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ORIGINAL PAPER

A Newborn Screening System Based on Service-Oriented Architecture Embedded Support Vector Machine

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Abstract The clinical symptoms of metabolic disorders are rarely apparent during the neonatal period, and if they are not treated earlier, irreversible damages, such as mental retardation or even death, may occur. Therefore, the practice of newborn screening is essential to prevent permanent disabilities in newborns. In the paper, we design, implement a newborn screening system using Support Vector Machine (SVM) classifications. By evaluating metabolic substances data collected from tandem mass spectrometry (MS/MS), we can interpret and determine whether a newborn has a metabolic disorder. In addition, National Taiwan University Hospital Information System (NTUHIS) has been developed and implemented to integrate heterogeneous platforms, protocols, databases as well as applications. To expedite adapting the diversities, we deploy Service-Oriented Architecture (SOA) concepts to the newborn screening system based on web services. The system can be embedded seamlessly into NTUHIS.

Keywords Web services · Newborn screening · Service-Oriented Architecture · Tandem mass spectrometry · Support Vector Machine

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Introduction

Background

National Taiwan University Hospital (NTUH) initiated its investigation on newborn screening in 1981, and has received and carried on for screening newborn metabolic diseases nationwide since July, 1985. As medical science progressing, more and more advanced newborn screening tests are issued, required. To meet the demands, the hospital has developed and launched the Second Generation Newborn Screening Information System (SGNSIS) [1, 2] to improve, enhance the effectiveness of the system while dealing with large and complex data as well as leading to faster and more accurate diagnoses.

As applying the SGNSIS nationwide in Taiwan, innovations and refinements of the screening methodology using modern tandem mass spectrometry (MS/MS) becomes

increasingly important. MS/MS can quantify concentrations of up to 35 metabolites simultaneously from a single blood spot [3–5]. Consequently, it leads to high dimensional data for each newborn. Thus, there are two issues raised.

First, the classic cut-off value screening technique can not perform adequately or accurately while handling high dimensional data. Moreover, the manipulating strategies of multi-tiered cut-off schemes [6–8] without conjunction with clinical observations, additional sampling simultaneously, lower sensitivities, specificities or predictive values for metabolic disorder diseases can occur. For instance, the accuracy of MMA (Methylmalonic Acidemia) is between 56~73% [9]. The inadequate accuracy can cause newborns losing the opportunities to be treated earlier if they have the metabolic disorder diseases [10].

Secondly, the initiation of screening tests is based upon the past clinical experience of the targeted diseases. Undoubtedly, most screening programs, including MS/MS, can detect subtle variances of the diseases [11]. The natural history of those variances is still unclearly revealed. Now MS/MS can provide large amount of data. Therefore, we can perform data mining processes in order to retrieve, classify more knowledge about those variances.

Related work

The introduction of tandem mass spectrometry (MS/MS) in Portuguese national neonatal screening lab (with over 110,000 samples/year) has led to the development of a new application—NeoScreen—which can help technicians to handle the large amount of data involved (more than 80 parameters/sample) and assist in the implementation of a reliable quality control procedure [12, 13]. The application architecture includes Data Acquisition, Processing, Visualization and Configuration. The Acquisition reads MS/MS files; the Processing analyzes individual samples, testing for possible diseases and storing results into the NeoScreen database; the Visualization converts data or results into graphical representations; the Configuration provides algorithms to identify metabolic diseases. Furthermore, the application provides a mathematical tool or editor. It can automatically generate metabolites expressions as well as dynamic adaptation of diagnostic criterion.

NeoMate [14] and PerkinElmer [15], both provide a complete Laboratory Information Management System (LIMS) for public health and biomedical research especially for expanded newborn screening. The key features encompass user friendly, customizable demographics entry, automation of specimen receiving, validation, tracking, instrument integration as well as quality control for quantitative measurements of screening results. In addition, PerkinElmer equips a flexible, wide range of facilities for selected samples' spectrum or chromatogram presentation and interrogation. The applications support useful mechanisms to simply the newborn screening daily operations.

Furthermore, owing to the amount and complexity of the generated MS/MS screening experimental data, machine learning techniques to investigate patterns for high-dimensional metabolic data are a must. The Support Vector Machine (SVM) is a new technique for data classification [16–18]. The classification task usually involves with training and testing data instances; by feeding the algorithms, SVM can construct classification rules, models with high discriminatory power. In addition, a comparison of the SVM to other classifiers has been conducted by Meyer, Leisch and Hornik [19]. The SVM indicates mostly significant performances both on classifications and regression tasks.

Methodologies

Machine learning techniques offer an obvious and promising approach to examine high dimensional data [20]. Thus, the goal of the paper is to design, implement a newborn screening analysis system. The system utilizes machine learning techniques, i.e., SVM, and mining knowledge to establish the classification models for metabolic disorders screenings and diagnoses. The models can generate high discrimination and improve prediction accuracies.

In addition, the SGNSIS [2] has been developed, deployed based on middleware, SOA technologies [21, 22], i.e., Web Services.NET [23, 24]. SOA represents the current pinnacle of interoperability, in which resources distributed over networks are available as individual, loosely-coupled and independent services [25–28]. SOA is a desirable and inevitable solution to integrate diverse platforms, database as well as further merging, extending into NTUHIS.

In the following sections of the paper, we first elaborate the design of the overall Web Services Newborn Screening System Architecture including SVM classification features. In "SVM web services components", detailed descriptions of system components, SVM modules, functionalities, as well as communication mechanisms among the components are illustrated. In "Integrated scenarios and implementation", an integrated SVM services with data flow scenario and sequence are provided. The measurements, experimental results are presented in "Experimental data flow and results". Finally, the paper discusses and concludes particularly in "Discussion" and "Conclusion".

SOA SVM screening system architecture

Overall architecture

The SOA-based SVM screening system architecture contains three major portions: the Client, the Server and the Database as

depicted in Fig. 1. The Client, which is accessed by physicians or healthcare practitioners, provides a friendly graphical user interface to interact with the Server and the Database. At the Server, we implement the SVM functionalities, such as SVM Training, SVM predicting, SVM scaling, and Data Access Logic, embedded under the Web Services.NET environment. The Database stores the Newborn Screening data collected from the MS/MS, the SVM classifiers, or the Trained Models generated by the training results. All system components utilize the eXtensible Markup Language (XML) format for exchanging messages, and the communication mechanism is based on a Simple Object Access Protocol (SOAP) over HTTP handled internally by the .NET [2, 9, 29, 30].

Authentication/authorization

Medical records including screening data and results must be protected from unauthorized access to comply with Health Insurance Portability and Accountability Act (HIPAA) regulations.

Figure 2 indicates that prior to the SVM screening users from Client Site must be authenticated and authorized. After validation, the SVM methods i.e., MS/MS data repository and transformation, SVM scaling as well as SVM predicting can be performed. Afterwards, the trained models will be calculated, stored in Database.

SVM web services components

The descriptions of the components are illustrated in this section.

SVM screening system approach

SVM Screening system activities are depicted in Fig. 3. In the diagram, after the experimental dataset (i.e., the Excel file) from MS/MS is transformed into a.Net DataSet. At the Screening Client site, the DataSet is randomly separated into two portions. One portion is the training data, which is used for constructing the Trained Model (1a). The other portion is used as the testing data for predicting (1b). Both data are temporarily placed at the Client Site for the training and predicting processes. The results can be analyzed and diagnosed to clarify the accuracy of the research.

In the diagram, while a Screening Client asking for testing (1b), the Server retrieves Training DataSet from the Database (2a:request & 3:response respectively). Both the

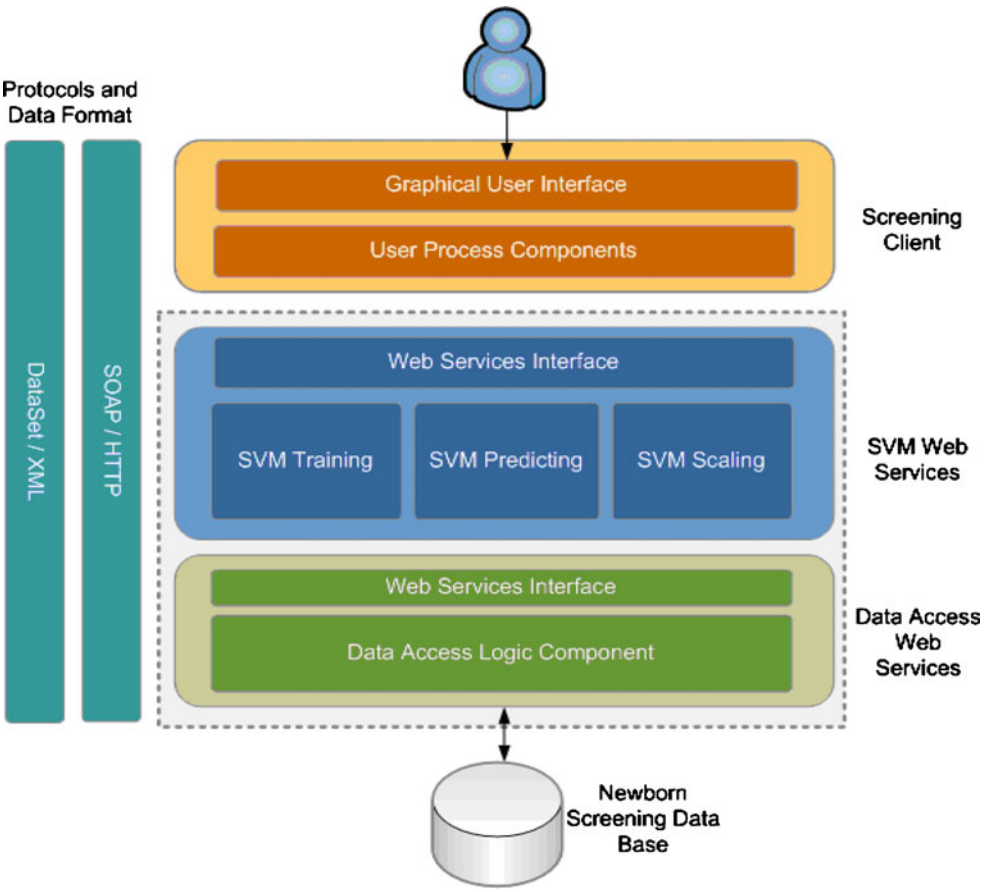

Fig. 1 Support vector machine screening system based on service-oriented architecture

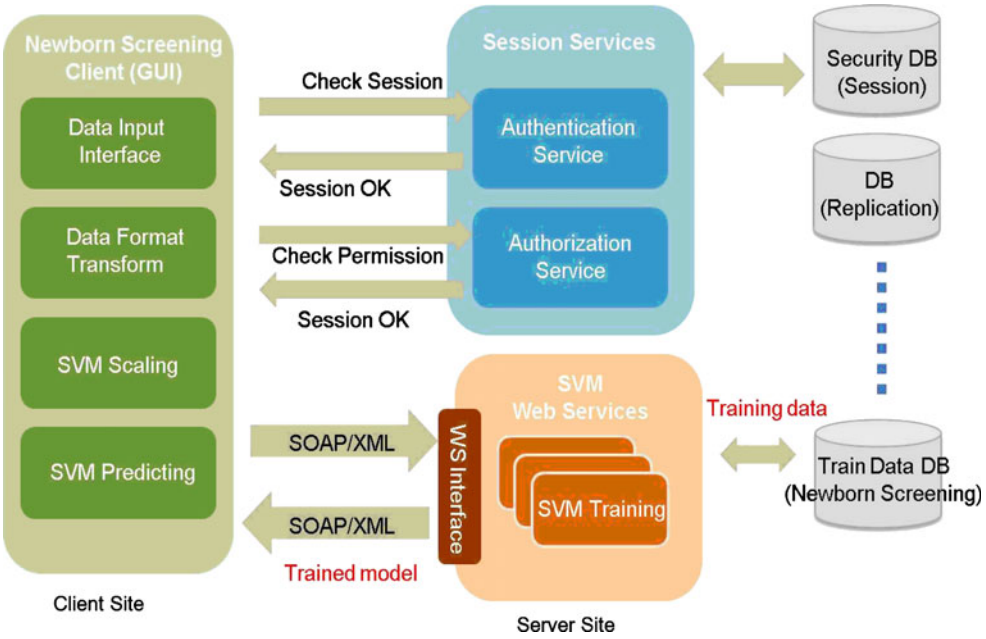

Fig. 2 Authentications and authorizations by session services

Testing DataSet and the Training DataSet need to be scaled (SVM Scaling Module) prior to passing to either SVM Training or SVM Predicting Modules in (2b & 5). According to the Scaled Training DataSet (5), the Trained Model will be generated, deposited into the Database (6). While constructing the classifier, the optimization processes are performed repeatedly to increase the accuracy of the Model. The accuracy of the SVM Model is largely dependent on the selection of the model parameters, i.e., C and Gamma. A Grid Search and an RBF (Radial Basis Function) kernel function with two parameters C and Gamma are used to optimize the model selection. During the computational iteration, the ranges of parameters, C and Gamma, are resizing accordingly [31]. Therefore, the classifier, or Trained Model, can accurately predict an unknown dataset, or the Testing DataSet. The SVM predicting module performs discriminating to a scaled Testing DataSet according to a Trained Model. The Trained Model is retrieved from the System Database, previously stored by the SVM Training Module (2b, 7:request & 8:response respectively).

Screening client site

The Screening Client is an application. It provides a friendly user graphical interface. The application supports functionalities as listed below:

1. Read or input the metabolic substances concentration data, an Excel file as shown in the left upper corner of Fig. 1, generated by the Tandem Mass Spectrometry. The application converts or transforms the file into a DataSet (the format required by .NET). The concentration data can be either a set of data retrieved from well known metabolic diseases to establish SVM Trained Model or a set of unknown data to be verified for diagnosis, analyzing later.
2. Invoke the SVM-Training Method and obtain the Trained Model, i.e., SVM classifier, as the return value. The Model is later stored into the Newborn Screening System Database.
3. Pass a newborn's DataSet and a Trained Model as parameters to the SVM Predicting Method; according to the Predicting result, determine whether the neonatal has metabolic disorder disease specified by the Trained Model.
4. Store the results into the Newborn Screening System Database.

SVM methods based on web services

The Server supports the following functionalities, methods.

1. SVM Training Method: the primary function: *svm_train*, indicated in Fig. 3, is to perform separating the metabolic substances DataSet retrieved from the Database, proceed optimizing, and generate the Trained Model. In the diagram, there are accessory functions to assist the training processes as well (Fig. 4).
2. SVM Predicting Method: the module performs predicting of a scaled Testing DataSet according to a Trained Model. The Trained Model is retrieved from the System Database, previously stored by the SVM Training Module (as shown in Fig. 1, (2), (7) & (8)). The Predicting Method returns the screening results, display them, and store them into the System Database for further analyses and diagnoses. The outcomes classify, or interpret the possibilities of metabolic disorder diseases.

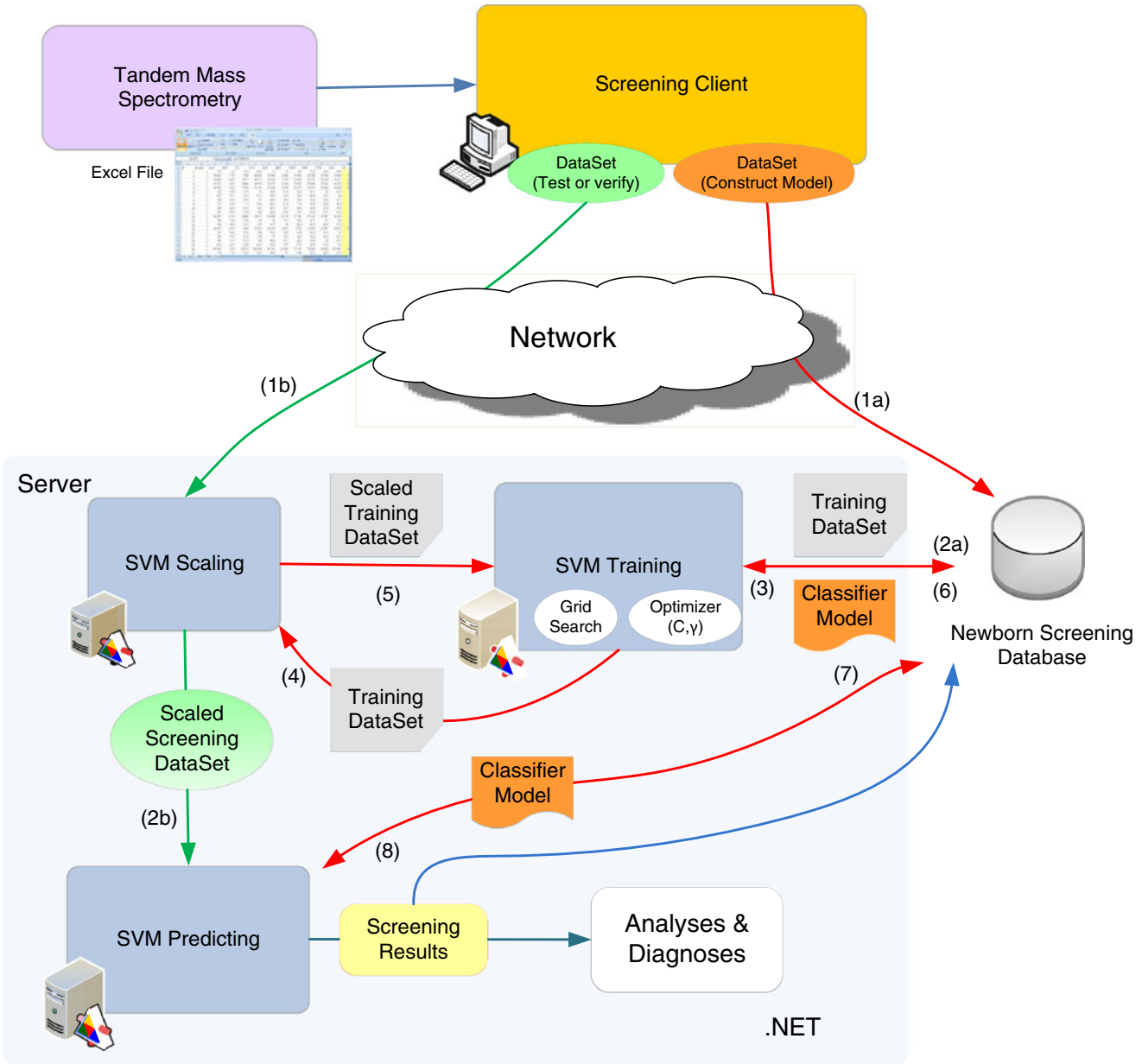

Fig. 3 SVM screening system activity diagram

3. SVM Scaling: the function is to avoid data attributes, either Testing DataSet or Training DataSet, in larger numeric ranges and induce calculating difficulties.
4. Data Access Services: the Services provide interfaces to either Clients or accessing the Newborn Screening System Database.

Integrated scenarios and implementation

The sequence diagrams for the SOA Newborn Screening System operational scenarios are depicted in Fig. 5. The System has integrated the SVM mechanisms, such as Training, Scaling, Predicting Modules, etc., under a Web Services.NET environment.

At first, the experimental dataset was collected according to an anonymous subset of all data obtained from the Newborn Screening Centre of NTUH between 2001 and 2006. Blood samples which had been taken within a few days of the newborns' birth were analyzed by MS/MS using a high throughput process, and the measured metabolic datasets (35 measured metabolites including amino acids, long fatty acid chains and acyl carnitines) were saved in Excel files and were stored in a database. This study primarily focuses on improving the accuracy of identifying the MMA (Methylmalonic Acidemia) metabolic

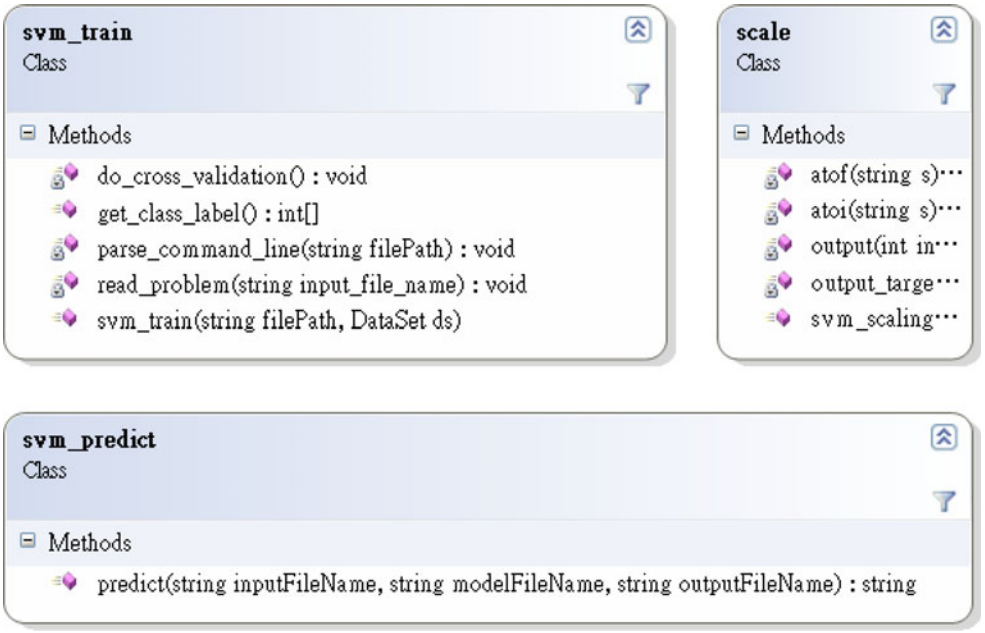

Fig. 4 SVM server functionalities

disease. This approach can definitely be extended to analyze other diseases as well.

First, by invoking the SVM Training Service, additional optimization processes occur repeatedly in order to obtain a highly accurate classifier. The classifier is then utilized by the SVM Predicting Service as an input parameter. Before activating both Services, the input datasets (either the Training DataSet or the Testing DataSet for prediction)

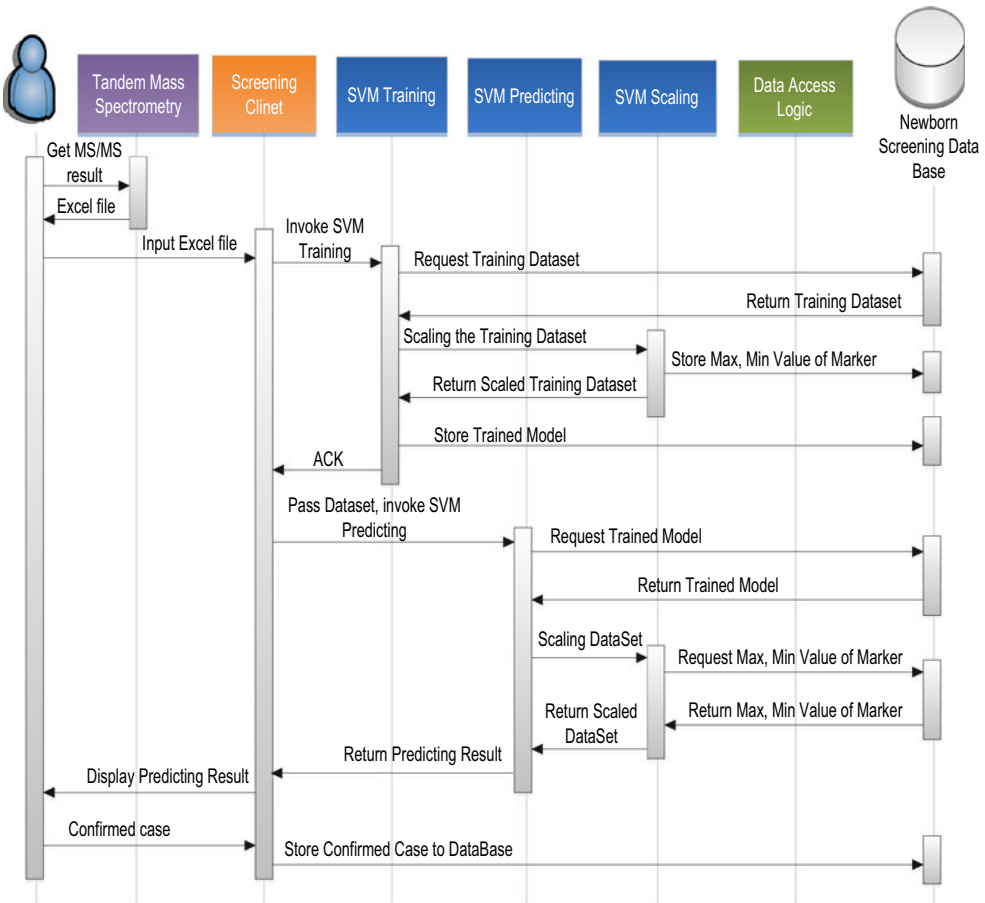

Fig. 5 System operational scenarios and sequences

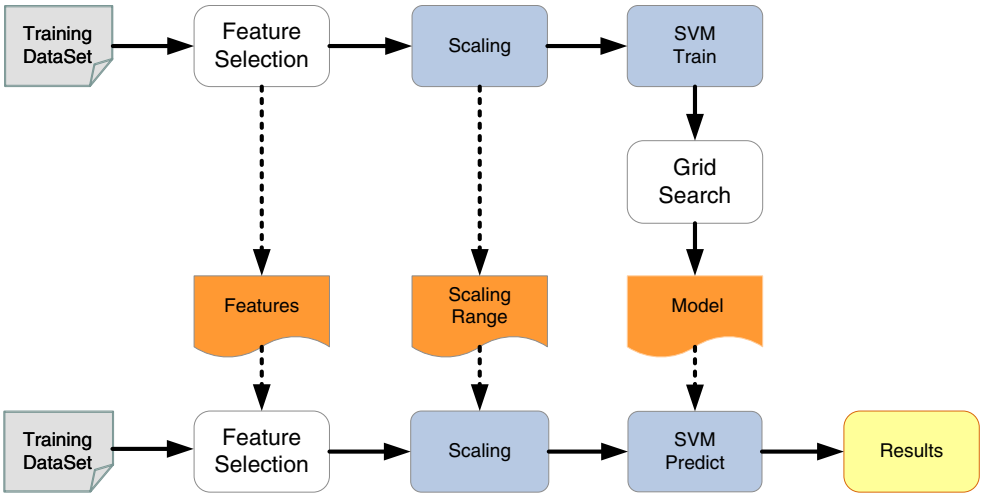

Fig. 6 Data flow model for newborn screening

are scaled via the SVM Scaling Service in order to avoid data attributes in large numerical ranges, which can induce calculation difficulties. Requests and responses among the associated components in the operational scenarios are clearly indicated in Fig. 5.

Experimental data flow and results

In the study, we propose a proper supervised classification data flow [18] to enhance the accuracy and sensitivity of Newborn Screening process, as depicted in Fig. 6. In the diagram, the Train Dataset undergoes learning to produce the SVM prediction model; the New Dataset processes the same methods to obtain the prediction result according to the trained model. Before training or predicting, the dataset is preprocessed by the MS/MS machine. The Feature Selection part will generate the most relevant features by a Pearson-like formula [32]. The Scaling method is used to avoid biasing and to improve computing efficiency. The SVM machine learning with Grid Search as well as Cross validation then generates the prediction model for the New Dataset [33].

During the experiment, we focused on the Methylmalonic Acidemia (MMA) metabolic disorder preliminarily. We collected 360 newborn samples gained from Newborn Screening Centre of National Taiwan University Hospital between 2001 and 2006. All the samples are divided into three parts, 1/2 for Train DataSet, 1/4 for the Validation DataSet, the rest for predicted New DataSet. The effectiveness of the classifiers is summarized in Table 1.

In the Table 1, the first four rows present the cases that used traditional cut-off value screening method; the last row means the results from SVM web services proposed in this paper. The Sensitivity column shows the developed SVM method get the best 95.9% sensitivity. In Specificity column displays that the SVM approach achieves the highest 95.6% specificity compared with the classic cut-off technique listed in low 1–4. Similarly, it also indicates that SVM performs the highest accuracy as listed in the last column. Obviously, the SVM approach, using higher dimensional selected features method, demonstrates better discrimination power and increase the accuracy accordingly.

Discussion

The NTUH newborn screening Program has educational and monitoring mechanisms in place to prevent and investigate any possible problems [1]. However, it is still critical for health care providers to remain watchful for any signs or symptoms of these disorders in their patients. Any signs or symptoms of a disorder should be followed up immediately. The possibility of a disorder should not be ruled out solely on the basis of the newborn screening test result. A newborn screening result should not be considered diagnostic, and cannot replace the individualized evaluation and diagnosis of an infant by a well-trained, knowledgeable healthcare provider. Undoubtedly, the timely delivery of complete and accurate information can enhance the opportunities to immunize the newborns. Performance: SVM pilot stage education cannot be obtained. After integration

Table 1 The sensitivity, specificity and accuracy results detected on the experiment results

Metabolites (MMA)	Sensitivity (%)	Specificity (%)	Accuracy (%)
C3	81.4	76.2	73.1
C2	67.7	88.5	63.2
C3/C2	76.0	90.6	56.7
C4DC	70.4	84.8	68.6
SVM	95.9	95.6	96.8

with HIS, We can provide detailed performance of evaluation data.

The purpose of newborn screening test is to sort out apparently healthy individuals who have a disease from those who probably do not. However, screening programs are, by nature, imperfect. In setting cutoffs, a balance must be struck between time, money, anxiety caused by false positives, and an acceptable number of missed cases. On one hand, laboratory advances in tandem mass spectrometry make it possible to screen newborns for many rate inborn errors of metabolism. This raises many policy issues including screening's cost-effectiveness, ethics, quality, and oversight. On the other hand, new techniques in genetics surveillance have facilitated an improved public health approach to the detection of, and interventions offered for, a range of important genetic conditions. Over the past 10 years, scientific advances associated with genetic have been increasing at an explosive rate. This has meant that an increasing number of diagnostic, predictive and carrier tests are available, for instance, leaning towards data mining technologies.

Conclusion

Based on SOA concepts, we developed three main functions of the SVM (i.e., training, predicting, scaling) using Web Services techniques. The design inherited SOA flexibilities and will provide additional cooperation for further integration and deployment.

In the study, we also proposed a Newborn Screening System that predicts whether the newborn has metabolic disorder diseases based on modified Support Vector Machines (SVM) classifier. Applying the architecture, the predicting accuracy of MMA can be improved from 56~73% (cut-off value approach) to over 96%, the sensitivity can be improved from 70~81% to over 95%.

Up to now, the MS/MS newborn screening at the NTUH has accumulated around 400,000 pieces of data in 5 years. The NTUH has dedicated the manpower to digitize the paper data, and after the data is converted, they provide opportunities to apply the SVM-based Screening System for classifying other metabolic disorder diseases and to obtain higher discrimination accuracies. Ultimately, the System can replace the classic cut-off value screening technique.

The newborn screening programs in Taiwan are continuing to refine and expand their Newborn Screening Services. There are many research projects ongoing, for instances, the particular interests are: (1) congenital adrenal hyperplasia; (2) glucose-6-phosphate dehydrogenase deficiency; (3) galactosemia; (4) congenital hypothyroidism; (5) Fabry disease; 6) Pompe disease. In the future, we hope that this successful mining experience with MS/MS newborn screening may be extended to other newborn diseases.

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