Use of signatures to create probability maps of brain tissues in health and disease – a new diagnostic tool?

Uporaba statističnih podpisov za izdelavo verjetnostnih map zdravih in obolelih možganov - nov diagnostični pripomoček?

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Abstract

Segmentation of brain MRI into white matter, gray matter, cerebrospinal fluid, skull, and other categories is an integral part of MRI analysis. To date, most widely used segmentation approaches require the use of population-based spatial segmentation priors, mostly to improve robustness to shading artifacts and noise. Prior generation requires a set of segmented volumes from a population similar to the one to be studied, and an alignment approach for aligning brains from multiple subjects.

Aim: In this paper we present a method for generating segmentation priors that is insensitive to noise and field bias and does not require registration to a template space.

Methods: Our approach relies on using signatures, a set of local descriptive statistics, computed over multiple spatial scales. In the training process, signatures of each tissue are clustered into representative sub-classes. Representative signatures are the median of signatures in each subclass. In a new dataset, voxel signatures are compared to the set of representative signatures and tissue classification priors are generated using Bayes' rule and total probability.

Results: These signature-based probability maps can replace spatially-based population priors in segmentation. We also show that signature similarity can be used interactively to delineate brain lesions, such as tumours, thereby facilitating diagnostic procedures.

Conclusions: Voxel signatures consisting of spatial texture information across multiple scales, can be used either as simple similarity measure to select tissue of the same type or to create tissue prior probability maps that can be used in brain segmentation and in other clinically relevant procedures.

Izvleček

Analiza magnetnoresonančnih (MR) slik možganov temelji na prepoznavanju možganske sivine, beline, likvorja in lobanje. Številne anomalije lahko izkušen diagnostik hitro in dobro prepozna, mnogo težje pa je oceniti obseg anomalije in spremljati njene spremembe po zdravljenju. Avtomatska segmentacija možganov z uporabo programske opreme je zato izrednega pomena za objektivno analizo MR slik. Preprosto povedano so dosedanje metode segmentacije temeljile na «normaliziranih« oz. »standardnih« možganih, ki se uporabljajo kot model za proces »učenja« računalniških programov za segementacijo. Avtomatska analiza slike torej temelji na »priorjih«, to je izhodiščih, iz katerih se program »uči« prepoznavati posamezne strukture v možganih. To je še zlasti pomembno zato, ker razni artefakti senčenja in šum v MR sliki povzroče, da intenziteta signala po celotni rezini in celotni pregledani prostornini možganov ni homogena. V praksi to pomeni, da sta si lahko npr. intenziteti signalov beline in sivine na posameznih vokslih, to je prikazanih prostorninskih delčkih tkiva, v raznih predelih MR slike enaki in jih ni možno prepoznati samo po tem merilu. Priorji omogočijo, da se standardni možgani »preslikajo« na možgane preiskovanca, kar izboljša avtomatsko analizo slike. Na MR slikah možganov normalnih prostovoljcev je tak postopek natančen in hiter, odpove pa lahko pri večjih anomalijah v možganih. Naš pristop k analizi slike, ki ga opisujemo v tem prispevku, pa je bil drugačen. Želeli smo se izogniti omejitvam, ki jih prinašajo priorji, ki temelje na standardnih možganih. Izdelali smo izvirno metodo analize slike z razvojem programa, ki prepozna značilne podpise posameznih vokslov v MR sliki na osnovi intenzitete signala in njegove soseščine. Priorje na osnovi »standardnih možganov« torej nadomestimo s priorji, ki so v bistvu značilni podpisi preiskovančevih možganov. Te

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značilne podpise nato uporabimo v nadaljnjih postopkih obdelave slike. Naša metoda omogoča popolnoma nove pristope k segmentiranju možganov. Program torej izdela verjetnostne mape sestavin možganov vsakega posameznega preiskovanca in s tem omogoča analizo možganov tudi ob prisotnosti večjih anomalij. Izkazalo se je, da z analizo značilnih podpisov preiskovančevih možganov lahko tudi prepoznamo posamezne patološke spremembe in celo njene posamezne dele, kar lahko bistveno prispeva k hitrosti, objektivnosti in natančnosti diagnostike.

Introduction

Diagnostic imaging is one of the most important approaches in the assessment of a patient's disease, and also in the follow up of treatment effects. Magnetic Resonance Imaging (MRI), compared to other diagnostic imaging methods, offers high spatial resolution and good discrimination of soft tissues while being non-invasive. The rich anatomy information provided by MRI is very useful in many imaging applications such as the quantitative clinical studies of pathology,[1,2] diagnosis,[3-6] localization of pathology,[7] study of anatomical structures and the derivation of anatomical atlases[8] and priors.[9] In addition, treatment planning[10-12] and computer integrated surgery[13] increasingly rely on MR imaging methods.

Although visual inspection of MR images can often yield an accurate diagnosis, there are several conditions where a more objective method for the assessment of pathology is needed. Even the evaluation of an easily recognizable pathology, such as brain tumours, becomes more complicated when a quantitative measurement is needed. Manual segmentation followed by volumetry is the usual choice, but it is a tedious and time-consuming approach. Measurement of the extent of brain tissue atrophy or quantisation of a diffusely spread pathology is even more complicated and therefore tedious manual procedures are unsuitable for the clinical practice where more rapid and accurate measurements are needed.

Most common delineation of normal brain is into 3 classes: cerebrospinal fluid (CSF), gray matter (GM) and white mater (WM). This seems easy at first look, but in practice, noise and field inhomogeneity cause the same tissue type to have non-uniform intensity over the whole volume. Those shading artifacts might not affect visual recognition of tissue borders, but they cause significant problems to automatic segmentations that are based on voxel intensity distributions.[14]

To make the segmentation robust to such artifacts, most if not all current brain segmentation approaches (SPM,[15] FSL,[16,17] FreeSurfer[18,19]) rely on a pre-computed anatomical atlas providing a priori information about the spatial distribution of tissue types. These priors are generated by combining segmentations of a large number of MRI volumes aligned to a common space. To make use of these spatial priors, one needs

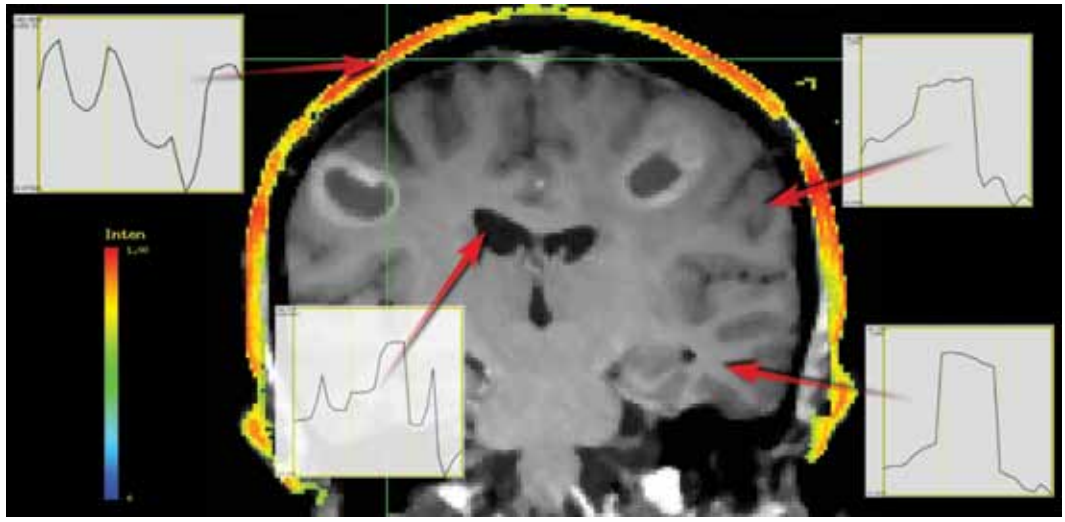

Figure 1: Highlight of skull tissue using voxel signature similarity. Colored overlay represent voxels whose signature had a Spearman correlation with that of the voxel at the cross hair (top left graph) at 0.6 or higher. Red arrows point to sample tissue locations with different signatures.

to align the volume to be segmented to the common space, a process which is itself sensitive to noise, and to shading artifacts as recently detailed by Ashburner et al.[15]

Brain abnormality seen on MRI can result from various diseases, and segmenting of pathologically altered brain images needs to be done carefully. Generally, as reflected in imaging, one could group brain anomalies into three groups. The first group comprises gross anatomical changes that can be caused by neoplastic diseases, cysts, abscesses, and other anomalies that change the anatomy of the brain. The second group of anomalies is characterized by "normal" anatomy, but changes in signal intensity on MR images (typical for multiple sclerosis–MS). The third group of changes is represented by "normal" anatomy, but different proportions of CSF, GM and WM (degeneration in disease, thickening of GM under some physiological conditions etc.). Segmentation procedures that rely on priors from normal brain atlases are most suited for the third group of brain image changes. Registration of an "average" brain to an observed normal brain is relatively easy, but problems arises when anomalies are present.

Here we propose a new method for generating segmentation priors. The proposed method is insensitive to shading artifacts because of its reliance on local measures, and does not require registration to a template. This greatly reduces the number of parameters to optimize during segmentation. Our approach relies on using local texture information computed over multiple spatial scales, rather than spatial location. We are also showing that this information can be used to categorize different tissues, including brain lesions.

Methods

Patients, volunteers, and standards.

The analysis of images was performed on data obtained from previous studies on patients and volunteers on tomographs GE Signa 1,5 T and Siemens Magnetom Trio A Tim Systems 3 T at the Faculty of Medicine, Ljubljana. Informed consent and permission to use the data obtained by MR imaging has been obtained in accordance with a protocol approved by the Ethical Committee of the Republic of Slovenia (Republiška komisija za zdravniško etiko). In addition, a set of manually segmented T1 volumes was obtained from the Internet Brain Segmentation Repository (IBSR) Center for Morphometric Analysis at Massachusetts General Hospital, which makes the data available for the assessment of different segmentation method (http://www.cma.mgh.harvard.edu/ibsr/).

We hypothesize that voxels of similar tissue types and local texture will exhibit similar signatures and that signature similarity can be used to generate classification priors. Figure 1 illustrates signatures and signature similarity. Each graph shows the signature from a different location in the brain. The colored portions show brain voxels whose signatures were correlated at 0.6 or higher with the signature at the crosshair voxel on the top left. This highlighting of tissue

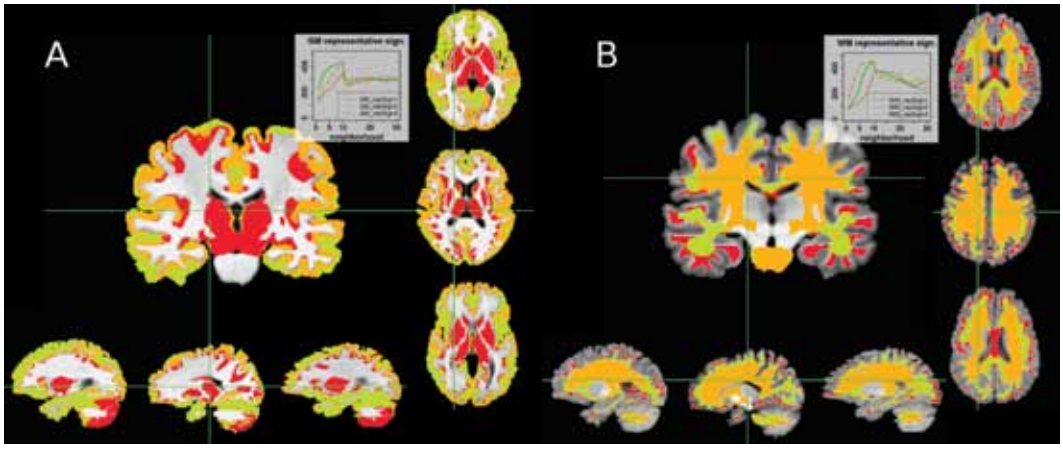

Figure 2: Sample clustering of gray and white matter into 3 subclusters in the learning process. Clustering of signatures into three different types of gray/white matter was consistent across all volumes used in the learning process. Note striking similarity in panel A between the basal ganglia and cerebellar cortex (red cluster). Characteristic clusters are also found in the temporal lobe and partly in the frontal cortex (green cluster). White matter on panel B also shows different signatures in the cortico-cortical "U" connections, pyramidal and extrapiramidal tract, and in the temporal lobe. Graphs show representative signatures from each tissue type.

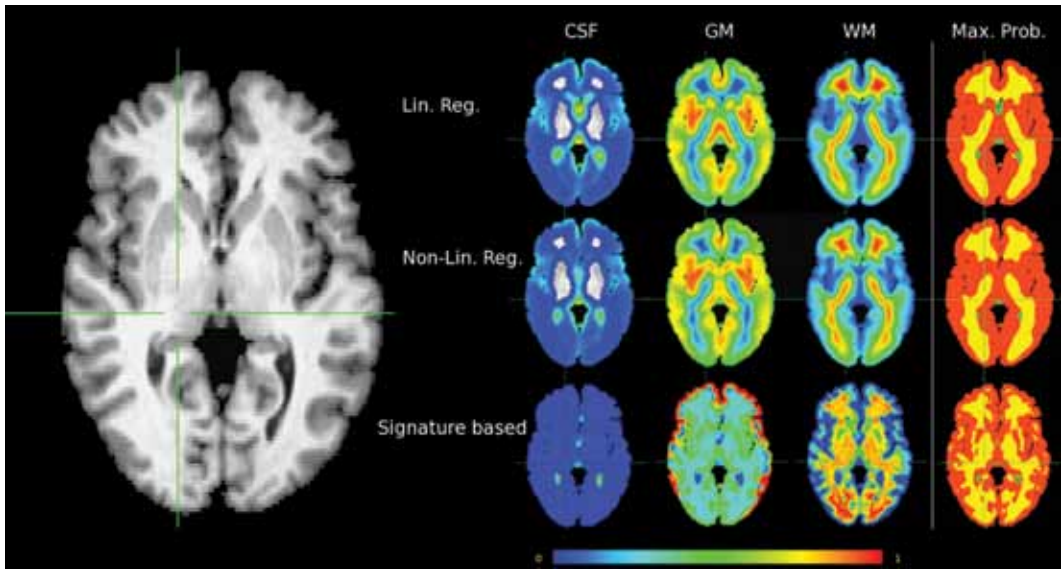

Figure 3: Probability maps of CSF, GM, WM, and class of maximum probability (Max. Prob.) of the sample brain shown on the left. The maps were produced with different methods (Linear registration of average probability map - first row, Non-linear registration – second row and probability maps computed with our approach – third row). The last column shows maps of the tissue type with the maximum probability.

around the skull is not based on individual voxel intensity, but rather on the distribution of voxel intensities over multiple spatial scales. In the remainder of this work, we focus on brain tissue only. However, the method can readily be extended to non-brain tissue as well.

Training Process

To determine which signatures best represent a tissue type, we use the manually segmented volumes to separate computed signatures by GM, WM and CSF. However, not all voxels of the same tissue type will exhibit similar signatures. For example, gray matter tissue will have different signatures on the surface of the brain (cortex) versus the basal ganglia or the brain stem. Thus, each tissue class can have multiple representative signatures, which can be identified by a clustering approach. We cluster signatures of each tissue class using k-means into 3 or 4 clusters [adaptation of Cluster 3.0 by Michiel de Hoon from Human Genome Center, University of Tokyo]. The centroid of each cluster forms one of the representative signatures $\vec{s}_i$ of the parent class.

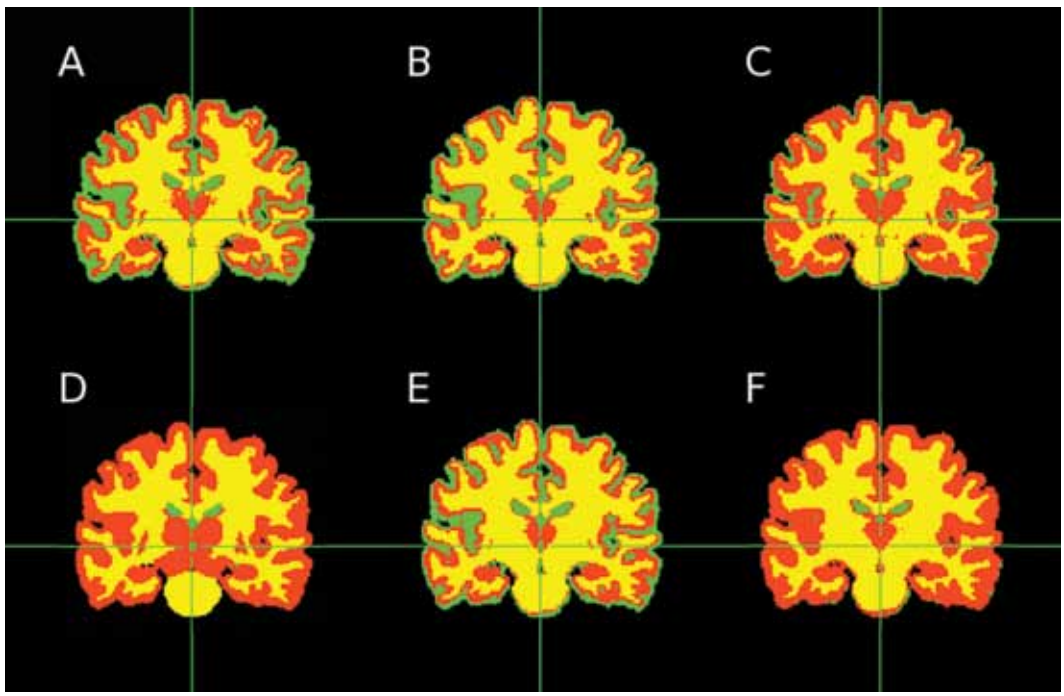

Figure 4: Segmentation of brain using various priors with segmentation tool FAST. (A) Segmentation without using probability maps, (B) with spatial priors only for initializing the segmentation procedure, (C) using spatial priors for final segmentation, (D) manually segmented from IBSR, (E) using signature-based priors for initializing segmentation, and (F) with signature-based priors for final segmentation. WM (red) is well represented in all cases but GM (orange) is often misclassified as CSF (green) in A, B and E where priors were not used for final segmentation.

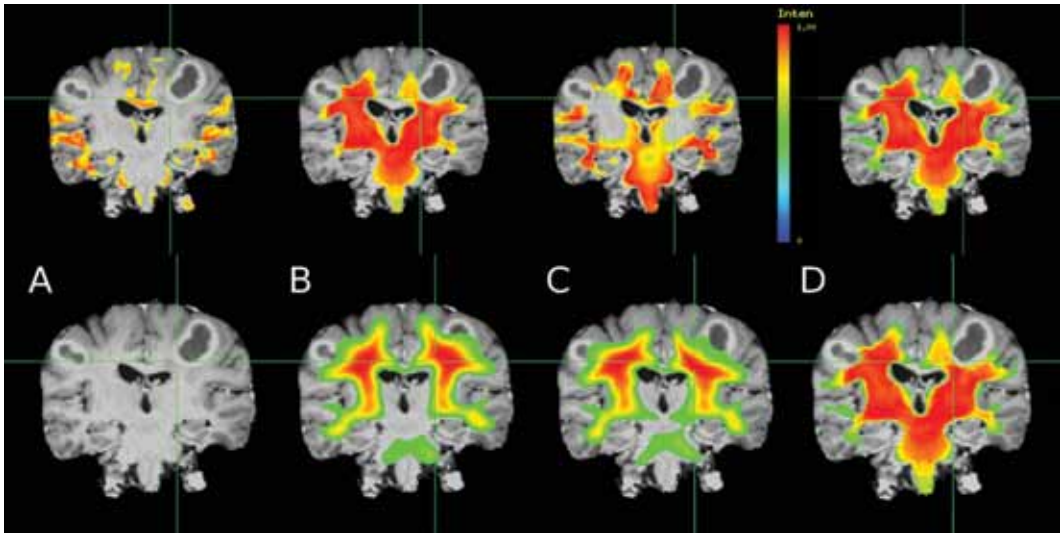

Figure 5: Accuracy of generation and registration of probability maps in brain with two large metastases. First row is showing (from left to right) three WM partial probability maps and final probability map produced by maximum of the weighted first three probability maps. In the second row panel A shows T1 coronal slice of brain with 2 lesions; Panel B shows overlaid average WM probability map based on linear registration of average brain template – the lesion was not "recognized"; panel C shows nonlinear registration of average probability map that gives a bit better results than linear registration; panel D shows our probability map generated from signatures. Our method recognizes both lesions as not belonging to WM, which would normally be present on this position in healthy brain.

Figure 2 shows in panel A the clustering results of gray matter tissue, and in panel B those of white matter tissue.

The similarity between signatures is inversely proportional to the distance between them. Using the training dataset, we model the distribution of distances in each subclass to each of the representative signatures using the Gamma function. These distance distributions are used to estimate $p(\delta_{i,r}|c_i=k)$, the probability of observing a distance from a voxel's signature from representative signature r, given that voxel's membership in class k.

Processing steps described above were implemented with AFNI [20] software package and its R[21] library extension http://afni.nimh.nih.gov.

To compare tissue probability maps obtained from voxel signatures to those obtained on spatial registration, we register T1 volumes to the space of the probability templates distributed with FSL [17] using both linear (FLIRT [22]) and non linear registration (FNIRT).

Results and discussion

Figure 3 shows tissue probability maps obtained by linear registration and nonlinear registration to the spatial priors template, and those computed from signatures of IBSR volume 7 using training results derived from IBSR volume 9.

In this case, average probability maps aligned by linear registration[22] overestimated the likelihood of CSF (especially frontally) and underestimated that of WM. Nonlinear registration yielded improved results, but population based likelihood map cannot reflect the higher level of detail found in an individual brain. In contrast, signature-based likelihood maps better reflect individual anatomy. To test whether they can replace population-based spatial priors, we used them as priors in FSL's FAST[17] segmentation tool (FMRIB Centre, University of Oxford, UK). Figure 4 shows a sample segmentation result with population-based spatial priors, and with signature-based ones. Dice metrics for both CSF and GM classification were improved with signature-derived priors from 0.23 to 0.56, and 0.87 to 0.9, respectively. Across all 18 IBSR volumes, classification of CSF, and GM improved by an average of 96 % and 1 %, however classification of WM decreased by 4 % suggesting that the procedure requires further optimization.

We also wanted to test the usefulness of our probability maps on pathologically altered brain as first results showed great detailed structures that average maps could not (see Figure 3, last column). Here we show that partial probability maps can give better results than using registration of average probability map. We used three representative signatures for computing similarities and later probabilities (first row in Figure 5). Compilation of these three probability maps gives reliable representation of all WM in the brain of a patient with two metastatic

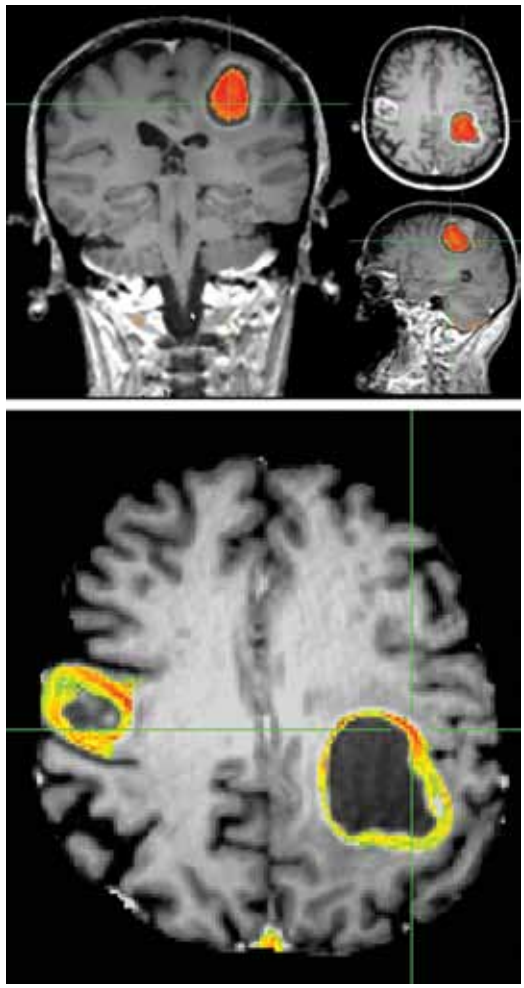

Figure 6: Recognition of tumor tissue by use of signature similarity. A reference voxel is selected at the cross hair, and colored overlay highlights voxels with similar signatures. Note how the vast majority of similar signatures belong in the cyst (first panel). The solid tumor tissue, which has similar signal intensity as the white matter, can also be delineated (second panel).

lesions (Fig. 5 D), avoiding the metastases that are not "recognized" by methods using linear and non-linear registration of average probability maps–priors.

Another use of the signatures is to compute similarity maps based on interactive selection of a reference voxel's signature. For example, Fig. 6 shows a metastatic lesion with necrotic region surrounded by viable tumor tissue. The selection of a reference voxel can trigger a computation of similarity between its signature and that of each other voxel in the brain.

Note how selecting a voxel in the cystic region (Fig. 6 top) reveals that voxels with most similar signatures lie within the cyst itself. If the similarity was based on signal intensity alone, then much of the gray matter would be considered similar to the voxel in the cyst. This interactive similarity detection approach can simplify the manual process of cyst delineation and volume estimation, which is especially important for monitoring the effects of therapeutic procedures such as radiotherapy and/or chemotherapy. Similarly, the viable tumor tissue is also well recognized by our signature similarity technique (Fig. 6 bottom), and it is well distinguished from white matter and gray matter, although the signal intensity of WM and tumor tissue is similar over the entire volume of slices.

Conclusions

By using voxel signatures consisting of spatial texture information across multiple scales, we can create tissue prior probability maps that can be used in brain segmentation. The approach does not require the use prior maps based on segmented brain data from a known population, nor registration to a template space. Furthermore, signatures can be used for interactive delineation of structures where the use of voxel intensity

Appendix

The essential part of our approach relies on what we term a voxel's signature. This is a collection of descriptive statistics computed over multiple spatial scales and arrayed into a vector $\vec{s}_i$ as shown in (Eq.1).

Eq1: $$\vec{s}_i = [\, stat_1(Y_{i1}), stat_1(Y_{i2}), \ldots stat_1(Y_{in}), stat_2(Y_{i1}), \ldots, stat_2(Y_{in}), \ldots, stat_m(Y_{in})]$$

i – voxel index

$\vec{s}_i$ – signature = a vector of m descriptive statistics over n multiple spatial scales

y_i – voxel intensity

Y_{ij} – Set of voxel intensities inside a sphere of j mm and centered around voxel i;

$stat_k(Y)$ –a statistic computed over set Y. In this work, we used the three statistics of median, median absolute deviation, and skew.

alone would fail. The results presented here constitute a proof of concept for the use of voxel signatures in generating template-independent priors for MRI segmentation, although further improvements are possible. The results also allow the conclusion, that our approach can be used for the delineation of brain pathology, as well as for other studies of brain morphology.

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