Medical Informatics Europe '97
C. Pappas et al. (Eds.)
IOS Press, 1997

Studies of Responsiveness in the R-EGFR and Rcerb-B2 Oncogenes Spaces: a Customized Application for Thyroid Lesions

Arijan Šiška[a] B. Sc., Ankica Babić[b] Ph. D., Nikola Pavešić[a] Ph. D.

a) Faculty of Electrical Engineering, Tržaška 25, Ljubljana
b) Department of Biomedical Engineering, Medical Informatics, Linköping University, Sweden

Abstract

Among verity of diagnostic approaches suitable for clinical analysis of thyroid lesions, the two oncogenes (R-EGFR and Rcerb-B2) are believed to be of discriminative power. In a retrospectively collected patient material we have defined different lesion types (normal tissue, benign and malignant tumours). Those were taken as class definitions in analysis performed to assign discriminating performance. Standard multivariate statistics has not performed satisfactory partly due to the data distribution and partly due to presence of the noise. Therefore we have developed a method for the classification purpose, which was based on principle of minimising generalised classification error. Results of the separation between carcinoma and normal tissue reached accuracy 70%, other classification attempts ended up in poor results. In general, misclassifications could be explained with the data quality (noise) and, when it came to benign lesions, with responsiveness of the oncogenes to tumour tissues.

Introduction

Follow up of patients with thyroid related complications is done with a purpose of controlling benign lesions and disclosing malignant processes. Routinely performed tests include a specific laboratory profile, histological and cytological examination. Exposition of the oncogenes is expected to be a sophisticated measure reflecting subtle changes in the tissue[1,2,3]. Aim of the present study was to assess this performance by means of statistical and other applicable methods. We approached this problem in a common manner by finding classification rules for the known data sets which could be then hypothetically used to diagnose new cases.
We studied thyroid lesions of 97 patients, 61 (62%) with benign and 37 (38%) with malignant changes.

2D formulation of the classification

Univariate and multivariate statistics were used to explore the patient material with respect to a great number of clinical and diagnostic features. The data distribution suggested nonparametric tests to be performed, and additional efforts to discriminate the groups. Due to the noise in data, most likely caused by time span in which patients were treated, preliminary accuracies were not high. Therefore, we had decided to search for more efficient classifiers, thus we have chosen a 2D representation. That meant that the diagnostic problem was turned into a problem of dividing-partitioning a set of points that belong to different classes in N dimensional space. This partitioning can be done in various ways of which the simplest and most intuitive might be to partition by means of linear functions or hyper planes. We are dividing N dimensional space with N-1 dimensional hyper planes into two subspaces. If we recursively divide subspaces into smaller subspaces, we get a hierarchical division of space with hyper planes into arbitrary number of parts or classes. Such division is called binary space partition. Hierarchical structure of division planes is called BSP tree. Problem can best be viewed in the 2D plane. Points are two dimensional, division planes are 1 dimensional lines. Subsequent generalisation into N dimensional problem is easy and can be derived later. All is a part of a larger class of classification problems some of which hypothesise about measured data distribution functions or pay a lot of attention to special points which reside near the border [4,5,6].

Classification Method

First of all, to define fitness of the proposed division, we have to ask ourselves: "How good does this line divides the plane?". Let us first define the error function E. This is a function that, for a given set of points in the plane, and with each point having defined a class membership, and given proposed dividing line, produces a

real number. That is our measure of error, i.e. criterion of fitness for the given dividing line. The smaller error, the better division. Formally we can define the function E as:

$$E:\{k,n,p_1,p_2,\ldots,p_n,c_1,c_2,\ldots,c_n\} \mapsto e$$

where k and n are linear function coefficients, p_i are points on the plane, c_i are class indexes and e is the error value. Error function defines the behavior of the dividing line. Out of all possible functions we must extract a class of functions that have some sort of meaning. Some attributes of the error function can be intuitively recognized:

- points-samples p_i are equivalent and error function is invariant with respect to these points. If we shuffle the points' indexes, for example, the error should remain the same.
- if we put all points from the first class into the second class, and all points from second class into first class, error should remain the same.
- error function is depended on a signed distance of point p_i from the line: this distance can be defined as Euclidean distance or: $(p_i\text{-}[O,n]).[k,-1]$, which is a principle of linear discrimination described in [5].

Following the above, we developed error function E, that is defined as a sum of errors that single points produce:

$$e = \sum_i f\left(\left(\left(p_i - [0,n]\right).[k,-1]\right) * c_i\right)$$

As we can see from the equation, there is a function f acting as a modifier of the error of a single point. This function is a generalization of the principle of peceptron criterion function [5]. Minimizing this criterion-error function is our goal.

There are only two unknown variables in the equation k and n, that define the dividing line. Our task is to find such parameters that minimize error e.

Method as just described can be viewed as a penalty method. We prescribe the penalty line has to pay if it sets itself on the "wrong side" of the point. When we minimize error function we actually try to enforce restrictions upon line placement.

What we are basically interested in is such an error function, that counts the wrongly classified points-samples. In this case we are minimizing number of miss-classified points. Function f in that case is defined as a step function. This function is not continuous and that fact can pose a real problem to various algorithms for finding a minimum.

If we chose f to be a right linear function we effectively get the method of minimizing perception criterion function [5].

At this point it is probably interesting to notice, that if we put $f(x) = x^2$ we practically get a method of placing a linear regression function through the points. We are looking for a linear function that has minimum square distance to the points. Of curse in this case there is no classification taking place since function f is symmetrical with respect to the y coordinate axis and therefore in a way blind to the point's class.

We can also define different f, with following properties:

- separate left and right side of the y axis in the coordinate system, by being small in the left side and growing large on the right side
- are continuous

Let us take a look at the Table 1.

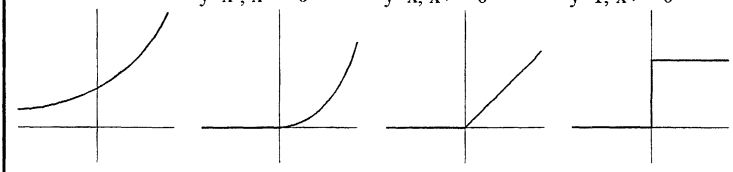
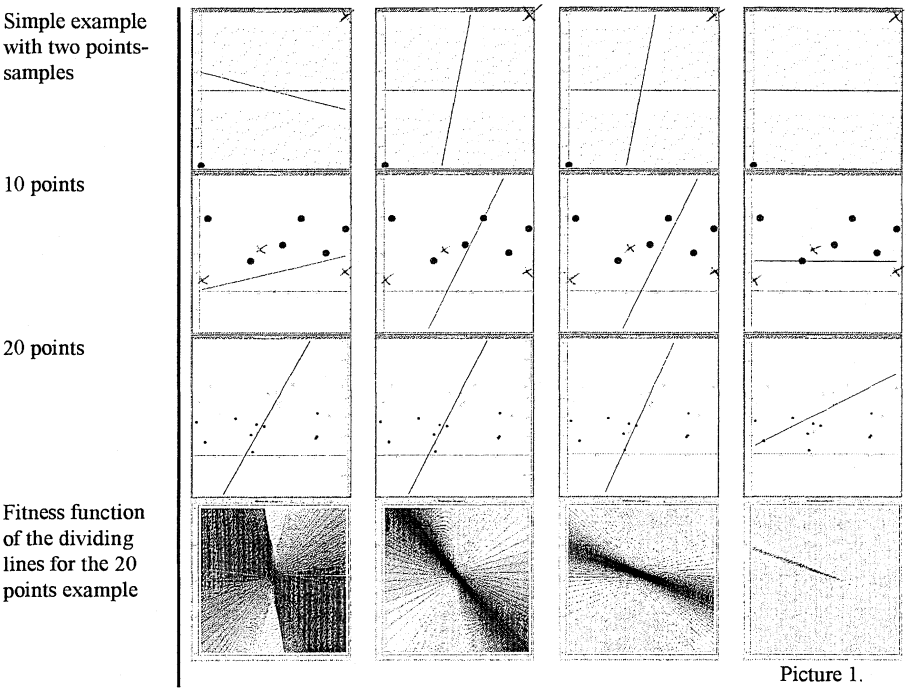
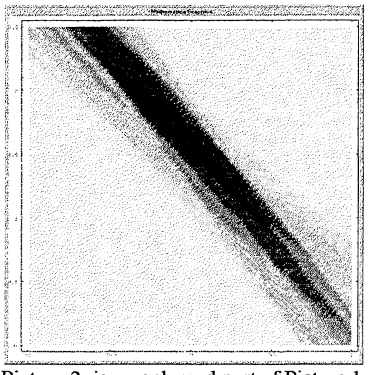
function f	Exponential function	Right Square function	Right Linear function	Step function
definition	$y=e^x$	$y=0,\ x<0$ $y=x^2,\ x>=0$	$y=0,\ x<0$ $y=x,\ x>=0$	$y=0,\ x<0$ $y=1,\ x>=0$
function graph				

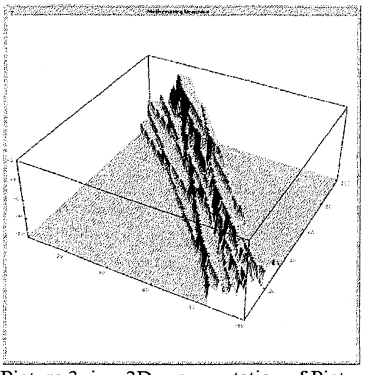
Table 1. A graphical presentation of choices for the f function and its corresponding effect on derivation of minimal error dividing line - classification criterion.



Picture 1.



Picture 2. is an enlarged part of Picture 1



Picture 3. is a 3D representation of Picture 2.

Enlarged part of the Picture 1. and its three dimensional display clearly suggest a difficulty of finding extreme of the error-fitness function with f being a step function. The error function is not continuous which makes it practically impossible to locate a minimum point. Even if the step function f is theoretically our ideal goal, since error function returns a number of miss-classified samples and that being the only relevant number to us, its use is clearly limited, since many algorithms for minimization depend on using derivation or gradient of the error function. This is something we cannot do if error function is not continuous.

As a compromise solution it is suggested to take a right linear function [5]. This would make error function continuous and enable use of gradient methods, but still derivation of the error function is not continuous and that makes it impossible to use second derivation in the minimization process. Still the fitness relief for both right linear function and step function are similar enough, to make us believe that we can get away by using right linear function for function f instead of the real thing.

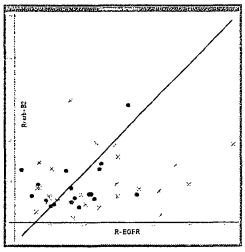
There are many different algorithms which find extreme points or minimum of the given function, and it is certainly not the point of this paper to go into many details regarding these methods. At this point genetic algorithms should be mentioned as a promising direction.

What we have come up with in this test example is a fairly simple method that tries to minimize parameters separately, first k than n, and then the whole scheme repeats. At first steps at which parameters are changed are big, then they gradually get smaller and smaller. Since fitness landscapes in our example are simple, this procedure works well enough. However more research in this part would be required to produce more accurate results faster, or prove there can be no significantly more accurate results.
We hoped that the method described will be less influenced by necessary noise in the data, since it does not necessarily tries to put all the points on the right side of the classification line, but it tries to minimize an error criterion. By introducing noise into data we hoped classification line will not change it's position very much. This robustness for noise was one of our goals.
All the programming was done in the Mathematica [7],[8]. programming environment. It is not very fast, but it is flexible enough for us the make that trade-off. This is especially important when trying out lot's of different algorithms.

Results

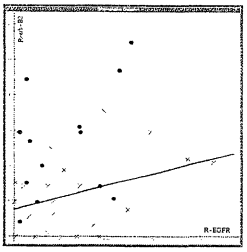
We applied our procedures to the real data. As a function f we used right linear function. Points are plotted in the plane, where X axis represents R-EGFR oncogene measurement and Y axis represents Rcerb-B2 oncogene measurement. An example of the classification is given in the pictures 4 and 5.
Points were separated into two classes by the following criteria:

class 1 (bright crosses) under the line: Benign tumours;
class 2 (dark points) above the line: Normal tissue;
dividing line: y=1.738*x-50;
classification error: 22 miss-classified samples out of 46



Picture 4.

class 1 (bright crosses) under the line: Malignant tumours;
class 2 (dark points) above the line: Normal tissue;
dividing line: y=0.137*x+15;
classification error: 12/39



Picture 5.

We evaluated our method with standard linear regression tests. These tests helped us find any relationship between the class of a point and its corresponding R-EGFR and Rcerb-B2 parameter.
An acceptably high accuracy of 70% supports an expectation that the oncogenes could distinguish carcinomas form normal tissue. As it could have been expected, response of the oncogenes was weak when dealing with benign tumours and normal tissue. However, unpaired t-test analysis found a few significant relations between the oncogenes and the lesion classes. In general, misclassifications could be explained with the data quality (noise) and with responsiveness of the oncogenes to certain type of tumour tissue.

Acknowledgements

Authors are grateful to Drs Prof. Marija Us-Krasovec, Ph.D., and Vera Kloboves-Prevodnik, M.Sc., for involving us in an interesting clinical discussion on diagnostic efficacy of the R-EGFR and Rcerb-B2 oncogenes which had initiated the present research.

References

[1] Willliam C. Dougali et. al., The neu-onkogene: signal transduction pathways, transformation mechanisms and evolving therapies
[2] Lori Jardines et. al., neu(c-erbB-2/HER2) and the Epidermal Growth Factor Receptor (EGFR) in Breast Cancer, Farhobiology 1993:61:268-252
[3] Giovanni Pauletti et. al., Detection and quantitation of HER-2/neu gene amplification in human breast cancer archival material using flourescence in situ hybridization, Oncogene 1996 13:63-72
[4] Pavešič N., Razpoznavanje vzorcev, in Slovene, ZAFER, 1992
[5] Duda R. O., Hart P. E., Pattern Classification and Scene Analysis, a Wiley Interscience Publication, 1973
[6] Niemann H., Pattern Analysis and Understanding, Springer-Verlag, 1981
[7] Gray J. W. Mastering Mathematica: Programming Methods and Applications, AP Professional, 1994
[8] Wolfram S., The Mathematica Book, Third Edition, Cambridge University Press, 1996