parameters of the models by the optimizer. We focused on the four historically popular regimens with 32 associated treatment objectives involving the four most important clinical variables (potency, adherence, adverse effects, and future drug options). The learning targets for the objectives were produced by two expert AIDS physicians on the project, and their averaged overall agreement rate was 70.6%. The system's learning ability and new regimen suitability prediction capability were tested under various conditions of clinical importance. The prediction accuracy was found between 84.4% and 100%. Finally, we retrospectively evaluated the system using 23 patients treated by 11 experienced nonexpert faculty physicians and 12 patients treated by the two experts at our AIDS Clinical Center in 2001. The overall exact agreement between the 13 physicians' selections and the system's choices was 82.9% with the agreement for the two experts being both 100%. For the seven mismatched cases, the system actually chose more appropriate regimens in four cases and equivalent regimens in another two cases. It made a mistake in one case. These (preliminary) results show that 1) the System outperformed the nonexpert physicians and 2) it performed as well as the expert physicians did. This learning and prediction approach, as well as our original FDES theory, is general purpose and can be applied to other medical or nonmedical problems.

Index Terms—Artificial intelligence, discrete event systems, fuzzy discrete event systems, fuzzy logic, HIV/AIDS treatment.

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I. INTRODUCTION

TREATMENT decision-making is a complex and challenging undertaking for virtually all diseases or disease states [7], [16], [29]. Many symptoms, diagnoses, and treatment outcomes are inherently imprecise, immeasurable or poorly quantifiable, and subjective with a high degree of uncertainty. Moreover, a clinician's subjective judgment always plays a vital role. Randomized controlled clinical trials are a superior method of determining the best treatment options on average for a group of patients but, often, the variations in treatment options are so numerous that it is not feasible to conduct controlled clinical trials capable of comparing all treatment variations in all patient subpopulations. In addition, differences among the randomized populations and individual patients may make the results of controlled clinical trials less relevant to many medical practices. Consequently, medical decision-making is highly dependent on expert opinions in an attempt to arrive at optimal treatment outcomes for specific patients.

The considerable complexities of human immunodeficiency virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) treatment provide a prime example of these issues. The United Nations estimates that 38 million people worldwide are infected with HIV and that more than 22 million have died [15]. To combat the disease, the most recent United Nations Program on HIV/AIDS/World Health Organization annual AIDS epidemic update (www.unaids.org) was launched late 2005 around the world. HIV infection rates are decreasing in several countries, but the global number of people living with HIV continues to rise. The continued expansion of the HIV pandemic makes it unlikely that the growth in medical personnel will be able to keep pace with the need for expertise in antiretroviral therapy, particularly in the poorer nations. Furthermore, HIV/AIDS treatment is, unfortunately, among one of the most complex treatments for any disease, with treatment failures resulting in diminished future treatment options for both treated patients and those infected with treatment-resistant HIV virus strains [3], [11]. Although the U.S. Department of Human Health and Services HIV/AIDS treatment guidelines cover the first-round combination antiretroviral therapy and describe a conceptual approach to the more complex second (or subsequent) rounds, they do not provide individualized treatment advice and must be frequently updated as treatment options evolve. In this regard, computer software that can utilize clinical information to recommend regimens that will be sufficiently potent, well tolerated, and taken on schedule by an HIV-infected person would be a great advance. Such a software advisory tool will be very useful not only to nonexpert AIDS physicians in the U.S.

but also to resource-poor nations whose access to antiretroviral drugs is increasing.

To achieve this goal, however, a systematic decision-making and optimization technology capable of handling all the aforementioned technical difficulties must be developed first. We have recently combined the merits of fuzzy systems technology [1], [3], [12], [24], [27], [32], [41], [42], [46], [50] with the advantages of conventional discrete event system (DES) technology [5] and have established a theoretical framework for a comprehensive theory of fuzzy DES (FDES) [19], [20]. We have generalized the conventional (crisp) finite automaton model to fuzzy finite automaton model. These developments aimed at applications to diverse fields with medicine being one of them.

We have applied this technology to create a regimen selection system, called AIDS-FDES, that prescribes combination antiretroviral therapy for HIV/AIDS patients receiving the first-round treatment [21]–[23], [47]–[49]. A patient who is about to start his/her first round is called “treatment-naive.” The differences between a treatment-naive patient and a patient receiving a subsequent round of treatment include (much) more uncertainties on drug resistance, treatment adherence, and the extent of side effects due to treatment. By regimen, we mean a combination of antiretroviral drugs to be taken by the patient. Our retrospective evaluation of the system using qualifying patients treated in our AIDS Clinical Center showed that the overall exact agreement between the actual prescribed regimens and the choices selected by the system was 82.9%.

Compared to the existing literature (e.g., [1], [6], [17], [28], [31], [33], [39], and [45]), the advantages of our FDES approach are as follows. Unlike the neural networks methodology [16], [36], which is a “black-box” approach from input–output standpoint, the reasoning chain between the input variables and the final decision in our approach is easily understandable to humans. All the parameters of the system have clear and intuitive meanings. Compared to the expert systems paradigm (e.g., [1], [13], [17], [31], [34], and [38]–[40]), our approach has better capabilities of representing and using knowledge even in the face of weak consensus and also is more readily and easily upgradeable to new knowledge. Additionally, as shown next, self-learning is inherent to FDES (this is not the case for the expert-system methodology, for which learning can be difficult to realize). These are practically important features particularly for medicinal applications.

HIV/AIDS treatments are rapidly changing owing to new antiretroviral drugs, evolving regimens, emerging technologies (e.g., genotype resistance testing and pharmacogenetics), and updated knowledge of HIV pathogenesis. Consequently, the U.S. HIV/AIDS treatment guidelines are modified several times per year to reflect the changes [11]. Logically, in order for any decision-making assistant system to be truly clinically useful, it must be refined or redesigned frequently to reflect the reality. Such a task, nevertheless, can not only be laborious and time consuming but also costly. Alternatively, the system should be so developed that it has the ability to predict the physician’s treatment selections involving a new regimen by learning his/her prior treatment choices on the previously available regimens. Such a learning system would be more practical and require less technical effort and minimal involvement of clinical experts to maintain and upgrade. Additionally, it is sometimes

desirable to quantitatively estimate the clinical utility of an anticipated new drug or regimen, even before its existence, relative to the existing ones.

This paper presents our further effort in establishing a self-learning FDES framework as well as in developing the AIDS-FDES system into a self-learning regimen selection system (early preliminary results were reported in [48]). The application-independent general-learning principle will be described so are the retrospective evaluation results involving real patients. The theory on nonlearning aspects of AIDS-FDES and its performance for selecting the first-round regimens have been addressed in detail in our previous papers [21]–[23], [47], [49] and will be minimally outlined in this paper for brevity.

II. SELF-LEARNING HIV/AIDS REGIMEN SELECTION SYSTEM

A. Brief Introduction to HIV/AIDS Treatment

We concentrate on combination antiretroviral therapy because it is the only effective long-term treatment strategy at present and has resulted in significant declines in mortality and morbidity in patients with HIV/AIDS. The essential components of effective antiretroviral therapy include the following: 1) selecting a regimen that is sufficiently potent to suppress replication of an individual patient’s HIV; 2) maximizing patient adherence to the prescribed regimen; 3) minimizing or managing drug toxicity so that patients can continue to use medications at their full doses; and 4) selecting regimens that maximize the chance of success with subsequent antiretroviral regimens. Selection of sufficiently potent regimens is based on such factors as baseline plasma HIV ribonucleic acid (RNA) levels, CD4+ lymphocyte counts, knowledge of prior treatment history, and the results of HIV resistance testing combined with expert interpretation and advice. Balancing all of these factors is complex and inexact. Published outcomes data support the role of expertise in utilization of the therapies. Published treatment guidelines recommend that expert opinion be sought regarding the initiation of therapy and selection of antiretroviral regimens and for decisions to change regimens. The clinical objective for a treatment-naive patient is to indefinitely suppress HIV replication to the lowest achievable level.

This paper involved naive patients treated at our AIDS Clinic Center in 2001 using the four most frequently prescribed regimens at the Center at that time (Table I). The four regimens constituted about 40% of the regimens prescribed for naive patients in that year. The reason for using the historically popular regimens, as opposed to the current popular regimens, was the availability of the patients needed for the retrospective evaluation of AIDS-FDES. Older regimens are replaced by newer ones rather quickly as new AIDS drugs emerge. Hence, it was difficult to accumulate within a short period of time (e.g., nine months) a sufficiently large number of patients for a fully powered retrospective study. This limitation existed even though our clinic at present has 1638 patients, 1251 of which (i.e., 76%) are receiving treatment.

A physician must consider many factors when selecting an antiretroviral treatment regimen for a patient. In our FDES scheme, the primary four clinical parameters germane to this decision are as follows: 1) anticipated potency of the regimen; 2) anticipated adherence for the patient under the regimen;

TABLE I
VALUES OF FOUR CLINICAL VARIABLES INTRINSIC TO FOUR
HISTORICALLY POPULAR FIRST-ROUND HIV/AIDS
TREATMENT REGIMENS

Regimen No.	Drugs	Potency	Adherence	Adverse Events	Future Drug Options
1	nelfinavir + zidovudine/lamivudine	85%	55%	30%	80%
2	efavirenz + zidovudine/lamivudine	90%	80%	20%	60%
3	nevirapine + zidovudine/lamivudine	85%	85%	20%	65%
4	abacavir/zidovudine /lamivudine	80%	90%	10%	85%

3) prognosis for adverse events under the regimen; and 4) expected future drug options due to the potential for development of resistance to the regimen [33], [37], [43], [44]. We use the literature-cited percentage of patients who achieve plasma HIV RNA less than 400 copies/mL after 48 weeks of treatment as our measure of potency [9]. Adherence is a very complicated issue involving many factors impacting the patient’s ability to comply with the prescribed regimen [35]. In addition to being associated with poor short-term virological response, insufficient adherence accelerates development of drug-resistant HIV. We define adherence as expected percentage of drug doses prescribed by the physician that are actually taken by the patient weekly for each regimen. Adverse events in this paper are defined as undesirable side effects (grades 1 to 2) and toxicities (grades 3 and 4) [8]. All these clinical grades are well defined in the medical literature. Such levels of adverse events can make it difficult for some patients to continue a regimen [25]. The final primary parameter is the future drug options that are available after the current treatment is no longer viable. Virologic failure is commonly associated with emergence of drug-specific resistance mutations [7], [14]. Genotypic resistance testing is currently widely used to measure mutations on the reverse transcriptase and/or protease genes that impart complete or partial resistance to HIV. In this paper, the future drug options parameter is defined as the approximate percentage of drugs remaining that have efficacy in the presence of detected or expected mutations already selected.

Table I summarizes the estimated intrinsic characteristics of each regimen. The estimation data were compiled following a thorough review of the relevant medical literature (e.g., outcomes of various clinical trials) and a lengthy interview process with the HIV/AIDS experts on our project team. Accordingly, each percentage in Table I is a (subjective) summarization of the clinical “possibility” for the parameter.

B. Self-Learning Regimen Selection System

Fig. 1 shows the configuration of the AIDS-FDES system. There are three major system components: 1) a treatment objectives classifier; 2) fuzzy finite state machine models for treatment regimens; and 3) a genetic-algorithm-based regimen selection optimizer. A more general self-learning FDES theory is given later.

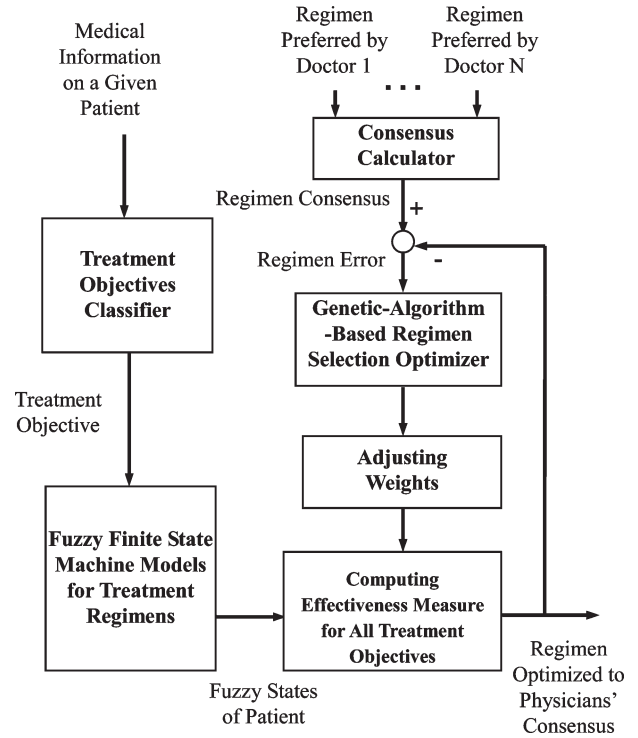


Fig. 1. Block diagram of the self-learning regimen selection system AIDS-FDES.

1) *Treatment Objectives Classifier*: A treatment objective is a combination of characteristics that a doctor must consider when choosing a regimen. These characteristics include the anticipated potency (classified into two levels—medium or high), adherence (challenging, moderate, or easy), adverse events (very low, low, or medium), and future drug options (medium or high) that are desired for the regimen to be selected. There are 32 clinically valid combinations of these characteristics among the total of 36 possibilities. However, this total is theoretical only and four of the combinations must be excluded because they are untenable from a clinical standpoint. These are the “medium” potency and “medium” future drug options when adherence is either “moderate” or “challenging” and adverse events is either “medium” or “low.” Thus, the actual total number of valid combinations is 32.

Each combination is a treatment objective. The role of the classifier is to assign a typical patient to one of the 32 treatment objectives. We exclude small numbers of the nontypical patients with special clinical challenges (e.g., pregnant patients and patients with liver disease, pancreatic disease, or neuropathy). There are nine simple classification rules defined through knowledge acquisition with our AIDS experts. Patient’s CD4 cell counts and HIV RNA level are used to determine treatment potency needed. Next are three of the nine rules.

- 1) If $CD4 < 50$ or if $CD4$ is 50–200 and $HIV\ RNA > 100\ 000$, then high potency is desired.
- 2) If $CD4$ is 50–200 and $HIV\ RNA < 100\ 000$ or if $CD4 > 200$ and $HIV\ RNA \geq 100\ 000$, then high or medium potency is desired.
- 3) If $CD4 > 200$ and $HIV\ RNA < 100\ 000$, then medium potency is desired.

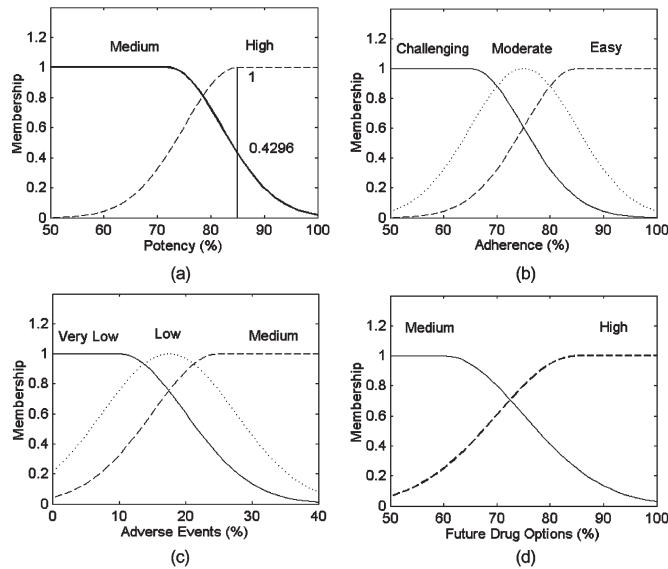


Fig. 2. Definitions of fuzzy sets for the four clinical variables. (a) Potency, (b) adherence, (c) adverse events, and (d) future drug options.

High potency is usually desired. This, however, is not always true because high potency may be ranked lower priority than other factors when immune function is good and/or viral copy number is not high.

The adherence requirement is based on five objective patient factors documented in the literature and consistent with our experience: 1) whether the patient’s age is younger than 24 (adolescents have a documented poor adherence rate); 2) whether the patient is homeless; 3) whether the patient is currently using any illegal drugs or drinking excessive alcohol; 4) whether the patient is mentally ill; and 5) whether the patient has missed clinic visit more than once in the past 12 months. Each of these five factors has been shown to negatively affect adherence (e.g., [29] and [30]). Patient tolerance of adverse events is quantified using each individual patient’s risk factors for cardiovascular disease, because antiretroviral therapy is known to increase these risks through modification of blood-lipid levels, promotion of glucose intolerance or diabetes, and perhaps other factors [10]. Determination of the relative importance of preserving future drug options involves balancing the need for maximally potent regimens [consideration of current HIV RNA levels and extent of immunosuppression (CD4 counts)] against the need to preserve future drug options.

2) *Fuzzy Finite State Machine Models for Treatment Regimens*: There are four FDES components, one for each of the four clinical variables. Correspondingly, there are four fuzzy state vectors, representing the state of “potency,” “adherence,” “adverse events,” and “future drug options,” respectively. Prescribing a treatment regimen for a patient is a crisp event, which causes the changes of state vectors in the four fuzzy automata. The changes are described by state transition matrices. There are a total of 16 different state transition matrices for the four regimens. Each element in a transition matrix is a number between zero and one to describe the possibility of transferring from one fuzzy state to another.

To generate these possibilities, we use Table I and fuzzy sets defined for each of the four clinical variables (Fig. 2). The

fuzzy sets are empirically defined according to the knowledge obtained from the literature as well as from our AIDS experts. They are defined subjectively but also intuitively—the values of the clinical variables are used to define the “key points” of the fuzzy sets (i.e., the tuning point where the membership first becomes one from less than one). For instance, the potency values for the four regimens in Table I range from 80% to 90%. Thus, the turning point for “high” potency is chosen at 85%, whereas that for “medium” potency is set at 75%. We chose the Gaussian type of fuzzy sets, because this type is one of the most widely used ones and worked well in our application.

If one draws a line perpendicular to the potency axis at 85%, which is the potency for Regimen 1, the intersection of the line with the “medium” fuzzy set is 0.4296 and with the “high” fuzzy set is one [Fig. 2(a)]. This process is similar to the fuzzification process used for fuzzy controller input variables [46]. Normalization of these membership values gives 0.3005 and 0.6995, respectively. Thus, the first row of the state transition matrix for the potency of Regimen 1 is obtained as

$$B = \begin{matrix} & \begin{matrix} \text{Initial} & \text{Medium} & \text{High} \end{matrix} \\ \begin{matrix} \text{Initial} \\ \text{Medium} \\ \text{High} \end{matrix} & \begin{bmatrix} 0 & 0.3005 & 0.6995 \\ 0 & 0.3 & 0.7 \\ 0 & 0.6 & 0.4 \end{bmatrix} \end{matrix} \quad (1)$$

Hence, the possibility of transferring from “initial” state to “medium” state is 0.3005 and from “initial” state to “high” state is 0.6995. The membership values in the second and third rows, assigned empirically based on clinical experience and knowledge, are not needed in this paper because our current clinical focus is on the first round—we begin with the “initial” state, not the “medium” or “high” states. The numbers in the second and third rows in (1) are arbitrary and are for illustration purpose only. Logically, the possibility for transferring from “initial” state to “initial” state, “medium” state to “initial” state, and “high” state to “initial” state is zero.

The other 15 state transition matrices can be obtained in the same manner using Table I and Fig. 2.

As the result of prescribing a regimen, we will have four newly modified fuzzy state vectors, one for “potency,” one for “adherence,” one for “adverse events,” and one for “future drug options.” The new vectors are computed by the maximum fuzzy composition operation using the four initial state vectors and the “potency,” “adherence,” “adverse events,” and “future drug options” state transition matrices specific to the regimen. The new state vectors represent the state of “potency,” “adherence,” “adverse events,” and “future drug option” are denoted as S_1 , S_2 , S_3 , and S_4 , respectively.

For example, the new potency state vector relative to the initial state vector (i.e., $[1 \ 0 \ 0]$) after Regimen 1 is applied is calculated as

$$\begin{aligned} S_1 &= [1 \ 0 \ 0] \circ B \\ &= [\max(0, 0), \max(0.3005, 0), \max(0.6995, 0)] \\ &= [0 \ 0.3005 \ 0.6995] \end{aligned} \quad (2)$$

where the symbol \circ stands for fuzzy reasoning operation. This means that the new state is 0.3005 for “medium” potency and 0.6995 for “high” potency.

The new state vectors contain memberships for different fuzzy sets. For the decision-making purpose, each vector needs to be converted to a number (i.e., defuzzification [46]). For this purpose, each vector is multiplied by a weight vector: $S_1 \cdot W_1$ for potency, $S_2 \cdot W_2$ for adherence, $S_3 \cdot W_3$ for adverse events, and $S_4 \cdot W_4$ for future drug options, where W_1 to W_4 are the weight vectors. In this paper, there are a total of ten weight vectors containing 26 adjustable weights (see “Adjusting Weights” block in Fig. 1). The dimension of the weight vectors is consistent with that of the corresponding state vectors. For instance, since S_1 is 1×3 , W_1 should be 3×1 . If the weight vector for “high” potency is $W_1 = [0 \ 0.3 \ 0.7]^T$, it would mean that the emphasis is on “high” with a weight of 0.7, but “medium” potency is also factored in with a lower weight of 0.3. Each vector is normalized to one (i.e., the sum of the membership values is one).

The models need to consider the 32 treatment objectives in determining which regimen would be deemed to be the best one for a given patient. For each objective, every regimen should be evaluated. Thus, a proper effectiveness measure E needs to be developed for gauging different regimens in optimizing decision-making. We have developed a weighted summation method that calculates the weighted summation of the four vectors for a balanced optimal decision-making (see “Computing Effectiveness Measure for All Treatment Objectives” block in Fig. 1)

$$E = \beta_1 \cdot S_1 \cdot W_1 + \beta_2 \cdot S_2 \cdot W_2 + \beta_3 \cdot S_3 \cdot W_3 + \beta_4 \cdot S_4 \cdot W_4 \quad (3)$$

where β_1 , β_2 , β_3 , and β_4 are the weights for potency, adherence, adverse events, and future drug options, respectively. In this paper, we consider all the four clinical variables to be equally important, making $\beta_1 = \beta_2 = \beta_3 = \beta_4 = 1$. In some applications, one may want to heavily emphasize more on certain variable. When this is the case, the corresponding weight should be higher and different weights will have different values.

Let us now put what has been described above together and make a more complete example. Assume that Regimen 1 is applied to one of the 32 combinations, which is “high” potency, “challenging” adherence, “medium” adverse events, and “medium” future drug options. Suppose that the computed new state vectors for potency, adherence, adverse events, and future drug options are, respectively

$$\begin{aligned} S_1 &= [0 \ 0.3050 \ 0.6995] \\ S_2 &= [0 \ 0.0777 \ 0.3482 \ 0.5741] \\ S_3 &= [0 \ 0.2467 \ 0.3943 \ 0.3590] \\ S_4 &= [0 \ 0.8004 \ 0.1996]. \end{aligned}$$

In addition, suppose that $W_1 = [0 \ 0 \ 1]^T$ for “high” potency, $W_2 = [0 \ 0.2069 \ 0.5402 \ 0.2529]^T$ for “challenging” adherence, $W_3 = [0 \ 0.1250 \ 0.3304 \ 0.5446]^T$ for “medium” adverse events, and $W_4 = [0 \ 0.4767 \ 0.5233]^T$ for “medium” future drug options. Hence, the value of E for

Regimen 1 being applied to this particular objective can be computed using (3)

$$\begin{aligned} E &= [0 \ 0.3050 \ 0.6995] \times [0 \ 0 \ 1]^T \\ &\quad + [0 \ 0.0777 \ 0.3482 \ 0.5741] \\ &\quad \times [0 \ 0.2069 \ 0.5402 \ 0.2529]^T \\ &\quad + [0 \ 0.2467 \ 0.3943 \ 0.3590] \\ &\quad \times [0 \ 0.1250 \ 0.3304 \ 0.5446]^T \\ &\quad + [0 \ 0.8004 \ 0.1996] \\ &\quad \times [0 \ 0.4767 \ 0.5233]^T = 1.8915. \end{aligned} \quad (4)$$

For each of the 32 treatment objectives, there are four E values, one for a regimen. The regimen with the highest E value is considered as the first-choice regimen, whereas the lowest the fourth-choice regimen. It is not meaningful to compare E values computed for different treatment objectives.

3) *Genetic-Algorithm-Based Regimen Selection Optimizer:* The role of the genetic-algorithm-based regimen selection optimizer is to optimize regimen selection through adjusting the weights to optimize the overall effective measure—to find such 26 weights that minimize the overall differences represented by an objective function (more precisely, the sum of differences) between the regimens selected by the models and those selected by the two AIDS experts on this project for the 32 treatment objectives. For each objective, the difference is zero if they agree and one if they do not.

The genetic algorithm was designed as follows. Each of the 26 weights was represented by a string of six-bit binary numbers of zeros and ones. These strings were connected to form a 156-bit-long string, each of which represented a weight vector. After creation in each generation, the weights in each weight vector were always normalized so that their sum was one. Each generation of the weights contained ten 156-bit strings. The weights of the first generation were created randomly because we did not have any prior knowledge on weights. A new generation was created in the following way. The two strings whose objective function values were the largest were used to form ten strings of next generation. One random crossover was applied to the two strings, and the resulting strings became two new strings in the next generation (random distribution was uniform and random number was in $[0, 1]$). This process repeated until all ten new strings were created. Then, one random mutation occurred to each of the ten strings, changing zero to one or one to zero at one location. The mutation probability was set at 0.006 as we experimentally determined this value to be adequate.

The ten sets of new weight vectors were then applied to formula (3) to compute their E values. For each of the 32 treatment objectives, the regimen with the highest E value was regarded as the preferred regimen of the AIDS-FDES system. The weight values kept evolving in this way until the objective function stopped changing appreciably (e.g., 0.1%). We should point out that this genetic algorithm was quite basic, whose performance was adequate at this stage of the system development. Clearly, other evolutionary optimization techniques as well as other optimization paradigms, such as simulated annealing and intelligent particle swarm, can also be used for our purpose. We did not pursue them because we wanted to focus on FDES development itself.

A 2.0-GHz PC and MATLAB software were used to implement the system. Depending on the initial weights and the learning task, the computing time took between a couple of minutes and up to 30 min.

4) *Theory of Self-Learning Fuzzy Discrete Systems*: Supervised learning is actually achieved via the optimizer. Learning performs in the form of adjusting the weights. The values of S_1, S_2, S_3 , and S_4 in (3) can always be computed as long as the percentage values of potency, adherence, adverse events, and future drug options of a regimen are available. Interestingly, the regimen can be real or hypothetical. One just needs to use them, along with the learned weights, to compute the E values for the four regimens with respect to the 32 treatment objectives. For each objective, one can use the regimen with the highest E value as the choice of AIDS-FDES. We have adopted this approach to learning/predicting the role that the presumptively unknown regimens play in regimen selection. Note that the existence of the prediction/learning capability is intrinsic to our FDES approach and is, in the case of HIV/AIDS treatment, independent of the numbers of clinical variables, fuzzy sets, and the form of the effective measure function, among other things.

We now present a general theory of self-learning FDES and do so in the context of the HIV/AIDS treatment to make it easier to understand. The theory is general-purpose and is applicable to other problems, medical or not.

Assume that there are M regimens, each of which has the same N clinical variables to be considered for the patient (e.g., potency). The variables are represented by $A_i, i = 1, \dots, N$. All the variable values are known (e.g., adherence is 85%). We denote the value of A_i of the j th regimen by $a_{ij}, j = 1, \dots, M$. Excluding the initial state, there exist P_i states for A_i , and each state is described by a fuzzy set F_{ki} , where $k = 1, \dots, P_i$. These states, along with the initial state, define a state transition matrix, designated as B_{ij} that represents A_i of the j th regimen. The dimension of B_{ij} is $(P_i + 1) \times (P_i + 1)$. The values of some elements in B_{ij} are determined by fuzzifying a_{ij} [e.g., the first row in (1)], whereas the rest are determined empirically via other means. For each regimen, there are N state transition matrices, one for each of the N variables. Thus, there exist $M \times N$ different state transition matrices for the M regimens.

The total number of different state combinations (i.e., all the theoretically possible treatment objectives) in the regimen selection process is $\Omega^* = \prod_{i=1}^N P_i$. Some of these objectives, though, may not be clinically sensible. Excluding them, we use Ω to represent the total number of the objectives that are clinically reasonable.

The current state for A_i is described by a $1 \times (P_i + 1)$ state vector, designated as S_{hij} , whose first element always represents the initial state (one if the system is in this state and zero otherwise), and the rest of the elements are memberships of the fuzzy sets F_{ki} for the P_i states. The index $h, 1 \leq h \leq \Omega$, indicates which clinical objective is considered when arriving at the state due to the occurrence of an event. The current state vector is updated to form a new state vector after an event takes place, and it can be computed using the max-product composition operation (or some other appropriate composition operation such as the max–min operation, if preferred)

$$S_{hij} = S_{hij} \circ B_{ij}.$$

The memberships for different fuzzy sets in each S_{hij} are then combined to produce a single number (i.e., defuzzification) in a weighted averaging fashion by a weight vector W_{ki} of $(P_i + 1) \times 1$ dimension whose first weight element corresponds to the initial state and is always set to zero. The resulting number, calculated by $S_{hij} \cdot W_{ki}$, represents the contribution of a specific A_i toward a particular treatment objective for the j th regimen. There are P_i different weight vectors, one for each of the P_i different states (i.e., F_{ki}). Since the weight vectors are $(P_i + 1) \times 1$ dimension and each P_i needs a weight vector, excluding the weights for the initial state, the total number of weights is

$$\Psi = \sum_{i=1}^N P_i^2. \tag{5}$$

For the models for AIDS treatment given in the last section, the parameters are as follows: $M = 4$ (four regimens), $N = 4$ [four clinical variables: potency (A_1), adherence (A_2), adverse events (A_3), and future drug options (A_4)], $P_1 = 2$ [two states for potency—“high” (F_{11}) and “medium” (F_{21})], $P_2 = 3$ [three states for adherence—“easy” (F_{12}), “moderate” (F_{22}), and “challenging” (F_{32})], $P_3 = 3$ [three states for adverse events—“medium” (F_{13}), “low” (F_{23}), and “very low” (F_{33})], $P_4 = 2$ [two states for future drug options—“high” (F_{14}) and “medium” (F_{24})]. $\Omega^* = 36$ and $\Omega = 32$ (because four objectives are not clinically sensible). $\Psi = 26$ weight vectors (W_{ki} for $F_{ki}, 1 \leq k \leq 3$, and $1 \leq i \leq 4$).

The effectiveness measure for the j th regimen when the h th treatment objective is considered is defined as follows:

$$E_{hj} = f(S_{h1j} \cdot W_{k1}, \dots, S_{hNj} \cdot W_{kN}), \quad 1 \leq k \leq P_i \tag{6}$$

where f is a (nonlinear) function whose particular form depends on the practical application of interest. If the linear function is chosen for the weighted summation/averaging of all the A_i 's, one attains

$$E_{hj} = \sum_{i=1}^N \beta_i S_{hij} \cdot W_{ki} + \beta_0 \tag{7}$$

where constant coefficient $\beta_i, i = 1, \dots, N$, represents the relative importance of A_i , as compared to the rest of the variables, in the effective measure. β_0 is a constant offset. According to the clinical results we have obtained so far, the linear function is appropriate for our AIDS treatment study. It may be a good choice for other applications as well and probably should be considered as the first choice due to its simplicity.

For more complex decision-making, the linear function may not be good enough, and nonlinear function will be needed. As an example (unrelated to AIDS treatment), if two variables are involved and the decision boundaries are supposedly known to be in the form of the XOR function (a well-known test for the early era of neural networks research in the 1960s [26]), then the following second-order polynomial effectiveness measure will meet the requirement

$$E_{hj} = S_{h1j} \cdot W_{k1} + S_{h2j} \cdot W_{k2} - 2S_{h1j} \cdot W_{ki} \cdot S_{h2j} \cdot W_{k2}. \tag{8}$$

For more complex problems, higher order polynomials or nonlinear functions may be used.

In the case of AIDS treatment, the ultimate goal for the fuzzy finite state machine models is that, for every treatment objective (i.e., $h = 1, \dots, \Omega$), the regimen with the highest effectiveness measure value is the same as the one selected by the expert or experts. It can be difficult, if not impossible, to manually set the values of all the design parameters correctly if the number is large. Alternatively, a (stochastic) optimization technique should be utilized, such as the genetic algorithm that we used.

It is a well-known fact that conventional DES technology is a general-purpose tool for modeling and control of a broad class of real-world applications. FDES technology generalizes some aspects of the classical DES technology and thus is also a general tool. Since the self-learning capability is inherent in FDES, it is logical to reason that it is applicable to any application that is suitable to FDES. This is to say that the self-learning theory is application-independent and is valuable not only to medicine but also to other fields such as engineering. The AIDS treatment application provides a concrete example.

The outcome of $E_{h,j}$ is determined by the following adjustable design components:

- 1) the fuzzy sets F_{ki} ;
- 2) the membership values in the state transition matrices B_{ij} ;
- 3) the weight vectors W_{ki} for the defuzzification;
- 4) the form of f and the coefficients in it for computing $E_{h,j}$.

The fuzzy sets and the state transition matrices have clear physical meanings. Thus, they should be defined using the knowledge and experience of the domain experts. As for f , one may try the linear function first. If it does not work well, one may then try polynomials or other common nonlinear functions. It is well known that automatic learning of a non-parametric component of any system is challenging. This is the case for many other techniques where the system designer has to empirically select a structure (e.g., neural networks), a kernel (e.g., support vector machines), or a basis function (e.g., wavelets) that are most proper to the problem in hand to be solved. For our particular application, the linear function performs adequately, and the values of its coefficients can be easily determined owing to their clear meanings (equal importance for the four clinical variables leads to the equal value of one). Hence, the component that should first be attempted for automated learning is the weight vectors W_{ki} , which is what we did.

C. Evaluation of System's Learning and Prediction Capabilities

The learning by the system belongs to the category of "supervised learning." As such, the correct regimen selection for every treatment objective (i.e., "training data set") must be made available by experts (e.g., AIDS experts). This is a laborious task that requires rich experience, skills, and knowledge as well as a lot of time and, hence, can be very expensive. This is particularly true if the number of treatment objectives and regimens is large, and multiple experts are involved. In [21]–[23], [47], and [49], our studies involved 32 treatment objectives, four regimens, and two AIDS experts, requiring a

total of 128 regimen selections for each physician. Our two AIDS experts had to spend a substantial amount of time (several hours per expert) to create the 256 treatment choices. We used this set of training data to establish the feasibility of using the system to match the experts' choices by automatically adjusting the 26 weights. That was the objective and focus of the early nonlearning studies.

However, to make the system truly clinically useful we must significantly expand the scope of this paper to meet the challenges imposed by the fast evolution of HIV/AIDS treatments. As stated above, the Department of Health and Human Services HIV/AIDS treatment guidelines are modified several times per year and new regimens become available annually. Hence, just maintaining a well-developed nonlearning system of any kind to keep pace with the medical developments would be very challenging, laborious, and costly. That led us to address the following practical issues.

- 1) Among the $M \cdot \Omega$ treatment choices that each expert has to decide on the preferred selections, is it possible that he/she will only need to give out a fraction of them (for example, only 30%), and the system will then use the information to predict the rest of the doctor's choices?
- 2) If the values of the N clinical variables are updated due to the latest knowledge advance or we are given these values for a new regimen that the system has never seen before or has just become existence, can the system predict the expert's regimen choices?
- 3) Can the system still accomplish the above predictions in the face of weak consensus and significant contradictions among the experts that make the selections?
- 4) Can these predictions be verified not only by the experts' regimen choices for the Ω treatment objectives but also by the real historical prescriptions that physicians, expert or not, actually gave to the patients?

Below, we will provide answers to all these questions. There were two steps in the evaluation. We first evaluated the performance of the models with the weights learned by the genetic algorithm optimizer. We then used the patients in our AIDS patient database to assess retrospectively the self-learning and prediction capabilities of the entire system.

1) "Gold Standard" Regimen Training Data Made by AIDS Experts for Learning: In order to generate the labeled training data to be used by the genetic algorithm to learn the weights, AIDS experts A and B on our team were presented with information on the four clinical variables. For each of the 32 treatment objectives, each expert was asked to rate the appropriateness of each of the four regimens using a ten-point scoring system—ten being the most appropriate with increments of 0.5 based on his clinical experiences (Table II). This scoring was done without knowledge of the response of the other expert. The scores reflected their choices—the regimen with the highest score was the first choice, and the lowest score the last choice (if two scores were equal, we randomly picked up one of the two regimens involved). For each treatment objective, the four scores were converted to four rankings of the regimens (they are the numbers in the parentheses after each score in Table II). They established a "gold standard" for the optimizer to tune the weights so that the regimens selected by the models

TABLE II
 REGIMENS ASSIGNED BY AIDS EXPERTS A AND B FOR THE APPROPRIATENESS SCORES (1–10) (COLUMNS 5 TO 11) OF EACH OF THE FOUR REGIMENS REGARDING THE 32 TREATMENT OBJECTIVES REPRESENTED BY THE 32 COMBINATIONS OF THE FOUR LEFTMOST COLUMNS. THE NUMBERS IN THE PARENTHESES AFTER EACH SCORE REPRESENT THE CORRESPONDING RANKINGS (1–4). ALSO MARKED ARE THE TEN SELECTED TREATMENT OBJECTIVES (SEE THE LAST COLUMN) USED IN LEARNING SETTING 3)

Treatment Objectives				Regimen 1		Regimen 2		Regimen 3		Regimen 4		10 selected objectives for Learning Setting 3
Potency	Adherence	Adverse Events	Future Drug Options	Expert A	Expert B	Expert A	Expert B	Expert A	Expert B	Expert A	Expert B	
High	Easy	Medium	High	5.5 (4)	6.0 (2)	7.0 (1)	4.0 (3)	6.5 (2)	3.5 (4)	6.5 (3)	9.0 (1)	X
High	Easy	Medium	Medium	6.5 (4)	3.0 (4)	9.0 (1)	9.0 (1)	8.5 (2)	8.5 (2)	6.5 (3)	8.0 (3)	
High	Easy	Low	High	5.5 (4)	3.5 (4)	6.5 (1)	5.0 (2)	6.0 (3)	4.5 (3)	6.5 (2)	9.0 (1)	
High	Easy	Low	Medium	6.5 (4)	4.0 (4)	8.5 (1)	8.5 (1)	8.0 (2)	8.0 (2)	6.5 (3)	7.0 (3)	
High	Easy	Very Low	High	5.0 (4)	3.0 (4)	6.5 (1)	7.0 (2)	5.5 (3)	6.0 (3)	6.0 (2)	9.0 (4)	
High	Easy	Very Low	Medium	6.0 (4)	2.0 (4)	8.5 (1)	8.0 (2)	7.5 (2)	7.5 (3)	6.0 (3)	8.5 (1)	X
High	Moderate	Medium	High	6.5 (4)	7.0 (2)	8.0 (1)	6.0 (3)	7.5 (2)	5.0 (4)	6.5 (3)	8.5 (1)	X
High	Moderate	Medium	Medium	6.5 (4)	7.0 (4)	10.0 (1)	9.0 (1)	9.5 (2)	8.5 (2)	7.5 (3)	8.0 (3)	
High	Moderate	Low	High	6.5 (4)	7.0 (2)	7.5 (1)	5.0 (3)	7.0 (2)	4.0 (4)	6.5 (3)	9.0 (1)	
High	Moderate	Low	Medium	7.5 (3)	6.0 (4)	9.5 (1)	8.5 (1)	9.0 (2)	8.0 (2)	6.5 (4)	7.5 (3)	
High	Moderate	Very Low	High	3.0 (4)	3.0 (4)	7.5 (1)	5.0 (2)	6.5 (2)	4.0 (3)	6.0 (3)	9.0 (1)	
High	Moderate	Very Low	Medium	7.0 (3)	3.0 (4)	9.5 (1)	8.0 (2)	8.5 (2)	7.5 (3)	6.0 (4)	8.5 (1)	X
High	Challenging	Medium	High	7.5 (2)	9.0 (1)	8.0 (1)	4.0 (3)	7.5 (3)	3.5 (4)	6.5 (4)	8.5 (2)	X
High	Challenging	Medium	Medium	8.5 (3)	7.0 (3)	10.0 (1)	9.0 (1)	9.5 (2)	8.5 (2)	6.5 (4)	6.5 (4)	
High	Challenging	Low	High	7.5 (2)	7.5 (2)	7.5 (1)	4.0 (3)	7.0 (3)	3.5 (4)	6.5 (4)	9.0 (1)	
High	Challenging	Low	Medium	8.5 (3)	6.5 (4)	9.5 (1)	9.0 (1)	9.0 (2)	8.5 (2)	6.5 (4)	7.0 (3)	
High	Challenging	Very Low	High	7.0 (2)	3.0 (4)	7.5 (1)	5.0 (2)	6.5 (3)	4.0 (3)	6.5 (4)	8.5 (1)	
High	Challenging	Very Low	Medium	8.0 (3)	3.0 (4)	9.5 (1)	8.0 (2)	8.5 (2)	7.5 (3)	6.5 (4)	9.0 (1)	X
Medium	Easy	Medium	High	6.5 (4)	7.0 (2)	7.0 (2)	4.5 (4)	7.0 (3)	5.0 (3)	8.0 (1)	9.5 (1)	X
Medium	Easy	Medium	Medium	7.5 (4)	5.0 (4)	9.0 (1)	8.0 (3)	9.0 (2)	8.5 (2)	8.0 (3)	9.0 (1)	
Medium	Easy	Low	High	6.5 (2)	5.0 (2)	6.5 (4)	4.0 (4)	6.5 (3)	3.0 (3)	8.0 (1)	9.5 (1)	
Medium	Easy	Low	Medium	7.5 (4)	2.0 (4)	8.5 (1)	8.0 (3)	8.5 (2)	8.5 (2)	8.0 (3)	9.5 (1)	
Medium	Easy	Very Low	High	3.0 (4)	3.0 (4)	6.5 (2)	4.5 (3)	6.0 (3)	5.0 (2)	7.5 (1)	9.5 (1)	
Medium	Easy	Very Low	Medium	7.0 (4)	3.0 (4)	8.5 (1)	7.0 (3)	8.0 (2)	7.5 (2)	7.5 (3)	9.5 (1)	X
Medium	Moderate	Medium	High	7.5 (4)	9.0 (2)	8.0 (2)	3.5 (4)	8.0 (3)	4.0 (3)	8.0 (1)	9.5 (1)	
Medium	Moderate	Low	High	7.5 (4)	7.5 (2)	7.5 (2)	3.5 (4)	7.5 (3)	4.0 (3)	8.0 (1)	9.5 (1)	X
Medium	Moderate	Very Low	High	7.0 (4)	3.0 (4)	7.5 (2)	3.5 (3)	7.0 (3)	4.0 (2)	7.5 (1)	9.5 (1)	
Medium	Moderate	Very Low	Medium	8.0 (3)	3.0 (4)	9.5 (1)	8.0 (3)	9.0 (2)	8.0 (2)	7.5 (4)	9.5 (1)	
Medium	Challenging	Medium	High	8.5 (1)	9.0 (2)	8.0 (3)	6.0 (3)	8.0 (4)	5.0 (4)	8.0 (2)	9.5 (1)	
Medium	Challenging	Low	High	8.5 (1)	9.0 (2)	7.5 (3)	4.0 (3)	7.5 (4)	3.5 (4)	8.0 (2)	9.5 (1)	
Medium	Challenging	Very Low	High	8.0 (1)	3.0 (4)	7.5 (3)	3.5 (3)	7.0 (4)	4.0 (2)	7.5 (2)	9.5 (1)	
Medium	Challenging	Very Low	Medium	9.0 (3)	6.0 (4)	9.5 (1)	8.0 (3)	9.0 (2)	8.0 (2)	7.5 (4)	9.5 (1)	X

TABLE III
 UNDER VARIOUS PRESCRIBING CONDITIONS, MEASURES OF EXACT AGREEMENT BETWEEN THE TWO AIDS EXPERTS (THE SECOND ROW) AND MEASURES OF EXACT AGREEMENT BETWEEN EACH OF THE TWO EXPERTS AND THEIR CONSENSUS (THE THIRD AND FOURTH ROWS)

	Prescribing all 4 regimens	Prescribing 3 of the 4 regimens (excluding Regimen 1)	Prescribing 3 of the 4 regimens (excluding Regimen 2)	Prescribing 3 of the 4 regimens (excluding Regimen 3)	Prescribing 3 of the 4 regimens (excluding Regimen 4)	Mean agreement rate
Exact agreement between experts A and B	37.5%	37.5%	43.8%	34.4%	62.5%	43.1%
Exact agreement between expert A and consensus of experts A & B	65.6%	59.4%	71.9%	68.8%	71.9%	67.5%
Exact agreement between expert B and consensus of experts A & B	71.9%	75%	68.8%	65.6%	87.5%	73.8%

would match as closely as possible to those chosen by the experts individually.

It is well appreciated that expert clinicians often disagree. For this paper, the consensus scores and the corresponding rankings were calculated as follows (“Consensus Calculator” in Fig. 1). Each score of expert A was divided by the standard deviation of all his scores. The same was done to the scores of expert B. We then computed the average score of the two experts for every treatment objective and every regimen. Each average score was subsequently divided by the standard deviation of all the 128 average scores. The resulting score was then subtracted from the mean of all the 128 final average scores, and the result was added five to shift the distribution in order to avoid negative numbers. The results represent the consensus scores of the two experts. Finally, the scores were converted to rankings (they are not shown here due to the space limit but can be calculated based on Table II). One advantage of scoring first and then converting scores to rankings was that it provided a continual, and thus more accurate, measure of agreement (or disagreement) between the experts, possibly forming a better consensus for the models. By consensus, we mean a measure that describes an overall agreement between the physicians, rather than the more strict exact agreement. Consider two scenarios for a treatment objective: 1) expert A chooses Regimen X as the first-choice regimen while expert B selects the same regimen as the second-choice regimen and 2) expert A prefers Regimen X as the first-choice regimen while expert B picks this regimen as the fourth-choice. The consensus in the first scenario is obviously much higher than that in the second scenario. Note that the exact agreement in both cases is 0%.

According to Table III derived from Table II, the exact agreements between experts A and B on treatment regimen choices under various settings were marginal, ranging from 34.4% to 62.5% with the mean being only 43.1%. Moreover, their consensus differed quite markedly from either of them with the mean overall agreements being 67.5% and 73.8%, respectively.

The consensus rankings as well as the rankings of the individual experts given in Table II established a “gold standard” for the optimizer to tune the weights so that the regimens selected by the models would match as closely as possible to the

first-choice regimens chosen by the experts individually or to the first-choices of the consensus regimens. To make the system practically useful, such data have to be used for the learning no matter how much the experts differ in their treatment-regimen selections.

2) *Settings for Evaluating System’s Learning/Prediction Capabilities*: The following settings were employed that reflected a variety of practical needs and addressed the four issues raised at the beginning of Section II-C.

Learning Setting 1) For each set of three drawn from the original four regimens (for a total of four such sets), we provided the resulting models with the four clinical variables of the absent regimen and either the 32 consensus choices of experts A and B or the choices of the individual experts for all the 32 objectives.

Learning Setting 2) For each set of two drawn from the original four regimens (for a total of six such sets), we provided the resulting models with the four clinical variables of the two absent regimens and either the 32 consensus choices of experts A and B or the choices of the individual experts for all the 32 objectives.

Learning Setting 3) For each set of two drawn from the original Regimens 2, 3, and 4 (for a total of three such sets; Regimen 1 was excluded due to lack of patients needed for Learning Setting 4), we provided the resulting models with the four clinical variables of the absent regimen and ten consensus choices of experts A and B for the ten of the 32 treatment objectives.

Learning Setting 4) Retrospectively evaluated the performance of the system using patients in our AIDS patient database after the system had learned under Learning Setting 3).

TABLE IV
PREDICTION RESULTS ACHIEVED AFTER THE SYSTEM LEARNED UNDER CONDITION OF LEARNING SETTING 1). EACH NUMBER REPRESENTS THE AVERAGE OF FOUR RESULTS OBTAINED USING FOUR DIFFERENT RANDOM INITIAL CONDITIONS FOR THE LEARNING

	Predicting Regimen 1 using Regimens 2, 3 & 4	Predicting Regimen 2 using Regimens 1, 3 & 4	Predicting Regimen 3 using Regimens 1, 2 & 4	Predicting Regimen 4 using Regimens 1, 2 & 3	Mean prediction accuracy
Accuracy of System-predicted choices vs. expert A's choices	96.9%	93.8%	100%	100%	97.7%
Accuracy of System-predicted choices vs. expert B's choices	100%	100%	100%	100%	100%
Accuracy of System-predicted choices vs. consensus of experts A & B	93.8%	85.4%	96.9%	100%	94%

TABLE V
PREDICTION RESULTS ACHIEVED AFTER THE SYSTEM LEARNED UNDER CONDITION OF LEARNING SETTING 2). EACH NUMBER REPRESENTS THE AVERAGE OF OUR RESULTS OBTAINED USING FOUR DIFFERENT RANDOM INITIAL CONDITIONS FOR THE LEARNING

	Predicting Regimens 1 using Regimens 2 & 3	Predicting Regimens 1 using Regimens 2 & 4	Predicting Regimens 1 using Regimens 3 & 4	Predicting Regimens 2 using Regimens 1 & 3	Predicting Regimens 2 using Regimens 1 & 4	Predicting Regimens 2 using Regimens 3 & 4	Predicting Regimens 3 using Regimens 1 & 2	Predicting Regimens 3 using Regimens 1 & 4	Predicting Regimens 3 using Regimens 2 & 4	Predicting Regimens 4 using Regimens 1 & 2	Predicting Regimens 4 using Regimens 1 & 3	Predicting Regimens 4 using Regimens 2 & 3	Mean prediction accuracy
Accuracy of System-predicted choices vs. expert A's choices	100%	100%	100%	100%	100%	97.8%	100%	100%	100%	100%	100%	100%	99.8%
Accuracy of System-predicted choices vs. expert B's choices	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Accuracy of System-predicted choices vs. consensus of experts A & B	90.6%	100%	100%	90.6%	96.9%	96.9%	90.6%	100%	96.9%	96.9%	100%	90.6%	96.9%

The selection of the ten treatment objectives out of the 32 was not random. The selected objectives were considered to be representative (see Table II). They involved “high” and “medium” potency six and four times, respectively; “easy,” “moderate,” and “challenging” adherence 4, 3, and 3 times, respectively; “medium,” “low,” and “very low” adverse events 4, 1, and 5 times, respectively; and “high” and “medium” future drug options five times each. Hence, the distribution of these fuzzy set terms is somewhat uniform.

The learning conditions became progressively more challenging from Learning Settings 1)–3), as the number of training regimens involved decreased, and the training information on the physician’s preferred choices is less accessible to AIDS-FDES. For these three settings, the treatment objective classifier was irrelevant as the learning involved with the other two system components only. For every regimen set in these settings, different initial conditions were generated randomly for the genetic algorithm. The weights subsequently learned were utilized to evaluate the prediction abilities of the system for the learning setting.

Learning Setting 4) involved our institution’s clinical HIV/AIDS database developed since early 1994. It contained information on more than 4500 patients, of whom approximately 1600 were active (i.e., they were currently being treated at our AIDS Clinic). Of the patients, 85% were African-American; 30% were women. Mostly of the patients were from the City of Detroit whose population in 2000 was, as found by the U.S. census conducted in that year, about 951 000 (81.6%

Black or African-Americans, 12.3% White, 5% Hispanic or Latino, and 1.1% others). The percentage of families below the federal poverty level was 21.7%. As for education, the census showed 69.6% high school graduate or higher and 11% having the Bachelor’s degree or higher. In 2001, there were 98 treatment-naïve patients who started antiretroviral therapy at our AIDS Center, and we selected this patient population for the evaluation [the system used weights learned under learning setting 3)]. Of these patients, 35 of them used one of the three regimens in Table I (Regimens 2 to 4), and it is this group of patients that was used in this paper. Thirteen experienced AIDS faculty physicians prescribed medicine for these patients, with experts A and B treating four and eight patients, respectively. The remaining 11 AIDS physicians, who were not experts, treated 23 patients with the mean and standard deviation of patients per physician being 2 and 1.97, respectively. We are aware that from a statistical point of view, larger patient sample sizes are desired. However, due to the rapid evolution of regimens, it is very difficult to achieve such sample sizes for retrospective comparisons using actually prescribed regimens. The fact that, among the four regimens that were popular in 2001, only the first regimen still remains a frequently used option today illustrates this point.

III. SYSTEM EVALUATION RESULTS

Tables IV–VII show the learning and prediction outcomes for the four learning settings. The prediction results involving

TABLE VI
PREDICTION RESULTS ACHIEVED AFTER THE SYSTEM LEARNED UNDER CONDITION OF LEARNING SETTING 3). EACH NUMBER REPRESENTS THE AVERAGE OF FOUR RESULTS OBTAINED USING FOUR DIFFERENT RANDOM INITIAL CONDITIONS FOR THE LEARNING

	Predicting Regimen 2 using Regimens 3 & 4	Predicting Regimen 3 using Regimens 2 & 4	Predicting Regimen 4 using Regimens 2 & 3	Mean prediction accuracy
Accuracy of System-predicted choices vs. consensus choices of experts A & B	89.8%	85.9%	84.4%	86.7%

TABLE VII
RETROSPECTIVE EVALUATION RESULTS UNDER CONDITION OF LEARNING SETTING 4) THAT INVOLVES 35 PATIENTS TREATED AT FOUR AIDS CLINIC IN 2001

	After Regimen 2 was learned using Regimens 3 & 4	After Regimen 3 was learned using Regimens 2 & 4	After Regimen 4 was learned using Regimens 2 & 3	Mean agreement rate
Agreement between choices made by the System and regimens prescribed by 2 experts and 11 non-experts	80% (28/35)	82.9% (29/35)	85.7% (30/35)	82.9%
Agreement between choices made by the System and regimens prescribed by expert A	100% (4/4)	100% (4/4)	100% (4/4)	100%
Agreement between choices made by the System and regimens prescribed by expert B	100% (8/8)	100% (8/8)	100% (8/8)	100%

the two experts individually were achieved using two different sets of weight vectors learned using the optimizer so that the models were allowed to optimize their decisions to match experts A and B individually. In contrast, only one set of weight vectors was used whenever the prediction was to best match the consensus of the two experts. Each result in Tables IV–VI is the average of four results obtained using four different random initial conditions for the learning. The prediction accuracy in these tables is defined as the number of choices correctly predicted by the system as compared to the experts’ choices divided by the total number of predictions made by the system.

The prediction results in these tables are self-explanatory and the table captions describe what they are. Overall, the results are excellent cross the learning settings. It is worth pointing out that, even though the exact agreements between the two experts were rather weak and the mean agreement rate was only 43.1% (Table III), the learning and prediction using such information still went successfully as compared to the consensus choices of the two experts (i.e., the last row in Tables IV and V and entire Table VI) with the mean prediction accuracy being from 86.7% to 96.9%. The mean prediction accuracy in Table VI was slightly lower (86.7%) because only ten of the 32 treatment objectives were involved in the learning. In contrast, the higher mean prediction accuracies in Table IV (94%) and Table V (94.8% and 96.9%) were obtained when all the 32 treatment objectives participated in the learning.

The retrospective evaluation of the clinical cases produced promising results as the mean agreement rate was 82.9% for the 13 physicians while the exact agreement with experts A and B was both at 100%. The exact agreement for the remaining 11 nonexperts not involved in the system training ranged from

69.6% (16/23) to 73.9% (17/23) to 78.3% (18/23), impressive results given the fact that physician opinion can be quite divergent for treatment decisions of such complexity. Our experts also carefully examined the seven mismatched cases between the system and the nonexpert physicians in these three circumstances. They deemed that the system actually chose a more appropriate regimen for four of them. In the two of the three remaining cases, either party’s choice would be reasonable. Only in one case, what the system chose was inappropriate.

IV. CONCLUSION

We established a novel learning FDES framework, based on which the AIDS-FDES system was developed for the initial round of combination antiretroviral therapy for HIV/AIDS. In addition to the self-learning capability, other particularly promising aspects of the FDES approach, as compared with the existing technologies (e.g., expert systems and neural networks), include effective and flexible representations of expert’s imprecise and uncertain knowledge and expectations, dynamic treatment optimization, and easy adaptation to new therapy strategy. Furthermore, this approach is capable of representing knowledge and learning even in the face of weak consensus collected from a group of physicians holding diverse or contradictory opinions. While these attributes are desirable for any area of therapeutic decision-making, they are particularly desirable for HIV/AIDS treatments because they are the most complex and are rapidly evolving. We have studied learning and prediction performances under various clinically realistic settings involving four historically popular treatment regimens, including those retrospectively confirmed by the patient cases in our AIDS patient database. The results show that the system performed as well as the expert physicians did but outperformed the nonexpert AIDS physicians.

This learning FDES framework is general purpose that can be utilized to solve a wide range of practical problems in medicine, engineering, and other domains.

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