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An Extended Fuzzy Discrete Event System For Hiv/aids Treatment Regimen Selection

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AN EXTENDED FUZZY DISCRETE EVENT SYSTEM FOR HIV/AIDS TREATMENT REGIMEN SELECTION

by

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INTRODUCTION

The number of human immunodeficiency virus (HIV) infected people is large and widespread. The Joint United Nations Programme on HIV/AIDS (UNAIDS) released the 2008 UNAIDS report on the global acquired immunodeficiency syndrome (AIDS) epidemic, stating that an estimated 30-36 million people are living with HIV worldwide. More than 20 million people have died. Most of the individuals with this disease reside in developing nations [54,72]. The HIV-infected patients need timely and lifelong medical treatment in order to live. The expense of such treatment is even high in those lesser developed nations [14,17,18,57]. Additionally, there are not enough physicians with HIV/AIDS expertise to properly prescribe the appropriate and potentially life-saving drugs. This shortage leads to a significant number of deaths. Prescribing the right drugs can increase the HIV-infected patients' lifespan.

1.1 Problem Statement

The challenge in treating most diseases is to optimize medical decision-making. HIV/AIDS is an extremely severe disease. An HIV/AIDS patient has individual characteristics such as genetic traits, reaction to the side effects of drugs, and overall prognosis. Many symptoms and diagnoses are vague in their definitions and hard to measure. Treatment outcomes are also subjective, with some degree of uncertainty. To address treatment decisions for an individual

patient, a clinician gathers all these variables into a clinical decision process and then a treatment decision is judged. Expert opinions play a significant role in optimizing treatment outcomes for specific patients. Many variables and factors involved in the medical treatment could cause physicians with inconsistent treatment decision-making.

In HIV/AIDS treatment, the highly active antiretroviral therapy (HAART) is an efficient therapy that can improve a patient's mortality and morbidity [38]. A combination of two or three drugs from three drug classes, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs), is used in HAART to suppress the viral load caused by HIV-infected CD4+ cells. When infected, the CD4+ cells are unable to signal the immune response cells (i.e., cytotoxic lymphocytes) in order to eliminate infection. The patient can retain low viral load and high population of CD4+ cells that would be the ideal clinical situation in HIV therapy. The desired drugs should provide such results with a minimum of side effects and toxicities (e.g., [38] listed common side effects and toxicities of anti-HIV drugs). Modeling the interaction between the viral load, CD4+ cells and the immune response cells was studied widely. That study included [35,37,43], [49]-[51], and their models were based on differential equations.

Clinical studies as well as empirical studies demonstrate that the patient must be strict with medication adherence to achieve levels of low viral load and high CD4+ cells. Taking less than 75-80% of the regimen prescription is

considered as poor adherence, causing an underestimate of treatment effect. The patient's individual characteristics and the treatment regimen affect patient adherence. Additionally, [40] provided other factors associated with patient adherence.

The technical approaches that contribute to treatment decision-supporting, especially in HIV/AIDS treatment, mainly include statistical methods [35]-[37], expert systems [8,10,48], and fuzzy discrete event systems theory [22,25,31,34]. The statistical methods were employed to estimate the unknown parameters in HIV dynamic models based on differential equations. Bayesian approach [35,36,39,42] is a powerful statistical method to estimate dynamic parameters for complex HIV dynamic models without closed-form solutions available, but it is complicated in application. Conversely, the expert system approach sometimes referred to as knowledge-based approach is designed using either rule-based or case-based reasoning methods to emulate the performance of treatment professionals. In the expert system the representation of knowledge is intuitive and reasoning sequences of decisions are understandable. The expert system usually employs the probability theory to describe the uncertainties of clinical parameter characteristics. When merging to artificial neural network [8,9,15], the expert system gained profit on self-learning capabilities being able to handle frequent update of existing knowledge or inclusion of new knowledge. The expert system could be combined with fuzzy set theory [1]-[3] (e.g., [47,71]). That theory provided the expert system capable of handling the uncertainties in form of fuzzy

rules and memberships. The physician knowledge is subjective, and a consensus among a group of individual physicians is difficult and rarely achieved. Extracting and representing the consensus knowledge from diverse opinions into a usable form like the IF-THEN rules for the expert system would be complicated and costly.

Recently, the theory of fuzzy discrete event systems (FDES) [12,13] was established and studied with the retrospective HIV/AIDS patients for the treatment regimen selection [22], [25]-[27], [31]. FDES theory merges the fuzzy system technology with the discrete event systems (DES) technology [4]. The DES is used to model a system which is described by sequences of events that involves changes of system states. Theoretically, the changes of the states would be occupied completely when the corresponding events take place. An evaluation of the state change can be mathematically described by a transition function (e.g., a partial function). A deterministic automaton can be used as a model of DES. On the other hand, a model of FDES is represented by a fuzzy automaton. FDES allows partial changes of states when the event occurs. The transition function involving fuzzy logic operations (e.g., max-product, max-min) will be employed to describe such changes of states. For example, for a partial change of states, in the medical field, saying a patient's illness is bad would be vague because the bad condition may mean something different for different people. After a treatment event (e.g., prescribing a drug), the patient's illness seems to be improved, which is between bad and fair state. The incomplete change of the illness states will

associate partially with corresponding states (i.e., saying 40% bad state and 60% fair state) in a state transition matrix. Such uncertainties and vagueness of the patient's illness state and state transition can be handled by the FDES but not the DES, showing that FDES is capable of handling a system with uncertainties and vagueness of the state and state transition.

The HIV/AIDS treatment regimen selection system is an interesting example of clinical applications achieved using FDES approach. Some important features of the application in concise details are given in the next session. This FDES-based system provided intuitive physical meanings of the parameter representation. The sequence process from beginning to end is easy, conceptual understanding for people. However, the situation of collecting consensuses may be undergone in difficult environments, especially in the biomedical field, and so may not be successful. This potential focused our attentions on how to correct this situation. Moreover, the HIV/AIDS epidemic is a global problem. Most of those suffering from this epidemic live in poor countries where the expertise of the physicians is limited and so the prescribed treatment is inefficient. The FDES-based system could provide a significant tool for HIV/AIDS treatment decisions.

1.2 Fuzzy Discrete Event System (FDES) in HIV/AIDS Treatment Regimen Selection System

In the antiretroviral therapy, two major concerns in drug selection are choosing ones with sufficient ability to suppress the HIV replication and those that minimize side effects. Complying with these goals would slow down viral

resistance in HIV/AIDS patients with the proper doses, thus prolonging their lives. The combination of drugs used in antiretroviral therapy (i.e., HAART) for HIV-infected patients is called a regimen. The HIV/AIDS specialists can prescribe proper regimens for specific characteristics of the patients. However, the prescriptions of the appropriate regimens could be inconsistent if the specialists deal with similar characteristics of patients time after time. The support system for treatment regimen selection (i.e., FDES-based system) providing a solution for such problem would be preferred by those specialists. In the FDES-based system, FDES theory was applied in HIV/AIDS treatment regimen selection system [22] being implemented in Fuzzy Finite State Models block illustrated in Figure 1.1. Three regimens were prescribed to patients. Each regimen consisted of Combivir (CBV) and one another drug, Efavirenz (EFV), Nevirapine (NVP), or Abacavir (ABC), shown in Table 1.1 with corresponding percentages of four clinic-considered parameters. Potency of the regimen, expected patient adherence to the regimen, adverse events (side effects and toxicities), and future drug options due to failure of the current regimen were the clinical parameters used in the model that needed to be defined and balanced by an HIV/AIDS specialist.

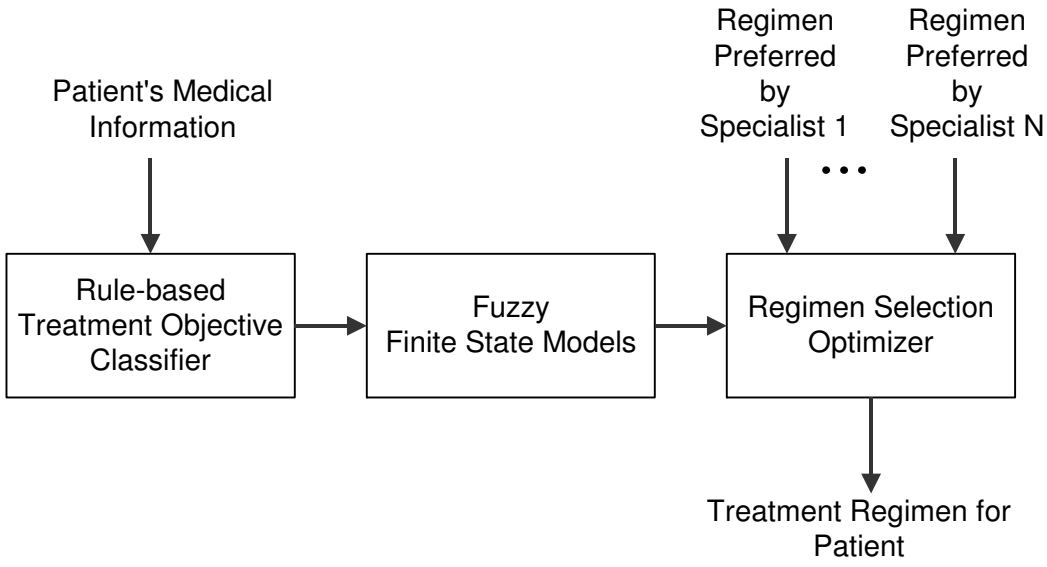


Figure 1.1: Block diagram of the FDES-based regimen selection system

Table 1.1: Values of four clinical parameters of the three HIV/AIDS treatment regimens

	Potency	Adherence	Adverse Events	Future Drug Options
Regimen 1: CBV+EFV	90%	80%	20%	60%
Regimen 2: CBV+NVP	85%	85%	20%	65%
Regimen 3: CBV+ABC	80%	90%	10%	85%

1.2.1 Fuzzy Sets in HIV/AIDS Treatment System

In the application of FDES theory to the HIV/AIDS treatment regimen selection system, four clinical parameters were primarily used in optimizing an antiretroviral treatment regimen for HIV-infected patients. These parameters are the regimen's expected potency, the patient's expected adherence along with the regimen, adverse events (e.g., side effects, toxicities) caused by the regimen, and future drug options due to the drug-resistance that develops from the current regimen.

Potency parameter is used to indicate a regimen capable of suppressing the HIV replication. As shown in Table 1.1, the measure of potency uses the percentage of patients who achieve clinical trials of plasma HIV RNA below a baseline (i.e., less than 400 copies/mL) after 48 weeks of treatment. Adherence is complicated and involves various factors that a patient faces in order to comply with the antiretroviral therapy. Effectively, at least 95% of the prescribed regimen doses are recommended for the patients to get desired outcomes of the treatment [55]. However, the HIV/AIDS studies indicate patients follow, at most, only 70% of prescribed regimens. Insufficient adherence cannot maintain suppression of HIV replication in an appropriate way and furthermore causes rapid development of drug-resistant HIV.

Adherence was defined as the expected percentage of doses of regimen prescribed by HIV/AIDS specialists that the patient would take faithfully each week. Adverse events were defined as the risk in the form of the undesired side

effects and toxicities to the patient under the regimen. Some medical information and physical behavior were considered, involving, for example, patient's age, gender, cholesterol, blood pressure, diseases like diabetes or hepatitis, etc. Finally, if the current regimen failed to maintain the suppression of HIV RNA replication and led to the development of resistance to the regimen, what is the feasibility that new regimens would be available for effective antiretroviral treatment? That is the definition of the clinical parameters of future drug options.

In the FDES system, each of four parameters was fuzzified by type-1 fuzzy sets defined according to HIV/AIDS specialists' knowledge as well as the clinical literatures. These type-1 fuzzy sets served to represent specialists' consensus. Unfortunately, more often in clinical practice, specialists with distinct knowledge and expertise may have a difficult time reaching a consensus. As an example, the fuzzy sets "Medium" and "High" shown in Figure 1.2 are two fuzzy variables for the regimen's future drug options parameter. The other three clinical parameters; potency, "Medium" and "High"; adherence: "Challenging", "Moderate", and "Easy"; and adverse events: "Very low", "Low", and "Medium", were fuzzified using similar type-1 fuzzy sets.

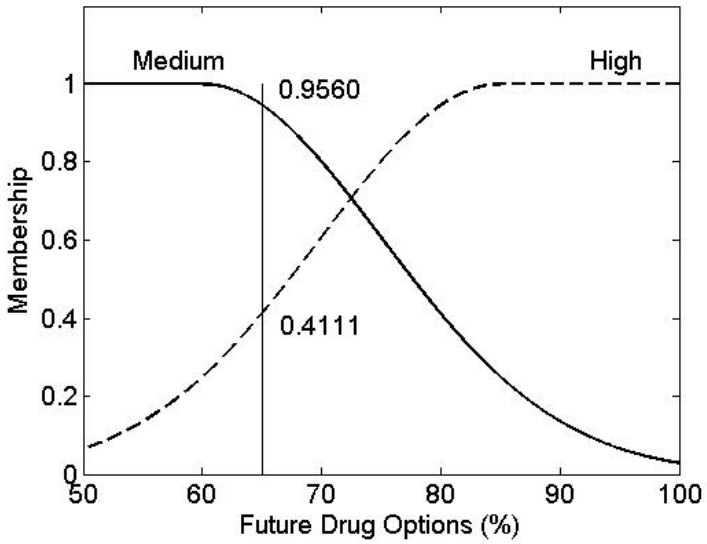


Figure 1.2: Two type-1 fuzzy sets defined for future drug options in the FDES system. In case of regimen 2, after fuzzification of the 65%, 0.9560 and 0.4111 are obtained as memberships for “Medium” and “High”.

1.2.2 FDES-Based Model for HIV/AIDS Treatment System

A fuzzy automaton can be used to model the FDES describing various parameters available and their potential output. The Fuzzy Finite State Model, a part in HIV/AIDS treatment system in Figure 1, is an example of the use of the fuzzy automaton. Generally, the fuzzy automaton (*G*) [7,12,13,16], [19]-[21], [23] can be expressed as $G = (Q, \Sigma, \delta, q_0)$. The formula describes how a state in the system changes from a current one to the next one when an event occurs. The current state q is a vector $q=[v_1, v_2, \ldots, v_n]$ in the fuzzy state space $Q=[0, 1]^n$, where $v_i \in [0, 1]$ is the membership grade of the state *i* possibly taken in the

system. The $q_0 \in Q$ is the initial state vector. An event σ^k is in the set of events $\Sigma = \{\sigma^1, \sigma^2, ..., \sigma^m\}$ represented by a state transition matrix $\sigma^k = \left[\sigma_{ij}^k\right]_{n \times n}$, where $\sigma_{ij}^k \in [0, 1]$ states the chance of the system shifting from state *i* to state *j* when the event takes place. Consequently, the occurrence of the event σ^k causes the update of the current state vector *q*. This state transition would be described by δ. The update (next) state vector q' can be computed by $q' = q \circ \sigma^k$, where $\circ$ a fuzzy logic operation is defined by δ.

The FDES model may consist of *N* fuzzy automata: G_1 G_2 … G_N. Their corresponding state vectors and event sets are denoted by q_1 q_2 … q_N and Σ_1 Σ_2 … Σ_N, respectively. For instance, there were four automata in the FDES-based regimen selection system. Each was modeled for each of the clinical parameters. The state vectors could be either 1×3 vector or 1×4 vector, for instance, adherence state vector has four components: initial, challenging, moderate, and easy, with the initial state vector represented by [1 0 0 0]. (Numbers in the second, third, and fourth place are membership grade for “Challenging”, “Moderate”, and “Easy”, respectively). Since prescribing a regimen referred to the occurrence of events in the system, thus each of the four sets would have three events (three given regimens).

1.2.3 Optimization in the FDES-Base Treatment System

All the events in the FDES-based system can be assumed to be either disabled and/or enforced. Controllable events are events that can be disabled,

whereas enforceable events are those events that can be enforced. To optimize FDES is to disable some controllable events and/or enforce some enforceable events. The forward-looking tree was employed for an optimal control online shown in Figure 1.3. After each of the events occurs, the controller will assess the possible consequent state of the system and determine which events are to be disabled and/or enforced.

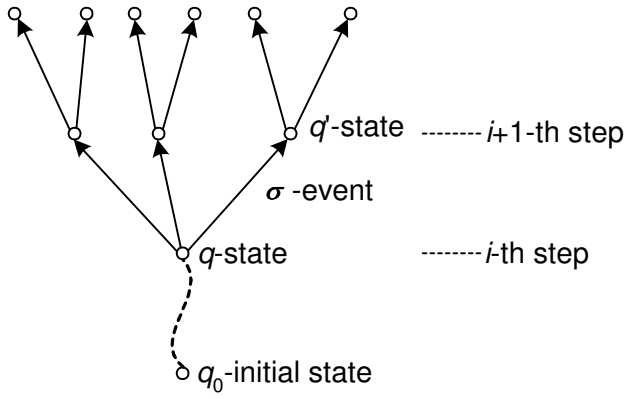


Figure 1.3: For FDES, *q* and *q'* in an example forward-looking tree for optimal control synthesis are fuzzy states represented by a vector containing the fuzzy state vectors.

Each node in the forward-looking tree for an FDES represents a fuzzy state. The fuzzy state (node) *q* in Figure 1.3 is a vector containing the fuzzy state vectors: $q = [q_1, q_2, ..., q_N]$. Occurrence of an event leads to movement of a fuzzy state. In Figure 1.3 the occurrence of the event σ causes the movement of the

fuzzy state *q* to a new fuzzy state: $q' = [q_1', q_2', ..., q_N']$, where q_i' is obtained by either $q_i' = q_i \circ \sigma$, $\sigma \in G_i$ or $q_i' = q_i$, $\sigma \notin G_i$.

Let *h* be a node in the forward-looking tree and designed as $h = (q, s)$, where *q* is the corresponding fuzzy state (vector of the fuzzy state vectors) and *s* is the sequence of events leading to the expected node from the initial fuzzy state q_0. Furthermore, each node in the forward-looking tree can be calculated for the performance index, cost measure or other specified measurements. The effectiveness measure and cost measure are two common measurements for a branch as defined for its terminal nodes in the forward-looking tree for the FDES in HIV/AIDS treatment system. The effectiveness measure and cost measure for a node $h = (q, s)$ can be expressed as $E(h) = f(q, s) = f([q_1, q_2, ..., q_N], s)$ and $C(h) = g(q, s) = g([q_1, q_2, ..., q_N], s)$, respectively, where *f* and *g* are the functions.

For the HIV/AIDS treatment, the term of optimization used is to maximize the effectiveness of the expected treatment regimens for a given cost of the treatment regimen. Therefore, the optimization problem for characterized state or node h of the forward-looking tree for the HIV/AIDS treatment system can be expressed as

$$\max_{Tr(h)} E(h), \text{ such that } C(h) < L \tag{1.1}$$

where *Tr*(*h*) is the forward-looking tree beginning at node *h*, *L* is a given number of the limited cost, and $C(h) < L$ is the constraint of cost persistently maintaining during the optimization execution.

The level of the complex optimization depends upon the length of the forward-looking tree *Tr*(*h*). A node which is several levels apart from the beginning would have more complexity of optimization. Usually for the HIV/AIDS treatment, one or two levels of the optimization which corresponds to one or two rounds of the treatment are desired. A treatment is considered to be the same round of the treatment if the drug or regimen is used without changing.

1.3 Issues on Representations of Physicians' Expertise in FDES-Based HIV/AIDS Treatment Regimen Selection System

As the compilation of many complicated factors, the FDES-based system can be considered to be the complex treatment system. All these factors were constructed based on the specialists' knowledge and experience as well as clinical literatures. Extracting knowledge and experience from specialist domains is a significant task. It is not easy for the specialists to express their opinions quantitatively. Accurate conversion of the expertise domains into a useable form for the system is a technical difficulty that the system developer encounters. In the FDES-based framework, point estimates (crisp numbers) and type-1 fuzzy sets are the FDES-useable forms describing subjectivity and imprecision in specialists' knowledge and experience.

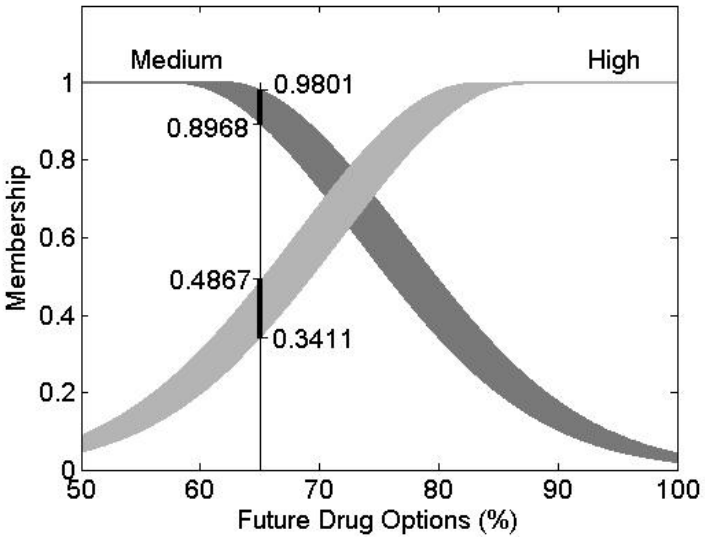
In the knowledge acquisition for regimen's characteristics, the HIV/AIDS specialist was asked to estimate and give a percentage of clinical parameters for all regimens used in the medical treatment, for example, such as those shown in Table 1.1. The percentages represented the specialist's best point estimates of

the regimen's anticipated clinical parameters. As seen, these numbers were uncertainties, as no such true values existed in the literature. If the specialist was allowed to use interval numbers (e.g., potency is [80%, 90%] for regimen 2), fuzzy numbers (e.g., potency is about 85%) or fuzzy sets, it would be a more realistic representation of the specialist's knowledge.

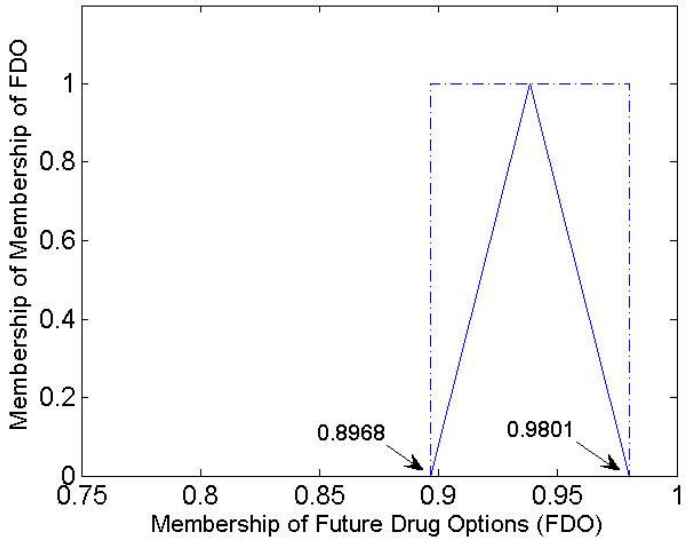
Since the absolute truth in HIV/AIDS treatment is mysterious and unknown, inequality respective to individual specialists' opinions should be potentially mentioned. This inequality is an issue when specialists in the team have different opinions. For example, specialist A's opinion on the potency of regimen 2 is 82%, whereas specialist B's opinion is 88%. To meet the requirements for the FDES-based system, the compromising consensus must be conducted. The specialists' agreement would be 85% potency of regimen 2. If they insist on their own numbers, the potency consensus would not be achieved. The FDES-based system could not work under this situation.

Furthermore, the interval value [80%, 90%] or the fuzzy number, around 85%, would represent remarkably the diverse opinions. The issue is similar when the HIV/AIDS specialists define the fuzzy sets for the four clinical parameters. For instance, the fuzzy sets in Figure 1.2 represented the consensus of the specialists' opinions describing the future drug options parameter characteristic of the system changing from initial state to "High" or "Medium" state. Failing to reach consensus and insisting on using different fuzzy sets cannot be handled by the current FDES-based system. The issue may exist in the specialist domains dealing with equal

respective expertise among differences. Without doubt, such a problem of obtaining consensuses occurs in the biomedical field. The second issue seems to be a conflict of consensus achievement that would cause the first order fuzzy sets (i.e., type-1 fuzzy set) insufficient representation of the specialists' knowledge.



(a)



(b)

Figure 1.4: Type-2 fuzzy sets in EFDES system as defined, for example, for future drug options: (a) the primary memberships with footprints of uncertainty of the type-2 fuzzy sets “Medium” and “High”, (b) the secondary membership function for

the fuzzy set “Medium” at future drug options of 65% is triangular (solid line) or rectangular (dotted line) as assumed the fuzzy sets is an interval type-2 fuzzy set.

To handle this situation and accomplish the knowledge acquisition of such specialists’ distinct opinions, the higher order fuzzy sets need to be utilized. Type-2 fuzzy set, one order higher than type-1 fuzzy set, can be described by a membership function of memberships over an entire universe of discourse which is called a secondary membership function. The membership function is now called a primary membership function. Type-2 fuzzy set [6,11,30,53,54,67,68] contains an infinite number of type-1 fuzzy sets (i.e., the primary membership functions) creating a footprint of uncertainty (FOU) [6,52] as shown in Figure 1.4(a) that would characterize diversities and uncertainties of the specialists’ knowledge. The footprint of uncertainty can be described by an upper primary membership function and a lower primary membership function which bind countless type-1 membership functions. A second membership function shown in Figure 1.4(b) can be defined over the primary membership grades at a particular value of the universe of discourse (i.e., at 65% future drug options). A type-2 fuzzy set which has equal secondary memberships is named an interval type-2 fuzzy set.

Type-3 fuzzy set [6] is one order higher than type-2 fuzzy set. A third membership function can be defined over the second memberships in the same manner as defining the secondary membership function over the primary

memberships. The higher the order of the fuzzy set, the more complicated the system. At present, the type-3 or higher orders fuzzy sets have not been implemented in practice.

Alternatively, if type-1 fuzzy set could be derived as a 2-D function: y=f(x)), then type-2 fuzzy set would be derived as a 3-D function: z=f(x,y). The one dimension beyond type-1 fuzzy set for type-2 fuzzy set could be supplemented for capturing the specialists' different opinions. Therefore, type-2 fuzzy set is the simplest among higher order fuzzy sets and would be effective enough to be applied to such a task. Thus the current FDES-based framework needs to be expanded in order to deal with type-2 fuzzy sets. The theory of the extended FDES (EFDES) is an approach in handling type-2 fuzzy sets to capture such specialists' knowledge. The development of the new HIV/AIDS treatment regimen system under the implementation of the EFDES theory is significantly concerned as a new aspect of the decision-supporting system. The EFDES theory utilizes type-2 fuzzy sets to parameters or factors considered with imprecision and uncertainties applying not only for medical fields but others as well.

As is known, the update of the HIV/AIDS treatment guidelines several times per year would reflect the treatment complexity. Approval of new antiretroviral regimens for the treatment, for example, would cause such updates. For the new approved regimens, the knowledge acquisition process will be required for the decision-supporting system. At this point, the system with the capacity of self-learning will be preferable. As mentioned above, another issue on performance of

the new system under the EFDES theory would arise. The skepticism issue is that under the EFDES-based framework, whether the HIV/AIDS treatment regimen selection system constructed with or without the capability of self-learning could handle the diversities and uncertainties of specialists' knowledge and could provide as such a good performance.

The way to disclose or key this skepticism problem is to construct such an EFDES-base decision-supporting system with or without self-learning function using the patients' medical information and specialist domains implemented in the FDES-based system as the basis of system data; the performance of the EFDES-based system can be verified.

1.4 Extended Fuzzy Discrete Event System (EFDES) Theory [24,33]

The EFDES theory can be modeled by a fuzzy automaton (*G*) which is mathematically expressed as $G = (Q,\ \Sigma,\ \delta,\ \mathbf{q}_0)$, where *Q* is the set of fuzzy state vectors. The *k*-th fuzzy state vector $\mathbf{q}_k$ ($\mathbf{q}_k \in Q$) is mathematically represented as $\mathbf{q}_k = [{}^kV_1 \quad {}^kV_2 \quad \cdots \quad {}^kV_N]$, where *N* is the total number of fuzzy states and ${}^kV_i$ is a fuzzy set with the universe of discourse [0, 100%]. Fuzzy state $\mathbf{q}_0$ is an initial fuzzy state vector. Σ is the set of fuzzy events. A fuzzy event $\boldsymbol{\sigma}_j$, ($\boldsymbol{\sigma}_j \in \Sigma$), is a fuzzy state transition matrix. The matrix is in the form of

$$\sigma_j = \begin{bmatrix} {}^jA_{11} & \cdots & {}^jA_{1N} \\ \vdots & \ddots & \vdots \\ {}^jA_{N1} & \cdots & {}^jA_{NN} \end{bmatrix}, 1 \le j \le M\ , \tag{1.2}$$

where ${}^{j}A_{mn}$, $1 \le m,n \le N$, is a fuzzy set characterizing the transition from one state (*m*-state), to another state (*n*-state) when the *j*-th event occurs. The universe of discourse of ${}^{j}A_{mn}$ ranges from 0 to 100% on the x-axis and the corresponding membership ranges from 0 to 1 on the y-axis. *M* is the total number of possible events.

δ is a transition mapping that describes how to obtain a new fuzzy state vector from a current fuzzy state vector and a fuzzy event transition matrix. It can be mathematically represented as $\delta : Q \circ \Sigma \to Q$, where $\circ$ is a fuzzy logic operation [1,5,28,69,70] (e.g., max-product() and max-min() etc). Thus, the new fuzzy state vector is determined from $\mathbf{q}_{k+1} = \mathbf{q}_k \circ \boldsymbol{\sigma}_j$. Since the max-product operation is desirable for the EFDES-based system, the equation becomes $\mathbf{q}_{k+1} = \max(\mathbf{q}_k \times \boldsymbol{\sigma}_j)$ in which ${}^{k+1}V_n$ is determined by

$$\begin{aligned} {}^{k+1}V_n &= \max_{1 \le i \le N}\left({}^{k}V_i \times {}^{j}A_{in}\right) \\ &= \max\left({}^{k}V_1 \times {}^{j}A_{1n}, {}^{k}V_2 \times {}^{j}A_{2n}, \ldots, {}^{k}V_N \times {}^{j}A_{Nn}\right), \end{aligned} \tag{1.3}$$

where $\times$ refers to product() operation.

Like the FDES theory used in the HIV/AIDS treatment regimen selection, the EFDES theory will be implemented in the Fuzzy Finite State Model named Extended Fuzzy Finite State Models. Similar to the FDES-based system, the fuzzy state model of the EFDES-based system consists of four fuzzy automata, each of which corresponds to one of the four parameters, i.e., potency, adherence,

adverse events, and future drug options. The fuzzy states of the automata are defined as follows: the fuzzy automaton for potency has three states: initial, medium, and high; the fuzzy automaton for adherence has four states: initial, challenging, moderate, and easy; the fuzzy automaton for adverse events has four states: initial, very low, low, and medium; the fuzzy automaton for future drug options has three states: initial, medium, and high. The interpretation of each state, except initial state, should be associated with the corresponding parameters of regimens. For example, the “high” state in the fuzzy automaton for potency means the anticipated high potency of the regimen. A fuzzy event occurs when a treatment regimen is prescribed for a patient. This prescription leads to a transition of a fuzzy state vector from the current fuzzy state to the next fuzzy state. A detailed computational example of the fuzzy automata will be discussed later in the next chapter.

1.5 Adaption of EFDES Theory into FDES-Based HIV/AIDS Treatment Regimen Selection System

As in the previous section, the potential issues could have faced the current FDES-based HIV/AIDS treatment regimen selection system in which the specialists’ domains of knowledge were captured in the form of the consensuses (i.e., estimated points for the clinical parameter characteristic of the treatment regimens and type-1 fuzzy sets for the treatment regimen’s clinical parameter definitions) that may not be achieved as usual. The FDES-based system was discussed in the literature by [22], which provided the great details in the

implementation of the theory of fuzzy discrete event system to the HIV/AIDS treatment regimen selection system. Conducting the clinical parameters (e.g., regimen's potency) in the useable forms for the system was demonstrated in the paper along with the forward-looking tree as an optimal control online approach discussed by [22] as well. The regimen effectiveness neglecting the treatment cost was the considered factor used for the optimization utilized with the genetic algorithm. The FDES-based system employed the 35 retrospective patients' medical information in the evaluation of the performance of the system.

In order to overcome such possible conflicts, the FDES-based system needs to be modified and generalized into the EFDES-based system. [24,33] demonstrated how to extend the FDES theory to the EFDES theory. The EFDES theory uses the fuzzy automaton as a model. Unlike the FDES, the elements in fuzzy state vectors could be crisp numbers in [0, 1], interval numbers, or fuzzy sets in general in which the prior two could be treated as special cases. [24,33] provided illustrative examples on how to obtain the fuzzy event transition matrices when applying the EFDES theory to the HIV/AIDS treatment regimen selection system. As in the examples in the next chapter (i.e., three different situations), two cases utilized the type-2 fuzzy sets with either crisp numbers or fuzzy sets to capture diversities and uncertainties of the specialists' knowledge and experience in determining the fuzzy event transition matrices.

The system capable of self-learning is preferred significantly, as frequent updates of the information, such as the HIV/AIDS treatment in which guidelines

change several times in each year and the new regimens become available, as well. Paper [31] discussed the FDES-based system with self-learning ability that could be achieved by adjusting parameter weights via the Optimizer. In the paper four regimens were involved in learning for the system used in the initial round of the HIV/AIDS treatment regimen selection. The information of the experts' knowledge on those regimens and patients' clinical data used in the FDES-based system would be implemented into the EFDES-based system in order to evaluate the system performance.

1.6 Research Objectives

Representing a consensus of physician experts' domains of knowledge with a useable form by utilizing type-1 fuzzy set in the HIV/AIDS treatment regimen selection system that is less acceptable in term of human sense and has a chance of being unachievable among respective experts' distinct opinions, this dissertation presents the utilization of EFDES theory and type-2 fuzzy set to handle the consensus of the experts' distinct opinions used in the system providing more realistic representation of expert knowledge and as good as the system performance of utilizing type-1 fuzzy set.

CHAPTER 2

EFDES-BASED HIV/AIDS TREATMENT REGIMEN SELECTION SYSTEM

Developing the FDES-based regimen selection system, HIV/AIDS specialists must compromise to reach consensus in terms of the parameter values and the type-1 fuzzy sets (e.g., Table 1.1 and Figure 1.1). If different specialists insist on using different parameter values or different fuzzy sets, then an FDES system cannot be constructed. To accommodate such needs, type-2 fuzzy sets [6, 30] provide a solution. This solution led recently to development of an extended fuzzy discrete event system (EFDES) theory [33]. It is capable of handling a parameter value in the form of type-1 fuzzy set or interval and a type-1 fuzzy set in the form of a type-2 fuzzy set. In this research work, we will employ the EFDES theory to investigate seven distinct scenarios shown in Table 2.1. For the specialist domains, either type-1 fuzzy sets or type-2 fuzzy sets are used to represent the definitions of clinical parameters, whereas crisp numbers, interval numbers, type-1 fuzzy sets and type-2 fuzzy sets are served to represent the parameter characteristics of the regimens.

Table 2.1: Specialist Domains in the FDES and EFDES-Based System

	Fuzzy Set Type for the Clinical Parameter Definitions	Value Type for the Clinical Parameter Characteristics
FDES theory	Type-1 fuzzy sets	Crisp numbers
EFDES theory		
Scenario 1	Type-1 fuzzy sets	Interval numbers
Scenario 2	Type-1 fuzzy sets	Type-1 fuzzy sets
Scenario 3	Type-1 fuzzy sets	Type-2 fuzzy sets
Scenario 4	Type-2 fuzzy sets	Crisp numbers
Scenario 5	Type-2 fuzzy sets	Interval numbers
Scenario 6	Type-2 fuzzy sets	Type-1 fuzzy sets
Scenario 7	Type-2 fuzzy sets	Type-2 fuzzy sets

2.1 EFDES-Based HIV/AIDS Treatment Regimen Selection System

The block diagram of the EFDES-based HIV/AIDS treatment regimen selection system is illustrated in Figure 2.1. Its structure is similar to the FDES-based system as mentioned in the Introduction. The major difference between the EFDES-based system and the FDES-based system is that the EFDES theory is now used to implement the Extended Fuzzy Finite State Models shown in Figure 2.1. Concisely, each block of the EFDES-based system will be explained as follows.

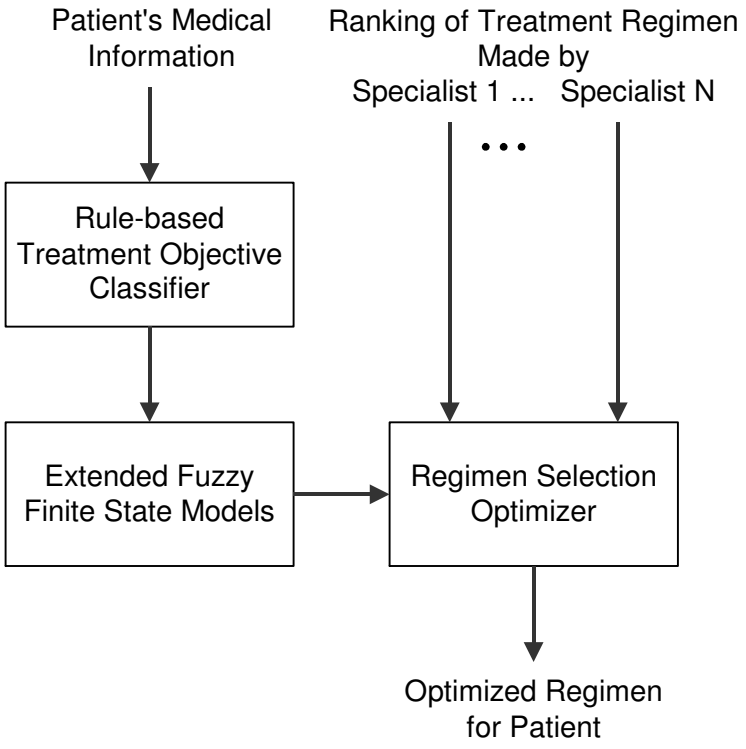


Figure 2.1: Block diagram of the EFDES-based HIV/AIDS treatment regimen selection system

2.1.1 Rule-Based Treatment Objective Classifier

The task of the rule-based classifier is to map a patient to one of the 32 objectives based on his/her medical condition. Each objective is a combination of the four clinical parameters. Potency, adherence, adverse events and future drug options are the clinical parameters which an HIV/AIDS specialist considers when assigning which regimen to prescribe. Each clinical parameter is composed of stated variables: “medium” and “high” for potency, “challenging”, “moderate”, and

Table 2.2: Patient's 32 clinical treatment objectives [22,31]

Objective class no.	Potency	Adherence	Adverse events	Future drug options
1	High	Easy	Medium	High
2	High	Easy	Medium	Medium
3	High	Easy	Low	High
4	High	Easy	Low	Medium
5	High	Easy	Very low	High
6	High	Easy	Very low	Medium
7	High	Moderate	Medium	High
8	High	Moderate	Medium	Medium
9	High	Moderate	Low	High
10	High	Moderate	Low	Medium
11	High	Moderate	Very low	High
12	High	Moderate	Very low	Medium
13	High	Challenging	Medium	High
14	High	Challenging	Medium	Medium
15	High	Challenging	Low	High
16	High	Challenging	Low	Medium
17	High	Challenging	Very low	High
18	High	Challenging	Very low	Medium
19	Medium	Easy	Medium	High
20	Medium	Easy	Medium	Medium
21	Medium	Easy	Low	High
22	Medium	Easy	Low	Medium
23	Medium	Easy	Very low	High
24	Medium	Easy	Very low	Medium
25	Medium	Moderate	Medium	High
26	Medium	Moderate	Low	High
27	Medium	Moderate	Very low	High
28	Medium	Moderate	Very low	Medium
29	Medium	Challenging	Medium	High
30	Medium	Challenging	Low	High
31	Medium	Challenging	Very low	High
32	Medium	Challenging	Very low	Medium

“easy” for adherence, “very low”, “low”, and “medium” for adverse events and “medium” and “high” for future drug options, called a treatment objective. Practically, there are a total of 32 clinical treatment objectives. Four combinations are excluded because of the absurd situation in the treatment. For instance, the second treatment objective is the combination of “high” potency, “easy” adherence, “medium” adverse events and “medium” future drug options. The complete list of the treatment objectives is displayed in Table 2.2. The rules used by the classifier were constructed with the help of the HIV/AIDS specialists as a document according to [22] in which only two specialists were involved.

In the classifier the patient’s CD4+ cell counts and HIV RNA level 56,58] were used to determine the regimen’s expected potency and future drug options needed. The rules for these two clinical parameters applied from [22,29] as follows are:

- **Potency**

If a patient’s CD4+ counts <50 cell/µL, then high expected potency of the regimen is desired.

If a patient’s CD4+ counts from 50 to 200 cell/µL, and a patient’s HIV RNA >100,000 copies/ml, then high expected potency of the regimen is desired.

If a patient’s CD4+ counts from 50 to 200 cell/µL, and a patient’s HIV RNA <100,000 copies/ml, then either high or medium expected potency of the regimen is desired.

If a patient's CD4+ counts > 200 cell/μL, and a patient's HIV RNA ≥100,000 copies/ml, then high expected potency of the regimen is desired.

If a patient's CD4+ counts > 200 cell/μL, and a patient's HIV RNA <100,000 copies/ml, then medium expected potency of the regimen is desired.

- **Future drug options**

If a patient's CD4+ counts ≥ 350 cell/μL, then high expected future drug options of the regimen is desired.

If a patient's CD4+ counts from 200 to 350 cell/μL, and a patient's HIV RNA <100,000 copies/ml, then high expected future drug options of the regimen is desired.

If a patient's otherwise conditions, then medium expected future drug options of the regimen is desired.

In order to classify a patient into which regimen's expected adherence, we need to answer questions about the criteria involving the patient's behavior and medical information. There are 5 questions to be asked: 1) if a patient's age is less than 25 year old, 2) if a patient is homeless, 3) if a patient uses any illegal or narcotic drugs or excessive alcohol, 4) if a patient has a mental illness, and 5) if a patient missed more than one clinic visit in the last year. The number of questions with which the corresponding patient complies is used to determine the adherence characteristic. Following are the rules used as guidelines for the regimen's expected adherence.

- **Adherence**

If a patient complies with two or more questions, then easy expected adherence of the regimen is desired.

If a patient complies with only one question, then either easy or moderate expected adherence of the regimen is desired.

If a patient complies with no questions, then any expected adherence of the regimen characteristic is desired.

- **Adverse events**

One of three treatment characteristics of adverse events (i.e., medium, low and very low) the classifier assigns as the regimen's expected adverse events for a treatment objective deals with a patient's risk of diseases, which include diabetes, hepatitis and cardiovascular disease. The patient with one or both of diabetes and hepatitis diseases will be avoided classifying with regimen's medium expected adverse events.

Table 2.3: Cardiovascular Disease Risk Assessment Scoring

Risk Factor		Risk points	
		Men	Women
Age, years	<34	-1	-9
	35-39	0	-4
	40-44	1	0
	45-49	2	3
	50-54	3	6
	55-59	4	7
	60-64	5	8
	65-69	6	8
	70-74	7	8
Total cholesterol, mg/dL	<160	-3	-2
	160-199	0	0
	200-239	1	1
	240-279	2	2
	≥280	3	3
HDL cholesterol, mg/dL	<35	2	5
	35-44	1	2
	45-49	0	1
	50-59	0	0
	≥60	-2	-3
Systolic blood pressure, mm Hg	<120	0	-3
	120-129	0	0
	130-139	1	1
	140-159	2	2
	≥160	3	3
Diabetes	No	0	0
	Yes	2	4
Smoking	No	0	0
	Yes	2	2

Table 2.4: Risk Estimates for Cardiovascular Disease as Determined Framingham Scoring

Age	Below average risk		average risk		Moderately above average risk		High risk	
years	man	woman	man	woman	man	woman	man	woman
30-34	<1	<4	1	4	2-4	5	>4	>5
35-39	<3	<5	3	5	4-6	6-7	>6	>7
40-44	<4	<6	4	6	5-6	7-8	>6	>8
45-49	<6	<7	6	7	6	8-10	>7	>10
50-54	<6	<9	7	9	8	10-12	>8	>12
55-59	<8	<10	8	10	9	11-15	>9	>15
60-64	<9	<11	9	11	10	12-16	>10	>16
65-69	<10	<12	10	12	11	13-16	>11	>16
70-74	<11	<13	11	13	12	14-16	>12	>16

The risk estimates of cardiovascular disease is derived by using the Framingham risk score [73,74] obtained by assessing the risk points of all risk factors shown in Table 2.3 that the individual associates with the risk of the cardiovascular disease. Then Table 2.4 is used to label the risk of the scores. For example, a 44-year male patient with a Framingham risk score of 4 will be labeled with average risk for the cardiovascular disease. With the risk label, the patient will be classified using the rules as follows:

If a patient is below average risk, then any adverse events of the regimen characteristic is desired.

If a patient is average risk, then either low or very low expected adverse events of the regimen is desired.

If a patient is above average risk, then very low expected adverse events of the regimen is desired.

Finally, all risks of diabetes, hepatitis and cardiovascular disease need to be evaluated to adopt which one has the most impact.

As mentioned above in the rules for an individual's clinical parameters, those rules need to meet clinical rules in order to classify a patient into a treatment objective. The clinical rules are

If potency is high, then adherence is either moderate or challenging

If potency is medium, then adherence is either easy or moderate

If potency is high, then adverse events are either medium or low

If potency is medium, then adverse events are very low

If a patient's adherence complies with at least one issue, then future drug options must be high.

In case of conflicts, potency must be the first priority choice. The second priority is adherence mapping with the easiest adherence level available. The last priority is adverse events mapping with the lowest adverse events level available.

2.1.2 Extended Fuzzy Finite State Models

The fuzzy finite state models for the FDES-based system describe the sequences of the change of states when the corresponding events occur. In the HIV/AIDS treatment, a naïve patient's state will change partially from a pre-treated state (an initial state) to a treated state (a next state) when an event of receiving a particular regimen happens. Correspondingly, the four clinical fuzzy state vectors

(parameters) of the model change to new fuzzy state vectors through fuzzy state transition matrices. The characteristics of the clinical parameters and the definitions of the corresponding state variables (e.g., the vertical line of the characteristic of the future drug options for regimen 2 and the fuzzy set definitions in Figure 1.1) are needed to construct the fuzzy state transition matrix. The new fuzzy state vector is determined by applying a fuzzy logic operation on the current fuzzy state with the fuzzy state transition matrix. This change of fuzzy states can be modeled by a fuzzy automaton. [13,22,25] provide great details.

2.1.3 Regimen Selection Optimizer

In the EFDES-based system, the interesting optimization issue is to maximize the expected HIV/AIDS treatment effectiveness without considering the treatment cost [41]. Therefore, at the nodes of the forward-looking tree, the L could be assumed to be infinity. We merely implemented an effectiveness measure introduced in [22,25] in order to search for regimens that best match those selected by the AIDS specialists for the 32 treatment objectives. The effectiveness measure (*E*) is computed in terms of the weighted average of the state vectors. It can be mathematically expressed by

$$E = def(S_P) \cdot w_P^T + def(S_A) \cdot w_A^T + def(S_E) \cdot w_E^T + def(S_F) \cdot w_F^T, \qquad (2.1)$$

where S_P, S_A, S_E and S_F are the next fuzzy state vectors for potency, adherence, adverse events and future drug options, respectively, whereas *def* () is defuzzification operation [6,56,57,63,64] which generates a crisp number (i.e., the

middle point of the interval) from each of the fuzzy elements (i.e., the intervals) of the fuzzy state vectors and w_P, w_A, w_E and w_F are their corresponding weight vectors. The weight vector for a parameter is the same regardless of regimens.

To demonstrate an example, assume the regimen 2 with the scenario 4 of the specialist domains is prescribed to a patient classified to one of 32 treatment objectives saying “high” potency, “moderate” adherence, “medium” adverse events, and “high” future drug options. Let the fuzzified next fuzzy state vectors for potency, adherence, adverse events, and future drug options respectively be

S_P=[Z [0.3246 0.5460] [0.9802 1.000]],

S_A=[Z [0.0889 0.1977] [0.4578 0.7066] [0.9802 1.000]],

S_E=[Z [0.4867 0.7261] [0.9523 0.9785] [0.7827 0.9559]],

S_F=[Z [0.8968 0.9801] [0.3411 0.4867]].

where Z is the singleton fuzzy number 0. Then the defuzzification of the next fuzzy state vectors can be obtained as

def(S_P)=[0 0.4353 0.9901],

def(S_A)=[0 0.1433 0.5822 0.9901],

def(S_E)=[0 0.6064 0.9654 0.8693],

def(S_F)=[0 0.9384 0.4139].

Furthermore, assume that the weight vectors for “high” potency is w_P=[0 0.2031 0.7969], for “moderate” adherence w_A=[0 0.1484 0.6523 0.1992], for

"medium" adverse events w_E=[0 0.2422 0.3086 0.4492], and for "high" future drug options w_F=[0 0.1836 0.8164]. The effectiveness measure for the regimen 2 with the scenario 4 of the specialist domains applied to the patient can be determined using the equation (2.1).

$$E=[0\ 0.4353\ 0.9901][0\ 0.2031\ 0.7969]^T$$
$$+[0\ 0.1433\ 0.5822\ 0.9901][0\ 0.1484\ 0.6523\ 0.1992]^T$$
$$+[0\ 0.6064\ 0.9654\ 0.8693][0\ 0.2422\ 0.3086\ 0.4492]^T$$
$$+[0\ 0.9384\ 0.4139][0\ 0.1836\ 0.8164]^T$$
$$= 2.8212$$

For each treatment objective, three effectiveness measure values can be computed: E_1 for regimen 1, E_2 for regimen 2 and E_3 for regimen 3. They are used by the models to rank the three regimens. The regimen with the highest value is the first choice regimen and the lowest value is the last choice.

To rank the three regimens, we need to adjust the 10 weight vectors for the four parameters. There are 26 adjustable weights (i.e., $2\times2+3\times3+3\times3+2\times2$) used for computing the effectiveness measures. The goal of the regimen selection optimizer is to search for a set of 26 weights that make the rankings of the three regimens made by the models best match those made by the specialists for the 32 treatment objectives. The 26 weights were arranged for the 32 treatment objectives regarding Table 2.2, as shown in Table 2.5.

Table 2.5: Optimal weight vectors for four parameters for 32 treatment objectives

Treatment Objective No.	Optimal weight vector for four clinical parameters			
	Potency, (w_P)	Adherence, (w_A)	Averse Events, (w_E)	Future Drug Options , (w_F)
1	[0 W1 W2]	[0 W5 W8 W11]	[0 W14 W17 W20]	[0 W23 W24]
2	[0 W1 W2]	[0 W5 W8 W11]	[0 W14 W17 W20]	[0 W25 W26]
3	[0 W1 W2]	[0 W5 W8 W11]	[0 W15 W18 W21]	[0 W23 W24]
4	[0 W1 W2]	[0 W5 W8 W11]	[0 W15 W18 W21]	[0 W25 W26]
5	[0 W1 W2]	[0 W5 W8 W11]	[0 W16 W19 W22]	[0 W23 W24]
6	[0 W1 W2]	[0 W5 W8 W11]	[0 W16 W19 W22]	[0 W25 W26]
7	[0 W1 W2]	[0 W6 W9 W12]	[0 W14 W17 W20]	[0 W23 W24]
8	[0 W1 W2]	[0 W6 W9 W12]	[0 W14 W17 W20]	[0 W25 W26]
9	[0 W1 W2]	[0 W6 W9 W12]	[0 W15 W18 W21]	[0 W23 W24]
10	[0 W1 W2]	[0 W6 W9 W12]	[0 W15 W18 W21]	[0 W25 W26]
11	[0 W1 W2]	[0 W6 W9 W12]	[0 W16 W19 W22]	[0 W23 W24]
12	[0 W1 W2]	[0 W6 W9 W12]	[0 W16 W19 W22]	[0 W25 W26]
13	[0 W1 W2]	[0 W7 W10 W13]	[0 W14 W17 W20]	[0 W23 W24]
14	[0 W1 W2]	[0 W7 W10 W13]	[0 W14 W17 W20]	[0 W25 W26]
15	[0 W1 W2]	[0 W7 W10 W13]	[0 W15 W18 W21]	[0 W23 W24]
16	[0 W1 W2]	[0 W7 W10 W13]	[0 W15 W18 W21]	[0 W25 W26]
17	[0 W1 W2]	[0 W7 W10 W13]	[0 W16 W19 W22]	[0 W23 W24]
18	[0 W1 W2]	[0 W7 W10 W13]	[0 W16 W19 W22]	[0 W25 W26]
19	[0 W3 W4]	[0 W5 W8 W11]	[0 W14 W17 W20]	[0 W23 W24]
20	[0 W3 W4]	[0 W5 W8 W11]	[0 W14 W17 W20]	[0 W25 W26]
21	[0 W3 W4]	[0 W5 W8 W11]	[0 W15 W18 W21]	[0 W23 W24]
22	[0 W3 W4]	[0 W5 W8 W11]	[0 W15 W18 W21]	[0 W25 W26]
23	[0 W3 W4]	[0 W5 W8 W11]	[0 W16 W19 W22]	[0 W23 W24]
24	[0 W3 W4]	[0 W5 W8 W11]	[0 W16 W19 W22]	[0 W25 W26]
25	[0 W3 W4]	[0 W6 W9 W12]	[0 W14 W17 W20]	[0 W23 W24]
26	[0 W3 W4]	[0 W6 W9 W12]	[0 W15 W18 W21]	[0 W23 W24]
27	[0 W3 W4]	[0 W6 W9 W12]	[0 W16 W19 W22]	[0 W23 W24]
28	[0 W3 W4]	[0 W6 W9 W12]	[0 W16 W19 W22]	[0 W25 W26]
29	[0 W3 W4]	[0 W7 W10 W13]	[0 W14 W17 W20]	[0 W23 W24]
30	[0 W3 W4]	[0 W7 W10 W13]	[0 W15 W18 W21]	[0 W23 W24]
31	[0 W3 W4]	[0 W7 W10 W13]	[0 W16 W19 W22]	[0 W23 W24]
32	[0 W3 W4]	[0 W7 W10 W13]	[0 W16 W19 W22]	[0 W25 W26]

A genetic algorithm in MATLAB's Direct Search Toolbox is employed to perform the task. The objective function $f = \alpha_1 M_1 + \alpha_2 M_2 + \alpha_3 M_3$, where M_i (i=1, 2, 3) is how many the first-choice, second-choice and third-choice regimens ranked by the models match those ranked by the two specialists. α_i represents the relative importance and we use α_1=1, α_2=0.01 and α_3=0.001. In clinical practice, the first choice is much more important than the other two choices. To terminate the optimization process when running the genetic algorithm, either the tolerative changing of the objective function value or the number of generations can be conditionally applied. We prefer the latter in which the termination condition is set to 1,600 generations. That is, the optimization process stops after 1,600 generations. *f* represents agreement between the models and the AIDS specialists.

After the 26 optimal weights are obtained, the rankings of the three regimens for the 32 treatment objectives can be made using these weights. As a result, the EFDES models establish a table of regimen choices for the 32 objective classes. Once a patient is classified into an objective, his/her treatment regimen can be found in the table.

2.2 Genetic Algorithm

Genetic algorithm is an optimization algorithm inspired by the process observed in natural selection. Genetic algorithm attempts to duplicate the process and utilize it for solving optimization problems. Genetic algorithm performs random searches through a given set of individuals to find the best one with respect to a

given criteria expressed in terms of an objective function or usually regarded as a fitness function. The individuals with better fitness values will contribute to the next population. From the current population the individuals are randomly selected to be parents in order to produce the children for the next generation. A genetic algorithm will modify a population of individuals from generation to the next generation. This successive process provides population evolvement toward an optimal solution.

Genetic algorithm uses three kinds of rules to create the next generation; selection rules choose the individuals as parents contributing to the population for the next generation. Crossover rules merge two parents to create children for the next generation, and mutation rules make random change to parents to form children.

This research implements the genetic algorithm in MATLAB's Direct Search Toolbox. There are three types of children that the algorithm creates for the next generation: elite children, crossover children, and mutation children.

Elite children are the individuals with the best fitness values in the current generation. These individuals grant privilege to the next generation.

Crossover children are created by combining pairs of parents in the current population. The crossover function selects the gene and its coordinate from one of the two parents to form the child gene at the same position. There are 26 adjustable weights which need to be optimized in this research. Each of them is in the form of a string of 8-bit binary numbers. The connection of these strings

provides a 208-bit-long string that represents a weight vector or an individual. With the crossover fraction of 0.5, the child receives the first half, 104-bit string, from one of two parents and the second half from the other. We use the crossover fraction of 0.75 for weight optimizing in this research.

Mutation children are the children who receive the mutative genes from their parents. To create mutation children, the algorithm provides random change of the parent genes. We use the algorithm default setting that adds a random vector from a Gaussian distribution to the parent vectors.

2.3 Fuzzy Sets for the Representation of the Specialist Domains

2.3.1 Defined Fuzzy Set Types of Four Clinical Parameters

According to [22], the type-1 fuzzy sets defined for the four clinical parameters in the FDES-based treatment regimen system took advantage of semi-Gaussian functions which could provide modest changes of the membership grades. In this research of the EFDES-based treatment regimen system, those defined type-1 fuzzy sets will be employed and regarded as the references for the upper and lower primary membership functions used to define type-2 fuzzy sets with the secondary membership grades.

The interval type-2 fuzzy set is a specific type-2 fuzzy set with a unit secondary membership grade that is the one for the investigation. Generally, the upper and lower primary membership functions are used to describe the type-2 fuzzy set. The area bounded by these two primary membership functions creates a footprint of uncertainty (FOU). Mathematical representations for the boundaries

of the footprint of uncertainties for the four clinical parameters are ordinarily listed in Table 2.6 and theirs corresponding graphical representations of the type-2 fuzzy sets when Δm equals to 2% are shown in Figure 2.2 as well. As Δm equals to zero, the interval type-2 fuzzy sets reduces to the type-1 fuzzy sets.

Table 2.6: Boundary membership Functions of the Foot of Uncertainties of the type-2 fuzzy sets for the Four Clinical Parameters

Clinical Parameters		Boundary Functions of FOU
Potency	High	$\begin{cases} 1, & x > m_{PH},\ m_{PH} = 85 \pm \Delta m \\ e^{-\frac{1}{2}\left(\frac{x-m_{PH}}{10}\right)^2}, & x \le m_{PH},\ m_{PH} = 85 \pm \Delta m \end{cases}$
	Medium	$\begin{cases} e^{-\frac{1}{2}\left(\frac{x-m_{PM}}{10}\right)^2}, & x > m_{PM},\ m_{PM} = 72 \pm \Delta m \\ 1, & x \le m_{PM},\ m_{PM} = 72 \pm \Delta m \end{cases}$
Adherence	Easy	$\begin{cases} 1, & x > m_{AE},\ m_{AE} = 85 \pm \Delta m \\ e^{-\frac{1}{2}\left(\frac{x-m_{AE}}{10}\right)^2}, & x \le m_{AE},\ m_{AE} = 85 \pm \Delta m \end{cases}$
	Moderate	$e^{-\frac{1}{2}\left(\frac{x-75}{\sigma_{AM}}\right)^2},\quad \sigma_{AM} = 10 \pm \Delta m, -\infty < x < \infty$
	Challenging	$\begin{cases} e^{-\frac{1}{2}\left(\frac{x-m_{AC}}{10}\right)^2}, & x > m_{AC},\ m_{AC} = 65 \pm \Delta m \\ 1, & x \le m_{AC},\ m_{AC} = 65 \pm \Delta m \end{cases}$
Adverse Event	Medium	$\begin{cases} 1, & x > m_{EM},\ m_{EM} = 25 \pm \Delta m \\ e^{-\frac{1}{2}\left(\frac{x-m_{EM}}{10}\right)^2}, & x \le m_{EM},\ m_{EM} = 25 \pm \Delta m \end{cases}$
	Low	$e^{-\frac{1}{2}\left(\frac{x-17.5}{\sigma_{VL}}\right)^2},\quad \sigma_{VL} = 10 \pm \Delta m, -\infty < x < \infty$
	Very Low	$\begin{cases} e^{-\frac{1}{2}\left(\frac{x-m_{VV}}{10}\right)^2}, & x > m_{VV},\ m_{VV} = 10 \pm \Delta m \\ 1, & x \le m_{VV},\ m_{VV} = 10 \pm \Delta m \end{cases}$
Future Drug Options	High	$\begin{cases} 1, & x > m_{FH},\ m_{FH} = 85 \pm \Delta m \\ e^{-\frac{1}{2}\left(\frac{x-m_{FH}}{15}\right)^2}, & x \le m_{FH},\ m_{FH} = 85 \pm \Delta m \end{cases}$
	Medium	$\begin{cases} e^{-\frac{1}{2}\left(\frac{x-m_{FM}}{15}\right)^2}, & x > m_{FM},\ m_{FH} = 60 \pm \Delta m \\ 1, & x \le m_{FM},\ m_{FH} = 60 \pm \Delta m \end{cases}$

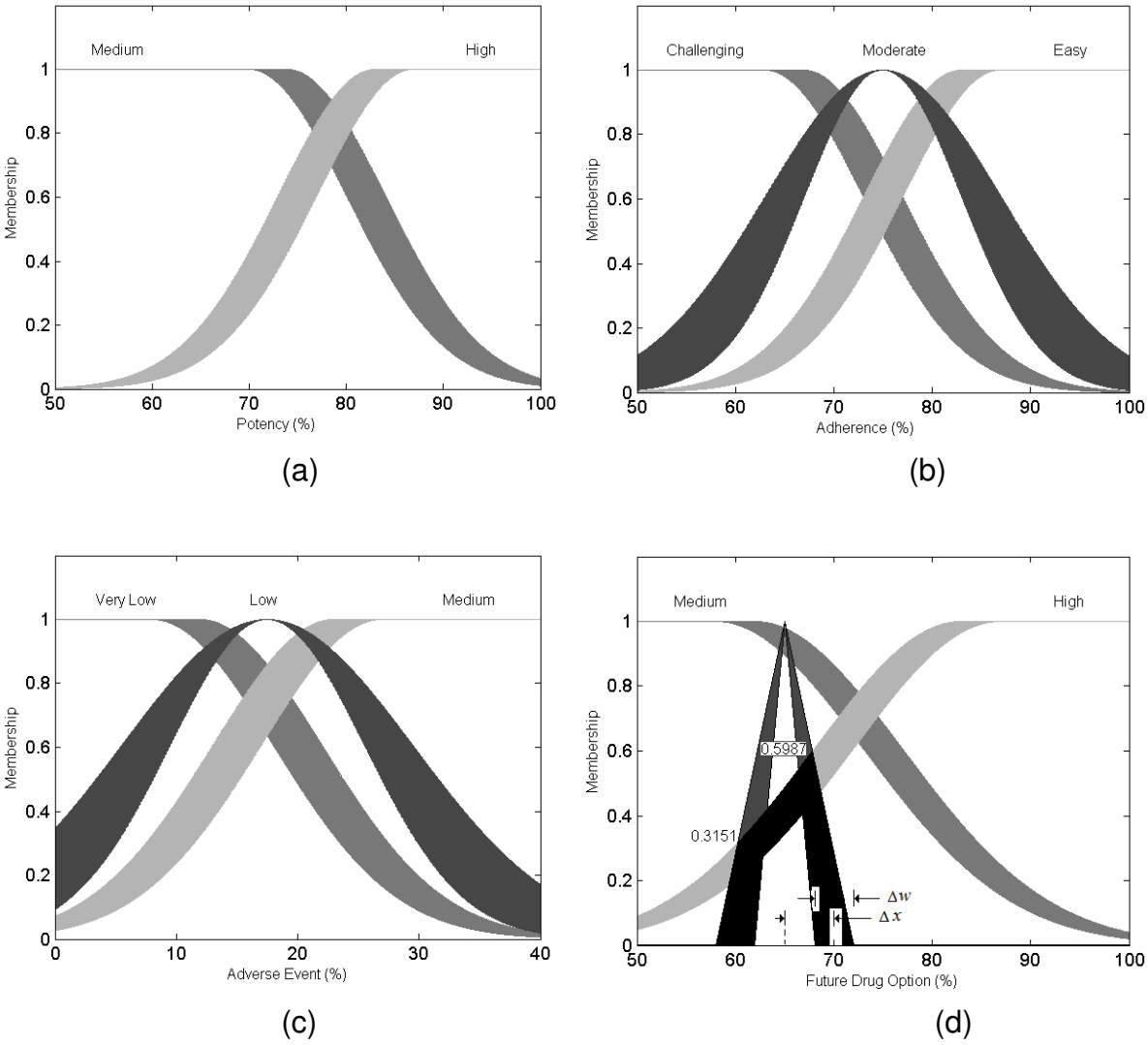
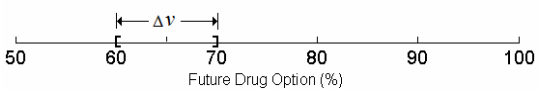


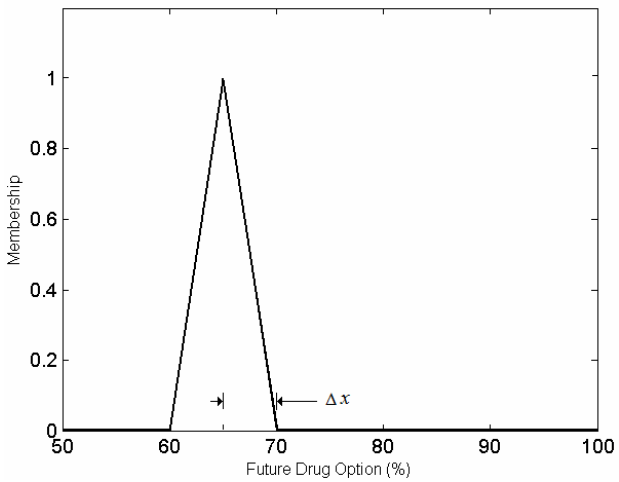
Figure 2.2: Graphical representations of the FOUs of the corresponding type-2 fuzzy sets with Δm being 2% according to Table 2.6. Also, an example demonstration of the fuzzification process shown in (d) in which the black area of FOU fuzzified from the "High" future drug options and the characteristic of future drug options for a particular regimen represented by the interval type-2 fuzzy set and its FOU shown as a shade of the triangular shape with Δx being 5% and Δw being 4%.

2.3.2 Fuzzy Sets for the Parameter Characteristic of the Regimen

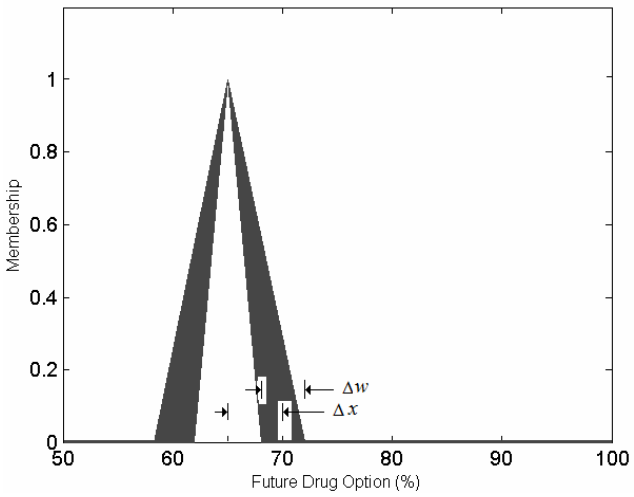
In order to express the specialist domains of the clinical parameter characteristics of the particular regimens, not only including crisp numbers used in the FDES-based system, but also extending to interval numbers, type-1 fuzzy sets and type-2 fuzzy sets that will be employed in the EFDES-based system. The fuzzy sets or the fuzzy numbers are constructed based on the estimated value (crisp) of the clinical characteristics of the regimens as the center points. Note that the interval numbers are not the fuzzy numbers but can be treated as a special case of the fuzzy numbers. These symmetrical shapes of the fuzzy numbers are illustrated in Figure 2.3 with specific variables that we use to assign values hereafter. For example, the interval number with Δv being 10% for the regimen 2 will refer to [80%, 90%] for potency, [80%, 90%] for adherence, [15%, 25%] for adverse events, and [60%, 70%] for the future drug options as illustrated in Figure 2.3 (a). Jointly, Δx and Δw are used to specify FOU of the symmetrical triangular type-2 fuzzy sets. Shown in Figure 2.3 (c) is FOU of future drug options for the regimen 2 with Δx being 5% and Δw being 4% and FOUs of other parameters for the regimen 2 use the same values as well. As Δw equals to zero, the interval type-2 fuzzy sets reduces to the type-1 shown in Figure 2.3 (b).



(a)



(b)



(c)

Figure 2.3: Specific variables used to describe the fuzzy numbers of the clinical characteristics of the regimens. (a) Δv used for the interval numbers (i.e., a special case of the fuzzy numbers), (b) Δx used for symmetrical triangular type-1 fuzzy sets, and (c) Δx and Δw used for FOU of the symmetrical type-2 fuzzy sets.

2.4 Determine the Fuzzy Event Transition Matrices in Different Situations of Specialists' Knowledge Representations

Four clinical parameters need to be models by four fuzzy automata. Seven scenarios need to be investigated in the EFDES-based regimen selection system. As the special case of the EFDES-based system, the case of the FDES-based system (i.e., type-1 fuzzy sets for definitions of parameters and crisp numbers for regimens characteristics) was clearly explained in detailed information [22] that then will be ignored here. In the seven different scenarios, we merely demonstrate that the fuzzy automata for future drug options are the combinations of the clinical parameter definitions in the forms of type-1 fuzzy sets and type-2 and the parameter characteristics in the forms of crisp number, interval number, type-1 fuzzy set and type-2 fuzzy set. Only regimen 2 is used in computing the fuzzy event transition matrices.

2.4.1 Type-1 Fuzzy Sets for the Parameter Definitions and Interval Numbers for the Parameter Characteristics (scenario 1)

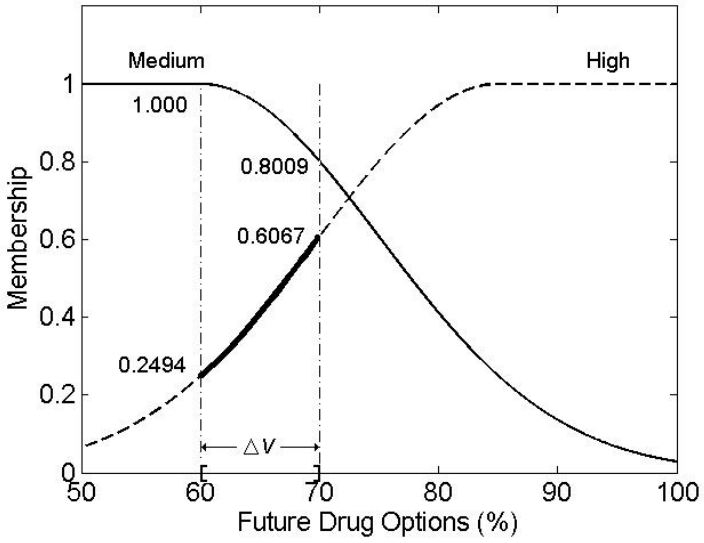


Figure 2.4: Determining the fuzzy event transition matrix for regimen 2 under the scenario 1

In this scenario an interval number instead of a crisp number is considered to describe diverse experts' opinions on the clinical factors. The crisp number can be a consensus of the experts' opinions but not each of them. The distinct opinions with different crisp numbers can be windowed into the interval number in which the opinions have the same weights. The interval number used in the EFDES-based system is illustrated in Figure 2.4. Its center at the value of the parameter characteristic value in Table 1.1 and Δv equals to 10% for regimen 2 which is the one in Figure 2.4. The fuzzy operation named fuzzification is processed to these two clinical parameters. The fuzzy sets for fuzzification for

future drug options are type-1 fuzzy sets. Their mathematical definitions (μ_{FH} for "High" and μ_{FM} for "Medium") are

$$\mu_{FH}(x) = \begin{cases} 1, & x > 85 \\ e^{-\frac{1}{2}\left(\frac{x-85}{15}\right)^2}, & x \le 85 \end{cases}, \qquad \mu_{FM}(x) = \begin{cases} e^{-\frac{1}{2}\left(\frac{x-60}{15}\right)^2}, & x > 60 \\ 1, & x \le 60 \end{cases} \tag{2.2}$$

In the EFDES-based system, the initial state vectors in the fuzzy automata have similar initial conditions. For instance, the fuzzy automaton for future drug options has the initial state vector $q_0 = [1/1 \quad Z \quad Z]$, where 1/1 and Z are singleton fuzzy numbers 1 and 0, respectively. The change of a patient's states occurs when he/she follows a regimen.

The fuzzy state transition matrix for future drug options for the first-round treatment is

$$\sigma_1 = \begin{matrix} \\ Initial \\ Medium \\ High \end{matrix} \begin{matrix} \begin{matrix} Initial & Medium & High \end{matrix} \\ \begin{bmatrix} Z & {}^1F_{12} & {}^1F_{13} \\ Z & Z & Z \\ Z & Z & Z \end{bmatrix} \end{matrix}$$

where ${}^1F_{12}$ and ${}^1F_{13}$ are type-1 fuzzy sets representing the transition of fuzzy states from the Initial state to the Medium state and High state, respectively.

Figure 2.4 will be utilized to obtain ${}^1F_{13}$. The dark and thick curve in the figure is its membership function:

$$\mu_{FHx}(x) = e^{-\frac{1}{2}\left(\frac{x-85}{15}\right)^2}, \quad x \in [60, 70], \tag{2.3}$$

which is the result of applying the standard fuzzy intersection to the fuzzy set "High" and the interval number depicted in Figure 2.4 over the universe of discourse ranging from 50 to 100. According to [33], the range of $\mu_{FHx}(x)$, which is from 0.2494 to 0.6067, will be assigned as the domain of fuzzy set for ${}^1F_{13}$. This is a special case involving only the domain of the fuzzy set (i.e., the interval [0.2494, 0.6067]). This result is because the membership of ${}^1F_{13}$ is calculated or obtained from the secondary membership of $\mu_{FHx}(x)$, which can be regarded as 1 since $\mu_{FHx}(x)$ is a type-1 fuzzy set. So, ${}^1F_{13}$ is the interval [0.2494, 0.6067]. We do the same procedure in order to obtain ${}^1F_{12}$. Finally, the fuzzy state transition matrix is

$$\sigma_1 = \begin{bmatrix} Z & [0.8009, 1] & [0.2494, 0.6067] \\ Z & Z & Z \\ Z & Z & Z \end{bmatrix}.$$

Consequently, we compute the next state by

$$q_1 = q_0 \circ \sigma_1 = [\, Z \quad [0.8009, 1] \quad [0.2494, 0.6067]]$$

The same process can be applied to other regimens as well as to other fuzzy automata: potency, adherence, and adverse events.

The result of interval numbers in the fuzzy state vectors need to be reduced to crisp numbers. We use the middle point of the interval [45] for this purpose.

This result is the case for the next six scenarios. Then the fuzzy state vectors are ready for the Regimen Selection Optimizer.

2.4.2 Type-1 Fuzzy Sets for the Parameter Definitions and Type-1 Fuzzy Sets for the Parameter Characteristics (Scenario 2)

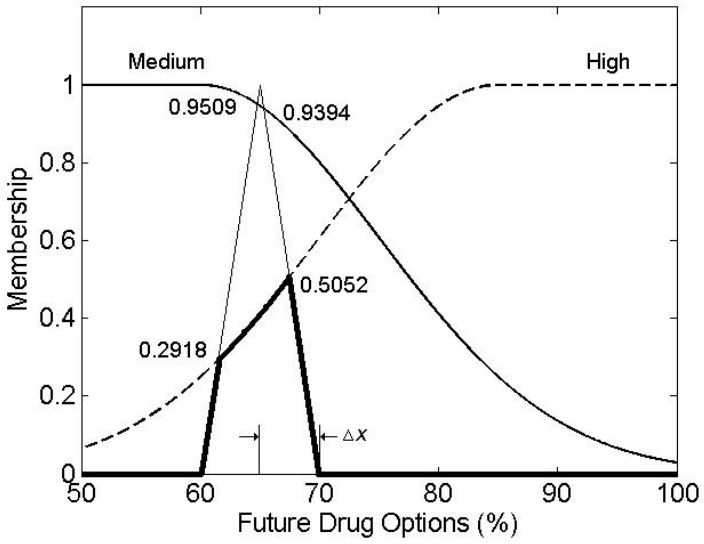


Figure 2.5: Determining the fuzzy event transition matrix for regimen 2 under the scenario 2

A fuzzy number instead of a crisp number used in FDES-based system is employed to describe diverse experts' opinions on the clinical factors. The fuzzy number in this scenario for the EFDES-based system is a symmetrical triangular type-1 fuzzy set as illustrated in Figure 2.5. Its center is the value of the parameter characteristic value in Table 1.1 and Δx equals to 5% for regimen 2 that is the one in Figure 2.5. The fuzzy sets for fuzzification for future drug options are type-1 fuzzy sets, and their mathematical definitions are the same shown in scenario 1.

Initial state vector $q_0 = [1/1 \quad Z \quad Z]$ and the fuzzy state transition matrix are the same for the first-round treatment.

$$\sigma_1 = \begin{matrix} \\ Initial \\ Medium \\ High \end{matrix} \begin{matrix} \begin{matrix} Initial & Medium & High \end{matrix} \\ \begin{bmatrix} Z & {}^1F_{12} & {}^1F_{13} \\ Z & Z & Z \\ Z & Z & Z \end{bmatrix} \end{matrix}$$

Figure 2.5 will be utilized to obtain ${}^1F_{13}$. The dark and thick curve in the figure is its membership function:

$$\mu_{FHx}(x) = \begin{cases} 0.2x - 12, & x \in [60, 61.459] \\ e^{-\frac{1}{2}\left(\frac{x-85}{15}\right)^2}, & x \in [61.459, 67.474] \\ 14 - 0.2x, & x \in [67.474, 70] \\ 0, & elsewhere \end{cases}, \tag{2.4}$$

which is the result of applying the standard fuzzy intersection (i.e., min()) to the fuzzy set “High” and the fuzzy number depicted in Figure 2.4 over the universe of discourse ranging from 50 to 100. According to [33], the range of $\mu_{FHx}(x)$, which is from 0 to 0.5052, will be assigned as the domain of fuzzy set for ${}^1F_{13}$. This domain is a special case involving only the domain of the fuzzy set (i.e., the interval [0, 0.5052]). This result is because the membership of ${}^1F_{13}$ is calculated or obtained from the secondary membership of $\mu_{FHx}(x)$, which can be regarded as 1, since $\mu_{FHx}(x)$ is a type-1 fuzzy set. Therefore, ${}^1F_{13}$ is the interval [0, 0.5052]. We use the same procedure in order to obtain ${}^1F_{12}$. Finally, the fuzzy state transition matrix is

$$\sigma_1 = \begin{bmatrix} Z & [0, 0.9509] & [0, 0.5052] \\ Z & Z & Z \\ Z & Z & Z \end{bmatrix}.$$

Consequently, we compute the next state by

$$q_1 = q_0 \circ \sigma_1 = [\, Z \quad [0, 0.9509] \quad [0, 0.5052]]$$

2.4.3 Type-1 Fuzzy Sets for the Parameter Definitions and Type-2 Fuzzy Sets for the Parameter Characteristics (Scenario 3)

The symmetrical triangular type-1 fuzzy set in the scenario is not adequate to capture the diverse experts' opinions if they have their own triangular type-1 fuzzy sets on clinical factors. The conflict made by different experts can be managed by employing a type-2 fuzzy set with equal second membership grades (i.e., interval type-2). The type-2 fuzzy set can be thought of as blurring the triangular type-1 fuzzy set in the scenario 2, and it creates an FOU. The FOUs shown in Figure 2.6 for future drug options are bounded by the lower and upper primary membership functions whose mathematical expressions are equation (2.5) and equation (2.6), with Δv and Δw being 5% and 2%, respectively, as

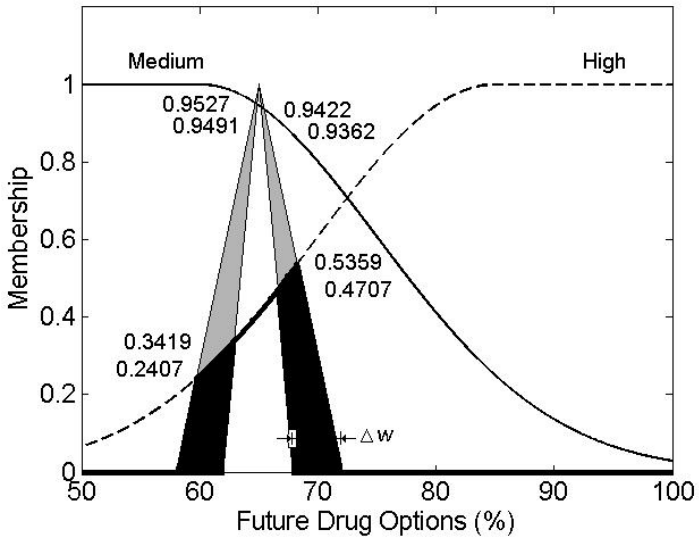


Figure 2.6: Determining the fuzzy event transition matrix for regimen 2

under the scenario 3

$$\mu_{\overline{Tri}}(x)=\begin{cases}1+\dfrac{x-65}{\Delta v+0.5\Delta w}, & 65-\Delta v-0.5\Delta w\le x<65\\ 1-\dfrac{x-65}{\Delta v+0.5\Delta w}, & 65\le x<65+\Delta v+0.5\Delta w\\ 0, & elsewhere\end{cases} \tag{2.5}$$

$$\mu_{\underline{Tri}}(x)=\begin{cases}1+\dfrac{x-65}{\Delta v-0.5\Delta w}, & 65-\Delta v+0.5\Delta w\le x<65\\ 1-\dfrac{x-65}{\Delta v-0.5\Delta w}, & 65\le x<65+\Delta v-0.5\Delta w\\ 0, & elsewhere\end{cases} \tag{2.6}$$

where $\mu_{\overline{Tri}}(x)$ and $\mu_{\underline{Tri}}(x)$ are the respective upper and lower primary membership functions for the type-2 fuzzy set used to describe the diverse experts' opinions on the clinical parameter characteristics.

In this scenario, the experts agree upon the type-1 fuzzy sets of the clinical parameter definitions. To obtain ${}^1F_{12}$ and ${}^1F_{13}$, we have to process the fuzzy operation of the symmetrical triangular type-2 fuzzy set and the type-1 fuzzy sets for "Medium" and "High", respectively. Applying the fuzzy intersection on the type-2 fuzzy set and the type-1 fuzzy set for "High", it results in an FOU which is the deep dark region shown in Figure 2.6. The FOU is bounded by the upper primary membership function in equation (2.7) and the lower primary membership function in equation (2.8) described below:

$$y_{\overline{FH}}(x) = \begin{cases} 1 + \dfrac{x-65}{7}, & x \in [58, 59.685] \\ e^{-\frac{1}{2}\left(\frac{x-85}{15}\right)^2}, & x \in [59.685, 68.248] \\ 1 - \dfrac{x-65}{7}, & x \in [68.248, 72] \\ 0, & elsewhere \end{cases} \tag{2.7}$$

$$y_{\underline{FH}}(x) = \begin{cases} 1 + \dfrac{x-65}{3}, & x \in [62, 63.026] \\ e^{-\frac{1}{2}\left(\frac{x-85}{15}\right)^2}, & x \in [63.026, 66.588] \\ 1 - \dfrac{x-65}{3}, & x \in [66.588, 68] \\ 0, & elsewhere \end{cases} \tag{2.8}$$

where $y_{\overline{FH}}$ and $y_{\underline{FH}}$ are the respective upper and lower primary membership functions of "High" for future drug options of regimen 2.

Unlike the first two scenarios, the range of the primary membership grades of the type-2 fuzzy set (the dark region in Figure 2.6) assigned for the domain of fuzzy set for ${}^1F_{13}$, as well as the membership function, can be determined by using the height type-reducer method [6,30]. The membership function for the reduced type-1 fuzzy set $(\psi(y))$ can be represented by

$$\psi(y) = \sup_x \varphi(x, y), \tag{2.9}$$

where *y* is the primary membership grade and φ is the secondary membership function of the type-2 fuzzy set, the result of applying a fuzzy intersection on two fuzzy sets. The $\sup_x()$ operation gives the highest grades of $\varphi(x, y)$ for *x* in the universe of discourse.

Applying equation (2.9) to the type-2 fuzzy set (the dark region for "High" in Figure 2.6) over the universe of discourse for *x* from 50 to 100 will result in the value of the primary grade changing from 0 to 0.5359 and the corresponding membership grade equal to 1. Therefore, ${}^1F_{13}$ can be represented by the interval [0, 0.5359]. We employ the same procedure for "Medium" and yield its associated interval [0, 0.9527] for ${}^1F_{12}$.

Hence, the fuzzy state transition matrix is represented as

$$\sigma_1 = \begin{bmatrix} Z & [0, 0.9527] & [0, 0.5359] \\ Z & Z & Z \\ Z & Z & Z \end{bmatrix}.$$

The next state vector can be determined by

$$q_1 = q_0 \circ \sigma_1 = \begin{bmatrix} Z & [0, 0.9527] & [0, 0.5359] \end{bmatrix}.$$

2.4.4 Type-2 Fuzzy Sets for the Parameter Definitions and Crisp Numbers for the Parameter Characteristics (Scenario 4)

The experts are allowed to define individually the state using different type-1 fuzzy sets. The diverse definitions made by different experts can be captured by a type-2 fuzzy set with equal second membership grades. The type-2 fuzzy set can be thought of blurring the type-1 fuzzy set in the scenario 1, and it creates an FOU. The FOUs of “High” and “Medium” shown in Figure 2.7 for future drug options are bounded by the lower and upper primary membership functions whose mathematical expressions are equation (2.10) and equation (2.11) with Δm being 2%.

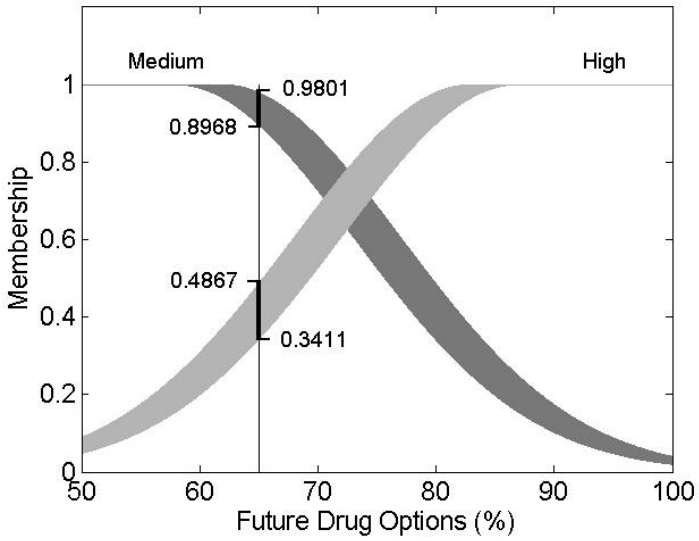


Figure 2.7: Determining the fuzzy event transition matrix for regimen 2 under the scenario 4

$$\mu_{\overline{FH}}(x)=\begin{cases}1, & x>m_{FH},\ m_{FH}=85-\Delta m\\ e^{-\frac{1}{2}\left(\frac{x-m_{FH}}{15}\right)^2}, & x\le m_{FH},\ m_{FH}=85-\Delta m\end{cases}$$
$$\mu_{\underline{FH}}(x)=\begin{cases}1, & x>m_{FH},\ m_{FH}=85+\Delta m\\ e^{-\frac{1}{2}\left(\frac{x-m_{FH}}{15}\right)^2}, & x\le m_{FH},\ m_{FH}=85+\Delta m\end{cases} \quad (2.10)$$

$$\mu_{\overline{FM}}(x)=\begin{cases}e^{-\frac{1}{2}\left(\frac{x-m_{FM}}{15}\right)^2}, & x>m_{FM},\ m_{FM}=60+\Delta m\\ 1, & x\le m_{FM},\ m_{FM}=60+\Delta m\end{cases}$$
$$\mu_{\underline{FM}}(x)=\begin{cases}e^{-\frac{1}{2}\left(\frac{x-m_{FM}}{15}\right)^2}, & x>m_{FM},\ m_{FM}=60-\Delta m\\ 1, & x\le m_{FM},\ m_{FM}=60-\Delta m\end{cases} \quad (2.11)$$

where $\mu_{\overline{FH}}(x)$ and $\mu_{\underline{FH}}(x)$ are the respective upper and lower primary membership functions for “High” and $\mu_{\overline{FM}}(x)$ and $\mu_{\underline{FM}}(x)$ are the upper and lower primary membership functions for “Medium”, respectively.

In this scenario, the experts agree upon the crisp numbers of the clinical parameters. To obtain ${}^1F_{12}$ and ${}^1F_{13}$, we draw a vertical line at a parameter value (i.e., 65% future drug options in Figure 2.7). The intersections of the line and the lower and upper primary membership functions of the two type-2 fuzzy sets create two intervals: one for “Medium” and the other for “High”. These intervals are the ranges of the primary membership grades for “Medium” and “High” and so will be used as the domains of fuzzy sets for ${}^1F_{12}$ and ${}^1F_{13}$, respectively. The membership grades for ${}^1F_{12}$ and ${}^1F_{13}$ over those range equal to 1. We normally represent this kind of a type-1 fuzzy set (i.e., an interval type-1 fuzzy set) by its domain of the fuzzy set. Hence, in Figure 2.7 the interval [0.8968, 0.9801] for “Medium” is for ${}^1F_{12}$ and the interval [0.3411, 0.4867] for “High” is for ${}^1F_{13}$. We therefore obtain the fuzzy state transition matrix,

$$\sigma_1 = \begin{bmatrix} Z & [0.8968, 0.9801] & [0.3411, 0.4867] \\ Z & Z & Z \\ Z & Z & Z \end{bmatrix}.$$

Consequently, the next state vector is

$$q_1 = q_0 \circ \sigma_1 = [\, Z \quad [0.8968, 0.9801] \quad [0.3411, 0.4867]].$$

2.4.5 Type-2 Fuzzy Sets for the Parameter Definitions and Interval Numbers for the Parameter Characteristics (Scenario 5)

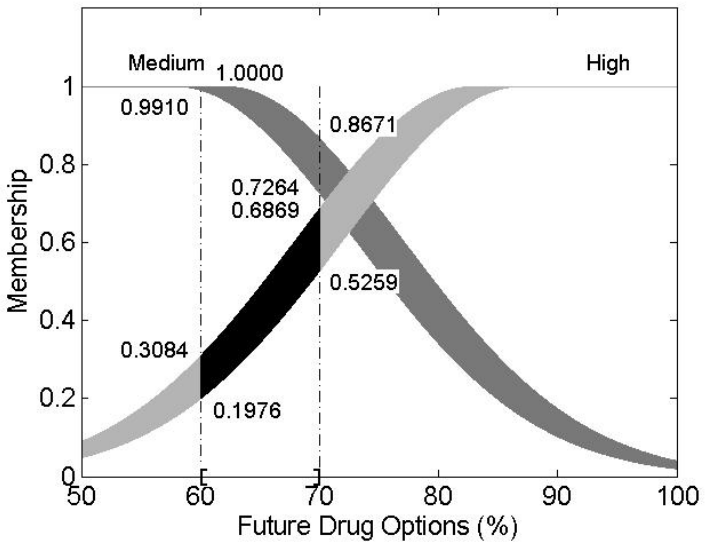


Figure 2.8: Determining the fuzzy event transition matrix for regimen 2 under the scenario 5

In this scenario, the type-2 fuzzy sets employed in scenario 4 are preferred to capture the distinct experts' opinions on the clinical parameter definitions for future drug options as shown in Figure 2.7. The interval number employed in scenario 1 is used to represent the range largely over the deviation of experts' opinions on the clinical factors for a regimen. This number is the combination of the scenario 1 and the scenario 4 as illustrated in Figure 2.8. The interval type-2 fuzzy set is described by the FOU with unity of the secondary membership grade. The FOUs of "High" and "Medium" for future drug options are bounded by the lower and upper primary membership functions whose mathematical expressions

are the same equation (2.10) and equation (2.11), with Δm being 2%. The interval number of which Δv equals 10% for regimen 2 shown in Figure 2.8 has a center at the value of the parameter characteristic value in Table 1.1.

Applying the fuzzy intersection on the interval number and the type-2 fuzzy set for "High", its result is an FOU which is the deep dark region shown in Figure 2.8. The foot of uncertainty is bounded by the upper primary membership function in equation (2.12) and the lower primary membership function in equation (2.13) given below:

$$\mu_{\overline{FH}}(x) = \begin{cases} [0.1976, 0.3084], & x = 60 \\ e^{-\frac{1}{2}\left(\frac{x-m_{FH}}{15}\right)^2}, & 60 < x < 70,\ m_{FH} = 83 \\ [0.5259, 0.6863], & x = 70 \end{cases} \tag{2.12}$$

$$\mu_{\underline{FH}}(x) = e^{-\frac{1}{2}\left(\frac{x-m_{FH}}{15}\right)^2}, \quad 60 \le x \le 70,\ m_{FH} = 87 \tag{2.13}$$

where $\mu_{\overline{FH}}(x)$ and $\mu_{\underline{FH}}(x)$ are the respective upper and lower primary membership functions for "High", and $\mu_{\overline{FM}}(x)$ and $\mu_{\underline{FM}}(x)$ are the upper and lower primary membership functions for "Medium", respectively.

Applying equation (2.9) to the type-2 fuzzy set with the FOU (the dark region for "High" in Figure 2.8) over the universe of discourse for *x* from 50 to 100 will result in the value of the primary grade changing from 0.1976 to 0.6863 and the corresponding membership grade equals 1. Therefore, ${}^1F_{13}$ can be represented

by the interval [0.1976, 0.6863]. We construct the same procedure for the "Medium" and yield its associated interval [0.7264, 1] for ${}^{1}F_{12}$.

Hence, the fuzzy state transition matrix is represented as

$$\sigma_1 = \begin{bmatrix} Z & [0.1976, 0.6863] & [0.7264, 1] \\ Z & Z & Z \\ Z & Z & Z \end{bmatrix}.$$

The next state vector can be determined by

$$q_1 = q_0 \circ \sigma_1 = \begin{bmatrix} Z & [0.1976, 0.6863] & [0.7264, 1] \end{bmatrix}.$$

2.4.6 Type-2 Fuzzy Sets for the Parameter Definitions and Type-1 Fuzzy Sets for the Parameter Characteristics (Scenario 6)

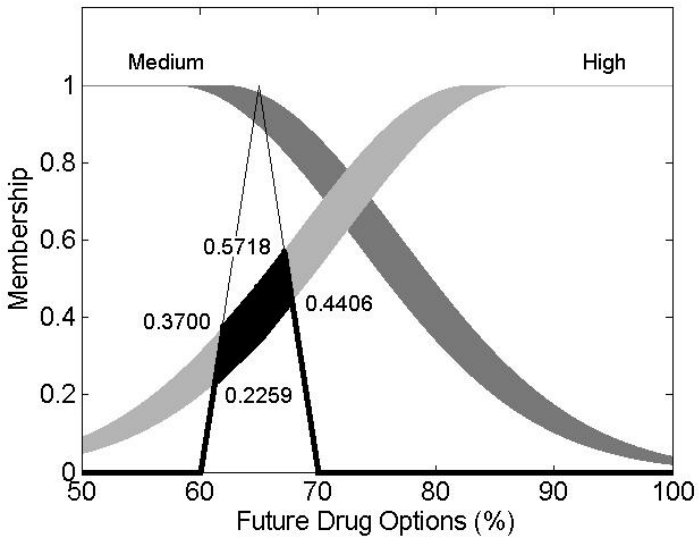


Figure 2.9: Determining the fuzzy event transition matrix for regimen 2 under the scenario 6

This scenario is the combination of scenario 2 and scenario 4. While the consensus of the diverse definitions of state is defined by type-2 fuzzy sets, the clinical parameters for a regimen are defined as symmetrical triangular type-1 fuzzy sets. Applying the fuzzy intersection on the triangular type-1 fuzzy set and the type-2 fuzzy set for "High", it results in an FOU which is the deep dark region shown in Figure 2.9. The FOU is bounded by the upper primary membership function in equation (2.14) and the lower primary membership function in equation (2.15) given below:

$$y_{\overline{FH}}(x) = \begin{cases} 0.2x - 12, & x \in [60, 61.850] \\ e^{-\frac{1}{2}\left(\frac{x-83}{15}\right)^2}, & x \in [61.850, 67.141] \\ 14 - 0.2x, & x \in [67.141, 70] \\ 0, & elsewhere \end{cases} \tag{2.14}$$

$$y_{\underline{FH}}(x) = \begin{cases} 0.2x - 12, & x \in [60, 61.129] \\ e^{-\frac{1}{2}\left(\frac{x-87}{15}\right)^2}, & x \in [61.129, 67.797] \\ 14 - 0.2x, & x \in [67.797, 70] \\ 0, & elsewhere \end{cases} \tag{2.15}$$

where $y_{\overline{FH}}$ and $y_{\underline{FH}}$ are the respective upper and lower primary membership functions of "High" for future drug options of regimen 2.

The range of the primary membership grades of the type-2 fuzzy set (the dark region in Figure 2.9) assigned for the domain of fuzzy set for ${}^1F_{13}$ as well as the membership function can be determined by using the height type-reducer

method expressed in the equation (2.9). As the interval type-2 fuzzy set has the secondary membership grade of the interval type-2 fuzzy set equals 1, the equation (2.9) will determine the highest primary membership grade for each value of x in the universe of discourse.

Applying equation (2.9) to the type-2 fuzzy set (the dark region for “High” in Figure 2.6) over the universe of discourse for *x* from 50 to 100 will result in the value of the primary grade changing from 0 to 0.5718 and the corresponding membership grade equal to 1. Therefore, ${}^{1}F_{13}$ can be represented by the interval [0, 0.5718]. We employ the same procedure for the “Medium” and yield its associated interval [0, 0.9812] for ${}^{1}F_{12}$.

Hence, the fuzzy state transition matrix is represented as

$$\sigma_1 = \begin{bmatrix} Z & [0, 0.9812] & [0, 0.5718] \\ Z & Z & Z \\ Z & Z & Z \end{bmatrix}.$$

The next state vector can be determined by

$$q_1 = q_0 \circ \sigma_1 = \begin{bmatrix} Z & [0, 0.9812] & [0, 0.5718] \end{bmatrix}.$$

2.4.7 Type-2 Fuzzy Sets for the Parameter Definitions and Type-2 Fuzzy Sets for the Parameter Characteristics (Scenario 7)

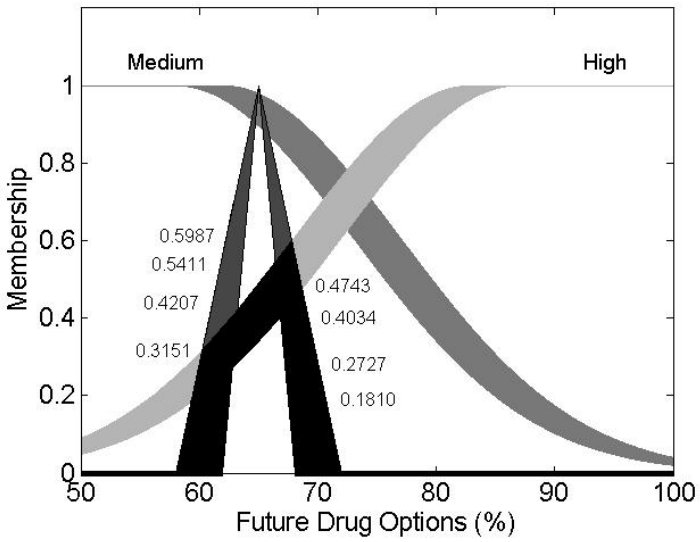


Figure 2.10: Determining the fuzzy event transition matrix for regimen 2 under the scenario 7

This scenario is the combination of scenario 3 and scenario 4. While the consensus of the diverse definitions of parameter state is defined by type-2 fuzzy sets, the clinical parameters for a regimen are defined as symmetrical triangular type-2 fuzzy sets. Their FOUs are depicted in Figure 2.10 and their boundary functions, the upper primary membership function and the lower primary membership function, have mathematical expressions in scenario 3 (equation (2.5) and (2.6)) and scenario 4 (equation (2.10) and (2.11)) for the clinical parameter and the definitions of parameter state, respectively.

Applying the fuzzy intersection on the triangular type-2 fuzzy set and the type-2 fuzzy set for “High” results in an FOU which is the deep dark region shown in Figure 2.10. The FOU is bounded by the upper primary membership function in equation (2.16) and the lower primary membership function in equation (2.17) given below:

$$y_{\overline{FH}}(x)=\begin{cases}1+\dfrac{x-65}{7}, & x\in[58,\,60.207]\\ e^{-\frac{1}{2}\left(\frac{x-83}{15}\right)^2}, & x\in[60.207,\,67.809]\\ 1-\dfrac{x-65}{7}, & x\in[67.809,\,72]\\ 0, & elsewhere\end{cases} \tag{2.16}$$

$$y_{\underline{FH}}(x)=\begin{cases}1+\dfrac{x-65}{3}, & x\in[62,\,62.818]\\ e^{-\frac{1}{2}\left(\frac{x-87}{15}\right)^2}, & x\in[62.818,\,66.790]\\ 1-\dfrac{x-65}{3}, & x\in[66.790,\,68]\\ 0, & elsewhere\end{cases} \tag{2.17}$$

where $y_{\overline{FH}}$ and $y_{\underline{FH}}$ are the respective upper and lower primary membership functions of “High” for future drug options of regimen 2.

The equation (2.9) for the height type-reducer method is used to determine the range of the primary membership grades of the type-2 fuzzy set (the dark region in Figure 2.10) assigned for the domain of fuzzy set for ${}^{1}F_{13}$, as well as the

membership function. The second membership grade of the interval type-2 fuzzy set is 1.

Applying equation (2.9) to the type-2 fuzzy set (the dark region for “High” in Figure 2.10) over the universe of discourse for *x* from 50 to 100 will result in the value of the primary grade changing from 0 to 0.5987 and the corresponding membership grade equal to 1. Therefore, ${}^{1}F_{13}$ can be represented by the interval [0, 0.5987]. We employ the same procedure for the “Medium” and yield its associated interval [0, 0.9818] is for ${}^{1}F_{12}$.

Hence, the fuzzy state transition matrix is represented as

$$\sigma_1 = \begin{bmatrix} Z & [0, 0.9818] & [0, 0.5987] \\ Z & Z & Z \\ Z & Z & Z \end{bmatrix}.$$

The next state vector can be determined by

$$q_1 = q_0 \circ \sigma_1 = \begin{bmatrix} Z & [0, 0.9818] & [0, 0.5987] \end{bmatrix}.$$

2.5 Retrospective patient data

The patient database [22, 31] was from the HIV/AIDS center founded in 1994. Clinical information of More than 4500 patients was collected. Since 1998 various highly active antiretroviral therapy regimens have been provided to patients. Clinical information of 35 patients used in this research was from the 98 treatment-naïve patients who received one of three treatment regimens for antiretroviral therapy at the AIDS clinical center in 2001. The data of all 35

patients was extracted from the database shown in Table 2.7-2.8. Table 2.10 was the regimen-choice of three treatment regimens for the 32 treatment objectives assigned by specialist A and B individually.

Table 2.7: 35 retrospective patients with their clinical information of physicians, CD4+ counts, HIV RNA, age, gender, and homelessness treated at AIDS Clinical Center in 2001

Patient No.	Physician	CD4+ (cell/μL)	HIV RNA (copies/mL)	Age (years)	Gender	Homeless
1	PHYSICIAN 1	81	8500	35	Male	No
2	EXPERT A	777	15000	32	Female	No
3	PHYSICIAN 2	64	300	36	Male	No
4	EXPERT B.	63	750000	55	Male	No
5	PHYSICIAN 3	210	60000	49	Male	No
6	PHYSICIAN 2	350	10000	48	Female	No
7	EXPERT A	512	100000	38	Male	No
8	PHYSICIAN 2	50	375000	49	Male	No
9	EXPERT B.	180	8500	48	Male	No
10	PHYSICIAN 1	10	85000	34	Male	No
11	EXPERT A	380	15000	36	Male	No
12	PHYSICIAN 4	532	125000	24	Male	Yes
13	PHYSICIAN 2	48	175000	42	Male	No
14	PHYSICIAN 5	135	400000	51	Male	No
15	PHYSICIAN 1	164	30000	45	Male	No
16	PHYSICIAN 6	288	225000	40	Female	No
17	PHYSICIAN 7	255	30000	32	Male	No
18	PHYSICIAN 4	440	25000	35	Male	No
19	PHYSICIAN 7	315	100000	33	Male	No
20	PHYSICIAN 3	575	15000	23	Male	No
21	PHYSICIAN 5	306	40000	40	Male	No
22	PHYSICIAN 8	714	750000	27	Male	No
23	EXPERT B.	480	6500	44	Female	No
24	PHYSICIAN 1	575	35000	25	Female	No
25	EXPERT B.	510	275000	33	Male	No
26	PHYSICIAN 6	644	3500	49	Male	Yes
27	EXPERT B.	656	2000	44	Male	No
28	EXPERT B.	45	725000	27	Male	No
29	PHYSICIAN 9	81	275000	43	Female	No
30	EXPERT B.	50	10000	40	Male	No
31	PHYSICIAN 10	24	150000	42	Male	No
32	PHYSICIAN 3	11	250000	38	Male	No
33	EXPERT A	342	2500	38	Male	No
34	PHYSICIAN 11	40	750000	70	Male	No
35	EXPERT B.	162	100000	43	Male	No

Table 2.8: 35 retrospective patients with their clinical information of behavior on illegal drugs or alcohol, mental illness problems, clinic visits, smoking, diabetes, and hepatitis B treated at AIDS Clinical Center in 2001

Patient No.	Active abuse	Mental illness	Clinic visit Missed >1	Smoking	Diabetes	Hepatitis B
1	Yes	No	No	Yes	No	No
2	No	No	No	No	No	No
3	No	No	No	No	No	No
4	No	Yes	No	No	No	No
5	Yes	No	No	Yes	No	No
6	Yes	Yes	Yes	No	No	No
7	Yes	No	Yes	No	No	No
8	No	No	No	No	No	No
9	No	No	No	No	No	No
10	Yes	No	No	Yes	No	Yes
11	No	No	Yes	No	No	No
12	Yes	No	No	No	No	No
13	Yes	Yes	No	No	No	No
14	Yes	No	Yes	Yes	Yes	Yes
15	No	No	No	Yes	No	No
16	Yes	No	No	Yes	Yes	No
17	No	No	No	Yes	No	No
18	Yes	Yes	No	Yes	No	No
19	No	No	No	Yes	No	No
20	No	No	Yes	No	No	No
21	Yes	Yes	Yes	Yes	No	No
22	Yes	No	Yes	Yes	No	No
23	Yes	No	No	Yes	No	No
24	No	No	No	No	No	No
25	Yes	Yes	No	Yes	No	No
26	No	Yes	No	No	No	No
27	No	No	No	Yes	No	No
28	Yes	No	No	Yes	Yes	No
29	Yes	No	No	Yes	No	No
30	No	No	No	No	No	No
31	No	No	No	No	No	No
32	No	No	No	No	No	No
33	No	No	No	No	No	Yes
34	No	No	No	No	No	No
35	No	Yes	No	No	No	No

Table 2.9: 35 retrospective patients with their clinical information of hepatitis C, total cholesterol, HDL cholesterol, blood pressure, and given medicines treated at AIDS Clinical Center in 2001

Patient No.	Hepatitis C	Cholesterol (mg/dL)	HDL (mg/dL)	Blood Pressure (mm Hg)	Medications
1	Yes	<100	<20	147	Regimen 3
2	No	144	44	105	Regimen 3
3	No	223	69	132	Regimen 3
4	No	<100	<20	99	Regimen 3
5	No	166	43	138	Regimen 3
6	Yes	107	34	113	Regimen 3
7	No	165	<20	114	Regimen 3
8	No	<100	<20	131	Regimen 3
9	No	198	53	136	Regimen 1
10	No	156	<20	122	Regimen 3
11	No	142	45	121	Regimen 3
12	No	189	62	126	Regimen 3
13	No	<100	<20	120	Regimen 3
14	No	159	36	141	Regimen 3
15	No	<100	<20	120	Regimen 1
16	No	154	43	119	Regimen 3
17	No	196	56	154	Regimen 2
18	No	129	<20	110	Regimen 3
19	No	<100	<20	132	Regimen 3
20	No	<100	<20	120	Regimen 1
21	No	139	33	137	Regimen 3
22	No	168	34	95	Regimen 3
23	Yes	133	52	112	Regimen 3
24	No	149	<20	135	Regimen 3
25	No	<100	<20	118	Regimen 3
26	No	172	35	139	Regimen 2
27	No	141	30	118	Regimen 3
28	No	108	<20	105	Regimen 3
29	No	<100	<20	133	Regimen 3
30	No	<100	<20	105	Regimen 3
31	No	192	32	115	Regimen 1
32	No	143	<20	104	Regimen 3
33	No	171	42	134	Regimen 3
34	No	163	21	160	Regimen 2
35	No	<100	<20	115	Regimen 3

Table 2.10: Regimens assigned by AIDS expert A and B for the preferable regimen-choices regarding the 32 treatment objectives

Treatment Objectives				1st choice		2nd choice		3rd choice	
Potency	Adherence	Adverse Events	Future Drug Options	Expert A	Expert B	Expert A	Expert B	Expert A	Expert B
High	Easy	Medium	High	1	3	2	1	3	2
High	Easy	Medium	Medium	1	1	2	2	3	3
High	Easy	Low	High	1	3	3	1	2	2
High	Easy	Low	Medium	1	1	2	2	3	3
High	Easy	Very Low	High	1	3	3	1	2	2
High	Easy	Very low	Medium	1	3	2	1	3	2
High	Moderate	Medium	High	1	3	2	1	3	2
High	Moderate	Medium	Medium	1	1	2	2	3	3
High	Moderate	Low	High	1	3	2	1	3	2
High	Moderate	Low	Medium	1	1	2	2	3	3
High	Moderate	Very Low	High	1	3	2	1	3	2
High	Moderate	Very low	Medium	1	3	2	1	3	2
High	Challenging	Medium	High	1	3	2	1	3	2
High	Challenging	Medium	Medium	1	1	2	2	3	3
High	Challenging	Low	High	1	3	2	1	3	2
High	Challenging	Low	Medium	1	1	2	2	3	3
High	Challenging	Very Low	High	1	3	2	1	3	2
High	Challenging	Very low	Medium	1	3	2	1	3	2
Medium	Easy	Medium	High	3	3	1	2	2	1
Medium	Easy	Medium	Medium	1	3	2	2	3	1
Medium	Easy	Low	High	3	3	2	2	1	1
Medium	Easy	Low	Medium	1	3	2	2	3	1
Medium	Easy	Very Low	High	3	3	1	2	2	1
Medium	Easy	Very Low	Medium	1	3	2	2	3	1
Medium	Moderate	Medium	High	3	3	1	2	2	1
Medium	Moderate	Low	High	3	3	1	2	2	1
Medium	Moderate	Very Low	High	3	3	1	2	2	1
Medium	Moderate	Very Low	Medium	1	3	2	2	3	1
Medium	Challenging	Medium	High	3	3	1	1	2	2
Medium	Challenging	Low	High	3	3	1	1	2	2
Medium	Challenging	Very Low	High	3	3	1	2	2	1
Medium	Challenging	Very Low	Medium	1	3	2	2	3	1

2.6 Simulation Results

The EFDES-based regimen selection system was implemented by using MATLAB. The medical information on the same 35 patients used in the FDES-based system was put into the system. We did experiments under the seven scenarios and evaluated the system's performance in terms of retrospectively matching the 35 patients' actual prescriptions. Twelve of the 35 patients were treated by the two HIV/AIDS experts. These two expert physicians involved in the system development (e.g., weighting the regimens for each of 32 treatment objectives). The remaining 23 patients were treated by 11 HIV/AIDS experts without contributing to system training, those results in the mean and standard deviation of patients per expert being 2 and 1.97, respectively.

The results are shown in Table 2.11, 2.11, 2.12 and Table 2.14, where the meanings of Δm, Δx, Δw, and Δv are given above (e.g., Figure 2.2 and Figure 2.3). Table 2.15 contains all seven scenarios that provide the patients' details of regimens experimentally assigned by the system against the historical prescriptions.

Table 2.11: First-choice regimens assigned by the EFDES-based system model against the actual regimens given to the 35 patients under scenario 1, 2, and 3

Patient No.	Objectives	Given Regimens	Assigned Regimens												
			Expert A	Expert B	The EFDES- Based System Model										
					Scenario 1 Δv (%)			Scenario 2 Δx (%)			Scenario 3 Δx, Δw (%)				
					2	6	10	1	3	5	1,2	3,2	3,4	5,2	5,4
1	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
2	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
3	10	3	1	1	1	1	1	1	1	1	1	1	1	1	1
4	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3
5	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
6	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
7	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
8	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3
9	10	1	1	1	1	1	1	1	1	1	1	1	1	1	1
10	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3
11	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
12	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
13	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3
14	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3
15	10	1	1	1	1	1	1	1	1	1	1	1	1	1	1
16	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3
17	23	2	3	3	3	3	3	3	3	3	3	3	3	3	3
18	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
19	24	3	1	3	1	1	1	1	1	3	1	1	1	1	1
20	23	1	3	3	3	3	3	3	3	3	3	3	3	3	3
21	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
22	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
23	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
24	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
25	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
26	23	2	3	3	3	3	3	3	3	3	3	3	3	3	3
27	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
28	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3
29	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3
30	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
31	10	1	1	1	1	1	1	1	1	1	1	1	1	1	1
32	10	3	1	1	1	1	1	1	1	1	1	1	1	1	1
33	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3
34	10	2	1	1	1	1	1	1	1	1	1	1	1	1	1
35	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3

Table 2.12: First-choice regimens assigned by the EFDES-based system model against the actual regimens given to the 35 patients under scenario 4 and 5

Patient No.	Objectives	Given Regimens	Assigned Regimens														
			Expert A	Expert B	The EFDES- Based System Model												
					Scenario 4 Δm (%)			Scenario 5 Δm, Δv (%)									
					1	2	3	1,2	1,6	1,10	2,2	2,6	2,10	3,2	3,6	3,10	
1	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
2	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
3	10	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
4	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3	3	
5	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
6	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
7	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
8	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3	3	
9	10	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
10	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3	3	
11	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
12	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
13	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3	3	
14	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3	3	
15	10	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
16	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3	3	
17	23	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
18	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
19	24	3	1	3	1	1	1	1	1	1	1	1	1	1	1	1	
20	23	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
21	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
22	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
23	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
24	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
25	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
26	23	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
27	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
28	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3	3	
29	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3	3	
30	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
31	10	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
32	10	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
33	23	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
34	10	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
35	9	3	1	3	3	3	3	3	3	3	3	3	3	3	3	3	

Table 2.13: First-choice regimens assigned by the EFDES-based system model against the actual regimens given to the 35 patients under scenario 6

Patient No.	Objectives	Given Regimens	Assigned Regimens										
			Expert A	Expert B	The EFDES- Based System Model								
					Scenario 6 Δm, Δx (%)								
					1,1	1,3	1,5	2,1	2,3	2,5	3,1	3,3	3,5
1	23	3	3	3	3	3	3	3	3	3	3	3	3
2	23	3	3	3	3	3	3	3	3	3	3	3	3
3	10	3	1	1	1	1	1	1	1	1	1	1	1
4	9	3	1	3	3	3	3	3	3	3	3	3	3
5	23	3	3	3	3	3	3	3	3	3	3	3	3
6	23	3	3	3	3	3	3	3	3	3	3	3	3
7	23	3	3	3	3	3	3	3	3	3	3	3	3
8	9	3	1	3	3	3	3	3	3	3	3	3	3
9	10	1	1	1	1	1	1	1	1	1	1	1	1
10	9	3	1	3	3	3	3	3	3	3	3	3	3
11	23	3	3	3	3	3	3	3	3	3	3	3	3
12	23	3	3	3	3	3	3	3	3	3	3	3	3
13	9	3	1	3	3	3	3	3	3	3	3	3	3
14	9	3	1	3	3	3	3	3	3	3	3	3	3
15	10	1	1	1	1	1	1	1	1	1	1	1	1
16	9	3	1	3	3	3	3	3	3	3	3	3	3
17	23	2	3	3	3	3	3	3	3	3	3	3	3
18	23	3	3	3	3	3	3	3	3	3	3	3	3
19	24	3	1	3	1	1	1	1	1	1	1	1	1
20	23	1	3	3	3	3	3	3	3	3	3	3	3
21	23	3	3	3	3	3	3	3	3	3	3	3	3
22	23	3	3	3	3	3	3	3	3	3	3	3	3
23	23	3	3	3	3	3	3	3	3	3	3	3	3
24	23	3	3	3	3	3	3	3	3	3	3	3	3
25	23	3	3	3	3	3	3	3	3	3	3	3	3
26	23	2	3	3	3	3	3	3	3	3	3	3	3
27	23	3	3	3	3	3	3	3	3	3	3	3	3
28	9	3	1	3	3	3	3	3	3	3	3	3	3
29	9	3	1	3	3	3	3	3	3	3	3	3	3
30	23	3	3	3	3	3	3	3	3	3	3	3	3
31	10	1	1	1	1	1	1	1	1	1	1	1	1
32	10	3	1	1	1	1	1	1	1	1	1	1	1
33	23	3	3	3	3	3	3	3	3	3	3	3	3
34	10	2	1	1	1	1	1	1	1	1	1	1	1
35	9	3	1	3	3	3	3	3	3	3	3	3	3

Table 2.14: First-choice regimens assigned by the EFDES-based system model against the actual regimens given to the 35 patients under scenario 7

Patient No.	Objectives	Given Regimens	Assigned Regimens									
			Expert A	Expert B	The EFDES- Based System Model							
					Scenario 7 Δm, Δx, Δw (%)							
					1,1,2	1,3,2	1,3,4	1,5,2	1,5,4	2,1,2	2,3,2	2,3,4
1	23	3	3	3	3	3	3	3	3	3	3	3
2	23	3	3	3	3	3	3	3	3	3	3	3
3	10	3	1	1	1	1	1	1	1	1	1	1
4	9	3	1	3	3	3	3	3	3	3	3	3
5	23	3	3	3	3	3	3	3	3	3	3	3
6	23	3	3	3	3	3	3	3	3	3	3	3
7	23	3	3	3	3	3	3	3	3	3	3	3
8	9	3	1	3	3	3	3	3	3	3	3	3
9	10	1	1	1	1	1	1	1	1	1	1	1
10	9	3	1	3	3	3	3	3	3	3	3	3
11	23	3	3	3	3	3	3	3	3	3	3	3
12	23	3	3	3	3	3	3	3	3	3	3	3
13	9	3	1	3	3	3	3	3	3	3	3	3
14	9	3	1	3	3	3	3	3	3	3	3	3
15	10	1	1	1	1	1	1	1	1	1	1	1
16	9	3	1	3	3	3	3	3	3	3	3	3
17	23	2	3	3	3	3	3	3	3	3	3	3
18	23	3	3	3	3	3	3	3	3	3	3	3
19	24	3	1	3	1	1	1	1	1	1	1	1
20	23	1	3	3	3	3	3	3	3	3	3	3
21	23	3	3	3	3	3	3	3	3	3	3	3
22	23	3	3	3	3	3	3	3	3	3	3	3
23	23	3	3	3	3	3	3	3	3	3	3	3
24	23	3	3	3	3	3	3	3	3	3	3	3
25	23	3	3	3	3	3	3	3	3	3	3	3
26	23	2	3	3	3	3	3	3	3	3	3	3
27	23	3	3	3	3	3	3	3	3	3	3	3
28	9	3	1	3	3	3	3	3	3	3	3	3
29	9	3	1	3	3	3	3	3	3	3	3	3
30	23	3	3	3	3	3	3	3	3	3	3	3
31	10	1	1	1	1	1	1	1	1	1	1	1
32	10	3	1	1	1	1	1	1	1	1	1	1
33	23	3	3	3	3	3	3	3	3	3	3	3
34	10	2	1	1	1	1	1	1	1	1	1	1
35	9	3	1	3	3	3	3	3	3	3	3	3

Table 2.14: (*continued*) First-choice regimens assigned by the EFDES-based system against the actual regimens given to the 35 patients under scenario 7

Patient No.	Objectives	Given Regimens	Assigned Regimens								
			Expert A	Expert B	The EFDES- Based System Model						
					Scenario 7 $\Delta m, \Delta x, \Delta w$ (%)						
					2,5,2	2,5,4	3,1,2	3,3,2	3,3,4	3,5,2	3,5,4
1	23	3	3	3	3	3	3	3	3	3	3
2	23	3	3	3	3	3	3	3	3	3	3
3	10	3	1	1	1	1	1	1	1	1	1
4	9	3	1	3	3	3	3	3	3	3	3
5	23	3	3	3	3	3	3	3	3	3	3
6	23	3	3	3	3	3	3	3	3	3	3
7	23	3	3	3	3	3	3	3	3	3	3
8	9	3	1	3	3	3	3	3	3	3	3
9	10	1	1	1	1	1	1	1	1	1	1
10	9	3	1	3	3	3	3	3	3	3	3
11	23	3	3	3	3	3	3	3	3	3	3
12	23	3	3	3	3	3	3	3	3	3	3
13	9	3	1	3	3	3	3	3	3	3	3
14	9	3	1	3	3	3	3	3	3	3	3
15	10	1	1	1	1	1	1	1	1	1	1
16	9	3	1	3	3	3	3	3	3	3	3
17	23	2	3	3	3	3	3	3	3	3	3
18	23	3	3	3	3	3	3	3	3	3	3
19	24	3	1	3	1	1	1	1	1	1	1
20	23	1	3	3	3	3	3	3	3	3	3
21	23	3	3	3	3	3	3	3	3	3	3
22	23	3	3	3	3	3	3	3	3	3	3
23	23	3	3	3	3	3	3	3	3	3	3
24	23	3	3	3	3	3	3	3	3	3	3
25	23	3	3	3	3	3	3	3	3	3	3
26	23	2	3	3	3	3	3	3	3	3	3
27	23	3	3	3	3	3	3	3	3	3	3
28	9	3	1	3	3	3	3	3	3	3	3
29	9	3	1	3	3	3	3	3	3	3	3
30	23	3	3	3	3	3	3	3	3	3	3
31	10	1	1	1	1	1	1	1	1	1	1
32	10	3	1	1	1	1	1	1	1	1	1
33	23	3	3	3	3	3	3	3	3	3	3
34	10	2	1	1	1	1	1	1	1	1	1
35	9	3	1	3	3	3	3	3	3	3	3

Table 2.15: Comparison of 35 patients' prescribed regimen with those assigned by the EFDES-based system

	Δm	Δx	Δw	Δv	Number of first-choice regimens matched with prescribed regimens for the 35 patients
Scenario 1				2%	28
				6%	28
				10%	28
Scenario 2		1%			28
		3%			28
		5%			29
Scenario 3		1%	2%		28
		3%	2%		28
		3%	4%		28
		5%	2%		28
		5%	4%		28
Scenario 4	1%				28
	2%				28
	3%				28
Scenario 5	1%			2%	28
	1%			6%	28
	1%			10%	28
	2%			2%	28
	2%			6%	28
	2%			10%	28
	3%			2%	28
	3%			6%	28
	3%			10%	28

Table 2.15: (*continued*) Comparison of 35 patients' prescribed regimen with those assigned by the EFDES-based system

	Δm	Δx	Δw	Δv	Number of first-choice regimens matched with prescribed regimens for the 35 patients
Scenario 6	1%	1%			28
	1%	3%			28
	1%	5%			28
	2%	1%			28
	2%	3%			28
	2%	5%			28
	3%	1%			28
	3%	3%			28
	3%	5%			28
Scenario 7	1%	1%	2%		28
	1%	3%	2%		28
	1%	3%	4%		28
	1%	5%	2%		28
	1%	5%	4%		28
	2%	1%	2%		28
	2%	3%	2%		28
	2%	3%	4%		28
	2%	5%	2%		28
	2%	5%	4%		28
	3%	1%	2%		28
	3%	3%	2%		28
	3%	3%	4%		28
	3%	5%	2%		28
	3%	5%	4%		28

2.7 Discussion

Specialist A treated patient numbers 2, 7, 11 and 33, whereas the specialist B treated the patient numbers 4, 9, 23, 25, 27, 28, 30 and 35. The clinical information of 35 retrospective patients is in Table 2.7-2.10. In all seven scenarios, the first-choice treatment regimens computed by the EFDES system match the regimens selected by the two specialists for the 12 patients 100% of times. This result may indicate that the system captures and represents the diverse knowledge of these two specialists well.

As shown in the result tables, most agreement between the computer and the actual prescriptions is 80% (28 out of 35), exempting scenario 2 with Δx being 5% which is 82.9% (29 out of 35). To obtain such high numbers of 29 first-choice matching regimens, the system assigned the right regimen (i.e., regimen 3) to patient number 19 with the treatment objective: “medium” potency, “easy’ adherence, “very low” adverse events, and “medium” future drug options. Under other scenarios, patient number 19 was assigned with regimen 1 instead. Unfortunately, this case has never again been observed since the first time. Basically, an initial condition value for the genetic algorithm is randomly generated which takes time to initiate the right one. It will take even more time when dealing with a large dimension of the initial values like the one in the EFDES-based system. The system normally provides 80% matching.

The uncertainties of the fuzzy state vectors like those in the seven scenarios need to be represented in a form of the certainties done by

defuzzification and then will be used for the Regimen Selection Optimizer. For instance, $def([Z \quad [0, 0.9509] \quad [0, 0.5052]])$ is [0 0.4754 0.2526], according to equation (2.3.1.2) for the future drug options for regimen 2 (Figure 2.4) in scenario 2 and the corresponding normalized state vector is [0 0.6530 0.3470]. While the normalized state vector for the future drug options for the FDES-based in Figure 1.1 is [0 0.6993 0.3007], the closest normalized state vector [0 0.6963 0.3037] is obtained from scenario 4 when Δx equals 1% and the farthest normalized state vector [0 0.6209 0.3791] is obtained from scenario 6 when Δm and Δx equal 3% and 5%, respectively. The system model shows that the Regimen Selection Optimizer for the EFDES-based system is able to handle at least those ranges of uncertainties in Table 2.11. For example, normalized state vectors for future drug options for regimen 2 are in the range from [0 0.6209 0.3791] to [0 0.6963 0.3037] that result in the same number of matching regimens (28 out of 35).

The normal level of performance is a bit lower than the FDES-based system, which is 82.9% (29 out of 35). However, that level shows the benefit of the EFDES system providing the domain experts with the ability to use their individual diverse knowledge and expertise. The equality respective is kept to those experts.

CHAPTER 3

SELF-LEARNING EFDES-BASED HIV/AIDS TREATMENT REGIMEN SELECTION SYSTEM

The EFDES-based HIV/AIDS treatment selection system with static mode (i.e., without self-learning mode) is a part of the research work. It has been studied and experimented, as the results have shown in the previous chapter. An adaptation of the HIV disease to a new environment would be remarkable as recognized by the revising of the HIV/AIDS treatment every few years. How to adapt the ability of self-learning to the system would be another challenging task. The theory of self-learning for the fuzzy discrete event system would be contributed in the development of the EFDES-based system with self-learning.

Adding a self-learning ability to the EFDES-based system will make the system even more useful where the evaluation of the HIV/AIDS treatment changes rapidly. The EFDES-based system with self-learning will be developed, and the complete system will then be used as an HIV/AIDS treatment decision-supporting system that will give huge benefits to those clinical institutes with limited numbers of the HIV/AIDS specialists.

3.1 EFDES-Based HIV/AIDS Regimen Selection System with Self-Learning

The approach of the self-learning system will utilize the theory of the self-learning fuzzy discrete system [31]. There will be four regimens involved in the system for self-learning. Each of them has the same four clinical parameters:

potency, adherence, adverse events, and future drug options. As mentioned in the previous chapter, without regarding the initial state, there are two states (e.g., medium and high) for potency, three for adherence, three for adverse events and two for future drug options. Theoretically, the combinations of the four clinical parameters generate 36 treatment objectives, but only 32 treatment objectives exist clinically. One of them will be labeled on a patient when classified. Which regimen to be assigned will be the one with the highest effectiveness measure computed by the system. Under the EFDES-based system, in general, the fuzzification of a fuzzy state vector of which components can be a type-1 fuzzy set or an interval number may need defuzzification into a crisp state vector in order to compute the effectiveness measure. The mathematical expression of the effectiveness measure (E) for the j-th regimen regarding the h-th treatment objective can be defined in a form of the function as

$$E_{hj} = f(S_{h1j} \cdot W_{k1}, ..., S_{hnj} \cdot W_{kn}), \quad 1 \le k \le P_n, \quad 1 < n < 4, \tag{3.1}$$

where *f* is a function. S_{hnj} is a new fuzzy state vector when an event occurs (i.e., prescribing a regimen), which is obtained by performing fuzzy logic operation (i.e., max-product) to the current fuzzy state vector with a state transition matrix. The four clinical parameters considered are indicated by n and P_n is the number states of the corresponding parameter (e.g., P_1=2 for medium and high for potency). Finally, W_{kn} is the weight vector corresponding to S_{hnj}.

The linear function in the form of the weighted average of clinical parameters will be utilized as a predicting function. With the same significant given to all clinical parameters, the linear function can be expressed as

$$E_{hj} = \sum_{n=1}^{4} S_{hnj} \cdot W_{kn} + C_0 \tag{3.2}$$

where C_0 is a constant offset.

In the equation (3.2), only the weight vector W_{kn} will be considered as a part of the system to be learned. The self-learning EFDES-based system can be adapted as shown in Figure 3.1. In order to prove the adapted system model, sets of data need to be acquired for the system training. There are four data-learning settings. Their criteria of these various data settings are in the following section.

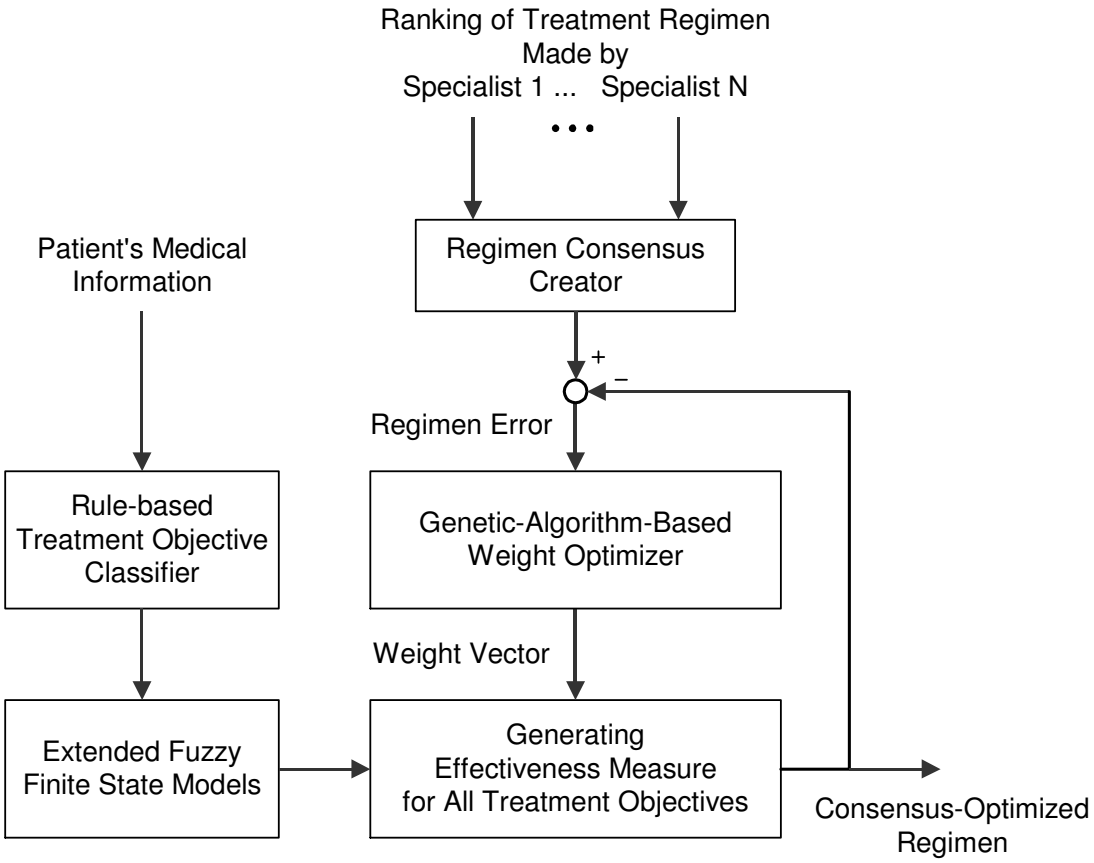


Figure 3.1: Block diagram of the EFDES-based HIV/AIDS treatment selection system with self-learning

3.2 Settings for the Self-Learning System Evaluation

As from the clinical data base as well as in [31], the four treatment regimens, the three regimens in Table 1.1 and the regimen which consisted of Combivir (CBV) and Nelfinavir (NEV), will be used for the self-learning system. Table 3.1 provides the clinical parameter characteristics of these four treatment regimens. Each of the four regimens with points individually given by two AIDS

experts for all 32 treatment objectives in Table 3.2-3.3 would be data for data-learning setting. The AIDS experts rated the four regimens following the instruction of a 10-point scoring with increments of 0.5. The highest score is 10. The experts' preference of regimens for the treatment objective was indicated in the form of scores rated among the four regimens. The regimen with the highest score was the most preferable as the first choice. In the case of the same scores, one of the regimens involved was selected randomly.

Table 3.1: Four clinical parameters of the four HIV/AIDS treatment regimens

	Potency	Adherence	Adverse Events	Future Drug Options
Regimen 1: CBV+NEV	85%	55%	30%	80%
Regimen 2: CBV+EFV	90%	80%	20%	60%
Regimen 3: CBV+NVP	85%	85%	20%	65%
Regimen 4: CBV+ABC	80%	90%	10%	85%

Table 3.2: Regimens assigned by AIDS experts A and B for the preferable scores of regimen 1 and regimen 2 regarding the 32 treatment objectives. Also marked are the 10 selected treatment objectives used in Learning Setting 3 [31]

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

Table 3.3: Regimens assigned by AIDS experts A and B for the preferable scores of regimen 3 and regimen 4 regarding the 32 treatment objectives. Also marked are the 10 selected treatment objectives used in Learning Setting 3 [31]

Treatment Objectives				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	
High	Easy	Medium	High	6.5	3.5	6.5	9.0	X
High	Easy	Medium	Medium	8.5	8.5	6.5	8.0	
High	Easy	Low	High	6.0	4.5	6.5	9.0	
High	Easy	Low	Medium	8.0	8.0	6.5	7.0	
High	Easy	Very Low	High	5.5	6.0	6.0	9.0	
High	Easy	Very low	Medium	7.5	7.5	6.0	8.5	X
High	Moderate	Medium	High	7.5	5.0	6.5	8.5	X
High	Moderate	Medium	Medium	9.5	8.5	7.5	8.0	
High	Moderate	Low	High	7.0	4.0	6.5	9.0	
High	Moderate	Low	Medium	9.0	8.0	6.5	7.5	
High	Moderate	Very Low	High	6.5	4.0	6.0	9.0	
High	Moderate	Very low	Medium	8.5	7.5	6.0	8.5	X
High	Challenging	Medium	High	7.5	3.5	6.5	8.5	X
High	Challenging	Medium	Medium	9.5	8.5	6.5	6.5	
High	Challenging	Low	High	7.0	3.5	6.5	9.0	
High	Challenging	Low	Medium	9.0	8.5	6.5	7.0	
High	Challenging	Very Low	High	6.5	4.0	6.5	8.5	
High	Challenging	Very low	Medium	8.5	7.5	6.5	9.0	X
Medium	Easy	Medium	High	7.0	5.0	8.0	9.5	X
Medium	Easy	Medium	Medium	9.0	8.5	8.0	9.0	
Medium	Easy	Low	High	6.5	3.0	8.0	9.5	
Medium	Easy	Low	Medium	8.5	8.5	8.0	9.5	
Medium	Easy	Very Low	High	6.0	5.0	7.5	9.5	
Medium	Easy	Very Low	Medium	8.0	7.5	7.5	9.5	X
Medium	Moderate	Medium	High	8.0	4.0	8.0	9.5	
Medium	Moderate	Low	High	7.5	4.0	8.0	9.5	X
Medium	Moderate	Very Low	High	7.0	4.0	7.5	9.5	
Medium	Moderate	Very Low	Medium	9.0	8.0	7.5	9.5	
Medium	Challenging	Medium	High	8.0	5.0	8.0	9.5	
Medium	Challenging	Low	High	7.5	3.5	8.0	9.5	
Medium	Challenging	Very Low	High	7.0	4.0	7.5	9.5	
Medium	Challenging	Very Low	Medium	9.0	8.0	7.5	9.5	X

There are four data-learning settings as follows which will be conducted to evaluate the EFDES- based system's prediction capabilities.

- **Data-learning setting 1**

In this data setting 1, a set of three regimens would be drawn from the pool of the four regimens. Thus, it provides 4 sets of the three regimens contributing with the consensus choices of specialist A and B or the individual choices of specialist A and B for all the 32 treatment objectives that the system would learn from and then predict the choices of the undrawn regimen regarding the 32 treatment objectives. For instance, the system would predict the choice of the regimen 1 for all 32 treatment objectives after learning the set of [Regimen 2, Regimen 3, Regimen 4]. Eventually, these four sets consisted of [Regimen 2, Regimen 3, Regimen 4], [Regimen 1, Regimen 3, Regimen 4], [Regimen 1, Regimen 2, Regimen 4], and [Regimen 1, Regimen 2, Regimen 3].

- **Data-learning setting 2**

In this data setting 2, a set of two regimens would be drawn from the pool of the four regimens. Thus, it provides 6 sets of the two regimens contributing with the consensus choices of specialist A and B or the individual choices of specialist A and B regarding the 32 treatment objectives that the system would learn from and then predict the choices of the undrawn regimen for all the treatment objectives. For instance, the system would predict the choice of the Regimen 1 for all 32 treatment objectives after learning each of two different sets; [Regimen 2, Regimen 3] and [Regimen 2, Regimen4]. These six sets consisted of [Regimen 1,

Regimen 2], [Regimen 1, Regimen 3], [Regimen 1, Regimen 4], [Regimen 2, Regimen 3], [Regimen 2, Regimen 4], and [Regimen 3, Regimen 4].

- **Data-learning setting 3**

In this data setting 3, a set of two regimens would be drawn from the pool of the three regimens: Regimen 2, Regimen 3, and Regimen 4. That drawing provides 3 sets of the two regimens contributing with the consensus choices of specialist A and B regarding ten selected treatment objectives that the system would learn from and then predict the choices of the undrawn regimens for 32 treatment objectives. Those treatment objectives marked in the last column in Table 3.2-3.3 were the selected treatment objectives used for this learning setting. The system would predict the choice of Regimen 2, Regimen 3, and Regimen 4 for all the 32 treatment objectives after learning the set of [Regimen 3, Regimen 4], [Regimen 2, Regimen4], and [Regimen 2, Regimen3], respectively.

- **Data-learning setting 4**

In this data setting 4, it would be the same as the data setting 3. There were three sets of two regimens drawn from the pool of the three regimens: Regimen 2, Regimen 3, and Regimen 4. The system would learn each of these three sets under the 32 treatment objectives and then predict the choices of regimens for the 35 retrospective patients under their treatment objectives involved.

Table 3.4: Rankings of the consensus of AIDS experts A & B for the four regimens regarding the 32 treatment objectives

Treatment Objectives				Rankings of Consensus of Experts A & B			
Potency	Adherence	Adverse Events	Future Drug Options	Regimen 1	Regimen 2	Regimen 3	Regimen 4
High	Easy	Medium	High	3	2	4	1
High	Easy	Medium	Medium	4	1	2	3
High	Easy	Low	High	4	2	3	1
High	Easy	Low	Medium	4	1	2	3
High	Easy	Very Low	High	4	2	3	1
High	Easy	Very low	Medium	4	1	2	3
High	Moderate	Medium	High	3	1	4	2
High	Moderate	Medium	Medium	4	1	2	3
High	Moderate	Low	High	2	3	4	1
High	Moderate	Low	Medium	3	1	2	4
High	Moderate	Very Low	High	4	2	3	1
High	Moderate	Very low	Medium	4	1	2	3
High	Challenging	Medium	High	1	3	4	2
High	Challenging	Medium	Medium	3	1	2	4
High	Challenging	Low	High	1	3	4	2
High	Challenging	Low	Medium	3	1	2	4
High	Challenging	Very Low	High	4	2	3	1
High	Challenging	Very low	Medium	4	1	2	3
Medium	Easy	Medium	High	2	4	3	1
Medium	Easy	Medium	Medium	4	2	1	3
Medium	Easy	Low	High	2	3	4	1
Medium	Easy	Low	Medium	4	3	2	1
Medium	Easy	Very Low	High	4	2	3	1
Medium	Easy	Very Low	Medium	4	2	3	1
Medium	Moderate	Medium	High	2	4	3	1
Medium	Moderate	Low	High	2	4	3	1
Medium	Moderate	Very Low	High	4	2	3	1
Medium	Moderate	Very Low	Medium	4	1	2	3
Medium	Challenging	Medium	High	1	3	4	2
Medium	Challenging	Low	High	1	3	4	2
Medium	Challenging	Very Low	High	2	3	4	1
Medium	Challenging	Very Low	Medium	4	1	2	3

3.3 Performance Evaluation with Simulation

To learn the information on the four clinical parameters assigned by the AIDS experts A and B shown in Table 3.2 and Table 3.3, it needed to be in the form of score rankings used by the genetic algorithm. Four rankings of the regimen for each of the 32 treatment objectives would create a table of expert choices for the weight optimizer to search the weights so that it would provide the most possible matching of the first-choice regimens assigned by the system and selected by the expert individually.

The consensus scores of the distinct scores rated by two AIDS experts were calculated in the manner done in [31]. Each score of the individual expert was divided by the corresponding standard deviation. We then needed to calculate the average score for every treatment objective and every regimen. There would be the results of 128 average scores of the two experts for the 32 treatment objectives and the four regimens. These average scores represented the consensus of the two experts and were converted to rankings. The score rankings of the consensus of experts A and B is shown in Table 3.4. The highest average score was ranked as 1 and the lowest average score was ranked as 4.

The exact agreements among two AIDS experts on regimen choice for the treatment objectives were derived from Table 3.2 and Table 3.3, and their measures under various settings were shown in Table 3.5. Also, the agreement between each of the experts and their consensus from Table 3.4 were included in Table 3.5. The EFDES system performance was evaluated under four various

learning settings as imitating medical situations which would be encountered. Basically, these situations would arise as new regimens become available. The system would predict the new regimens based on clinical information for existing available regimens provided by AIDS experts. The first two learning settings occupied all completed information for the existing regimens provided by the experts. The performance prediction after the system learned these two settings were shown in Table 3.6-3.14. Learning setting 3 occupied some information for the existing regimens provided by the experts. After learning, the system generated the prediction results shown in Table 3.15-3.17. Learning setting 4 involved 35 historical treatment patients. The prediction results against the given regimens to the patients after learning setting 4 was learned shown in Table 3.18-3.26. The corresponding optimal weight vectors were shown in Table 3.27-3.32.

Table 3.5: Measures of exact agreement between two experts and measure of exact agreement between each of the two experts and their consensus under various prescribing conditions.

Exact agreement between	Prescribing					Mean rate
	all 4 regimens	3 of the 4 regimens (excluding Regimen 1)	3 of the 4 regimens (excluding Regimen 2)	3 of the 4 regimens (excluding Regimen 3)	3 of the 4 regimens (excluding Regimen 4)	
expert A and expert B	37.5%	46.9%	46.9%	37.5%	50.0%	43.8%
expert A and consensus of experts A&B	62.5%	65.6%	78.1%	65.6%	75.0%	69.4%
expert B and consensus of experts A&B	68.8%	75.0%	68.8%	68.8%	75.0%	71.3%

Table 3.6: Prediction results achieved after the EFDES-based system learned under condition of learning setting 1 compared with expert A's choices.

Scenario					Accuracy of System-prediction Choices vs. Expert A's Choices				
	Δm	Δx	Δw	Δv	Predicting Regimen 1 using Regimen 2, 3 & 4	Predicting Regimen 2 using Regimen 1, 3 & 4	Predicting Regimen 3 using Regimen 1, 2 & 4	Predicting Regimen 4 using Regimen 1, 2 & 3	Mean prediction
Scenario 1				6%	30 (93.8%)	30 (93.8%)	32 (100%)	26 (81.3%)	29.5 (92.2%)
				10%	31 (96.9%)	29 (90.6%)	32 (100%)	26 (81.3%)	29.5 (92.2%)
Scenario 2		3%			29 (90.6%)	29 (90.6%)	32 (100%)	26 (81.3%)	29.0 (90.6%)
		5%			29 (90.6%)	29 (90.6%)	32 (100%)	26 (81.3%)	29.0 (90.6%)
Scenario 3		3%	4%		32 (100%)	29 (90.6%)	28 (71.9%)	26 (81.3%)	28.8 (89.8%)
		5%	4%		31 (96.9%)	29 (90.6%)	32 (100%)	26 (81.3%)	29.5 (92.2%)
Scenario 4	1%				30 (93.8%)	29 (90.6%)	32 (100%)	26 (81.3%)	29.3 (91.4%)
	2%				30 (93.8%)	32 (100%)	32 (100%)	26 (81.3%)	30.0 (93.8%)
Scenario 5	1%			6%	31 (96.9%)	29 (90.6%)	32 (100%)	32 (100%)	31.0 (96.9%)
	1%			10%	32 (100%)	31 (96.9%)	32 (100%)	26 (81.3%)	30.3 (94.5%)
	2%			6%	30 (93.8%)	29 (90.6%)	32 (100%)	32 (100%)	30.8 (96.1%)
	2%			10%	30 (93.8%)	32 (100%)	32 (100%)	32 (100%)	31.5 (98.4%)
Scenario 6	1%	3%			30 (93.8%)	29 (90.6%)	32 (100%)	26 (81.3%)	29.3 (91.4%)
	1%	5%			32 (100%)	29 (90.6%)	32 (100%)	26 (81.3%)	29.8 (93.0%)
	2%	3%			30 (93.8%)	31 (96.9%)	30 (93.8%)	26 (81.3%)	29.3 (91.4%)
	2%	5%			31 (96.9%)	30 (93.8%)	28 (87.5%)	26 (81.3%)	28.8 (89.8%)
Scenario 7	1%	3%	4%		29 (90.6%)	28 (87.5%)	32 (100%)	26 (81.3%)	28.8 (89.8%)
	1%	5%	4%		29 (90.6%)	29 (90.6%)	32 (100%)	26 (81.3%)	29.0 (90.6%)
	2%	3%	4%		29 (90.6%)	31 (96.9%)	32 (100%)	26 (81.3%)	29.5 (92.2%)
	2%	5%	4%		29 (90.6%)	29 (90.6%)	32 (100%)	26 (81.3%)	29.0 (90.6%)
Average					30.2 (94.4%)	29.7 (92.7%)	31.5 (98.4%)	26.9 (84.1%)	29.6 (92.4%)

Table 3.7: Prediction results achieved after the EFDES-based system learned under condition of learning setting 1 compared with expert B's choices

Scenario					Accuracy of System-prediction Choices vs. Expert B's Choices				
	Δm	Δx	Δw	Δv	Predicting Regimen 1 using Regimen 2, 3 & 4	Predicting Regimen 2 using Regimen 1, 3 & 4	Predicting Regimen 3 using Regimen 1, 2 & 4	Predicting Regimen 4 using Regimen 1, 2 & 3	Mean prediction
Scenario 1				6%	32 (100%)	30 (93.8%)	31 (96.9%)	32 (100%)	31.3 (97.7%)
				10%	31 (96.9%)	30 (93.8%)	32 (100%)	32 (100%)	31.3 (97.7%)
Scenario 2		3%			32 (100%)	32 (100%)	30 (93.8%)	32 (100%)	31.5 (98.4%)
		5%			32 (100%)	30 (93.8%)	31 (96.9%)	32 (100%)	31.3 (97.7%)
Scenario 3		3%	4%		31 (96.9%)	32 (100%)	32 (100%)	30 (93.8%)	31.3 (97.7%)
		5%	4%		32 (100%)	32 (100%)	31 (96.9%)	32 (100%)	31.8 (99.2%)
Scenario 4	1%				32 (100%)	32 (100%)	32 (100%)	32 (100%)	32.0 (100%)
	2%				31 (96.9%)	30 (93.8%)	32 (100%)	32 (100%)	31.3 (97.7%)
Scenario 5	1%			6%	32 (100%)	32 (100%)	32 (100%)	29 (90.6%)	31.3 (97.7%)
	1%			10%	32 (100%)	31 (96.9%)	31 (96.9%)	29 (90.6%)	30.8 (96.1%)
	2%			6%	31 (96.9%)	32 (100%)	32 (100%)	29 (90.6%)	31.0 (96.9%)
	2%			10%	32 (100%)	32 (100%)	32 (100%)	32 (100%)	32.0 (100%)
Scenario 6	1%	3%			32 (100%)	26 (81.3%)	28 (87.5%)	32 (100%)	29.5 (92.2%)
	1%	5%			32 (100%)	32 (100%)	32 (100%)	31 (96.9%)	31.8 (99.2%)
	2%	3%			31 (96.9%)	28 (87.5%)	32 (100%)	28 (87.5%)	29.8 (93.0%)
	2%	5%			31 (96.9%)	32 (100%)	32 (100%)	32 (100%)	31.8 (99.2%)
Scenario 7	1%	3%	4%		32 (100%)	28 (87.5%)	30 (93.8%)	31 (96.9%)	30.3 (94.5%)
	1%	5%	4%		32 (100%)	30 (93.8%)	30 (93.8%)	31 (96.9%)	30.8 (96.1%)
	2%	3%	4%		32 (100%)	32 (100%)	32 (100%)	32 (100%)	32.0 (100%)
	2%	5%	4%		32 (100%)	30 (93.8%)	32 (100%)	31 (96.9%)	31.3 (97.7%)
Average					31.7 (99.1%)	30.7 (95.8%)	31.3 (97.8%)	31.1 (97.0%)	31.2 (97.5%)

Table 3.8: Prediction results achieved after the EFDES-based system learned under condition of learning setting 1 compared with the consensus of experts A&B

Scenario					Accuracy of System-prediction Choices vs. Consensus of Experts A & B				
	Δm	Δx	Δw	Δv	Predicting Regimen 1 using Regimen 2, 3 & 4	Predicting Regimen 2 using Regimen 1, 3 & 4	Predicting Regimen 3 using Regimen 1, 2 & 4	Predicting Regimen 4 using Regimen 1, 2 & 3	Mean prediction
Scenario 1				6%	31 (96.9%)	31 (96.9%)	31 (96.9%)	31 (96.9%)	31.0 (96.9%)
				10%	31 (96.9%)	30 (93.8%)	31 (96.9%)	29 (90.6%)	30.3 (94.5%)
Scenario 2		3%			28 (87.5%)	31 (96.9%)	31 (96.9%)	30 (93.8%)	30.0 (93.8%)
		5%			31 (96.9%)	31 (96.9%)	31 (96.9%)	29 (90.6%)	30.5 (95.3%)
Scenario 3		3%	4%		31 (96.9%)	30 (93.8%)	31 (96.9%)	28 (87.5%)	30.0 (93.8%)
		5%	4%		31 (96.9%)	29 (90.6%)	30 (93.8%)	28 (87.5%)	29.5 (92.2%)
Scenario 4	1%				30 (93.8%)	30 (93.8%)	31 (96.9%)	29 (90.6%)	30.0 (93.8%)
	2%				29 (90.6%)	30 (93.8%)	31 (96.9%)	29 (90.6%)	29.8 (93.0%)
Scenario 5	1%			6%	31 (96.9%)	30 (93.8%)	31 (96.9%)	30 (93.8%)	30.5 (95.3%)
	1%			10%	31 (96.9%)	31 (96.9%)	31 (96.9%)	28 (87.5%)	30.3 (94.5%)
	2%			6%	31 (96.9%)	30 (93.8%)	31 (96.9%)	28 (87.5%)	30.0 (93.8%)
	2%			10%	31 (96.9%)	30 (93.8%)	31 (96.9%)	31 (96.9%)	30.8 (96.1%)
Scenario 6	1%	3%			31 (96.9%)	30 (93.8%)	31 (96.9%)	29 (90.6%)	30.3 (94.5%)
	1%	5%			31 (96.9%)	29 (90.6%)	31 (96.9%)	30 (93.8%)	30.3 (94.5%)
	2%	3%			31 (96.9%)	31 (96.9%)	31 (96.9%)	28 (87.5%)	30.3 (94.5%)
	2%	5%			30 (93.8%)	29 (90.6%)	29 (90.6%)	28 (87.5%)	29.0 (90.6%)
Scenario 7	1%	3%	4%		30 (93.8%)	29 (90.6%)	31 (96.9%)	29 (90.6%)	29.8 (93.0%)
	1%	5%	4%		31 (96.9%)	29 (90.6%)	29 (90.6%)	28 (87.5%)	29.3 (91.4%)
	2%	3%	4%		30 (93.8%)	29 (90.6%)	30 (93.8%)	29 (90.6%)	29.5 (92.2%)
	2%	5%	4%		30 (93.8%)	31 (96.9%)	30 (93.8%)	30 (93.8%)	30.3 (94.5%)
Average					30.5 (95.3%)	30.0 (93.8%)	30.7 (95.8%)	29.1 (90.8%)	30.1 (93.9%)

Table 3.9: Prediction results for Regimen 1 and Regimen 2 achieved after the EFDES-based system learned under condition of learning setting 2 compared with expert A's choices

Scenario					Accuracy of System-prediction Choices vs. Expert A's Choices					
					Predicting					
	Δm	Δx	Δw	Δv	Regimen 1 using Regimen 2 & 3	Regimen 1 using Regimen 2 & 4	Regimen 1 using Regimen 3 & 4	Regimen 2 using Regimen 1 & 3	Regimen 2 using Regimen 1 & 4	Regimen 2 using Regimen 3 & 4
Scenario 1				6%	31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
				10%	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
Scenario 2		3%			31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
		5%			31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
Scenario 3		3%	4%		31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
		5%	4%		31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
Scenario 4	1%				31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%				32(100%)	31(96.9%)	32(100%)	31(96.9%)	32(100%)	32(100%)
Scenario 5	1%			6%	31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	1%			10%	32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	2%			6%	32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	2%			10%	32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
Scenario 6	1%	3%			32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	1%	5%			31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	2%	3%			31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	2%	5%			31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
Scenario 7	1%	3%	4%		32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	1%	5%	4%		31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	2%	3%	4%		31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	2%	5%	4%		31(96.9%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
Average					31.3(97.8%)	31.9(99.8%)	32(100%)	31.1(97.2%)	31.8(99.4%)	32(100%)

Table 3.10: Prediction results for Regimen 3 and Regimen 4 achieved after the EFDES-based system learned under condition of learning setting 2 compared with expert A's choices

Scenario					Accuracy of System-prediction Choices vs. Expert A's Choices					
					Predicting					
	Δm	Δx	Δw	Δv	Regimen 3 using Regimen 1 & 2	Regimen 3 using Regimen 1 & 4	Regimen 3 using Regimen 2 & 4	Regimen 4 using Regimen 1 & 2	Regimen 4 using Regimen 1 & 3	Regimen 4 using Regimen 2 & 3
Scenario 1				6%	32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
				10%	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
Scenario 2		3%			32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
		5%			31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
Scenario 3		3%	4%		32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
		5%	4%		31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
Scenario 4	1%				32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%				31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
Scenario 5	1%			6%	32(100%)	29(90.6%)	32(100%)	32(100%)	32(100%)	32(100%)
	1%			10%	32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%			6%	32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%			10%	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
Scenario 6	1%	3%			32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)
	1%	5%			32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%	3%			31(96.9%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%	5%			31(96.9%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
Scenario 7	1%	3%	4%		31(96.9%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
	1%	5%	4%		31(96.9%)	31(96.9%)	32(100%)	32(100%)	32(100%)	30(93.8%)
	2%	3%	4%		32(100%)	32(100%)	30(93.8%)	32(100%)	32(100%)	32(100%)
	2%	5%	4%		31(96.9%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
Average					31.6(98.8%)	31.4(98.0%)	31.9(99.5%)	32(100%)	32(100%)	31.9(99.7%)

Table 3.11: Prediction results for Regimen 1 and Regimen 2 achieved after the EFDES-based system learned under condition of learning setting 2 compared with expert B's choices

Scenario					Accuracy of System-prediction Choices vs. Expert B's Choices					
					Predicting					
	Δm	Δx	Δw	Δv	Regimen 1 using Regimen 2 & 3	Regimen 1 using Regimen 2 & 4	Regimen 1 using Regimen 3 & 4	Regimen 2 using Regimen 1 & 3	Regimen 2 using Regimen 1 & 4	Regimen 2 using Regimen 3 & 4
Scenario 1				6%	32(100%)	32(100%)	31(96.9%)	32(100%)	31(96.9%)	32(100%)
				10%	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
Scenario 2		3%			32(100%)	31(96.9%)	31(96.9%)	32(100%)	32(100%)	32(100%)
		5%			32(100%)	31(96.9%)	31(96.9%)	32(100%)	31(96.9%)	32(100%)
Scenario 3		3%	4%		32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)	30(93.8%)
		5%	4%		32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)
Scenario 4	1%				32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%				32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
Scenario 5	1%			6%	32(100%)	31(96.9%)	31(96.9%)	32(100%)	32(100%)	32(100%)
	1%			10%	32(100%)	32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)
	2%			6%	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%			10%	32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
Scenario 6	1%	3%			32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	30(93.8%)
	1%	5%			32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%	3%			32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%	5%			32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)	28(87.5%)
Scenario 7	1%	3%	4%		32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
	1%	5%	4%		32(100%)	32(100%)	32(100%)	32(100%)	31(96.9%)	28(87.5%)
	2%	3%	4%		32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)
	2%	5%	4%		32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
Average					32(100%)	31.7(98.9%)	31.7(98.9%)	32(100%)	31.8(99.4%)	31.4(98.1%)

Table 3.12: Prediction results for Regimen 3 and Regimen 4 achieved after the EFDES-based system learned under condition of learning setting 2 compared with expert B's choices

Scenario					Accuracy of System-prediction Choices vs. Expert B's Choices					
					Predicting					
	Δm	Δx	Δw	Δv	Regimen 3 using Regimen 1 & 2	Regimen 3 using Regimen 1 & 4	Regimen 3 using Regimen 2 & 4	Regimen 4 using Regimen 1 & 2	Regimen 4 using Regimen 1 & 3	Regimen 4 using Regimen 2 & 3
Scenario 1				6%	32(100%)	31(96.9%)	32(100%)	31(96.9%)	32(100%)	32(100%)
				10%	32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
Scenario 2		3%			32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
		5%			32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
Scenario 3		3%	4%		32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
		5%	4%		32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
Scenario 4	1%				32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	2%				31(96.9%)	32(100%)	30(93.8%)	32(100%)	32(100%)	32(100%)
Scenario 5	1%			6%	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
	1%			10%	32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	2%			6%	32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	2%			10%	32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
Scenario 6	1%	3%			32(100%)	32(100%)	32(100%)	31(96.9%)	32(100%)	32(100%)
	1%	5%			31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%	3%			32(100%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%	5%			32(100%)	32(100%)	28(87.5%)	31(96.9%)	32(100%)	32(100%)
Scenario 7	1%	3%	4%		32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
	1%	5%	4%		32(100%)	32(100%)	32(100%)	30(93.8%)	32(100%)	32(100%)
	2%	3%	4%		32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%	5%	4%		32(100%)	32(100%)	32(100%)	32(100%)	32(100%)	32(100%)
Average					31.9(99.7%)	31.9(99.5%)	31.7(99.1%)	31.5(98.3%)	32(100%)	32(100%)

Table 3.13: Prediction results for Regimen 1 and Regimen 2 achieved after the EFDES-based system learned under condition of learning setting 2 compared with the consensus of experts A & B

Scenario					Accuracy of System-prediction Choices vs. Consensus of Experts A & B					
					Predicting					
	Δm	Δx	Δw	Δv	Regimen 1 using Regimen 2 & 3	Regimen 1 using Regimen 2 & 4	Regimen 1 using Regimen 3 & 4	Regimen 2 using Regimen 1 & 3	Regimen 2 using Regimen 1 & 4	Regimen 2 using Regimen 3 & 4
Scenario 1				6%	29(90.6%)	31(96.9%)	32(100%)	30(93.8%)	30(93.8%)	32(100%)
				10%	29(90.6%)	32(100%)	32(100%)	30(93.8%)	30(93.8%)	31(96.9%)
Scenario 2		3%			29(90.6%)	32(100%)	32(100%)	29(90.6%)	30(93.8%)	32(100%)
		5%			29(90.6%)	32(100%)	32(100%)	30(93.8%)	30(93.8%)	31(96.9%)
Scenario 3		3%	4%		29(90.6%)	31(96.9%)	32(100%)	30(93.8%)	30(93.8%)	31(96.9%)
		5%	4%		29(90.6%)	32(100%)	32(100%)	30(93.8%)	30(93.8%)	32(100%)
Scenario 4	1%				28(87.5%)	31(96.9%)	32(100%)	30(93.8%)	30(93.8%)	31(96.9%)
	2%				30(93.8%)	31(96.9%)	32(100%)	30(93.8%)	30(93.8%)	32(100%)
Scenario 5	1%			6%	29(90.6%)	31(96.9%)	32(100%)	30(93.8%)	29(90.6%)	31(96.9%)
	1%			10%	29(90.6%)	32(100%)	32(100%)	30(93.8%)	30(93.8%)	32(100%)
	2%			6%	29(90.6%)	32(100%)	32(100%)	30(93.8%)	31(96.9%)	32(100%)
	2%			10%	29(90.6%)	31(96.9%)	32(100%)	30(93.8%)	31(96.9%)	31(96.9%)
Scenario 6	1%	3%			30(93.8%)	31(96.9%)	32(100%)	30(93.8%)	30(93.8%)	31(96.9%)
	1%	5%			30(93.8%)	31(96.9%)	32(100%)	30(93.8%)	29(90.6%)	31(96.9%)
	2%	3%			29(90.6%)	32(100%)	32(100%)	30(93.8%)	29(90.6%)	32(100%)
	2%	5%			27(84.4%)	31(96.9%)	32(100%)	30(93.8%)	29(90.6%)	32(100%)
Scenario 7	1%	3%	4%		29(90.6%)	31(96.9%)	32(100%)	30(93.8%)	30(93.8%)	32(100%)
	1%	5%	4%		29(90.6%)	32(100%)	32(100%)	30(93.8%)	30(93.8%)	31(96.9%)
	2%	3%	4%		30(93.8%)	31(96.9%)	32(100%)	30(93.8%)	29(90.6%)	32(100%)
	2%	5%	4%		30(93.8%)	32(100%)	32(100%)	29(90.6%)	29(90.6%)	31(96.9%)
Average					29.1(90.9%)	31.5(98.3%)	32(100%)	29.9(93.4%)	29.8(93.1%)	31.5(98.4%)

Table 3.14: Prediction results for Regimen 3 and Regimen 4 achieved after the EFDES-based system learned under condition of learning setting 2 compared with the consensus of experts A & B

Scenario					Accuracy of System-prediction Choices vs. Consensus of Experts A & B					
					Predicting					
	Δm	Δx	Δw	Δv	Regimen 3 using Regimen 1 & 2	Regimen 3 using Regimen 1 & 4	Regimen 3 using Regimen 2 & 4	Regimen 4 using Regimen 1 & 2	Regimen 4 using Regimen 1 & 3	Regimen 4 using Regimen 2 & 3
Scenario 1				6%	28(87.5%)	31(96.9%)	31(96.9%)	31(96.9%)	32(100%)	29(90.6%)
				10%	30(93.8%)	31(96.9%)	32(100%)	31(96.9%)	32(100%)	29(90.6%)
Scenario 2		3%			30(93.8%)	31(96.9%)	32(100%)	32(100%)	32(100%)	31(96.9%)
		5%			29(90.6%)	31(96.9%)	32(100%)	30(93.8%)	32(100%)	30(93.8%)
Scenario 3		3%	4%		29(90.6%)	31(96.9%)	32(100%)	32(100%)	32(100%)	29(90.6%)
		5%	4%		30(93.8%)	31(96.9%)	31(96.9%)	30(93.8%)	32(100%)	29(90.6%)
Scenario 4	1%				30(93.8%)	31(96.9%)	32(100%)	29(90.6%)	32(100%)	29(90.6%)
	2%				29(90.6%)	31(96.9%)	31(96.9%)	31(96.9%)	32(100%)	31(96.9%)
Scenario 5	1%			6%	29(90.6%)	32(100%)	31(96.9%)	30(93.8%)	32(100%)	32(100%)
	1%			10%	30(93.8%)	31(96.9%)	32(100%)	32(100%)	32(100%)	32(100%)
	2%			6%	30(93.8%)	31(96.9%)	32(100%)	31(96.9%)	32(100%)	31(96.9%)
	2%			10%	29(90.6%)	31(96.9%)	32(100%)	30(93.8%)	32(100%)	31(96.9%)
Scenario 6	1%	3%			28(87.5%)	31(96.9%)	31(96.9%)	31(96.9%)	32(100%)	29(90.6%)
	1%	5%			29(90.6%)	31(96.9%)	31(96.9%)	31(96.9%)	32(100%)	28(87.5%)
	2%	3%			30(93.8%)	31(96.9%)	32(100%)	30(93.8%)	32(100%)	31(96.9%)
	2%	5%			28(87.5%)	31(96.9%)	32(100%)	30(93.8%)	32(100%)	29(90.6%)
Scenario 7	1%	3%	4%		29(90.6%)	32(100%)	31(96.9%)	31(96.9%)	32(100%)	30(93.8%)
	1%	5%	4%		30(93.8%)	32(100%)	32(100%)	31(96.9%)	32(100%)	29(90.6%)
	2%	3%	4%		30(93.8%)	31(96.9%)	32(100%)	31(96.9%)	32(100%)	28(87.5%)
	2%	5%	4%		30(93.8%)	32(100%)	31(96.9%)	30(93.8%)	32(100%)	31(96.9%)
Average					29.4(91.7%)	31.2(97.5%)	31.6(98.8%)	30.7(95.9%)	31.9(99.8%)	29.9(93.4%)

Table 3.15: Prediction results achieved after the EFDES-based system learned under condition of learning setting 3 compared with expert A's choices

Scenario					Accuracy of System-prediction Choices vs. Expert A's Choices			
	Δm	Δx	Δw	Δv	Predicting Regimen 2 using Regimen 3 & 4	Predicting Regimen 3 using Regimen 2 & 4	Predicting Regimen 4 using Regimen 2 & 3	Mean prediction
Scenario 1				6%	25 (87.1%)	26 (81.3%)	23 (71.9%)	24.7 (77.1%)
				10%	28 (87.5%)	28 (87.5%)	23 (71.9%)	26.3 (82.3%)
Scenario 2		3%			22 (68.8%)	25 (78.1%)	23 (71.9%)	23.3 (72.9%)
		5%			23 (71.9%)	26 (81.3%)	23 (71.9%)	24.0 (75.0%)
Scenario 3		3%	4%		25 (78.1%)	24 (75.0%)	23 (71.9%)	24.0 (75.0%)
		5%	4%		21 (65.6%)	24 (75.0%)	23 (71.9%)	22.7 (70.8%)
Scenario 4	1%				25 (78.1%)	25 (78.1%)	23 (71.9%)	24.3 (76.0%)
	2%				23 (71.9%)	23 (71.9%)	23 (71.9%)	23.0 (71.9%)
Scenario 5	1%			6%	27 (84.4%)	26 (81.3%)	23 (71.9%)	25.3 (79.2%)
	1%			10%	27 (84.4%)	27 (84.4%)	23 (71.9%)	25.7 (80.2%)
	2%			6%	27 (84.4%)	28 (87.5%)	23 (71.9%)	26.0 (81.3%)
	2%			10%	24 (75.0%)	24 (75.0%)	23 (71.9%)	23.7 (74.0%)
Scenario 6	1%	3%			21 (65.6%)	24 (75.0%)	23 (71.9%)	22.7 (70.8%)
	1%	5%			24 (75.0%)	24 (75.0%)	23 (71.9%)	23.7 (74.0%)
	2%	3%			20 (62.5%)	22 (68.8%)	23 (71.9%)	21.7 (67.7%)
	2%	5%			23 (71.9%)	23 (71.9%)	23 (71.9%)	23.0 (71.9%)
Scenario 7	1%	3%	4%		21 (65.6%)	23 (71.9%)	23 (71.9%)	22.3 (69.8%)
	1%	5%	4%		25 (78.1%)	29 (90.6%)	23 (71.9%)	25.7 (80.2%)
	2%	3%	4%		23 (71.9%)	24 (75.0%)	23 (71.9%)	23.3 (72.9%)
	2%	5%	4%		24 (75.0%)	24 (75.0%)	23 (71.9%)	23.7 (74.0%)
Average					23.9 (74.7%)	25.0 (78.0%)	23.0 (71.9%)	24.0 (74.8%)

Table 3.16: Prediction results achieved after the EFDES-based system learned under condition of learning setting 3 compared with expert B's choices

Scenario					Accuracy of System-prediction Choices vs. Expert B's Choices			
	Δm	Δx	Δw	Δv	Predicting Regimen 2 using Regimen 3 & 4	Predicting Regimen 3 using Regimen 2 & 4	Predicting Regimen 4 using Regimen 2 & 3	Mean prediction
Scenario 1				6%	23 (71.9%)	25 (78.1%)	26 (81.3%)	24.7 (77.1%)
				10%	26 (81.3%)	26 (81.3%)	22 (68.8%)	24.7 (77.1%)
Scenario 2		3%			26 (81.3%)	26 (81.3%)	21 (65.6%)	24.3 (76.0%)
		5%			25 (78.1%)	20 (62.5%)	20 (62.5%)	21.7 (67.7%)
Scenario 3		3%	4%		26 (81.3%)	26 (81.3%)	25 (78.1%)	25.7 (80.2%)
		5%	4%		22 (68.8%)	26 (81.3%)	23 (71.9%)	23.7 (74.0%)
Scenario 4	1%				26 (81.3%)	22 (68.8%)	21 (65.6%)	23.0 (71.9%)
	2%				22 (68.8%)	26 (81.3%)	23 (71.9%)	23.7 (74.0%)
Scenario 5	1%			6%	26 (81.3%)	24 (75.0%)	27 (84.4%)	25.7 (80.2%)
	1%			10%	26 (81.3%)	26 (81.3%)	22 (68.8%)	24.7 (77.1%)
	2%			6%	26 (81.3%)	26 (81.3%)	23 (71.9%)	25.0 (78.1%)
	2%			10%	26 (81.3%)	26 (81.3%)	29 (90.6%)	27.0 (84.4%)
Scenario 6	1%	3%			26 (81.3%)	26 (81.3%)	22 (68.8%)	24.7 (77.1%)
	1%	5%			22 (68.8%)	26 (81.3%)	23 (71.9%)	23.7 (74.0%)
	2%	3%			23 (71.9%)	26 (81.3%)	19 (59.4%)	22.7 (70.8%)
	2%	5%			26 (81.3%)	20 (62.5%)	24 (75.0%)	23.3 (72.9%)
Scenario 7	1%	3%	4%		24 (75.0%)	26 (81.3%)	20 (62.5%)	23.3 (72.9%)
	1%	5%	4%		25 (78.1%)	25 (78.1%)	25 (78.1%)	25.0 (78.1%)
	2%	3%	4%		26 (81.3%)	25 (78.1%)	25 (78.1%)	25.3 (79.2%)
	2%	5%	4%		26 (81.3%)	26 (81.3%)	22 (68.8%)	24.7 (77.1%)
Average					24.9 (77.8%)	25.0 (78.0%)	23.1 (72.2%)	24.3 (76.0%)

Table 3.17: Prediction results achieved after the EFDES-based system learned under condition of learning setting 3 compared with the consensus of experts A&B

Scenario					Accuracy of System-prediction Choices vs. Consensus of Experts A & B			
	Δm	Δx	Δw	Δv	Predicting Regimen 2 using Regimen 3 & 4	Predicting Regimen 3 using Regimen 2 & 4	Predicting Regimen 4 using Regimen 2 & 3	Mean prediction
Scenario 1				6%	25 (78.1%)	26 (81.3%)	22 (68.8%)	24.3 (76.0%)
				10%	26 (81.3%)	24 (75.0%)	25 (78.1%)	25.0 (78.1%)
Scenario 2		3%			26 (81.3%)	24 (75.0%)	26 (81.3%)	25.3 (79.2%)
		5%			26 (81.3%)	26 (81.3%)	23 (71.9%)	25.0 (78.1%)
Scenario 3		3%	4%		26 (81.3%)	26 (81.3%)	23 (71.9%)	25.0 (78.1%)
		5%	4%		23 (71.9%)	21 (65.6%)	22 (68.8%)	22.0 (68.8%)
Scenario 4	1%				26 (81.3%)	26 (81.3%)	24 (75.0%)	25.3 (79.2%)
	2%				22 (68.8%)	26 (81.3%)	21 (65.6%)	23.0 (71.9%)
Scenario 5	1%			6%	25 (78.1%)	24 (75.0%)	25 (78.1%)	24.7 (77.1%)
	1%			10%	26 (81.3%)	26 (81.3%)	25 (78.1%)	25.7 (80.2%)
	2%			6%	22 (68.8%)	23 (71.9%)	22 (68.8%)	22.3 (69.8%)
	2%			10%	20 (62.5%)	26 (81.3%)	24 (75.0%)	23.3 (72.9%)
Scenario 6	1%	3%			26 (81.3%)	26 (81.3%)	20 (62.5%)	24.0 (75.0%)
	1%	5%			26 (81.3%)	25 (78.1%)	22 (68.8%)	24.3 (76.0%)
	2%	3%			23 (71.9%)	23 (71.9%)	21 (65.6%)	22.3 (69.8%)
	2%	5%			26 (81.3%)	21 (65.6%)	22 (68.8%)	23.0 (71.9%)
Scenario 7	1%	3%	4%		26 (81.3%)	21 (65.6%)	20 (62.5%)	22.3 (69.8%)
	1%	5%	4%		25 (78.1%)	26 (81.3%)	22 (68.8%)	24.3 (76.0%)
	2%	3%	4%		26 (81.3%)	25 (78.1%)	20 (62.5%)	23.7 (74.0%)
	2%	5%	4%		25 (78.1%)	26 (81.3%)	26 (81.3%)	25.7 (80.2%)
Average					24.8 (77.5%)	24.6 (76.7%)	22.8 (71.1%)	24.0 (75.1%)

Table 3.18: First-choice regimens predicted by the EFDES-based system model after regimen 2 was learned using regimens 3 & 4 against the actual regimens given to the 35 patients under scenarios 1, 2, 3, 4, and 5

Patient No.	Objectives	Given Regimens	Expert A	Expert B	Predicted regimens after regimen 2 was learned using regimens 3 & 4									
					Scenario 1 Δv (%)		Scenario 2 Δx (%)		Scenario 3 Δx, Δw (%)		Scenario 4 Δm (%)		Scenario 5 Δm, Δv (%)	
					6	10	3	5	3,4	5,4	1	2	1,6	1,10
1	23	4	4	4	4	4	4	4	4	4	4	4	4	4
2	23	4	4	4	4	4	4	4	4	4	4	4	4	4
3	10	4	2	2	2	2	2	2	2	2	2	2	2	2
4	9	4	2	4	4	4	4	4	4	4	4	4	4	4
5	23	4	4	4	4	4	4	4	4	4	4	4	4	4
6	23	4	4	4	4	4	4	4	4	4	4	4	4	4
7	23	4	4	4	4	4	4	4	4	4	4	4	4	4
8	9	4	2	4	4	4	4	4	4	4	4	4	4	4
9	10	2	2	2	2	2	2	2	2	2	2	2	2	2
10	9	4	2	4	4	4	4	4	4	4	4	4	4	4
11	23	4	4	4	4	4	4	4	4	4	4	4	4	4
12	23	4	4	4	4	4	4	4	4	4	4	4	4	4
13	9	4	2	4	4	4	4	4	4	4	4	4	4	4
14	9	4	2	4	4	4	4	4	4	4	4	4	4	4
15	10	2	2	2	2	2	2	2	2	2	2	2	2	2
16	9	4	2	4	4	4	4	4	4	4	4	4	4	4
17	23	3	4	4	4	4	4	4	4	4	4	4	4	4
18	23	4	4	4	4	4	4	4	4	4	4	4	4	4
19	24	4	2	4	4	4	4	4	4	4	4	4	4	4
20	23	2	4	4	4	4	4	4	4	4	4	4	4	4
21	23	4	4	4	4	4	4	4	4	4	4	4	4	4
22	23	4	4	4	4	4	4	4	4	4	4	4	4	4
23	23	4	4	4	4	4	4	4	4	4	4	4	4	4
24	23	4	4	4	4	4	4	4	4	4	4	4	4	4
25	23	4	4	4	4	4	4	4	4	4	4	4	4	4
26	23	3	4	4	4	4	4	4	4	4	4	4	4	4
27	23	4	4	4	4	4	4	4	4	4	4	4	4	4
28	9	4	2	4	4	4	4	4	4	4	4	4	4	4
29	9	4	2	4	4	4	4	4	4	4	4	4	4	4
30	23	4	4	4	4	4	4	4	4	4	4	4	4	4
31	10	2	2	2	2	2	2	2	2	2	2	2	2	2
32	10	4	2	2	2	2	2	2	2	2	2	2	2	2
33	23	4	4	4	4	4	4	4	4	4	4	4	4	4
34	10	3	2	2	2	2	2	2	2	2	2	2	2	2
35	9	4	2	4	4	4	4	4	4	4	4	4	4	4

Table 3.19: First-choice regimens predicted by the EFDES-based system model after regimen 2 was learned using regimens 3 & 4 against the actual regimens given to the 35 patients under scenarios 5, 6, and 7

Patient No.	Objectives	Given Regimens	Expert A	Expert B	Predicted regimens after regimen 2 was learned using Regimens 3 & 4									
					Scenario 5 Δm, Δv (%)		Scenario 6 Δm, Δx (%)				Scenario 7 Δm, Δx, Δw (%)			
					2,6	2,10	1,3	1,5	2,3	2,5	1,3,4	1,5,4	2,3,4	2,5,4
1	23	4	4	4	4	4	4	4	4	4	4	4	4	4
2	23	4	4	4	4	4	4	4	4	4	4	4	4	4
3	10	4	2	2	2	2	2	2	2	2	2	2	2	2
4	9	4	2	4	4	4	4	4	4	4	4	4	4	4
5	23	4	4	4	4	4	4	4	4	4	4	4	4	4
6	23	4	4	4	4	4	4	4	4	4	4	4	4	4
7	23	4	4	4	4	4	4	4	4	4	4	4	4	4
8	9	4	2	4	4	4	4	4	4	4	4	4	4	4
9	10	2	2	2	2	2	2	2	2	2	2	2	2	2
10	9	4	2	4	4	4	4	4	4	4	4	4	4	4
11	23	4	4	4	4	4	4	4	4	4	4	4	4	4
12	23	4	4	4	4	4	4	4	4	4	4	4	4	4
13	9	4	2	4	4	4	4	4	4	4	4	4	4	4
14	9	4	2	4	4	4	4	4	4	4	4	4	4	4
15	10	2	2	2	2	2	2	2	2	2	2	2	2	2
16	9	4	2	4	4	4	4	4	4	4	4	4	4	4
17	23	3	4	4	4	4	4	4	4	4	4	4	4	4
18	23	4	4	4	4	4	4	4	4	4	4	4	4	4
19	24	4	2	4	4	4	3	4	4	4	4	4	4	3
20	23	2	4	4	4	4	4	4	4	4	4	4	4	4
21	23	4	4	4	4	4	4	4	4	4	4	4	4	4
22	23	4	4	4	4	4	4	4	4	4	4	4	4	4
23	23	4	4	4	4	4	4	4	4	4	4	4	4	4
24	23	4	4	4	4	4	4	4	4	4	4	4	4	4
25	23	4	4	4	4	4	4	4	4	4	4	4	4	4
26	23	3	4	4	4	4	4	4	4	4	4	4	4	4
27	23	4	4	4	4	4	4	4	4	4	4	4	4	4
28	9	4	2	4	4	4	4	4	4	4	4	4	4	4
29	9	4	2	4	4	4	4	4	4	4	4	4	4	4
30	23	4	4	4	4	4	4	4	4	4	4	4	4	4
31	10	2	2	2	2	2	2	2	2	2	2	2	2	2
32	10	4	2	2	2	2	2	2	2	2	2	2	2	2
33	23	4	4	4	4	4	4	4	4	4	4	4	4	4
34	10	3	2	2	2	2	2	2	2	2	2	2	2	2
35	9	4	2	4	4	4	4	4	4	4	4	4	4	4

Table 3.20: First-choice regimens predicted by the EFDES-based system model after regimen 3 was learned using regimens 2 & 4 against the actual regimens given to the 35 patients under scenarios 1, 2, 3, 4, and 5

Patient No.	Objectives	Given Regimens	Expert A	Expert B	Predicted regimens after regimen 3 was learned using regimens 2 & 4									
					Scenario 1 Δv (%)		Scenario 2 Δx (%)		Scenario 3 Δx, Δw (%)		Scenario 4 Δm (%)		Scenario 5 Δm, Δv (%)	
					6	10	3	5	3,4	5,4	1	2	1,6	1,10
1	23	4	4	4	4	4	4	4	4	4	4	4	4	4
2	23	4	4	4	4	4	4	4	4	4	4	4	4	4
3	10	4	2	2	2	2	2	2	2	2	2	2	2	2
4	9	4	2	4	4	4	4	4	4	4	4	4	4	4
5	23	4	4	4	4	4	4	4	4	4	4	4	4	4
6	23	4	4	4	4	4	4	4	4	4	4	4	4	4
7	23	4	4	4	4	4	4	4	4	4	4	4	4	4
8	9	4	2	4	4	4	4	4	4	4	4	4	4	4
9	10	2	2	2	2	2	2	2	2	2	2	2	2	2
10	9	4	2	4	4	4	4	4	4	4	4	4	4	4
11	23	4	4	4	4	4	4	4	4	4	4	4	4	4
12	23	4	4	4	4	4	4	4	4	4	4	4	4	4
13	9	4	2	4	4	4	4	4	4	4	4	4	4	4
14	9	4	2	4	4	4	4	4	4	4	4	4	4	4
15	10	2	2	2	2	2	2	2	2	2	2	2	2	2
16	9	4	2	4	4	4	4	4	4	4	4	4	4	4
17	23	3	4	4	4	4	4	4	4	4	4	4	4	4
18	23	4	4	4	4	4	4	4	4	4	4	4	4	4
19	24	4	2	4	3	4	4	4	4	4	4	4	4	4
20	23	2	4	4	4	4	4	4	4	4	4	4	4	4
21	23	4	4	4	4	4	4	4	4	4	4	4	4	4
22	23	4	4	4	4	4	4	4	4	4	4	4	4	4
23	23	4	4	4	4	4	4	4	4	4	4	4	4	4
24	23	4	4	4	4	4	4	4	4	4	4	4	4	4
25	23	4	4	4	4	4	4	4	4	4	4	4	4	4
26	23	3	4	4	4	4	4	4	4	4	4	4	4	4
27	23	4	4	4	4	4	4	4	4	4	4	4	4	4
28	9	4	2	4	4	4	4	4	4	4	4	4	4	4
29	9	4	2	4	4	4	4	4	4	4	4	4	4	4
30	23	4	4	4	4	4	4	4	4	4	4	4	4	4
31	10	2	2	2	2	2	2	2	2	2	2	2	2	2
32	10	4	2	2	2	2	2	2	2	2	2	2	2	2
33	23	4	4	4	4	4	4	4	4	4	4	4	4	4
34	10	3	2	2	2	2	2	2	2	2	2	2	2	2
35	9	4	2	4	4	4	4	4	4	4	4	4	4	4

Table 3.21: First-choice regimens predicted by the EFDES-based system model after regimen 3 was learned using regimens 2 & 4 against the actual regimens given to the 35 patients under scenarios 5, 6, and 7

Patient No.	Objectives	Given Regimens	Expert A	Expert B	Predicted regimens after regimen 3 was learned using Regimens 2 & 4									
					Scenario 5 Δm, Δv (%)		Scenario 6 Δm, Δx (%)				Scenario 7 Δm, Δx, Δw (%)			
					2,6	2,10	1,3	1,5	2,3	2,5	1,3,4	1,5,4	2,3,4	2,5,4
1	23	4	4	4	4	4	4	4	4	4	4	4	4	4
2	23	4	4	4	4	4	4	4	4	4	4	4	4	4
3	10	4	2	2	2	2	2	2	2	2	2	2	2	2
4	9	4	2	4	4	4	4	4	4	4	4	4	4	4
5	23	4	4	4	4	4	4	4	4	4	4	4	4	4
6	23	4	4	4	4	4	4	4	4	4	4	4	4	4
7	23	4	4	4	4	4	4	4	4	4	4	4	4	4
8	9	4	2	4	4	4	4	4	4	4	4	4	4	4
9	10	2	2	2	2	2	2	2	2	2	2	2	2	2
10	9	4	2	4	4	4	4	4	4	4	4	4	4	4
11	23	4	4	4	4	4	4	4	4	4	4	4	4	4
12	23	4	4	4	4	4	4	4	4	4	4	4	4	4
13	9	4	2	4	4	4	4	4	4	4	4	4	4	4
14	9	4	2	4	4	4	4	4	4	4	4	4	4	4
15	10	2	2	2	2	2	2	2	2	2	2	2	2	2
16	9	4	2	4	4	4	4	4	4	4	4	4	4	4
17	23	3	4	4	4	4	4	4	4	4	4	4	4	4
18	23	4	4	4	4	4	4	4	4	4	4	4	4	4
19	24	4	2	4	4	4	3	4	4	4	3	4	4	4
20	23	2	4	4	4	4	4	4	4	4	4	4	4	4
21	23	4	4	4	4	4	4	4	4	4	4	4	4	4
22	23	4	4	4	4	4	4	4	4	4	4	4	4	4
23	23	4	4	4	4	4	4	4	4	4	4	4	4	4
24	23	4	4	4	4	4	4	4	4	4	4	4	4	4
25	23	4	4	4	4	4	4	4	4	4	4	4	4	4
26	23	3	4	4	4	4	4	4	4	4	4	4	4	4
27	23	4	4	4	4	4	4	4	4	4	4	4	4	4
28	9	4	2	4	4	4	4	4	4	4	4	4	4	4
29	9	4	2	4	4	4	4	4	4	4	4	4	4	4
30	23	4	4	4	4	4	4	4	4	4	4	4	4	4
31	10	2	2	2	2	2	2	2	2	2	2	2	2	2
32	10	4	2	2	2	2	2	2	2	2	2	2	2	2
33	23	4	4	4	4	4	4	4	4	4	4	4	4	4
34	10	3	2	2	2	2	2	2	2	2	2	2	2	2
35	9	4	2	4	4	4	4	4	4	4	4	4	4	4

Table 3.22: First-choice regimens predicted by the EFDES-based system model after regimen 4 was learned using regimens 2 & 3 against the actual regimens given to the 35 patients under scenarios 1, 2, 3, 4, and 5

Patient No.	Objectives	Given Regimens	Expert A	Expert B	Predicted regimens after regimen 4 was learned using regimens 2 & 3									
					Scenario 1 Δv (%)		Scenario 2 Δx (%)		Scenario 3 Δx, Δw (%)		Scenario 4 Δm (%)		Scenario 5 Δm, Δv (%)	
					6	10	3	5	3,4	5,4	1	2	1,6	1,10
1	23	4	4	4	4	4	4	4	4	4	4	4	4	4
2	23	4	4	4	4	4	4	4	4	4	4	4	4	4
3	10	4	2	2	2	2	2	2	2	2	2	2	2	2
4	9	4	2	4	4	4	4	4	4	4	4	4	4	4
5	23	4	4	4	4	4	4	4	4	4	4	4	4	4
6	23	4	4	4	4	4	4	4	4	4	4	4	4	4
7	23	4	4	4	4	4	4	4	4	4	4	4	4	4
8	9	4	2	4	4	4	4	4	4	4	4	4	4	4
9	10	2	2	2	2	2	2	2	2	2	2	2	2	2
10	9	4	2	4	4	4	4	4	4	4	4	4	4	4
11	23	4	4	4	4	4	4	4	4	4	4	4	4	4
12	23	4	4	4	4	4	4	4	4	4	4	4	4	4
13	9	4	2	4	4	4	4	4	4	4	4	4	4	4
14	9	4	2	4	4	4	4	4	4	4	4	4	4	4
15	10	2	2	2	2	2	2	2	2	2	2	2	2	2
16	9	4	2	4	4	4	4	4	4	4	4	4	4	4
17	23	3	4	4	4	4	4	4	4	4	4	4	4	4
18	23	4	4	4	4	4	4	4	4	4	4	4	4	4
19	24	4	2	4	2	2	4	4	2	2	2	4	4	4
20	23	2	4	4	4	4	4	4	4	4	4	4	4	4
21	23	4	4	4	4	4	4	4	4	4	4	4	4	4
22	23	4	4	4	4	4	4	4	4	4	4	4	4	4
23	23	4	4	4	4	4	4	4	4	4	4	4	4	4
24	23	4	4	4	4	4	4	4	4	4	4	4	4	4
25	23	4	4	4	4	4	4	4	4	4	4	4	4	4
26	23	3	4	4	4	4	4	4	4	4	4	4	4	4
27	23	4	4	4	4	4	4	4	4	4	4	4	4	4
28	9	4	2	4	4	4	4	4	4	4	4	4	4	4
29	9	4	2	4	4	4	4	4	4	4	4	4	4	4
30	23	4	4	4	4	4	4	4	4	4	4	4	4	4
31	10	2	2	2	2	2	2	2	2	2	2	2	2	2
32	10	4	2	2	2	2	2	2	2	2	2	2	2	2
33	23	4	4	4	4	4	4	4	4	4	4	4	4	4
34	10	3	2	2	2	2	2	2	2	2	2	2	2	2
35	9	4	2	4	4	4	4	4	4	4	4	4	4	4

Table 3.23: First-choice regimens predicted by the EFDES-based system model after regimen 4 was learned using regimens 2 & 3 against the actual regimens given to the 35 patients under scenarios 5, 6, and 7

Patient No.	Objectives	Given Regimens	Expert A	Expert B	Predicted regimens after regimen 4 was learned using Regimens 2 & 3									
					Scenario 5 Δm, Δv (%)		Scenario 6 Δm, Δx (%)				Scenario 7 Δm, Δx, Δw (%)			
					2,6	2,10	1,3	1,5	2,3	2,5	1,3,4	1,5,4	2,3,4	2,5,4
1	23	4	4	4	4	4	4	4	4	4	4	4	4	4
2	23	4	4	4	4	4	4	4	4	4	4	4	4	4
3	10	4	2	2	2	2	2	2	2	2	2	2	2	2
4	9	4	2	4	4	4	4	4	4	4	4	4	4	4
5	23	4	4	4	4	4	4	4	4	4	4	4	4	4
6	23	4	4	4	4	4	4	4	4	4	4	4	4	4
7	23	4	4	4	4	4	4	4	4	4	4	4	4	4
8	9	4	2	4	4	4	4	4	4	4	4	4	4	4
9	10	2	2	2	2	2	2	2	2	2	2	2	2	2
10	9	4	2	4	4	4	4	4	4	4	4	4	4	4
11	23	4	4	4	4	4	4	4	4	4	4	4	4	4
12	23	4	4	4	4	4	4	4	4	4	4	4	4	4
13	9	4	2	4	4	4	4	4	4	4	4	4	4	4
14	9	4	2	4	4	4	4	4	4	4	4	4	4	4
15	10	2	2	2	2	2	2	2	2	2	2	2	2	2
16	9	4	2	4	4	4	4	4	4	4	4	4	4	4
17	23	3	4	4	4	4	4	4	4	4	4	4	4	4
18	23	4	4	4	4	4	4	4	4	4	4	4	4	4
19	24	4	2	4	4	4	2	2	4	2	4	2	2	4
20	23	2	4	4	4	4	4	4	4	4	4	4	4	4
21	23	4	4	4	4	4	4	4	4	4	4	4	4	4
22	23	4	4	4	4	4	4	4	4	4	4	4	4	4
23	23	4	4	4	4	4	4	4	4	4	4	4	4	4
24	23	4	4	4	4	4	4	4	4	4	4	4	4	4
25	23	4	4	4	4	4	4	4	4	4	4	4	4	4
26	23	3	4	4	4	4	4	4	4	4	4	4	4	4
27	23	4	4	4	4	4	4	4	4	4	4	4	4	4
28	9	4	2	4	4	4	4	4	4	4	4	4	4	4
29	9	4	2	4	4	4	4	4	4	4	4	4	4	4
30	23	4	4	4	4	4	4	4	4	4	4	4	4	4
31	10	2	2	2	2	2	2	2	2	2	2	2	2	2
32	10	4	2	2	2	2	2	2	2	2	2	2	2	2
33	23	4	4	4	4	4	4	4	4	4	4	4	4	4
34	10	3	2	2	2	2	2	2	2	2	2	2	2	2
35	9	4	2	4	4	4	4	4	4	4	4	4	4	4

Table 3.24: Retrospective evaluation results after the EFDES-based system learned under condition of learning setting 4 involving 35 patients treated at AIDS Clinic in 2001

Scenario					Matching between regimen choices predicted by EFDES-based system and regimens prescribed by 2 experts and 11 non-experts			
	Δm	Δx	Δw	Δv	After Regimen 2 was learned using Regimen 3 & 4	After Regimen 3 was learned using Regimen 2 & 4	After Regimen 4 was learned using Regimen 2 & 3	Mean prediction
Scenario 1				6%	29 (82.9%)	28 (80.0%)	28 (80.0%)	28.3 (81.0%)
				10%	29 (82.9%)	29 (82.9%)	28 (80.0%)	28.7 (81.9%)
Scenario 2		3%			29 (82.9%)	29 (82.9%)	29 (82.9%)	29.0 (82.9%)
		5%			29 (82.9%)	29 (82.9%)	29 (82.9%)	29.0 (82.9%)
Scenario 3		3%	4%		29 (82.9%)	29 (82.9%)	28 (80.0%)	28.7 (81.9%)
		5%	4%		29 (82.9%)	29 (82.9%)	28 (80.0%)	28.7 (81.9%)
Scenario 4	1%				29 (82.9%)	29 (82.9%)	28 (80.0%)	28.7 (81.9%)
	2%				29 (82.9%)	29 (82.9%)	29 (82.9%)	29.0 (82.9%)
Scenario 5	1%			6%	29 (82.9%)	29 (82.9%)	29 (82.9%)	29.0 (82.9%)
	1%			10%	29 (82.9%)	29 (82.9%)	29 (82.9%)	29.0 (82.9%)
	2%			6%	29 (82.9%)	29 (82.9%)	29 (82.9%)	29.0 (82.9%)
	2%			10%	29 (82.9%)	29 (82.9%)	29 (82.9%)	29.0 (82.9%)
Scenario 6	1%	3%			28 (80.0%)	28 (80.0%)	28 (80.0%)	28.0 (80.0%)
	1%	5%			29 (82.9%)	29 (82.9%)	28 (80.0%)	28.7 (81.9%)
	2%	3%			29 (82.9%)	29 (82.9%)	29 (82.9%)	29.0 (82.9%)
	2%	5%			29 (82.9%)	29 (82.9%)	28 (80.0%)	28.7 (81.9%)
Scenario 7	1%	3%	4%		29 (82.9%)	28 (80.0%)	29 (82.9%)	28.7 (81.9%)
	1%	5%	4%		29 (82.9%)	29 (82.9%)	28 (80.0%)	28.7 (81.9%)
	2%	3%	4%		29 (82.9%)	29 (82.9%)	28 (80.0%)	28.7 (81.9%)
	2%	5%	4%		28 (80.0%)	29 (82.9%)	29 (82.9%)	28.7 (81.9%)
Average					28.9 (82.6%)	28.85 (82.4%)	28.5 (81.4%)	28.8 (82.1%)

Table 3.25: Retrospective evaluation results after the EFDES-based system learned under condition of learning setting 4 involving 35 patients against expert A's regimen choices

Scenario					Matching between regimen choices predicted by EFDES-based system and regimens prescribed by expert A			
	Δm	Δx	Δw	Δv	After Regimen 2 was learned using Regimen 3 & 4	After Regimen 3 was learned using Regimen 2 & 4	After Regimen 4 was learned using Regimen 2 & 3	Mean prediction
Scenario 1				6%	4 (100%)	4 (100%)	4 (100%)	4 (100%)
				10%	4 (100%)	4 (100%)	4 (100%)	4 (100%)
Scenario 2		3%			4 (100%)	4 (100%)	4 (100%)	4 (100%)
		5%			4 (100%)	4 (100%)	4 (100%)	4 (100%)
Scenario 3		3%	4%		4 (100%)	4 (100%)	4 (100%)	4 (100%)
		5%	4%		4 (100%)	4 (100%)	4 (100%)	4 (100%)
Scenario 4	1%				4 (100%)	4 (100%)	4 (100%)	4 (100%)
	2%				4 (100%)	4 (100%)	4 (100%)	4 (100%)
Scenario 5	1%			6%	4 (100%)	4 (100%)	4 (100%)	4 (100%)
	1%			10%	4 (100%)	4 (100%)	4 (100%)	4 (100%)
	2%			6%	4 (100%)	4 (100%)	4 (100%)	4 (100%)
	2%			10%	4 (100%)	4 (100%)	4 (100%)	4 (100%)
Scenario 6	1%	3%			4 (100%)	4 (100%)	4 (100%)	4 (100%)
	1%	5%			4 (100%)	4 (100%)	4 (100%)	4 (100%)
	2%	3%			4 (100%)	4 (100%)	4 (100%)	4 (100%)
	2%	5%			4 (100%)	4 (100%)	4 (100%)	4 (100%)
Scenario 7	1%	3%	4%		4 (100%)	4 (100%)	4 (100%)	4 (100%)
	1%	5%	4%		4 (100%)	4 (100%)	4 (100%)	4 (100%)
	2%	3%	4%		4 (100%)	4 (100%)	4 (100%)	4 (100%)
	2%	5%	4%		4 (100%)	4 (100%)	4 (100%)	4 (100%)
Average					4 (100%)	4 (100%)	4 (100%)	4 (100%)

Table 3.26: Retrospective evaluation results after the EFDES-based system learned under condition of learning setting 4 involving 35 patients against expert B's regimen choices

Scenario					Matching between regimen choices predicted by EFDES-based system and regimens prescribed by expert B			
	Δm	Δx	Δw	Δv	After Regimen 2 was learned using Regimen 3 & 4	After Regimen 3 was learned using Regimen 2 & 4	After Regimen 4 was learned using Regimen 2 & 3	Mean prediction
Scenario 1				6%	8 (100%)	8 (100%)	8 (100%)	8 (100%)
				10%	8 (100%)	8 (100%)	8 (100%)	8 (100%)
Scenario 2		3%			8 (100%)	8 (100%)	8 (100%)	8 (100%)
		5%			8 (100%)	8 (100%)	8 (100%)	8 (100%)
Scenario 3		3%	4%		8 (100%)	8 (100%)	8 (100%)	8 (100%)
		5%	4%		8 (100%)	8 (100%)	8 (100%)	8 (100%)
Scenario 4	1%				8 (100%)	8 (100%)	8 (100%)	8 (100%)
	2%				8 (100%)	8 (100%)	8 (100%)	8 (100%)
Scenario 5	1%			6%	8 (100%)	8 (100%)	8 (100%)	8 (100%)
	1%			10%	8 (100%)	8 (100%)	8 (100%)	8 (100%)
	2%			6%	8 (100%)	8 (100%)	8 (100%)	8 (100%)
	2%			10%	8 (100%)	8 (100%)	8 (100%)	8 (100%)
Scenario 6	1%	3%			8 (100%)	8 (100%)	8 (100%)	8 (100%)
	1%	5%			8 (100%)	8 (100%)	8 (100%)	8 (100%)
	2%	3%			8 (100%)	8 (100%)	8 (100%)	8 (100%)
	2%	5%			8 (100%)	8 (100%)	8 (100%)	8 (100%)
Scenario 7	1%	3%	4%		8 (100%)	8 (100%)	8 (100%)	8 (100%)
	1%	5%	4%		8 (100%)	8 (100%)	8 (100%)	8 (100%)
	2%	3%	4%		8 (100%)	8 (100%)	8 (100%)	8 (100%)
	2%	5%	4%		8 (100%)	8 (100%)	8 (100%)	8 (100%)
Average					8 (100%)	8 (100%)	8 (100%)	8 (100%)

Table 3.27: Weight vectors optimized by the EFDES-based system model after regimen 2 was learned using regimens 3 & 4 regarding to regimen-choice prediction against the actual regimens given to the 35 patients under scenarios 1, 2, 3, 4, and 5

Optimal weight vectors after regimen 2 was learned using regimens 3 & 4										
$[W1 \ldots W26]^T$	Scenario 1 Δv (%)		Scenario 2 Δx (%)		Scenario 3 Δx, Δw (%)		Scenario 4 Δm (%)		Scenario 5 Δm, Δv (%)	
	6	10	3	5	3,4	5,4	1	2	1,6	1,10
W1	0.9961	0.9648	0.8984	0.9258	0.5547	0.9063	0.9844	0.9609	0.9063	0.9844
W2	0.0039	0.0352	0.1016	0.0742	0.4453	0.0938	0.0156	0.0391	0.0938	0.0156
W3	0.6061	0.5664	0.5938	0.7148	0.3828	0.7148	0.6719	0.2344	0.4258	0.7852
W4	0.3984	0.4336	0.4063	0.2852	0.6172	0.2852	0.3281	0.7656	0.5742	0.2124
W5	0.5595	0.2550	0.3576	0.3948	0.1365	0.4167	0.3856	0.1476	0.2471	0.6165
W6	0.0000	0.2114	0.0766	0.0798	0.0310	0.1173	0.1753	0.1518	0.1174	0.1091
W7	0.2259	0.0615	0.1429	0.0361	0.0283	0.1335	0.0000	0.0320	0.0000	0.2166
W8	0.1389	0.2928	0.4778	0.3333	0.2415	0.2014	0.4280	0.1978	0.4431	0.2756
W9	0.2485	0.3307	0.3527	0.3568	0.4028	0.3464	0.3506	0.7855	0.5563	0.5477
W10	0.3283	0.2062	0.4125	0.7590	0.7767	0.3552	0.5309	0.4306	0.4838	0.4679
W11	0.3016	0.4522	0.1646	0.2718	0.6220	0.3819	0.1864	0.6546	0.3098	0.1080
W12	0.7515	0.4579	0.5708	0.5634	0.5662	0.5363	0.4740	0.0627	0.3263	0.3432
W13	0.4458	0.7323	0.4447	0.2048	0.1950	0.5113	0.4691	0.5374	0.5162	0.3155
W14	0.4962	0.2220	0.3063	0.0942	0.4655	0.2884	0.3538	0.2977	0.2920	0.2253
W15	0.2519	0.3067	0.2584	0.0376	0.1418	0.3352	0.0769	0.3531	0.4734	0.2319
W16	0.2458	0.1186	0.1062	0.0072	0.1889	0.0000	0.1179	0.0443	0.2704	0.0980
W17	0.3295	0.4379	0.5023	0.4448	0.3103	0.4775	0.2028	0.3550	0.5487	0.4660
W18	0.1325	0.2073	0.5084	0.3145	0.3014	0.2700	0.2154	0.0323	0.0000	0.3831
W19	0.0085	0.4787	0.2080	0.2862	0.1940	0.2072	0.1282	0.3986	0.2704	0.3358
W20	0.1742	0.3401	0.1914	0.4610	0.2241	0.2340	0.4434	0.3473	0.1593	0.3086
W21	0.6156	0.4860	0.2331	0.6478	0.5567	0.3948	0.7077	0.6146	0.5266	0.3851
W22	0.7458	0.4027	0.6858	0.7065	0.6171	0.7928	0.7538	0.5571	0.4591	0.5662
W23	0.9766	0.9141	0.9023	0.8750	0.9063	0.8867	0.9219	0.9102	0.9180	0.9023
W24	0.0234	0.0859	0.0977	0.1250	0.0938	0.1133	0.0781	0.0898	0.0820	0.0977
W25	0.4531	0.5977	0.5234	0.5156	0.5273	0.5078	0.4805	0.4297	0.5977	0.5898
W26	0.5469	0.4023	0.4766	0.4844	0.4727	0.4922	0.5195	0.5703	0.4023	0.4102

Table 3.28: Weight vectors optimized by the EFDES-based system model after regimen 2 was learned using regimens 3 & 4 regarding to regimen-choice prediction against the actual regimens given to the 35 patients under scenarios 5, 6, and 7

Optimal weight vectors after regimen 2 was learned using regimens 3 & 4										
$[W1 \ldots W26]^T$	Scenario 5 Δm, Δv (%)		Scenario 6 Δm, Δx (%)				Scenario 7 Δm, Δx, Δw (%)			
	2,6	2,10	1,3	1,5	2,3	2,5	1,3,4	1,5,4	2,3,4	2,5,4
W1	0.7031	0.6953	0.9414	0.8242	0.9883	0.9570	0.9180	0.8477	0.9844	0.9922
W2	0.2969	0.3047	0.0586	0.1758	0.0117	0.0430	0.0820	0.1523	0.0156	0.0078
W3	0.1211	0.5742	0.8906	0.3906	0.8594	0.6875	0.6133	0.4023	0.7031	0.4219
W4	0.8789	0.4258	0.1094	0.6094	0.1406	0.3125	0.3867	0.5977	0.2969	0.5781
W5	0.4316	0.5556	0.7041	0.4044	0.4279	0.3481	0.4254	0.3977	0.3657	0.0227
W6	0.0246	0.1147	0.0000	0.0162	0.0178	0.0706	0.0426	0.0000	0.0063	0.0000
W7	0.0373	0.0000	0.1028	0.3941	0.0246	0.0860	0.0649	0.1904	0.0205	0.1199
W8	0.2188	0.0480	0.2633	0.1444	0.0349	0.3038	0.0263	0.2917	0.0926	0.8333
W9	0.5055	0.2907	0.6184	0.6757	0.8994	0.0118	0.4134	0.2185	0.5104	0.7360
W10	0.4959	0.4533	0.0356	0.3501	0.4676	0.4507	0.3052	0.4729	0.6404	0.1901
W11	0.3495	0.3964	0.0325	0.4511	0.5372	0.3481	0.5482	0.3106	0.5417	0.1439
W12	0.4699	0.5947	0.3816	0.3081	0.0828	0.9176	0.5441	0.7815	0.4833	0.2640
W13	0.4668	0.5467	0.8617	0.2558	0.5078	0.4633	0.6299	0.3367	0.3390	0.6901
W14	0.4387	0.0158	0.1241	0.4140	0.3825	0.5850	0.4918	0.5943	0.3907	0.5356
W15	0.0741	0.1231	0.4124	0.0149	0.1866	0.0333	0.0887	0.0335	0.0472	0.3312
W16	0.2679	0.1388	0.2339	0.0032	0.2137	0.1229	0.0255	0.0217	0.0758	0.2792
W17	0.3467	0.6474	0.8459	0.1646	0.3257	0.0751	0.2951	0.2547	0.1589	0.0627
W18	0.5714	0.1415	0.2372	0.3358	0.2935	0.5917	0.0000	0.5223	0.1635	0.4183
W19	0.1518	0.0239	0.3387	0.1812	0.1945	0.3455	0.0727	0.2446	0.0000	0.1484
W20	0.2146	0.3368	0.0301	0.4214	0.2919	0.3399	0.2131	0.1509	0.4505	0.4017
W21	0.3545	0.7354	0.3504	0.6493	0.5199	0.3750	0.9113	0.4442	0.7893	0.2505
W22	0.5804	0.8373	0.4274	0.8155	0.5918	0.5316	0.9018	0.7337	0.9242	0.5724
W23	0.9023	0.9844	0.9570	0.8594	0.9492	0.9648	0.9609	0.9922	0.9063	0.9531
W24	0.0977	0.0156	0.0430	0.1406	0.0508	0.0352	0.0391	0.0078	0.0938	0.0469
W25	0.4141	0.3789	0.1250	0.3789	0.6523	0.6484	0.4063	0.4648	0.5078	0.3164
W26	0.5859	0.6211	0.8750	0.6211	0.3477	0.3516	0.5938	0.5352	0.4922	0.6836

Table 3.29: Weight vectors optimized by the EFDES-based system model after regimen 3 was learned using regimens 3 & 4 regarding to regimen-choice prediction against the actual regimens given to the 35 patients under scenarios 1, 2, 3, 4, and 5

Optimal weight vectors after regimen 3 was learned using regimens 3 & 4										
$[W1 \ldots W26]^T$	Scenario 1 Δv (%)		Scenario 2 Δx (%)		Scenario 3 Δx, Δw (%)		Scenario 4 Δm (%)		Scenario 5 Δm, Δv (%)	
	6	10	3	5	3,4	5,4	1	2	1,6	1,10
W1	0.8516	0.9883	0.8125	0.9961	0.8242	0.9414	0.9531	0.9453	0.9766	0.7422
W2	0.1484	0.0117	0.1875	0.0039	0.1758	0.0586	0.0469	0.0547	0.0234	0.2578
W3	0.0117	0.0742	0.5430	0.4180	0.4531	0.3945	0.5664	0.2070	0.2695	0.3633
W4	0.9883	0.9258	0.4570	0.5820	0.5469	0.6055	0.4336	0.7930	0.7305	0.6367
W5	0.6284	0.4048	0.4257	0.4668	0.4542	0.4882	0.3830	0.3674	0.3991	0.4671
W6	0.0764	0.0026	0.0633	0.0000	0.0361	0.0808	0.1182	0.0056	0.0339	0.0160
W7	0.0118	0.0036	0.1444	0.0857	0.1655	0.1514	0.0320	0.1807	0.2733	0.1963
W8	0.2020	0.0661	0.4119	0.4487	0.3250	0.1706	0.1491	0.5116	0.2363	0.4362
W9	0.6545	0.3641	0.6051	0.3307	0.0201	0.4377	0.7389	0.6704	0.2000	0.3590
W10	0.2835	0.1511	0.5802	0.4514	0.5374	0.2771	0.4160	0.7695	0.4990	0.3458
W11	0.1696	0.5291	0.1624	0.0845	0.2208	0.3412	0.4679	0.1209	0.3646	0.0967
W12	0.2691	0.6332	0.3316	0.6693	0.9438	0.4815	0.1429	0.3239	0.7661	0.6250
W13	0.7047	0.8453	0.2754	0.4629	0.2971	0.5714	0.5520	0.0498	0.2277	0.4579
W14	0.4092	0.3661	0.4836	0.2043	0.3991	0.4658	0.3410	0.3761	0.4289	0.4008
W15	0.3584	0.0915	0.0102	0.1754	0.1368	0.1083	0.0975	0.2500	0.0701	0.0436
W16	0.2158	0.0437	0.0052	0.0867	0.0060	0.1343	0.0947	0.2901	0.0000	0.2964
W17	0.3175	0.3178	0.0922	0.5489	0.0540	0.1065	0.4276	0.2495	0.4444	0.3175
W18	0.0050	0.2465	0.2653	0.3578	0.0211	0.4509	0.4665	0.4239	0.4227	0.5047
W19	0.1612	0.2216	0.1510	0.2704	0.0299	0.0813	0.4474	0.1533	0.3473	0.0240
W20	0.2733	0.3161	0.4242	0.2468	0.5469	0.4278	0.2314	0.3743	0.1267	0.2817
W21	0.6366	0.6620	0.7245	0.4668	0.8421	0.4408	0.4359	0.3261	0.5072	0.4517
W22	0.6230	0.7347	0.8438	0.6429	0.9641	0.7845	0.4579	0.5566	0.6527	0.6796
W23	0.8984	0.9453	0.8555	0.9297	0.7695	0.8672	0.9609	0.9492	0.9688	0.8711
W24	0.1016	0.0547	0.1445	0.0703	0.2305	0.1328	0.0391	0.0508	0.0313	0.1289
W25	0.1719	0.2383	0.4297	0.4766	0.3359	0.4375	0.5469	0.5000	0.3555	0.4336
W26	0.8281	0.7617	0.5703	0.5234	0.6641	0.5625	0.4531	0.5000	0.6445	0.5664

Table 3.30: Weight vectors optimized by the EFDES-based system model after regimen 3 was learned using regimens 3 & 4 regarding to regimen-choice prediction against the actual regimens given to the 35 patients under scenarios 5, 6, and 7

Optimal weight vectors after regimen 3 was learned using regimens 3 & 4										
$[W1 \ldots W26]^T$	Scenario 5 Δm, Δv (%)		Scenario 6 Δm, Δx (%)				Scenario 7 Δm, Δx, Δw (%)			
	2,6	2,10	1,3	1,5	2,3	2,5	1,3,4	1,5,4	2,3,4	2,5,4
W1	0.8750	0.7266	0.9648	0.9375	0.8828	0.8711	0.8750	0.8750	0.9375	0.9805
W2	0.1250	0.2734	0.0352	0.0625	0.1172	0.1289	0.1250	0.1250	0.0625	0.0195
W3	0.1719	0.2266	0.4570	0.6055	0.7813	0.4727	0.6289	0.5625	0.6016	0.5156
W4	0.8281	0.7734	0.5430	0.3945	0.2188	0.5273	0.3711	0.4375	0.3984	0.4844
W5	0.5457	0.4128	0.3730	0.4104	0.2670	0.3711	0.4530	0.4497	0.3198	0.4990
W6	0.0126	0.0659	0.0453	0.1703	0.0664	0.0204	0.0041	0.1039	0.0080	0.0233
W7	0.2527	0.1480	0.0282	0.2188	0.1159	0.0409	0.2143	0.1884	0.0676	0.1474
W8	0.3370	0.0000	0.5000	0.3918	0.5668	0.3377	0.4384	0.3073	0.4291	0.1598
W9	0.7573	0.4516	0.4887	0.1731	0.7345	0.3852	0.1317	0.0390	0.4987	0.4067
W10	0.6374	0.3935	0.1975	0.0997	0.3123	0.3534	0.5652	0.1594	0.1351	0.1579
W11	0.1174	0.5872	0.1270	0.1978	0.1662	0.2913	0.1086	0.2430	0.2510	0.3412
W12	0.2301	0.4826	0.4660	0.6566	0.1991	0.5944	0.8642	0.8571	0.4933	0.5699
W13	0.1099	0.4585	0.7743	0.6814	0.5718	0.6058	0.2205	.06522	0.7973	0.6947
W14	0.3353	0.3646	0.4517	0.2121	0.3997	0.5395	0.3822	0.0868	0.4016	0.5195
W15	0.0279	0.0996	0.0215	0.1189	0.1881	0.1447	0.0174	0.0404	0.1041	0.1689
W16	0.0078	0.0000	0.0979	0.1406	0.0718	0.0000	0.0699	0.0090	0.0123	0.1667
W17	0.4651	0.4827	0.2437	0.5939	0.2147	0.2719	0.3030	0.6497	0.3951	0.1273
W18	0.0906	0.5125	0.5161	0.3351	0.0321	0.0675	0.0348	0.1324	0.0372	0.3406
W19	0.0196	0.3649	0.2723	0.1484	0.2241	0.0000	0.0294	0.0135	0.1399	0.0349
W20	0.1996	0.1527	0.3046	0.1939	0.3856	0.1886	0.3149	0.2635	0.2033	0.3532
W21	0.8815	0.3879	0.4624	0.5459	0.7798	0.7878	0.9478	0.8272	0.8587	0.4905
W22	0.9725	0.6351	0.6298	0.7109	0.7040	1.0000	0.9007	0.9776	0.8477	0.7984
W23	0.9688	0.8984	0.9375	0.8633	0.8672	0.9727	0.8633	0.8047	0.9531	0.9531
W24	0.0313	0.1016	0.0625	0.1367	0.1328	0.0273	0.1367	0.1953	0.0469	0.0469
W25	0.1758	0.3945	0.4883	0.5273	0.6016	0.4336	0.3906	0.3906	0.4844	0.4961
W26	0.8242	0.6055	0.5117	0.4727	0.3984	0.5664	0.6094	0.6094	0.5156	0.5039

Table 3.31: Weight vectors optimized by the EFDES-based system model after regimen 4 was learned using regimens 3 & 4 regarding to regimen-choice prediction against the actual regimens given to the 35 patients under scenarios 1, 2, 3, 4, and 5

Optimal weight vectors after regimen 4 was learned using regimens 3 & 4										
$[W1 \ldots W26]^T$	Scenario 1 Δv (%)		Scenario 2 Δx (%)		Scenario 3 Δx, Δw (%)		Scenario 4 Δm (%)		Scenario 5 Δm, Δv (%)	
	6	10	3	5	3,4	5,4	1	2	1,6	1,10
W1	0.8125	0.8242	0.8281	0.9883	0.9805	0.9766	0.8633	0.9180	0.7188	0.9336
W2	0.1875	0.1758	0.1719	0.0117	0.0195	0.0234	0.1367	0.0820	0.2812	0.0664
W3	0.7266	0.6758	0.6055	0.7656	0.8359	0.9453	0.7773	0.4102	0.3047	0.6641
W4	0.2734	0.3242	0.3945	0.2344	0.1641	0.0547	0.2227	0.5898	0.6953	0.3359
W5	0.1103	0.0435	0.2248	0.2010	0.1006	0.0963	0.0725	0.3196	0.1304	0.3399
W6	0.2015	0.0946	0.1986	0.0475	0.1374	0.0495	0.2115	0.1010	0.0222	0.0891
W7	0.1522	0.0559	0.0763	0.0401	0.1072	0.1141	0.0279	0.0000	0.0314	0.0000
W8	0.4766	0.1706	0.0906	0.1127	0.4043	0.5652	0.4352	0.5434	0.3681	0.4644
W9	0.7839	0.7027	0.4513	0.4727	0.7863	0.4346	0.7038	0.7981	0.5817	0.7442
W10	0.6505	0.5155	0.4322	0.4114	0.4239	0.3747	0.2351	0.8659	0.2780	0.1307
W11	0.4131	0.7860	0.6846	0.6863	0.4951	0.3385	0.4923	0.1370	0.5014	0.1957
W12	0.0147	0.2027	0.3502	0.4798	0.0763	0.5159	0.0846	0.1010	0.3961	0.1667
W13	0.1972	0.4286	0.4915	0.5485	0.4688	0.5112	0.7371	0.1341	0.6906	0.8693
W14	0.1117	0.1852	0.0729	0.3145	0.3441	0.6675	0.4222	0.0417	0.4425	0.1532
W15	0.4390	0.0306	0.0000	0.1701	0.0952	0.4986	0.0765	0.0969	0.2831	0.3710
W16	0.2149	0.3484	0.1284	0.2900	0.1107	0.2730	0.4563	0.0028	0.2874	0.2072
W17	0.7011	0.7444	0.3576	0.3585	0.2847	0.0157	0.2997	0.4091	0.1692	0.5065
W18	0.0528	0.4311	0.4144	0.5773	0.2143	0.0220	0.4074	0.2602	0.3108	0.1734
W19	0.2829	0.2628	0.1318	0.1382	0.4777	0.1009	0.1944	0.3583	0.0323	0.3750
W20	0.1872	0.0704	0.5694	0.3270	0.3713	0.3168	0.2781	0.5492	0.3883	0.3403
W21	0.5081	0.5383	0.5856	0.2526	0.6905	0.4793	0.5160	0.6429	0.4062	0.4556
W22	0.5022	0.3888	0.7399	0.5718	0.4117	0.6261	0.3492	0.6389	0.6804	0.4178
W23	0.8555	0.9258	0.7031	0.9258	0.8945	0.9922	0.9023	0.8750	0.8281	0.8984
W24	0.1445	0.0742	0.2969	0.0742	0.1055	0.0078	0.0977	0.1250	0.1719	0.1016
W25	0.0547	0.5977	0.4766	0.7539	0.2773	0.1328	0.2813	0.4492	0.4570	0.6523
W26	0.9453	0.4023	0.5234	0.2461	0.7227	0.8672	0.7188	0.5508	0.5430	0.3477

Table 3.32: Weight vectors optimized by the EFDES-based system model after regimen 4 was learned using regimens 3 & 4 regarding to regimen-choice prediction against the actual regimens given to the 35 patients under scenarios 5, 6, and 7

Optimal weight vectors after regimen 4 was learned using regimens 3 & 4										
$[W1 \ldots W26]^T$	Scenario 5 Δm, Δv (%)		Scenario 6 Δm, Δx (%)				Scenario 7 Δm, Δx, Δw (%)			
	2,6	2,10	1,3	1,5	2,3	2,5	1,3,4	1,5,4	2,3,4	2,5,4
W1	0.6328	0.9844	0.8125	0.8906	0.9844	0.9141	0.8945	0.8125	0.9688	0.9844
W2	0.3672	0.0156	0.1875	0.1094	0.0156	0.0859	0.1055	0.1875	0.0312	0.0156
W3	0.3906	0.5234	0.7344	0.8711	0.8008	0.8906	0.8555	0.7578	0.8711	0.7539
W4	0.6094	0.4766	0.2656	0.1289	0.1992	0.1094	0.1445	0.2422	0.1289	0.2461
W5	0.1525	0.4122	0.0136	0.1303	0.2735	0.0305	0.1353	0.0841	0.1696	0.2374
W6	0.0823	0.1280	0.0132	0.1586	0.1527	0.0173	0.0352	0.0389	0.1449	0.0913
W7	0.0102	0.0604	0.0282	0.0316	0.0600	0.1000	0.0870	0.0997	0.1461	0.0202
W8	0.4159	0.2020	0.2678	0.2515	0.2531	0.3807	0.4244	0.4425	0.3743	0.0091
W9	0.3591	0.2720	0.8987	0.3793	0.4466	0.5446	0.5352	0.8198	0.6996	0.3053
W10	0.5563	0.5165	0.3548	0.5854	0.2067	0.0688	0.5761	0.3196	0.5205	0.1869
W11	0.4315	0.3857	0.7186	0.6182	0.4735	0.5888	0.4403	0.4735	0.4561	0.7534
W12	0.5586	0.6000	0.0881	0.4621	0.4008	0.4381	0.4297	0.1413	0.1555	0.6034
W13	0.4334	0.4231	0.6169	0.3829	0.7333	0.8313	0.3370	0.5806	0.3333	0.7929
W14	0.3877	0.2899	0.4574	0.1287	0.1319	0.5753	0.3351	0.0874	0.0853	0.3803
W15	0.0815	0.2000	0.0435	0.3725	0.2417	0.4884	0.1198	0.0986	0.1671	0.3565
W16	0.2686	0.1837	0.2763	0.0344	0.1010	0.0240	0.1596	0.0956	0.2042	0.1923
W17	0.3111	0.3445	0.1064	0.3458	0.5852	0.2226	0.2193	0.5336	0.4167	0.2356
W18	0.5778	0.2833	0.0725	0.0196	0.2384	0.2300	0.4392	0.0563	0.1813	0.0783
W19	0.3039	0.2493	0.2538	0.5413	0.2500	0.7560	0.3245	0.4886	0.2222	0.3487
W20	0.3012	0.3655	0.4362	0.5255	0.2830	0.2021	0.4456	0.3789	0.4980	0.3840
W21	0.3407	0.5167	0.8841	0.6078	0.5199	0.2817	0.4410	0.8451	0.6516	0.5652
W22	0.4275	0.5669	0.4699	0.4243	0.6490	0.2200	0.5160	0.4158	0.5736	0.4590
W23	0.7813	0.8945	0.8750	0.8438	0.8359	0.9922	0.8398	0.7852	0.7813	0.8906
W24	0.2188	0.1055	0.1250	0.1563	0.1641	0.0078	0.1602	0.2148	0.2188	0.1094
W25	0.6055	0.5078	0.3398	0.2109	0.6250	0.0781	0.7383	0.5078	0.2852	0.7227
W26	0.3945	0.4922	0.6602	0.7891	0.3750	0.9219	0.2617	0.4922	0.7148	0.2773

3.4 Discussion

Two different sets of weight rankings made by two AIDS physician experts individually involved in the prediction results were used in learning by the systems to optimize their regimen choices to match expert A and B individually. Additionally, the prediction result involved used a consensus set of weight rankings that systems learned and predicted best match the consensus of the two experts. Each prediction result in Tables 3.6-3.18 was the highest match of three prediction results obtained using three different random initials. The prediction accuracy is defined as the ratio of the number of choices on which the system made right predictions as compared to the expert's choices and the total number of the prediction choices.

There were seven scenarios under the self-learning EFDES experiments. The descriptions on the tables made the prediction results with understandable contents. The overall prediction results were high levels of satisfaction that the models could provide under the variety of the seven scenarios with the different learning settings. The prediction results using data-learning setting 1 provided the mean accuracy from 84.1% to 98.4% with the overall mean being 92.4% and from 95.8% to 99.1%, with the overall mean being 95.8% as compared to expert A's choices and expert B's choices, respectively. The prediction accuracy depended on which regimens were used in learning. The system learning by using regimen 1, regimen 2, and regimen 4 would provide the best prediction result as compared

to the expert A's choices, but using regimen 2, regimen 3, and regimen 4 would provide the best one as compared to expert B's choices.

The prediction results as compared to the consensus choices of the two experts under the condition of data-learning setting 1 came with the accuracy from 90.8% to 95.8% with the overall mean being 93.9%, while their exact agreement rate was 43.8%. As compared to the consensus choices of the two experts under the conditions of data learning-setting 3, only ten of the 32 treatment objectives were contributed to the system learning that would lead to the lower mean prediction accuracy of 75.1% in Table 3.17, as compared to those mean prediction accuracy of 93.9% and 96.0% under the condition of data-learning setting 1 and data-learning setting 2, respectively. The prediction results using data-learning setting 3 provided the mean accuracy from 71.9% to 78.0%, with the overall mean being 74.8% and from 72.2% to 78.0%, with the overall mean being 76.0% as compared to expert A's choices and expert B's choices, respectively. The fewer numbers of treatment objectives used in the system learning that contained information of the expert's preferred choices would cause the lower mean prediction accuracy results either for the consensus of experts or an individual.

The retrospective evaluation results of the 35 historical patient cases shown in Table 3.18-3.23 were obtained by providing the system with data-learning setting 4 including regimen 2, regimen 3, and regimen 4. The system optimized weight vectors from learning each regimen using other two regimens to predict the

regimen-choices for the 35 retrospective patients. The average agreement rates for seven scenarios were from 81.4% to 82.6%, with the overall average agreement rate of 82.1% for the 35 patients treated by 13 AIDS physicians. The overall mean agreement rate was 100% for expert A and expert B individually, while the agreement rate for the remaining 11 AIDS physicians was 72.8%. The exact agreement the system could provide was a high level of satisfaction above 80%.

Seven patients with mismatching regimens assigned by the system were treated by non-system AIDS physicians. Three patients were classified with “high” potency that the system assigned regimen 2. It should be the appropriate regimen choice because regimen 2 could provide the most expected potency agreed with two AIDS experts’ regimen choice. Similarly, the system assigned regimen 4 as the same regimen two AIDS experts selected for other three patients classified with “medium” potency and “high” future drug options. Regimen 4 provided the lowest expected potency and the most expected future drug options that would be considered as a better regimen choice the system selected. Only one patient was the system assigned the right regimen choice rated from 50% to 90% under the seven scenarios.

CHAPTER 4

SUMMARY AND FUTURE DIRECTIONS

4.1 Summary and Conclusion

The HIV/AIDS-EFDES system was based on applying the extended fuzzy discrete event system theory for optimal decision-making in HIV/AIDS treatment regimen selection. The system extended the FDES framework for HIV/AIDS treatment regimen selection, especially in the case of the initial round of combination antiretroviral therapy for HIV/AIDS. In the new EFDES framework, the type-2 fuzzy set was employed in representing the expert domain of knowledge and experiences with imprecision and uncertainties. All system parameters with intuitive meaning used in the FDES framework were contributed in the EFDES framework as well. The EFDES-based system would keep simple and understandable steps of the procedures from the beginning through to the final step of the decision-making. The change from one state to another in the sense of the forward-looking tree provides the treatment with a dynamic optimization process. The representations of experts' knowledge and regimen information in the terms of type-2 fuzzy sets would be more flexible as consensus of diverse opinions with equal respect. Adding or updating clinical parameters could be done with ease.

HIV/AIDS treatment is a complicated strategy involving not only the patient's clinical participation but drug resistances. Frequent updating of treatment

guidelines many times in the past few years reflected the fast evolution of scientific knowledge on HIV/AIDS as a complex and severe disease. Research on developing HIV/AIDS drugs is on the fast track. Optimizing new weight vectors for a new HIV/AIDS regimen can be readily achieved when clinical parameter information on the potency, adherence, adverse events, and future drug options are provided by the HIV/AIDS experts. The system needs little time to be updated as new regimens become accessible.

The HIV/AIDS-EFDES system provided impassive decision-making on selecting proper regimens for the retrospective patients in the initial round of the HIV/AIDS treatment. Twenty eight of 35 patients with the correctly selected regimens were in overall exact agreement under seven scenarios. Two HIV/AIDS physician experts were involved in the system development with three regimens in treatment.

Self-learning is another significant feature of the HIV/AIDS-EFDES system. The self-learning system is able to predict outcomes for a new regimen with little required information on clinical trials. For example, only the potency, adherence, adverse events, and future drug options are required for the system to predict decision-making on a new fourth regimen among three other existing regimens. The retrospective performances of the HIV/AIDS-EFDES system's self-learning provided an overall mean prediction rate under seven scenarios about 28 out of 35 given prescriptions. These system predictions were obtained under

experimental environments of weak experts' consensus and uncertainties of knowledge represented in the term of type-2 fuzzy sets.

In conclusion, we applied the extended fuzzy discrete event theory for optimal decision-making on treatment regimen selection for naïve HIV/AIDS patients with highly active antiretroviral therapy. This HIV/AIDS EFDES system extended the FDES framework with use of the type-2 fuzzy sets to represent the uncertainties of clinical domains of diverse experts' knowledge and experiences. Historically, three treatment regimens used in the model evaluation generated the agreement between experts and models with better results as compared to the agreement among experts. The retrospective performance of the system with the real patients treated in AIDS Clinic in 2001 provided the impassive promising results. The performance of the system's self-learning was tested under various clinically possible settings for seven different scenarios involving four historical treatment regimens. The results show that in some certain circumstances, depending on which treatment regimens were learned, the models' average prediction would be more accurate at the satisfaction level of more than 99%. The retrospective performance of the system provided overall mean accuracy around 82% (28.8/35). That result was as good as the FDES-based system's performance. However, the EFDES-based system would earn a benefit on the management of diverse and uncertainty of the experts' knowledge and expertise.

4.2 Future Directions

In the application of the EFDES theory to HIV/AIDS treatment regimen selection system, Type-2 fuzzy sets were allowed to play important role in extracting the expert's knowledge and experiences into useable forms. The effectiveness measure was only used for online optimal control synthesis of the system to provide an appropriated treatment therapy. In realistic, there is an expense of the treatment therapy. What the treatment therapy a patient receives depends on his financial support. The cost of treatment therapy will then be needed to consider along with the treatment effectiveness measure for the system optimal control.

There was an optimization problem in maximizing the overall matching between the treatment regimens assigned by the system and those regimens assigned by two AIDS experts for the 32 treatment objectives. The genetic algorithm in MATLAB's Direct Search Toolbox was employed to solve that kind of problem through adjusting 26 weights for four clinical parameters for all of the 32 treatment objectives. Other optimization approaches such as particle swarm optimization approach, simulated annealing method, etc., would be considered to be experimental search engines for the time-consuming task of optimizing the 26-dimensional vector space.

Finally, the challenge is the implementation of the EFDES-based system on the HIV/AIDS treatment selection for patients with the second round treatment.

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ABSTRACT

AN EXTENDED FUZZY DISCRETE EVENT SYSTEM FOR HIV/AIDS TREATMENT REGIMEN SELECTION

by

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HIV/AIDS is a global problem. Its treatment is dependent on the physician experts' opinion. A system which is capable of supporting the treatment decision will be desired. Recently, the HIV/AIDS treatment regimen selection system appeared in literature that utilized theory of fuzzy discrete event system (FDES) to capture the meaning of experts' knowledge; a form of consensus involving estimated points and type-1 fuzzy sets. The goal was to assign exact matching regimens as close as possible to those regimens preferred by the experts for patients. The system performance was 80% of satisfaction level with the 35 retrospective patients. Extracting experts' knowledge into the consensus forms would not be possible without being compromised by the experts. With equal respective experts, if one insists on his/her values, then the consensus would not be achieved. Conversely, the FDES theory would be no longer to handle such conflict. The theory of extended fuzzy discrete event system (EFDES) extended

the FDES theory that type-2 fuzzy sets would be allowed to be used in the system. This dissertation is to apply the EFDES theory to the HIV/AIDS treatment regimen selection system. Seven scenarios of the diversity of experts' knowledge representation were categorized for the system. The MATLAB was implemented to model the system. Genetic algorithm in MATLAB's Direct Search Toolbox was used to search an optimal vector of 26 weights for system parameters regarding the experts' regimen-choices. As the same input of the retrospective patient data for the FDES-based system, the overall means of simulation results of EFDES-based system demonstrated the degree of matching regimens being 80%. That result would be the same performance level of the FDES-based system as well. The EFDES-based system performance with self-learning provided the overall satisfaction level of above 80%. Moreover, the EFDES-based system with use of the type-2 fuzzy set gained the benefit on the extraction of diverse and uncertainty experts' knowledge and expertise.

AUTOBIOGRAPHICAL STATEMENT

KIATTISAK WONGSOPANAKUL

K. Wongsopanakul was born in Nakonsri Thumarat province, Thailand, on November 7, 1968. He received a Bachelor's degree in Electrical Engineering in 1991 from the Prince of Songkla University, Thailand, and a Master's degree in Electrical Engineering in 1993 from New York Institute of Technology, USA. One year later, he began his career as a lecturer in the Electrical Engineering Department, Prince of Songkla University. In 2002 he was awarded a scholarship from the same university to continue his studies. He joined the Biomedical Engineering Department, Wayne State University, Detroit, Michigan, and finished his Master's degree in 2005. He then transferred to the Electrical and Computer Engineering Department, Wayne State University, for the Doctor of Philosophy (Ph.D.) program.

Since fall 2007 he has been working on this dissertation under the supervision of Dr. Hao Ying. His dissertation involves applying the extended fuzzy discrete event system theory in decision-making system for HIV/AIDS treatment regimen selection. His work was published in the North American Fuzzy Information Processing Society (NAFIPS) conference.

After a long academic journey, he and his family members will be together once again. He will continue to work for the Prince of Songkla University.