EMBO Practical Course on Light Sheet Microscopy

Registration Techniques

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Motivation

Registration, that you have seen so far (in Stephans talk this morning)

- All images taken from the same individual
- Feature-based registration using point-to-point correspondences (bead or nuclei positions)
- Rigid/Affine transformation

What I will show

- Images from different individuals
- Mainly intensity-based registration
- Elastic transformation
Elastic Registration
Map Patterns from Many Individuals to a Common Atlas

Virtual Colocalization Studies
Manual Segmentation of Reference Brain
Automated Anatomical Assignment

Z 270

Z164

- dlx6a/6a:GFP
- emx3:YFP
- foxd3:GFP
- hb9:GFP
- hcrt:EGFP
- isl1:GFP
- nkd2.2a:GFP
- vmat2:GFP
- AcTub
- TH
- 3A10
Automated Anatomical Assignment
Elastic Registration

- Use the anatomy channel to **find the transformation**
- Use found transformation to **transform the pattern channel**

**New Recording**

Anatomy channel

Pattern channel

**Reference (Atlas)**

Anatomy channel

Pattern channel (aligned to atlas)
Registration Definition: Bring two images into spatial alignment

More technical:

- One “fixed image” and one “moving image”
- Find optimal transformation parameters, such that the “moving image” matches best the “fixed image”
- Output:
  - Transformation parameters
  - Transformed moving image
Registration Categories

Feature based Registration

- use manually or automatically detected **landmarks**
- compute transformation, such that “moving” and “fixed” **landmarks** are placed onto each other

Intensity based Registration

- Iteratively transform moving image and **compare image intensities** to find optimal alignment
Landmark Based Registration

Rigid transformation: minimize the **squared distance** between corresponding landmarks.
Landmark Based Registration

Elastic Transformation (here Thin-plate Splines): deform image, such that landmarks match exactly
Thin-Plate Splines (TPS) Example

new larva with landmarks

reference larva with landmarks
Central slice. magenta: reference larva, green: new larva
After Landmark-Based Elastic Registration

For images from different individuals, we can not do much better:
- usually only a few point-to-point correspondences are available!

Central slice. magenta: reference larva, green: new larva
Central slice. magenta: reference larva, green: new larva only brain region is considered
Intensity based Registration

How does a human register two images?

Fixed image

Moving Image on transparent slide
Registration Techniques
Registration Techniques
Registration Techniques
Parts of a Registration Algorithm

How does a human register two images?

Fixed image

Moving Image on transparent slide

Final registration
General Flow Chart for a Registration

- "Fixed image"
- "Moving image"

1. **Transformation**
2. **Compute Similarity**
   - Similarity score
   - Improved Transformation parameters
   - Transformed "Moving image"
3. **Optimizer**

Registration Techniques
The 3 Parts of a Registration Algorithm

A transformation model

- What can you do with the moving image.
  e.g. rigid transformation (corresponds to our slide) or elastic transformation (put moving image on a rubber skin)

A similarity measure

- Compare the gray values of fixed and moving image and output a score

An optimizer

- Algorithm to find the transformation parameters
Component 1: The Transformation

- Fixed image
- Moving image
- Transformation
- Compute Similarity
- Optimizer
- Improved Transformation parameters
- Transformed Moving image
- Similarity score
Typical Transformation Models

Translation only

- 2D images: **2 parameters** (shift in x and shift in y direction, denoted as \(u,v\))
- 3D images: **3 parameters** (shift in x, y, and z direction)

\[
B(x, y) = A(x + u, y + v)
\]

Rigid Transformation (shift and rotation)

- 2D images: **3 parameters** (shift x, shift y, rotation angle)
- 3D images: **6 parameters** (shift x, y, and z, rotation around x-, y- and z-axis)

\[
B(x, y) = A(x \cdot \cos \alpha - y \cdot \sin \alpha + u, \\
\quad x \cdot \sin \alpha + y \cdot \cos \alpha + v)
\]
Typical Transformation Models

Affine Transformation (shift, rotation, scale and skew)

- 2D images: 6 parameters
- 3D images: 12 parameters

\[
B(x, y) = A(a_1 x + a_2 y + u, \ a_3 x + a_4 y + v)
\]

Elastic Registration

- 2D images: 2 times the number of pixels
- 3D images: 3 times the number of voxels

\[
B(x, y) = A(x + u(x, y), \ y + v(x, y))
\]
Component 2: The Similarity Measure

"Fixed image"

"Moving image"

Transformation

Compute Similarity

Improved Transformation parameters

Transformed "Moving image"

Similarity score

Optimizer
Similarity Measures
Case 1: Identical Gray Values

e.g., transmitted light images of moving cells
### Similarity Measures for Intensity Based Registration

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### Similarity Measures for Intensity Based Registration

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Similarity Measures
Case 1: Identical Gray Values

Sum of Squared Differences (SSD)

- Compute **squared difference** between intensity of each **pixel** $a_i$ in the “fixed image” and intensity of the corresponding **pixel** $b_i$ in the transformed “moving image”
- **Sum up** for all pixels

$$SSD = \frac{1}{N} \sum_{i} (a_i - b_i)^2$$

- Standard Error model (assumes **Gaussian distribution of errors**)
- Allows **effective optimization** in certain algorithms
Similarity Measures
Case 1: Identical Gray Values

Sum of Absolute Differences (SAD)

- Compute **absolute difference** between intensity of each pixel \( a_i \) in the “fixed image” and intensity of the corresponding pixel \( b_i \) in the transformed “moving image”
- **Sum up** for all pixels

\[
SAD = \frac{1}{N} \sum_{i} |a_i - b_i|
\]

- Less sensitive to **outlier intensities** than SSD

Both methods only for images recorded under **identical conditions**!
Similarity Measures
Case 2: Gray Value Offset and Scale

e.g. fluorescent cells, over time with bleaching
Similarity Measures
Case 2: Gray Value Offset and Scale

Normalized Cross Correlation

- **Subtract the mean value** of each image
- Compute the **product** of each **pixel** \( a_i \) in the “fixed image” and the corresponding **pixel** \( b_i \) in the transformed “moving image” and **sum up** for all pixels
- **Normalize with standard deviation** of each Image

\[
NCC = \frac{1}{\sigma_a \cdot \sigma_b} \sum_i (a_i - \bar{a}) \cdot (b_i - \bar{b})
\]

- different intensity offsets (e.g. **background intensities**) are compensated
- different intensity scales (**contrast changes**) are compensated
- **Extension**: Compute mean and stddev only in a **local surrounding**: High **robustness**, even for very different contrast within the same image!
Similarity Measures
Case 3: Different Modalities

e.g. CT scan (X-Ray) and MRI scan (Magnetic Resonance)
Similarity Measures
Case 3: Different Modalities

Mutual Information

- Standard measure in **medical image registration**, when registering images from different modalities (e.g. CT and MRI)
- Allows **any dependencies of intensities** in the images (e.g. bones are white in CT and black in MRI)
- (we don't go into detail here)
Component 3: The Optimizer

- Fixed image
- Moving image
- Transformation
- Compute Similarity
- Optimizer
- Improved Transformation parameters
- Similarity score

"Fixed image":

"Moving image":

Transformed "Moving image":

Improved Transformation parameters:

"Fixed image":

"Moving image":

Compute Similarity:

Optimizer:

Similarity score:

Registration Techniques

O. Ronneberger, Uni Freiburg / 21.8.2014 / slide 42
Optimizers

The Optimizer searches the best Parameters.

- Intuitive visualisation of optimizer by drawing the **similarity measure as function of the parameters**
- For two parameters, you can think of **mountains**.
- Your job is to **find the peak**.
- But you are **blind**, you can explore the surrounding by feeling with your feet.
Best Neighbor Optimizer

1. Evaluate all **2n neighbors** of the current location

2. If **better than the current** value, set best neighbor as next location, repeat 1.

3. Otherwise **half the step size** and try again

4. **Abort** if step size or cost function difference **below limit**

Slow, but works very stable – only locations are chosen that have been evaluated
Gradient Descent Optimizer

If you can compute the gradient at your current position

1. determine **gradient** (that is, in with direction the mountain raises)

2. go as far **in that direction**, until it does not increase anymore

3. repeat steps 1,2 **until convergence**
Problem of these optimizers

Do you see the problem of all these optimizers?

Local maxima

Similarity measure

Parameter 1

Parameter 2
Higher Dimensional Parameter Spaces

- In reality there are usually much more than only 2 parameters (like in the mountain metaphor)
- Metaphor for 3 parameters: You dive in the ocean, and you have to find the warmest spot.
Put all together for 2D smiley registration

matlab demo:
Elastic Registration

“Fixed” image I

“Moving” Image J

Transformation T
Smoothness Term

- Transformation is described by a **vector field** (individual displacement vector for each voxel)
- Not all vector fields describe **reasonable deformations**
- **Neighboring points** should have similar displacement
- We need a **regularization**, that enforces a **smooth deformation**

![Un-smooth deformation](image1)

![Smother deformation](image2)

- Very important: **Optimize smoothness and image similarity simultaneously!** Many available software packages do this wrong.
Elastic Registration Flow Diagram

- "fixed image" I
- "moving image" J

1. **Apply Transformation**
2. **Compute Similarity**
3. **Compute Smoothness**
4. **Optimizer**

- Transformed "moving image" J'
- Weight for smoothness term $\lambda$

**Transformation T**
Problem with Gradient-based Optimization

Standard approach:
Optimize per position
1 continuous variable (3 comp)
- runs into “best” direction

Combinatorial approach:
Optimize per position
N binary variables
(with constraint: sum=1)
- checks many hypotheses

- Problem: In 3D not possible to store all these variables for each voxel:
  Number of voxels times number of displacement hypotheses

- Use grid based registration to reduce number of variables.
(c) Control points \( p_i \) (white) and corresponding regions \( \Omega_i \) (red)
Discretization:

- Regular grid of control points (nodes)
- At each control point discrete number of displacement hypotheses (labels)
- **Data term** → **unary term**: similarity measure of fixed image (red patch) and moving image (green patch) for the given displacement
- **Smoothness term** → **pairwise term**: difference of two neighboring displacement vectors
Dense displacement field

(e) Dense displacement field $U$ by cubic spline interpolation
Landmark-Based Pre-Registration

Central slice. magenta: reference larva, green: new larva

100µm
After Intensity Based Elastic Registration

Central slice. magenta: reference larva, green: new larva, only brain region is considered.
Results

- Use **FastPD solver** for combinatorial optimization (Komodakis et al. 2008)
  - Primal-Dual strategy, updates use fast graph-cut algorithm
- Very fast algorithm. In zebrafish setup **solver only takes a few seconds**. Most time is spent on computing the cross-correlations
- Only **two iterations** needed
- Overall computation time approx. **3 minutes** on a 6core Xeon
  - dataset with **1000x500x500 voxels** (3.6 million voxels after downscaling and masking)

Limitations

- Only **binary potentials possible** – i.e. in current implementation rotation is more expensive than shear
- Problem becomes **non-submodular** from second iteration on (i.e. same label on neighbouring control points has not a pairwise energy zero)
  - work-around used by Glocker et al: “fluid-like” registration...
- **More complex smoothness terms** make problem non-submodular also in first iteration
- Solution: Don't use FastPD (with graph cuts), but alpha expansion with **QPBO** --> much slower.
Conclusions

- Alignment of **different individuals** needs **intensity-based** registration with **elastic transformation**

- **Combinatorial optimization** makes elastic registration less susceptible for local optima.

- **Building block** for many further image analysis applications

- You can try the “vibez_elastic_registration” on saturday or sunday afternoon

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Thank you for your attention.