

LIFEx: a freeware for radiomic feature calculation in multimodality imaging to accelerate advances in the characterization of tumor heterogeneity

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ABSTRACT

Textural and shape analysis is gaining considerable interest in medical imaging, particularly to identify parameters characterizing tumor heterogeneity and to feed radiomic models. Here we present a free, multiplatform, and easy-to-use freeware called LIFEx, which enables the calculation of conventional, histogram-based textural and shape features from PET, SPECT, MR, CT, and US images, or from any combination of imaging modalities. The application does not require any programming skills and was developed for medical imaging professionals. The goal is that independent and multicenter evidence of the usefulness and limitations of radiomic features for characterization of tumor heterogeneity and subsequent patient management can be gathered. Many options are offered for interactive textural index calculation and for increasing the reproducibility among centers. The software already benefits from a large user community (more than 800 registered users), and interactions within that community are part of the development strategy.

STATEMENT OF SIGNIFICANCE

This study presents a user-friendly, multi-platform freeware to extract radiomic features from PET, SPECT, MR, CT, and US images, or any combination of imaging modalities.

Introduction

Texture analysis has been suggested since the early eighties as a way to extract relevant information characterizing tissue types from various medical images. Recently, there has been renewed interest in texture analysis in the context of tumor imaging (1), assuming that textural features could reflect intratumor heterogeneity, which is known to have important implications in cancer research (2). Texture analysis is also a key component of radiomics (3). Despite promising results, texture analysis has not yet been transferred to the clinic for several reasons, including a limited understanding of the biological meaning of the measured textural features, the lack of evidence of significant added value of textural features compared to more conventional indices in prospective studies, and the insufficient control of the false discovery rates (4). In addition, although various research software programs that enable the calculation of radiomic features (RF) have been developed (examples in Supplemental Table 1), easy-to-install and user-friendly software that can be easily interfaced with the Picture Archiving and Communication System is not yet widely available. Last, the use of RF in the clinics is hampered by the unavailability of widely validated radiomic models. The identification of robust radiomic models is complicated by the variability of feature values as a function of the acquisition device and acquisition protocols (5-8), although harmonization methods have recently been described (9).

In an effort to boost the promising research regarding the potential and use of textural analysis in medical imaging, we developed freeware dedicated to the easy calculation of RF from medical images that does not require any specific programming skills. The goal was to contribute to reproducible research (10) by offering the scientific and medical community a free and user-friendly way to access parameters that are considered as potential relevant biomarkers so that results from many investigators can be obtained and the role that textural analysis can play in image interpretation and radiomics can be clarified.

Here, we present the main characteristics of the software and two cases in which it was used. The free software was released in February 2016 and has already gathered more than 800 registered users around the world. The software comes with various resources (detailed documentation, video tutorials, list of bibliographic references) that are all available <http://www.lifexsoft.org>.

Overall features of the LIFEx software

LIFEx is a free Java application that does not rely on any commercial library and is implemented for Windows, Linux and Mac operating systems. Its installation is straightforward from the provided installation packages. Personalized user support is provided.

Elementary functionalities of LIFEx include the following:

- A graphical user interface (GUI) that is similar to the interface offered by scanner vendors.

The GUI supports keyboard shortcuts and mouse-driven operations and includes two main panels dedicated to the management of image series and volumes of interest (VOI) (Figure 1).

- A browser for reading DICOM images locally or over a DICOM network from DICOM nodes. Non-DICOM formats (NIFTI-1, JPG, TIFF, PNG, BMP) are also supported.

- A viewer supporting the synchronized display of coronal, sagittal and transaxial slices, the management of different image layers corresponding to different image series (for instance, PET and CT, or PET and MR, or T1 weighted MR and T2 weighted MR) and maximum intensity projection display. Mouse-driven navigation through an image volume in the 3 directions simultaneously is available. Time series can be displayed either as a set of images on a single screen or as a stack of images through which the user can navigate using the mouse button. The viewer supports interseries or intraseries supervised image registration.

- RF calculation using optimized memory access for sparse textural matrix computation.

Parallel thread execution is used to speed up the calculation by taking advantage of the available CPU power.

- Exportation of results in a system file supporting screenshots (PNG format), image-derived values (CSV or XLS formats), PDF booklets including sets of screenshots selected by the user, transformation matrix when image registration is performed (TXT), and VOI (NIFTI-1 format).

Radiomic feature calculations

In LIFEx, a so-called protocol is a set of elementary functions assembled into a logical workflow to produce a result. LIFEx includes a protocol dedicated to the calculation of RF from medical images with all the necessary tools (Figure 1).

Segmentation. Three options are available to define the VOI from which RF can be calculated. A VOI drawn using another software and stored as a RTSTRUCT object in a DICOM file or in NIFTI-1 format can be imported. The region can also be drawn manually with the 2D or 3D drawing tool or using a semi-automated segmentation method that operates in a previously drawn loose VOI including the target of interest or in the whole image. The segmentation methods currently offered are threshold-based methods accounting or not for background intensity and a click and draw option that creates a VOI from a seed point defined by the click using a region growing approach.

Radiomic index calculation. Some steps involved in the RF calculation significantly affect the results, including the VOI delineation, the quantization of the voxel values before textural index (TI) calculation, the voxel size, and the implementation of textural index calculation in 3D. Voxel value quantization reduces the number of intensity values in the VOI to a fixed set to mitigate the impact of noise on values and to decrease the size of the matrix used for some

TI calculations. Relative and absolute quantization are available in LIFEx, yielding significantly different results in terms of tissue type discrimination and value interpretation (11,12). Quantization can also be performed in a range defined by the mean and standard deviation voxel values in the VOI. As some TI values depend on the voxel size (13), in LIFEx, the user can specify the voxel size to be used for TI calculation. When the specified voxel size is different from the native one, the image is first resampled to the target voxel size using a Lagrangian polynomial of degree 5. Voxel value quantization is performed after the spatial resampling step if any. In its current version, LIFEx calculates 44 RF reflecting the VOI shape, the VOI voxel values, the histogram of VOI values, or the VOI textural content (See www.lifexsoft.org/index.php/resources/19-texture/radiomic-features for a list of all available RF). TI can be calculated in 2D for 2D regions of interest or in 3D for VOI, where the 3D extension strategy depends on the TI and is fully described in the technical appendix provided with the software (www.lifexsoft.org/index.php/resources/documentation).

LIFEx can be run either interactively or offline using a scripting mechanism. This option is especially relevant when repeated calculations must be performed to explore the impact of some parameters on the results. The script is a simple text file in which successive command lines specify the image filenames to be loaded, the region of interest filename(s) to be read, the settings to be used for the calculations of all radiomic features, and the filename in which the results should be saved. An example of the script is provided (www.lifexsoft.org/index.php/resources/documentation) and can be easily edited to one's own needs.

The integration of LIFEx in a complete radiomic workflow is illustrated in Figure 2.

Use cases

Video 1 shows a real-time complete example of radiomic feature calculation from a PET/MR scan where the same VOIs are used to extract PET and MR radiomic features, demonstrating the ease of use of the software. The same process can be applied to any combination of image series and/or parametric image series to obtain a complete multimodality radiomic description of the tumor features.

In a second case study, we show how LIFEx can be used to demonstrate the impact of the voxel size on some RF values in 18F-FDG PET scans of 109 patients with breast cancer (age range [28-90] years, mean \pm 1 SD = 57 \pm 15). This study was approved by the institutional ethics committee and all the patient's data were analyzed retrospectively and anonymously, thus the need for patient approval was waived. Patients were all scanned on a Philips Gemini TF PET/CT scanner, 83 \pm 10 min (range [64-108] min) after the injection of 18F-FDG (3 MBq/kg). PET images were obtained with 1.45 min per bed position and reconstructed using a list-mode iterative algorithm (Blob-Ordered-Subsets-Time-Of-Flight, 2 iterations, 33 subsets). For each patient, five volumes of interest (23 mL in volume each) were drawn in healthy regions, namely, the liver, spleen, lung, muscle and fatty tissue and in the primary tumor (40% intensity threshold). The RF values were calculated using three different voxel sizes using a script: that of the original images (voxel size = 4 x 4 x 4 mm³) and 2 x 2 x 2 mm³ and 1 x 1 x 1 mm³. Supplemental Figure 1 clearly shows that some RF values highly depend on the voxel size used for the calculation, unlike the standardized uptake value that is always used in the clinic. These results demonstrate the need to account for voxel size in radiomic model design and application.

Beyond these two examples, LIFEx has been used in a number of publications

(www.lifexsoft.org/index.php/resources/publications-journal-papers,

www.lifexsoft.org/index.php/resources/publications-conference-abstracts, Supplemental

Table 2) with biological and clinical impacts. Images from various PET, CT, MR and US

from different imaging devices (list on [www.lifexsoft.org/index.php/resources/76-list-of-](http://www.lifexsoft.org/index.php/resources/76-list-of-systems-as-lifex-compatible)

[systems-as-lifex-compatible](http://www.lifexsoft.org/index.php/resources/76-list-of-systems-as-lifex-compatible)) have been processed. Sample PET/CT, PET/MR and US data

are provided at <http://www.lifexsoft.org/index.php/resources/data-files> for newcomers to try

the software.

Discussion

LIFEx has been designed as an easy-to-install and user-friendly software enabling RF

calculations from medical images and including many options and large flexibility in terms of

parameter settings, without the need for any programming skills. By offering it as a free and

multi-platform (Mac, Windows and Linux) tool, the goal is to make radiomic feature

calculation accessible to a large community of imaging professionals so that independent and

multicenter evidence of the usefulness and limitations of RF for tumor heterogeneity

characterization and subsequent patient management can be gathered. LIFEx is an evolving

tool (currently V4.00) in which new functions are constantly added as texture analysis and

radiomics develop. Feedback from users and interactions with the radiomic community are

part of the development strategy.

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References

1. Alic L, Niessen WJ, Veenland JF Quantification of heterogeneity as a biomarker in tumor imaging: a systematic review. *PLoS ONE* 2014;**9**: e110300.
2. Fisher R, Pusztai L, Swanton C. Cancer heterogeneity: implications for targeted therapeutics. *Br J Cancer* 2013;**108**:479-85.
3. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images are more than pictures, they are data. *Radiology* 2016;**278**:563-77.
4. Chalkidou A, O'Doherty MJ, Marsden PK. False discovery rates in PET and CT studies with texture features: a systematic review. *PLoS One* 2015;**10**:e0124165.
5. Nyflot MJ, Yang F, Byrd D, Bowen SR, Sandison GA, Kinahan PE. Quantitative radiomics: impact of stochastic effects on textural feature analysis implies the need for standards. *J Med Imaging* 2015;**2**:041002.
6. Yan J, Chu-Shern JL, Loi HY, Khor LK, Sinha AK, Quek ST, Tham IW, Townsend D. Impact of image reconstruction settings on texture features in 18F-FDG PET. *J Nucl Med* 2015;**56**:1667-73.
7. Zhao B, Tan Y, Tsai WY, Qi J, Xie C, Lu L, Schwartz LH. Reproducibility of radiomics for deciphering tumor phenotype with imaging. *Sci Rep* 2016;**6**:23428.
8. Reuzé S, Orlhac F, Chargari C, Nioche C, Limkin E, Riet F, Escande A, Haie-Meder C,

- Dercle L, Gouy S, Buvat I, Deutsch E, Robert C. Prediction of cervical cancer recurrence using textural features extracted from 18F-FDG PET images acquired with different scanners. *Oncotarget* 2017; **8**:43169-43179.
9. Orhac F, Boughdad S, Philippe C, Stalla-Bourdillon H, Nioche C, Champion L, Soussan M, Frouin F, Frouin V, Buvat I. A post-reconstruction harmonization method for multicenter radiomic studies in PET. *J Nucl Med* 2018;**59**: in press (doi: 10.2967/jnumed.117.199935)
10. Fomel S, Claerbout J. Introduction: reproducible research. *Comput Sci Eng* 2009;**11**:5-9.
11. Leijenaar RT, Nalbantov G, Carvalho S, van Elmpt WJ, Troost EG, Boellaard R, Aerts HJ, Gillies RJ, Lambin P. The effect of SUV discretization in quantitative FDG-PET radiomics: the need for standardized methodology in tumor texture analysis. *Sci Rep* 2015;**5**:11075.
12. Orhac F, Soussan M, Chouahnia K, Martinod E, Buvat I. 18F-FDG PET-derived textural indices reflect tissue-specific uptake pattern in non small cell lung cancer. *Plos One* 2015;**10**:e0145063.
13. Orhac F, Thézé B, Soussan M, Boisgard R, Buvat I. Multi-scale texture analysis: from 18F-FDG PET images to pathological slides. *J Nucl Med* 2016;**57**:1823-28.

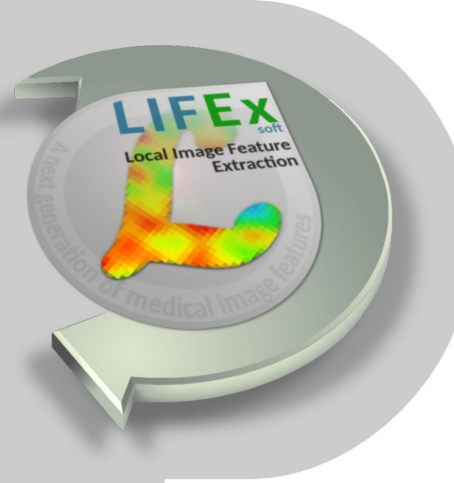
Figure legends

Figure 1: Snapshot of the LIFEx user interface.

Figure 2: Workflow of the radiomic processes in which LIFEx can be involved. LIFEx operation (green circular arrow) can be used to calculate radiomic features that are part of the learning workflow (light purple arrow) to derive a radiomic model. LIFEx can also be used to produce the radiomic features entering a radiomic model for decision support (decision workflow, blue arrow).

Video 1: Demonstration of the use of LIFEx for radiomic feature extraction from a PET/MR scan

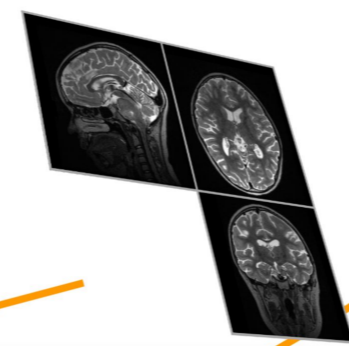
http://www.lifexsoft.org//images/phocagallery/documentation/ProtocolTexture/TutorialMovies/TextureProtocolPETMR_yuv420p.mp4



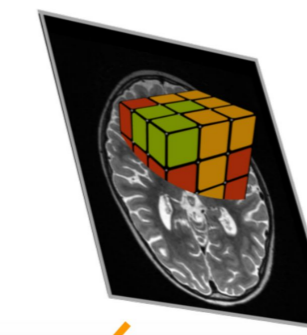
Screenshot of LIFEX

start

1) Image acquisition
 DICOM: PET, NM, MR, CT, US
 Others: Nifti-1, BMP, TIF, PNG, JPG

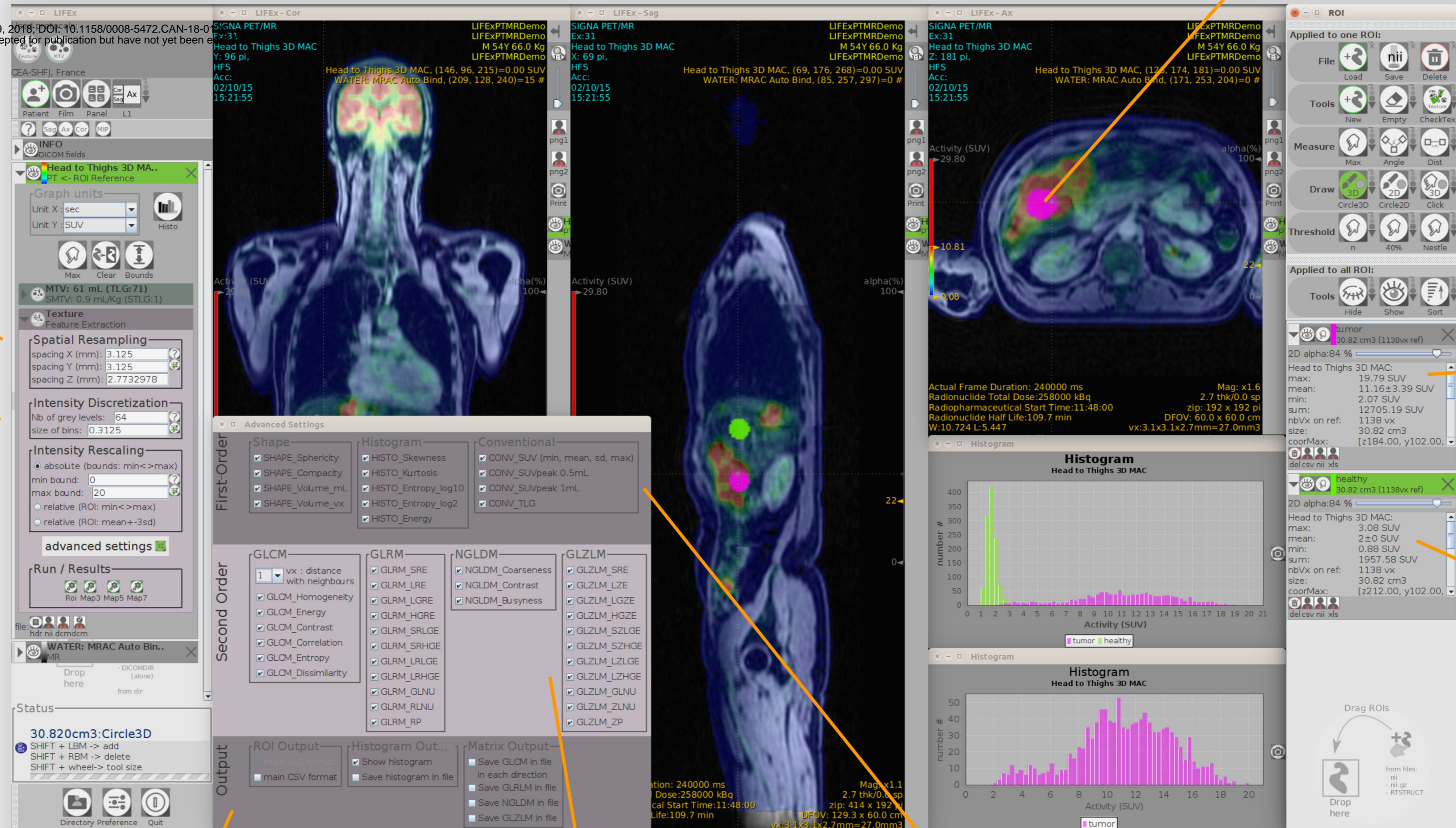


2) Loading images
 Axial, Coronal, Sagittal



3) Loading ROI or drawing ROI

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5.1) Spatial resampling
 spX, spY, spZ

5.2) Intensity discretization

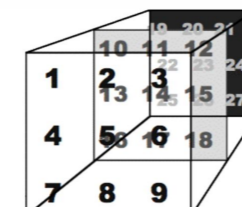
5.3) Intensity rescaling
 absolute
 relative
 mean+3SD

4.1) Values extracted from ROI C1

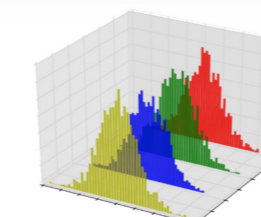
4.2) Values extracted from ROI C2

1.3 2.1 4.0
 6.3 3.7 4.2
 2.4 3.2 7.1
 9.0 9.6 4.6
 2.3 1.2 4.4

6.3) Radiomic features
 Output of LIFEX



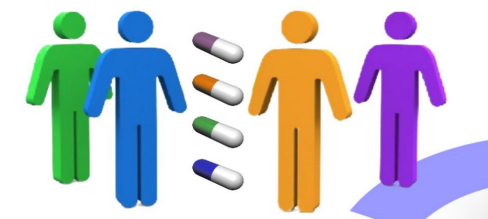
6.2) Texture matrices
 GLCM, GLRM
 NGLDM, GLZLM



6.1) First-order statistics
 shape, histogram,
 min, max, mean, peak

Workflow for exploiting radiomic biomarkers

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Treatment personalization

Decision support

Running the prediction model

start

1) Image acquisition
 DICOM: PET, NM, MR, CT, US
 Others: Nifti-1, BMP, TIF, PNG, JPG

2) Loading images
 Axial, Coronal, Sagittal

3) Loading ROI or drawing ROI

4) Extraction of basic stats from ROI

5.1) Spatial resampling
 spX, spY, spZ

5.2) Intensity discretization

5.3) Intensity rescaling
 absolute
 relative
 mean+3SD

6.1) Calculation of first-order statistics
 shape, histogram,
 min, max, mean, peak

6.2) Calculation of texture matrices
 GLCM, GLRM
 NGLDM, GLZLM

6.3) Radiomic features
 Output Data

Prediction model

Machine learning
 random forest, SVM,
 clustering,
 neural network,
 etc

Omics, etc:
 Genomics,
 Proteomics,
 Clinical data,
 Immunohistochemistry

Radiomic-based workflow

Decision workflow

Learning workflow

LIFEx workflow

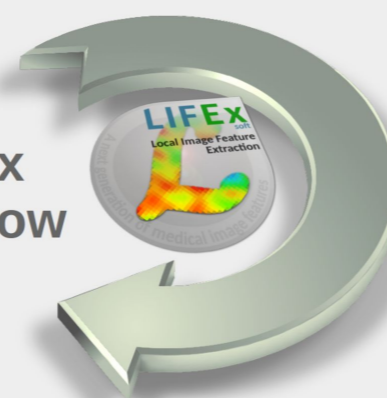


Figure 2

Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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