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Cluster analysis for dynamic PET studies

Introduction

Cluster analysis is a data-lead technique that can be used to partition pixel time-activity curves (TACs) obtained from a dynamic PET data into a smaller number of clusters. The aim of clustering is to partition the data according to a certain criteria in such a way that the tissue TACs within a cluster are similar to each other but are dissimilar to those drawn from other clusters.

This report reviews applications of cluster analysis found in literature. Clustering methods introduced here are a method based on a mixture model, a method based on least-squares distance measure, a hierarchical *K*-means method, a method based on Markov random field model and a method based on low-order moments of voxel concentration histories.

Clustering method based on a mixture model

In their article, Ashburner et al. from London and Manchester introduce a clustering algorithm based on a mixture model (Hartigan, 1975) and modified to accommodate dynamic PET data [Ashburner et al. 1996]. Underlying assumptions of the model are that the dynamic data has a known number (k) of characteristics underlying TAC shapes and that each pixel TAC constitutes one of these shapes scaled by a constant, with superimposed Gaussian noise. The noise is assumed to be stationary within each time frame but can vary from frame to frame.

The data is partitioned according to its probability of belonging to each of the k clusters and the partition is based purely on the shape of the pixel TACs. Each of the clusters is described by a multinormal distribution whose parameters are a mean pixel vector, a diagonal covariance matrix common to all clusters and the number of pixel TACs constituting the distribution. The clustering algorithm is based on estimating the likelihood of each pixel TAC being drawn from each of the distributions and updating the distributions according to the properties of the pixels of which they are composed.

Examples of the method's application are given in [^{11}C]flumazenil studies and the made modifications to the original algorithm are discussed, as well the underlying assumptions.

It has been noticed that the method does not always give a convincing partition of the images and one reason to this might be that the real data may form a continuum rather than distinct clusters. It is also worth noticing that the number of clusters k is a user-defined parameter and different choices of it usually lead to different outputs. Effects of such facts as partial volume and movement artefacts are discussed and it is pointed out that all these preceding facts need to be taken into account when interpreting the results of the analysis.

It is concluded that the introduced technique is nonetheless of great value as an exploratory tool in the characterization of dynamic data sets.

Ashburner et al. introduce also a short example of using cluster analysis in an ^{18}F-fluorodeoxyglucose study of a glioma [Ashburner et al. 1995].

R.N. Gunn and his co-workers from London and Amsterdam present a method for quantification of ligand-receptor binding at the voxel level using a simplified reference tissue model and cluster analysis [Gunn et al. 1998]. Cluster analysis (Ashburner et al. 1996) is used to classify voxel time-activity curves in order to automatically extract the reference tissue time course.

An example of using cluster analysis is given of a [^{11}C]WAY 100635 study. Because the kinetics of the radioligand in the reference tissue is the fastest (excluding any blood volume effects), it is possible to determine this region with the clustering method. In the study, the cluster image corresponding to the cerebellum was identified easily and thresholded at $p > 0.75$, which produced a cerebellum mask. This mask was applied to the dynamic PET data to produce a reference TAC to be used as an input function in the reference tissue model.

The conclusion of the report is that the cluster analysis together with compartmental analysis provides a powerful tool for the parametric imaging of PET radioligand binding and delivery. It is also stated that the data lead approach enables the segmentation of the reference tissue with minimal observer bias compared to the manual definition of a reference region of interest.

R. Myers et al. from London consider cluster analysis in the analysis of clinical [^{11}C]PK11195 PET [Myers et al. 1999]. In the case of PK11195, no single anatomical region can be considered as free of specific signal and thus modelling by using a reference tissue as an input function is not possible. Cluster analysis (Ashburner et al. 1996) was used to segment the dynamic data to get the reference TAC that can be used as an input function to the simplified reference tissue model.

It is reported that for most subjects studied one or two dominant clusters of the ten routinely produced represent normal kinetics. The normal kinetics was determined by comparing the shape of the TAC with the one from control brains.

The conclusion of the study is that cluster analysis of dynamic data may provide a viable means of generating an input function to the simplified reference tissue model in the analysis of [^{11}C]PK11195 clinical data.

R.B. Banati et al. report results of studying quantitative imaging of microglia as a measure of disease activity in multiple sclerosis using [^{11}C](R)-PK11195 PET [Banati et al. 2000]. Binding of [^{11}C](R)-PK11195 was measured with a simplified reference tissue model. When using a reference tissue model, the reference input kinetics is usually derived from an anatomical structure that is devoid of specific lingand binding, such as the cerebellum. However, in multiple sclerosis the tissue pathology is often widespread and thus it might not be possible to define unequivocally normal reference tissue. That is why Banati et al. used cluster analysis (Ashburner et al. 1996) to extract a normal ligand kinetic to serve as a reference input function.

In clustering, voxels of the raw dynamic data were segmented into clusters based on the shape of their concentration time-activity curves. Whether a TAC extracted by cluster analysis from the raw dynamic data of a patient was suitable to serve as the patient's normal ligand kinetics was assessed by testing for dissimilarity with the previously established normal population kinetic (χ^2 test, $p < 0.05$).

A.Gerhard et al. report results of using [^{11}C](R)-PK11195 PET imaging in a study of microglial activation in multiple system atrophy [Gerhard et al. 2003]. They used cluster analysis for the extraction and identification of a normal reference input function in the same way as Banati et al. did in their study.

Clustering method based on a weighted least squares distance measure

K.-P. Wong et al. describe an approach to automatically segment dynamic PET images using cluster analysis [Wong et al. 2002]. The study is motivated by their work on a modelling approach where several regions of interest (ROIs) of distinct kinetics are required and manual delineation of ROIs restrain the reproducibility of the modelling technique.

Clustering method introduced is based on a weighted least-squares distance measure and each tissue TAC is allocated to the nearest cluster centroid according to a defined distance criterion. The process is repeated for all tissue TACs until there is no reduction in the weighted least-squares distance measure when moving a tissue TAC from a cluster to another. On convergence, the cluster centroids are mapped back to the original data space for all voxels. In the model used, the number of clusters is a user-defined parameter and initial cluster centroid in each cluster is selected randomly to ensure that all clusters are nonempty. The underlying assumption is that there is a finite number of kinetics in the data. In the study, clustering was performed independently on each slice.

The method proposed in this article is similar to the one introduced by Ashburner et al. [Ashburner et al. 1996] in that there is a finite number of kinetics present in the dynamic PET data. The difference is that the algorithm of Ashburner et al. maximises the probability of an arbitrarily selected TAC belonging to a specified cluster while the method proposed by Wong et al. minimises the weighted least-squares distance for an arbitrarily selected TAC to its cluster centroid.

The optimal cluster centroids are not known beforehand. There may be several local minima in the solution space and thus authors point out that restarting the algorithm with different initial cluster centroids may be needed to identify the best possible minimum. An incorrect initial cluster centroid selection (e.g. a noisy outlier is chosen) may result in a cluster with a single member. This can also be avoided by rerunning the algorithm with different initial cluster centroids or by defining a lower bound on the final number of members in a cluster.

Methods to determine the optimum number of clusters based on the given dataset are discussed because the optimum number of clusters is not known beforehand. Authors suggest that information-theoretic criteria such as Akaike information criteria (AIC) and Schwartz criterion (SC) could be used when determining the optimal number of clusters. It is pointed out that when using these kinds of criteria it must be explored that the probability distribution function used is appropriate for the observed data.

Validation of the segmentation scheme was examined by simulating a dynamic 2-[^{11}C]thymidine PET study and three examples are given on [^{18}F]fluorodeoxyglucose (FDG) PET studies with patients having brain tumour or lung cancer. In human studies the location of tumours and the rim of increased glucose uptake are identified correctly by the clustering algorithm with the optimal value of clusters (defined by AIC and SC criteria). The extracted TACs obtained by cluster analysis and manual ROI delineation were fitted to the three-compartment FDG model using nonlinear least squares method. It is reported that there was a close agreement between the parameter estimates for the tissue TACs obtained by different methods (extracted and manually delineated) in terms of the estimate and the coefficient of variation.

The authors state that a limitation of the proposed algorithm is that it cannot differentiate anatomical structures that are unconnected but have similar kinetics. It is also suggested that further studies are required to investigate tissue heterogeneity in cluster analysis. Nonetheless it is reported that the results suggest that cluster analysis can automatically segment tissues in dynamic PET studies and has the potential to replace manual ROI delineation for some applications.

In their paper, K.-P. Wong et al. investigate the feasibility of using the kinetics extracted by cluster analysis for non-invasive quantification of physiological parameters [Wong et al. 2000]. Clustering method is the one introduced by Wong et al. 2002.

Simulations done with a slice of the numerical Hoffman brain phantom are reported. The Hoffman brain phantom was modified using a template consisting of five different kinetics (grey matter, white matter, thalamus, tumour in white matter and an adjacent hypometabolic region in left middle temporal gyrus). It is reported that the clustering algorithm performed well in extracting the underlying tissue kinetics in grey matter, white matter and tumour. However, the kinetics in thalamus and the hypometabolic region were not separated from those in grey and white matter but this is not considered surprising because their kinetics are very similar in the raw PET images.

It is concluded that the results reported show that the tissue TACs can be extracted automatically by using cluster analysis since the method can segment tissues of different kinetics in PET data. Automatic extraction of ROIs is considered a reliable alternative to manual ROI delineation and by using cluster analysis it is also possible to minimise the subjectivity of manual ROI delineation and the method also ensures that the extracted TACs have distinct kinetics.

Hierarchical K-means cluster analysis

Liptrot et al. from Denmark propose an alternative to arterial blood sampling in quantification of brain tracer uptake, metabolism or binding [Liptrot et al 2004]. The proposed method is to use a blood vessel time activity curve extracted directly from dynamic PET scans by cluster analysis instead of blood sampling. The authors have used clustering to (semi)automatically extract only those voxels that belong to the brain vasculature and the clustering method used is a *K*-means clustering analysis.

The goal of the proposed clustering method is to minimise within-class variance of each cluster by assigning each individual voxel time course in turn to the nearest cluster according to the simple Euclidian distance measure. Cluster centres are created from the mean of all their members. The process is iterated from some randomly generated initial conditions until a stable partition is found. In this study, a hierarchical clustering was performed. In the first step, the data was partitioned into a few clusters such that the number of clusters was that where the vasculature was first segmented out as a separate cluster. In the second step, this vasculature cluster was extracted and put through the clustering process to select as pure a sample of the vasculature as possible. The result of the clustering was a single cluster advocated as a representative ROI of the vasculature. The vasculature TAC was then formed as the average time series of all the voxel members.

In the study, the validity of using a vasculature TAC as a possible replacement for the standard arterial cannulation was assessed by comparing the results of modelling the binding parameters of the [^{18}F]-altanserin after a bolus injection using a cluster-derived estimate of the vasculature TAC with those from arterial and venous blood sampling. Cluster-determined input curve was used in Logan plot analysis and compared with the arterial and venous blood samples. It is stated that the results of performing kinetic modelling using the proposed alternative to blood sampling compare favourably with those obtained via arterial sampling, more so than those obtained via venous sampling. It is hence concluded that cluster input curves can substitute the arterial one without any significant difference in the output parameters.

It is pointed out that there are some limitations and underlying assumptions as well other issues to be considered when applying the proposed clustering method. Such issues as partial volume effects, movement and noise issues are discussed. It is also stated that the agreement with the arterial inputs varies depending on the size of the cluster and that is why the clustering process is seen as a process requiring some refinement to improve the results. In the model, it is assumed that user determines the number of clusters beforehand but it is difficult to define the right number of clusters. Using an incorrect number of clusters can lead to meaningless results and hence such methods as measures of within-class variance, information criteria and initial assumptions concerning the upper and lower limits of the number of clusters are proposed to be used when choosing the number of clusters.

It is concluded that the use of cluster analysis on a PET data set could obviate the requirement for arterial cannulation when determining the input function for kinetic modelling of tracer behaviour.

Clustering method based on Markov random field model

J. L. Chen et al. introduce a segmentation algorithm based on a Markov random field model for the voxel class labels [Chen et al. 2001]. The aim is to use segmentation technique to extract the reference tissue model input function automatically from the PET data volume. Most of the techniques used to segment PET images rely on the statistical assumption that the time-activity curves are independent although there is typically a high degree of correlation between voxels close to each other. Markov random field models provide a way to incorporate spatial interaction between voxels in the segmentation process.

The paper considers a two-dimensional model. An example is given on synthetic data and the results of the independent voxel segmentation using EM algorithm and the results of dependent voxel segmentation based on Markov random field model are compared. The results of the comparison show that using the Markov random field model reduces the voxel misclassification error and also the estimated centre vectors are closer to the true centre vectors. The algorithm was also applied to real PET data obtained with the ligand [^{11}C](R)-PK11195. Also in this case the results of independent voxel clustering and Markov random field based clustering were compared. It is concluded that although the performance evaluation is difficult for a real data set, the Markov random field model based segmentation results look better in terms of visual inspection.

The proposed algorithm is an approximate EM algorithm with hidden class information being modelled as a Markov random field. In the model, there is a parameter that controls the degree of correlations between voxels and the choice of an appropriate parameter value depends on the images being considered. Also the number of clusters is a parameter to be chosen. It is stated that the choices of parameter values can be made by experimenting or by using computing methods like Markov chain Monte Carlo method.

It is concluded that the result for synthetic image shows that the Markov random field model based segmentation performs better than the independent-voxel segmentation in terms of both the image segmentation accuracy and parameter estimation. The performance of the proposed method on real PET data is also considered promising.

Clustering method based on low order moments of voxel concentration histories

Y.Kimura et al. [Y.Kimura et al. 1999] introduce a model-based clustering method to generate parametric images. The aim of using clustering is to reduce noise in parametric images. The basic idea of the clustering method is to average over voxels whose concentration histories have the same shape.

It is stated that the formation of parametric images has two major drawbacks that are long computation times and low statistical precision (i.e. parametric images are quite noisy). A clustering method based on low order moments of the voxel concentration histories that will average over kinetic curves having the same shape and thus improve the noise level without degrading spatial resolution is proposed. Clustering theory is developed for a two-parameter single-compartment model that can be described by differential equation of the form

$$\frac{dC(t)}{dt} = K_1 C_a(t) - k_2 C(t).$$

Function *C(t)*, which denotes the tracer concentration in the compartment, can be solved from the previous differential equation and clustering is based on the ratio of 0^{th} and first moments of *C(t).* It is shown that the ratio of moments is a function of parameter k_2 (i.e. the clearance rate of the

tracer in the compartment) only and thus voxels having a similar ratio of moments have similar parameter k_2 and thus also similar shape of kinetic curves. Hence, voxels with similar ratio of moments can be grouped into classes or clusters of voxels. In addition to previously mentioned advantages of using clustering, also the number of parameter estimations is reduced from one per voxel to one per cluster and thus computation of parametric images is also more rapid.

According to this theory of clustering, a stepwise method to create parametric images is introduced and it mainly consists of two steps: a cluster-based operation and voxel-based operation on each cluster. Also results of computer simulations as well as human study are reported. It is concluded that the ratio of 0^{th} and first moments has desirable properties as clustering statistics but it is also pointed out that extensions to more complicated models with more parameters requires additional clustering criteria. It is reported that the estimation of parameters K_1 and k_2 is unbiased especially for a noise level of a typical clinical study and estimation error is no larger than in the conventional non-clustering method. Hence it is seen that the key feature of clustering is the reduction of estimation noise. It is also pointed out that the choice of clustering method deserves careful consideration. In this study the ratios of moments were sorted in ascending order and clusters with equal numbers of voxels were used. It is concluded on the basis of experiments that a few hundred to 1000 voxels per cluster is an appropriate cluster size.

It is concluded that the advantages of the method proposed are the possibility to create parametric images without loss of the original spatial resolution, fast computation, the possibility of unbiased averaging of the parameters within a ROI on the parametric images and the fact that the estimation error is no larger than in the conventional method.

In his paper [Kimura 2004] Y. Kimura presents a general scheme for voxel-based kinetic analysis in PET where an unobserved clustering algorithm of the Mixture Gaussian Model is applied to categorize dynamic data according to their kinetic parameters. Parameter estimation is then invoked to averaged PET data in a cluster and thus the bad noise statistics in voxel-based PET data and large calculation times required for voxel-based kinetic analysis can be overcome. In this papers Kimura's algorithm Clustering Analysis for Kinetics (reviewed above in the case of one-tissue two-compartment model) is applied to FDG studies.

It is reported that a statistical clustering algorithm using Mixture Gaussian Model is applied to construct groups in which the voxels have almost same kinetic parameters of k_2 and k_3 and then an averaged TAC is used for further model analysis. Clustering algorithm is invoked hierarchically, which means that TACs are first group into four clusters and then each cluster is divided into a further four clusters and so on, until there are no clusters that include more than 500 voxels. It is concluded that averaging can develop the noise level of TAC and grouping can reduce the number of estimated TACs.

Kim et al. [Kim et al. 2004] present a method that can generate parametric images of both cerebral blood flow (CBF) and vascular volume (V_0), with improvement of image quality, by a single computational procedure. The method is applied to a $H_2{}^{15}O$ PET study.

The presented method is based on the two-compartment model and it employs linear least square algorithm for parameter estimation and cluster analysis for suppressing noise on image data. In the presentation of the clustering method the authors refer to the article of Kimura et al. [Kimura et al. 1999].

It is reported that the results of computer simulations show that the use of clustering reduced the error in the estimation of both CBF and V_0 values and the noise on generated images of both parameters compared with those without clustering. Also the PET study shows that the proposed method incorporating clustering could generate both images of CBF and V_0 with improvement of image quality.

It is concluded that the presented method could generate parametric images of CBF and V_0 simultaneously with improvement of image quality and computation time. The method could provide the image if CBF value with an acceptable range of error and the image of V_0 value improved in quality by means of clustering. However, it is reported that the estimate of V_0 is very sensitive to the error in delay and dispersion in input function as well as noise on image data and thus the accurate pixel-by-pixel estimation of V_0 value cannot be achieved in actual fact. It is however concluded that the presented method has the potential to make a contribution to an improved diagnosis of cerebral vascular disease and activation.

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