Using Topological Data Analysis for diagnosis pulmonary embolism

 $\sf Matteo\ Rucco^{*1}$, Lorenzo $\sf Falsetti^2$, $\sf Damir\ Herman^3$, $\sf Tanya\ Petrossian^3$, $\sf Emanuela\ Merelli^1$, $\sf Cinzia\ Nitti^2$, $\sf Aldo\ Salvi^2$

Email: Matteo Rucco*- matteo.rucco@unicam.it; Lorenzo Falsetti - lorenzo.falsetti@ospedaliriuniti.marche.it; Damir Herman - damir@ayasdi.com; Tanya Petrossian - tanya@ayasdi.com; Emanuela Merelli - emanuela.merelli@unicam.it; Cinzia Nitti - c.nitti@ospedaliriuniti.marche.it; Aldo Salvi - a.salvi@ospedaliriuniti.marche.it;

Abstract

Background

Pulmonary Embolism (PE) is a common and potentially lethal condition. Most patients die within the first few hours from the event. Despite diagnostic advances, delays and underdiagnosis in PE are common. Moreover, many investigations pursued in the suspect of PE result negative and no more than 10% of the pulmonary angio-CT scan performed to confirm PE confirm the suspected diagnosis. To increase the diagnostic performance in PE, current diagnostic work-up of patients with suspected acute pulmonary embolism usually starts with the assessment of clinical pretest probability using plasma d-Dimer measurement and clinical prediction rules. One of the most validated and widely used clinical decision rules are the Wells and Geneva Revised scores. However, both indices have limitations. We aimed to develop a new clinical prediction rule (CPR) for PE based on a new approach for features selection based on topological concepts and artificial neural network.

Results

Filter or wrapper methods for features reduction cannot be applied to our dataset: the application of these algorithms can only be performed on datasets without missing data. Alternatively, eliminating rows with null

¹University of Camerino, School of Science and Technology, Computer Science Division, Camerino, IT

²Internal and Subintensive Medicine of Ospedali Riuniti - Ancona, IT

³Ayasdi, Inc. Palo Alto, CA

^{*}Corresponding author

values in the dataset would reduce the sample size significantly and result in a covariance matrix that is singular. Instead, we applied Topological data analysis (TDA) to overcome the hurdle of processing datasets with null values missing data. A topological network was developed using the Iris software (Ayasdi, Inc., Palo Alto). The PE patient topology identified two flares in the pathological group and hence two distinct clusters of PE patient populations. Additionally, the topological netowrk detected several sub-groups among healthy patients that likely are affected with non-PE diseases. to be diagnosed properly even though they are not affected by PE, in a next study we will introduce also the survival curves for the patients. TDA was further utilized to identify key features which are best associated as diagnostic factors for PE and used this information to define the input space for a back-propagation artificial neural network (BP-ANN). It is shown that the area under curve (AUC) of BP-ANN is greater than the AUCs of the scores (Wells and revised Geneva) used among physicians.

Conclusions

The results demonstrate topological data analysis and the BP-ANN, when used in combination, can produce better predictive models than Wells or revised Geneva scores system for the analyzed cohort. The new CPR can help physicians to predict the probability of PE. A web-version of the BP-ANN has been published and it can be tested at the address http://cuda.unicam.it

Keywords

Clinical Prediction Rule (CPR), Pulmonary Embolism, Topological Data Analysis, Artificial Neural Network (ANN), Computer Aided Detection CAD

Background

A novel computer-aided diagnosis for Pulmonary Embolism

Several statistical and machine learning techniques have been proposed in the literature to deal with output of implicit or explicit rules and good classification performance [1,2]. Most available techniques, such as linear discriminant approaches, multilayer perceptrons or support vector machines, are able to achieve a good degree of provisional accuracy but these methods lack accuraccy sufficient for the implementation of computer-aided diagnosis (CAD) for pulmonary embolism diagnosis. Different studies have been developed for CAD system predicting development of PE in patients. Tang et al used data from the Shangai Xin Hua Hospital, Tourassi et al and Patil S used the data collected from the collaborative study of the *Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED)* and built neural network [3,4]. To improve the

performance of a CAD we built a new system based on topological data analysis and statistical approach for features selection to define the input space for theartificial neural network. The result of the CAD must be interpreted as a new CPR that might be used to assign a probability of an occurrence of PE [5].

Pulmonary Embolism

Pulmonary embolism (PE) is a relatively common and potentially lethal condition, affecting a proportion between 0.04% and 0.09% of the general population [6,7], and ranging, in most of the cohorts of outpatients with suspected PE, between 8% and 12% [8,9]. Among patients who die of PE, the largest part is observed in the first few hours from the acute event [10]. Despite diagnostic advances, delays in PE diagnosis are common and represent an important issue [11]. As a cause of sudden death, PE is second only to arrhythmic death. Among survivors, recurrent embolism and death can be prevented with prompt diagnosis and therapy. Current clinical guidelines suggest to perform a first-level, clinical stratification based upon patient's history, clinical findings and, in some cases, physician's judgment. For this purpose, several clinical prediction rulers (CPR) have been suggested and validated, and are currently in use in common clinical practice [8,9,12]. Subsequent management of the patient relies mainly on this stratification. Patients at high-risk for PE should immediately undergo a computed tomography pulmonary angiography (CTPA), while patients with intermediate or low pretest probability should be tested for high-sensitive dDimer assay [12]. Only patients with increased dDimer levels should be further investigated with second level examinations. CTPA is currently the most widely accepted imaging method recommended to confirm a suspect diagnosis of PE. However, increasing evidences and its direct and indirect costs suggest a limitation in its use: CTPA has been associated to increased risk of secondary cancer from radiation exposure [13] and contrast-induced nephropathy [14]. Another interesting point is that current use of 64-slices detectors has increased the frequency of subsegmental PE diagnoses: this finding, in the absence of a documented deep vein thrombosis (DVT), may cause clinical uncertainty, and lead to unnecessary therapies [15]. Echocardiography is currently recommended for shocked patients with high suspect of PE. For haemodinamically stable patients it is currently recommended only to better stratify the prognosis by detecting right ventricle dysfunction (RVD) [12]. Biomarkers such as BNP and troponin are used to assess disease severity and associated to right ventricle overload or damage, but are currently not included in diagnostic algorithms.

Clinical Prediction Rules

The extreme aspecificity and the variety of the clinical presentation and symptoms and the slenderness of the clinical signs of PE are cause on a side of the proven underdiagnosis on the other of an excess of negative examinations performed. The positive CTPA rate is very low - less than 15% of the overall number of exams performed for suspected acute PE [16]. Recent studies have demonstrated the safety of rejecting the diagnosis of PE by the combination of a low clinical probability, assessed by a CPR, and a normal quantitative d-Dimer test result, thereby decreasing the need for further diagnostic radiological imaging in up to 30% of patients [17]. The most widely used CPRs are the Wells rule (table on page 18) and the Geneva Revised score [10] The Wells score has three different risk categories, and more recently it has been simplified assuming two risk categories with a cutoff set to 4. Perrier et al has been successful in generating a model based solely on objective parameters using the Geneva Revised score [12]. This CPR is easily standardizable and has been validated internally and externally, although less extensively than the Wells rule. Both scores appeared to have a comparable predictive value for PE. Regardless of the rule being performed, the proportion of patients with PE is around 10% for low probability, 30% for moderate probability and 65% for high clinical probability category. It is important to note that these scores have severe limitations. The Wells rule includes the physician's judgment of whether an alternative diagnosis is more likely than PE [11, 12] This criterion, which carries a major weight in the score, is subjective and cannot be standardized. Moreover, it has been suggested that the predictive value of the Wells rule is derived primarily from its subjective component [18]. The Geneve Revised score is based on 13 entirely objective variables, requires a blood gas analysis while breathing room air. Interestingly, these parameters have only been evaluated for patients in ED with a clinical performance result not superior to the Wells score.

Topological data analysis

Topological Data Analysis (TDA) is a method to analyze multidimensional, complex data primarily driven by geometry. TDA is a result of over a decade of research in applications of pure mathematics to practical problems. The main idea of this approach is that the shape of the data in an abstract multidimensional space drives the analysis by exploring the parallelism of a large number of machine learning algorithms. The three fundamental concepts of TDA are independence of coordinate systems; insensitivity to deformation; and compressed representation [19]. A typical example of insensitivity to deformation would be writing in a different font as long as the underlying meaning is preserved, while compressed representation refers to approximating a complex shape such that of a circle with a hexagon. Using a mathematical concept of lenses [20], data can be projected onto a subspace suitable for visualization. The topological features of the subspace are then inspected with traditional statistical approaches such as Kolmogorov-Smirnov or t-test analysis. We applied TDA to the clinical data of patients suspected of high risk of PE and used shapes of the generated topological networks on page 16 to identify different subgroups of patients and features that statistically significantly explain the observed differences. We used the TDA-derived features as input into artificial neural network analysis.

Artificial Neural Network

A complex system may be decomposed into simpler elements, in order to be able to understand it. Also simple elements may be gathered to produce a complex system in line with the approach divide et impera. Networks are one approach for achieving this. There are a large number of different types of networks, but they all are characterized by the following components:

- a set of nodes
- connections between nodes.

The nodes can be treated as computational units. They receive inputs, and process them to obtain an output. The connections determine the information flow between nodes. The interactions of nodes though the connections lead to a global behavior of the network, which cannot be observed in the elements of the network. This global behavior is said to be emergent, meaning that the abilities of the network supersede the ones of its elements. Networks can be used as very powerful tool because many systems can be assembled into a systems-like network space, applications including proteins, computers, and communities. One type of network uses nodes as artificial neurons, and an artificial neuron is a computational model inspired by the natural neurons. Natural neurons receive signals through synapses located on the dendrites or membrane of the neuron. When the signals received are strong enough (greater than a certain threshold), the neuron is activated and emits a signal though the axon. This can activate a cascade process. The complexity of real neurons is highly abstracted when modeling artificial neurons. These basically consist of inputs, which are multiplied by weights, and then computed by a mathematical function that determines the activation of the neuron. Another function computes the output of the artificial neuron (sometimes in dependence of a certain threshold). Weights can also be negative, so we can say that the signal is inhibited by the negative weight. Depending on the weights, the computation of the neuron will be different. By adjusting the weights of an artificial neuron we can obtain the output we want for specific inputs. If we scale an ANN to hundreds or thousands of neurons, it is both complicated and labor intensive to manually discover all the necessary weights. However, by identifying algorithms to adjust the weights of the ANN in order to obtain the desired output from the network. This process of adjusting weights is called learning or training [3] [21] [22]. The number of ANN types and uses is very high; hence, there are hundreds of different models considered as ANNs. The differences among them can be related to functions, the accepted values, the topology of network, and/or the learning algorithms, etc. We applied backpropagation algorithm to perform a layered feed-forward ANNs. This allows us to organize the artificial neurons in layers to send their signals "forward", and propagate errors backwards. The network receives inputs by neurons in the input layer, and the output of the network is given by the neurons on an output layer. There may be one or more intermediate hidden layers. The backpropagation algorithm uses supervised learning, which means that we provide the algorithm with examples of the inputs and outputs we want the network to compute, and then the error (difference between actual and expected results) is calculated. The benefit of using backpropagation algorithm is that this error is reduced until the ANN learns the training data. The training begins with random weights, and the goal is to adjust them so that the error will be minimal. Further mathematical explanations are detail in [23] and [24].

Statistical concepts

Kolmogorov-Smirnov Test

In statistics, the Kolmogorov–Smirnov test (K–S test) is a nonparametric test for the equality of continuous, one-dimensional probability distributions that can be used to compare a sample with a reference probability distribution (one-sample K–S test), or to compare two samples (two-sample K–S test). The Kolmogorov–Smirnov statistic quantifies a distance between the empirical distribution function of the sample and the cumulative distribution function of the reference distribution, or between the empirical distribution functions of two samples. The null distribution of this statistic is calculated under the null hypothesis that the samples are drawn from the same distribution (in the two-sample case) or that the sample is drawn from the reference distribution (in the one-sample case). In each case, the distributions considered under the null hypothesis are continuous distributions but are otherwise unrestricted. The two-sample KS test is one of the most useful and general nonparametric methods for comparing two samples, as it is sensitive to differences in both location and shape of the empirical cumulative distribution functions of the two samples [25].

Receiver Operating Characteristic

Both Artificial Neural Networks and the two scores (Wells and Revised Geneva) were evaluated by using receiver-operating characteristic (ROC) analysis. Medical tests play a vital role in modern medicine not only for confirming the presence of a disease but also to rule out the disease in individual patient. A test with two outcome categories such as test + and test - is known as dichotomous, whereas more than two categories such as positive, indeterminate and negative called polytomous test. The validity of a dichotomous test compared with the gold standard is determined by sensitivity and specificity [26]. The Receiver Operating Characteristic (ROC) curve is the plot that displays the full picture of trade-off between the sensitivity (true positive rate) and (1-specificity) (false positive rate) across a series of inherent validity of a diagnostic test. This curve is useful in:

- evaluating the discriminatory ability of a test to correctly pick up diseased and non-diseased subjects;
- finding optimal cut-off point to least misclassify diseased and non-diseased subjects;
- comparing efficiency of two or more medical tests for assessing the same disease;
- comparing two or more observers measuring the same test

Total area under ROC curve is a single index for measuring the performance a test. The larger AUC - Area Under Curve - , the better is overall performance of the medical test to correctly identify diseased and non-diseased subjects. Equal AUCs of two test represent similar overall performance of tests but this does not necessarily mean that both the curves are identical [27].

Jaccard Similarity Coefficient

The Jaccard Similarity coefficient is a statistic used for comparing the similarity and diversity of sample sets. The Jaccard coefficient measures similarity between sample sets, and it is defined as [28]:

$$J = \frac{|DD \cap AD|}{|DD \cup AD|} \tag{1}$$

where:

- Doctor diagnosis -DD.
- ANN diagnosis AD.

Results

Topological data analysis results

Topologial data analysis was applied on the PE dataset to generate the network in figure (see on page 16) using AYASDI-Iris (Ayasdi, Inc, Palo Alto). We color in red the pathological patients and in blue the healthy group. IRIS highlighted two flares and a longer tail in the pathological group. From the comparison of the two flares we selected a sub-set of features characterized with high Kolmogorov- Smirnov and low p-value (see table on page 20). The information extracted from the comparison of the two flares is that there is a sub-group of patients who is characterized by the recurrence risk to be affected by PE. IRIS detected some sub-groups among healthy patients, which present other diseases to be diagnosed properly even though they are not affected by PE.

Comparison of AUC: Wells, Geneva and ANN

From the patients' dataset we random selected 152 patients: 101 pathological and 51 healthy and we studied the discriminatory ability of the system. Tables 5 and 6 on page 20 show the performance of three classifier: Wells score, revised Geneva score and the ANN model. Any of the three AUC was statistically significant different. The comparative study of three AUCs has been made with the software MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium) [29]. The AUCs of Revised Geneva and Wells score obtained from the analysed dataset are directly comparable with the results previously published in literature by other groups [30]. Figure (see on page 16 and on page 17) showed the ROC curves of three classifiers, they were evaluated by leave-one-out method [31]. The difference between the AUC of the new classifier both with revised Geneva's AUC and Wells' AUC was statistically significant at the 95% confidence level, P-value < 0.0001 and P-value = 0.0025 respectively. Instead, the difference between revised Geneva's AUC and Wells' AUC is not statistically relevant: P-value = 0.1456. Thus, the network's discriminant power is significantly. The Jaccard coefficient for the ANN is J=0.88 as every informatics system also the ANN-classifier is affected by the round problem, i.e. the probability value of occurrence of PE in range [0.45; 0.5) is rounded to 0.5 then the patient is classified as pathological. At the state of the art we left to the physician the final judgment over this situations [32–35].

Conclusions

The study derives a new CPR for pulmonary embolism and evaluating patients' cohort characteristic with a topological approach. The new CPR has been obtained training an artificial neural network on the input formed by a set of features selected by Iris. Iris extracted new knowledge from the patients' dataset by the application of an innovative approach for data analysis: Topological Data Analysis. Our results show that the feature selection strategy is beneficial for the performance improvement of an ANN trained on the analyzed cohort. A three-layer neural network can be trained to successfully perform the diagnostic task. In conclusion a system based on Iris and an ANN can form the basis of a CAD system to assist physicians with the right stratification of patients. A web-version of the BP-ANN has been published and it can be tested at the address http:\\cutocuta.unicam.it. In the future we will perform a validation of the system both increasing the number of patients in the dataset and using different cohorts, we will perform a comparison study among artificial neural networks and other classification systems. Our dataset allowed us to increase the clinical performance of about 20%

Methods

Patients and patients' dataset preparation

From a cohort of 1500 patients accepted in the department of Intensive and Subintesive medicine from 2009 to 2012 at Ospedali Riuniti di Ancona, a total of 987 patients of average age 70 years were included. The inclusion criteria for this study were that the patients at least were recorded with Wells score, Revised Geneva score, d-Dimer and blood gas PO_2 , the cutoff of d-Dimer was 230ng/ml. For each patients 26 variables were collected (see table on page 19). In these patients, the diagnosis of PE and the exclusion of PE were made by angio-CT. Among these, 793 had PE and 147 did not have PE. Characteristics of the history, objective data from the physical examination and the outcome of d-Dimer analysis were tabulated for each patient. To improve the interpretability of our data the logarithm transformation has been applied to d-Dimer and WBC (white blood count). In the present work we analyzed only outpatients. The patients' dataset was processed using topological data analysis with Ayasdi IRIS specifications. Ayasdi IRIS-ready data files are composed of rows and columns. The calculations are performed on a row-by-row basis and the results elucidate the columns (features) that best define and explain particular groups of rows. The Ayasdi Iris data format is a matrix with unique column headers and unique row identifiers. Column headers must uniquely identify the columns. In contrast, the column that uniquely identifies the rows may be in any column position, it does not have to be the first or the last column.

Classical approaches for feature selection

Filter or wrapper methods for features reduction can not be applied to our dataset: the application of these algorithms can be done on a dataset without missing data. The elimination of rows with null values from our dataset would reduce extremily the number of samples and the covariance matrix is singular (ill conditioned) [36].

Topological Data Analysis: features selection

From the patients' dataset we selected only d-Dimer, Revised Geneva score and Wells score for the analysis and Variance Normalized Euclidean as metric function (equation 2). The Variance Normalized Euclidean metric is utilized when data are comprised of disparate quantities that are not directly comparable. The filters were L-Infinity centrality, which assigns to each point the distance to the point most distant from it, and final diagnosis. L-infinity centrality, is defined for a data point x to be the maximum distance from x to any other data point in the set. Large values of this function correspond to points that are far from the center of the data set (equation 3). It is also useful to use some filters that are not geometric, in that they do depend on a coordinate representation, such as coordinates in principal component or projection pursuit analysis. The parameters of the configuration were: resolution 60, gain 3.0x, equalized on (see figure on page 16) [19].

$$D(h_1, h_2) = \sqrt{\sum_{i=1}^{d} \frac{(h_1(i) - h_2(i))^2}{\sigma_i^2}}$$
 (2)

$$f(x) = \max_{x \in X} d(x, y) \tag{3}$$

Artificial Neural Network Architecture

The neural network used in our study had a three-layer, feed-forward architecture and was trained by using the back-propagation algorithm with the sigmoid activation function. According to this learning scheme, the network tries to adjust its weights so that for every training input it can produce the desidered output. During the training phase, the network is presented with pairs of input-output patterns: supervised learning. It has been shown that this technique minimizes the mean squared error (MSE) between the decider and the actual network output following an intentive gradient search technique. The input of the network is a subset of the patient's dataset formed with all the patients but only with selected features by TDA (see table on page 20). Specifically our network had a hidden layer with 3 nodes, and an output layer with a single decision node. The network was trained to output 1 if PE was present and 0 if not. In this study,

the network's output was interpreted as the probability of PE being present. In addition, input data were scaled to -1 and +1. The learning rate was selected to be 0.5 and the momentum coefficient to be 0.9, the optimal number of iterations (epochs) have been found equal to 660 after the execution of 100 trials with the permutations of rows in the patients' dataset.

Softwares

IRIS

Topological data analysis has been performed using the Iris software [37], properties of Ayasdi Inc. Iris uses the concepts of metric and lenses. Metric is a distance or similarity measure between point. Lenses are mathematical functions through which you see the data points. Different lenses emphasizing different aspects of the dataset and different networks will be generated. Lens executes the division of data points in overlapping bins. Through the bins, the data are clustered. Each cluster is represented by a node, default node size is proportional to the number of data points in the cluster. IRIS connects nodes when corresponding clusters have common data points. During IRIS exploration there are two parameters attached to the lens that allow you to control how the data is divided in the bins. One of these is resolution which corresponds to the number of bins is put into:

- low resolution: coarse view of data;
- high resolution: detailed view and possibly fragmented into singletons.

Another lens parameter is gain. Gain controls how much overlap there is between bins. Increasing the gain increases the number of edges in the output. Oversampling highlights relationship within the data. Finally the commands equalize distributes the data points in the bins so that each bin has an equal number of data points.

RULEX 2.0

The ANN has been implemented by the Rulex software suite [38]. The Rulex software, developed and commercialized by Impara srl, is an integrated suite for extracting knowledge from data through statistical and machine learning techniques. An intuitive graphical interface allows to easily apply standard and advanced algorithms for analyzing any dataset of interest, providing the solution to classification, regression and clustering problems. To build classifiers we used a number of graphical components provided by Rulex 2.0. We utilized Visualization and editing components to visualize and export the confusion matrix, the

training and validation sets, the results of the classifier, to access statistical data (e.g. Covering, Error and Relevance).

List of abbreviations

CPR: clinical predictive rule, CAD: computer aided detection, ANN: artificial neural network, TDA: topological data analysis, PE: pulmonary embolism, DVT: deep venous thrombosis, angio-CT: angiography computed tomography, K-S or KS: Kolmogorov-Smirnov test, ROC: receiver operating characteristic, FP: false positive, TN: true negative, FN: false negative, TP: true positive, DD: doctor diagnosis, AD: artificial neural network dianosis, AUC: area under curve, WBC: white blood count, MSE: mean sqared error,

Competing interests

Damir Herman and Tanya Petrossian are employees of Ayasdi, Inc. and hold stock in the company. The authors declare that they have no competing interests.

Author's contributions

Emanuela Merelli, Aldo Salvi, Lorenzo Falsetti and Cinzia Nitti and conceived the project, supervised the study. Lorenzo Falsetti wrote the clinical background. Matteo Rucco designed the experimental flowchart, performed the computer experiments and wrote the manuscript.

Acknowledgements

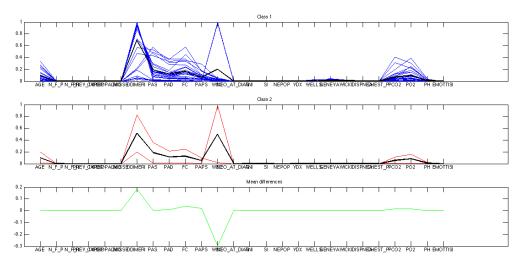
We acknowledge the department of Internal and Subintensive medicine of Ospedali Riuniti di Ancona - Torrette for the patients' dataset, the financial support of the Future and Emerging Technologies (FET) programme within the Seventh Framework Programme for Research of the European Commission, under the FET- Proactive grant agreement TOPDRIM (Topology-driven methods for multievel complex systems), number FP7-ICT-31812, Francesco Vaccarino and Giovanni Petri from ISI foundation for their introduction to algebraic topology and complex networks. Impara s.r.l. and Ayasdi Inc. for their software products. A special thanks is extended to Damir Herman for his support during the TDA.

References

- 1. Cangelosi D, Blengio F, Versteeg R, Eggert A, Garaventa A, Gambini C, Conte M, Eva A, Muselli M, Varesio L: Logic Learning Machine creates explicit and stable rules stratifying neuroblastoma patients. *BMC Bioinformatics* 2013, 14(Suppl 7):S12.
- 2. Kotsiantis SB, Zaharakis ID, Pintelas PE: Machine learning: a review of classification and combining techniques. Artif. Intell. Rev. 2006, 26(3):159–190, [http://dx.doi.org/10.1007/s10462-007-9052-3].
- 3. Tourassi G, Floyd C, Sostman H, Coleman R: Acute pulmonary embolism: artificial neural network approach for diagnosis. *Radiology* 1993, **189**:555–558.
- 4. Patil S: Neural network in the clinical diagnosis of acute pulmonary embolism. Chest 1993, 1:1685–1689
- 5. Tang L, Wang L, Pan S, Su Y, Chen Y: A neural network to pulmonary embolism aided diagnosis with a feature selection approach. In *Biomedical Engineering and Informatics (BMEI)*, 2010 3rd International Conference on, Volume 6 Oct:2255–2260.
- 6. Tagalakis V, Patenaude V, Kahn S, S S: Incidence of and Mortality from Venous Thromboembolism in a Real-world Population: The Q-VTE Study Cohort. Am J Med 2013, 126(9):832.e13–21. [Doi: 10.1016/j.amjmed.2013.02.024. Epub 2013 Jul 3. PubMed PMID: 23830539].
- 7. Silverstein M, Heit J, Mohr D, Petterson T, O'Fallon W, Melton Lr: Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998, 158(6):585–93. [PubMed PMID: 9521222].
- 8. Wells P, Anderson D, Rodger M, Stiell I, Dreyer J, Barnes D, Forgie M, Kovacs G, Ward J, Kovacs M: Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med.* 2001, 135(2):98–107. [PubMed PMID: 11453709].
- 9. Wolf S, McCubbin T, Nordenholz K, Naviaux N, Haukoos J: Assessment of the pulmonary embolism ruleout criteria rule for evaluation of suspected pulmonary embolism in the emergency department. Am J Emerg Med 2008, 26(2):181–5. [Doi: 10.1016/j.ajem.2007.04.026. PubMed PMID: 18272098].
- 10. Wood K: Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. *Chest* 2002, **121**(3):877–905.
- 11. Kline J, Hernandez-Nino J, Jones A, Rose G, Norton H, Camargo CJ: Prospective study of the clinical features and outcomes of emergency department patients with delayed diagnosis of pulmonary embolism. Acad Emerg Med. 2007, 14(7):592–8.
- 12. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, Bengel F, Brady A, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand J: ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008, 29(18):2276–315. [Doi: 10.1093/eurheartj/ehn310. Epub 2008 Aug 30. PubMed PMID: 18757870].
- 13. Einstein A, Henzlova M, Rajagopalan S: Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *JAMA* 2007, **298**:317–323.
- 14. Mitchell A, Kline J: Contrast nephropathy following computed tomography angiography of the chest for pulmonary embolism in the emergency department. J Thromb Haemost 2007, 5:50-54.
- 15. Brunot S, Corneloup O, Latrabe V, Montaudon M, Laurent F: Reproducibility of multi-detector spiral computed tomography in detection of sub-segmental acute pulmonary embolism. *Eur.Radiol.* 2005, 15:2057–2063.
- 16. Haap M, Gatidis S, Horger M, Riessen R, Lehnert H, Haas C: Computed tomography angiography in patients with suspected pulmonary embolism-too often considered? Am J Emerg Med 2012, 30(2):325–30.
- 17. Beck K, Holzschuh J: Schattauer GmbH Verlag für Medizin. Naturwissenschaften The Science of Nature 2011.

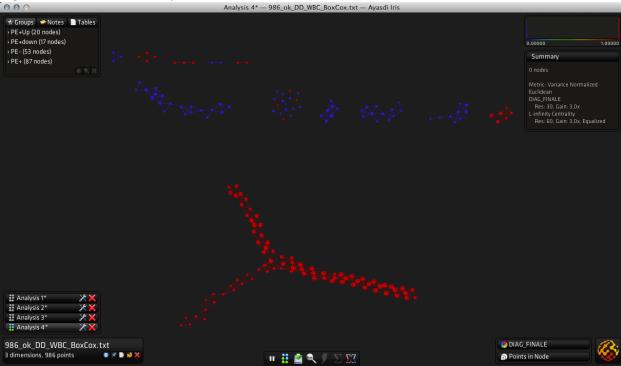
- 18. Sanchez O, Trinquar L, Caille V, Couturaud F, Pacouret, G Meneveau N, Verschuren F, Roy P, Parent F, Righini M, Perrier A, Lorut C, Tardy B, Benoit M, Chatellier G, Meyer G: **Prognostic factors for pulmonary embolism: the prep study, a prospective multicenter cohort study.** Am J Respir Crit Care Med. 2010, 15(181(2)):168–73.
- 19. Lum P, Singh G, Lehman A, et al: Extracting insights from the shape of complex data using topology. Scientific Reports Nature 2013, 3:561-577.
- 20. Singh G, Memoli F, Carlsson G: **Topological Methods for the Analysis of High Dimensional Data Sets and 3D Object Recognition**. In *Symposium on Point Based Graphics*. Edited by Botsch M, Pajarola R, Chen B, Zwicker M, Eurographics Association 2007:91–100.
- 21. Lippmann R: An introduction to computing with neural nets. ASSP Magazine, IEEE Apr, 4(2):4-22.
- 22. Rosenblatt F: Principles of neurodynamics. Perceptrons and the theory of brain mechanisms. Washington: Spartan Books 1962.
- 23. Rojas R: Neural Networks: A Systematic Introduction 1996.
- 24. Kauffman SA: The Origins of Order: Self-Organization and Selection in Evolution. New York: Oxford University Press 1993.
- 25. **Kolmogorov-Smirnov** test [http://www.encyclopediaofmath.org/index.php/Kolmogorov\OT1\ textendashSmirnov_test].
- 26. Hanley J, McNeil B: The Meaning and Use of the Area under a Receiver Operating Characteristic (ROC) Curve. Radiology. 1982, 143:29–36.
- 27. McClish DK: Analyzing a Portion of the ROC Curve. Medical Decision Making 1989, 9:190-195.
- 28. Jaccard Coefficient [http://www.stanford.edu/~maureenh/quals/html/ml/node68.html].
- 29. MedCalc [http://www.medcalc.org/].
- 30. Penaloza A, Melot C, Motte S: Comparison of the Wells score with the simplified revised Geneva score for assessing pretest probability of pulmonary embolism. Thromb Res 2011, 127(2):81–4.
- 31. Picard R, Cook D: Cross-Validation of Regression Models. *Journal of the American Statistical Association*. 1984, **79**(387):575–583.
- 32. DeLong E, DeLong D, Clarke-Pearson D: Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988, 44:837–845.
- 33. Griner P, Mayewski R, Mushlin A, Greenland P: **Selection and interpretation of diagnostic tests and procedures.** Annals of Internal Medicine 1981, **94**:555–600.
- 34. Metz C: Basic principles of ROC analysis. Seminars in Nuclear Medicine. Annals of Internal Medicine 1978, 8:283–298.
- 35. Zweig M, Campbell G: Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clinical Chemistry 1993, 39:561–577.
- 36. Lloyd NT, Bau D: **NUMERICAL LINEAR ALGEBRA**. In *Clinical Chemistry*, iii edition, UK: Society for Industrial and Applied Mathematics 1997:xii+361.
- 37. Ayasdi-Iris [http://www.ayasdi.com].
- 38. Rulex 2.0 [http://www.impara-ai.com/].

Figures Figure 1 - Parallel plots and mean difference



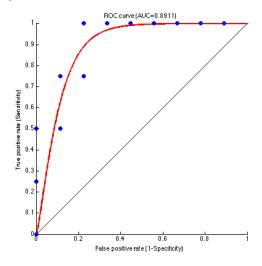
Blu lines: parallel plot for pathological patients. Red lines: parallel plot for healthy patients. Green line: difference between mean values of the previous parallel plot; only d-Dimer and WBC exhibit a relevant difference between two classes, but it is not enough to diagnose pulmonary embolism.

Figure 2 - AYASDI-Iris Analysis



IRIS highlighted two flares in the pathological group. That means there are two cluster of patients in the PE population (red groups), also IRIS detected some sub-groups among healthy patients, which present other diseases to be diagnosed properly even though they are not affected by PE (blue groups).

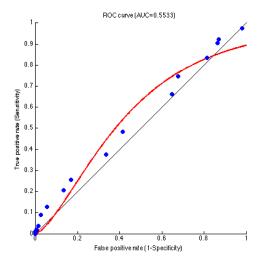
Figure 3 - ANN



Comparison study of ROC curves: the AUC obtained with the new classifier is greater then the AUCs from

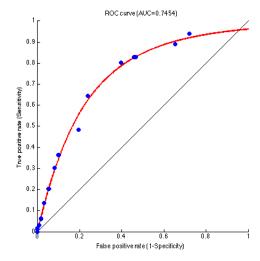
the other two CPRs.

Figure 4 - Revised Geneva



ROC curve of Revised Geneva score.

Figure 5 - Score Wells



ROC curve of Wells score.

Tables

Table 1 - Revised Geneva Score

Variable	Points
Predisposing factors	
Age > 65 years	+1
Previous Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE)	+3
Surgery or fracture within 1 month	+2
Active malignacy	+2
Symptons	
Unilateral lower limb pain	+3
Haemoptysis	+2
Clinical signs	
Heart rate	
75-94 beats/min	+3
$\geq 95 \text{ beats/min}$	+5
Pain on lower limb deep vein at palpation an unilateral oedema	+4
Clinical probability	Total
Low	0-3
Intermediate	4-10
High	≥11

Table 2 - Wells Score

Points
+1.5
+1.5
+1
+1
+1.5
+3
+3
Total
0 - 1
2 - 6
≥ 7
Total
0 - 4
>4
ļ

Table 3 - Dataset

	Features	Clinical Significance
1	ID	Patient's identifier
2	Age	With the increase of the age, increase the incidence
3	Number Predictive Factors	Absolute number of predictive factors
4	Number Risk Fac- tors	Absolute number of risk factors
5	Previous DVT	A previous DVT / PE is a risk factor repeated infringement DVT / PE
6	Palpitations	Aspecific symptom. If it implies a tachycardia could be associated with DVT / PE
7	Coughs	Symptom very nonspecific but frequently present in patients with DVT / PE
8	d-Dimer	A value of d-Dimer $< 230ng/ml$ is associated with a low risk / absent of DVT / PE. A very high value is associated with a high risk of DVT / PE
9	Systolic Pressure (PAS)	A low PAS is present in patients with DVT / PE and hemodynamic shock
10	Diastolic Pressure (PAD)	In cardiogenic shock with DVT / PE is low, sometimes undetectable. By itself has no value despite of the PAS
11	Heart Rate (FC)	In the patient with TVP / EP tachycardia is often found
12	Mean Pulmonary Artery Pressure (PAPS)	It is one of the criteria of right ventricular dysfunction. It can be normal in the case of EP low entity.
13	White Blood Cells Counter (WBC)	The value increases with inflammatory forms (pneumonia, etc) that can be confused with DVT / PE
14	Cancer at diagnosis	It is a risk factor for DVT / EP recognized
15	Troponin	It is a marker of myocardial infarction or heart failure and can be confused with DVT / PE
16	Shockindex	It is the ratio between PAS and FC, if it is greater than 1 is indicative of shock
17	Cancer	It is a risk factor for DVT / EP recognized
18	Right Ventricular Dsfunction (RVD)	Right ventricular overload in the course of DVT / PE
19	Score Wells	
20	Score Revised Geneva	
21	Score Wicki	
22	Dyspnea	Main symptom in DVT / PE
23	Chest pain	Chest pain is present in myocardial infarction, in pleural effusion, in the high DVT / PE
24	pCO2	Associated with low pO2 may be suggestive of DVT / PE
25	pO2	Associated with low pCO2 may be suggestive of DVT / PE
26	рН	In DVT / EP pH is usually normal
27	Final Diagnosis	Final physicians' diagnosis

Table 4 - Extracted Features

	Features	Clinical Significance	
1	Age	With the increase of the age, increase the incidence	
2	d-Dimer	A value of d-Dimer $< 230ng/ml$ is associated with a	
		low risk / absent of DVT / PE. A very high value is	
		associated with a high risk of DVT / PE	
3	Systolic	A low PAS is present in patients with DVT / PE and	
	Pressure	hemodynamic shock	
	(PAS)		
4	Heart Rate	In the patient with TVP / EP tachycardia is often	
	(FC)	found	
5	Mean Pul-	It is one of the criteria of right ventricular dysfunc-	
	monary	tion. It can be normal in the case of EP low entity.	
	Artery Pres-		
	sure (PAPS)		
6	Shockindex	It is the ratio between PAS and FC, if it is greater	
		than 1 is indicative of shock	
7	Score Re-		
	vised Geneva		
8	Score Wells		
9	pO2	Associated with low pCO2 may be suggestive of DVT	
		/ PE	

Table 5 - Performance of classifiers

iable of terrormance or classificity				
Comparison of classifier				
	AUC	Standard Error (SE)	95% Confidence Interval	
ANN	0,891	0,0383	0,838 to 0,899	
Revised Geneva	0,5533	0,0485	0,420 to 0,610	
Wells	0,7454	0,0473	0,538 to 0,753	

Table 6 - Comparison of AUCs

•	
ANN - Geneva	
Difference between areas	0,337
95% Confidence Interval	0,168 to 0,386
Significance level	P < 0,0001
ANN - Wells	
Difference between areas	0,1456
95% Confidence Interval	0,0565 to 0,266
Significance level	P = 0,0025
Revised Geneva - Wells	
Difference between areas	0,1921
95% Confidence Interval	0,0421 to 0,212
Significance level	P = 0,1456