pyKNEEr: An image analysis workflow for open and reproducible research on femoral knee cartilage

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https://sbonaretti.github.io/

Open and reproducible research

- Openness and computational reproducibility are recent movements in research (Woelfle 2011, Bollen 2015)
- They are essential to researchers to assess value of scientific claims and confidently build on previous work (Sandve 2013)
- Transparent *image-based* research is crucial to provide reliable answers to biological questions (Poldrack 2017)
- Other communities, e.g. neuroimaging, largely benefit from open-access tools (Gorgolewski 2011)

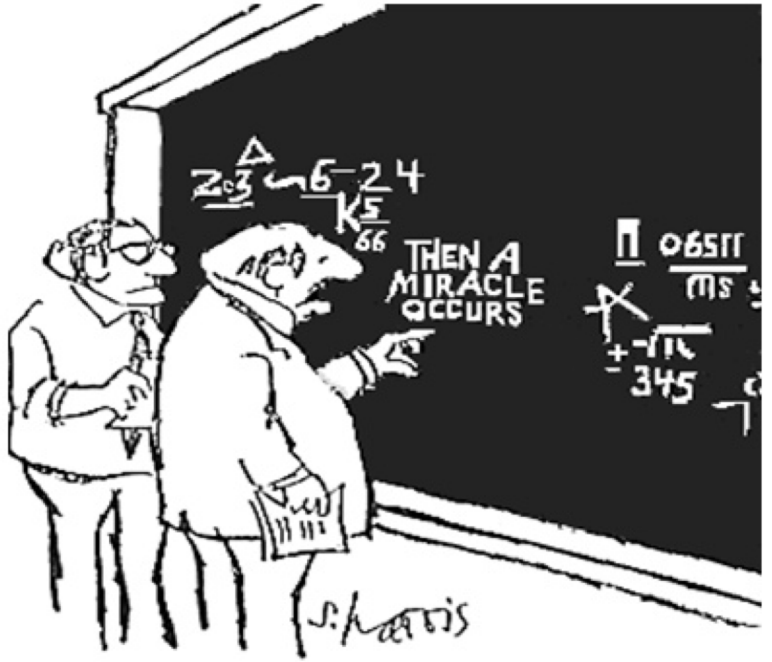


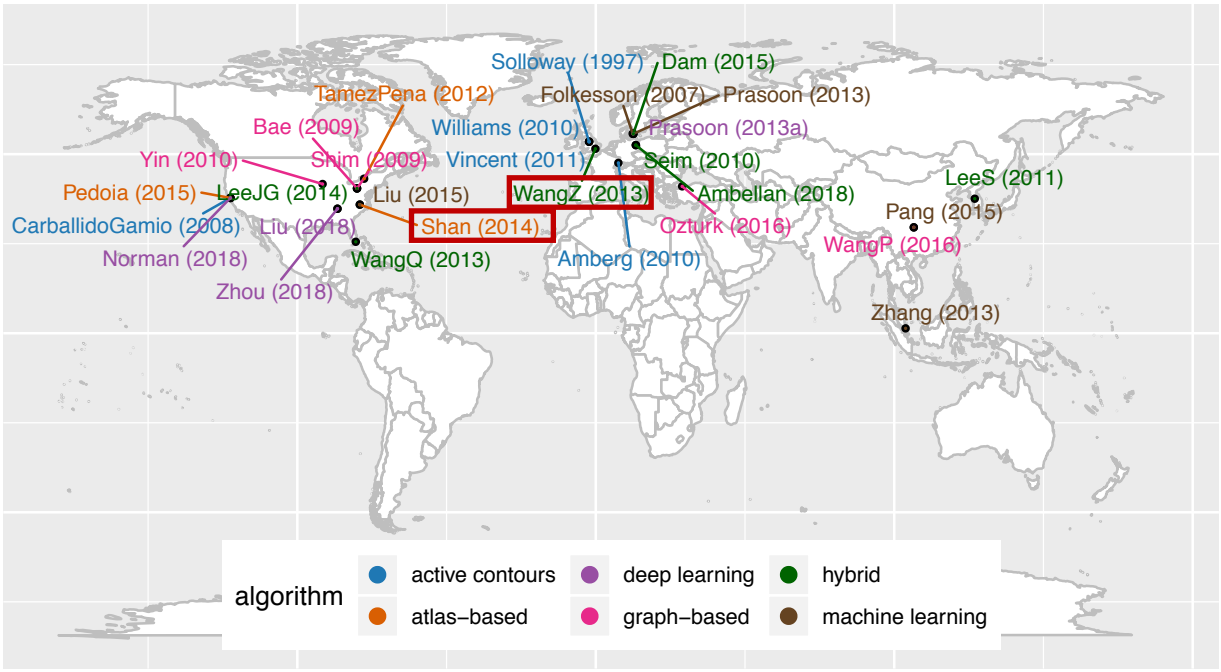
Image-based analysis of femoral knee cartilage

- In knee OA, analysis of femoral cartilage from MR images has assumed an important role (Hafezi-Nejad 2018)

- Analysis workflows include:
  - Preprocessing
  - Segmentation
  - Morphology and Relaxometry

- Segmentation is a major challenge
  - Of 29 segmentation algorithms, only 2 have open source code (Wang 2013, Shan 2014)

Literature map of femoral knee cartilage segmentation



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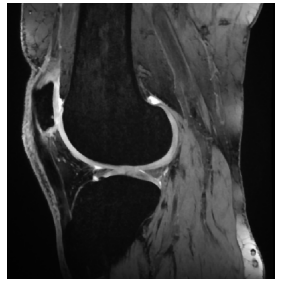
Openness of *pyKNEEr*

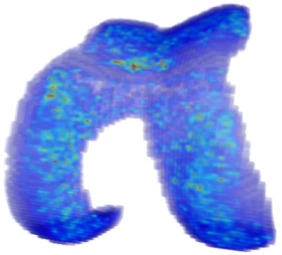
- Code written in *python*
- Use of open file formats
  - *.mha, .txt, .csv*
- Modular structure to favor code expansion
- Reuse of developed code
  - Intensity preprocessing from Shan et al., *elastix*
- Available on GitHub
  - GNU GPLv3 license and DOI

I. Preprocessing

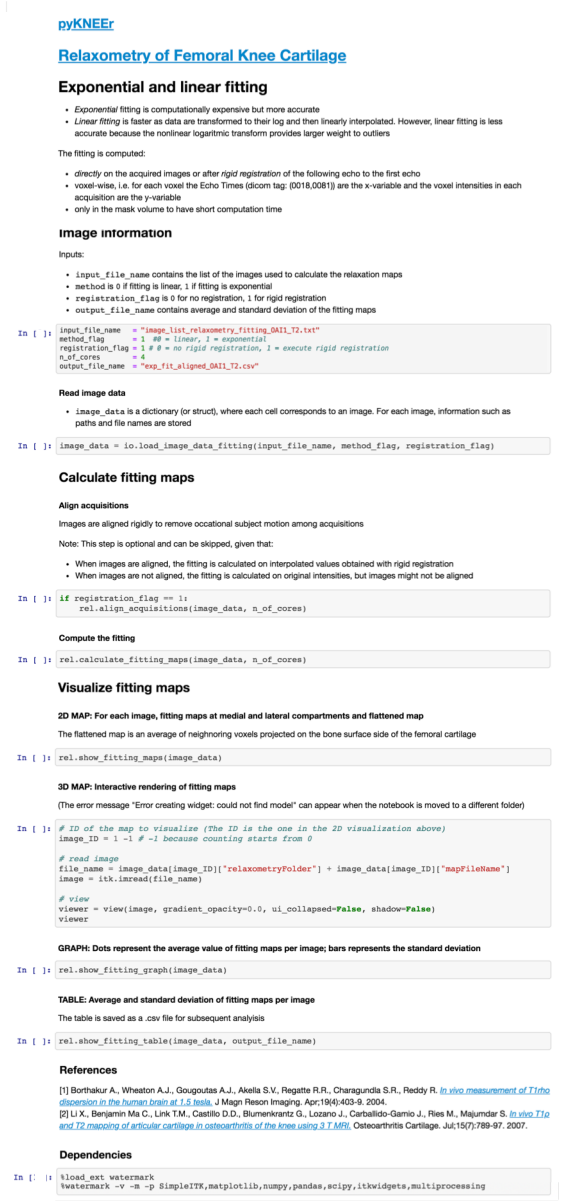


II. Segmentation

III. Analysis



Reproducibility: Jupyter notebook



pyKNEEr

Relaxometry of Femoral Knee Cartilage

Exponential and linear fitting

- *Exponential* fitting is computationally expensive but more accurate
- *Linear fitting* is faster as data are transformed to their log and then linearly interpolated. However, linear fitting is less accurate because the nonlinear logaritmic transform provides larger weight to outliers

The fitting is computed:

- *directly* on the acquired images or after *rigid registration* of the following echo to the first echo
- voxel-wise, i.e. for each voxel the Echo Times (dicom tag: (0018,0081)) are the x-variable and the voxel intensities in each acquisition are the y-variable
- only in the mask volume to have short computation time

Image information

Inputs:

- `input_file_name` contains the list of the images used to calculate the relaxation maps
- `method` is 0 if fitting is linear, 1 if fitting is exponential
- `registration_flag` is 0 for no registration, 1 for rigid registration
- `output_file_name` contains average and standard deviation of the fitting maps

In [ ]:
```
input_file_name   = "image_list_relaxometry_fitting_OAI1_T2.txt"
method_flag       = 1  ## 0 = linear, 1 = exponential
registration_flag = 1 # 0 = no rigid registration, 1 = execute rigid registration
n_of_cores        = 4
output_file_name  = "exp_fit_aligned_OAI1_T2.csv"
```

Read image data

- `image_data` is a dictionary (or struct), where each cell corresponds to an image. For each image, information such as paths and file names are stored

In [ ]:
```
image_data = io.load_image_data_fitting(input_file_name, method_flag, registration_flag)
```

Calculate fitting maps

Align acquisitions

Images are aligned rigidly to remove occational subject motion among acquisitions

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Compute the fitting

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Visualize fitting maps

2D MAP: For each image, fitting maps at medial and lateral compartments and flattened map

The flattened map is an average of neighnoring voxels projected on the bone surface side of the femoral cartilage

In [ ]:
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3D MAP: Interactive rendering of fitting maps

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image = itk.imread(file_name)

# view
viewer = view(image, gradient_opacity=0.0, ui_collapsed=False, shadow=False)
viewer
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GRAPH: Dots represent the average value of fitting maps per image; bars represents the standard deviation

In [ ]:
```
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TABLE: Average and standard deviation of fitting maps per image

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In [ ]:
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References

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```

- Open-source web application integrating
  - Live code
  - Narrative text with equations
  - Visualizations
- Versatile
- Easy to share among researchers

Reproducibility of *pyKNEEr*: Jupyter notebook

pyKNEEr

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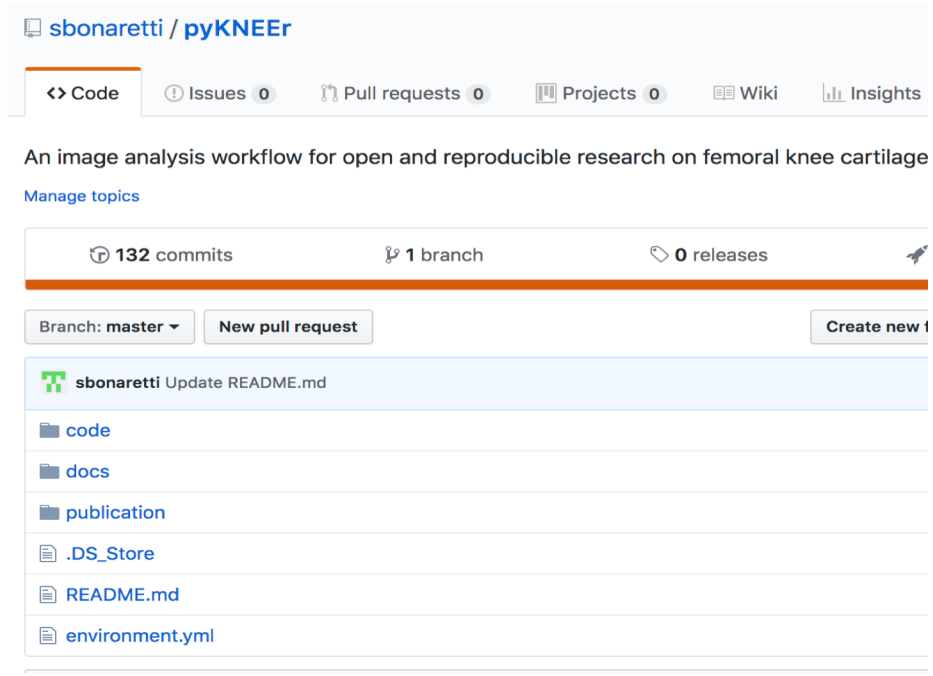

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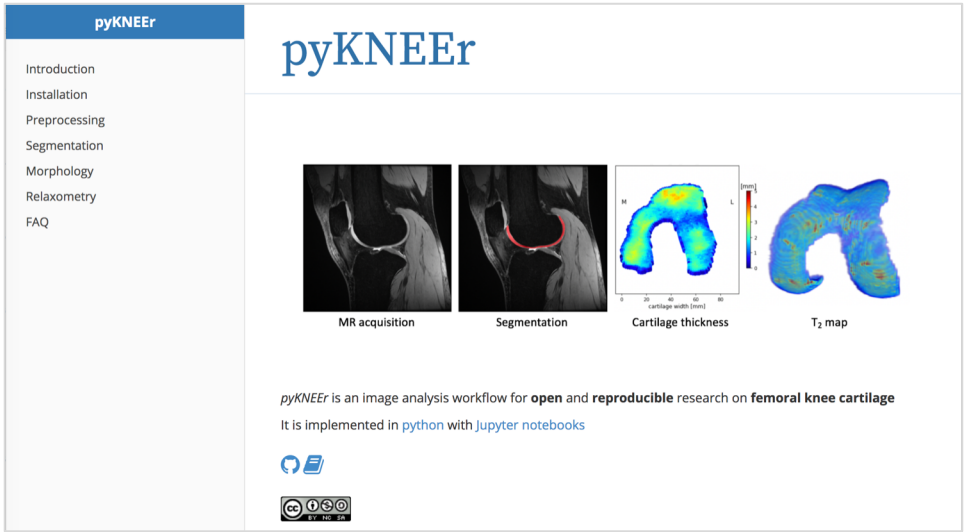

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1. Link to GitHub repository
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4. User inputs

```
input_file_name
./original/
001/BL
left
002/BL
left
003/BL
right
004/BL
left
005/BL
right
006/BL
left
007/BL
left
008/BL
left
009/BL
right
010/BL
left
011/BL
left
012/BL
right



n_of_cores

output_file_name

...
```

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3. Introduction

Image information

Inputs:

- `input_file_name` contains the list of the images used to calculate the relaxation maps
- `method` is 0 if fitting is linear, 1 if fitting is exponential
- `registration_flag` is 0 for no registration, 1 for rigid registration
- `output_file_name` contains average and standard deviation of the fitting maps

4. User inputs

In [ ]:
```
input_file_name   = "image_list_relaxometry_fitting_OAI1_T2.txt"
method_flag       = 1  ## 0 = linear, 1 = exponential
registration_flag = 1 # 0 = no rigid registration, 1 = execute rigid registration
n_of_cores        = 4
output_file_name  = "exp_fit_aligned_OAI1_T2.csv"
```

Read image data

- `image_data` is a dictionary (or struct), where each cell corresponds to an image. For each image, information such as paths and file names are stored

In [ ]:
```
image_data = io.load_image_data_fitting(input_file_name, method_flag, registration_flag)
```

Calculate fitting maps

Align acquisitions

Images are aligned rigidly to remove occational subject motion among acquisitions

Note: This step is optional and can be skipped, given that:

- When images are aligned, the fitting is calculated on interpolated values obtained with rigid registration
- When images are not aligned, the fitting is calculated on original intensities, but images might not be aligned

In [ ]:
```
if registration_flag == 1:
    rel.align_acquisitions(image_data, n_of_cores)
```

Compute the fitting

In [ ]:
```
rel.calculate_fitting_maps(image_data, n_of_cores)
```

5. Commands with narrative

Visualize fitting maps

2D MAP: For each image, fitting maps at medial and lateral compartments and flattened map

The flattened map is an average of neighnoring voxels projected on the bone surface side of the femoral cartilage

In [ ]:
```
rel.show_fitting_maps(image_data)
```

3D MAP: Interactive rendering of fitting maps

(The error message "Error creating widget: could not find model" can appear when the notebook is moved to a different folder)

In [ ]:
```
# ID of the map to visualize (The ID is the one in the 2D visualization above)
image_ID = 1 -1 # -1 because counting starts from 0

# read image
file_name = image_data[image_ID]["relaxometryFolder"] + image_data[image_ID]["mapFileName"]
image = itk.imread(file_name)

# view
viewer = view(image, gradient_opacity=0.0, ui_collapsed=False, shadow=False)
viewer
```

GRAPH: Dots represent the average value of fitting maps per image; bars represents the standard deviation

In [ ]:
```
rel.show_fitting_graph(image_data)
```

TABLE: Average and standard deviation of fitting maps per image

The table is saved as a .csv file for subsequent analysis

In [ ]:
```
rel.show_fitting_table(image_data, output_file_name)
```

References

[1] Borthakur A., Wheaton A.J., Gougoutas A.J., Akella S.V., Regatte R.R., Charagundla S.R., Reddy R. *In vivo measurement of T1rho dispersion in the human brain at 1.5 tesla.* J Magn Reson Imaging. Apr;19(4):403-9. 2004.
[2] Li X., Benjamin Ma C., Link T.M., Castillo D.D., Blumenkrantz G., Lozano J., Carballido-Gamio J., Ries M., Majumdar S. *In vivo T1ρ and T2 mapping of articular cartilage in osteoarthritis of the knee using 3 T MRI.* Osteoarthritis Cartilage. Jul;15(7):789-97. 2007.

Dependencies

In [ ]:
```
%load_ext watermark
%watermark -v -m -p SimpleITK,matplotlib,numpy,pandas,scipy,itkwidgets,multiprocessing
```

Cartilage Thickness

Separating subcondral surface and articular surface of cartilage

To calculate cartilage thickness, first the cartilage surface is extracted from the binary mask. Then subcondral surface and articular surface are divided in two separate point clouds

```
morph.separate_cartilage_surfaces(image_data, n_of_cores)
```

Visual check

Subcondral bone surface (yellow) and articular surface (blue) are visualized as flattened point clouds. The flattening is with respect to a cylinder interpolated into the cartilage surface [2]

```
morph.show_cartilage_surfaces(image_data)
```

Calculating cartilage thickness

Assign the chosen algorithm

```
morph.algorithm(image_data, thickness_algo)
```

Calculate thickness

```
morph.calculate_thickness(image_data, n_of_cores)
```

Reproducibility of *pyKNEEr*: Jupyter notebook

pyKNEEr

Relaxometry of Femoral Knee Cartilage

Exponential and linear fitting

- *Exponential* fitting is computationally expensive but more accurate
- *Linear fitting* is faster as data are transformed to their log and then linearly interpolated. However, linear fitting is less accurate because the nonlinear logaritmic transform provides larger weight to outliers

The fitting is computed:

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- voxel-wise, i.e. for each voxel the Echo Times (dicom tag: (0018,0081)) are the x-variable and the voxel intensities in each acquisition are the y-variable
- only in the mask volume to have short computation time

Image information

Inputs:

- `input_file_name` contains the list of the images used to calculate the relaxation maps
- `method` is 0 if fitting is linear, 1 if fitting is exponential
- `registration_flag` is 0 for no registration, 1 for rigid registration
- `output_file_name` contains average and standard deviation of the fitting maps

```
input_file_name   = "image_list_relaxometry_fitting_OAI1_T2.txt"
method_flag       = 1  ## 0 = linear, 1 = exponential
registration_flag = 1 # 0 = no rigid registration, 1 = execute rigid registration
n_of_cores        = 4
output_file_name  = "exp_fit_aligned_OAI1_T2.csv"
```

Read image data

- `image_data` is a dictionary (or struct), where each cell corresponds to an image. For each image, information such as paths and file names are stored

```
image_data = io.load_image_data_fitting(input_file_name, method_flag, registration_flag)
```

Calculate fitting maps

Align acquisitions

Images are aligned rigidly to remove occational subject motion among acquisitions

Note: This step is optional and can be skipped, given that:

- When images are aligned, the fitting is calculated on interpolated values obtained with rigid registration
- When images are not aligned, the fitting is calculated on original intensities, but images might not be aligned

```
if registration_flag == 1:
    rel.align_acquisitions(image_data, n_of_cores)
```

Compute the fitting

```
rel.calculate_fitting_maps(image_data, n_of_cores)
```

Visualize fitting maps

2D MAP: For each image, fitting maps at medial and lateral compartments and flattened map

The flattened map is an average of neighnoring voxels projected on the bone surface side of the femoral cartilage

```
rel.show_fitting_maps(image_data)
```

3D MAP: Interactive rendering of fitting maps

(The error message "Error creating widget: could not find model" can appear when the notebook is moved to a different folder)

```
# ID of the map to visualize (The ID is the one in the 2D visualization above)
image_ID = 1 -1 # -1 because counting starts from 0

# read image
file_name = image_data[image_ID]["relaxometryFolder"] + image_data[image_ID]["mapFileName"]
image = itk.imread(file_name)

# view
viewer = view(image, gradient_opacity=0.0, ui_collapsed=False, shadow=False)
viewer
```

GRAPH: Dots represent the average value of fitting maps per image; bars represents the standard deviation

```
rel.show_fitting_graph(image_data)
```

TABLE: Average and standard deviation of fitting maps per image

The table is saved as a .csv file for subsequent analysis

```
rel.show_fitting_table(image_data, output_file_name)
```

References

[1] Borthakur A., Wheaton A.J., Gougoutas A.J., Akella S.V., Regatte R.R., Charagundla S.R., Reddy R. *In vivo measurement of T1rho dispersion in the human brain at 1.5 tesla.* J Magn Reson Imaging. Apr;19(4):403-9. 2004.
[2] Li X., Benjamin Ma C., Link T.M., Castillo D.D., Blumenkrantz G., Lozano J., Carballido-Gamio J., Ries M., Majumdar S. *In vivo T1ρ and T2 mapping of articular cartilage in osteoarthritis of the knee using 3 T MRI.* Osteoarthritis Cartilage. Jul;15(7):789-97. 2007.

Dependencies

```
%load_ext watermark
%watermark -v -m -p SimpleITK,matplotlib,numpy,pandas,scipy,itkwidgets,multiprocessing
```

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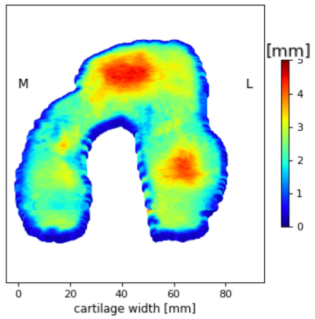
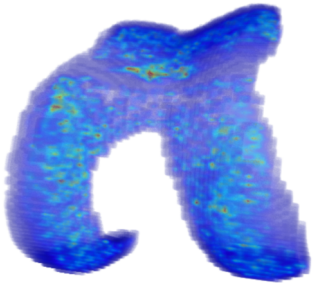
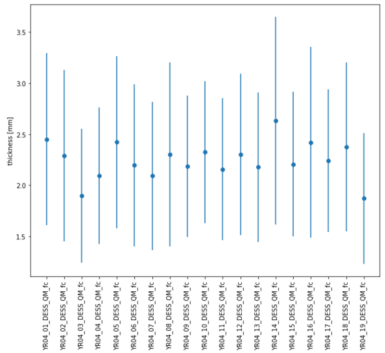
Qualitative visualizations



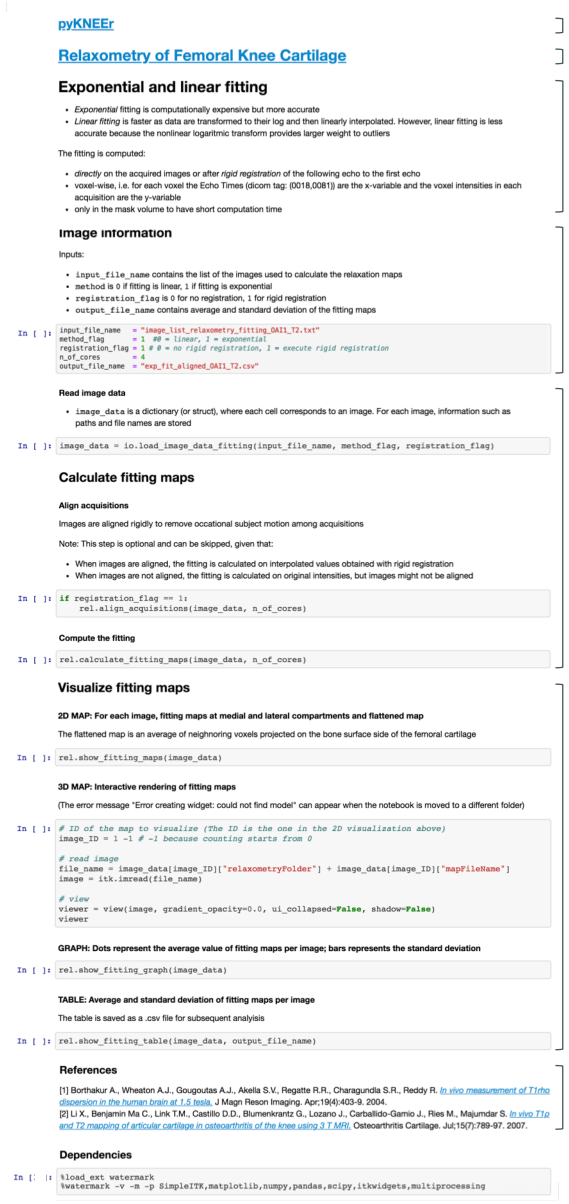


Quantitative visualizations



	Subjects	averageThickness	std.dev
1	YR04_01_DESS_QM_fc_thickness_1	2.45	0.84
2	YR04_02_DESS_QM_fc_thickness_1	2.29	0.84
3	YR04_03_DESS_QM_fc_thickness_1	1.90	0.65
4	YR04_04_DESS_QM_fc_thickness_1	2.09	0.67
5	YR04_05_DESS_QM_fc_thickness_1	2.42	0.84
6	YR04_06_DESS_QM_fc_thickness_1	2.20	0.79
7	YR04_07_DESS_QM_fc_thickness_1	2.09	0.72
8	YR04_08_DESS_QM_fc_thickness_1	2.30	0.90
9	YR04_09_DESS_QM_fc_thickness_1	2.19	0.69
10	YR04_10_DESS_QM_fc_thickness_1	2.32	0.70
11	YR04_11_DESS_QM_fc_thickness_1	2.16	0.69
12	YR04_12_DESS_QM_fc_thickness_1	2.30	0.79
13	YR04_13_DESS_QM_fc_thickness_1	2.18	0.73
14	YR04_14_DESS_QM_fc_thickness_1	2.63	1.02
15	YR04_15_DESS_QM_fc_thickness_1	2.21	0.71
16	YR04_16_DESS_QM_fc_thickness_1	2.42	0.93
17	YR04_17_DESS_QM_fc_thickness_1	2.24	0.70
18	YR04_18_DESS_QM_fc_thickness_1	2.38	0.82
19	YR04_19_DESS_QM_fc_thickness_1	1.87	0.64

Reproducibility of *pyKNEEr*: Jupyter notebook



pyKNEEr

Relaxometry of Femoral Knee Cartilage

Exponential and linear fitting

- *Exponential* fitting is computationally expensive but more accurate
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The fitting is computed:

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- voxel-wise, i.e. for each voxel the Echo Times (dicom tag: (0018,0081)) are the x-variable and the voxel intensities in each acquisition are the *y*-variable
- only in the mask volume to have short computation time

Image information

Inputs:

- `input_file_name` contains the list of the images used to calculate the relaxation maps
- `method` is 0 if fitting is linear, 1 if fitting is exponential
- `registration_flag` is 0 for no registration, 1 for rigid registration
- `output_file_name` contains average and standard deviation of the fitting maps

In [ ]:
```
input_file_name   = "image_list_relaxometry_fitting_OAI1_T2.txt"
method_flag       = 1  ## 0 = linear, 1 = exponential
registration_flag = 1 # 0 = no rigid registration, 1 = execute rigid registration
n_of_cores        = 4
output_file_name  = "exp_fit_aligned_OAI1_T2.csv"
```

Read image data

- `image_data` is a dictionary (or struct), where each cell corresponds to an image. For each image, information such as paths and file names are stored

In [ ]:
```
image_data = io.load_image_data_fitting(input_file_name, method_flag, registration_flag)
```

Calculate fitting maps

Align acquisitions

Images are aligned rigidly to remove occational subject motion among acquisitions

Note: This step is optional and can be skipped, given that:

- When images are aligned, the fitting is calculated on interpolated values obtained with rigid registration
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In [ ]:
```
if registration_flag == 1:
    rel.align_acquisitions(image_data, n_of_cores)
```

Compute the fitting

In [ ]:
```
rel.calculate_fitting_maps(image_data, n_of_cores)
```

Visualize fitting maps

2D MAP: For each image, fitting maps at medial and lateral compartments and flattened map

The flattened map is an average of neighnoring voxels projected on the bone surface side of the femoral cartilage

In [ ]:
```
rel.show_fitting_maps(image_data)
```

3D MAP: Interactive rendering of fitting maps

(The error message "Error creating widget: could not find model" can appear when the notebook is moved to a different folder)

In [ ]:
```
# ID of the map to visualize (The ID is the one in the 2D visualization above)
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# read image
file_name = image_data[image_ID]["relaxometryFolder"] + image_data[image_ID]["mapFileName"]
image = itk.imread(file_name)

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viewer = view(image, gradient_opacity=0.0, ui_collapsed=False, shadow=False)
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```

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In [ ]:
```
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```

TABLE: Average and standard deviation of fitting maps per image

The table is saved as a .csv file for subsequent analysis

In [ ]:
```
rel.show_fitting_table(image_data, output_file_name)
```

References

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Dependencies

In [ ]:
```
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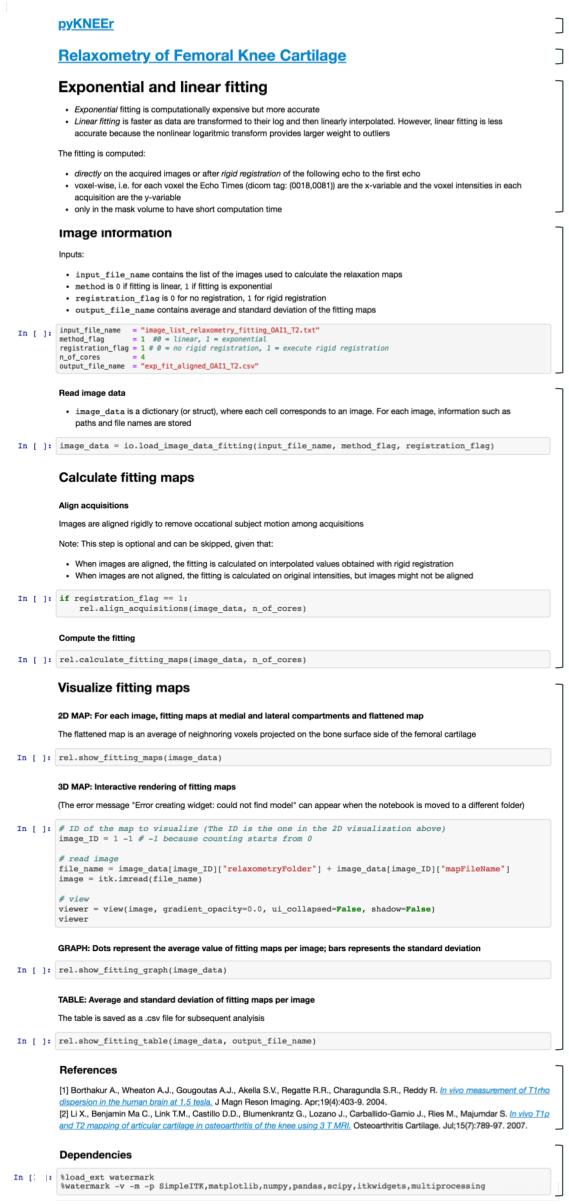
Reproducibility of *pyKNEEr*: Jupyter notebook



pyKNEEr

Relaxometry of Femoral Knee Cartilage

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```
input_file_name   = "image_list_relaxometry_fitting_OAI1_T2.txt"
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```
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    rel.align_acquisitions(image_data, n_of_cores)
```

Compute the fitting

```
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```

Visualize fitting maps

2D MAP: For each image, fitting maps at medial and lateral compartments and flattened map

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```
rel.show_fitting_maps(image_data)
```

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```
# ID of the map to visualize (The ID is the one in the 2D visualization above)
image_ID = 1 -1 # -1 because counting starts from 0

# read image
file_name = image_data[image_ID]["relaxometryFolder"] + image_data[image_ID]["mapFileName"]
image = itk.imread(file_name)

# view
viewer = view(image, gradient_opacity=0.0, ui_collapsed=False, shadow=False)
viewer
```

GRAPH: Dots represent the average value of fitting maps per image; bars represents the standard deviation

```
rel.show_fitting_graph(image_data)
```

TABLE: Average and standard deviation of fitting maps per image

The table is saved as a .csv file for subsequent analysis

```
rel.show_fitting_table(image_data, output_file_name)
```

References

[1] Borthakur A., Wheaton A.J., Gougoutas A.J., Akella S.V., Regatte R.R., Charagundla S.R., Reddy R. *In vivo measurement of T1rho dispersion in the human brain at 1.5 tesla.* J Magn Reson Imaging. Apr;19(4):403-9. 2004.
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Dependencies

```
%load_ext watermark
%watermark -v -m -p SimpleITK,matplotlib,numpy,pandas,scipy,itkwidgets,multiprocessing
```

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Dependencies

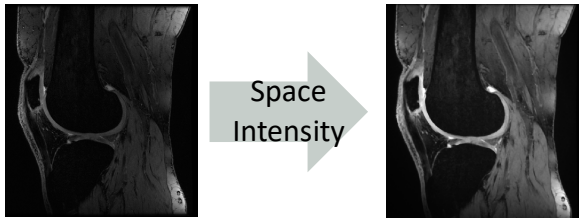
```
%load_ext watermark
%watermark -v -m -p matplotlib,numpy,pandas,scipy
```

```
CPython 3.7.1
IPython 7.2.0

matplotlib 2.2.3
numpy 1.16.1
pandas 0.24.1
scipy 1.2.1

compiler   : Clang 4.0.1 (tags/RELEASE_401/final)
system     : Darwin
release    : 17.7.0
machine    : x86_64
processor  : i386
CPU cores  : 4
interpreter: 64bit
```

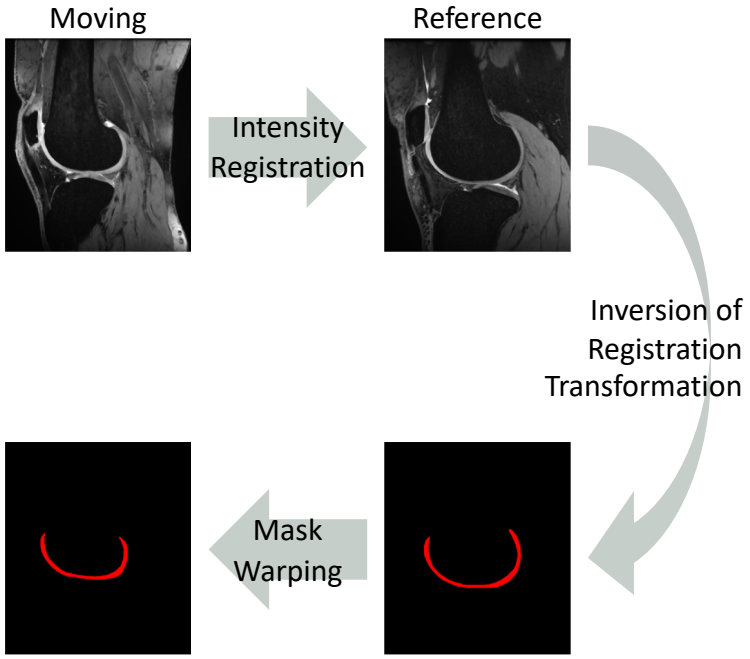
→ Reproducibility of computational environment

Algorithms in *pyKNEEr*

I. Preprocessing

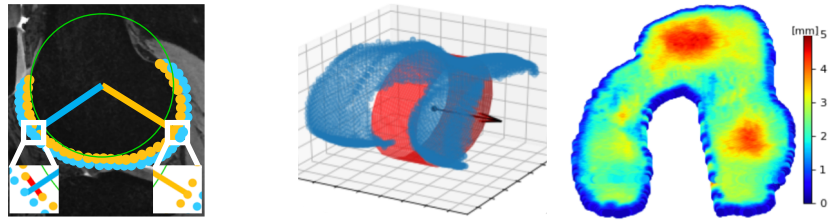


II. Segmentation

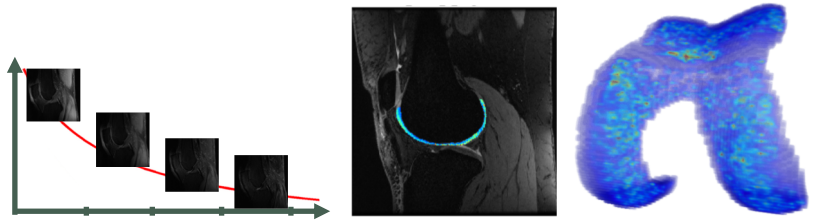


III. Analysis

Morphology



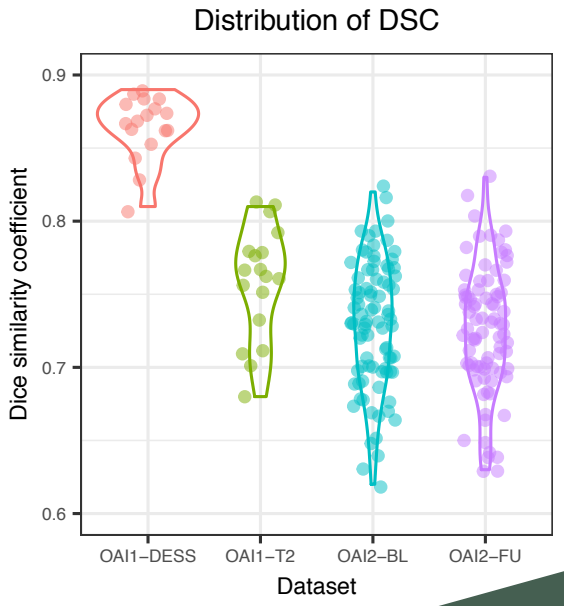
Relaxometry

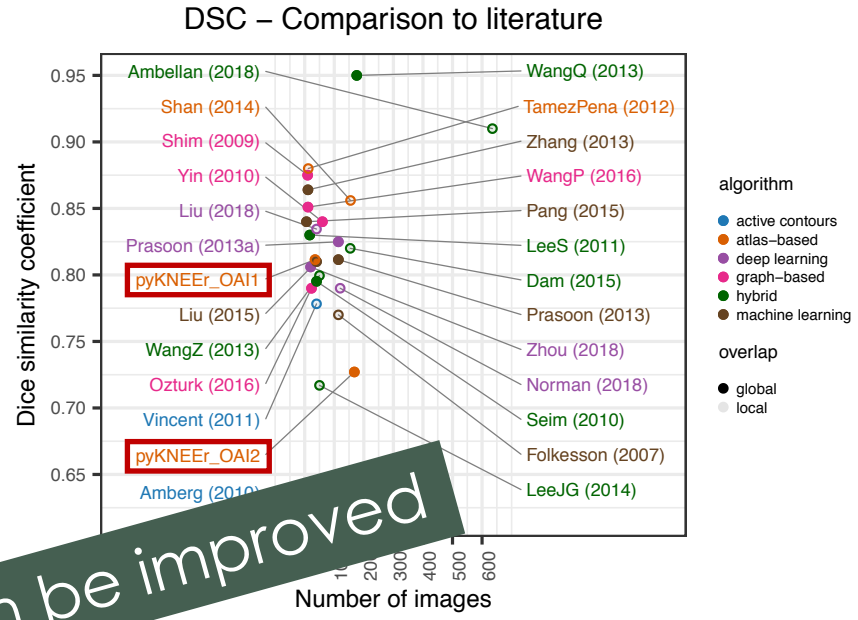


Validation experiments

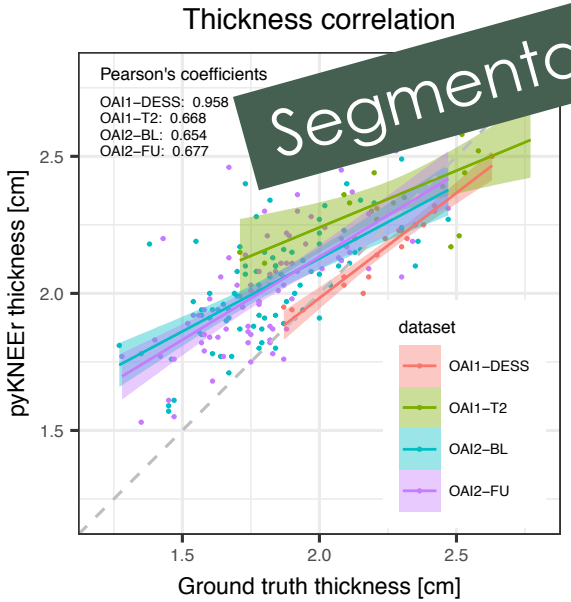
- OAI1: 19 subjects
  - OAI1-DESS
  - OAI1-T2
  - G. Truth: atlas-based (TamezPena 2012)
- OAI2: 88 subjects
  - OAI2-DESS BL
  - OAI2-DESS FU
  - G. Truth: AAM (Vincent 2011)

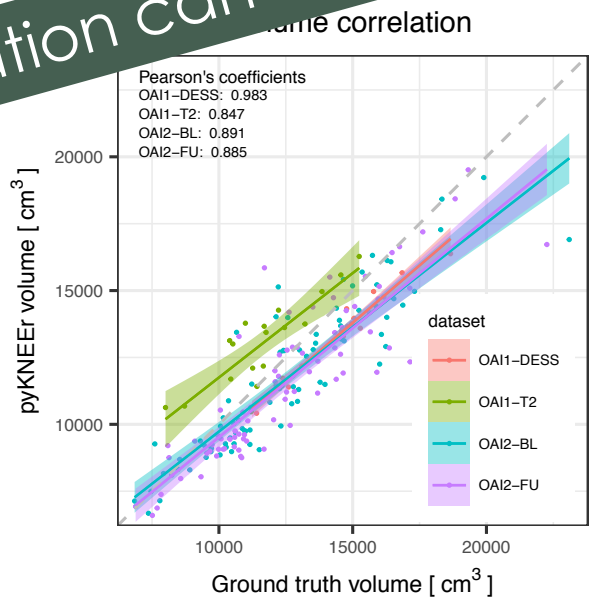
Data on Zenodo
Code on GitHub
Analysis on binder
Paper on bioRxiv

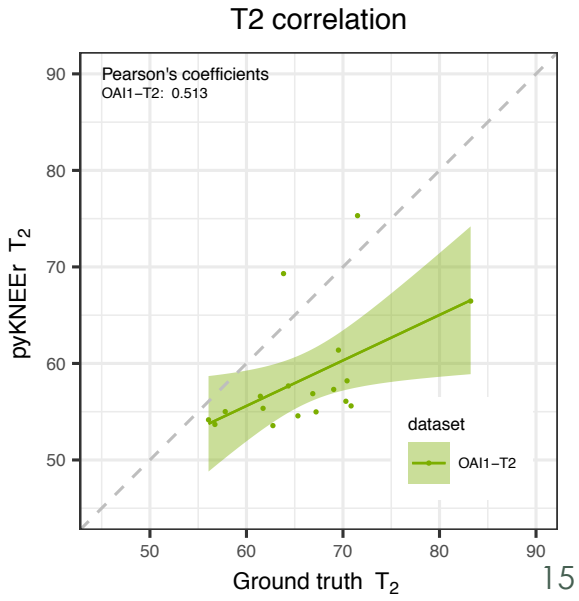




Segmentation can be improved





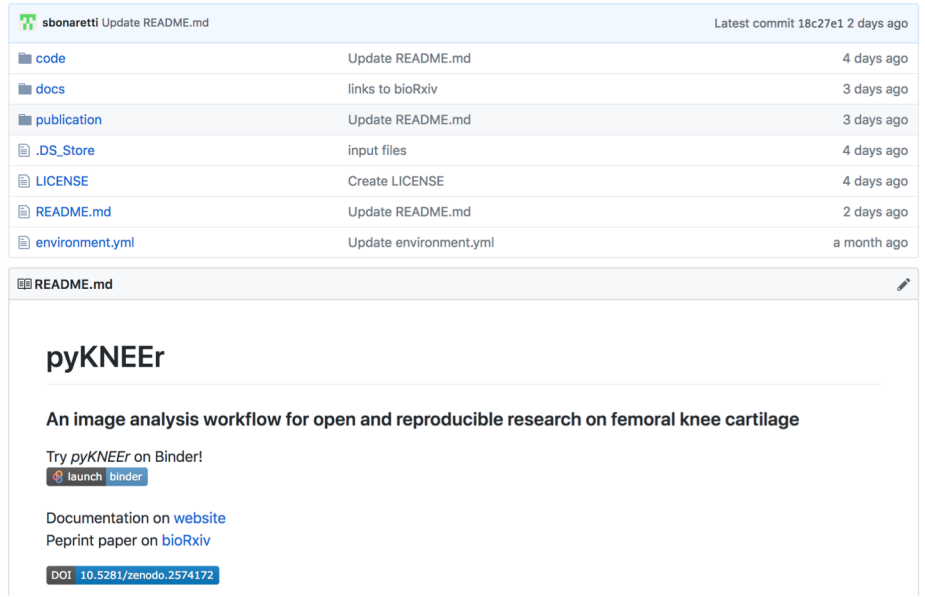


Discussion

- *pyKNEEr* can facilitate transparent research
  - Open source
  - Notebooks can be shared among researchers
  - Notebooks can be linked to publications

- Do you want to use *pyKNEEr*?
  - Go to terminal and type: `pip install pyKNEEr`
  - Download Jupyter notebooks from GitHub
  - Follow the instruction on the documentation (demo)

- Do you want to contribute to *pyKNEEr*?
  - Go to GitHub and create a branch
  - Implement your contribution
    - Segmentation: Machine and deep learning, hybrid, …
    - Thickness algorithms: surface normal vectors, potential field lines, …
    - Other knee tissues: tibial cartilage, patellar cartilage, menisci, …
  - Send a pull request and your code will be merged to the main project



https://github.com/sbonaretti/pyKNEEr

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pyKNEEr: An image analysis workflow for open and reproducible research on femoral knee cartilage

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