Image analysis challenges in translational molecular imaging research

Boudewijn P.F. Lelieveldt
Division of Image Processing
department of Radiology,
Leiden University Medical Center
Leiden, the Netherlands

Dept of Intelligent Systems
Delft University of Technology
Delft, the Netherlands

Content

- Introduction small animal imaging
  - New possibilities compared to clinical imaging
  - New image analysis challenges
- Analysis of follow-up studies
- Fusion of heterogeneous imaging data
- Applications
  - Monitoring metastasis formation
  - Improving cancer surgery
Acknowledgements

Martijn van de Giessen
Jouke Dijkstra
Julien Milles
Martin Baiker
Martin Wildeman
Artem Khmelinskii
Paulien Stegehuis
Hans Reiber
Division of Image Processing
department of Radiology, LUMC

Marcel Reinders, Emile Hendriks
Pattern Recognition &
bioinformatics group
Delft University of Technology

Wiro Niessen, Erik Meijering,
Esben Plenge, Dirk Poot
BIGR, Erasmus Medical Center

Clemens Lowik
Eric Kajzoi, Thomas Snoeks
Ivo Que, Pieter van Driel
Experimental Molecular Imaging
department of Radiology
LUMC

Charl Botha
Peter Kok
Visualization Group
Delft University of Technology

Alexander Vahrmeijer
Bob Schaafsma
Joost van der Vos
Merlijn Hutteman
Peter Kuppen, Cees Sier
Cock van der Velde
department of Surgery
LUMC

Division of Image Processing

- knowledge driven segmentation
- registration
- Information fusion
In-vivo small animal imaging

Micro-PET ($\mu$PET)
Positron Emission Tomography

Micro-CT ($\mu$CT)
Computed Tomography

Micro-SPECT ($\mu$SPECT)
Single Photon Emission
Computed Tomography

Micro-MRI ($\mu$MRI)
Magnetic Resonance Imaging

FLI
Fluorescence Imaging

BLI
Bioluminescence Imaging

Optical Imaging

Bioluminescence: (photons generated by conversion of a substrate)

Luciferin + ATP + $O_2 \rightarrow$ Oxyluciferin + light (photons)

luciferase
BLI: insert luciferase gene in cells

Xenograft, cancer cells, bacteria, parasites

Transgenic animal

Basic Method

Tag Cell
Tag Gene
Image
Digitize
Quantify
Archive

Slide courtesy of Xenogen
- Luciferase labeled breast cancer cells

- Luciferase labeled malaria parasites

Ploemen e.a., PLOS One, 4(11): e7881
New (switchable) contrast mechanisms

- Promoter gene
  - Switch of a gene, activated by transcription factors
- Reporter gene
  - Gene that codes for a detectable protein when a specific biochemical process happens

Activatable contrast mechanisms

Promoter gene
  “Switch” of a gene, activated by transcription factors

Insulin promoter \[\rightarrow\] Insulin

Transcription factor

Insulin promoter \[\rightarrow\] Reporter gene
Effect of bone marrow ablation and 1,25(OH)₂D₃ on human osteocalcin expression
VEGFR2-luc-KI mice

- After 9-10 days fire fly luciferase activity can be seen indicating the start of tumor angiogenesis (the angiogenic switch)

Site of sc injection of wt LL/2 tumor cells

Fluorescence imaging

- Fluorophore is either
  - injected
  - bound to ligand that targets specific proteins
  - cleaved by disease-specific enzyme
  - encoded in reporter gene

Compared to BLI:
+ possible without dna insertion, easier translation to human apps
+ more near-infra-red probes: deeper light penetration
- less sensitive due to autofluorescence signals
Real-time optical imaging

 Courtesy of Clemens Lowik, Ivo Que, Eric Kaijzel, LUMC, Leiden

Real-time multispectral imaging

 Movie recorded with O2View multi-spectral camera
Integrated imaging

Structure

µMRI
µCT
µPET
µSPECT
BLI
FLI
...

Function

µMRI
µCT
µPET
µSPECT

Biochemistry

Integrated imaging: translation

Structure

µMRI
µCT
µPET
µSPECT
BLI
FLI
...

Function

µMRI
µCT
µPET
µSPECT

Biochemistry

In humans
What are new image analysis challenges compared to clinical imaging?

Data heterogeneity....

due to image structure and contrast mechanism
...whole-body imaging...

- Posture not standardized over time
  - How to handle large pose variations in arms and legs?
  - Separate coincidental shape changes from disease changes

---

High-throughput follow-up data...

- 3D BLI
- Micro-PET 100-300
- Micro-CT >1000
- Time
...New quantification needs...

- Optical signal location and concentration
  - correct for photon scatter & absorption
  - requires registered tissue atlas & inverse modeling
  - in real-time?

...overlapping color spectra....

- Spectra from multiple “colors” overlap: how to separate?
... coupling of imaging to omics ...

Bohland e.a., Methods vol 50, pp 105-112, 2010

...Data Integration...

Interpretation:
- Integrated
- Multiple time points
- Quantitative
- Automatic

Micro-CT
>1000

Time

Micro-PET
100-300

3D BLI
- Adaptations to three standard atlases
  - define individual bones
  - define joint type and rotation centers

MOBY¹  Digimouse²  Bai rat atlas³

Articulated registration: µCT

- Registration criterion governed by
  - Strong image feature
  - Kinematic constraints imposed by model

Skeleton registration results

“Atlas-based whole-body segmentation of mice from low-contrast µCT data”, Medical Image Analysis, vol. 14(6), pp 723-737, 2010
CT-fluorescence: manual landmarks

Rigid BLI / CT registration

Multi-view BLI (Xenogen 3D)

Micro-CT (Skyscan 1178)
Articulated registration: µSPECT


Articulated atlas-to-BLI registration

M. Wildeman, M. Baiker, M.J.T. Reinders, C.W.G.M. Liwick, J.H.C. Reiber, B.P.F. Lelieveldt,
Something is changing, but what?
Find the differences....

Find the differences....

Source: http://www.ronruelle.com/mw.html
Use atlas to normalize posture

Articulated Planar Reformation

P.Kok, M. Baiker, E.A. Hendriks, F.H. Post, J. Dijkstra, C.W.G.M. Löwik, B.P.F. Lelieveldt, C.P. Botha,
“Articulated Planar Reformation for change visualization in small animal imaging”, IEEE Transactions on
Visualization and Computer Graphics, vol. 16(6), pp1396-1404, 2010
New idea? Not really....

Follow-up data: side-by-side view

P.Kok, M. Baiker, E.A. Hendriks, F.H. Post, J. Dijkstra, C.W.G.M. Lutwiek, B.P.F. Lelieveldt, C.P. Botha,
“Articulated Planar Reformation for change visualization in small animal imaging”, IEEE Transactions on
Visualization and Computer Graphics, vol. 16(6), pp1396-1404, 2010
Multi-modal comparison


Integrated data exploration

Integrated quantification

Image level

Registration

Template level

Data fusion

Imaging Modalities

T0

Te
Automated VOI selection


Integrated imaging: translation

Structure

µMRI
µCT
µPET
µSPECT
BLI
FLI
...

Function

Biochemistry

In humans
Applications

- Monitoring breast cancer metastases
- Improving cancer surgery

Fused interactive visualization
Interactive MR-superresolution

Automated VOI selection


Automated bone volume measurement

Applications

- Monitoring breast cancer metastases
- Improving cancer surgery

Improving breast cancer surgery

**Start:**
Find lymph node

**End:**
Check for tumor remnants

- Problems:
  - Sentinel lymphnode difficult to find
  - Difference between healthy tissue / tumor not visible
Improving breast cancer surgery

Detection

Visualization

Excitation

Emission

Probe

MI: More effective oncological surgery

John Frangioni, Boston, USA, www.frangionilabs.org
LUMC: SLN mapping in breast cancer

Liver metastases in colon cancer

Movie courtesy of dr Alexander Vahrmeijer, LUMC
Camera system: Artemis, Quest Medical Imaging
Liver metastases in colon cancer

Movie courtesy of dr Alexander Vahrmeijer, LUMC
Camera system: Artemis, Quest Medical Imaging

Probe validation: ProSense

Before injection

After 24 hours
Fusion with Micro-CT

Targeted tracer development

Prosense

Epcam
Outlook

Integrated data exploration

Integrated quantification

Data fusion

Template level

Registration

Image level

Imaging Modalities

Time

New modality

T_e