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A novel liver perfusion analysis method

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Abstract— **In this paper we apply level set segmentation to aid in automating the clinical challenge of measuring the contrast agent concentration in liver perfusion time series. For this, we apply implicit contour methods to time series of two-dimensional MRI images to yield accurate measurements of local image properties located relative to the shape of the liver across all images in the series. Our results show that Level Set Methods can be used to provide the necessary segmentation shape data to reliably measure local image intensities positioned relative to this shape throughout a time series, where the location and shape of the object to be tracked changes.**

Keywords—**Liver perfusion, segmentation, level set methods**

I. Introduction

For certain illnesses related to the liver the blood flow to the liver has to be studied. By injecting a contrast agent into the patients body while taking MRI images in fixed time intervals, the concentration of the contrast agent can be studied while it flows through the patients body. A short time after the injection the contrast agent reaches the liver and the MRI images at that time can reveal important information about the blood supply condition of the liver for that patient. This information can lead to a more accurate diagnosis. The overall procedure is called liver perfusion.

Part of automating the above process can be modeled as a two dimensional registration problem, where the liver is the object of interest that is registered between the images. The more important problem is what to use as input to the registration mechanism. We use the segmented liver shape and now describe previous work on segmentation algorithms for two dimensional MRI images.

An excellent discussion of medical image segmentation algorithms including level set methods is Suri et al. [7] and [8]. The introduction of level set techniques into the field of medical image segmentation is due to Malladi in [2]. Malladi used the curvature and the gradient of the image convolved with a Gaussian as a potential field to guide the evolution of the level set function. Our segmentation approach is based on his work, using a refined speed function. We have not found literature concerning the automation of perfusion measurements by incorporating level set methods for segmentation.

The current method to perform liver perfusion measurements is manual, because the patient breathes throughout the series and the liver moves vertically in a coronal view. As such the position of the blood vessel to be studied has to be marked in every single image to extract a local intensity from which the concentration curve of the contrast agent is deduced. The curve is used for further diagnosis.

In this paper we describe an automated method to locate the perfusion area within the time series of two-dimensional MRI images and present first results of the method applied to perfusion series. We have not found prior methods in the literature specific to liver perfusion measurements. Our method is novel in that it (a) combines segmentation results with a simple and efficient registration scheme specific to liver perfusion, (b) requires no manual interaction after a manual initialization and (c) can deal with small errors in the segmented shape.

II. Review

Now we briefly review the fundamental methods we use, the Fast Marching Method (FMM) and the Narrow band level set method.

A. Fast Marching Method

The Fast Marching Method (FMM) is an algorithm to efficiently solve curve and surface evolution problems. Consider a closed curve that evolves under a fixed-sign normal speed $F(x,y)$ dependent only on the position (x,y) in the computational domain. The curve either expands outward all the time or moves inward all the time and once a point has been crossed by the curve it will never be crossed again. Then, the Eikonal equation can be given as $|\nabla T|F = 1$, where $T(x,y)$ is the arrival time at which the curve or surface crosses the given point (x,y). The Eikonal equation states the relationship that the gradient of arrival time is inversely proportional to the speed of the surface (Malladi & Sethian, 1996). The Fast Marching Method explicitly constructs the solution $T(x,y)$ for all points (x,y) in the domain. The complexity for N points is $O(N \log N)$ and the algorithm generalizes naturally to three or more dimensions. The original paper about the Fast Marching Method is from Sethian and Adalsteinsson [1]. Since then, the Fast Marching Method has been intensively studied, the most detailed study is given by Sethian himself in [6].

B. Narrow band Level set method

The level set method deals with the representation and evolution of closed interfaces, such as curves and surfaces.

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In the level set framework, the interface is embedded into a function of a dimensionality one higher than the original interface. Most often the signed distance function is used as embedding function, where the zero crossings of the function values represent the original interface. This implicit representation has many advantages. For one, geometric properties such as the local curvature κ and the normal vector $\vec{N}$ can be easily determined. Most importantly, the evolution of the curve under the initial value problem $\phi_t + F|\nabla\phi| = 0$, where ϕ is the embedding function, ϕ_t its derivate over time and F is the speed function, can be solved iteratively. The speed function can be dependent on time dependent properties of the interface, such as the local curvature and on external forces not related to the interface.

First introduced by Osher and Sethian in [5], since then it has been extensively used in image processing and medical image segmentation [6, 4]. The full level set method represents the curve on a discrete computational domain by assigning each point (i, j) in the domain a corresponding function value $\phi_{i,j}$. If one is interested only in the evolution and representation of the curve itself as opposed to the entire computational domain, it is enough to define ϕ within only a small boundary around the zero level contour (ZLC). This reduces the computational complexity significantly and is known as the Narrow band Level Set Method.

III. METHODOLOGY

We developed a segmentation process for liver shape segmentation employing three steps. The first step locates a seed point for the segmentation in every image. The second step applies the Fast Marching Method to the original image at the given seed point to yield a first approximation of the liver shape. In the third step, this shape is used to initialize a level set segmentation step, which introduces a curvature reducing term to improve the segmentation results and repair local irregularities in the segmented shape. We now describe the steps in detail.

A. Locating the seed point

The seed point marks the initial curve position in the image. The initial curve is then evolved to segment the shape of the liver. The location of the segmentation seed point is found semi-automatic: for one image, the radiologist manually marks the segmentation seed point, and for all other images it is located using the following robust, but liver-specific method.

In the MRI perfusion series, there are two patterns, (a) the top of the liver shape is well contrasted to the background, and (b) as the patient breathes throughout the series, the liver moves only vertically. Combining these patterns, we construct a simple method to locate the seed point: for every image a gradient magnitude is extracted and slightly mean smoothed inside a vertical strip at the horizontal position of the initial seed point. The maximum gradient magnitude is located in the strip, and a fixed Δy is added to its vertical position. The value of Δy is determined once in the original image, for which we already know the seed point location.

B. Fast Marching Method segmentation step

The FMM segmentation step takes as input all the images and a single seed point for each image. As result, a segmented liver shape is returned as a bitmap, where a positive truth value indicates the pixel belongs to the liver. The FMM algorithm is fairly straightforward and the only flexible part is the definition of the speed function to use and the stopping criteria. The speed function determines the propagation speed in normal direction for any point in the computational domain. The stopping criteria tells us when to stop the segmentation. The speed function we use for the FMM segmentation step is a biased variation of the well known speed function used in [2,3]. We first define

$$F_{base}(x,y) = \frac{1.0}{1.0 + \left|S_k \cdot \nabla\left(G_\sigma * I_{x,y}\right)\right|^{S_p}}$$

which is the interface propagation speed in normal direction based on the gradient magnitude image. The gradient image $\nabla\left(G_\sigma * I_{x,y}\right)$ is the Sobel approximated gradient of the original image I convolved with a Gaussian of width σ. σ, S_k and S_p are constants and we had good results using $\sigma = 3.0$, $S_k = 13.0$ and $S_p = 2.0$ for the series examined. The speed image is generated from F_{base} by using it in the Gaussian-biased speed function F_{FMM}, which is defined

$$F_{FMM}(x,y) = e^{-\frac{(1-F_{base}(x,y))^2}{2\sigma^2}}$$

with σ being the standard deviation. A large value leads to a slow cutoff, while a small value reduces small values to zero. We use a value of $\sigma = 0.3$. Because the FMM cannot incorporate curvature dependent information, a segmentation using the unbiased speed function F_{base} could leak out of the liver shape where the gradient is locally weak. By using a cautious bias or threshold we limit the risk of leaking in exchange for a higher probability to not cover the entire liver shape in the first segmentation step. The stopping criteria for the FMM segmentation is simply a constant of the area size, which corresponds to the number of iterations of the FMM. The value is configurable but we

choose a default of 1500 elements, which yielded good results.

C. Level set segmentation step

The input to the level set evolution step is the first rough FMM segmentation result. In this step we incorporate a regularizing curvature term to smooth the shape, remove holes and refine the segmentation result. The result is the level set signed distance map for the entire computational domain.

We employ a convergent speed function based on the reaction-diffusion equation introduced by Tek and Kimia in [9]. It has both a regularizing diffusion term and a reaction term that attracts the curve to the gradient of the image. By selectively employing a "pushback" force term upon only the reaction term, we are able to stop the curve from crossing strong gradients in the image, except where the term resulting from the regularization condition is stronger. The speed function we use is

$$F_C(x,y,t) = (F_{base}(x,y) - s)\beta_0 - F_{base}(x,y)\beta_1 \kappa_{x,y,t}$$

with $s = 0.3$, $\beta_0 = 0.5$ and $\beta_1 = 0.5$. The diffusion term using the negative curvature, removes any small local irregularities the FMM segmentation has left over, such as sharp corners and single non-shape points within the shape stemming from to noise in the original image. Globally it leads a smoother overall shape. We use a fixed number of evolution time steps of $\Delta t = 0.2$. To improve the results of the FMM segmentation, we found 120 time steps a good value.

D. Perfusion area localization

We now introduce a new method to locate the perfusion area in each image given the segmented liver shape. In this method, the radiologist first marks the perfusion area in one image. Afterwards, this area is automatically located in all remaining images.

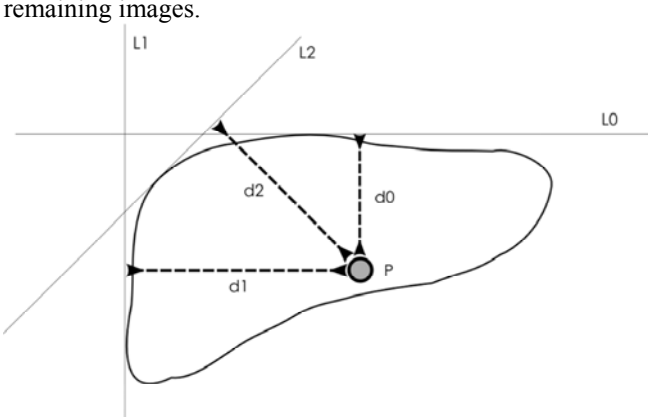

Fig. 1. . A point *P* defined by a three element distance vector *(d0, d1, d2)* relative to the lines L1, L2 and L3.

Consider the point P in figure 1. Assume for now, we know for sure the absolute position of P in the image and that we have a good segmentation result of the liver shape. Then, we define a set of non-parallel lines $L = \{L_0, L_1, \ldots, L_n\}$. For each line L_k we determine the following for the image I : 1. the distance $d(P_{x,y}, L_k, I)$ of every point $P_{x,y}$ within the segmented liver shape to L_k and 2. the shortest distance $d_s(L_k, I)$ among all $d(P_{x,y}, L_k, I)$. Then, any point within the liver in an image I can be represented as a *line relative distance vector*:

$$D_{P_{x,y}}(I) := \begin{pmatrix} d(P_{x,y}, L_0, I) - d_s(L_0, I) \\ \ldots \\ d(P_{x,y}, L_n, I) - d_s(L_n, I) \end{pmatrix}$$

As reference lines we use lines which always have their minimum distance point at the boundary of the shape where the segmentation result is of good quality. For example by using a horizontal line above the liver as distance measurement line, the resulting component in the distance vector will accurately reflect the relative position to the top of the liver because there is a strong gradient response at the top of the liver.

To obtain an absolute coordinate given $D_P(I_p)$ for the initial radiologist-marked image I_p and the segmentation results for all other slices, we determine the position within or nearby the segmented shape that minimizes an error term., which describes how much the distance vector for a point (x_0, y_0) in image I_0 diverges geometrically from the distance vector of the original known perfusion area point (x_p, y_p) in the radiologist-marked image I_p :

$$\varepsilon(x_0, y_0, I_0) := \left| D_{P_{x0,y0}}(I_0) - D_{P_{xp,yp}}(I_p) \right|$$

After the minimizing error point is located, the perfusion area is approximated as a circle area centered around the point. Because the liver shape is deformed only slightly throughout the series and the circle area is invariant to rotation, it is a simple but sufficient approximation. For each image, the resulting perfusion intensity is the mean value of all the MRI intensity values within the circle area. The perfusion intensity values are smoothed over time using a Gaussian with $\sigma = 3.0$.

IV. RESULTS

To evaluate our implementation of the proposed method, we created a new C implementation of the Narrow band level set method and the FMM and a prototype GUI in C#. We evaluate the performance of the proposed method on twelve perfusion series of two-dimensional 256x256 MRI images taken with a GE Medical Systems Genesis Signa system at the Shanghai First People Hospital. They show the patients

abdomen in coronal view. The imaging parameters are the following: slice thickness 15.0, repetition time 4.7, echo time 1.2, magnetic field strength 15000, flip angle 60 degrees. The series consist of 50 to 60 pictures each.

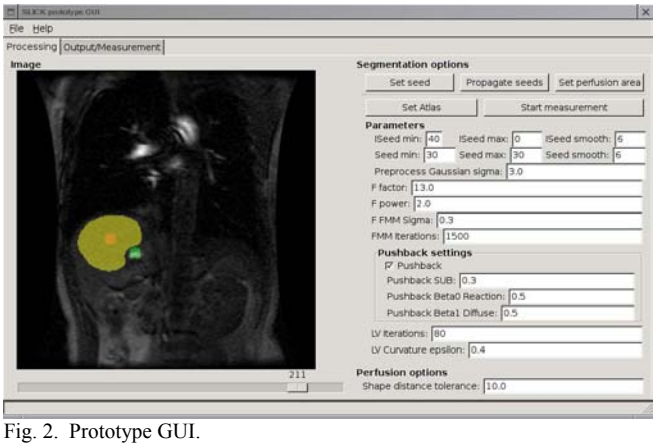

Fig. 2. Prototype GUI.

The evaluation procedure is as follows. In the GUI (figure 2), one particular good image of the series is selected and the seed point and the perfusion area is manually marked. The segmentation and perfusion measurement process is started, producing the intensity curve.

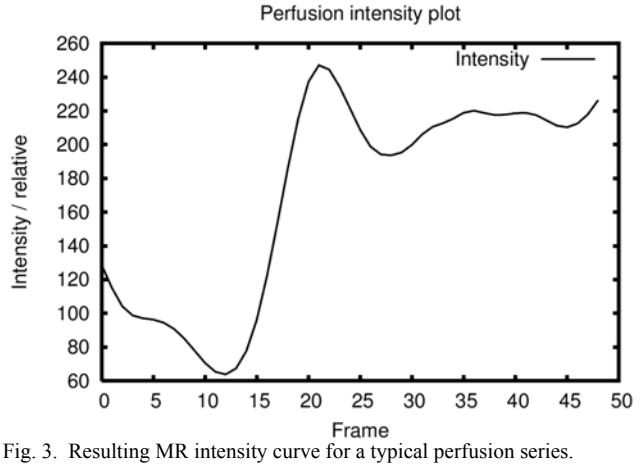

Fig. 3. Resulting MR intensity curve for a typical perfusion series.

The output intensity curve for a typical series is shown in figure 3. Around the 15th image, when the contrast agent reaches the liver, a strong response can be seen clearly.

TABLE I
PERFUSION SERIES ERROR TERMS

Series	Images	Error mean	Error max.	Error std. dev.
1	60	0.94	3.53	0.78
2	60	1.03	3.53	0.71
3	60	3.00	6.00	2.08

In table I we analyze the error terms for three series. Interpreting the error values as the geometric distance from an optimal fit, the low mean error values for all the series indicates a good perfusion area localization success, which is confirmed by manually inspecting the processed images. For the runtime performance evaluation a combined measurement of 240 frames is used. The system is a Pentium-M 1500Mhz, 512Mb RAM system.

TABLE II
RUNTIME PERFORMANCE RESULTS

Step	time	time per image
Locating seed point	44s	0.183s
FMM/LV segmentation	443s	1.845s
Locating perfusion area	23s	0.095s
Total	510s	2.125s

V. CONCLUSION

We proposed and evaluated a combined segmentation and registration method to image intensity curves from positions relative to the liver shape. For this we developed a simple and robust registration method which maps the perfusion area to a minimum error fit coordinate in each image.

The results have been verified for its overall clinical value by radiologists. We confirmed that the combined FMM and Narrow band Level Set Methods based segmentation approach is computationally efficient.

Further research is needed to draw conclusions about the performance of the proposed method in case the segmented objects have a more complex shape or vary considerably across the images in the series, such as the heart.

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