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Application of Shape Analysis on 3D Images - MRI of Renal Tumors

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Abstract. The image recognotion and the classification of objects according to the images are more in focus of interests, especially in medicine. A mathematical procedure allows us, not only to evaluate the amount of data per se, but also ensures that each image is processed similarly. Here in this study, we propose the power of shape analysis, in conjunction with neural networks for reducing white noise instead of searching an optimal metric, to support the user in his evaluation of MRI of renal tumors. Therapy of renal tumors in childhood bases on therapy optimizing SIOP(Society of Pediatric Oncology and Hematology)-study protocols in Europe. The most frequent tumor is the nephroblastoma. Other tumor entities in the retroperitoneum are clear cell sarcoma, renal cell carcinoma and extrarenal tumors, especially neuroblastoma. Radiological diagnosis is produced with the help

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of cross sectional imaging methods (computertomography CT or Magnetic Resonance Images MRI). Our research is the first mathematical approach on MRI of retroperitoneal tumors (n=108). We use MRI in 3 planes and evaluate their potential to differentiate other types of tumor by Statistical Shape Analysis. Statistical shape Analysis is a methology for analyzing shapes in the presence of randomness. It allows to study two- or more dimensional objects, summarized according to key points called landmarks, with a possible correction of size and position of the object. To get the shape of an object without information about position and size, centralisation and standardisation procedures are used in some metric space. This approach provides an objective methodology for classification whereas even today in many applications the decision for classifying according to the appearance seems at most intuitive.

We determine the key points or three dimensional landmarks of retroperitoneal tumors in childhood by using the edges of the platonic body (C60) and test the difference between the groups (nephroblastoma versus non-nephroblastoma).

Keywords. Neural networks, radiology, shape analysis.

MSC: 51, 62-07, 62-Pxx, 92-08.

1 Introduction

6.2 % of pediatric malignant tumors concern the kidney. The most frequent renal tumor in childhood is the nephroblastom (Wilms-tumor). Therapy of renal tumors bases on therapy optimizing studies of SIOP-study protocols in Europe. The main objective of these therapy trials is the treatment of patients according to well-defined risk groups in order to achieve the highest cure rates, to decrease the frequency and intensity of acute and late toxicity and to minimize the cost of therapy, as it is described by Schenk (2008)[31]. Hence, the SIOP studies focus on the issue of preoperative therapy.

The important subject of preoperative chemotherapy is the initiation of therapy based on the radiological diagnosis without further histology by e.g. biopsy of the tumor according to [31]. Detection of the tumor mostly is possible with sonography, whereas the final diagnosis is achieved after further sectional image techniques, in MRI or CT. Advantages of MRI are a high contrast resolution in soft tissue and the avoidance of radiation exposure, which is of importance in pediatric patients. Despite the high number of MRI investigations for kidney tumors

in infancy, a falsely applied chemotherapy could not be totally prevented so far. The last concluded SIOP 93-01/GPOH study showed false diagnosis in 5.7 % (incl. malignant non Wilmśtumors). The risk rate of a preoperative chemotherapy in benign kidney lesions was at 1.3 %.

The nephroblastoma is to be demarcated from the renal parenchyma by its pseudocapsula. This pseudocapsula corresponds to compressed renal tissue at the edge of tumor and appears hypointense in T2 weighted sequences. Because of this pseudocapsule, the tumor is often quite good to discriminate from surrounding kidney parenchyma.

There are different kinds of tumors in childhood: nephroblastoma, clear cell sarcoma, congenital mesoblastic nephroma and renal cell carcinoma. Main differential diagnosis is the neuroblastoma with a growth next to the kidney in the suprarenal gland or in the paravertebral sympathetic nervous system. Different tumor growth results in different tumor shape.The clinician wants to get an accurate diagnosis by imaging studies.

Wilms´ tumors show a displacing growth behavior. The vena cava is frequently compressed by large tumor volumes. Diagnosis is based on morphological findings such as intra or extrarenal growth, calcifications, possible pseudocapsula, structure of the tumor in imaging with or without cysts, relation to retroperitoneal vessels, size of the tumor and complications as tumorthrombus in the inferior vena cava or metastases in other organs. Additional clinical syndrome associations and age of the patients, position, volume are also very important. Every other criterion for a better differentiation of different kind of tumors in childhood are of great importance to minimize the number of wrong therapies. Empirically, the tumor shape is visualized by the radiologist, but is not evaluated in a scientific way in nephroblastomas in comparison to other retroperitoneal tumors. Up till now, the shape of the tumor is only visualized in preoperative 3D-visualizations in the single patient for better surgical planning, as it is already shown in Günther et al.(2004).

Not only in medicine, but also in a wide variety of disciplines it is of great practical importance to measure, to describe and compare the shapes of objects. In general terms, the shape of an object, data set, or image can be defined as the total of all information that is invariant under translations, rotation and isotropic rescaling. The field of shape analysis involves methods for the study of the shape of objects where location, rotation and scale can be removed. The two- or more dimensional objects are summarized according to key points called landmarks. This approach provides an objective methodology for classification, whereas,

even today in many applications the decision for classifying according to the appearance seems at most intuitive.

Statistical shape analysis is concerned with methodology for analyzing shapes in the presence of randomness. It is a mathematical procedure to get the information of two- or more dimensional objects with a possible correction of size and position of the object. Therefore objects with different size and/or position can be compared with each other and classified. In order to get the shape of an object without information about position and size, centralisation and standardisation procedures are used in some metric space.

Interest in shape analysis began in 1977[19]. D.G. Kendall published a note in which he introduced a new representation of shapes as elements of complex projective spaces. K.V. Mardia on the other hand investigated the distribution of the shapes of triangles generated by certain point processes, and in particular considered whether towns in a plain are spread regularly with equal distances between neighbouring towns. The full details of this elegant theory which contains interesting areas of research for both probabilists and statisticians where was published by D. Kendall 1977[19] and F. Bookstein 1986[2]. The details of the theory and further developments can be found in the textbooks by C.G. Small 1996 [34] and I.L. Dryden & K.V. Mardia 1998 [5].

In this paper, we describe one interesting application of statistical shape analysis [7] [13]: the classification of renal tumors in childhood. In contrast to many application called also "Shape Analysis" we have to determine a mean shape, representative for a group of objects, and not only to detect an already known shape. This kind of shape analysis has nothing to do with an image recognition or restoring like in [6]. In our first approach[9] to Shape analysis we use only Euclidean distance, furthermore we consider, that we also have to reflect on non-Euclidean transformations: The renal tumor is limited by spleen or liver , the rest of the kidney, the spine and retroperitoneal vessels. To reduce the variance in the data the Neural Networks are used previoulsy. In contrast to our ideas Neural Networks are more used so far in opposition to stochastic models.

In [9] it was shown that every landmark has another meaning for differentiating the tumors. Only for the influence of the landmarks on the general shape there are no results in [11].

In consequence of a different influence of the landmarks, especially a different variance, we would have to find an optimal metric to describe it and to differentiate our group of objects. Instead of this procedure we

are using for the first time neural networks in this paper to reduce the white noise in terms of variance to improve our results in differentiation.

Firstly, we will propose the field of application, at second a short introduction to the idea of Neural Networks and Shape Analysis is given and thirdly the results of this procedure are discussed.

2 Application in Medicine on Wilms-Tumors

In the special case of oncology there is no theoretical medical reason to select a specific group of landmarks for differentiation. All landmarks in this research have to be selected by an explorative procedure.

Nephroblastoma (Wilms' tumor) is the typical tumor of the kidneys appearing in childhood. Therapy is organized in therapy-optimizing studies of the Society of Paediatric Oncology and Haematology (SIOP) in Europe. Indication of preoperative chemotherapy is based on radiological findings. The preferred radiological method is sonography and MRI. Both methods avoid radiation exposure, which is of great importance in childhood. Preoperative chemotherapy is performed without prior biopsy.

Information of the images of magnetic resonance tomography, especially the renal origin of a tumor and the mass effect with displacement of other organs, is needed for diagnosis. Next to nephroblastomas other tumors of the retroperitoneum exist, which are difficult to differentiate. Renal tumors in childhood are classified in three stages of malignancy (I, II, III). Typical Wilms tumors mostly belong in stage II. In stage II different subtypes of nephroblastoma tissue exist.

In our sample of tumors in childhood,there are four main different types of retroperitoneal tumours: nephroblastoma, neuroblastoma, clear cell sarcoma, and renal cell carcinoma. Renal cell carcinomas are very rare in childhood. They represent the typical tumors of adult patients. They have no high sensitivity for chemotherapy. Clear cell sarcomas are very rare in childhood and are characterized by high malignancy. Neuroblastoma is the main differential diagnosis to nephroblastoma. It is the typical tumor of the sympathetic nervous system and suprarenal glands. Infiltration of the kidney is possible. The tumor grows with encasement of vessels. Due to the high importance of radiological diagnosis for therapy, it is of great interest to find markers for a good differentiation of tumors. Misclassification leads to a useless therapy, to waste of time and all resources. Additionally, it results in an useless therapy and stress for the patient.

In the following figure 1 the data by using MRI are shown:

Figure 1: Data by using MRI[16]

It depends a lot on the user, if the data for a patient can be used. There should be enough slides in an equal distance to measure the object.

Our collected sample of 155 cases is a part of the study of the SIOP in Germany. Different kind of hospitals take part in this study. In 2009-2011 108 patients of the nephroblastoma study SIOP 2001- GPOH are analyzed in this study. The patients are on the average around 4 years old ($\overline{x} = 4.21$;; $\sigma = 4.301$; $\tilde{x} = 2.868$);. In our sample of tumors in childhood, there are four major types of retroperitoneal tumours: nephroblastoma (n=85), neuroblastoma (n=10), clear cell sarcoma (n=4) and renal cell carcinoma (n=5), furthermore three rhabdoid tumors and one angiomyolipoma.

3 Neural Network

Neural networks have been developed originally in order to understand the cognitive processes [1]. Nowadays there are a lot of applications of neural networks as a mathematical method in quite different disciplines.

The term "neural networks" points to the model of a nerve cell, the neuron, and the cognitive processes carried and driven by the network of interacting neurons. A neuron perceives chemical and physical excitement from the environment by its dendrites. The neuron is processing this incoming data and sending the information to other neurons via axons and synapses.

The neuron:

McCulloch and Pitts implemented the biological processes of a nerve cell for the first time in a mathematical way [25]. Nerve cells have to access and process incoming data in order to evaluate target information. Therefore the corresponding neural networks are called supervised neural networks. An unsupervised neural network has no target and is similar to a cluster algorithm.

The data consists of n variables $x_1, \ldots, x_n$ on binary scale. For data processing, the ith variable x_i is weighted with w_i. Normalized with $|w_i| \leq 1$, the multiplication of x_i with w_i determines the relevance of x_i for a target y. The value w_i reflects the correlation between the input variable and the target, the sign indicating the direction of the influence of the input variable on the target. Weighting the input variables for a target variable is similar to discriminant analysis.

The critical quantity for the neuron is the weighted sum of input variables

$$q := \sum_{i=1}^{n} w_i \cdot x_i = w_1 \cdot x_1 + ... + w_n \cdot x_n. \tag{1}$$

For a target y with binary scale, a threshold S is needed. Crossing the threshold yields 1 and falling below the threshold yields 0. Hence the activation function F can be written as

$$F(q) \quad = \quad \begin{cases} 1, & \text{if } \ x > S \\ 0, & \text{if } \ x \leq S \end{cases} \quad . \tag{2}$$

In comparison to discriminant analysis, for neural networks the threshold S has to be assigned, depending on properties of the target; it can not be derived from the data in a straightforward manner. Neural networks usually include no assumption about the data. Rather they are a numerical method.

With the input of the activation function, we obtain $y = F(q)$ as

$$y \quad = \quad 1, \quad \text{if } \ \sum_{i=1}^{n} w_i \cdot x_i > S, \tag{3}$$

$$y \quad = \quad 0, \quad \text{if } \ \sum_{i=1}^{n} w_i \cdot x_i \leq S. \tag{4}$$

To simulate all logical more than one layer is necessary. In our case we are only interessted in a one-layer procedure. Now the neural network performs a training step by modifying the weights of all input layers.

The learning mechanism the weights is determined by the target distance measure

$$E = \frac{1}{2}\sum_{i=1}^{n}(y_i - \tilde{y}_i)^2 \ . \tag{5}$$

The weights are changed according to the steepest descent, i.e.

$$\nabla_{w_i} E \ := \ \frac{\partial E}{\partial w_i} \ , \tag{6}$$

$$\tag{7}$$

With a learning rate α, which should be adapted to the data, the weights are changed as follows:

$$w_i^{new} = w_i^{old} - \alpha \cdot \nabla_{w_i} E \ , \tag{8}$$

We get a Matrix W.The necessary number of iterations depends on the requirements posed by the data, the user, and the discipline. Instead of the error function (5) we are using the variance in our data.

$$\sum_{j=1}^{k} d(W \cdot x_j, \overline{x})^2 \tag{9}$$

We try to find an optimal variance for differentiating our groups. That means, that we calculate an arithmetic mean in every iteration and then we weight all landmarks of every objects in the direction to a reduced variance.

4 Shape Analysis

The idea of a shape goes already back to Plato [26] (424/423 BC 348/347 BC). Plato has assumed that we recognize and order all objects in our world by knowing the shape. Knowing the representative shape of a group of objects leads us to a tool for differentiation. The procedure is shown in the following figure:

In step 1 we have to remove the location of the objects to compare them. We centre both objects. In step 2 we have to standardize them by using the Euclidean norm. In step 3 we have to remove the rotation and now in step 4 we can recognize that both objects have the same shape.

To compare the standardized and centered sets of landmarks after minimizing the variance, we have to define the mean shape of all the

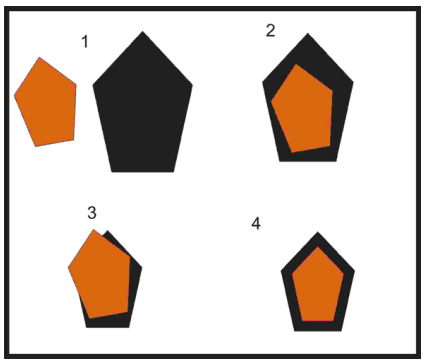

Figure 2: Procedure of Shape Analysis[16]

objects and a distance function which allows us to evaluate how "near" every object is from this mean shape.

The term "mean" is used here in the sense of Fréchet (1948). It can be described by the following steps: If X denotes a random variable defined on a probability space $(\Omega, \mathcal{F}, \mathcal{P})$ with values in a metric space (Ξ, d), an element $m \in \Xi$ is called a mean of $x_1, x_2, ..., x_k \in \Xi$ if

$$\sum_{j=1}^{k} d(x_j, m)^2 = \inf_{\alpha \in \Xi} \sum_{j=1}^{k} d(x_j, \alpha)^2. \tag{10}$$

That means that the "mean shape" is defined as the shape with the smallest variance of all shapes in a group of objects. For computing the mean shape we use the algorithm of Ziezold[36]. Asymptotically our used distance is equal to the procrustean distance[36].

For testing the mean shape on its relevance in most of the cases an assumption about the distribution and minimum of cases are given. In our case we have a small sample and we cannot prove our assumptions about the distribution. The test of Ziezold (1994) is one possibility to solve this problem. It can be described in following steps:

1. Step: Definition of the set of objects

There is one set $M = \{o_1, \ldots, o_N\}$ that can be divided into two subsets:

Objects with the characteristics A:
$A^{sample} = \{o_1, \ldots, o_n\} = \{a_1, \ldots, a_n\}$, and
Objects with the characteristics B:
$B^{sample} = \{o_{n+1}, \ldots, o_N\} = \{b_1, \ldots, b_{N-n}\}$.

The subset A is a realisation of a distribution P and the subset B is an independent realisation of a distribution Q.

Hypothesis: $H_0 : P = Q$

Alternative: $H_1 : P \neq Q$

Define the *level of significance* α. If the probability for H_0 is smaller, we neglect H_0 and assume H_1.

2. Step: Computing the mean shape

The mean shape is calculated by means of the algorithm of Ziezold (1994). Let m_0 denote the mean shape of the subset A.

3. Step: Computing the u-value

$$u_0 = \sum_{j=1}^{n} card\big(b_k : d(b_k, m_0) < d(a_j, m_0)\big)$$

is calculated by the given sets.

4. Step: Determination of all the possibilities of dividing the set into two subset with the same proportion or a random number of possibilities

5. Step: Comparing the u_0-value to all u-values calculated in step 4. Computing the rank (small u-value mean a small rank).

6. Step: Calculate the p-value for H_0

$p_{r=i} = \frac{1}{n_{sample}}$ for $i = 1, \ldots, n_{sample}$, where r is the rank for which we assume a rectangular distribution and n_{sample} a randomized sample of all possibilities.

The same results are there after obtained also for the subset B.

5 Results and Conclusions

To get $3D$ landmarks we construct from $2D$-images a three dimensional object of the tumor. Then we take as landmarks the cut-points between the surface of the tumor and the vector of the edge of the platonic body C60, as shown in figure 3.

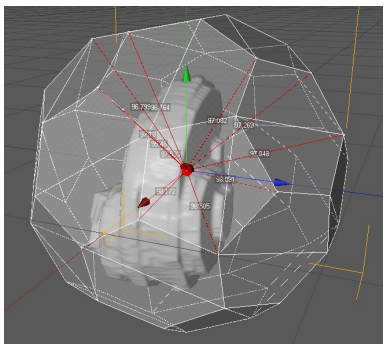

Figure 3: 3D-Landmarks as cut points between the edge of a platonic body and the surface of the tumor[16]

After standardization, centering and minimizing the variance by weighting the landmarks of every object we get for the mean shape of Wilms versus Non-Wilms as in figure 4 an u_0-value of 270. In comparison to all 199 spot tests of 85 objects of total 108 we get as minimum of the u-value 275 and as maximum 721. Hence we get for our order a p-value of $0,005$.

In the other direction Non-Wilms versus Wilms we get an u_0-value of 691 as in figure 5. As well we compare this value to 199 random values and we get a value for $p = 0,02$. In both direction we get a significant $(\alpha = 0,05)$ value.

In comparison of figure 4 to figure 5 the representative object for a diagnosis can be shown. The representative object in 5 is not so useful in describing in consequence of heterogenity.

Our first approach on applying Shape Analysis on the field of oncology shows us only a tendency of differentiation . A tool for ordering the objects was missing. Hence, we combined it and we get

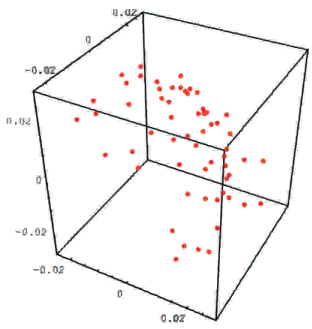

Figure 4: Mean Shape of Wilms[16]

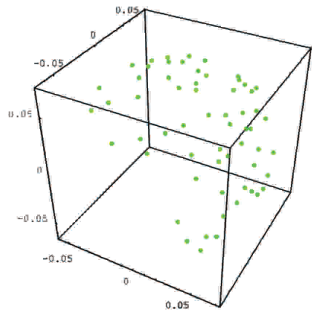

Figure 5: Mean Shape of Non-Wilms[16]

the following results: The Logistic Regression classifies 20 of 21 non-nephroblastoma correctly as non-nephroblastoma and 81 of 82 nephroblastoma as nephroblastoma by using the age of the patient, the position and the distance to the mean shape. All in all 98.1% of all patients can be classified correctly by our procedure. Nagelkerkes R is over 0.98. So our model is significant. After minimizing the variance by using Neural Networks we get in both direction useful results. Therefore, our application shows, that Neural Networks should be used more in combination with stochastic models. The white noise in the data, useless for differentiating, could be reduced.

The sample of 108 patients equates to the total population with renal tumors per year. Hence our results give a new approach for a support in diagnosis. Furthermore we get a correct classification of over 90% by using Logistic Regression.

In contrast to other studies, as an example[6], in Shape Analysis we are searching a representative shape called mean shape for every relevant group. We are not interessted in restoring images by known shapes of objects. Our procedure for testing the mean shape includes only the assumption of uniform distribution and can be used also in the case of a small sample size. In comparison to [36] we have extended our application by $3D$ and by combining neural networks with stochastic models to reduce white noise. White noise in our data is the consequence of image quality.

Furthermore we are using our mathematical procedure on a field in medicine, where decisions according to images are necessary to get a suitable therapy. Our procedure could be a first approach to develop a tool for diagnosis according to the images and the whole known data of all patients in all hospitals. Especially, in the light of the sample of 108 patients with renal tumors, which equates e.g. to the total pediatric population in Germany per year, our results give a new approach for a support in diagnosis.

Further studies with an extension on $4D$ are a future option, especially to study change of tumor shape during chemotherapy. Another important study object should be the shape analysis in organs with fast movements, e.g. shape of heart ventricles or aorta during cardiac cycle.

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