"LIBRA": a Publically Available Software Solution for Fully-Automated Mammographic Density Assessment

By Dr. A Gastounioti, Dr. O H Maghsoudi, Dr. C Vachon, Dr. E F Conant & Dr. D Kontos

This article provides an overview of LIBRA, a publically available software solution for fully-automated mammographic density assessment. LIBRA has been increasingly utilized around the world in multiple studies examining mammographic density and breast cancer risk. Here, we summarize representative studies and discuss the latest software extensions of LIBRA as well as future directions.

INTRODUCTION

Breast cancer is the most common cancer in women worldwide, and mammographic density (MD) is one of the strongest breast cancer risk factors [1]. MD reflects the mammographic appearance of the breast, with different proportions of fibroglandular and fatty tissue as the basic components of breast parenchymal tissue [2]. Women with high MD have a 3 — 5-fold increased breast cancer risk as compared to women with low MD [1]. Moreover, MD is also associated with decreased mammographic sensitivity due to "masking" or obscuration of tumors by areas of dense breast tissue [3-6].

The most commonly used method to assess MD in clinical practice is the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) lexicon [7]. According to the ACR BI-RADS lexicon, MD is visually graded by the radiologist into one of four categories,

Type A: almost entirely fatty;

Type B: scattered fibroglandular densities;

Type C: heterogeneously dense; and

Type D: extremely dense [7].

However, BI-RADS density assessments are subjective and limited by a large degree of inter- and intra-reader variability. To overcome the subjective nature of visual BI-RADS MD assessment, fully automated software tools that generate robust and reproducible quantitative measures [8] have been made available by commercial vendors [9, 10] and the research community [11]. Such software packages usually provide both absolute as well as percentage metrics of the amount of mammographically dense tissue in the breast. In addition to generating reproducible quantitative metrics, these tools provide continuous values of MD, rather than a categorical assessment, which may also allow for more refined, density-based breast cancer risk stratification as well as assessment of changes in MD.

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Among the widely-used fully-automated tools for MD assessment, the "Laboratory for Individualized Breast Radiodensity Assessment (LIBRA)" has been developed at the University of Pennsylvania, and is a publically available MD estimation software solution based on a published algorithm for digital mammography images [11]. Since LIBRA made its first public appearance in 2015, it has been used by multiple institutions around the world. As of now, we estimate that LIBRA has been applied to >150,000 mammograms. In this article, we will provide an overview of LIBRA, including a review of key application studies, latest software extensions, and future directions.

THE LIBRA SOFTWARE

LIBRA was developed to be a fully-automated method for area-based MD estimation from full-field digital mammography (FFDM) images, and has, thus far, been validated to work on Hologic and GE Healthcare FFDM systems [11].

Briefly, LIBRA first applies an edge-detection algorithm to delineate the boundary of the breast and the boundary of the pectoralis muscle, which together define the breast tissue area. Following the segmentation of the breast, an adaptive multi-class fuzzy c-means algorithm is applied to identify and partition the breast tissue area, into multiple regions (i.e., clusters) of similar gray-level image intensity. These clusters are then aggregated by a pre-trained support-vector machine classifier to the final dense tissue area [Figure 1]. By

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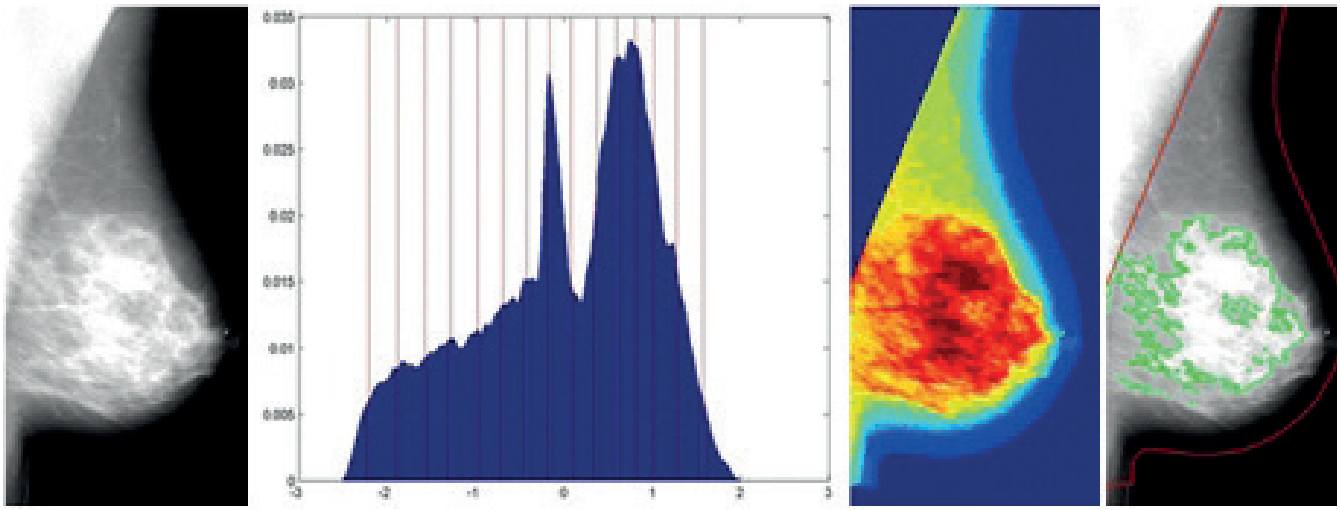

Figure 1. Mammographic density estimation example using LIBRA. From left to right: digital mammography image, image intensity histogram and cluster centers, color-coded image clustering result, and final spatial segmentation map with the breast region outlined in red and the dense tissue segmentation outlined in green [11].

calculating the area of dense pixels, LIBRA provides an estimate of the total absolute dense tissue area (DA), while normalizing DA by the total breast area results in breast percent density (PD%).

Besides being publically available, LIBRA has the important advantage of being applicable to both raw (i.e., "FOR PROCESSING") and vendor post-processed (i.e., "FOR PRESENTATION") FFDM images. This is very important since most clinical practices do not archive raw images due to cost and storage constraints, leaving only the processed FFDM image data available for retrospective analysis. Furthermore, LIBRA generates a spatial segmentation map [Figure 1] which allows the user to confirm the estimated MD and may also provide valuable insights about breast regions driving breast cancer risk.

LIBRA was first publically released in 2015, as a pre-compiled stand-alone executable to ensure platform-wide compatibility; source files were also made available for development purposes. In 2017, LIBRA was also integrated into the Cancer Imaging Phenomics Toolkit (CaPTk) [12], a publically available software platform for analysis of radiographic images of cancer, developed at the University of Pennsylvania. Through CaPTk, LIBRA has two modes of operations: (1) an interactive mode with Graphical-User-Interface where the user can select a single FFDM image or a batch of FFDM images for processing and

(2) a command-line interface amenable to batch processing and scripting.

Since its first release, LIBRA has had continuously increasing community engagement. As of now (September 20) LIBRA has received >565 downloads from multiple institutions worldwide [Figure 2a]. Moreover, studies related to the development of LIBRA and scientific discoveries obtained via LIBRA usage (28 publications) [11, 13-39] have collectively received >556 citations following a trend of exponential increase [Figure 2b]. In total, we estimate that LIBRA has been applied to >150,000 mammographic FFDM images worldwide.

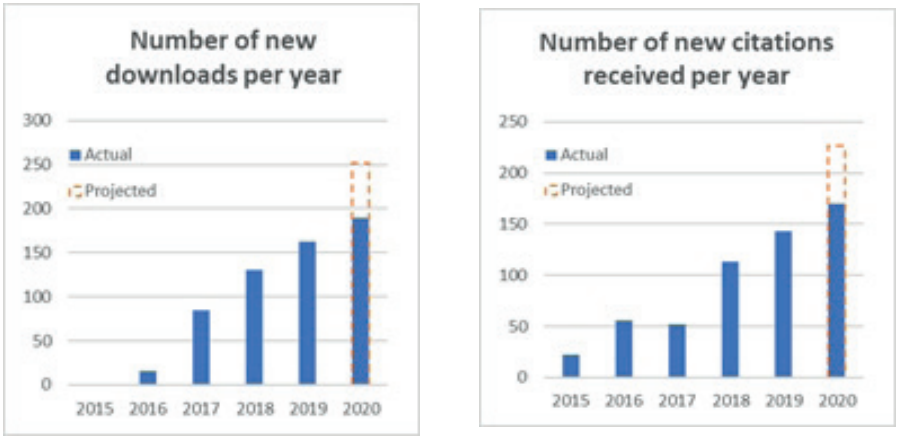

Figure 2a. LIBRA-related downloads and **2b.** Citations as of September 2020.

KEY STUDIES USING LIBRA TO QUANTITATE MAMMOGRAPHIC DENSITY

LIBRA has been utilized in various studies of MD. These studies include a large cohort study with 9,498 women within the "Population-based Research Optimizing Screening through Personalized Regimens" (PROSPR) Network of the National Cancer Institute (NCI) of the National Institutes of Health (NIH), where LIBRA revealed MD disparities between different ethnic groups [15]. Additional key studies have focused on associations of MD measures with other established risk factors [13] and inflammatory markers [20], as well as on quantifying MD changes due to aspirin use [19] and bariatric surgery [16].

Moreover, LIBRA MD measures have consistently shown positive associations with breast cancer in several case-control studies conducted by the University of Pennsylvania, the London School of Hygiene and Tropical Medicine, the University of Melbourne, and Lund University [17, 18, 28, 29], all focusing on density estimates from the contralateral breast at the time of breast cancer diagnosis. For instance, in a US study with raw FFDM images from a racially diverse sample of 106 breast cancer cases and 318 controls (Ethnicity: 57% Caucasian; 22% African American; 3% Asian; 18%

Table 1. LIBRA density distributions and associations with breast cancer in the latest case-control study by the Mayo Clinic[14].

	Breast cancer cases (n = 437)	Controls (n = 1225)	OR*
Raw FFDM images			
LIBRA PD%	11.4 (10.5) [3.8, 58.6]	10.8 (8.8) [2.9, 52.2]	1.2 (1.1, 1.4)
LIBRA DA	19.8 (11.4) [3.5, 90.5]	18.7 (11.3) [4.4, 83.1]	1.1 (1.0, 1.3)
Processed FFDM Images			
LIBRA PD%	16.8 (16.9) [2, 69.3]	14.9 (14.3) [1.7, 77.9]	1.3 (1.1, 1.5)
LIBRA DA	25.9 (17.3) [7.2, 98.9]	23.1 (13.8) [5.8, 121.8]	1.2 (1.1, 1.4)

Note. Data are median values, with interquartile ranges in parentheses and ranges in brackets. * Odds ratios (ORs) per SD and C-statistics were calculated from models adjusted for age and body-mass index. Numbers in parentheses are 95% confidence intervals. FFDM: full-field digital mammography; PD%: percent density; DA: dense area.

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Other/Unknown), the authors reported strong associations between breast cancer and the LIBRA-derived percent density, LIBRA PD% (Odds Ratio, OR per standard deviation, SD = 2.6 (95% CI: 1.8-3.9)) and Dense Area, DA (OR = 2.6 per SD (95% CI: 1.9-3.6))(29). High ORs) with increased MD were also reported in a Korean study evaluating LIBRA on 398 breast cancer cases and 737 controls, where LIBRA DA demonstrated an OR (per SD) of 1.7 (95% CI: 1.4-2.2)(17).

Moreover, LIBRA has been evaluated in European populations where it demonstrated:

(a) an OR of 1.32 (95% CI: 1.1-1.6) for PD% extracted from processed images of 414 breast cancer cases and 684 controls [18], as well as

(b) statistically significant differences in PD% change over time between breast cancer cases and controls [28].

The latest case-control study of LIBRA by the Mayo Clinic [14) was the first to examine LIBRA density measures as risk factors on mammograms that had been acquired years prior to the diagnosis of breast cancer. Using 437 women diagnosed with breast cancer and 1225 controls, the study reported significant associations of LIBRA density measures with breast cancer risk on both raw and processed FFDM images [Table 1]. LIBRA density estimates were also strongly correlated to those from established commercial and research breast density programs, such as Volpara [9] (r = 0.85-0.90) and Cumulus [40, 41] (r = 0.77-0.84), p<0.001 for both.

Furthermore, LIBRA is part of an ongoing international challenge evaluating MD measurements in a large dataset of 1650 cases and 1929 controls from five contributing sites in Australia, Malaysia, Norway, the UK and the USA [42].

LATEST LIBRA SOFTWARE EXTENSIONS AND FUTURE DIRECTIONS

FFDM has been rapidly being replaced by digital breast tomosynthesis (DBT) for breast cancer screening. DBT, also an x-ray imaging modality, creates reconstructed quasi-3D images of the breasts from a series of low-dose, 2D projection images acquired at different angles [43, 44]. In many facilities, DBT screening is also being performed with "synthetic 2D mammograms" reconstructed from the DBT acquisition making the FFDM component of the screening study obsolete [45]. To follow such advancements in breast cancer screening, LIBRA has been

"...future priorities are the extensive validation of LIBRA for DBT, including larger, multi-site and multi-racial populations, which will pave the way to the first public release of the DBT version of LIBRA..."

retrained for area-based density evaluation from synthetic mammograms [37]. Moreover, LIBRA has been recently extended for volumetric density estimation (VBD) from 3D reconstructed slices acquired with DBT [33].

Briefly, the DBT VBD algorithm works in three steps:

1) initial segmentation of the dense tissue in raw DBT projection images,

2) use of these segmented projection images to build a 3D density likelihood map, with the statistical likelihood of dense tissue in each voxel and

3) refinement of the dense tissue segmentation in the 3D reconstructed DBT data using texture analysis and a pre-trained multi-feature classifier to identify blurring effects.

Summing the dense voxel volumes provides total absolute dense volume (DV), while normalizing DV by the total breast volume defines volumetric breast percent density (VPD%).

Future evaluation will focus on examination of LIBRA density measures on FFDM images acquired years prior to the diagnosis of breast cancer. Other future priorities are the extensive validation of LIBRA for DBT, including larger, multi-site and multi-racial populations, which will pave the way to the first public release of the DBT vesrion of LIBRA. Furthermore, we aim to also look into comparisons and potential integration with more refined breast parenchymal complexity features which are complementary to the amount or percent of dense tissue in the breast and are provided by emerging radiomic and deep learning methodologies [31, 46-48].

CONCLUSION

LIBRA is a publically available software solution for area-based MD assessment

from both raw and processed digital mammograms and has also been recently extended for MD estimation with DBT images. LIBRA has been increasingly utilized around the world in various studies, confirming MD as a robust risk factor. LIBRA is integrated into the CaPTk platform and can be downloaded from NITRC (*www.nitrc.org/projects/cbica_libra/*) and GitHub (*https://github.com/CBICA/CaPTk*).

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