First Trimester Diagnosis of Trisomy-21 Using Artificial Neural Networks

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Abstract—**A chromosomal disorder caused by the presence of all or part of an extra 21st chromosome is known as the Down syndrome, or trisomy 21, or trisomy G. In the last fifteen years it has become possible to observe these features by ultrasound examination in the third month of intrauterine life. About 75% of trisomy 21 fetuses have absent nasal bone.**

In the present work, neural network schemes that have been applied to a large data base of findings from ultrasounds of fetuses, aiming at generating a predictor for the risk of Down syndrome are reported. A number of feed forward neural structures, both of standard multilayer and multi-slab types were tried to find the best for prediction. The database was composed of 23513 cases of fetuses in UK, provided by the Fetal Medicine Foundation in London. For each pregnant woman, 19 parameters were measured or recorded. Out of these, 11 parameters were considered as the most influential at characterizing the risk for this type of chromosomal defect.

The best results obtained were with a multi-slab neural structure. In the training set there was a correct classification of the 98.9% cases of trisomy 21 and in the guidance (test) set 100%. The prediction for the totally unknown verification test set was 93.3%.

Keywords— **Trisomy 21, Down syndrome, neural networks.**

I. Introduction

During the last 35 years, extensive research has aimed at developing a non-invasive method for prenatal diagnosis based on the isolation and examination of fetal cells found in the maternal circulation. Examination of fetal cells from maternal peripheral blood is however, more likely to find an application as a method for assessment of risk, rather than the non-invasive prenatal diagnosis of chromosomal defects. In addition to this, there is contradictory evidence concerning the concentration of cell-free fetal DNA in trisomy 21 pregnancies. Invasive techniques on the other hand require invasive testing and thus increase the risk of miscarriage even if this is carried out by an appropriately trained and experienced operator [1].

In the 1990s, screening by a combination of maternal age and fetal nuchal translucency (NT) thickness at 11 to 13+6 weeks of gestation was introduced. This method has now shown to identify about 75% of affected fetuses for a screen-positive rate of about 5% [2].

Subsequently, maternal age was combined with fetal NT and maternal serum biochemistry (free β-hCG and PAPP-A) in the first-trimester to identify about 85-90% of affected fetuses. The level of free β-hCG in maternal blood normally decreases with gestation. In trisomy 21 pregnancies free β-hCG is increased. The level of maternal blood normally increases with gestation and in trisomy 21 pregnancies the level is decreased.

In 2001, it was found that in 60-70% of fetuses with trisomy 21 the nasal bone is not visible by ultrasound at 11 to 13+6 weeks and preliminary results suggest that this finding can increase the detection rate of the first trimester scan and serum biochemistry to more than 95%.

The risk for trisomies in women who have had a previous fetus or child with a trisomy is higher than the one expected on the basis of their age alone. In women who had a previous pregnancy with trisomy 21, the risk of recurrence in the subsequent pregnancy is 75% higher than the maternal and gestational age-related risk for trisomy 21 at the time of testing. Thus, for a woman aged 35 years who has had a previous baby with trisomy 21, the risk at 12 weeks of gestation increases from 1 in 249 to 1 in 87 [1].

The Fetal Medicine Foundation (FMF) which is a UK registered charity has established a process of training and quality assurance for the appropriate introduction of NT screening into clinical practice.

An automatic and user friendly tool is suggested to build using artificial neural networks and trained with the data that was collected by FMF during recent years.

Such a tool may improve the detection of chromosomal defects, as for instance a reliable predictor or a method for the effective and early identification of an abnormality. This tool would be of great help to obstetricians and of course to pregnant women and unborn children.

In recent years, neural networks and other computationally intelligent techniques have been used as medical diagnosis tools aiming at achieving effective medical decisions incorporated in appropriate medical support systems [3], [4], [5]. Neural networks in particular have proved to be

quite effective and also have resulted in some relevant patents [6], [7].

II. Data

The data were obtained from the greater London area and South-East England, for pregnant women attending routine clinical and ultrasound assessment for the risk for chromosomal abnormalities.

This assessment was performed by measurements of the fetal nuchal translucency thickness, the maternal serum free human chorionic gonadotropin (fhCG) and the serum pregnancy-associated plasma protein A (PAPP-A) at 11 to 13+6 weeks of gestation. Gestational age was derived from the fetal crown-rump length (CRL).

The database was composed of 23513 cases. These were provided by the Fetal Medicine Foundation (FMF) in London. For each case, 19 parameters that were presumed to contribute to diagnosis were recorded.

Based on recommendations from medical experts, some data (parameters) were excluded in the study. At the end, only 11 parameters out of the total of 19 were ultimately considered to be the most influential at characterizing the risk of chromosomal defect occurrence, and those were used in the built-up of the neural predictor. These parameters are shown in Table 1.

Table 1 Parameters used for the first trimester diagnosis of trisomy 21

Maternal age
CRL, Crown Rump Length (mm)
GA, Gestation Age when the CRL was measured (in days)
Previous T21 (yes or no)
NT, Nuchal Translucency (mm)
FHR, Fetus Heard Rate
NB, Nasal Bone (normal, abnormal)
TF, Tricuspid Flow from RA to RV (normal, abnormal)
DV, Ductus Venosus Flow (normal, abnormal)
Serum marker PAPP-A
β-hCG, Human Chorionic Gonadotropin

Those parameters were encoded in appropriate numerical scales that could make the neural processing to be most effective.

A guidance test set of 109 cases was extracted and used to test the progress of training and thus guide the training towards better generalizations and classification yields. This data set included 25 cases (23%) of fetuses that were abnormal. Also, a verification data set having 93 cases out of which 15 were with abnormality (16%), was extracted to be used as totally unknown data set to the neural network, and thus to be used for checking the prediction capabilities of each attempted network. The data set under examination is very difficult to study because of its unbalanced nature; it has 23513 cases from which 23296 are normal and 217 are the abnormal. The nature of this problem makes the use of artificial neural networks more interesting since their ability to handle such complex problems will be demonstrated.

III. Neural predictor

A number of feed forward neural structures, both standard multilayer of varying number of layers and neurons per layer, as well as multi-slab of different structures, sizes, and activation functions, were systematically tried for the prediction. This was done in a planned and systematic manner so that the best architecture would be obtained.

Ultimately a multislab neural structure having five slabs that were connected as depicted in Figure 1 was selected and used.

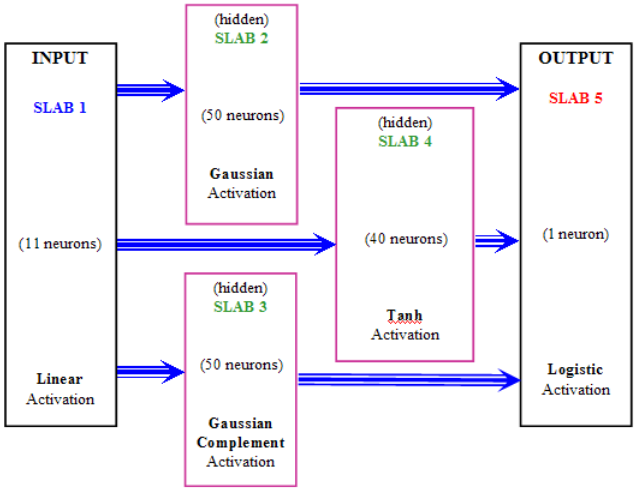

Fig. 1. The neural structure that was ultimately selected and used for the first trimester diagnosis of chromosomal defects

Based on extensive previous experience, all the weights were initialized to 0.3, while the learning rate was the same for all connections, having value of 0.1. Similarly, the momentum rate was 0.2 for all links.

The guidance test set was applied at the end of each epoch to test the progress of training. If the results of the testing at epoch *e* were better than those at epoch *e*–1, the weights were saved and kept as a better set.

The training progress was monitored in order to observe whether there was improvement during the application of the training and test set data. For most of the network struc-

tures attempted, there was little generalization improvement after about 1500 epochs.

IV. Results

Following a rigorous investigation of different neural structure topologies, sizes and initial conditions, a structure of the form of Figure 1 gave the best results which are summarized in Tables 2 and 3 below. The size of the various data sets used for the training and verification are shown in Table 2.

Table 2. Data sets used for the development of the neural predictor of trisomy 21

Total number of cases	23513
Normal cases	23296
T21 cases	217
Training set cases	23311
Training set, normal cases	23134
Training set, T21 cases	177
Test set cases	109
Test set, normal cases	84
Test set, T21 cases	25
Verification set cases	**93**
Verification set, normal cases	**78**
Verification set, T21 cases	**15**

The results obtained for the neural structure described before are given in Table 3.

Table 3. Results of data sets used for the development of the neural predictor of trisomy 21

SET	SIZE	% of total cases
Training set correct cases	23307	99.9
Training set T21 correct cases	175	98.9
Test set correct cases	109	100.0
Training set T21 correct cases	25	100.0
Verification set correct cases	**92**	**98.9**
Verification set T21 correct cases	**14**	**93.3**

It is seen that a high correct classification of 98.9% was obtained for all the cases of the totally unknown verification set. In this set there were 15 unknown cases of trisomy 21, and 14 (93.3%) were correctly predicted.

The correlation coefficient for this unknown verification data set was 95.5%.

V. Conclusions and future work

The results summarized in Table 3 are very encouraging because they give a 100% diagnostic yield during testing and 93.3% diagnostic yield to a totally unknown T21 data set. It should be mentioned that we have not came across to any previous work that is using artificial neural networks for handling this problem. Statistical techniques were used however, with results of lower performance. The results obtained in this study are to our knowledge, the highest recorded in the literature.

The study is currently under further development for improvement and in addition other chromosomal defects are being studied, namely T-18, T-13, and Turner Syndrome with additional data from FMF, about these cases [1]. It is aimed to develop with the help of the doctors from the clinic, a full diagnostic tool that will be user friendly and that it will cover the whole spectrum of chromosomal deficiencies during the first trimester.

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