### MRI Techniques for Noninvasive Monitoring of Transplanted Organs José M. F. Moura

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# Outline

- MRI at CMU
- Goals of research:
  - Monitoring transplanted organ function
    - Automatic segmentation
    - Organ function
- Transplanted organs in animal models:
  - Kidneys
  - Heart



# Centers with Bioimaging Interests





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# **NMR Center for Biomedical Research**

- Founded in 1986, NIH funded since 1988
- 1 of 7 NIH NCRR Biomedical Research Resource Centers for NMR MRI/ MRS – now through NBIB
- Only one exclusively devoted to small animal models
- 8400 sq. ft. facility at Mellon Institute
- Jointly administered by CMU/ Pitt
- Director: Prof. Chien Ho (Biological Sc.)
- Renewed September 1<sup>st</sup>/ 2003-August 31<sup>st</sup>/ 2008



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### **NMR Center**

- NMR Center: MRI and MRS instruments
  - 1 Brucker 11.7 T, 8.9 cm vertical bore (microimaging small animal mice, high resolution)
  - 2 Brucker Avance DRX (4.7 T and 7.0 T) MRI/MRS
  - Home-built 2.35 T MRI/MRS
  - Brucker Minispec .47 T NMR Instrument
  - 4 High resolution multinuclear NMR spectrometers (300, 500, 600 MHz)
  - All equipped with gradient capability
- Animal research:
  - Surgical and physiological monitoring equipment (microscopes, pumps, ventilators, electrocautery, gas analyzers, ...)
- Computing and data processing facilities



<b>Goals</b> Scientific Goal	<b>Noninvasive MRI Methodology for Early Detection of Organ Malfunction</b>
	<b>Transplanted</b> organs – early detection of rejection <b>Kidney</b> and <b>heart</b> small animal models
<b>Research Goal</b>	Signal/Image Processing Alg. for <i>Automatic</i> Detection of Organ Malfunction
Task 1:	Automatic organ segmentation
Task 2:	Automatic detection of organ rejection
Cha	llenges: low contrast, clutter, missing edge info



# **Kidneys**





# Block Diagram of Kidney Segmentation Algorithm







### **MRI Data**

USPIO enhanced dynamic MRI: ultra-small superparamagnetic iron oxide

(6 mg Fe/kg body weight )

**Groups of rats** 

- a. Normal BN (n = 5)
- **b.** Normal DA (n = 5)
- c. isograft (n = 4)
- **d.** allograft (n = 6)



Image size: 64×64 Frame number: 128 Imaging time: 43 Sec



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### **Perfusion Signal: Organ Segmentation**



Observation: distinct dynamic features



### **Perfusion Signal: Function Monitoring**



Right (native)
 Left (transplanted)



• MSD: Maximum Signal Decrease

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- t<sub>MSD</sub> : Time of occurrence of MSD
- Wash-in slope



# **Segmentation Algorithm**





# Preprocessing

- Mean:  $\bar{I}(x, y) = \frac{1}{L} \sum_{t=1}^{L} I(x, y, t)$
- Zero mean signal:  $\tilde{I}(x, y, t) = I(x, y, t) \bar{I}(x, y)$
- Average correlation coefficient  $\overline{C}(x, y) = (1/8) \sum_{(p,q) \in A(x,y)} \frac{\sum_{t=1}^{L} \widetilde{I}(x, y, t) \widetilde{I}(p, q, t)}{\sqrt{\sum_{t=1}^{L} \widetilde{I}(x, y, t)^{2}} \sqrt{\sum_{t=1}^{L} \widetilde{I}(p, q, t)^{2}}}$



Second order neighborhood structure





### **Locate the Kidneys**





**MRI** sequence

**Single image:**  $\overline{C}(x, y)$ 

### Kidneys are roughly located: Energy minimization by level set



# **Normal rats: Cortex segmentation**

#### **Energy minimization by level set**

- C: boundary of a set
- $\Omega_{i}$ : inside of curve C
- $\Omega_{o}$ : outside of curve C

**Vector representation** 



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- $\widetilde{\mathbf{I}}(x, y) = \left[\widetilde{I}(x, y, 1), \widetilde{I}(x, y, 2), \dots \widetilde{I}(x, y, L)\right]$
- $\overline{\mathbf{I}}_i$ : average zero mean vector inside curve C
- $\overline{\mathbf{I}}_{o}$ : average zero mean vector outside curve C



### **Energy Minimization: Cortex**

• Energy functional  $E(C) = \mu \cdot Length(C)$  $+ \lambda_{1} \int dis^{2} (\tilde{\mathbf{I}}(\mathbf{x}, \mathbf{y}), \bar{\mathbf{I}}_{i}) dx dy$ Integral over space  $+ \lambda_{2} \int dis^{2} (\tilde{\mathbf{I}}(\mathbf{x}, \mathbf{y}), \bar{\mathbf{I}}_{o}) dx dy$ Integral over time sequence dis<sup>2</sup>( $\mathbf{\widetilde{I}}(x_1, y_1), \mathbf{\widetilde{I}}(x_2, y_2)$ ) = sin<sup>2</sup> $\frac{\theta}{2} = \frac{1 - \cos \theta}{2}$  $\cos\theta = \frac{\sum_{t=1}^{L} \widetilde{I}(x_{1}, y_{1}, t) \widetilde{I}(x_{2}, y_{2}, t)}{\sqrt{\sum_{t=1}^{L} \widetilde{I}(x_{1}, y_{1}, t)^{2}} \sqrt{\sum_{t=1}^{L} \widetilde{I}(x_{2}, y_{2}, t)^{2}}}$ 



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 $\mathbf{\tilde{I}}(x_2, y_2)$  $\theta$  $\mathbf{\widetilde{I}}(x_1, y_1)$ 

Level set method to minimize energy functional



### **Transplanted Kidneys**

**Energy minimization by region growing** 

 $R_p$ : *p*th region;  $N_{\text{Re}g}$ : total number of regions

 $N_p$ : total number of pixels in *p*th region



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$$\bar{I}^{p}(t) = \frac{1}{N_{p}} \sum_{(x,y)\in R_{p}} I(x,y,t); \quad \bar{\mathbf{I}}^{p} = \left[\bar{I}^{p}(1), \bar{I}^{p}(2), \cdots, \bar{I}^{p}(L)\right]: \text{ average signal}$$

c(p,q): correlation coefficient between two neighboring regions

$$= c(\bar{\mathbf{I}}^{p}, \bar{\mathbf{I}}^{q}) = \frac{\sum_{t=1}^{L} \left[\bar{I}^{p}(t) - \frac{1}{L} \sum_{t=1}^{L} \bar{I}^{p}(t)\right] \left[\bar{I}^{q}(t) - \frac{1}{L} \sum_{t=1}^{L} \bar{I}^{q}(t)\right]}{\sqrt{\sum_{t=1}^{L} \left[\bar{I}^{p}(t) - \frac{1}{L} \sum_{t=1}^{L} \bar{I}^{p}(t)\right]^{2}} \sqrt{\sum_{t=1}^{L} \left[\bar{I}^{q}(t) - \frac{1}{L} \sum_{t=1}^{L} \bar{I}^{q}(t)\right]^{2}}}$$

 $\alpha$ : threshold to stop merging



# **Region-growing**

- 1. For each region, find the average perfusion signal  $\overline{\mathbf{I}}^{p}$ ,  $p = 1, 2, ..., N_{\text{Re}g}$
- 2. For each pair of neighboring regions, calculate c(p,q) between  $\overline{\mathbf{I}}^{p}$  and  $\overline{\mathbf{I}}^{q}$



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- 3. Merge  $R_{p^*}$  with  $R_{q^*}$  s.t.  $(p^*, q^*)$  maximizes c(p, q)
- 4. Update the average temporal sequence

$$\overline{\mathbf{I}}^{p^*} = \frac{N_p}{N_p + N_q} \overline{\mathbf{I}}^p + \frac{N_q}{N_p + N_q} \overline{\mathbf{I}}^q$$

5. Continue merging until  $\max c(p,q) < \alpha$ 



Second order neighborhood structure



### **Experimental Results**

MR instrument: 4.7-T Bruker AVANCE DRX TR = 3.45ms; TE = 2.1ms Data matrix size =  $64 \times 38$ USPIO: ultra-small superparamagnetic iron oxide Dose: 6 mg Fe/kg body weight

#### Four groups of rats

- a. Normal BN (n = 5)
- b. Normal DA (n = 5)
- c. Isograft BN $\rightarrow$ BN (n = 4)
- d. Allograft DA $\rightarrow$ BN (n = 6)



Image size: 64×64 Image number: 128 Imaging time: 43 Sec



### Normal rats: No transplantation







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### Task1: Automatic Kidney Segmentation Renal Perfusion Signal





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### **Task2: Monitoring Organ Function (Kidney)**



#### •Measure of dissimilarity: subspace distance

•Fit a parametric model (AR) to perfusion signal
•Determine (oscillatory) modes of perfusion signal
•Geometric distance between modes of transplanted and native kidneys



Subspace distance: 6 allograft & 4 isograft rats.



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# Movement Correction and Noise Reduction



Observed

Motion-free & Noiseless



# **Problem Formulation**

Given the observed image sequence g(i, j, t), find the image sequence f(i, j, t) that minimizes

$$E = \underbrace{\left\|g - Hf\right\|^{2}}_{\text{Motion correction}} + \underbrace{\alpha \left\|\nabla_{t}f\right\|_{W}^{2} + \beta \left\|\nabla_{tt}f\right\|_{W}^{2}}_{\text{Weighted temporal smoothness constraints}}$$

Assume the variance of the background noise is  $\sigma^2$ 

$$w(i, j, t) = \exp(1/2)\exp\left(-\frac{p(i, j, t)}{2\sigma^2}\right) \qquad \text{Selectively Smooth}$$
$$p(i, j, t) = \frac{1}{2m+1} \sum_{k=-m}^{m} (g(i, j, t+k) - \overline{g}(i, j, t))^2 \qquad \overline{g}(i, j, t) = \frac{1}{2m+1} \sum_{k=-m}^{m} g(i, j, t+k)$$



# Motion Model

Assumptions:

- 1. Breathing motion is vertical (head-to-feet) within 1 pixel
- 2. Motion of pixels along the same horizontal line are identical





# Motion Model (cont'd)

#### Model non-rigidity:

$$\forall j, \quad g(i,j,t) = \frac{1+d_t}{2} \lambda_{it} f(i-1,j,t) + (1-\lambda_{it}) f(i,j,t) + \frac{1-d_t}{2} \lambda_{it} f(i+1,j,t) + n(i,j,t)$$



 $\begin{cases} d_t = +1, & \text{head} \to \text{feet} \\ d_t = -1, & \text{head} \leftarrow \text{feet} \end{cases}$ 

$$\lambda_{it} = r^{(i-1)}\lambda_t, \quad 0 \le \lambda_t \le 1$$



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# Energy Minimization: matrix-vector form

 $E = (\mathbf{g} - \mathbf{H}\mathbf{f})^{\mathrm{T}} \boldsymbol{\Sigma}^{-1} (\mathbf{g} - \mathbf{H}\mathbf{f}) + \boldsymbol{\alpha} (\mathbf{D}_{1}\mathbf{f})^{\mathrm{T}} \mathbf{W} (\mathbf{D}_{1}\mathbf{f}) + \boldsymbol{\beta} (\mathbf{D}_{2}\mathbf{f})^{\mathrm{T}} \mathbf{W} (\mathbf{D}_{2}\mathbf{f})$ 

Keeping H fixed,

$$\mathbf{f}^* = \left[\mathbf{H}^{\mathrm{T}} \mathbf{\Sigma}^{-1} \mathbf{H} + \alpha \left(\mathbf{D}_1^{\mathrm{T}} \mathbf{W} \mathbf{D}\right)_1 + \beta \left(\mathbf{D}_2^{\mathrm{T}} \mathbf{W} \mathbf{D}\right)_2\right]^{-1} \mathbf{H}^{\mathrm{T}} \mathbf{\Sigma}^{-1} \mathbf{g}$$
  
Avoid inversion of a  $\left(N_i \times N_j \times N_t\right)^2$  matrix

Minimize two energy functions iteratively

$$E_1 = (\mathbf{\tilde{g}} - \mathbf{f})^{\mathrm{T}} \mathbf{\Sigma}^{-1} (\mathbf{\tilde{g}} - \mathbf{f}) + \alpha (\mathbf{D}_1 \mathbf{f})^{\mathrm{T}} \mathbf{W} (\mathbf{D}_1 \mathbf{f}) + \beta (\mathbf{D}_2 \mathbf{f})^{\mathrm{T}} \mathbf{W} (\mathbf{D}_2 \mathbf{f})$$
$$E_2 = (\mathbf{g} - \mathbf{H} \mathbf{f})^{\mathrm{T}} \mathbf{\Sigma}^{-1} (\mathbf{g} - \mathbf{H} \mathbf{f}), \quad \mathbf{\tilde{g}} = \mathbf{H}^{\mathrm{T}} \mathbf{g}$$



# Results

 $\alpha = 1, \beta = 2$ 





# Results (isograft)



Observed (g)

Recovered (f)



# Results (allograft)



Observed (g)

Recovered (f)



### Heart

- Heart segmentation
- Heart structures segmentation
- Motion tracking
- Data:
  - Untagged
  - Tagged



#### **Untagged Data: Active Contour Methods**

- Kass, Witkin & Terzopoulos: classical snakes, edge-based
- Cohen: balloon snake, edge-based + constant force
- Xu & Prince: snake edge-based +new potential force field, Gradient Vector Field, (GVF)
- Malladi, Sethian & Vemuri method: edge-based + constant force
- Chan & Vese method: region-based + piecewise constant model

#### **Problems with existing methods**

- Edge-based: only local information, sensitive to initial condition
- Initial contour must reside close enough to true boundary of the object, or contour will not move if no edge information is present, contour may be trapped at spurious edge points
- Adding an external constant force causes leakage where edge of the object boundary is weaker than added constant force
- Piece-wise constant model fails when the image has low contrast



#### **Automatic Heart Segmentation: Results Current Methods**

#### **Gradient Vector Field (Xu & Prince)**



Initial contour not close enough to desired left ventricular endocardium, contour converges to undesired boundary

Chest wall not segmented

#### **Chan & Vese Energy Minimization**

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Papillary muscles not segmented

**Problems:** low contrast, lack edge information, no prior on shape



### **Energy Minimization: Stochastic Active Contour**

- Stochastic model: Works with low contrast, segments chest wall
- **Region-based + Edge-based:** robust to contour's initial condition
- Prior knowledge about shape of heart: papillary muscle problem



**Minimization solution: PDE contour evolution & level sets** 

- Provides smooth and closed boundary
- Deformable: segments various anatomy parts
- High potential for tracking motion of heart



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#### **Region-based forces: Contour not trapped at spurious edge points**

Region Force:  $\lambda_1 = 3$  Ellipse force  $\lambda_2 = 0.50037$  All forces conbined



Region Force:  $\lambda_1 = 1$ 



Edge Force:  $\lambda_3 = 1$ 





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Ellipse force  $\lambda_2 = 0.010121_{All forces}$  conbined



Region-based forces: Contour keeps moving although edge information missing Electrical & Computer ENGINEERING

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# Region-based forces and edge-based forces: Balance keeps contour stationary at object boundary.







### **Automatic Heart Segmentation**





Contours tracked using Stochastic Active Contour Scheme





Contours tracked manually



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Contours tracked using Stochastic Active Contour Scheme



How good is automatic segmentation?



#### **Similarity Between Reference and Segmented Contours**

(Modified Chanfer) 
$$\sum_{(x,y)} S(x, y) \cdot \Gamma_r(x, y)$$
  
 $s(E_r, E_c) = \frac{(x,y)}{\sum_{(x,y)} S(x, y)}$   
Edge Similarity  
LV  
 $s(A,B) = \frac{2*n(A \cap B)}{n(A)+n(B)}$   
Area Similarity

0.6519 0 0.5103 0.47960.63710.586 0 0 0.9182 0 0.70750.8971 0.9331 0.6844 0 0 0.62860.61980.66900.69940.67410.72360.60700.518 0.93840.91450.92120.91830.89690.96320.90980.8601 0.52250.6857 0.6650 0.6529 0.6760 0.6591 0.6520 0.614 0.86070.92980.93910.86600.95470.91490.90130.8820.66180.49430.58450.58040.54650.68550.58780.578 0.94120.73910.84510.77440.85260.93580.8875 0.919  $0.6570\,0.54700.6428\,0.68310.63300.71410.49180.640$ 0.94230.85250.85410.90260.90520.95340.86120.928 0.58260.61360.69480.62820.71910.6210 0 0.423 0.89170.86780.94180.83280.93540.8462 0 0.7760

[0.6303 0.3480 0.6519 0.6131 0.6268 0.6047 0.6309 0.606₄ [0.8395 0.6414 0.8452 0.7297 0.8802 0.7987 0.8974 0.826† 0.63800.6199 0 0.2057 0.3030 0.5901 0.6262 0.606¢ 0.89270.8328 0 0.2820 0.3492 0.8953 0.9070 0.902 0.61360.47660.57570.56700.55860.67710.64750.587 0.8598 0.6315 0.8275 0.7955 0.7823 0.9182 0.9235 0.860 0.59250.32390.5202 0.3228 0.5477 0.6806 0.5583 0.636 0.81340.64700.56460.66910.84700.92730.83570.9070.65500.57130.51420.6326 0.44310.6500 0.5985 0.6490 0.90560.74520.74280.81850.79010.92620.86930.90030.5623 0.6041 0.5644 0.5378 0.4748 0.5754 0.6383 0  $0.8172\, 0.8047\, 0.6539\, 0.6988\, 0.7938\, 0.8888\, 0.9282$ 



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### Comparison

#### Contour tracked by our Active Contour scheme





# Contour tracked manually



Edge Similarity = 0.6500 Area Similarity = 0.9262

# Tagline Detection: tag centers

- Three types of tag centers:
  - Vertical taglines, horizontal taglines, and crossings of both taglines
  - Each type of tag centers is associated with a model







# Heart Segmentation

• Tagged Data



# **Key Observations**

- Tagline prediction
  - Predict initial tag positions based on motion between two previous frames

$$F_{i-1} \qquad F_i \qquad F_i \qquad F_{i+1}$$

- Motion of the taglines: sparse
  - Model movement and then construct dense displacement field



#### **Tagged Data: Heterotropic Heart Transplantation**

#### Isograft No Rejection



#### Allograft With Rejection



<u>Goal</u>: by monitoring the *motion* of every pixel in the heart, monitor the *function* of the heart

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<u>Challenge</u>: detect motion of every pixel in myocardium

### Heart Motion Detection

- Estimate dense motion of the heart from first detecting motion of taglines
- Expand motion of taglines to motion of every myocardial pixel.
- Many existing techniques:
  - Single tagline detection: nothing to prevent two taglines from occupying same physical position
  - Valuable correlations between adjacent taglines are ignored

### Data

- Transplanted rats with heterotropic working heart.
- Cardiac tagging achieved by a modified DANTE sequence.
- MRI scans were performed on a Bruker AVANCE DRX 4.7-T system.
- 8 to 12 frames per cardiac cycle.
- The size of each matrix is 256×256 pixels.

# Our Methodology

• Simultaneous detection of all tag lines: Energy \_\_\_\_\_ minimization

• Taglines motion (displacement) field

• Motion of myocardial pixels: dense motion field







# **Task2: Tagline Detection**

For each frame in cardiac cycle from diastole to systole:





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 $I_{v}$ 

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 $I_{H}$ 



 $I_{C}$ 

# **Tagline Detection: energy functional**

For the pixel (x,y) on a mesh, the energy functional is:





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### Tagline Detection: distance metrics





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$$\mathbf{I}_{V}(x, y) = \left[I(x, y-3), \dots, I(x, y), \dots, I(x, y+3)\right]^{T}$$
$$\operatorname{dis}(\mathbf{I}_{V}(x, y), \mathbf{I}_{V}^{T}) = \sin\frac{\theta}{2} = \sqrt{\frac{1-\cos\theta}{2}}$$



# Tagline Detection: internal energy

- Energy functional:  $E(\lbrace x_{ij}, y_{ij} \rbrace) = \sum_{(i,j)\in V} [\alpha_V E_{Vint}(x_{ij}, y_{ij}) + \beta_V D_V(x_{ij}, y_{ij})] + \sum_{\substack{(i,j)\in H}} [\alpha_H E_{Hint}(x_{ij}, y_{ij}) + \beta_H D_H(x_{ij}, y_{ij})] + \sum_{\substack{(i,j)\in C}} [\alpha_C E_{Cint}(x_{ij}, y_{ij}) + \beta_C D_C(x_{ij}, y_{ij})]$
- Control the smoothness of taglines A B C D



# Left Ventricle Tagline Detection



End of diastole

End of systole



### Dense Displacement Field Estimation

 The displacement field of the myocardial pixels is estimated based on the displacement field of the taglines.



• An affine model, **A**(*x*,*y*), is used to describe the motion of the myocardium locally.



# Affine Transform

• Determine the affine transform



• Predict the coordinates of the pixel in the next frame by  $\begin{bmatrix} x' \\ y' \end{bmatrix} = \mathbf{A}(x,y) \begin{bmatrix} x \\ y \\ 1 \end{bmatrix}$ 



### Dense Motion Estimation









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Tagline motion field Displacement field

Pixel affine motion model Dense motion field



#### Conclusions • Heart:

- Automatic segmentation: Untagged MRI
  - Energy minimization stochastic active contour method segments heart and its structures
- Motion detection: Tagged MRI
  - Energy minimization detects simultaneously *all* taglines.
  - Affine method estimates motion of *all* the myocardial pixels: dense motion estimate
- Kidney:
  - perfusion signal (automatic segmentation and organ monitoring)
- Future work:
  - monitor heart function by monitoring heart motion
  - 3D: heart and kidney



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