Intraoperative Registration of Pathology for Adjuvant Postoperative Radiotherapy

Project 4. Seminar Presentation
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Project Overview

- Problem: Radiation oncologists over-estimate region for post-operative radiotherapy
- Need: A way to track and analyze tissue deformation after tumor excision
- Solution: Intra-operatively add marks around pathology to pre-operative CT; register pre-operative CT to post-operative CT
B. B. Avants, C. L. Epstein, M. Grossman, and J. C. Gee,

“Symmetric Diffeomorphic Image Registration with Cross-Correlation: Evaluating Automated Labeling of Elderly and Neurodegerative Brain,”

Definitions 1

- **Diffeomorphism** – 1) invertible function, 2) maps one manifold to another, 3) is smooth and has a smooth inverse
- **Manifold** – a topological space; resembles Euclidean space near each point
- **Cross-correlation** – measure of the similarity of two waveforms as a function of a time-lag that is applied to one of the waveforms
- **Euler-Lagrange equations** – for finding stationary solutions/optimizations
- **Geodesic** – shortest path between elements in a space
Definitions 2

- **Dice statistic** – overlap ratio; measures difference in size and location between two segmentations
- **Pearson correlation** – measure of linear correlation (dependence) between two variables
- **Gradient descent** – optimization algorithm to find min by taking steps proportional to negative gradient of function at current point
- **FTD** – frontotemporal dementia, a neurodegenerative disorder
- **Sulcus** – depression in the surface of the brain
Introduction

• Purpose: Propose a new deformable registration method; compare to other methods using brain MRI data
• Novel symmetric image normalization (SyN) method
• Goals: Maximize cross correlation within space of diffeomorphic maps, provide necessary Euler-Lagrange equations
• Compare SyN to elastic method and ITK (Insight ToolKit) implementation of Thirion’s Demons method
Registration Methods: Demons

- Uses an approximate elastic regularizer to solve an optical flow problem
- One image is “fixed” and the other “moves” by bringing its level sets into correspondence with the fixed image
- Agreement between Demons labeling and manual labeling of images has been shown\(^1\)
Registration Methods: Symmetric Diffeomorphisms

- Constraints: $\text{Diff}_0$ with homeogenous BC’s; symmetric; invertible
- Advantages they afford: genuine symmetry; same path; sub-pixel accurate invertible transformations in discrete domain
- Assumptions: $x$ indicates identity position in image I and $z$ indexes identity position of same anatomy in image J; diffeomorphism maps homologous anatomy
Registration Methods: Symmetric Diffeomorphisms

Source: Avants et al.
Registration Methods: Symmetric Diffeomorphisms

- Obtaining deformation grids:
  \[
  \phi(x,1) = \phi(x,0) + \int_0^1 \nu(\phi(x,t),t) dt
  \]
  \[
  D(\phi(x,0),\phi(x,1)) = \int_0^1 \|\nu(x,t)\|_L dt
  \]

- Relationship between evolutions along diffeomorphism:
  \[
  \phi_1(x,1)I = J,
  \]
  \[
  \phi_2^{-1}(\phi_1(x,t),1-t)I = J,
  \]
  \[
  \phi_2(\phi_2^{-1}(\phi_1(x,t),1-t),1-t)I = \phi_2(z,(1-t)J,
  \]
  \[
  \phi_1(x,t)I = \phi_2(z,1-t)J,
  \]
Registration Methods: Symmetric Diffeomorphisms

- From last slide, similarity term:
  \[ |\varphi_1(x, t)I - \varphi_2(z, 1 - t)J|^2 \]

- Optimization problem:

\[
E_{\text{sym}}(I,J) = \inf_{\varphi_1} \inf_{\varphi_2} \int_{t=0}^{0.5} \left\{ \|u_1(x,t)\|_L^2 + \|u_2(x,t)\|_L^2 \right\} dt + \int_{\Omega} \left| I(\varphi_1(0.5)) - J(\varphi_2(0.5)) \right|^2 d\Omega.
\]
Subject to each \( \varphi_i \in \text{Diff}_0 \) the solution of:

\[
d\varphi_i(x,t)/dt = v_i(\varphi_i(x,t), t) \]

with \( \varphi_i(x,0) = \text{Id} \) and \( \varphi_i^{-1}(\varphi_i) = \text{Id}, \varphi_i(\varphi_i^{-1}) = \text{Id} \).
Registration Methods: Cross Correlation w. SyN

- Going further – using symmetric diffeomorphism to find spatiotemporal mapping that maximizes cross correlation
- Elastic method: similarities and differences
- Cross correlation (CC): adaptive to intensity; simple inputs; robust to unpredictable illumination, reflectance
- CC term:

\[ CC(\bar{I}, \bar{J}, x) = \frac{\langle \bar{I}, \bar{J} \rangle^2}{\langle \bar{I} \rangle \langle \bar{J} \rangle} = A^2 / BC, \]
Registration Methods: Cross Correlation w. SyN

- Optimization problem:

\[ E_{cc}(\bar{I}, \bar{J}) = \inf_{\phi_1} \inf_{\phi_2} \int_0^{\frac{1}{2}} \left\{ ||v_1(x,t)||^2_L + ||v_2(x,t)||^2_L \right\} dt + \int_\Omega CC(\bar{I}, \bar{J}, x) d\Omega. \]

Subject to each \( \phi_i \in Diff_0 \) the solution of:

\[ \frac{d\phi_i(x,t)}{dt} = v_i(\phi_i(x,t), t) \]

with \( \phi_i(x,0) = Id \) and \( \phi_i^{-1}(\phi_i) = Id, \phi_i(\phi_i^{-1}) = Id. \)
Registration Methods: Cross Correlation w. SyN

- Euler-Lagrange Equations:

\[
\nabla_{\phi_1(x,0.5)} E_{cc}(x) = 2L_1(x,0.5) + \frac{2A}{BC} (J(x) - \frac{A}{B} \bar{I}(x)) |D\phi_1| \nabla \bar{I}(x),
\]

\[
\nabla_{\phi_2(x,0.5)} E_{cc}(x) = 2L_2(x,0.5) + \frac{2A}{BC} (\bar{I}(x) - \frac{A}{C} \bar{J}(x)) |D\phi_2| \nabla \bar{J}(x).
\]

- Algorithm 1: Allows rapid computation of E.L. equations

1. Deform \( I \) by \( \phi_1(0.5) \) and \( J \) by \( \phi_2(0.5) \).
2. Calculate \( \bar{I} \) and \( \bar{J} \) from the result of step (1).
3. Calculate and store images representing \( A, B \) and \( C \).
Registration Methods: Cross Correlation w. SyN

- LPF method used to check that spatiotemporal maps satisfy ODE and invertibility constraints
- Algorithm 2:
  1. while $||\psi^{-1}(\varphi(x)) - x||_\infty > \varepsilon^2 r$ do
  2. Compute $v^{-1}(x) = \psi^{-1}(\varphi(x)) - x$.
  3. Find scalar $\gamma$ such that $||v^{-1}||_\infty = 0.5r$.
  4. Integrate $\psi^{-1}$ s.t. $\psi^{-1}(\tilde{y}, t)^+ = \gamma v^{-1}(\psi^{-1}(\tilde{y}, t))$.
  5. end while
Registration Methods: Cross Correlation w. SyN

- Algorithm 3: Overview of SyN method with CC
  1. Initialize $\varphi_1 = \mathbf{1}d = \varphi_1^{-1}$ and $\varphi_2 = \mathbf{1}d = \varphi_2^{-1}$.
  2. Repeat the following steps until convergence:
  3. Compute the CC as described in Algorithm 1.
  4. Compute each $\nu_i$ by smoothing the result of step (3) in this table.
  5. Update each $\varphi_i$ by $\nu_i$ through the ODE described by
     $\phi(x,t+\Delta t) \leftarrow \phi(x,t)+\Delta t \nu(\phi(x,t),t)$.
  6. Use Algorithm 2 to get the inverses of the $\varphi_i$.
  7. Generate the time 1 solutions from $\phi_1(1)=\phi_2^{-1}(\phi_1(x,0.5),0.5)$
     and $\phi_1^{-1}(1)=\phi_2(1)=\phi_1^{-1}(\phi_2(x,0.5),0.5)$.
Implementation in ITK and Testing

- Same ITK code base used by Demons; different similarity metric and transformation model
- Test cross correlation effectiveness by evaluating Demons vs Elastic
- Test SyN’s transformation model effectiveness by evaluating difference between
Data and Experiments

• 20 T1 MRI images, 10 elderly brains and 10 with FTD
• Template brain with labels of cortex, hippocampus, amygdala, cerebellum
• 60 deformable registrations: 1 per image per method
• Evaluation: Dice overlap ratios between automatic and manual (gold standard) structural segmentations
• Ratio of running times: Demons 1, elastic CC 4.2, SyN 5.5
Results and Discussion

Source: Avants et al.
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Results and Discussion

<table>
<thead>
<tr>
<th>Structure</th>
<th>Demons</th>
<th>Elastic XCor &gt; Demons</th>
<th>SyN XCor &gt; Elastic</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>temporal</em></td>
<td>Mean+Sigma: 0.76 +/- 0.021</td>
<td>0.81 +/- 0.02</td>
<td>0.84 +/- 0.019</td>
</tr>
<tr>
<td></td>
<td>Min - Max: [0.69-0.79]</td>
<td>[0.76-0.84]</td>
<td>[0.79-0.87]</td>
</tr>
<tr>
<td></td>
<td>Significance:</td>
<td>p&lt; 0.0001</td>
<td>p&lt; 0.0001</td>
</tr>
<tr>
<td><em>parietal</em></td>
<td>0.69 +/- 0.034</td>
<td>0.74 +/- 0.03</td>
<td>0.78 +/- 0.027</td>
</tr>
<tr>
<td></td>
<td>[0.62-0.73]</td>
<td>[0.68-0.79]</td>
<td>[0.70-0.83]</td>
</tr>
<tr>
<td></td>
<td>Significance:</td>
<td>p&lt; 0.0001</td>
<td>p&lt; 0.0001</td>
</tr>
<tr>
<td><em>occipital</em></td>
<td>0.78 +/- 0.030</td>
<td>0.79 +/- 0.024</td>
<td>0.83 +/- 0.022</td>
</tr>
<tr>
<td></td>
<td>[0.72-0.82]</td>
<td>[0.73-0.84]</td>
<td>[0.78-0.87]</td>
</tr>
<tr>
<td></td>
<td>Significance:</td>
<td>p &lt; 0.011</td>
<td>p&lt; 0.0001</td>
</tr>
<tr>
<td><em>hippocampus</em></td>
<td>0.62 +/- 0.070</td>
<td>0.72 +/- 0.036</td>
<td>0.72 +/- 0.038</td>
</tr>
<tr>
<td></td>
<td>[0.48-0.73]</td>
<td>[0.65-0.77]</td>
<td>[0.63-0.79]</td>
</tr>
<tr>
<td></td>
<td>Significance:</td>
<td>p&lt; 0.0001</td>
<td>p&lt;0.7</td>
</tr>
</tbody>
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## Results and Discussion

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<th>SyN XCor &gt; Elastic</th>
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</thead>
<tbody>
<tr>
<td>frontal</td>
<td>0.74 ± 0.026</td>
<td>0.81 ± 0.026</td>
<td>0.85 ± 0.024</td>
</tr>
<tr>
<td></td>
<td>[0.65-0.77]</td>
<td>[0.73-0.84]</td>
<td>[0.79-0.88]</td>
</tr>
<tr>
<td></td>
<td>p&lt; 0.0001</td>
<td>p&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>cerebellum</td>
<td>0.89 ± 0.012</td>
<td>0.89 ± 0.011</td>
<td>0.92 ± 0.011</td>
</tr>
<tr>
<td></td>
<td>[0.87-0.92]</td>
<td>[0.88-0.92]</td>
<td>[0.91-0.93]</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.2</td>
<td>p&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>amygdala</td>
<td>0.59 ± 0.053</td>
<td>0.73 ± 0.065</td>
<td>0.74 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>[0.5-0.68]</td>
<td>[0.59-0.81]</td>
<td>[0.63-0.81]</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt; 0.24</td>
<td></td>
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</tbody>
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Source: Avants et al.
Results and Discussion

- More exact comparison of volume measurements between registration and manual expert (gold standard)
- Sum voxel volumes assigned to each structure
- Only temporal, frontal, and parietal lobes because of differences between elderly and FTD brains
Results and Discussion

• Table 1: Pearson correlations between manual and algorithmic volume measures

<table>
<thead>
<tr>
<th>Structure</th>
<th>Corr(Man, Syn)</th>
<th>Corr(Man, Elas)</th>
<th>Corr(Man, Demon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal</td>
<td>0.86</td>
<td>0.69</td>
<td>0.79</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.89</td>
<td>0.67</td>
<td>0.71</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.71</td>
<td>0.42</td>
<td>0.66</td>
</tr>
</tbody>
</table>

• Table 2: Absolute volume error between manual and algorithmic volume measures

<table>
<thead>
<tr>
<th>Structure</th>
<th>VolErr(Man, Syn)</th>
<th>VolErr(Man, Elas)</th>
<th>VolErr(Man, Demon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal</td>
<td>8.4</td>
<td>9.2</td>
<td>8.7</td>
</tr>
<tr>
<td>Frontal</td>
<td>11.1</td>
<td>16.1</td>
<td>15.8</td>
</tr>
<tr>
<td>Parietal</td>
<td>7.9</td>
<td>9.3</td>
<td>7.9</td>
</tr>
</tbody>
</table>
Results and Discussion

Other results:

• No significant difference between minimum Jacobian of SyN vs Elastic CC
• No significant difference in volumes between FTD and elderly individuals
• Automated methods tend to overestimate volumes
• Though SyN outperforms other methods, still not able to claim accurate reproduction of manual labeling
Criticisms/Application to Project

- Dice statistic threshold is arbitrary
- SyN method not as quick/efficient as authors portray
- Will work well with CT to CT registration
- Maybe fixed post-op image and moving pre-op image more useful
- Volume overestimation better case than underestimation
- Good first step as registration algorithms improve
References

Dice statistic

\[ S(R_1, R_2) = \frac{2\#(R_1 \cap R_2)}{\#(R_1) + \#(R_2)}, \]