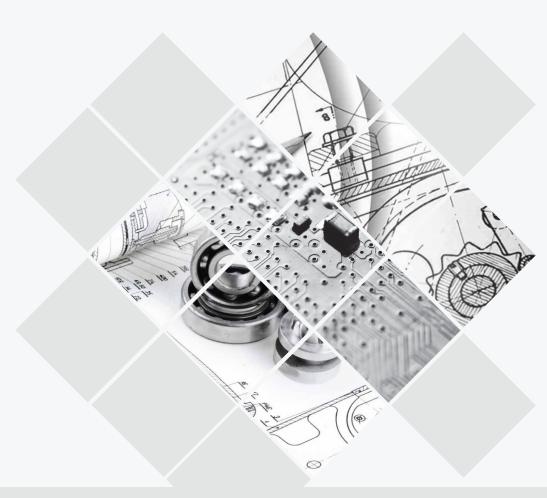


focal cortical dysplasia (FCD) lesion analysis with complex diffusion approach

Focal Cortical Dysplasia (FCD) is a neuronal migration disorder and is a major cause of medically refractory epilepsy. The most carefully collected data from international surveys indicate that about 1 adult in 200 suffers from recurrent epilepsy. Around 30% of brain epilepsy is due to FCD.



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Abstract

Identification of Focal Cortical Dysplasia (FCD) can be difficult due to the subtle MRIchanges. Though sequences like FLAIR (fluid attenuated inversion recovery) can detect a large majority of these lesions, there are smaller lesions without signal changes that can easily go unnoticed by the naked eye. The aim of this study is to improve the visibility of Focal Cortical Dysplasia lesions in the T1 weighted brain MRI images. In the proposed method, we used a complex diffusion based approach for calculating the FCD affectedareas. Based on the diffused image and thickness map, a complex map is created. Fromthis complex map; FCD areas can be easily identified. MRI brains of forty eight subjectsselected by neuroradiologists were given to computer scientists who developed thecomplex map for identifying the cortical dysplasia. The scientists were blinded to theMRI interpretation result of the neuroradiologist. The FCD could be identified in all thepatients in whom surgery was done, however three patients had false positive lesions. More lesions were identified in patients in whom surgery was not performed and lesionswere seen in few of the controls. These were considered as false positive. This computeraided detection technique using complex diffusion approach can help detect focal cortical dysplasia in patients with epilepsy.

Keywords: Complex Diffusion, Cortical Thickening, Epilepsy, Focal Cortical Dysplasia, MRI, Thickness Map

1. Introduction

Focal Cortical Dysplasia (FCD) is a neuronal migration disorder and is a major cause of medically refractory epilepsy. The most carefully collected data from international surveys indicate that about 1 adult in 200 suffers from recurrent epilepsy. Around 30% ofbrain epilepsy is due to FCD [1]. The histologic features of FCD range from milddisruption of the cortical organization to more severe forms with marked corticaldyslamination, voluminous balloon cells littered throughout the cortex and astrocytosis[2],[3]. During the last 35 years, developments in imaging, electroencephalography, and electrocorticography have allowed more patients with medically refractory epilepsy toundergo resective surgery [4]. Magnetic Resonance Imaging (MRI) plays a pivotal role in the presurgical evaluation of patients with intractable epilepsy. Although MRI has allowed the recognition of FCD in an increased number of patients, standard identifylesions in a large number of cases due due to their subtlety and the complexity of the cortexconvolution. Even with high resolution MRI, the lesional boundaries are often difficult todelineate by neuroimaging or on the basis of the macroscopic appearance of the cortexduring the surgical procedure. On T1-weighted MRI sequence, FCD is usually characterized by variable degrees of cortical thickening and reduced demarcation of the gray-white matter junction [5].FLAIR sequence shows hyperintensity of gray and subcortical white matter. Recently many computational models and image processingtechniques have been developed to improve the lesion detection [5] - [8] [26]. In all these models the above said FCD characteristics are used to identify the lesions. In the proposed method we used a combination of complex diffusion [9] and cortical thicknessmap for identifying FCD lesions.

Complex diffusion is a comparatively new Partial Differential Equation (PDE) basedmethod and can be applied for processing images. This is a generalization of diffusionand free Schrodinger equations [9]. Analysis of linear complex diffusion shows that generalized diffusion has properties of both forward and inverse diffusion. Whencomplex diffusion is applied to images, we will get details in real and imaginary planes.In real plane we will get smoothed areas of the image and in imaginary plane, the edgecomponents of the image. When non linear complex diffusion is applied to images, intraregion smoothing will occur before inter region smoothing. This property of non lineardiffusion will help to detect the blurring effect in Gray-White matter junction. The contrast difference between lesion tissues and nonlesional tissues can be increased by applying complex diffusion.

II. Materials and Methods

The 3D T1 weighted sequence images of fortyeight subjects were selected by the neuroradiologist. These included images of patients with intractable epilepsy due tocortical dysplasia and of subjects with normal brain MRI. There were 27 males and 21 females of age group 0.3 years to 55 years old. These images were given to the computerscientists, who were blinded about the MRI findings. The diagnosis of FCD was based onthe MRI imaging criteria of thickening of cortex, blurring of gray-white matter junctionand/or cortical and subcortical white matter hyperintensity. The MRI diagnosis of FCDwas made by neuroradiologists specializing in epilepsy imaging. The diagnosis was basedon an epilepsy MRI protocol consisting of axial and high resolution coronal T2 fast spin echo, axial and coronal FLAIR, 3D T1 weighted spoiled gradient, diffusion weighted andsusceptibility weighted imaging. Out of 48 subjects, 35 had

FCD and the rest had a normal MRI. The subjects with the normal MRI were selected by the neuroradiologists as the controls for the study. This age matched control subjects had undergone the same MRI imaging protocol. The computer scientists were informed about the inclusion of normal controls in the study but were not informed about the identity of imaging data of the controls. Ten of the patients underwent surgery and the pathological diagnosis of focal cortical dysplasia was made.

The MR images were acquired on a 1.5-T scanner (Siemens Medical Systems, Germany). The acquired 3D MRI data set consisted of approximately 120 T1 weightedcoronal slices with TR/TE/FOV/ flip angle of 11s/4.94s/23cm/15°, matrix size 256 x224, thickness 1.5 mm and pixel spacing 0.89 mm. Axial FLAIR images were a cquiredwith TR/TE/FOV/ slice thickness/interslice thickness of 9000s/109s/23 cm/5mm/1.5mmand matrix size of 256 x 224. In the proposed method we used a combination of complex diffusion and thickness map to identify lesions.

The following preprocessing steps are applied first.

- 1. The images were intensity normalized using a subject specific linear multiplier based on the median voxel-wise intensity [10], [11] of the image to an average control brain.
- 2. The scalp and lipid layers were removed from each image of the entire volume.mages are converted into axial slices before stripping scalp and lipid layers.Morphological operations such as dilation, erosion and connected componentanalysis are used for stripping scalp from brain MR images [12]-[14].

- 3. The possibility of FCD in cerebellum as a cause for intractable epilepsy iscomparatively negligible, so cerebellum is removed before processing to reduce false positives.
- 4. The next step is the segmentation of brain MRI into Gray Matter (GM), WhiteMatter (WM) and CSF. For this a Gaussian curve was used to fit each of the grayand white matter peaks in the histogram. The intensity threshold between grayand white matter was then automatically determined by the intersection of the two Gaussian curves, eliminating the reliance on the local minimum between the grayand white matter peaks [5].
- 5. Usually FCD affects the gray matter area. So searching for FCD is restricted togray matter area alone. The white matter and CSF is removed from the segmented image.

Once the preprocessing operations are completed, thickness map, complex diffused image and complex map are calculated. These methods are explained below.

A. Thickness Map Calculation

Cortical thickening and blurring effect in gray-white matter interface are the findingsseen in FCD. To calculate the cortical thickness, many methods are proposed in theliterature [14] – [19]. In the proposed method we used the method suggested earlier [16] in which cortical surface is considered as equipotential surface used in the mathematical description of electrostatic fields and described by Laplace's equation. This method solves Laplace's equation to construct trajectories passing through the cortical sheet connecting one surface to the other. A particular advantage of this approach is that for any path or trajectory there is mutual correspondence

between the points on the two surfaces regardless of the trajectory's starting point [20]. The method works by considering the cortex of each hemisphere to be a volume bounded by two surfaces, S and 'S. Laplace's equation (shown in eqn. 1) is solved over the area between S and 'S to calculate the scalar filed $_{W}$ [16].

$$\nabla^2 \psi = \frac{\partial^2 \psi}{\partial x^2} + \frac{\partial^2 \psi}{\partial y^2} + \frac{\partial^2 \psi}{\partial z^2} = 0 \tag{1}$$

In their method Jones. et. al [16] defined a potential $_{\psi}$ every where between two lines S and S' such that $_{\psi}$ = 0 on S and $_{\psi}$ = 10,000 on 'S. The resulting profile of is a smooth transition from $_{\psi}$ = 0 V on S to 10,000 V on 'S . The significant property of Laplace's equation is that nonintersecting intermediate lines, or isopotentials, with constant values between 0 V and 10,000 V must exist between S and 'S. Once the solution of $_{\psi}$ is obtained, filed lines are computed and normalized to

$$\Psi \qquad N = \frac{E}{\|E\|} \tag{2}$$

where $E = -\nabla \psi$ and N represents a unit vector field defined everywhere between S and S' which always points perpendicularly to the sublayer on which it sits [16]. Integratingin the direction defined by N at any point in the volume from one boundary to the other, provides the length of the trajectory and hence the cortical thickness.

B. Calculating Complex Diffused Image

For calculating complex diffused image, we used non-linear complex diffusion proposed by Gilboa et. al [9]. Complex diffusion is a generalization of diffusion and free Schrodinger equations.

The nonlinear complex diffusion is of the form

used non-linear complex diffusion proposed by Gilboa et. al [9]. Complex diffusion is a generalization of diffusion and free Schrodinger equations.

The nonlinear complex diffusion is of the form

$$I_{t} = \nabla \cdot (c(\operatorname{Im}(I))\nabla I) \tag{3}$$

where

$$c(\operatorname{Im}(I)) = \frac{e^{i\theta}}{1 + \left(\frac{\operatorname{Im}(I)}{k\theta}\right)^2} \tag{4}$$

 ∇ is the gradient and k is the threshold parameter. In the experiment we used k as 1.5.

When image is processed with complex diffusion, we will get low frequency components (plateaus) of the image in real plane and high frequency components (edges) in the imaginary plane. As iteration continues more high frequency components will move to imaginary plane. The component in the real and imaginary is equivalent to that of the image convolved with Gaussian and Laplacian of Gaussian (LOG).

In the proposed method we applied complex diffusion to the segmented gray matter with an iteration step of 40. The reasons for selecting nonlinear complex diffusion is that intra region smoothing will occur before inter region smoothing. So FCD areas and nonFCD areas in gray matter will diffuse separately. The advantage of using complex diffusion is that we can take advantage of imaginary part also. Figure 1 shows the real and imaginary parts of an FCD affected brain image.

C. Calculating Complex Map

In both thickness map and real part of the diffused image, the areas where thickness is more is represented with high intensity and in imaginary part the reverse. So to get a better view of thickness area, we derived the following equation for calculating complex map

$$Complex map = \frac{cortical \ thickness \times real \ part \ of \ complex \ diffusion}{imaginary \ part \ of \ complex \ diffusion} \tag{5}$$

When non-linear complex diffusion is applied to an image, the areas having similar properties will be grouped first (intra region smoothing occur before inter region smoothing, a property of non linear diffusion). The contrast between FCD areas and nonFCD areas will increase in the real plane after complex diffusion. The imaginary part of complex diffusion is almost equal to Laplacian of Gaussian (LOG), in which the borders will be highlighted. When the real part of the complex diffusion is divided with

imaginary part, all the smooth areas in the gray matter will also get enhanced (the areas other than edges), but when this result is weighted with cortical thickness, only the areas affected with FCDs highlighted. This process can be clearly understood from Fig 2. It can also be seen from the Fig 2 that there is a significant increase in the contrast difference

between lesion and non lesion areas in the gray matter.

III. Results

The computer scientists, who were blinded to the MRI findings, identified FCDs in 38 patients of the total 48 patients. This included the ten patients in whom surgery was done and a pathological diagnosis was made. The histopathology was Taylor- ballooncell dysplasia in the majority of patients. Table-1 illustrates the findings in these ten patients. In each patient the neuroradiologists reported the site of the lesion in T1 weighted and FLAIR sequences. There were two patients (patient 3 & 6) in whom the lesion was not visualised in the T1 weighted sequence, but was seen in the FLAIR sequence. In both these patients the lesion was small and subtle in the FLAIR sequence. The FCD area was highlighted after post processing in nine out of the ten surgically proved cases in the same location where the lesion was detected by the neuroradiologist. In three patients (patient 3, 6, 7) more areas were identified by the processing technique. In patient 6, the area identified by the neuroradiologist was not highlighted by the

postprocessing technique. Instead few other areas were highlighted. Since there was no clinical, neuropsychological or video-EEG correlations for the site of seizure onset and the additional areas highlighted by proposed method in the patients, these areas were considered false positives.

Among the rest of thirty eight MRI given to the computer scientists, the lesion was identified in twenty nine and nine were reported as normal. The results are summarised in the Table-2. The neuroradiologists had identified a cortical dysplasia in only twenty five of these 38 MRI. In five of these twenty five patients the neuroradiologists had reported the dysplasia based on a thickened cortex with poor grey – white matter distinction in the T1 weighted image. The FLAIR did not reveal any intralesional or subcortical signal changes. The lesion was detected in the same location by the neuroradiologist and the computer scientists in all the twenty five cases detected by both.

More lesions were shown by the computer scientists in eight patients. This included 4 patients in whom the neuroradiologist had reported a normal MRI and was taken as the controls of the study. After the report from the scientists the MRI images were reviewed by the neuroradiologists. But again these areas were not diagnosed as FCD. Hence these areas were considered to be radiological false positive area. Since these areas were considered as false positive based on the MRI findings and not on pathology, it is likely, though remote, that some of these areas may be truly areas of dysplasia. Except in one patient who was 3 months old, the image processing steps could be done without difficulty. In this infant the white matter myelination was not complete and hence there was difficulty in segmentation. The FCD was large in this patient and the lesion identified by the neuroradiologist corresponded with the lesion identified by the scientist.

IV. Discussion

While many techniques are being developed [5]-[8],[22][23] to enhance FCD lesions from MR images, our paper demonstrates the integration of two Partial Differential Equation (PDE) based methods (Thickness measurement of Jones et.al.) and Complex diffusion) to extract FCD areas. In most of the previous methods [5],[6],[22] thickness map along with gradient techniques are used to compute FCD areas. But byusing complex diffusion both blurring effect and gradient change can be computed in asingle step. Experimental results show that this hybrid mathematical model is a goodcandidate for FCD segmentation (Fig 3). The proposed method produces a mean contrastchange of around 16 times (between FCD areas and nearby tissues) than that of original image. The contrast change is computed by taking the mean intensity difference of the FCD areas and nearby tissues (gray matter) before and after processing. The t test analysis done on the results also shows that increase in contrast was significant (P=0.007).

In the surgically proved cases the proposed technique was correct in highlighting the site of lesion in ninety percent of patients. Most of the previously reported techniques had a detection rate of more than seventy percent [21]-[23]. In the patient in whom the lesion was not seen by proposed technique, there was no significant cortical thickening in the T1 images. However the neuroradiologist could diagnose FCD based on the subcortical FLAIR hyperintensity. This is an important fact because the automated image processing techniques base their detection mainly on T1 cortical thickening and poor greywhite matter distinction. At the same time small Taylor balloon cell cortical dysplasia can present with only subtle cortical hyperintensity in FLAIR and these techniques usually fail in these cases. Non balloon cell dysplasia which are more difficult to diagnose radiologically because of the absence of signal changes are the lesions in which the image processing techniques can help. We feel that the image

processing technique can also help in detecting heterotopic grey matter, another easily missed radiological entity. Studies have to be

missed radiological entity. Studies have to be done to prove this. Detection of cortical dysplasia by this technique can sometimes be difficult in infants especially before the myelination is complete in the T1 weighted images. The segmentation of the grey and white matter, which is one of the steps of this image processing technique, can be difficult as was noted in one of our patients. Though methods have been described for segmentation in the developing brain [27], we have not used this technique in our patient. Although potential false positives were significantly reduced in the complex map they were not completely eliminated. In some patients additional one or two areas were highlighted in the complex map. There is possibility that some false positives may in fact be true lesions of FCD. A review of the routine images and the map by the radiologist will increase the detectability of these lesions. Even though there is a significant reduction in false positives, its presence is still a problem in developing fully automated system for FCD detection. Removal of cerebellum and caudate nucleus in the pre-processing stage can further increase the accuracy of results. Recently some methods have been developed for removing caudate nucleus from MR images, but most of them depends on some atlas [24],[25].

V. Conclusion

Image processing techniques using complex diffusion approach can help detect focalcortical dysplasia. These lesions can be easily missed in the MRI studies done in patients as a work up for epilepsy. This computer aided detection technique can be used to identify the abnormal areas, following which the radiologist can survey all theMRIsequences to diagnose the area which are visually truly positive for the cortical dysplasia and which agrees with the neurophysiology and Positron Emission Tomography (PET). This technique is especially useful in patients in whom the routine MRI appears normal and adds to the diagnostic armamentarium of these patients. Larger studies using this technique with

validation of results are needed to understand the role of this technique in guiding placement of depth electrodes and serving as a complimentary technique to PET, neurophysiology and magnetoencephalography.

Table 1: Report in the surgically proved cases

Pt. No:	Sex	Age	Neuro radiology Report Location		Scientist Report	Histopathology
			T1	FLAIR	*Site	
1.	F	03Y	+	+	A	FCD- b c
2.	M	08Y	+	-	A	FCD
3.	F	18Y	+	+	A & C	FCD- b c
4.	M	25Y	+	+	A	FCD- b c
5.	M	19Y	+	+	A	FCD-bc
6.	F	25Y	-	+	B & C	FCD- b c
7.	F	28Y	+	+	A & C	FCD-bc
8.	M	27Y	+	+	A	FCD- b c
9.	M	06Y	+	+	A	FCD- b c
10.	M	37Y	+	-	A	FCD

*Site: A. corresponds to that identified by neuroradiologist.

B. does not correspond to that identified by neuroradiologist

C. more sites than that identified by neuroradiologist (which may be false positive)

+-seen

-- not seen

FCD - bc focal cortical dysplasia - balloon cell type

FCD Focal cortical dysplasia

Table 2: Summary of results of MRI whose surgery was not performed.

Number of patients: 38	
Neuroradiology report	
Number of patients in whom dysplasia was detected: 25	
Dysplasia detection based on FLAIR image alone: 20	
Dysplasia detection based on T1 weighted & FLAIR image: 25	
Normal MRI: 13	
Scientist Report	
Number of patients in whom dysplasia was detected: 29	
Normal MRI: 9	
Site of lesion detection	
Same as the site of lesion as detected by neuroradiologist: 25	
Additional sites detected: 8	

Figure Legends

Fig 1: (a) Scalp & Cerebellum removed MR Brain image, (b) & (c) are real and imaginary part of (a) after complex diffusion (5 iterations), (d) Gray matter segmented from (a), (e) & (f) are real and

imaginary part of (d) after complex diffusion (15iterations). The contrast difference between lesion and non-lesion areas can be easily identified from (e).

Fig 2: The proposed approach for FCD detection.

Fig 3: Figure shows the original and processed T1 MR Brain images. It can be seen that it is easy to identify the FCD areas from the images after processing it with the proposed approach.

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Fig 1

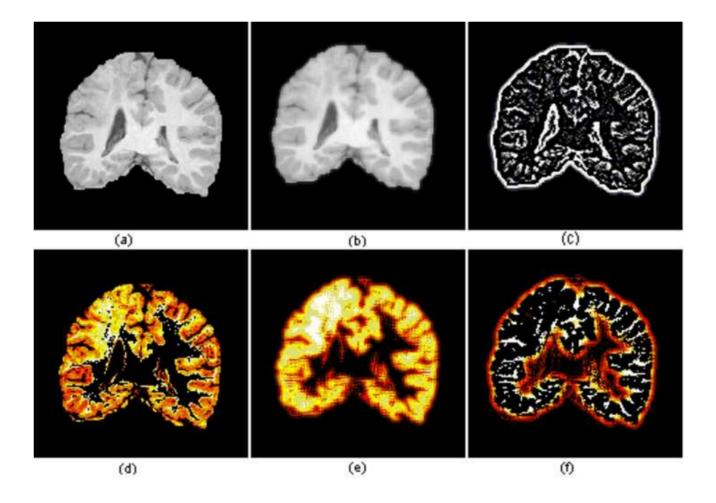


Fig 2

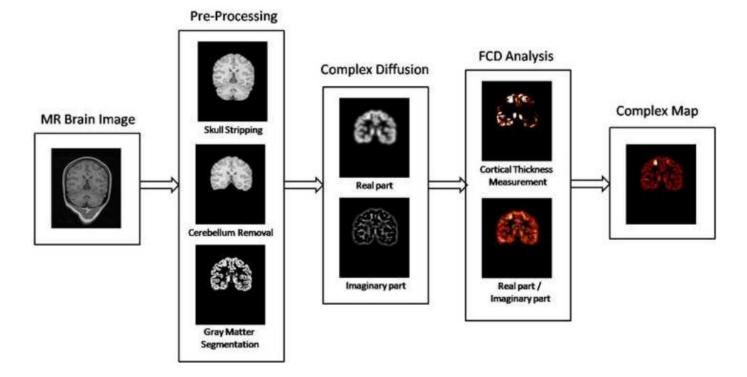
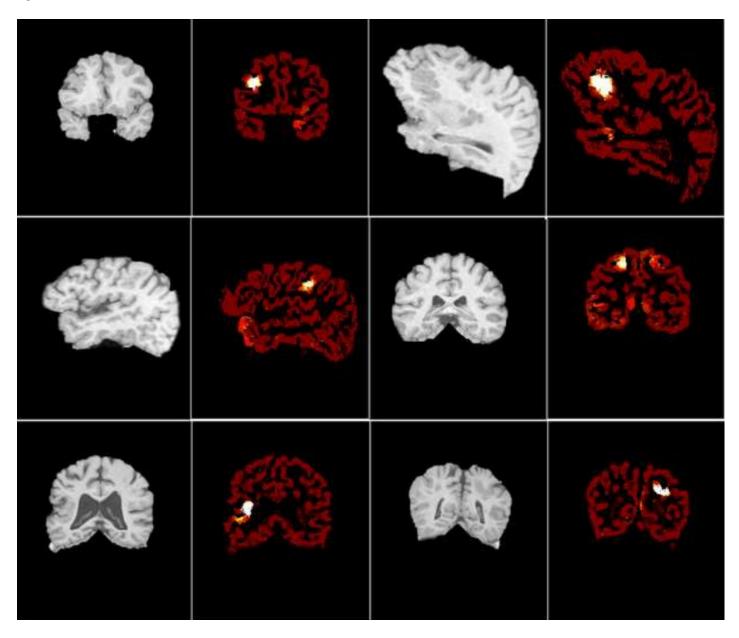


Fig3







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