International Journal of Innovative
Computing, Information and Control
Volume 8, Number 1(B), January 2012
 ISSN 1349-4198
pp. 779–790

EVALUATION OF INTELLIGENT SYSTEM TO THE CONTROL OF DIABETES

Shou-Wei Chien[1,2,3], Cho-Tsan Bau[4,5], Ker-Chung Lin[3], Kuo-An Wang[2]
Yung-Fu Chen[2,6,7,*] and Jong-Chen Chen[1,*]

[1]Department of Information Management
National Yunlin University of Science and Technology
No. 3, University Rd., Douliou, Yunlin 64002, Taiwan
g9523809@yuntech.edu.tw; *Corresponding author: jcchen@yuntech.edu.tw

[2]Department of Management Information Systems
[6]Institute of Biomedical Engineering and Material Sciences
Central Taiwan University of Science and Technology
No. 666, Buzih Rd., Beitun District, Taichung 40601, Taiwan
gawang@ctust.edu.tw; *Corresponding author: yfchen@ctust.edu.tw

[3]Department of Director Center, Nantou Hospital
Department of Health, Executive Yuan, Nantou 54062, Taiwan
direct@nant.doh.gov.tw

[4]Department of Information Management
Chaoyang University of Technology
No. 168, Jifong E. Rd., Wufong Township, Taichung 41349, Taiwan
s9733902@mail.cyut.edu.tw

[5]Department of Internal Medicine, Taichung Hospital
Department of Health, Executive Yuan, Taichung 403, Taiwan

[7]Department of Health Services Administration
China Medical University
No. 91, Hsueh-Shih Rd., Taichung 40402, Taiwan

Received September 2010; revised April 2011

Abstract. *Diabetes, which ranks 4th among the top ten causes of death in Taiwan, is one of the most important medical issues in the 21st century. However, for most diabetic patients, their blood sugar is not under good control, especially in ICUs. Good control of blood sugar may reduce the risk of sepsis to 34% for patients in ICUs. The importance of good blood sugar control for patients in ICUs is manifested by a significant reduction of mortality and morbidity. This study designed a clinical decision support system (CDSS) using a support vector machine (SVM) to predict if a critically ill patient can have good glucose control after insulin administration. A filter method based on logistic regression analysis (LRA) and a wrapper method based on recursive feature elimination (RFE) were adopted to select salient features from 10 variables for CDSS design. Data on 231 patients (2492 records) were collected covering four years from an ICU. Four significant variables* ($p < 0.05$) *using LRA in contrast to five ones using RFE algorithm, were selected. The results show that the predictive accuracy under cross-validation was 93.50% for features selected with LRA, and the accuracy, sensitivity and specificity with SVM-RFE were 95.75%, 92.71% and 99.81%, respectively. It could predict the outcome quite accurately after having injected a certain dose of insulin. The proposed system may help doctors effectively assess their patients in determining insulin dose for better glucose control in an ICU setting.*

Keywords: Diabetes, Logistic regression analysis, Clinical decision support system, Neural network, Support vector machine, Recursive feature elimination, Decision tree, Radial basis function network

1. **Introduction.** Diabetes is one of the most important global public health issues in the 21st century. In recent years, with the continually elevating living standards together with the changes in diet and living habits, the incidence of diabetes around the world has been increasing year by year. It has become a prevalent disease in civilized countries, with a global incidence of 190 million based on the statistics of the Global Diabetes Alliance [1]. In Taiwan, among all the chronic diseases, the prevalent rate of diabetes is ranked as one of the most prevalent diseases (4.3%) based on the 2005 statistics of Department of Health of Taiwan [2], and only second to hypertension. Diabetes, as the 4th leading cause of death in Taiwan, has the highest increasing rate among the 10 leading causes of death. The mortality rate related to diabetes increased, with 7.91, 34.67 and 42.5 per 100,000 people dying in 1980, 1997 and 2006, respectively [2]. Unfortunately, blood sugar levels of 2/3 of the patients were not under good control [2].

The etiology of diabetes is closely related to the function of the pancreas, which secrets insulin to regulate blood sugar levels in the human body. If the insulin secretion function of the pancreas is compromised, blood sugar levels will be imbalanced and can lead to diabetes. Generally, there are 2 types of diabetes: Type 1 and Type 2. Type 1 diabetes is related to insufficient production of insulin by the pancreas, while type 2 diabetes, in spite of normal insulin production, is caused by the resistance of cells to the reaction of insulin and prevents glucose from effectively entering into cells, thereby resulting in the elevation of blood sugar levels [3]. With various complications, such as cardiovascular, retinal and renal diseases, diabetes may incur enormous medical expense and social cost, causing a serious burden for many countries.

For patients facing diabetes, a cheerful mood is important [4], as is diet control and medication compliance to maintain blood sugar under the suggested level. However, most diabetic patients were unable to adequately control their blood sugar levels for several reasons. First of all, insufficient health education may make the patient unaware of the serious consequences of diabetes. The second reason is the difficulty in the overall control and adjustment of diet, exercise and medication. Thirdly, although various medications are available for controlling diabetes, there is still no cure, which may make patients lose patience for long-term therapy. Furthermore, available specialists are insufficient, leading to limited access to medical care and difficulty in seeking medical attention.

In addition to physiological status, the condition of a patient with a chronic disease will be influenced to a certain extent by the disease, remedy and mental condition. Therefore, we still could not identify any single indicator as the ideal guideline for determining the reasonable dosage for an individual patient. Currently, most of the decisions made by the physicians still rely on their professional judgments. Different medical staffs may adopt different medical remedies for the same patient. On the other hand, even with the same medical administration, different patients may react differently. Since error related to human judgment is inevitable and medical staffs may misjudge under some circumstances, determining how to achieve an effective control of patient's condition, how to discriminate well- and poorly-controlled patients, and the features related to a poor control will provide significant and valuable assistance to patients, physicians and healthcare education staffs.

2. Literature Reviews.

2.1. Intensive insulin therapy in ICU setting.

In contrast to conventional treatment whereby infusion of insulin is needed only if the blood sugar level rises to more than 215 mg/dl and the blood glucose is maintained at a level between 180 and 200 mg/dl, the intensive insulin therapy (IIT) intentionally maintains the blood glucose within 80-110 mg/dl [5]. Van den Berghe et al. [5] reported that IIT reduced mortality of critically ill ICU patients by 34%, bloodstream infections by 46%, acute renal failure by 41%, the median number of blood transfusions by 50%, and critically-ill polyneuropathy by 44%. Additionally, the need for prolonged ventilator support and the duration of ICU stay were also reduced if IIT was conducted [5]. However, the efficacy of IIT in reducing mortality of ICU patients is controversial according to more recent studies [6,7] and meta-analyses [8-10].

In contrast to surgical ICU, the mortality rate of medical ICU patients treated with IIT was not significantly reduced compared to conventional treatment [6]. However, similar to surgical ICU, the morbidity rate was significantly reduced in medical ICU with reduced newly acquired kidney injury, accelerated predicting from glucose control, and decreased length of stay in the ICU and hospital. More recently, the NICE-SUGAR study concluded that IIT did not reduce the mortality rate for critically ill patients in either surgical or medical ICU setting; in fact, IIT increased mortality among adults in the ICU [7], a result which differed from the finding of a meta-analysis study addressing the view that IIT did not affect mortality for critically ill adult patients [10]. By including NICE-SUGAR data, the meta-analysis conducted by Griesdale et al. [9] suggested that patients of surgical ICUs benefitted from IIT while patients in other ICU settings did not. The reasons behind such conflicting results are not clear. Reduced blood glucose level, increased administrated insulin, occurrence of hypoglycemia, methodological factors, or types of disease might be the factors causing such discrepancies [7,11].

Although the benefit of IIT in treating critically ill ICU patients is still controversial, it is widely believed that hyperglycemia is highly associated with increased mortality in critically ill patients [12-15]. The mortality rate of critically ill patients is closely related to blood glucose levels. For example, Krinsley [15] reported that mean and maximum glucose levels for non-survival patients were significantly higher than those for survival patients. The mortality rate increased progressively as glucose levels elevated. On the other hand, it was reported that the occurrence of hypoglycemia was frequently observed in IIT interventions [7,9,10]. Hypoglycemia might be the reason why the mortality rate of critically ill ICU patients administrated with IIT was higher than that of conventional treatment [7]. Hence, it is very important to find factors influencing blood glucose control and to design a clinical decision support system (CDSS) for an ICU setting.

2.2. **Automatic diagnosis of diabetes.** Barakat and Bradley [15] designed a model based on SVM to diagnose and predict Type II diabetes with an accuracy of 94%, sensitivity of 93% and specificity of 94%. On the other hand, a model proposed by Huang et al. [16] based on a C4.5 decision tree achieved an accuracy of 95% and sensitivity of 98% for efficient glucose control of diabetic outpatients. More recently, a model designed using linear discriminant analysis for feature selection and Morlet wavelet SVM for classifier design achieved an accuracy rate as high as 89.74% for diabetic diagnosis based on a Pima Indian women database [17].

Unfortunately, most of the aforementioned investigations only focused mainly on the prediction of glucose control for patients in outpatient settings [15-17]. To our knowledge, no study conducted so far has endeavored to find important factors for designing a CDSS to efficiently control blood glucose in ICU patients. In this study, our aim was to establish a model by adopting important factors which influence the efficiency of blood sugar control. Additionally, the relationship between the efficiency of blood sugar control and the administration of insulin dosage for individual ICU patients will also be explicated. Based on the established model, the predictive outcome of the blood sugar control can be used to adjust suitable dosage of administrated insulin for ICU patients; this should prove useful in reducing healthcare cost and elevating patient safety as well as the quality of service in ICU settings.

3. Materials and Methods.

The collected data were statistically analyzed with SPSS software package applied for descriptive and inferential analyses, followed by feature selection using filter (logistic regression analysis) and wrapper methods (recursive feature elimination) to obtain salient features for predictive model construction. Finally, models based on RBF network, decision tree J48, logistic regression, and SVM were constructed and compared that the best model was applied for clinical application. Cross validation scheme was applied to obtain accuracy, sensitivity, and specificity of the constructed models. Furthermore, area under ROC curve (AUC) was also used to assess the predictive performance.

3.1. Data collect.

A total of 2492 samples of data collected from 231 patients admitted to the ICU of a national hospital situated in central Taiwan from 2006 to 2009 were used for this study. All of the patients were diagnosed as Type 2 diabetes, showing the symptom of hyperglycemia. The diagnostic criteria of diabetes are as follows [3]: (1) Two times of venous blood sugar level after fasting over 140 mg/dl; (2) With a venous blood sugar level after fasting lower than 140 mg/dl, but the venous blood sugar level at 2 h after oral administration of 75 mg glucose (glucose tolerance test) is over 200 mg/dl; and (3) Frequently accompanied by the following classical complications: drinking more, urinating more and eating more, but still losing weight [3]. Data samples were collected every 4 h on average, within 48 h after the patients had been admitted to the ICU. Data were classified into 2 groups based on good or bad glucose control after insulin administration. A good glucose control trial indicated that the glucose level had been reduced to a level less than 140 mg/dl after insulin administration; otherwise it was classified as a bad trial. Each data sample consisted of 10 factors: age, gender, time from initial insulin administration, blood glucose level, surgical operation, heart rate, body temperature, administrated insulin dosage, coma scale and BMI. Models for predicting blood glucose level control after insulin administration were constructed using four different methods: i.e., RBF network, decision tree J48, simple logistic regression and support vector machine (SVM). Predictive results obtained from these models were compared that the best model will be applied for clinical application in an ICU setting.

3.2. Support vector machine (SVM).

Support vector machine (SVM) is a useful technique for data classification and regression; it has become an important tool for machine learning and data mining. In general, SVM has better performance compared with existing methods, such as neural networks and decision trees [17,19]. Recently, application of SVM in medicine has grown rapidly. For examples, it has been applied in the prediction of RNA-binding sites in proteins [20-22], discrimination of malignant and benign cervical lymph nodes [23-25], disease diagnosis using tongue images [26,27], diagnosis of cardiovascular disease [28] and breast cancer [29,30].

The goal of SVM is to separate multiple clusters with a set of unique hyperplanes having the widest margins to the boundary, consisting of support vectors, of each cluster. In contrast, each hyperplane which separates two clusters is not unique for other linear classifiers [31,32]. Given a two-class linearly separable problem, the hyperplane separating two classes leaving the maximum margin from both classes is represented as [33,34]:

$$g(\mathbf{x}) = \mathbf{w}^T\mathbf{x} + w_0 = 0 \tag{1}$$

in which $\mathbf{w}$ indicates the weights of the input vector $\mathbf{x}$ and w_0 is a bias term of the hyperplane. The training data of two classes can be represented as $(\mathbf{x}_i,\, y_i)$ with $\mathbf{x}_i \in \boldsymbol{R}^n$

and $y_i \in \{+1, -1\}$ for $i = 1, 2, \ldots, N$, in which sample $\mathbf{x}_i$ is an N-dimensional input vector and y_i is its corresponding label indicating the class of $\mathbf{x}_i$. By scaling the orthogonal vector $\mathbf{w}$ and bias w_0 in Equation (1) to make the values of g($\mathbf{x}$) at the nearest points in class 1 and class 2 equal to 1 and –1, respectively, the problem of obtaining the optimal hyperplane becomes a nonlinear quadratic optimization problem, which can be formulated as:

$$\begin{array}{ll} \underset{\mathbf{w},w_0}{\text{Min}} & \dfrac{\|\mathbf{w}\|^2}{2}, \\ \text{Subject to} & y_i\left(\mathbf{w}^T\mathbf{x}_i + w_0\right) \geq 1, \quad i = 1, 2, \ldots, N \end{array} \tag{2}$$

The problem can be solved by considering Lagrangian duality, and stated equivalently by its Wolfe dual representation form with the constraints satisfying the Karush-Kuhn-Tucker (KKT) conditions, i.e., $\partial L(\mathbf{w}, w_0, \lambda)/\partial \mathbf{w} = 0$, $\partial L(\mathbf{w}, w_0, \lambda)/\partial w_0 = 0$, $\lambda_i[y_i(\mathbf{w}^T\mathbf{x}_i + w_0) - 1] = 0$, and $\lambda_i \geq 0$ for $i = 1, \ldots, N$, as indicated in the following equation:

$$\text{Max} \;\; L(\mathbf{w}, w_0, \lambda) = \frac{\|\mathbf{w}\|^2}{2} - \sum\nolimits_{i=1}^{N} \lambda_i \left[y_i\left(\mathbf{w}^T\mathbf{x}_i + w_0\right) - 1\right] \tag{3a}$$

$$\text{Subject to} \;\; \mathbf{w} = \sum\nolimits_{i=1}^{N} \lambda_i y_i \mathbf{x}_i, \; \sum\nolimits_{i=1}^{N} \lambda_i y_i = 0 \;\text{ and }\; \lambda_i \geq 0 \;\text{ for }\; i = 1, \ldots, N \tag{3b}$$

where $L(\mathbf{w},\ w_0,\ \lambda)$ is a Lagrangian function and $\lambda = [\lambda_1, \lambda_2, \ldots, \lambda_N]$ is the vector of Lagrangian multipliers corresponding to the constraint in Equation (2). In contrast to Equation (2), the first two constraints in Equation (3b) become equality constraints and make the problem easier to handle. By substituting the first two constraints in Equation (3b) into Equation (3a), the problem is formulated as:

$$\begin{array}{ll} \underset{\lambda}{\text{Max}} & \left(\sum_{i=1}^{N} \lambda_i - \frac{1}{2}\sum_{i,j=1}^{N} \lambda_i\lambda_j y_i y_j \mathbf{x}_i^T\mathbf{x}_j\right), \\ \text{Subject to} & \sum_{i=1}^{N} \lambda_i y_i = 0 \;\text{ with }\; \lambda_i \geq 0, \quad i = 1, \ldots, N \end{array} \tag{4}$$

As soon as the Lagrangian multipliers have been obtained by maximizing the above equation, the optimal hyperplane can be obtained from $\mathbf{w} = \sum_{i=1}^{N} \lambda_i y_i \mathbf{x}_i$ shown in Equation (3b). Then, classification of a sample is performed based on the sign of the following equation:

$$f(\mathbf{x}) = \text{sgn}\left(\mathbf{w}^T\mathbf{x} + w_0\right) = \text{sgn}\left(\sum\nolimits_{i=1}^{Ns} \lambda_i y_i \mathbf{x}_i^T\mathbf{x}_i + w_0\right) \tag{5}$$

where Ns is the number of support vectors.

For a nonlinear classification problem, the optimization problem shown in Equation (2) is changed to Equation (6) with a penalty term being added:

$$\begin{array}{ll} \underset{\mathbf{w},w_0}{\text{Min}} & \left(\dfrac{\|\mathbf{w}\|^2}{2} + C\sum_{i=1}^{N} \xi_i\right), \\ \text{Subject to} & y_i\left(\mathbf{w}^T\phi(\mathbf{x}_i) + w_0\right) \geq 1 - \xi_i \;\text{ and }\; \xi_i \geq 0, \quad i = 1, 2, \ldots, N \end{array} \tag{6}$$

where C is a positive penalty parameter, variables ξ_i are used to weight the cost of misclassified samples, and $\phi(\mathbf{x}_i)$ is a function applied to map the training sample $\mathbf{x}_i$ to a higher dimensional space. For a vector $\mathbf{x} \in R^n$ in the original feature space, it is assumed that there exists a function ϕ for mapping $\mathbf{x} \in R^n$ to $\phi(\mathbf{x}) \in R^k$ with $k > n$. Then, the class of a sample can be determined from the following equation:

$$f(\mathbf{x}) = \text{sgn}\left[\mathbf{w}^T\phi(\mathbf{x}) + w_0\right] = \text{sgn}\left[\sum\nolimits_{i=1}^{Ns} \lambda_i y_i \phi\left(\mathbf{x}\right)^T \phi(\mathbf{x}_i) + w_0\right] \tag{7}$$

in which $\phi(\mathbf{x})^T\phi(\mathbf{x}_i)$ is the inner product needed for calculation, which is performed by a kernel function $K(\mathbf{x},\ \mathbf{z}) = \phi(\mathbf{x})^T\phi(\mathbf{z})$ a symmetric function, satisfying the following condition:

$$\int K(\mathbf{x},\mathbf{z})g(\mathbf{z})d\mathbf{x}d\mathbf{z} \geq 0 \text{ and } \int g(\mathbf{x})^2 d\mathbf{x} \leq \infty \tag{8}$$

Finally, the optimization problem in Equation (4) is reformulated as:

$$\begin{aligned} &\operatorname*{Max}_{\lambda} \left(\sum_{i=1}^{N} \lambda_i - \frac{1}{2} \sum_{i,j=1}^{N} \lambda_i \lambda_j y_i y_j K\left(\mathbf{x}_i^T \mathbf{x}_j\right) \right), \\ &\text{Subject to } \sum_{i=1}^{N} \lambda_i y_i = 0 \text{ with } 0 \leq \lambda_i \leq C \end{aligned} \tag{9}$$

For a nonlinear classifier, various kernels including polynomial, radial basis function, and hyperbolic tangent can be used for mapping the original sample space into a new Euclidian space with Mercer's conditions being satisfied. The linear classifier can then be designed for classification. Among them, radial basis function, as shown in the following equation, is the most widely used function, and is applied in this study for feature mapping.

$$K(\mathbf{x},\mathbf{z}) = \exp\left(-\gamma \left\|\mathbf{x}-\mathbf{z}\right\|^2\right) \tag{10}$$

3.3. **Feature selection.** Feature selection has the advantage of reducing the number of features and the size of storage requirements, decreasing training and computational time, facilitating data visualization and understanding, as well as improving predictive performance [35,36]. The algorithms of feature selection can often be classified into 3 approaches: filter, wrapper and embedded methods [34]. The filter method is a preprocessing procedure which selects a subset of features based on statistical measures independent of the designed classifiers. In contrast, the wrapper method assesses individual subsets of features in a recursive way by considering their predictive efficiency to a given classifier. It is more computationally intensive than the filter method, but is believed to be able to provide more efficient outcome. The subset with the smallest number of features achieving the highest predictive accuracy is used for classifier construction.

3.3.1. *Filter method based on logistic regression analysis.* LRA is a type of nonlinear regression which has been used to delineate the relationship between several independent variables, discrete or continuous, and a dependent discrete variable, dichotomous or multiple. For binary LRA, the dependent variable is dichotomous, while for multiple LRA, it is multiple. In contrast, the dependent variable of a multiple regression analysis is continuous. The dependent variable (y) is a linear combination of dependent variables (x_i) for a multiple regression, as shown in the following equation:

$$y = a + \sum_{i=1}^{n} b_i x_i + \varepsilon \tag{11}$$

in which a is the intercept of Y axis, b_i indicates the regression coefficient and ε is the prediction error. Therefore, a model constructed using multiple regression analysis can be represented as:

$$g(\mathbf{x}) = a + \sum_{i=1}^{n} b_i x_i \tag{12}$$

Hence, the prediction error $\varepsilon = y - g(\mathbf{x})$ indicates the difference between a measured value and the predicted value. Since the dependent variable of a binary LRA is dichotomous, i.e., 1 or 0, its modeling is based on the probability associated with the values of dependent variable, as formulated as natural logarithm of odd ratio in favor of $y = 1$ in the following equation:

$$\ln \frac{P(y=1|x_1, x_2, \ldots, x_n)}{P(y=0|x_1, x_2, \ldots, x_n)} = a + \sum_{i=1}^{n} b_i x_i \tag{13}$$

The above (Logit) transformation of the dependent variable converts a non-linear relationship between independent and dependent variables into a linear one. The SPSS 10.0

statistical software package was adopted to perform a statistical analysis of the acquired data. Descriptive statistics were first used to deal with the characteristics of the dataset with mean and standard deviation calculated for each continuous variable followed by inferential statistics. Frequency and percentage of each sub-type of a categorical variable were also calculated for further analysis. Inference statistics such as t-test was used to test significance of the continuous variables while a Pearson chi-square test was applied to test the dichotomous variables. The variables which are significantly different ($p < 0.05$) between good and bad glucose control were further studied using LRA. In the beginning, all 10 variables were analyzed using t-test and Pearson chi-square test for selecting salient continuous and discrete variables, respectively, followed by LRA to further select significant variables for training and testing using neural network, decision tree and support vector machine.

3.3.2. *Wrapper method based on recursive feature elimination.* The wrapper method assesses individual subsets of features in a recursive way by considering their predictive efficiency in regard to a given classifier. For a vector space with n features, a recursive feature elimination (RFE) algorithm removes unimportant features based on backward sequential selection by iteratively deleting one feature at a time, resulting in a sub-optimal combination of r ($r < n$) features with best predictive performance [34]. SVM-RFE starts with all features, and deletes features repeatedly until r features are left, which leads to the widest margin separating two classes. Weight magnitude, which is inversely proportional to the margin, is generally used as the ranking criterion in determining the importance of individual features. The eliminated feature p is the one which minimizes the variation of weight:

$$\|\mathbf{w}_{-p}\|^2 = \sum\nolimits_{i,j=0}^{N} \lambda_i \lambda_j y_i y_j K\left(\mathbf{x}_i^T \mathbf{x}_j\right) \tag{14}$$

In addition to weight or margin, other measures such as generalization error, gradient of weight and Fischer's ratio were also proposed for feature ranking [37]. In this study, mean cross validation accuracy was used as a measure of feature ranking for determining the eliminated feature in each iteration.

3.4. **Cross validation and system assessment.** First of all, the data were randomly divided into two subsets, in which good and bad glucose control samples are equally distributed, for cross validation to get the optimal SVM parameters, i.e., C (cost parameter) and γ (kernel parameter). In the validation stage, data were divided into 10 subsets (folds) for cross validation by fixing the SVM parameters to the values obtained in the previous step. In each iteration, 9 folds were used for training the model while the rest one used for validation. The procedure was repeated for 10 times, each used an individual fold for validation.

To assess the predictive performance of the models constructed by various artificial techniques, including RBF network, decision tree J48, simple logistic regression and SVM, the accuracy, sensitivity and specificity of the model were compared. In addition, area under ROC curve (AUC) was also used for sensitivity analyses. The best model will be adopted for future clinical applications.

4. **Results.**

4.1. **Feature selection.** The results of descriptive statistics and inference statistics of 2492 samples collected from 231 patients are shown in Table 1. As depicted in this table, 4 variables, including surgical operation, blood sugar, body mass index (BMI) and administrated insulin dose, are significantly different ($p < 0.05$) between good and bad glucose control groups. As shown in Table 2, after analysis using the filter method based on LRA, it was found that only 4 variables: blood sugar, body temperature, BMI and administrated insulin dose, were significant ($p < 0.05$); these were selected for CDSS construction. Notice that the variable surgical operation was replaced by body temperature after LRA.

Table 1. Statistic analyses of recorded data for feature selection (N = 2492)

Variables	Blood Sugar Control		
	Good (n = 1324)	Bad (n = 1168)	Significance (p-value)
Gender (male/female)	714/610	602/566	0.377
Age	74.37±12.34	74.78±11.01	0.339
Surgical operation (n/y)	195(14.7%)	122(10.4%)	0.001
Blood sugar (mg/dl)	281.44±110.45	236.42±95.08	< 0.001
Body temperature (°C)	36.51±0.89	36.55±0.84	0.167
Heart rate (BPM)	93.74±20.786	95.09±35.05	0.258
Body mass index (BMI)	22.13±4.10	22.57±3.98	0.007
Administrated insulin dose (unit/h)	8.12±5.56	8.51±5.59	< 0.001
Time from initial insulin administration (hours)	9.20±12.10	9.10±10.30	0.082
Glascow coma scale	8.11±4.11	8.26±4.22	0.36

Table 2. Significant variables after logistic regression analysis (LRA)

Variables	**B**	**S.E.**	**Wald**	***P*-value**
Gender	0.146	0.086	2.867	0.090
Age	0.00	0.004	0.000	0.988
Surgical operation	–0.140	0.134	1.095	0.295
Blood sugar (mg/dl)	–0.05	0.000	126.182	< 0.001
Body temperature (°C)	0.132	0.050	6.949	0.008
Heart rate (BPM)	0.003	0.002	2.389	0.122
Body mass index (BMI)	0.031	0.011	8.260	0.004
Administrated insulin dose (Unit/h)	0.037	0.008	19.225	< 0.001
Time from initial insulin administration (hours)	–0.001	0.000	3.877	0.203
Glascow coma scale	0.033	0.011	2.217	0.102
Constant	–5.231	1.859	7.917	0.005

To compare the features selected using LRA and SVM-RFE, it was found that 4 common features, i.e., blood sugar, body temperature, BMI and administrated insulin dose, were selected by two methods, while surgical operation was selected by SVM-RFE only.

4.2. **Predictive performance of blood glucose control.** In this study, we tested SVM models using different combinations of parameters C and γ, with a grid size of 0.1, to select the optimal parameters for constructing the CDSS with the greatest predictive accuracy. The parameters with best predictive performance are 5.8 and 19.3 for $\log_2 C$ and $\log_2 \gamma$, respectively. In addition, features selected using different methods of feature selection also affect the predictive performance because of different number, or combination, of selected features. As shown in Table 3, the predictive performance for the SVM model constructed using features selected based on wrapper method (5 features) is better than that of the filter method (4 features).

TABLE 3. Comparisons of accuracy, sensitivity, specificity, and AUC of models constructed with different AI techniques

AI Method	Feature Selection	Accuracy	Sensitivity	Specificity	AUC
RBFN	LRA	53.21%	53.29%	51.14%	0.518
Decision Tree J48	LRA	64.77%	65.97%	63.23%	0.721
Simple Logistic Regression	LRA	60.67%	60.68%	60.66%	0.645
SVM	LRA	93.50%	90.63%	97.36%	0.931
	RFE	95.75%	92.71%	99.81%	0.955

A comparison of predictive rates of CDSS models constructed using four different methods, i.e., RBF network, decision tree J48, logistic regression and SVM, with 2 feature selection method is demonstrated in Table 3. As indicated in this table, the SVM model achieves higher predictive rates than the other AI techniques. Furthermore, SVM model constructed using features selected with RFE (95.75%) achieves better performance than LRA (93.50%).

5. **Discussion.** Neural network and decision tree have been widely applied in designing decision support systems for clinical applications; some studies find that neural networks are better than decision tree [37-39], while others have opposite outcomes [40]. Recently, the application of SVM in medicine has grown rapidly; it has been applied in the prediction of RNA-binding sites in proteins [41], disease diagnosis using tongue images [26], discrimination of malignant and benign cervical lymph nodes [23], and diagnoses of cardiovascular disease [28]. Wu et al. [43] applied an artificial neural network and support vector machine to diagnose students' learning disabilities problem for students. Although their results showed that a neural network performs better than an SVM, other investigations reported that SVM in general has a better performance compared to neural network [44] and decision tree [18,33,44].

In this study, we compared the models constructed using RBF network, decision tree J48, simple logistic regression and SVM. The results show that CDSS constructed using SVM was the best in regard to glucose control prediction. The predicative accuracy of the model constructed using simple LRA is only 60.67%. The SVM model constructed with features selected using LRA, by contrast, achieves a predictive accuracy as high as 93.5% for the same dataset, which is only slightly lower than that of the SVM models constructed using 5 features selected with RFE (95.75%). There are two ways to change the nonlinear relationship between independent and dependent variables into a linear one, transforming either the independent or dependent variables. One possible reason for the low predictive accuracy of the LRA model might be that it transformed the dependent variable using a nonlinear logarithmic function and was constructed in the same dimensional space, while the SVM models transform the input variables to a space with higher dimensions using a nonlinear kernel before being classified linearly in the high-dimensional space.

For outpatient diagnosis of diabetes and prediction of glucose control, models designed with SVM [15] and decision tree [16] achieved very good performance with a predictive accuracy as high as 94% and 95%, respectively. However, a more recent study with a model constructed and validated based on the Pima Indian women database achieved a predictive rate of 89.74% only in regard to diabetic diagnosis [17]. Difference in database characteristics might be the reason causing such discrepancy. The database adopted in [15,16] containing data collected from both male and female outpatients, while the database in [17] referred to female data only. In contrast, the data investigated in this study were collected from female and male ICU patients who were more critically ill than the patients in [15,16]. Furthermore, compared to the previous investigations that the models were constructed based on database containing demographic data, history, and anthropometric measures collected from outpatients [15-17], the unique feature of the approach proposed in this study is that we endeavored on designing a CDSS for clinical application based on the data collected from more critically ill ICU patients. In addition to demographic data (Gender and age), history (surgical operation) and anthropometric measures (body temperature, heart rate, BMI and coma scale), the data used in this study also include intervention (administrated insulin dose and time from initial insulin administration). The main advantage is that the designed CDSS can be used to determine appropriate dose of insulin to be administrated to a critically ill patient so that good blood glucose controlled can be achieved in ICU setting, which in turn can elevate patient safety and improve healthcare quality. The deficiencies of this investigation are that the patients were recruited from medical ICU diagnosed with diabetes; other comorbidities such as cardiovascular and kidney diseases which might influence efficiency of glucose control were not considered. Further improvement can be made by recruiting patients with other morbidities to see if these factors affect efficiency of blood glucose control.

The conditions imposed to develop the main results are described as follows: (1) The good glucose control trial is based on testing if the glucose level has been reduced to a level less than 140 mg/dl; the case with hypoglycemia which should be treated as bad glucose control was not considered. (2) The data samples were collected every 4 h within 48 h after the patient had been admitted to the ICU; hyperglycemia and hypoglycemia caused by inappropriate insulin dose within such a long period might endanger the patient. Data collected every 1 h or 2 h might provide more valuable information for physicians to make quick decision in adjusting administrated insulin dose to alleviate hyperglycemia or to prevent hypoglycemia. (3) This study focused only on building a general model for predicting whether a trial will achieve good glucose control with a dose of administrated insulin; however, even with the same medical administration, different patients may react differently. Although BMI is an efficient anthropometric measure for discriminating patient characteristics, other factors such as insulin sensitivity of an individual should also be considered.

6. **Conclusions.** We proposed a CDSS constructed using SVM to accurately predict blood glucose control outcome for critically ill ICU patients with the accuracy, sensitivity, specificity and AUC of 95.75%, 92.71%, 99.81% and 0.955, respectively; it is good enough for clinical applications. To our best knowledge, in contrast to previous investigations which mainly focused on outpatient settings, our study is the first one emphasizes on the prediction of glucose control in the ICU setting.

It was observed that the wrapper (RFE) method has been demonstrated to be capable of obtaining a better combination of features with a better predictive performance than the filter (LRA) method. In the future, a program with GUI will be designed to assist physicians in decision-making for determining appropriate dose of administrated insulin for getting more efficient blood glucose control. The outcome of this investigation is expected to be able to significantly increase patient safety and reduce the healthcare costs, as well as to help doctors to effectively assess their patients regarding blood glucose control.

Acknowledgment. This work was supported in part by the National Science Council of Taiwan under grant NSC98-2410-H-039-003-MY2 and by National Nantou Hospital, Department of Health under grant CTU100-C-002.

REFERENCES

[1] The World Diabetes Foundation, *http://www.worlddiabetesfoundation.org/media(527,0)/*, 2011.

[2] *Bureau of Health Promotion, Department of Health, Taiwan*, http://www.bhp.doh.gov.tw/BHPnet/English/index.aspx, 2011.

[3] American Diabetes Association, Standards of medical care in diabetes-2011, *Diabetes Care*, vol.34, pp.s11-s61, 2011.

[4] V. K. Tsenkova, G. D. Love, B. H. Singer and C. D. Ryff, Coping and positive affect predict longitudinal change in glycosylated hemoglobin, *American Psychological Association,* vol.27, no.2, pp.s166-s171, 2008.

[5] G. Van den Berghe, P. Wouters, F. Weekers, C. Verwaest, F. Bruyninckx, M. Schetz, D. Vlasselaers, P. Ferdinande, P. Lauwers and R. Bouillon, Intensive insulin therapy in critically ill patients, *The New England Journal of Medicine*, vol.345, no.19, pp.1359-1367, 2001.

[6] G. Van den Berghe, A. Wilmer, G. Hermans, W. Meersseman, P. J. Wouters, I. Milants, E. Van Wijngaerden, H. Bobbaers and R. Bouillon, Intensive insulin therapy in the medical ICU, *The New England Journal of Medicine*, vol.354, no.5, pp.449-461, 2006.

[7] The NICE-SUGAR Study Investigators, Intensive versus conventional glucose control in critically Ill patients, *The New England Journal of Medicine*, vol.360, no.13, pp.1283-1297, 2009.

[8] A. G. Pittas, R. D. Siegel and J. Lau, Insulin therapy for critically ill hospitalized patients – A meta-analysis of randomized controlled trials, *Arch. Intern. Med.*, vol.164, 2004.

[9] D. E. G. Griesdale, R. J. de Souza, R. M. van Dam, D. K. Heyland, D. J. Cook, A. Malhotra, R. Dhaliwal, W. R. Henderson, D. R. Chittock, S. Finfer and D. Talmor, Intensive insulin therapy and mortality among critically ill patients: A meta-analysis including NICE-SUGAR study data, *Canadian Medical Association Journal*, vol.180, no.8, pp.821-827, 2009.

[10] R. S. Wiener, D. C. Wiener and R. J. Larson, Benefits and risks of tight glucose control in critically ill adults: A meta-analysis, *Database of Abstracts of Reviews of Effects*, vol.300, no.8, pp.933-944, 2008.

[11] G. Y. Gandhi, G. A. Nuttall, M. D. Abel, C. J. Mullany, H. V. Schaff, P. C. O'Brien, M. G. Johnson, A. R. Williams, S. M. Cutshall, L. M. Mundy, R. A. Rizza and M. M. McMahon, Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: A randomized trial, *American College of Physicians*, pp.233-243, 2007.

[12] J. Sung, G. V. Bochicchio, M. Joshi, K. R. Bochicchio, K. Tracy and T. Scalea, Admission hyperglycemia is predictive of outcome in critically ill trauma patients, *The Journal of Trauma*, vol.59, no.1, pp.80-83, 2005.

[13] B. W. Whitcomb, E. K. Pradhan, A. G. Pittas, M. C. Roghmann and E. N. Perencevich, Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations, *Critical Care Medicine*, vol.33, pp.2772-2777, 2005.

[14] S. C. Gale, C. Sicoutris, P. M. Reilly, C. W. Schwab and V. H. Gracias, Poor glycemic control is associated with increased mortality in critically ill trauma patients, *The American Surgeon*, vol.73, no.5, pp.454-460, 2007.

[15] J. S. Krinsley, Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients, *Mayo Foundation for Medical Education and Research*, vol.78, pp.1471-1478, 2003.

[16] Y. Huang, P. McCullagh, N. Black and R. Harper, Feature selection and classification model construction on type 2 diabetic patients' data, *Artificial Intelligence in Medicine*, vol.41, pp.251-262, 2007.

[17] D. Çalişir and E. Doğntekin, An automatic diabetes diagnosis system based on LDA-wavelet support vector machine classifier, *Expert Systems with Applications*, vol.38, pp.8311-8315, 2011.

[18] M. P. S. Brown, W. N. Grundy, D. Lin, N. Cristianini, C. W. Sugnet, T. S. Furey, M. Ares and D. Haussler, Knowledge-based analysis of microarray gene expression data using support vector machines, *Proc. of the National Academy of Sciences*, vol.97, no.1, pp.262-267, 2000.

[19] D. Decoste and B. Schölkopf, Training invariant support vector machines, *Machine Learning*, vol.46, pp.161-190, 2002.

[20] Z. Wang and M. Li, A hybrid coevolutionary algorithm for learning classification rules set, *ICIC Express Letters*, vol.4, no.2, pp.401-406, 2010.

[21] J. C. Hsu, Y. F. Chen, H. H. Lin, C. H. Li and X. Jiang, Construction of prediction module for successful ventilator weaning, *Lecture Notes in Artificial Intelligence*, vol.4570, pp.766-775, 2007.

[22] C. Liu, New evolutionary algorithm for multi-objective constrained optimization, *ICIC Express Letters*, vol.2, no.4, pp.339-344, 2008.

[23] J. Zhang, Y. Wang, Y. Dong and Y. Wang, Computer-aided diagnosis of cervical lymph nodes on ultrasonography, *Computers in Biology and Medicine*, vol.38, no.2, pp.234-243, 2008.

[24] Y. Mu and A. Sheng, Evolutionary diagonal recurrent neural network with improved hybrid EP-PSO algorithm and its identification application, *International Journal of Innovative Computing, Information and Control*, vol.5, no.6, pp.1615-1624, 2009.

[25] N. H. Barakat, A. P. Bradley and M. N. H. Barakat, Intelligible support vector machines for diagnosis of diabetes mellitus, *IEEE Transactions on Information Technology in Biomedicine*, vol.14, no.4, 2010.

[26] Z. Liu, D. Zhang, J. Yan, Q. L. Li and Q. Tang, Classification of hyperspectral medical tongue images for tongue diagnosis, *Computerized Medical Imaging and Graphics*, vol.31, no.8, pp.672-678, 2007.

[27] Y. E. Shao and B.-S. Hsu, Determining the contributors for a multivariate SPC chart signal using artificial neural networks and support vector machine, *International Journal of Innovative Computing, Information and Control*, vol.5, no.12(B), pp.4899-4906, 2009.

[28] J. H. Eom, S. C. Kim and B. T. Zhang, AptaCDSS-E: A classifier ensemble-based clinical decision support system for cardiovascular disease level prediction, *Expert Systems with Applications*, vol.34, no.4, pp.2465-2479, 2008.

[29] G. N. R. Jr and G. M. Edelman, Selective neural networks and their implications for recognition automata, *International Journal of Supercomputer Applications*, vol.1, pp.44-69, 1987.

[30] Z. Wang and M. Li, A Hybrid Coevolutionary algorithm for learning classification rules set, *ICIC Express Letters*, vol.4, no.2, pp.401-406, 2010.

[31] B. Dong, C. Cao and S. E. Lee, Applying support vector machines to predict building energy consumption in tropical region, *Energy and Buildings*, vol.37, no.5, pp.545-553, 2005.

[32] L. Lukas, A. Devos, J. A. K. Suykens, L. Vanhamme, F. A. Howe, C. Majós, A. Moreno-Torres, M. V. D. Graaf, A. R. Tate, C. Arús and S. V. Huffe, Brain tumor classification based on long echo proton MRS signal, *Artificial Intelligence in Medicine*, vol.31, no.1, pp.73-89, 2004.

[33] Z. Pian, L. Gao and L. Guo, A biologically plausible model of contour detection, *International Journal of Innovative Computing, Information and Control*, vol.5, no.9, pp.2541-2549, 2009.

[34] K. Polat, S. Gunes and A. Arslan, A cascade learning system for classification of diabetes disease: Generalized discriminant analysis and least square support vector machine, *Expert System with Applications*, vol.34, pp.482-487, 2008.

[35] I. Guyon and A. Elisseeff, An introduction to variable and feature selection, *Journal of Machine Learning Research*, vol.3, pp.1157-1182, 2003.

[36] G. P. Zhang, Neural networks for classification: A survey, *IEEE Transactions on Systems, Man, and Cybernetics – Part C: Applications and Reviews*, vol.30, no.4, pp.451-462, 2000.

[37] S. Maldonado and R. Weber, A wrapper method for feature selection using support vector machines, *Information Sciences*, vol.179, pp.2208-2217, 2009.

[38] I. Kurt, M. Ture and A. T. Kurum, Comparing performances of logistic regression, classification and regression tree, and neural networks for predicting coronary artery disease, *Expert Systems with Applications,* vol.34, no.1, pp.366-374, 2008.

[39] M. Ture, I. Kurt, A. T. Kurum and K. Ozdamar, Comparing classification techniques for predicting essential hypertension, *Expert Systems with Applications*, vol.29, no.3, pp.583-588, 2005.

[40] D. Delen, G. Walker and A. Kadam, Predicting breast cancer survivability: A comparison of three data mining methods, *Artificial Intelligence in Medicine*, vol.34, no.2, pp.113-127, 2005.

[41] J. Tong, P. Jiang and Z. Lu, A web-based server for prediction of RNA-binding sites in proteins, *Computer Methods and Programs in Biomedicine*, vol.90, no.2, pp.148-153, 2008.

[42] T. K. Wu, S. C. Huang and Y. R. Meng, Evaluation of ANN and SVM classifiers as predictors to the diagnosis of students with learning disabilities, *Expert Systems with Applications*, vol.34, no.3, pp.1846-1856, 2008.

[43] H.-C. Chen, C.-H. Hsu, P.-H. Chou, S.-H. Yang, C.-Y. Chang and M.-J. Wu, Neural network modeling for small DMFC bipolar plate stack system, *International Journal of Innovative Computing, Information and Control*, vol.5, no.12(B), pp.4765-4774, 2009.

[44] Y. LeCun, L. Jackel, L. Bottou, A. Brunot, C. Cortes, J. Denker and H. Drucker, Comparison of learning algorithms for handwritten digit recognition, *The International Conference on Artificial Neural Networks*, 1995.