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Sammba-MRI: a library for processing SmAll MaMmals BrAin MRI data in Python

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ABSTRACT

Small mammals neuroimaging offers incredible opportunities to investigate structural and functional aspects of the brain. Many tools have been developed in the last decade to analyse small animal data, but current softwares are less mature than the available tools that process human brain data. The Python package Sammba-MRI (SmAll MaMmals BrAin MRI in Python; http://sammba-mri.github.io) is designed to allow flexible and efficient use of existing methods and enables fluent scriptable analysis workflows, from raw data conversion to multimodal processing.

Keywords: Processing pipeline, MRI, registration, small animal Neuroimaging, Python

1 INTRODUCTION

The use of magnetic resonance imaging (MRI) methods in animals provides considerable benefits for improving our understanding of the brain structure and functioning in health and disease. The greatest advantages of preclinical MRI include group homogeneity and the opportunity to acquire a high amount of information repeated or modulated as needed. This added value, together with practical and ethical considerations, resulted in an increase of the use of small mammals MRI in research. However, while human brain imaging benefits from a large variety of high level software solutions for MRI preprocessing and analysis, preclinical MRI is left behind. There is currently an urgent need for efficient and collaborative tools that would facilitate the adoption and dissemination of standardized pre-processing strategies for small animal MRI.

2 TOOLS: PYTHON ECOSYSTEM AND NEUROIMAGING SOFTWARE PACKAGES

With its Free and Open Source Software (FOSS) dependency stack and its growing neuroimaging community Python has been naturally the language of choice for our package. The scientific Python libraries used in Sammba-MRI are NumPy (Oliphant, 2006), SciPy (Millman and Aivazis, 2011), the neuroimaging data analysis tools nibabel[1], Nilearn (Abraham et al., 2014) and Nipype (Gorgolewski et al., 2011). Visualization functionality depends on Matplotlib (Hunter, 2007) or Graphviz (Gansner and North, 2000), but neither is required to perform MRI data processing.

[1] https://nipy.org/nibabel/

Via Nipype, we utilize basic MRI preprocessing functions from AFNI (Cox, 1996), FSL (Jenkinson et al., 2012) and ANTs (Avants et al., 2009) packages. The dependency on the efficient but non open-source brain segmentation RATs tool (Oguz et al., 2014) is optional.

3 CODE DESIGN

Coding guidelines follow the model of Nilearn and other successfully adopted packages (e.g. Scikit-learn Pedregosa et al., 2011) to make the code-base understandable and easily maintainable[2]. Objects are used with parsimony : the different registration classes share all the same interface, and the brain extraction classes comply to the Nipype `BaseInterface`. Effort is made to keep the code uniformly formatted and to use consistent naming for the functions and parameters following the coding conventions of Nilearn. Preprocessing building blocks and pipelines are automatically tested on light MRI data samples to ensure code quality. Finally, the user is guided through Sammba-MRI with extensive documentation including installation instructions, API reference, pipelines graphs, and practical examples based on publicly available small animal neuroimaging datasets.

4 PREPROCESSING BRICKS

In this section, we provide a detailed explanation of the preprocessing building blocks (Figure 1).

4.1 DICOM to NIfTI conversion

Sammba-MRI allows to convert Bruker DICOM (digital imaging and communications in medicine) files to the standard Neuroimaging Informatics Technology Initiative format (NIfTI-1) and extracts extensive information using DCMTK package (Eichelberg et al., 2004). Bruker files conversion is an active development field, with various available tools handling DICOM (e.g. dicomifier[3]) or not (e.g. bru2nii[4], Bruker2nifti[5], bruker2nifti[6]).

[2] http://gael-varoquaux.info/programming/software-design-for-maintainability.html

[3] https://github.com/lamyj/dicomifier

[4] https://github.com/neurolabusc/Bru2Nii

[5] https://github.com/CristinaChavarrias/Bruker2nifti

[6] https://github.com/SebastianoF/bruker2nifti

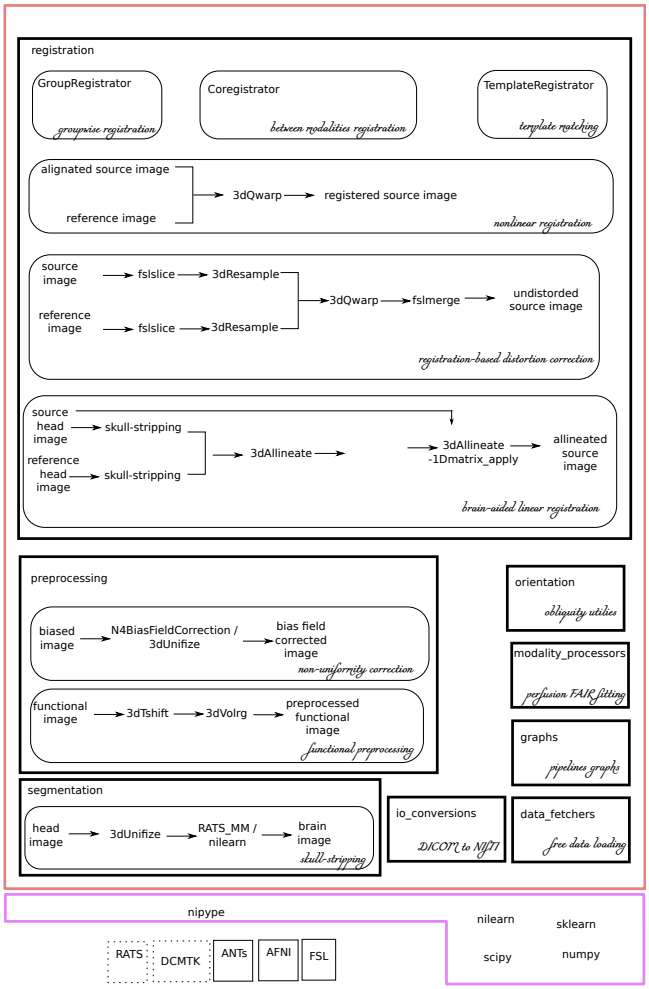

Figure 1. Sammba-MRI major modules.

Finally, ParaVision 360 with the latest patch 1.1 can export the NIFTI format since February 2019. Our implementation is meant to be a light helper function, allowing to handle the conversion on the fly. It has been tested only for Paravision 6 and a limited number of imaging sequences.

4.2 Bias field correction

Intensity non-uniformity modelling is essential in preclinical studies because the intensity gradient corrupting MR images becomes particularly pronounced at high field strengths (Boyes et al., 2008). Sammba-MRI relies on AFNI's `3dUnifize` to correct for intensity bias in anatomical images, and on `N4BiasFieldCorrection` function of the ANTs package (Tustison et al., 2010) for the other modalities. 3dUnifize is also used to aid brain extraction, as detailed in the following paragraph.

4.3 Skull-stripping

Skull-stripping is the critical early step in processing MRI images from small animals. Various automatic rodent-specific softwares (Chou et al., 2011; Oguz et al., 2014) or adaptations of human algorithms (Wood et al., 2013; AFNI's 3dskullstrip -rat) are freely available for research purposes. We choose to rely on the LOGISMOS-based graph segmentation (Yin et al., 2010) based on gray-scale mathematical morphology RATS software (Oguz et al., 2014) because of its good performance across a wide range of datasets (Sargolzaei et al., 2018). An alternative to the free but non-open source RATS tool is also available, based on an adaptation of the human histogram-based brain extraction method of Nilearn. This method can be used in any pipeline by setting the parameter `use_rats_tool` to `False`. Because intensity inhomogeneity can hamper the performance of automatic skull stripping, prior bias field correction is usually recommended (Sled et al., 1998) and is performed by default with `3dUnifize`. The helper function `brain_segmentation_report` from Sammba-MRI `segmentation` module allows to efficiently tune the initial intensity threshold used in bias correction by producing for a given set of thresholds 5 informative measures characterizing the extracted mask to bypass time consuming repetitive visual checks. The returned features consist of the total volume of the extracted mask, its anteroposterior length, its right-left width, and its inferior-superior hight as well as the sample Pearson's product-moment correlation coefficient between the brain mask image and its reflection with respect to the estimated mid-sagittal plane (Powell et al., 2016).

5 READY-TO-USE PIPELINES

Sammba-MRI proposes optimized pipelines to perform spatial registration to a population or standard reference template, inter-modalities registration and functional and perfusion MRI processing. State-of-the-art small animal registration pipelines available as FOSS are the Atlas-based Imaging Data Analysis of structural and functional mouse brain MRI (AIDAmri) (Pallast et al., 2019) package for the registration of functional and diffusion mouse brain MRI with the Allen Brain Reference atlas and the mouse-brain-optimized registration workflow (Ioanas et al., 2019) part of SAMRI package. Sammba-MRI pipelines have been tested throughout the different stages of their development process on various datasets from mouse, rat and mouse lemur and used in several publications from our lab (Garin et al., 2018; Nadkarni et al., 2019; Garin et al., 2019). All pipelines start with bias filed correction for the individual images. The registration itself relies on AFNI's `3dAllineate` and `3dQwarp` functions to estimate linear and nonlinear (piecewise polynomial C^1 diffeomorphism) transforms respectively between the source image and the reference image. Internal parameters of these functions have been optimized for small animal brains. We experienced a better performance when linear registration is performed on brain extracted images and nonlinear warps are computed using whole head images, and therefore followed this strategy across all the registration pipelines.

5.1 Template matching

Template matching is a necessary step for group studies. Several reference templates exist both for mouse and rat brains and the user needs to specify the path to the template of his choice to the `TemplateRegistrator` class from the `registration` module.

```
from sammba.registration import
    TemplateRegistrator
registrator = TemplateRegistrator(
    'dorr_t2.nii.gz',
    brain_volume=400)
registrator.fit('mouse01_t1.nii.gz')
```

We evaluated the registration accuracy of the proposed pipeline on the publicly available Brookhaven in vivo dataset, consisting of T2-weighted images of 12 C57BL/6J male adult mice and their segmentations in 20 brain regions (Ma et al., 2008). The scans were acquired using a 9.4 T Bruker scanner at 100 µm isotropic resolution. The public dataset had

incomplete files/segmentations for 2 subjects so the evaluation was limited to 10 subjects. Because the shared individual images have been pre-registered to one reference image, we submitted them to slight random quadratic deformations (Normally distributed coefficients with std=0.1 mm for translation, 0.1 degrees for rotation, 0.02 mm for scaling, 0.02 mm for shear and 0.005 mm for the remaining 31 polynomial coefficients) before performing the registration to the template. We then measured the regional overlap between each region in the average atlas and the transformed mice atlases using Dice similarity coefficient ($2\frac{|A \cap B|}{|A|+|B|}$) . For comparison purposes, the registration was also performed using SPM mouse (Sawiak et al., 2009). Figure 2 shows that Sammba-MRI pipeline achieves high overlap values and outperforms SPM mouse in the majority of cases.

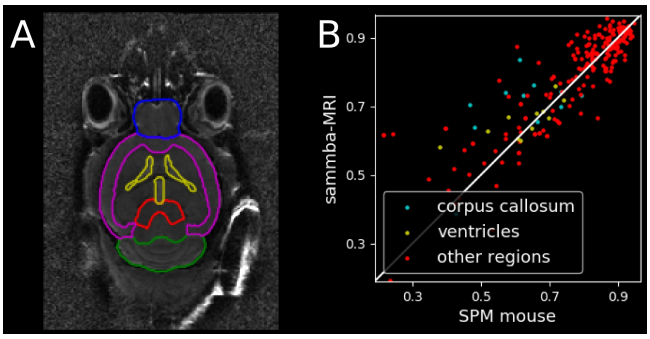

Figure 2. Registration to template of 10 C57 mice: **(A)** individual mouse anatomical image registered to the template with the contours of the average atlas superimposed as coloured lines; **(B)** Dice coefficient between each region in the average atlas and the transformed mice atlases (per region and animal).

5.2 Group-wise registration

Group-wise registration aims to align all images within a common space, resulting in an average brain that represents the commonalities among individual brain anatomies of a particular population. The use of cohort-specific templates eliminates possible bias toward external features and improves subsequent analyzes (De Feo and Giove, 2019). Sammba-MRI implements the multi-level, iterative scheme proposed by (Kovačević et al., 2005) to create a fine anatomical template from individual structural MRI scans. A first rough template is obtained by averaging bias corrected head images centred on their respective brain masks barycentres. Then the individual images are registered to this template. This process of successive averaging/registration is iterated while increasing the number of degrees of freedom of the estimated transform and updating the target template (see (Nadkarni et al., 2019) for a detailed description of the pipeline). The method adapts to different small animal species, e.g. mouse lemurs (Nadkarni et al., 2018), and allows the creation of high quality group average templates (Figure 3).

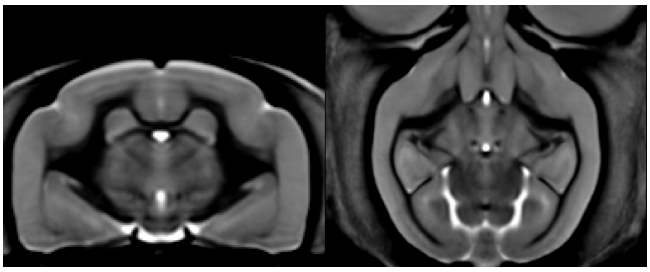

Figure 3. Mouse lemur template from 34 animals.

5.3 Multi-modal processing

In the context of the increasing use of multimodal imaging, several MRI techniques can be acquired from small animals, including structural imaging with different contrasts, blood-oxygenation-level-dependent (BOLD) and arterial spin labeling (ASL) MRI. In addition to the inherent difficulties in intermodality registration (Ashburner and Friston, 1997), severe image artifacts can corrupt the non anatomical scan resulting in a low signal-to-noise ratio (SNR). For instance, the echo planar imaging (EPI) technique widely used in functional MRI and perfusion imaging suffers nonlinear geometric and intensity distortions caused by static magnetic field inhomogeneity that worsen at higher field strengths and have a more dramatic impact on small brains (Hong et al., 2015).

Intra-subject registration between an anatomical scan and another modality is handled through the

Coregistrator class from the registration module.

```
from sammba.registration import
    Coregistrator
coregistrator = Coregistrator(
    brain volume =400)
```

5.3.1 Rigid-body registration

Since orientation is correctly handled through the DICOM to NIfTI conversion, the anatomical image is first reoriented to match the modality of interest. Both images then undergo intensity unification and brain extraction. A rigid body transform that minimizes normalized mutual information between the brain extracted images is finally estimated and applied to the whole head images.

```
coregistrator.fit_anat(
    'mouse01_t1.nii.gz')
coregistrator.fit_modality(
    'mouse01_t2.nii.gz')
```

5.3.2 Reorientation-only

It is possible that the source or/and the reference images are of insufficient quality to correctly estimate a rigid body transform. In this case, assuming that the head motion between the two acquisitions is low, it is better to only reorient the anatomical image to match the modality of interest.

```
coregistrator.fit_anat(
    'mouse01_t1.nii.gz')
coregistrator.fit_modality(
    'mouse01_t2.nii.gz',
    reorient_only=True)
```

5.3.3 Resting state BOLD fMRI processing

BOLD scans are preprocessed using the same usual steps for human data with optional slice timing correction, bias field correction, realignment to the first volume and computation of the temporal mean of all the volumes. The corresponding structural scan is then registered to the average BOLD scan. Since this is a critical step, the user can choose either to pursue with human-like pipeline by estimating a rigid body functional-to- structural transform and applying its inverse to the structural image, or to assume that the head motion between the two scans is negligible. In all cases, the transformed or not structural image is then reoriented to match the functional image. Next, the average functional image and the reoriented structural image are split into 2D slices along the z-direction (according to the slice geometry of the functional image) and each functional slice undergoes afterwards a nonlinear registration step to best match the corresponding structural slice. This per-slice registration corrects for EPI distortion while being more conservative than a global 3D nonlinear registration, to better manage large slice thickness in the BOLD acquisitions of small animals. Since geometric distortions are higher in the through plane direction due to the typically lower resolution than in- plane, the correction is still satisfactory.

5.3.4 ASL fMRI processing

ASL is an attractive method to image the vascular system by directly measuring blood flow. However, estimating the cerebral blood flow (CBF) in small animals is challenging due to the low SNR and lack of sensitivity (Kober et al., 2008). Sammba-MRI allows to preprocess functional ASL scans with the M0 scan used as the representative volume for registration. No between volume realignment is performed because of the usual poor SNR. For Bruker-FAIR (Flow-sensitive Alternating Inversion Recovery) EPI sequences, quantitative CBF maps can be estimated using `fair_to_proc` function from the `modality_processor` module.

5.4 Modality to template and vice versa

BOLD and ASL preprocessing can be performed in the individual space with `Coregistrator` or in template space with `TemplateRegistrator`. In the latter case, the structural-to-template warp, the functional-to-structural rigid body transform and the perslice functional-to-structural warps are combined and applied in a one-big-step transformation to the functional data to minimize interpolation errors. The `TemplateRegistrator` class encompasses an `inverse_transform_towards_modalit`

method to bring an image from the reference space to the individual's space.

5.5 Results

Resting state fMRI allows to study temporally synchronized BOLD oscillations reflecting functionally connected brain networks. As in human resting state fMRI, spatial networks can be extracted using Independent Components Analysis (ICA) and were successfully demonstrated in anaesthetized mice (Zerbi et al., 2015; Grandjean et al., 2019). We preprocessed the publicly shared functional data from 15 mice (2-3 months old) from Zerbi et al. (2015) paper with Sammba-MRI and performed a group ICA (Varoquaux et al., 2010) with 30 components. Relevant bilateral regions related to somatosensory, hippocampal, visual, basal ganglia, and sensorimotor networks. were obtained without additional data post-processing Figure 4. To illustrate the perfusion processing pipeline, we used perfusion FAIR images from 10 C57BL/6J mice (5-7 months) to quantify CBF. Figure 5 shows voxelwise map averaged across all individuals and regional absolute CBF values, all in agreement with the literature (Muir et al., 2008).

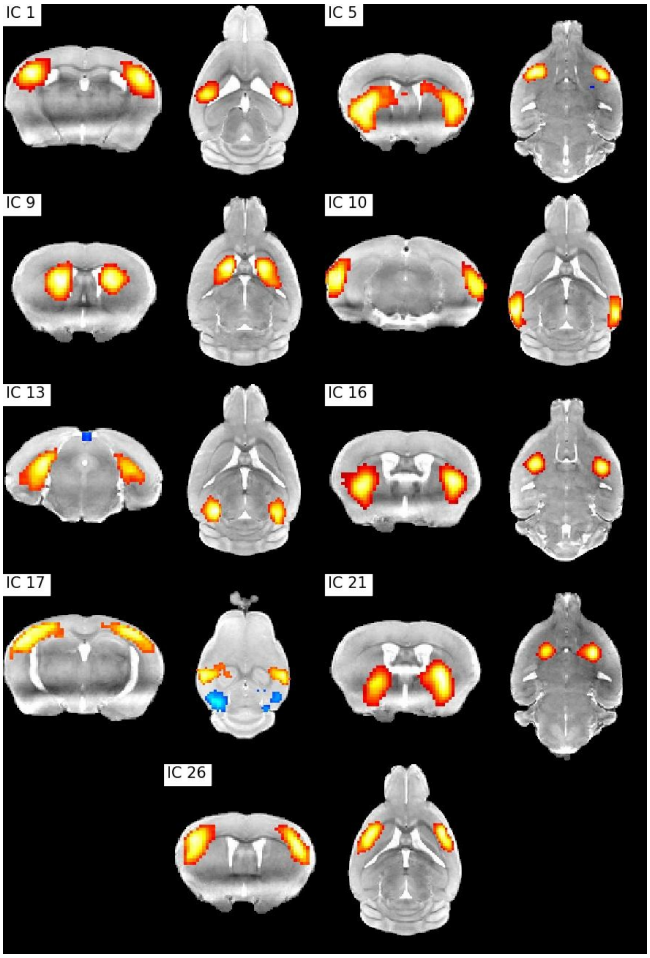

Figure 4. ICA bilateral components. IC 1: Barrel field (i) cortex, IC 5: Lateral striatum, IC 9: Dorsal striatum (i), IC 10: Visual cortex, IC1 3: Hippocampus, IC 16: Dorsal striatum (ii), IC 17: Barrel field (ii) cortex, IC 21: Ventral striatum, IC 26: Supplementary cortex

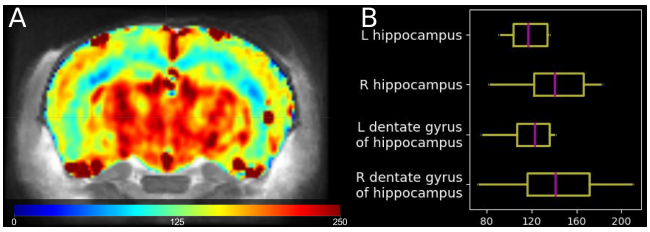

Figure 5. CBF from 10 C57 mice in ml/100g/min: **(A)** group average CBF map ; **(B)** individual regional CBF.

6 BIG DATA, REPRODUCIBILITY, COLLABORATION

The package design facilitates big data exploration: the user is able to run an entire analysis in a single Python script, rerunning pipelines is optimized through Nipype caching mechanism and long lasting steps (nonlinear warping, perfusion fitting) are executed in parallel. We believe that reproducibility in the neuroimaging field is not possible without making the acquired images and the preprocessing code available to the community. For this reason, Sammba-MRI promotes the sharing of MRI data by providing utility functions to download public small animal brain MRI datasets and relies on it for demoing the package capabilities. In order to encourage external contributions, our library source code is hosted on the open collaborative GitHub platform and distributed under the CeCILL v2.1 license, a FOSS license adapted to both international and French legal matters allowing anyone to make changes and redistribute it. Sammba-MRI supports GNU/Linux and Mac OS X operating systems (OS), used by over 70% of neuroimagers (Hanke and Halchenko, 2011).

7 CONCLUSION

By efficiently combining different existing human and animal neuroimaging tools, Sammba-MRI allows to tackle common processing issues in a fully automated fashion. High quality spatial registration can be easily performed, including template matching, between modalities registration as well as the creation of cohort-specific templates. Sammba-MRI also implements functional and perfusion MRI preprocessing methods and cerebral blood flow estimation for FLAIR perfusion images. Emphasis is put on code readability and ease of use to favour contributions from the community.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

SB, NN and MC contributed code to the project. NN, CG and MD contributed to data acquisition. SB wrote the manuscript with input from CG and NN. Every author read and approved the manuscript.

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DATA AVAILABILITY STATEMENT

The mouse lemur dataset can be automatically loaded through Sammba-MRI or directly from https://nitrc.org/projects/mouselemuratlas for the template and https://openneuro.org/datasets/ds001945 for the original anatomical images. The perfusion dataset will be made publicly available following publication.

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