

# A Fuzzy Discrete Event System Approach to Determining Optimal HIV/AIDS Treatment Regimens

Hao Ying, *Senior Member, IEEE*, Feng Lin, *Member, IEEE*, Rodger D. MacArthur, Jonathan A. Cohn, Daniel C. Barth-Jones, Hong Ye, and Lawrence R. Crane

**Abstract**—Treatment decision-making is complex and involves many factors. A systematic decision-making and optimization technology capable of handling variations and uncertainties of patient characteristics and physician's subjectivity is currently unavailable. We recently developed a novel general-purpose fuzzy discrete event systems theory for optimal decision-making. We now apply it to develop an innovative system for medical treatment, specifically for the first round of highly active antiretroviral therapy of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients involving three historically widely used regimens. The objective is to develop such a system whose regimen choice for any given patient will exactly match expert AIDS physician's selection to produce the (anticipated) optimal treatment outcome. Our regimen selection system consists of a treatment objectives classifier, fuzzy finite state machine models for treatment regimens, and a genetic-algorithm-based optimizer. The optimizer enables the system to either emulate an individual doctor's decision-making or generate a regimen that simultaneously satisfies diverse treatment preferences of multiple physicians to the maximum extent. We used the optimizer to automatically learn the values of 26 parameters of the models. The learning was based on the consensus of AIDS specialists A and B on this project, whose exact agreement was only 35%. The performance of the resulting models was first assessed. We then carried out a retrospective study of the entire system using all the qualifying patients treated in our institution's AIDS Clinical Center in 2001. A total of 35 patients were treated by 13 specialists using the regimens (four and eight patients were treated by specialists A and B, respectively). We compared the actually prescribed regimens with those selected by the system using the same available information. The overall exact agreement was 82.9% (29 out of 35), with the exact agreement with specialists A and B both at 100%. The exact agreement for the remaining 11 physicians not involved in the system training was 73.9% (17 out of 23), an impressive result given the fact that expert opinion can be quite divergent for treatment decisions of such complexity. Our specialists also carefully examined the six mismatched cases and deemed that the system actually chose a more appropriate regimen for four of them. In the other two cases, either would be reasonable choices. Our approach has the capabilities of generalizing, learning, and representing knowledge even in the face of weak consensus, and being readily upgrade-

able to new medical knowledge. These are practically important features to medical applications in general, and HIV/AIDS treatment in particular, as national HIV/AIDS treatment guidelines are modified several times per year.

**Index Terms**—Decision-making, discrete event systems, fuzzy logic, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) treatment.

## I. INTRODUCTION

TREATMENT decision-making for most diseases including human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is complex [1]. This is the case because every patient is unique, with his/her own history, set of genetic traits, predisposition to side effects, and prognosis. Additionally, many symptoms and diagnoses are inherently imprecise in their definition, and difficult to measure. Although clinical trials data provide excellent information regarding expected treatment outcomes for large groups of patients, the prediction of actual treatment outcomes and clinical courses for a particular individual patient may be subject to a considerable degree of uncertainty. With all these uncertainties inherent to the clinical decision process, a clinician's subjective judgment plays a vital role in making sound treatment decisions for individual patients. Various patient-specific factors make it difficult to objectively and quantitatively compare various treatment decisions made by different physicians for particular patients. Consequently, inconsistent and suboptimal treatment outcomes can occur even for quite similar patients. At present, a systematic decision-making and optimization technology capable of handling all these difficulties, although much desired clinically, is still not available.

### A. Major Technical Issues for Existing Methods

Statistical decision-making methods, such as the Bayesian Decision Theory [2], [3], are appropriate for groups of patients, but are complicated in application to individual patients when there are differences between the covariates that were used in developing multivariate models and the patient-specific factors that a physician wishes to consider in decision-making for a particular patient. Expert systems and other artificial intelligence (AI) approaches can contribute importantly to the selection of appropriate treatment options by applying the expert knowledge of treatment specialists to the complex task of selecting appropriate treatments for individual patients. Significant research

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H. Ying and F. Lin are with the Department of Electrical and Computer Engineering, Wayne State University, Detroit, MI 48202 USA (e-mail: hao.ying@wayne.edu; flin@ece.eng.wayne.edu).

R. D. MacArthur, J. A. Cohn, D. C. Barth-Jones, H. Ye, and L. R. Crane are with the Department of Medicine, Wayne State University, Detroit, MI 48202 USA (e-mail: rmacarthur@med.wayne.edu; jcohn@med.wayne.edu; dbjones@med.wayne.edu; hye@med.wayne.edu; lcrane@med.wayne.edu).

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efforts have been made in the past three decades for various clinical needs with varying degree of success (e.g., [4]), including those involving HIV/AIDS [5]–[9], [10], [40], [41]. The technical approaches include expert systems [3], [5], [10], [40], [41], statistical methods [2], [11], neural networks [12], [13], and artificial intelligence [11], [14], to name just a few. Other decision-making approaches include statistical pattern matching, decision trees, rule-based systems, and model-based schemes.

In the expert systems and other artificial intelligence approaches, uncertainty is usually represented by probability theory although other methods, such as the Dempster–Shafer theory [15] and the theory of endorsement [16], are also used. The traditional methods are effective in dealing with random/statistical information and uncertainty. Some of them are also capable of handling partial memberships. For systematic handling of deterministic uncertainty and subjective information, however, the more recently developed fuzzy set theory [17] is often a more effective methodology. Fuzzy set theory has been successfully used alone or combined with neural networks and expert systems to solve challenging biomedical problems in practice [18]–[21], some of which are difficult to solve without it. Regardless of application domains and technical fields, it has been widely documented and recognized in the literature that fuzzy logic provides an effective means for complex knowledge acquisition, interpretation, and representation.

The most important advantage of the neural network approach is its automatic learning capability. It is “model-free” and can learn from the existing data and extrapolates the result to make a prediction. However, it is also a “black-box” method in that the knowledge learned is encoded as neurons and weights of the connections between them, which is unintuitive and very difficult for humans to understand and interpret. Additionally, updating changing medical knowledge/parameters necessitates the periodic retraining of the network.

In comparison, the expert system approach is more intuitive in terms of knowledge representation. The reasoning chain of expert systems and the subsequent decisions are readily available and understandable. While the expert system paradigm is a powerful one, it has some deficiencies when applied to clinical medicine.

An expert system requires detailed knowledge, the acquisition of which can be time-consuming and challenging. Moreover, the knowledge acquired is physician-dependent. Consequently, the expert system developed may only emulate the expertise of the particular physician and may not be generalizable to cover another physician’s expertise.

Developing an expert system capable of emulating consensus of a group of physicians is difficult if the consensus knowledge is not explicitly available. This is challenging even when the knowledge of the individual doctors involved is available. Extracting consensus knowledge from diverse, sometimes even opposing, opinions of individual specialists and representing it in a form usable by an expert system (e.g., if–then rules) is not trivial whether this task is performed manually or by a computer program.

An expert system can be inflexible with poor self-learning ability and scalability. Inclusion of new knowledge or updating

of existing knowledge usually means manual redesign of at least a part of the system, sometimes even the whole system. This can cause serious application constraints. For instance, HIV/AIDS treatment strategy evolves quickly as our understanding of the disease and its treatment deepens. Presently, the U.S. Public Health Service HIV/AIDS treatment guidelines are being updated several times per year.

### B. Rationale for Our Approach

In searching for a more powerful decision-making technology that is not subject to these weaknesses, we have recently established a theoretical framework for a comprehensive theory of fuzzy discrete-event systems (fuzzy DES) by combining the merits of fuzzy systems technology with the advantages of the DES technology [22], [23]. To model fuzzy DES, we have generalized the conventional (crisp) finite automaton model to a fuzzy finite automaton model. This model is most convenient and simple for many applications, including medical applications.

The conventional DES are used to model systems that cannot be described by differential or difference equations, but must be described by sequences (traces) of events that record significant qualitative changes in the state of the system [24], [25]. Although conventional DES have been applied in many engineering fields, they are not adequate for some other fields. This is especially true when we consider biomedical applications in which the state and state transition of a system (e.g., a person’s health status) are always somewhat uncertain and vague even in a deterministic sense. Subjective human observation, judgment, and interpretation (e.g., by a physician or a patient) invariably play a significant role in describing the status of state, which is usually not crisp. For instance, saying the state of a patient is “fair” is vague and subjective. Similarly, the transition from one state to another is also vague. It is hard to say how exactly a patient’s condition has changed from “good” to “bad.” A suitable representation of the inherent subjectivity and uncertainty in appropriate fields like medicine, therefore, provided the rationale for our development of the fuzzy DES theory.

### C. Objectives of This Study

In the present paper, we use the fuzzy DES theory to develop a general-purpose decision-making and optimization technology that can produce optimized treatment decisions for any given patient based on subjective and uncertain information concerning the patient, treatment options available, and desired treatment outcomes. It addresses the above-mentioned three major issues of expert systems. (The self-learning aspect of our approach has been developed with the results being reported separately in [26]). We have applied this technology to create a regimen selection system that prescribes optimal antiretroviral therapy for HIV/AIDS patients who have never received such a treatment before (such patients are termed “treatment-naïve”). By optimal, we mean that the system can select the same treatment regimen as the expert AIDS physician does to produce the (expected) best treatment effect to the given patient. Some preliminary results obtained earlier were reported in [27]–[29].

The application of this technology to this problem is timely, as the United Nations estimates that until 2004, 38 million people worldwide are infected with HIV, and that more than 22 million have died [30]. Antiretroviral medications are becoming increasingly available in developing countries through financial support of donor nations and agencies; however, the lack of health care professionals with training and experience in their use is limiting access to treatment in the most severely impacted countries. 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, especially in the poor nations. Worse, HIV/AIDS treatment is one of the most complex treatments among all diseases because of the potential for the development of drug resistance mutations that can render potential treatment options ineffectual after such mutations occur [38]. A computer software that can utilize clinical information to recommend therapies that will be sufficiently potent, well tolerated, and taken on schedule by patients would be a great advance. Such a tool will be very useful not only to physicians in the United States but especially to resource-poor nations [30].

## II. FUZZY DISCRETE EVENT SYSTEM APPROACH TO HIV/AIDS TREATMENT

### A. Some Clinical Variables Important to HIV/AIDS Treatment and System Development

We focus on the highly active antiretroviral therapy (HAART) since it is the only effective long-term treatment strategy to date and has resulted in significant declines in mortality and morbidity in patients with HIV infection and AIDS [39]. The essential components of effective antiretroviral therapy include: 1) selecting a regimen that is sufficiently potent to suppress replication of a patient's HIV and 2) minimizing or managing drug toxicity so that the patient continues to use medications at their full doses. The 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 [31]. Balancing all these factors is complex and inexact; therefore, published treatment guidelines recommend that expert opinion be sought regarding initiation of therapy and selection of antiretroviral regimens, and for decisions to change regimens [32], [33]. The clinical objective for a treatment-naïve patient is to indefinitely suppress HIV replication to the lowest achievable level.

This paper considers patients treated in 2001. The drugs used as part of this paper are Efavirenz (EFV), Nevirapine (NVP), Abacavir (ABC), and Combivir (CBV, the brand name of the combination of two nucleoside analogues zidovudine and lamivudine). Each combination of drugs is called a treatment regimen and we have chosen to concentrate on three of the most commonly used regimens in 2001 (Table I).

A doctor must consider many factors when selecting a regimen for a patient. The primary four clinical parameters are: 1) anticipated potency of the regimen; 2) anticipated adherence for the patient under the regimen; 3) prognosis for adverse

TABLE I  
ESTIMATED CLINICAL CHARACTERISTICS INTRINSIC TO THREE HISTORICALLY WIDELY USED HIV/AIDS TREATMENT REGIMENS

	Potency	Adherence	Adverse Events	Future Drug Options
Regimen 1: EFV + CBV	90%	80%	20%	60%
Regimen 2: NVP + CBV	85%	85%	20%	60%
Regimen 3: ABC + CBV	80%	90%	10%	85%

events under the regimen; and 4) expected future drug options due to the potential for development of resistance to the regimen.

Potency measures how powerful a regimen is in suppressing the HIV replication. It is determined through clinical trials. In this paper, we use the percentage of patients who achieve plasma HIV RNA less than 400 copies/mL after 48 weeks of treatment as our measure of potency.

Adherence is a very important factor in antiretroviral therapy. Without adequate adherence, antiretroviral drugs will not be maintained at sufficient concentrations to suppress HIV replication and lower the plasma viral load. In addition to being associated with poor short-term virological response, insufficient adherence accelerates development of drug-resistant HIV. In order to achieve desirable treatment results, adherence to at least 95% of the prescribed treatment doses is necessary. Before prescribing a regimen, the clinician must consider the likelihood that the patient will adhere to the dosage schedule (total number of pills taken per day and dosing frequency). Adherence is a very complicated issue involving many factors impacting the patient's ability to comply with the prescribed regimen. We define adherence as the expected percentage of prescribed doses taken weekly for each regimen.

Adverse events in this paper are defined as undesirable side effects (grades 1 and 2) and toxicities (grades 3 and 4). 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. It should be underscored that many patients are likely to have complaints (usually minor) if precisely questioned and that adverse events can have a negative effect on adherence, potentially leading to treatment discontinuation or failure.

The last important parameter is the future drug options that are available after the current treatment is no longer viable. Even if an initially effective regimen is selected, over a period of time, there is a likelihood that the virus will eventually develop resistance to a drug (or drugs), leading to failure of the current regimen. Virologic failure is commonly associated with emergence of drug-specific resistance mutations. Genotypic resistance testing is currently widely used to measure mutations on the reverse transcriptase and/or protease genes that impart partial or complete resistance to the HIV. In this paper, future drug options is defined as the percentage of drugs remaining that have efficacy in the presence of detected or expected mutations already selected.

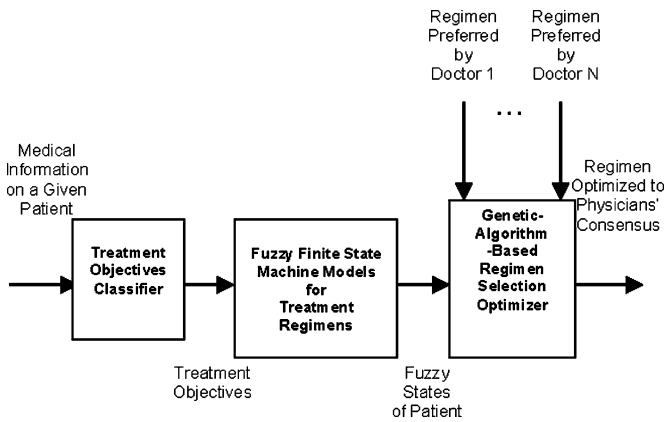


Fig. 1. Block diagram of the regimen selection system.

Table I summarizes the estimated intrinsic characteristics of each regimen used in this project for each of these four important parameters. The data supporting this assessment was compiled following a thorough review of the relevant medical literature (e.g., outcomes of various clinical trials) and a lengthy interview process of acquisition of the expert knowledge of the HIV/AIDS specialists on our project team [42]–[47]. Accordingly, each percentage in the table is a subjective summarization of the clinical possibility for the parameter.

Fig. 1 shows the configuration of our regimen selection system. There are three major components: 1) a treatment objective classifier; 2) fuzzy finite state machine models for treatment regimens; and 3) a genetic-algorithm-based regimen selection optimizer. We now describe each of the components.

### B. Design of Treatment Objective Classifier

A treatment objective is a combination of potency (medium or high), adherence (challenging, moderate, or easy), adverse events (very low, low, or medium), and future drug options (medium or high) that a doctor must consider when choosing a regimen. It is independent of treatment regimens. There are a total of 36 (i.e.,  $2 \times 3 \times 3 \times 2$ ) possible different combinations. 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.

The function of the classifier is to assign a typical individual patient (e.g., exclusion of pregnant patients) to one of the combinations using his/her clinical information. The simple classification rules were developed by our clinical AIDS experts. Specifically, each of the two experts first created a set of rules independently using his clinical knowledge and experience. It turned out that there were differences between the two groups of rules. Consequently, meetings were held to address the differences. They were resolved after careful examination and thorough debates, which led to the consensus rules used in the system development.

The patient’s CD4 cell counts and HIV RNA level are used to determine the treatment potency needed [34]. There are three simple rules:

If  $CD4 < 50$  or If  $CD4$  is 50–200 and  $HIV\ RNA > 100000$  then high potency is desired,

If  $CD4$  is 50–200 and  $HIV\ RNA < 100000$  or If  $CD4 > 200$  and  $HIV\ RNA \geq 100000$  then high or medium potency is desired,

If  $CD4 > 200$  and  $HIV\ RNA < 100000$  then medium potency is desired.

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.

Adherence requirement is based on five factors: 1) whether the patient’s age is younger than 24 (associated with a higher risk for nonadherence); 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 visits more than once in the last 12 months. If none of the factors is present, no adherence restriction will be placed to regimen selection. If one factor is present, the patient should be limited to the regimens with easy or moderate adherence. If more than one factor is identified, the patient should only take the easy adherence regimens.

Tolerance to adverse events partially depends on whether the patient has diabetes or hepatitis and is the patient’s individual risk for atherosclerotic coronary artery disease (because antiretroviral therapy may increase this risk). If the patient has either disease, he/she should be prescribed a regimen with very low or low adverse event potential. The cardiovascular risk is evaluated using a standard clinical quantification scheme covering such risk factors as patient’s age, gender, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, etc. The resulting points are translated to adverse event risk levels. The patient will be given a regimen with the smallest potential for adverse events among those attributed to diabetes, hepatitis, and the cardiovascular risk.

The determination of the relative importance of preserving future drug options involves balancing the consideration of current degree of HIV viral replication (HIV RNA levels) and extent of immunosuppression (CD4 counts) against the need to preserve future drug options. If the patient’s CD4 count is above 350 or if his/her CD4 counts are between 200 and 350, but the HIV RNA level is less than 100 000, then the patient’s immediate situation is not dire and the regimens with high future drug options should be selected. However, if the patient’s CD4 count falls below 200, or below 350 with a HIV RNA level greater than 100 000 or the HIV RNA level exceeds 100 000 regardless of the CD4 count, the patient’s condition is sufficiently serious to warrant the use of regimens with reduced (i.e., medium) future drug options.

### C. Fuzzy Finite State Machine Models for Treatment Regimens

1) *Theoretical Framework*: Before describing the models block in Fig. 1, we first provide a brief introduction to its

theoretical foundation, which is the fuzzy DES theory. This is to make this paper self-contained and more readable. For additional information, the reader is referred to our papers [22] and [23].

A fuzzy DES can be modeled by a fuzzy automaton, designated as  $G$ ,

$$G = (Q, \Sigma, \delta, q_o).$$

Here,  $Q = [0, 1]^n$  is the fuzzy state space with  $n$  being the number of states, and  $q_o \in Q$  is the initial state vector. A state vector  $q \in Q$  is a vector  $q = [v_1, v_2, \dots, v_n]$ , where  $v_i \in [0, 1]$  is the possibility (i.e., membership) that the system is in state  $i$ .  $\Sigma = \{\sigma^1, \sigma^2, \dots, \sigma^m\}$  is the set of events. Each event  $\sigma^k$  is represented by a state transition matrix  $\sigma^k = [\sigma_{ij}^k]_{n \times n}$ , where  $\sigma_{ij}^k$  is a number in  $[0, 1]$  representing the likelihood of the system moving from state  $i$  to state  $j$  when the event occurs.  $\delta$  describes the state (vector) transition: if the current state vector is  $q$  and event  $\sigma^k$  occurs, then the updated state vector  $q'$  is computed by  $q' = q \circ \sigma^k$ , where the symbol  $\circ$  represents some fuzzy operation specified by  $\delta$ . We have utilized the following max-product operation commonly used in fuzzy reasoning as a specific implementation of the fuzzy operation [22], [23]:

$$q' = q \circ \sigma^k = \max(q \times \sigma^k). \quad (1)$$

In general, a fuzzy DES to be controlled consists of  $N$  components, modeled by  $N$  fuzzy automata

$$G_1 \quad G_2 \quad \dots \quad G_N.$$

Their state vectors are denoted by  $q_1 \quad q_2 \quad \dots \quad q_N$  respectively. Their corresponding event sets are  $\Sigma_1 \quad \Sigma_2 \quad \dots \quad \Sigma_N$ , respectively, which may or may not be disjoint.  $\Sigma = \Sigma_1 \cup \Sigma_2 \cup \dots \cup \Sigma_N$  is the set of all the events in the system. We assume that some of these events can be disabled and/or enforced. The events that can be disabled are called controllable events whereas the events that can be enforced are called enforceable events. Control of a (fuzzy) DES is achieved by disabling some controllable events and/or enforcing some enforceable events. Note that the control mechanisms are crisp in that if an event is disabled, then its occurrence can be prevented with full certainty. Similarly, if an event is enforced, then it will definitely occur. The objective of optimal control is to minimize cost and/or maximize effectiveness for the (fuzzy) DES.

There are two different approaches to optimal control: online approach and offline approach. In a conventional DES, designing an optimal control online follows the steps shown later [35]: After each occurrence of events, the controller will evaluate the possible future execution of the DES and determine which events to be disabled and which ones to be enforced. Therefore, one can construct a forward-looking tree as shown in Fig. 2. For a crisp DES,  $q_o$ ,  $q$ , and  $q'$  in the figure should be understood as crisp states.

For a fuzzy DES, however, the way to construct this tree must be different from that for the crisp DES. This is because each node in the tree no longer represents a crisp state, but rather a fuzzy state. Conceptually, now  $q$  in Fig. 2 should be understood as a fuzzy state represented by a vector containing the state vectors:  $[q_1, q_2, \dots, q_N]$ . Note that the nature of an event should always be crisp regardless of DES or fuzzy DES. If the event  $\sigma$  in

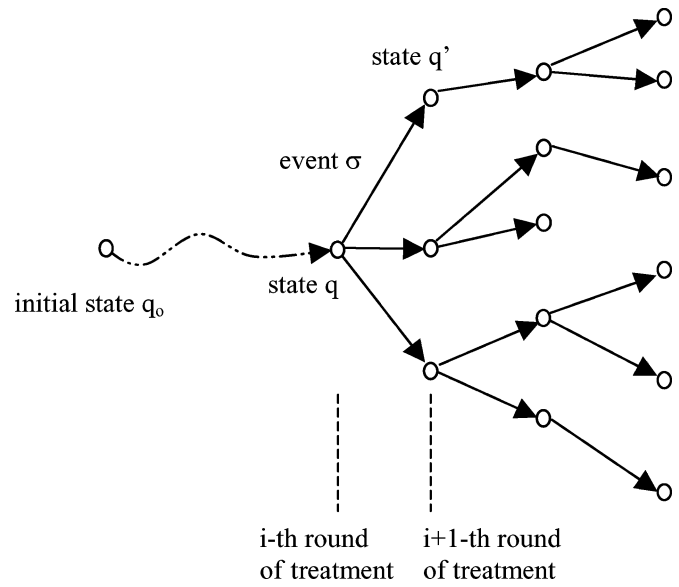


Fig. 2. Example forward-looking tree for online control synthesis. For a conventional DES,  $q$  and  $q'$  are crisp states. For a fuzzy DES,  $q$  and  $q'$  should be regarded as fuzzy states, each of which is represented by a vector containing the fuzzy state vectors.

Fig. 2 takes place, the vector of the state vectors will be changed to a new vector of the state vectors:  $q' = [q'_1, q'_2, \dots, q'_N]$ , where  $q'_i$  is calculated as follows. If  $\sigma$  is an event in  $G_i$ , then  $q'_i = q_i \circ \sigma$ . If  $\sigma$  is not an event in  $G_i$ , then  $q'_i = q_i$ .

Generally speaking, a node of a fuzzy DES can be denoted by  $h$  represented by the corresponding vector of fuzzy state vector  $q$  and a string  $s$  describing the sequence of events leading to the node from the initial state  $q_o$ , or by notation  $h = (q, s)$ . The root of the tree changes with events. It represents the current state of the system and the sequence of events executed so far. The main difference between a crisp DES tree and the corresponding fuzzy DES tree is that there are more branches in the fuzzy DES tree. This is the case because the system can now be partially in more than one state at the same time. Therefore, more events are possible at each node in the fuzzy DES tree. The size of the tree (i.e., the number of branches and their depths relative to the root) depends on the number of forward-looking steps desired for the optimization. Looking ahead further, of course, requires greater depth. This may produce better optimization results, but at the expense of more computing time and computer storage memory. For more efficient searches, a variable look-ahead policy may be used by specifying some intelligent terminating conditions.

After constructing the forward-looking tree for a fuzzy DES, one can calculate the effectiveness and cost measures for each node. For node  $h = (q, s)$ , the effectiveness measure and cost measures are, respectively,

$$E(h) = f(q, s) = f(q_1, q_2, \dots, q_N, s)$$

$$C(h) = g(q, s) = g(q_1, q_2, \dots, q_N, s)$$

where  $f$  and  $g$  are functions. We define the effectiveness and cost of a branch in the tree to be the effectiveness and cost of its terminal node. Mathematically, if branch  $\tau$  leads to the terminal node  $h$ , then  $E(\tau) = E(h)$  and  $C(\tau) = C(h)$ .

The optimization problem that we are interested in this paper is to maximize the anticipated HIV/AIDS treatment effectiveness for a given cost (i.e., the expense of the drugs used in the treatment). Simply speaking, if the system is in the state characterized by node  $h$  of the tree, then the optimization problem can be formulated as

$$\max_{T(h)} E(h), \text{ such that } C(h) < L$$

where  $T(h)$  denotes the forward-looking tree starting from  $h$ ,  $L$  is a (given) constant restricting the maximum cost, and  $C(h) < L$  means the cost must be less than  $L$  all the time during the optimization process. We should point out that we can only optimize the anticipated (or expected) treatment effectiveness because we do not know in reality which treatment will really be the most effective for any given patient. Thus, we can only maximize the subjective assessment of what our AIDS experts believe the most effective treatment will be under a given set of circumstances.

Obviously, the level of the optimization depends on the depth of  $T(h)$ . The simplest optimization is with respect to the nodes in the next level of the tree beyond  $h$ . For the HIV/AIDS treatment planning, this corresponds to the optimization with respect to one round of treatment (a treatment is considered to stay in the same round until a drug is changed). A more complex optimization is with respect to the nodes that are several levels beyond the current node, representing optimization with respect to several rounds of treatments. The procedures to solve the optimization problem for different branch depths are actually the same, as discussed later.

In the forward-looking tree  $T(h)$ , let us first identify all the nodes whose cost is greater than  $L$  and denote these “undesired nodes” as a set

$$UN(h) = \{h' \in T(h) : C(h') \geq L\}.$$

Obviously, our control must ensure that the system will never enter these undesired nodes. This corresponds to the safety problem in supervisory control theory for the conventional DES. To maximize the effectiveness, we identify the nodes whose effectiveness is the largest among all the nodes in the tree. The determination of the most effective nodes is related to how many levels of the nodes are involved in the optimization. We denote these nodes as the “most effective nodes” and mark them as a set

$$MN(h) = \{h' \in T(h) : \forall h'' \in T(h), E(h'') \leq E(h')\}.$$

We would like the system to reach these marked nodes, which is a liveness problem in conventional supervisory control theory. Therefore, after defining  $UN(h)$  and  $MN(h)$ , the optimization problem can be solved by solving a standard supervisory control problem of safety and liveness with  $UN(h)$  as the illegal states and  $MN(h)$  as the marked states. Since the control synthesis for such a problem has been addressed in the literature, we will not discuss it here further, except to note that the solution exists if the corresponding language is controllable [24].

In the application of this theory to the clinical decision-making reported in Section III, we will not consider the treat-

ment cost and will assume  $L = \infty$ . This is because as the first phase of this development, we are concentrating on the treatment for the HIV/AIDS patients in the United States, where the cost of the drugs is not a major consideration in determining which drug to use. Such considerations, nevertheless, will be important when we extend our research to cover the patients in the less resourceful regions of the world.

2) *Realization of Finite State Machine Models for Treatment Regimens:*

a) *Development of the Models:* We need to design the fuzzy DES components  $G_i$ , in particular, their state transition matrices. We have used the four clinical parameters mentioned in Section II-A as inputs to a fuzzy DES for treatment decision-making. Accordingly, there are four fuzzy DES components, one for each of the four parameters. Correspondingly, there are four fuzzy state vectors, denoted as  $q_1, q_2, q_3$ , and  $q_4$ , representing the state of “potency,” “adherence,” “adverse events,” and “future drug options,” respectively. Potency state vector  $q_1$  has three components: initial, medium, and high. Thus, it is a  $1 \times 3$  vector with the initial state being represented by  $[1 \ 0 \ 0]$  (the second and the third numbers represent memberships for “medium” and “high”, respectively). Adherence state vector  $q_2$  has four members (i.e., a  $1 \times 4$  vector): initial, challenging, moderate, and easy. The state vector for adverse events  $q_3$  is defined by four elements (i.e., a  $1 \times 4$  vector) labeled as: initial, very low, low, and medium. Finally, future drug options state vector  $q_4$  has three elements (i.e., a  $1 \times 3$  vector): initial, medium, and high. Note that, as described earlier, all the four vectors are fuzzy state vectors. For instance, if  $q_1 = [0.6 \ 0.4]$ , it means the treatment is in a state with membership/possibility of 0.6 for “medium” potency and 0.4 for “high” potency.

Prescribing a treatment regimen for a patient is a crisp event, which causes the changes of state vectors in the four fuzzy automata (that is, what is deemed to be likely to happen to the patient’s status with regard to potency, adherence, adverse events, and future drug options). The changes are described by state transition matrices. The dimension of the state transition matrices is as follows:  $3 \times 3$  for potency,  $4 \times 4$  for adherence,  $4 \times 4$  for adverse events, and  $3 \times 3$  for future drug options. The dimension is determined by the number of elements in the corresponding fuzzy state vector. There are a total of 12 different state transition matrices for the three regimens. Each element in a transition matrix is a number between 0 and 1 to describe the possibility of transferring from one fuzzy state to another.

To generate these possibilities/memberships, we use Table I and fuzzy sets defined for each of the four clinical variables (Fig. 3). The fuzzy sets are empirically defined according to the knowledge obtained from the literature as well as from our AIDS specialist physicians. Semi-Gaussian functions are used to produce the gradual changes of the possibilities. For each fuzzy set, two parameters need to be defined: 1) the turning point where the membership value starts to decrease from 1 and 2) how quickly the decrease should be. The first parameter is determined using the information in Table I. Take potency as an example. The potency for regimens 1, 2, and 3 is 90%, 85%, and 80%, respectively. Thus, it is reasonable to use 75%

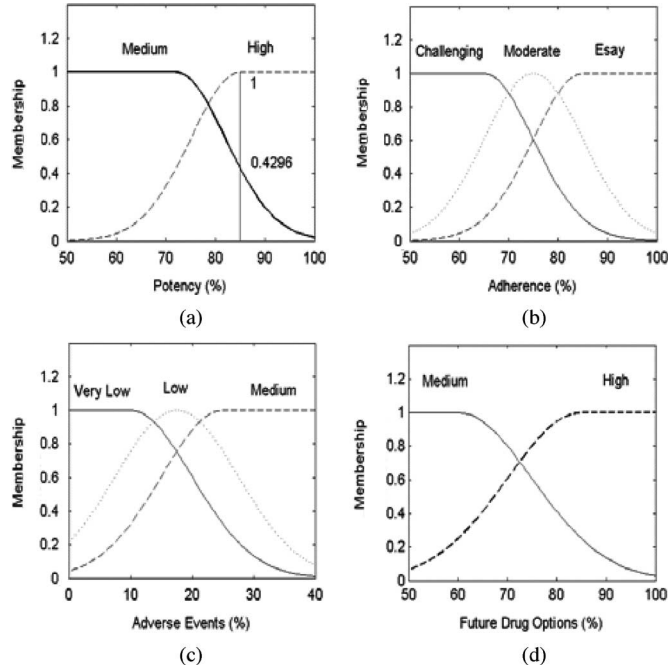


Fig. 3. Definitions of fuzzy sets for (a) potency, (b) adherence, (c) adverse events, and (d) future drug options. Also shown in (a) is the example fuzzification process for generating the memberships needed.

as the tuning point for the “medium” fuzzy set and 85% for the “high” fuzzy set (Fig. 3). To specify the second parameter, the membership value should not decrease too quickly or too slowly. We choose a modest decline for every fuzzy set. All the fuzzy sets are designed based on these principles. The resulting fuzzy sets are then inspected by the AIDS experts and adjustments are made, if necessary. Further fine tuning is performed to some of the fuzzy sets in the process of matching the system’s regimen choices to the experts’ choices. The mathematical definitions of the final fuzzy sets (Fig. 3) are summarized in Table II.

According to Table I, the potency for regimens 1, 2, and 3 is 90%, 85%, and 80%, respectively. If one draws a line perpendicular to the potency axis at 85% (which is the potency for regimen 2), the intersection of the line with the “medium” fuzzy set is 0.4296 and with the “high” fuzzy set is 1 [Fig. 3(a)]. This process is similar to the fuzzification process used for fuzzy controller input variables [19]. Normalization of these membership values gives 0.3005 and 0.6995, respectively. Thus, the state transition matrix for the potency of regimen 2 is obtained as

$$\psi = \begin{bmatrix} \textit{initial} & \textit{medium} & \textit{high} \\ 0 & 0.3005 & 0.6995 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{matrix} \textit{initial} \\ \textit{medium} \\ \textit{high} \end{matrix}$$

As illustrated, the labels are “initial” state, “medium” state, and “high” state for each row from left to right and the same names for each column from top to bottom. Hence, the possibility of transferring from the “initial” state to the “medium” state is 0.3005. The rest of the possibilities can be interpreted

TABLE II  
MATHEMATICAL DEFINITIONS OF THE FUZZY SETS FOR THE FOUR CLINICAL PARAMETERS (THEIR GRAPHICAL REPRESENTATIONS ARE GIVEN IN FIG. 3)

Potency	High	$\begin{cases} 1, & x > 85. \\ e^{-\frac{1}{2}\left(\frac{x-85}{10}\right)^2}, & x \leq 85. \end{cases}$
	Medium	$\begin{cases} e^{-\frac{1}{2}\left(\frac{x-72}{10}\right)^2}, & x > 72. \\ 1, & x \leq 72. \end{cases}$
Adherence	Easy	$\begin{cases} 1, & x > 85. \\ e^{-\frac{1}{2}\left(\frac{x-85}{10}\right)^2}, & x \leq 85. \end{cases}$
	Moderate	$e^{-\frac{1}{2}\left(\frac{x-75}{10}\right)^2}, \quad -\infty < x < \infty$
	Challenging	$\begin{cases} e^{-\frac{1}{2}\left(\frac{x-65}{10}\right)^2}, & x > 65. \\ 1, & x \leq 65. \end{cases}$
Adverse Events	Medium	$\begin{cases} 1, & x > 25. \\ e^{-\frac{1}{2}\left(\frac{x-25}{10}\right)^2}, & x \leq 25. \end{cases}$
	Low	$e^{-\frac{1}{2}\left(\frac{x-17.5}{10}\right)^2}, \quad -\infty < x < \infty$
	Very Low	$\begin{cases} e^{-\frac{1}{2}\left(\frac{x-10}{10}\right)^2}, & x > 10. \\ 1, & x \leq 10. \end{cases}$
Future Drug Options	High	$\begin{cases} 1, & x > 85. \\ e^{-\frac{1}{2}\left(\frac{x-85}{15}\right)^2}, & x \leq 85. \end{cases}$
	Medium	$\begin{cases} e^{-\frac{1}{2}\left(\frac{x-60}{15}\right)^2}, & x > 15. \\ 1, & x \leq 15. \end{cases}$

similarly. Note that the second and third rows are all 0’s because our study reported in this paper deals with the first round of treatment. Hence, we are in the “initial” state, not the “medium” state or “high” state. For treatment beyond the first round, the two rows would contain nonzero possibilities.

The other 11 state transition matrices can be obtained in the same manner using Table I and Fig. 3.

As the result of prescribing a regimen (which is a crisp event), 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 max-product operation (1) using the four initial state vectors and the “potency,” “adherence,” “adverse events,” and “future drug options” state transition matrices specific to the regimen. For example, the new potency state vector relative to the initial

state vector (i.e.,  $[1 \ 0 \ 0]$ ) after regimen 1 is calculated as

$$\begin{aligned} & [1 \ 0 \ 0] \circ \psi \\ &= [\max(0, 0, 0) \ \max(0.3005, 0, 0) \ \max(0.6995, 0, 0)] \\ &= [0 \ 0.3005 \ 0.6995]. \end{aligned}$$

This means the new state is 0.3005 for “medium” potency and 0.6995 for “high” potency.

*b) Development of Effectiveness Measure:* A proper effectiveness measure  $E(h)$  needs to be developed to gauge different regimens. It will also be used for optimizing decision-making.  $E(h)$  must work for all the possible combinations of conditions. The models need to consider the 32 combinations of the categories for potency, adherence, adverse events, and future drug options in determining which regimen would be deemed to be the best one for a given patient based on the available clinical trial evidence and expert knowledge. For each of the combinations, every regimen should be evaluated in searching for the best treatment. For each regimen, the event “applying the treatment regimen” will take four fuzzy DES components to yield four updated fuzzy state vectors. They represent the state of “potency,” “adherence,” “adverse events,” and “future drug option” and are denoted as  $\alpha, \beta, \gamma,$  and  $\lambda,$  respectively. As a result, three groups of new state vectors, one group for one regimen, will be produced for each combination. We use the optimization formalism presented in Section II-C-a to decide which regimen is expected to provide the most effective treatment outcome. The decision must involve all the four new state vectors simultaneously. Relative to the conventional DES theory, this optimization procedure may be viewed as a one-step look-ahead optimization of fuzzy DES.

We have developed a weighted average method that calculates the weighted average of the four vectors for a balanced optimal decision-making; i.e., the function  $f$  for computing  $E(h)$  is a weighted average function. For this purpose, we have defined two weight vectors for potency (one for “high” and one for “medium”), three weight vectors for adherence (one for “easy,” one for “moderate,” and one for “challenging”), three weight vectors for adverse events (one for “medium,” one for “low,” and one for “very low”), and two for future drug options (one for “high” and one for “medium”). The dimension of the weight vectors is the same as that of the corresponding state vectors. For example, if the weight vector for “high” potency is  $[0 \ 0.1 \ 0.9]$  (after transpose), it would mean that the emphasis is put on “high” with a weight of 0.9 but “medium” potency is also factored in with a lower weight of 0.1. Each vector is normalized to 1 (i.e., the sum of the membership values is 1). All the weight vectors are regimen-independent, i.e., different regimens use the same weight vectors.

For each combination, the effectiveness measure  $E(h)$  can be computed for each regimen by the weighted average of the new state vectors. Mathematically,

$$E(h) = \alpha \cdot W_P + \beta \cdot W_A + \gamma \cdot W_E + \lambda \cdot W_F \quad (2)$$

where  $W_P, W_A, W_E,$  and  $W_F$  are the weight vectors for potency, adherence, adverse events, and future drug options, respectively.

For a more complete example, let us assume that regimen 2 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

$$\begin{aligned} \alpha &= [0 \ 0.3050 \ 0.6995], \quad \beta = [0 \ 0.0777 \ 0.3482 \ 0.5741], \\ \gamma &= [0 \ 0.2467 \ 0.3943 \ 0.3590], \quad \lambda = [0 \ 0.8004 \ 0.1996], \end{aligned}$$

respectively. Also, suppose that the weight vector for “high” potency is  $W_P = [0 \ 0 \ 1]$ , for “challenging” adherence  $W_A = [0 \ 0.2069 \ 0.5402 \ 0.2529]$ , for “medium” adverse events  $W_E = [0 \ 0.1250 \ 0.3304 \ 0.5446]$ , and for “medium” future drug options  $W_F = [0 \ 0.4767 \ 0.5233]$  (all after vector transpose). Hence, the value of  $E(h)$  for regimen 1 applied to this particular combination can be computed using (2)

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

*c) Genetic-Algorithm-Based Regimen Selection Optimizer:* The role of this component is to optimize regimen selection through adjusting the weight vectors of the models guided by  $E(h)$ .

As indicated earlier, there were a total of 10 weight vectors. Each of them was normalized to 1. The weight vectors for potency, adherence, adverse events, and future drug options had two, three, three, and two adjustable weights, respectively. Therefore, there were a total of  $2 \times 2 + 3 \times 3 + 3 \times 3 + 2 \times 2 = 26$  adjustable weights. Our optimization objective was to find such 26 weights that would minimize the overall difference between the regimens selected by the models and those selected by two of the AIDS specialist physicians on this project for the 32 combinations of the categories of the four clinical variables. For clarity, they are labeled as specialists A and B. Their regimen selections are detailed in Section III-A. Optimizing the 26 weights through exhaustive search would take prohibitively long time. We instead turned to genetic algorithm technology for an efficient approach for searching the 26-dimensional parameter space.

The genetic algorithm was designed as follows. Compared to many genetic algorithms reported in the literature, ours was simple and basic. Nevertheless, we found it to be effective and adequate for our purpose. Each of the 26 weights is represented by a string of 6-bit binary numbers of 0s and 1s, thus the smallest change for each weight is  $1/64$ , or 0.0156. These strings are connected to form a 156-bit-long string, each of which represents a weight vector. After creation in each generation, the weights in each weight vector are always normalized so that their sum is 1.

The objective function for the weight optimization is

$$f = w_1 M_1 + w_2 M_2 + w_3 M_3 \quad (3)$$

where  $M_i, i = 1, 2, 3$ , is, for the 32 treatment objectives how many first-, second-, and third-choice regimens, as ranked by the system match the corresponding regimen rankings of the consensus of specialists A and B. Here,  $w_j$  represents the importance of each choice level. We set  $w_1 = 1, w_2 = 0.3$ , and  $w_3 = 0.1$ . The weighted agreement between the computer and physicians is represented by  $f$ .

Each generation of the weights contained 10 156-bit strings. The weights of the first generation were created randomly. A new generation was created in the following way. The two strings whose values of  $f$  are the largest are used to form 10 strings of the next generation (in case the two strings were identical, one of them would be replaced by the next best string that was different from them). One random crossover is applied to the two strings and the resulting strings become two new strings in the next generation. This process is repeated four more times until all 10 new strings are created. Then, one random mutation will occur to each of the 10 strings, changing 0 to 1 or 1 to 0 at one location. The mutation probability is 0.006.

The 10 sets of new weight vectors are then applied to (2) to compute their  $E$  values. For each of the 32 treatment objectives, the regimen with the highest  $E$  value is regarded as the first-choice regimen and the second highest as the second-choice, and the lowest as the last choice. Note that the magnitude of each  $E$  value is not important by itself, but it becomes significant when compared with the other three  $E$  values for the same treatment objective. Additionally,  $E$  values for different treatment objectives can be quite different. The weight values keep evolving in this way until the objective function value stops changing appreciably or until a preset number of generations have been reached.

A 2.0-GHz PC and MATLAB software were used to implement the proposed system.

### III. RESULTS OF SYSTEM EVALUATION

There were two steps in the evaluation. We first evaluated the performance of the models tuned by the optimizer and then assessed the system's performance.

#### A. Treatment Decisions Made by AIDS Specialists A and B and Calculation of Their Consensus

In order to generate labeled data to be used to learn the weights by the genetic algorithm, AIDS specialists A and B were presented with information on the above-mentioned four parameters critical to selection of an appropriate treatment regimen. All of the 32 possible combinations of these criteria were included with equal proportional representation in order to test the potential of the system without regard to the distribution of these criteria in any particular patient population. For each of the 32 combinations, each specialist was asked to rate the appropriateness of each of the three regimens using a 10-point score system—10 being the most appropriate and 0 the least for a regimen with an increment of 0.5 based on their clinical experiences. This rating was done without knowledge of the response of the other specialist. The scores reflected their choices—the regimen with the highest score was the first choice, and the lowest

TABLE III  
SCORES ASSIGNED BY AIDS SPECIALISTS A AND B FOR THE APPROPRIATENESS OF EACH OF THE THREE REGIMENS REGARDING THE 32 TREATMENT OBJECTIVES

Treatment Objective				Regimen 1		Regimen 2		Regimen 3	
Potency	Adherence	Adverse Events	Future Drug Options	Specialist A	Specialist B	Specialist A	Specialist B	Specialist A	Specialist B
High	Easy	Medium	High	7.0	4.0	6.5	3.5	6.5	9.0
High	Easy	Medium	Medium	9.0	9.0	8.5	8.5	6.5	8.0
High	Easy	Low	High	6.5	5.0	6.5	4.5	6.0	9.0
High	Easy	Low	Medium	8.5	8.5	8.0	8.0	6.5	7.0
High	Easy	Very Low	High	6.5	7.0	6.0	6.0	5.5	9.0
High	Easy	Very Low	Medium	8.5	8.0	7.5	7.5	6.0	8.5
High	Moderate	Medium	High	8.0	6.0	7.5	5.0	6.5	8.5
High	Moderate	Medium	Medium	10.0	9.0	9.5	8.5	7.5	8.0
High	Moderate	Low	High	7.5	5.0	7.0	4.0	6.5	9.0
High	Moderate	Low	Medium	9.5	8.5	9.0	8.0	6.5	7.5
High	Moderate	Very Low	High	7.5	5.0	6.5	4.0	6.0	9.0
High	Moderate	Very Low	Medium	9.5	8.0	8.5	7.5	6.0	8.5
High	Challenging	Medium	High	8.0	4.0	7.5	3.5	6.5	8.5
High	Challenging	Medium	Medium	10.0	9.0	9.5	8.5	6.5	6.5
High	Challenging	Low	High	7.5	4.0	7.0	3.5	6.5	9.0
High	Challenging	Low	Medium	9.5	9.0	9.0	8.5	6.5	7.0
High	Challenging	Very Low	High	7.5	5.0	6.5	4.0	6.5	8.5
High	Challenging	Very Low	Medium	9.5	8.0	8.5	7.5	6.5	9.0
Medium	Easy	Medium	High	7.0	4.5	7.0	5.0	8.0	9.5
Medium	Easy	Medium	Medium	9.0	8.0	9.0	8.5	8.0	9.0
Medium	Easy	Low	High	6.5	4.0	6.5	3.0	8.0	9.5
Medium	Easy	Low	Medium	8.5	8.0	8.5	8.5	8.0	9.5
Medium	Easy	Very Low	High	6.5	4.5	6.0	5.0	7.5	9.5
Medium	Easy	Very Low	Medium	8.5	7.0	8.0	7.5	7.5	9.5
Medium	Moderate	Medium	High	8.0	3.5	8.0	4.0	8.0	9.5
Medium	Moderate	Low	High	7.5	3.5	7.5	4.0	8.0	9.5
Medium	Moderate	Very Low	High	7.5	3.5	7.0	4.0	7.5	9.5
Medium	Moderate	Very Low	Medium	9.5	8.0	9.0	8.0	7.5	9.5
Medium	Challenging	Medium	High	8.0	6.0	8.0	5.0	8.0	9.5
Medium	Challenging	Low	High	7.5	4.0	7.5	3.5	8.0	9.5
Medium	Challenging	Very Low	High	7.5	3.5	7.0	4.0	7.5	9.5
Medium	Challenging	Very Low	Medium	9.5	8.0	9.0	8.0	7.5	9.5

score meant the last choice. The specialists could have directly ranked the regimens instead. One major 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 doctors, possibly forming a better consensus for the models. The scores are listed in Table III.

We then preprocessed the scores to standardize them between the two physicians. Each score of specialist A was divided by the standard deviation of all his scores in Table III. The same was done to the scores of specialist B. We then computed the average score of the two specialists for every combination and every regimen (the total number was  $32 \times 3 = 96$ ). The average scores were subsequently divided by the standard deviation of the 96 average scores. Then, the resulting scores were obtained by subtracting their mean (i.e., the mean of the 96 modified average scores) and adding 5 to shift the distribution in order to avoid negative numbers. The results formed the consensus scores of the two specialists. Finally, for each objective combination, the

TABLE IV

REGIMEN SELECTIONS MADE BY AIDS CLINICAL SPECIALISTS A AND B AND THE FUZZY DES MODULE FOR THE 32 COMBINATIONS OF THE FOUR CLINICAL PARAMETERS: (a) AGREEMENT BETWEEN THE TWO SPECIALISTS; (b) AGREEMENT BETWEEN SPECIALIST A AND THE FUZZY DES MODULE; AND (c) AGREEMENT BETWEEN SPECIALIST B AND THE FUZZY DES MODULE

Agreement		Regimens Ranked Using Scores of Specialist A		
		1st choice	2nd choice	3rd choice
Regimens Ranked Using Scores of Specialist B	1st choice	12	3	17
	2nd choice	13	13	6
	3rd choice	7	16	9

(a)

Agreement		Regimens Ranked Using Scores Computed by the Models		
		1st choice	2nd choice	3rd choice
Regimens Ranked Using Scores of Specialist A	1st choice	19	11	2
	2nd choice	4	16	12
	3rd choice	9	5	18

(b)

Agreement		Regimens Ranked Using Scores Computed by the Models		
		1st choice	2nd choice	3rd choice
Regimens Ranked Using Scores of Specialist B	1st choice	24	2	6
	2nd choice	6	22	4
	3rd choice	2	8	22

(c)

three scores were converted to three rankings of the regimens. They established a “gold standard” for the genetic algorithm to tune the weights so that the regimens selected by the models would match as closely as possible to those chosen by the doctors individually or jointly.

As we stated in Section I, treatment decision-making is partially art and partially science. It is well appreciated, and is frequently the norm, that expert clinicians will disagree to some extent with each other’s treatment choices. This was, indeed, the case for specialists A and B. While they were in complete agreement on the structure and parameter values of Table I containing the decision factors relevant to their selection of a regimen, they did not always select exactly the same regimen, so their agreement on treatment regimen choices was only moderate [see Table IV(a)]. We used the main diagonal of Table IV(a) as a measure of the consensus. The consensus was only 35.4% (34 out of 96). This lack of complete agreement between the physicians’ treatment choices still existed in spite of the fact that they had held many meetings to thoroughly discuss their thought processes regarding their treatment decisions.

### B. Evaluation of Performance of the Models Tuned by the Optimizer Against Regimen Selections of AIDS Specialists

We sought to demonstrate that the models, coupled with the optimizer, could select antiretroviral treatment regimens that were at least as acceptable to each HIV/AIDS specialist as the treatment selections made by the other AIDS specialists. The

models were evaluated in a blinded experiment comparing the treatment selections made by specialists A and B (Table III) with those made by the models in the following way.

We calculated the  $E(h)$  value determined by the models for each of the three regimens applied to each of the 32 combinations. This generated 96 values of  $E(h)$ . For each combination, the models ranked the three values of  $E(h)$  and labeled the regimens according to the corresponding values, from the highest to the lowest, as “first choice,” “second choice,” and “third choice,” providing the models’ optimal decision for the combination. Clinically speaking, however, the first choice is far more relevant and important than the other two choices.

In order to adjust for any agreement likely to occur simply by chance, a weighted Cohen’s Kappa [36] was used to measure the degree of agreement between the two specialists, and between the specialists and the models. The use of this statistics adjusts for the potentially substantial chance agreement that could occur if, for example, a single regimen was predominately preferred by both physicians. The weighted Kappa statistic made use of the full information contained in the ordinal rankings of the regimen suitability by the physicians and the models [37]. This measure, therefore, accounted for the fact that the agreement was better when physician A rated physician B’s first choice as his second choice, than would be the case if physician A had rated the regimen as his third choice. The null hypothesis was that the weighted Cohen’s Kappa for the two physician’s treatment selections relative to each other did not differ from the weighted Cohen’s Kappa for the physicians’ selections relative to the models.

When two separate sets of weight vectors were optimized using the genetic algorithm so that the models were allowed to optimize their decision to separately match specialists A or B individually, the exact agreements for the regimen selections were excellent—100% for each individual specialist.

We went further to develop a clinically more useful model that used only one set of fixed weight vectors to produce the treatment decision that could best match the consensus of a group of specialists (in our case, two specialists). The best consensus found by the genetic algorithm with one set of fixed weights for both specialists is shown in Table IV(a). This result indicated that the specialists exactly agreed on the treatment regimen in 35.4% (34 out of 96) of the evaluations, with a weighted Cohen’s Kappa of 0.10 (95% confidence interval was  $[-0.25, 0.16]$ ). This result indicated that the physicians’ agreement with each other’s treatment choices (beyond that expected by chance) was slight.

In contrast, the results for the physician’s selections relative to the models [Table IV(b) and (c)] indicated that the specialists exactly agreed with the treatment selection made by the models, developed using the consensus of the two physicians, in 63.0% (121 out of 192) of the evaluations and agreed within one preference level in 90.1% (173 out of 192) of the evaluations. Accordingly, the weighted Cohen’s Kappa for the agreement between either specialist and the models was good (0.50, with the 95% confidence interval being  $[0.37, 0.62]$ ), thus indicating that the physician’s agreement with the models’ choices (beyond that expected by chance) was substantial. The 95% confidence intervals for weighted Cohen’s Kappa for the physician’s agreement

with each other and their agreement with the models did not overlap, thus indicating that the  $p$ -value was less than 0.05 for the null hypothesis that these weighted Cohen's Kappa values were equal. These results demonstrate superior agreement between the physicians and the models coupled with the optimizer, as compared to their agreement with each other, thus demonstrating the system's ability to readily select those regimens for which there will be substantial agreement between independent experts as to the suitability of the proposed regimen.

### C. Retrospective Evaluation of Entire Regimen Selection System Using Patient Database

We then took our validation experiments to the next stage by using actual retrospective patient data to further evaluate the performance of the system relative to the expert opinions of specialists not involved in the training of the system. Our institution's clinical HIV/AIDS database was developed in early 1994. It contains information on more than 4500 patients, the majority of which was treated with various highly active antiretroviral therapy regimes since 1998. There are approximately 1600 active patients. The database, implemented in Microsoft Access 2000, contains information including laboratory, medication and diagnosis information, dates of hospitalization, death-related information, patient enrollment into clinical trials, and genotype testing.

In 2001, there were 98 treatment-naïve patients who started antiretroviral therapy in our AIDS Center. Thirty-five of them used one of the three regimens considered in this paper. Thirteen AIDS specialists prescribed medicine for these patients, with specialists A and B treating four and eight patients, respectively. The remaining 11 "nonsystem training" specialists treated 23 patients with the mean and standard deviation of patients per specialist being 2 and 1.97, respectively. We used these 35 patients to assess the performance of the system whose weight vectors were those learned by the genetic algorithm to achieve the best consensus [i.e., Table IV(b) and (c)].

We compared the regimens that the patients had actually received in our historical clinical database with the regimens selected as first choice regimens by our system using the same historical information about the patient's characteristics and conditions (the system was developed using the consensus of the two physicians). The overall exact agreement was 82.9% (29 out of 35) with an exact agreement with the historical decisions made by specialists A and B for their patients 100% for both specialists A and B. More importantly, the exact agreement for the remaining 11 "nontraining" physicians was an impressive 73.9% (17 out of 23). The extent of these exact agreements was particularly significant given the fact that the knowledge implemented in the system came only from two of the 13 specialists involved whose treatment consensus was rather modest. In general, HIV/AIDS specialists can be expected to disagree with each other fairly often, at least with regard to which treatment is most highly preferable. Hence, this substantial agreement with the historical decisions of the 11 "nontraining" specialists is a very encouraging result that demonstrates the generalization capabilities of our system.

We also further analyzed the six cases for which our system's choices disagreed with the historical choices of the clinicians. In four of the cases, the system chose a regimen that would be deemed more appropriate according to the clinical criteria defined by the training specialists (two patients with low CD4 counts should have received high potency regimens, and two patients with two risk factors for poor adherence should have received regimens with high future treatment options). In the other two cases, the clinicians and the system chose different regimens, but in our specialists' opinions either choice would have been reasonable choices for the patient. In light of this, our results provide promising evidence that the system may be capable of performing as well, or, in some select cases, perhaps better, than infectious disease physicians staffing an HIV clinic with regard to selection of appropriate treatment regimens.

### D. Discussion

Our methodology is novel and shares some of the same merits as certain AI methods. For instance, the reasoning chain between the input variables and final decision is transparent and easily understandable to humans. All the parameters of the system have clear and intuitive meanings. Our approach also offers some significant advantages. The optimization process of our system is dynamic because the forward-looking tree generated by the models changes from one state to another after each optimization step. An important feature of our approach is its promising capabilities of self-learning and representing knowledge even in the face of weak consensus, a crucial feature especially necessary to treatment of a complex disease. Another advantage is that the knowledge and information about regimens of interest are compactly represented and stored in the models. Including more clinical variable/parameters or changing the existing ones is not difficult, permitting easy knowledge upgrade and fast treatment strategy evolution. This is critically important for some diseases where scientific knowledge is rapidly evolving, such as HIV/AIDS. For example, new HIV/AIDS regimens are emerging on a regular basis as new AIDS drugs are developed and marketed. Because our system only requires information on the potency, adherence, adverse events, and future drug options of a new regimen [determined through clinical trials, and specialist'(s) regimen ratings] to update the weight vectors using the genetic algorithm, our system can be readily updated as new regimens become available without requiring substantial and time-consuming design changes.

In additional work reported elsewhere [26], we report on our system's ability to self-learn, by including an additional antiretroviral regimen—without the specialist's ratings for this fourth additional regimen being explicitly programmed. The technical basis for this self-learning technique is that each specialist's regimen ratings are related and thus partially contained in his ratings for the original three regimens being used by the system. They thus can be utilized to learn/predict the unknown ratings for the newly introduced regimen. The prediction accuracy in this experiment was always above 81%, and in some cases as high as 100%, depending on which regimen was treated as a new regimen to be learned and which ones were used as

old regimens. Arguably, achieving the same learning/prediction ability using the existing techniques (e.g., expert systems) would seem to be difficult (excepting the potential use of neural networks approach because of their unsuitable black box approach).

We are aware that from a statistical point of view, a larger patient sample size will be required for a more rigorous evaluation. However, due to the rapid evolution of treatment regimens, it is very difficult to achieve such a sample size for retrospective comparisons using actually prescribed regimens. The fact that none of the three regimens used in this paper remains a frequently used option today illustrates this point.

#### IV. CONCLUSION

We have developed a novel fuzzy DES approach to regimen selection of highly active antiretroviral therapy for treatment-naïve HIV/AIDS patients, which is the first application of the theory. Three historically widely used treatment regimens have been considered involving four essential clinical parameters for HIV treatment regimens, along with other patient-specific clinical variables. We have provided the details on how we have realized, designed, and tuned the system. Statistical evaluation of the results generated by the models tuned by the optimizer indicates significantly better agreement between the physicians and the models as compared to their agreement with each other, thus validating the models' performance. Additionally, the performance of the entire system was retrospectively assessed using all the qualifying patients treated in our AIDS Clinic in 2001, yielding very promising results with regard to the system's ability to arrive at treatment selection consistent with the expert opinions of physicians not involved in training of the system.

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#### REFERENCES

- [1] S. Quaglini, R. Bellazzi, C. Berzuini, M. Stefanelli, and G. Barosi, "Hybrid knowledge based systems for therapy planning," *Artif. Intell. Med.*, vol. 4, pp. 207–220, 1992.
- [2] T. Deutsch, E. Carson, and E. Ludwig, *Dealing with Medical Knowledge: Computers in Clinical Decision Making*. New York: Plenum, 1994.
- [3] E. H. Shortliffe, *MYCIN: Computer-Based Medical Consultations*. New York: Elsevier, 1976.
- [4] H. L. Bleich, "The computer as a consultant," *New Eng. J. Med.*, vol. 284, pp. 141–147, 1971.
- [5] B. Atalay, W. D. Potter, and D. Haburchak, "HIVPCES: A WWW-based HIV patient care expert system," in *Proc. 12th IEEE Symp. Comput.-Based Med. Syst.* Jun. 18–20, 1999, pp. 214–219.
- [6] L. X. Li and L. D. Xu, "An integrated information system for the intervention and prevention of AIDS," *Int. J. Biomed. Comput.*, vol. 29, pp. 191–206, 1991.
- [7] L. Ohno-Machado, E. Parra, S. B. Henry, S. W. Tu, and M. A. Musen, "AIDS2: A decision-support tool for decreasing physicians' uncertainty regarding patient eligibility for HIV treatment protocols," in *Proc. Annu. Symp. Comput. Appl. Med. Care*, 1993, pp. 429–433.
- [8] M. J. Pazzani, D. See, E. Schroeder, and J. Tilles, "Application of an expert system in the management of HIV-infected patients," *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.*, vol. 15, pp. 356–362, 1997.
- [9] C. Safran, D. M. Rind, F. Herrmann, C. Rury, E. Caraballo, K. Rippel, and H. Kowaloff, "The development of knowledge-based medical records for clinicians caring for patients with HIV infection," in *Proc. 7th World Congr. Med. Informat.*, 1992, pp. 495–500.
- [10] M. Sobesky and P. Le Beux, "An expert system for AIDS patients management," in *Proc. 7th World Congr. Med. Informat.*, 1992, pp. 490–494.
- [11] L. D. Xu, "A decision support system for AIDS intervention and prevention," *Int. J. Biomed. Comput.*, vol. 36, pp. 281–291, 1994.
- [12] H. B. Burke, D. B. Rosen, and P. H. Goodman, "Comparing artificial neural networks to other statistical methods for medical outcome prediction," in *Proc. 1994 IEEE World Congr. Comput. Intell.*, Jun. 27–Jul. 2, 1994, vol. 4, pp. 2213–2216.
- [13] N. K. Kwak and C. Lee, "A neural network application to classification of health status of HIV/AIDS patients," *J. Med. Syst.*, vol. 21, pp. 87–97, 1997.
- [14] C. Langlotz, L. Fagan, S. Tu, B. Sikic, and E. Shortliffe, "A therapy planning architecture that combines decision theory and artificial intelligence techniques," *Comput. Biomed. Res.*, vol. 20, pp. 279–303, 1987.
- [15] G. Shafer, *The Mathematical Theory of Evidence*. Princeton, NJ: Princeton Univ. Press, 1976.
- [16] P. R. Cohen and M. R. Grinberg, "A theory of heuristic reasoning about uncertainty," *AI Mag.*, pp. 17–23, Summer 1983.
- [17] L. A. Zadeh, "Fuzzy sets," *Inform. Control*, vol. 8, pp. 338–353, 1965.
- [18] H. Ying, M. McEachern, D. Eddleman, and L. C. Sheppard, "Fuzzy control of mean arterial pressure in postsurgical patients with sodium nitroprusside infusion," *IEEE Trans. Bio-Med. Eng.*, vol. 39, no. 10, pp. 1060–1070, Oct. 1992.
- [19] H. Ying, *Fuzzy Control and Modeling: Analytical Foundations and Applications*. New York: Wiley-IEEE, 2000.
- [20] S. Barro, R. Marin, and J. Kacprzyk, Eds., *Fuzzy Logic in Medicine*. Heidelberg, Germany: Physica Verlag, 2002.
- [21] J. N. Mordeson, D. S. Malik, and S. C. Cheng, *Fuzzy Mathematics in Medicine*. Heidelberg, Germany: Physica Verlag, 2000.
- [22] F. Lin and H. Ying, "Modeling and control of fuzzy discrete event systems," *IEEE Trans. Syst., Man, Cybern. B.*, vol. 32, no. 4, pp. 408–415, Aug. 2002.
- [23] —, "Fuzzy discrete event systems and their observability," in *Proc. Joint Int. Conf. 9th Int. Fuzzy Syst. Assoc. World Congr. and 20th North Amer. Fuzzy Inform. Process. Soc.*, Vancouver, BC, Canada, Jul. 25–28, 2001, pp. 1271–1276.
- [24] C. G. Cassandras and S. LaFortune, *Introduction to Discrete Event Systems*. Norwell, MA: Kluwer, 1999.
- [25] F. Lin and W. M. Wonham, "On observability of discrete event systems," *Inform. Sci.*, vol. 44, pp. 173–198, 1988.
- [26] H. Ying, F. Lin, X.-D. Luan, R. D. MacArthur, J. A. Cohn, D. C. Barth-Jones, H. Ye, and L. R. Crane, "A fuzzy discrete event system with self-learning capability for HIV/AIDS treatment regimen selection," in *Proc. North Amer. Fuzzy Inform. Process. Soc. Conf.*, Ann Arbor, MI, Jun. 22–25, 2005, pp. 820–824.
- [27] F. Lin, H. Ying, X.-D. Luan, R. D. MacArthur, J. A. Cohn, D. C. Barth-Jones, and L. R. Crane, "Control of fuzzy discrete event systems and its applications to clinical treatment planning," in *Proc. IEEE Conf. Decision Control*, Paradise Island, The Bahamas, Dec. 14–17, 2004, vol. 1, pp. 519–524.
- [28] X.-D. Luan, H. Ying, F. Lin, R. D. MacArthur, J. A. Cohn, D. C. Barth-Jones, H. Ye, and L. R. Crane, "A fuzzy discrete event system for HIV/AIDS treatment," in *Proc. IEEE Int. Conf. Fuzzy Syst.*, Reno, NV, May 22–25, 2005, pp. 167–172.
- [29] H. Ying, F. Lin, X.-D. Luan, R. D. MacArthur, J. A. Cohn, D. C. Barth-Jones, and L. R. Crane, "A fuzzy discrete event system for HIV/AIDS treatment planning," in *Proc. IEEE Int. Conf. Fuzzy Syst.*, Budapest, Hungary, Jul. 25–29, 2004, pp. 197–202.
- [30] Joint United Nations Programme on HIV/AIDS (UNAIDS), "2004 report on the global AIDS epidemic," UNAIDS Pub 04.16E, Jun. 2004.
- [31] F. M. Hecht, I. B. Wilson, A. W. Wu, R. L. Cook, and B. J. Turner, "Optimizing care for persons with HIV infection. Society of General Internal Medicine AIDS Task Force," *Ann. Intern. Med.*, vol. 131, pp. 136–143, 1999.
- [32] DHHS and Henry Kaiser Foundation Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. The living document. [Online]. Available: <http://www.hivatis.org> <http://www.hivatis.org>
- [33] C. L. Brosgart, T. F. Mitchell, R. L. Coleman, T. Dyner, K. E. Stephenson, and D. I. Abrams, "Clinical experience and choice of drug therapy for human immunodeficiency virus disease," *Clin. Infect. Dis.*, vol. 28, pp. 14–22, 1999.

- [34] R. D. MacArthur, G. Perez, S. Walmsley, J. Baxter, J. Neaton, and D. Wentworth, "CD4+ cell count is a better predictor of disease progression than HIV RNA level in persons with advanced HIV infection on highly active antiretroviral therapy," in *Proc. 8th Conf. Retroviruses Opportunistic Infect.* Feb. 4–8, 2001, vol. 8, no. 101, abstract no. 203.
- [35] S. L. Chung, S. LaFortune, and F. Lin, "Limited look ahead policies in supervisory control of discrete event systems," *IEEE Trans. Autom. Control*, vol. 37, no. 12, pp. 1921–1935, Dec. 1992.
- [36] A. M. Liebetrau, *Measure of Association*. Newbury Park, CA: Sage, 1983.
- [37] A. Agresti, *Categorical Data Analysis*. New York: Wiley, 1990.
- [38] M. Harris and J. S. Montaner, "Management of HIV-infected patients with multidrug-resistant virus," *Curr. HIV/AIDS Rep.*, vol. 1, no. 3, pp. 116–121, Sep. 2004.
- [39] F. J. Palella, Jr., K. M. Delaney, A. C. Moorman, M. O. Loveless, J. Fuhrer, G. A. Satten, D. J. Aschman, and S. D. Holmberg, "Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators," *New. Eng. J. Med.*, vol. 338, no. 13, pp. 853–860, Mar. 26 1998.
- [40] P. M. A. Sloom, A. V. Boukhanovsky, W. Keulen, A. Tirado-Ramos, and C. A. Boucher, "A grid-based HIV expert system," *J. Clin. Monit. Comput.*, vol. 19, no. 4–5, pp. 263–278, 2005.
- [41] R. H. Lathrop, N. R. Steffen, M. P. Raphael, S. Deeds-Rubin, M. J. Pazzani, P. J. Cimocho, D. M. See, and J. G. Tilles, "Knowledge based avoidance of drug resistant HIV mutants," *AI Mag.*, vol. 20, no. 1, pp. 13–25, Spring, 1999.
- [42] H. Jiang, S. G. Deeks, D. R. Kuritzkes, M. Lallemand, D. Katzenstein, M. Albrecht, and V. DeGruttola, "Assessing resistance costs of antiretroviral therapies via measures of future drug options," *J. Infect. Dis.*, vol. 188, pp. 1001–1008, 2003.
- [43] S. Walmsley, B. Bernstein, M. King, J. Arribas, G. Beall, P. Ruane, M. Johnson, D. Johnson, R. Lalonde, A. Japour, S. Brun, and E. Sun, "Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection," *New. Eng. J. Med.*, vol. 346, pp. 2039–2046, 2002.
- [44] J. C. Gathe, Jr., P. Ive, R. Wood, D. Schürmann, N. C. Bellos, E. DeJesus, A. Gladysz, C. Garriss, and J. Yeo, "SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir/ritonavir versus twice-daily nelfinavir in naïve HIV-1 infected patients," *AIDS*, vol. 18, pp. 1529–1537, 2004.
- [45] F. van Leth, P. Phanuphak, K. Ruxrungtham, E. Baraldi, S. Miller, B. Gazzard, P. Cahn, U. G. Laloo, I. P. van der Westhuizen, D. R. Malan, M. A. Johnson, B. R. Santos, F. Mulcahy, R. Wood, G. C. Levi, G. Reboredo, K. Squires, I. Cassetti, D. Petit, F. Raffi, C. Katlama, R. L. Murphy, A. Horban, J. P. Dam, E. Hassink, R. van Leeuwen, P. Robinson, F. W. Wit, and J. M. Lange, "Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: A randomized open-label trial, the 2NN Study," *Lancet*, vol. 17, pp. 1253–1263, 2004.
- [46] R. W. Shafer, L. M. Smeaton, G. K. Robbins, V. De Gruttola, S. W. Snyder, R. T. D'Aquila, V. A. Johnson, G. D. Morse, M. A. Nokta, A. I. Martinez, B. M. Gripshover, P. Kaul, R. Haubrich, M. Swingle, S. D. McCarty, S. Vella, M. S. Hirsch, and T. C. Merigan, "Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection," *New. Eng. J. Med.*, vol. 349, pp. 2304–2315, 2003.
- [47] D. Cooper and P. Yeni, "Virologic and immunologic outcomes at 3 years following initiation of ART with regimens containing a NNRTI or PI or both: The INITIO trial," presented at the 12th Conf. Retroviruses Opportunistic Infect., Boston, MA, Feb. 22–25, 2005.



**Hao Ying** (S'88–M'90–SM'97) received the B.S. and M.S. degrees in electrical engineering from Donghua University (formerly China Textile University), Shanghai, China, in 1982 and 1984, respectively, and the Ph.D. degree in biomedical engineering from the University of Alabama, Birmingham, in 1990.

From 1992 to 2000, he was on the faculty of the University of Texas Medical Branch, Galveston. Between 1998 and 2000, he was an Adjunct Associate Professor, Biomedical Engineering Program, University of Texas, Austin. He is currently a Professor in the Department of Electrical and Computer Engineering and a Full Member at Barbara Ann Karmanos Can-

cer Institute, Wayne State University, Detroit, MI. He is the author or coauthor of 73 peer-reviewed journal papers and 103 conference papers published in international journals and is the author of *Fuzzy Control and Modeling: Analytical Foundations and Applications* (IEEE Press, 2000). He has served as a Reviewer for more than 50 international journals.

Dr. Ying is an Elected Board Member of the North American Fuzzy Information Processing Society (NAFIPS). He is an Associate Editor for four international journals (*Dynamics of Continuous Discrete and Impulsive Systems—Series B: Applications and Algorithms*, *International Journal of Fuzzy Systems*, *International Journal of Approximate Reasoning*, and *Journal of Intelligent and Fuzzy Systems*) and a Member of the Journal Editorial Board of *Advances in Fuzzy Sets and Systems*. He has been a Guest Editor for four journals. He has been a Program Chair for the 2005 NAFIPS Conference. He has served as the Publication Chair for the 2000 IEEE International Conference on Fuzzy Systems and as a Program Committee Member for over 20 international conferences.



**Feng Lin** (S'86–M'87) received the B.Eng. degree from Shanghai Jiao-Tong University, Shanghai, China, in 1982, and the M.A.Sc. and Ph.D. degrees from the University of Toronto, Toronto, ON, Canada, in 1984 and 1988, respectively, all in electrical engineering.

From 1987 to 1988, he was a Postdoctoral Fellow at Harvard University, Cambridge, MA. Since 1988, he has been with the Department of Electrical and Computer Engineering, Wayne State University, Detroit, MI, where he is currently a Professor. He

has been a Consultant to General Motors, Ford, Hitachi, and other automobile companies. His current research interests include discrete-event systems, hybrid systems, robust control, and image processing.

Dr. Lin has served as an Associate Editor of the IEEE TRANSACTIONS ON AUTOMATIC CONTROL. Together with S. L. Chung and S. LaFortune, he coauthored a paper that received a George Axelby Outstanding Paper Award from the IEEE Control Systems Society. He was also the recipient of a Research Initiation Award from the National Science Foundation, an Outstanding Teaching Award from Wayne State University, a Faculty Research Award from ANR Pipeline Company, and a Research Award from the Ford Foundation.



**Rodger D. MacArthur** received the B.A. degrees in psychology and biology from Northwestern University, Evanston, IL, in 1977, the M.A. degree in experimental psychology from Columbia University, New York, NY, in 1979, and the M.D. degree from the College of Medicine, University of Illinois, Chicago, in 1983.

From 1978 to 1979, he was a National Science Foundation Graduate Research Fellow at Columbia University. From 1983 to 1986, he was an Intern in Internal Medicine at Case Western Reserve University, Cleveland, OH. From 1986 to 1988, he was a Fellow in Infectious Diseases at The Johns Hopkins Hospital, Baltimore, MD. Since 1995, he has been at Wayne State University, Detroit, MI, where he is currently an Associate Professor of Medicine and Director of Clinical Research. He is the author or coauthor of 57 peer-reviewed publications, chapter contributions, and reviews.

Dr. MacArthur is a Fellow of the Infectious Diseases Society of America. He was the recipient of the Wayne State University School of Medicine College Teaching Award in 2004. From 1989 to 1995, he was on the committee for the AIDS Task Force.

**Jonathan A. Cohn** received the M.D. degree from the State University of New York (SUNY), Brooklyn, in 1976, and the Master's degree in preventive medicine and epidemiology from the University of Maryland, College Park, in 1994.

From 1976 to 1977, he was an Intern in the Internal Medicine Residency Program at SUNY, Brooklyn. From 1978 to 1980, he was a Resident in Internal Medicine at Pacific Presbyterian Medical Center, San Francisco, CA. From 1980 to 1983, he was the Chief Resident at the center. From 1984 to 1986, he was a Fellow in Infectious Diseases and Immunology at Bellevue Medical Center, New York University, New York. Thereafter, he was with the Infectious Disease Division, Bellevue Medical Center, University of Maryland. Since 1997, he has been with Wayne State University, Detroit, MI, where he is currently an Associate Professor of Medicine.

Dr. Cohn is a Fellow of the American College of Physicians and a member of the Infectious Disease Society of America. He was the recipient of a Department of Medicine Teaching Award in 2004 and was included in the Best Doctors of America List for several years.



**Daniel C. Barth-Jones** received the B.S. degree in psychology from Wayne State University, Detroit, MI, in 1983, and the M.P.H. degree in general epidemiology and the Ph.D. degree in epidemiological science from the University of Michigan, Ann Arbor, in 1988 and 1999, respectively.

From 1988 to 1999, he was an Infection Control Practitioner, Biostatistician, Senior Statistician, and Consulting Epidemiologist in the healthcare industry. Since 2000, he has been with the Center for Healthcare Effectiveness Research and Departments of Internal Medicine and Community Medicine, Wayne State University, Detroit, MI, where he is currently an Assistant Professor. His current research interests include computer simulation, epidemic modeling, statistical disclosure control, and artificial intelligence applications for the biomedical, biostatistical, and epidemiological sciences.

Dr. Barth-Jones is a member of the American College of Epidemiology, the American Statistical Association, and the Society for Mathematical Biology. He is a participant in the World Health Organization/Joint United Nations Programme on HIV/AIDS Epidemiologic Reference Group on Estimates, Modeling, and Projections. He has also served as an Advisor for the World Health Organization on 11 occasions.

Dr. Barth-Jones is a member of the American College of Epidemiology, the American Statistical Association, and the Society for Mathematical Biology. He is a participant in the World Health Organization/Joint United Nations Programme on HIV/AIDS Epidemiologic Reference Group on Estimates, Modeling, and Projections. He has also served as an Advisor for the World Health Organization on 11 occasions.



**Hong Ye** received the B.Eng. degree in mechanical engineering from Wuhan University, Wuhan, China, in 1998, the M.S. degree in mechanical engineering from North China Electric Power University, Beijing, China, in 2002, and the M.A. degree in computer science from Wayne State University, Detroit, MI, in 2003.

Since 2004, she has been with the Division of Infectious Diseases, Department of Medicine, Wayne State University School of Medicine, Detroit, MI, as a Research Assistant.



**Lawrence R. Crane** received the M.D. degree from Wayne State University, Detroit, MI, in 1966.

He was a Resident in Internal Medicine at Henry Ford Hospital, Detroit, in 1967, and at the National Naval Medical Center, Bethesda, MD, in 1972. He was Fellow in Infectious Diseases at Wayne State University in 1974. Since then, he has been with the Division of Infectious Diseases, Department of Medicine, Wayne State University, where he is currently a Professor. He is also the Director of the Wayne State University/Detroit Medical Center

Adult HIV/AIDS Program. He is the author or coauthor of over 100 peer-reviewed publications and book chapters. He is the editor of a book and is a reviewer for numerous journal publications. His current research interests include HIV-related clinical trials.

Dr. Crane is a Fellow of the American College of Physicians and the Infectious Diseases Society of America. He is the recipient of numerous service and teaching awards and serves on several university and national committees.