Build Super-resolution Images with Aberration Correction and Ultrasound Localisation Microscopy

In the Ultrasound Imaging lecture, we introduced Ultrasound Localization Microscopy (ULM), an imaging modality that uses a contrast agent, microbubbles, to image the vasculature with unprecedented spatio-temporal resolution [1]. In this project, you will discover how the technique works in more details, and implement it on real research data from a recent high impact research paper [2]. Your objective will be to retrieve as much information as possible from raw ultrasound data, and to display it in a readable (and esthetical if possible) manner. You will then have to organize your work and your findings in the shape of a research paper.
In the first half of the project, your reflexion will be guided by specific questions and points to consider, but you are also expected to be creative to pass the different steps. Keep in mind that usually in research there is not a single solution for a given question. Any trial and implementation of your own will be appreciated if presented in a scientific manner: detailed explanation of the implementation, (quantitative/comparative) characterisation of the results, explanation of the limits, and ideas for improvements.

More precisely, for the evaluation you have to hand in:

1) A high quality image reconstructed from raw data, associated to the skull induced aberration law over the transducer width, in µs (.mat file)
2) A map of bubble positions, with a $\lambda/10$ resolution (.mat file)
3) A map of bubble velocities, with a $\lambda/10$ resolution (.mat file)
4) A document explaining your work and taking the form of a research article (4 pages max., following the plan: introduction, methods, results, discussion/conclusion).

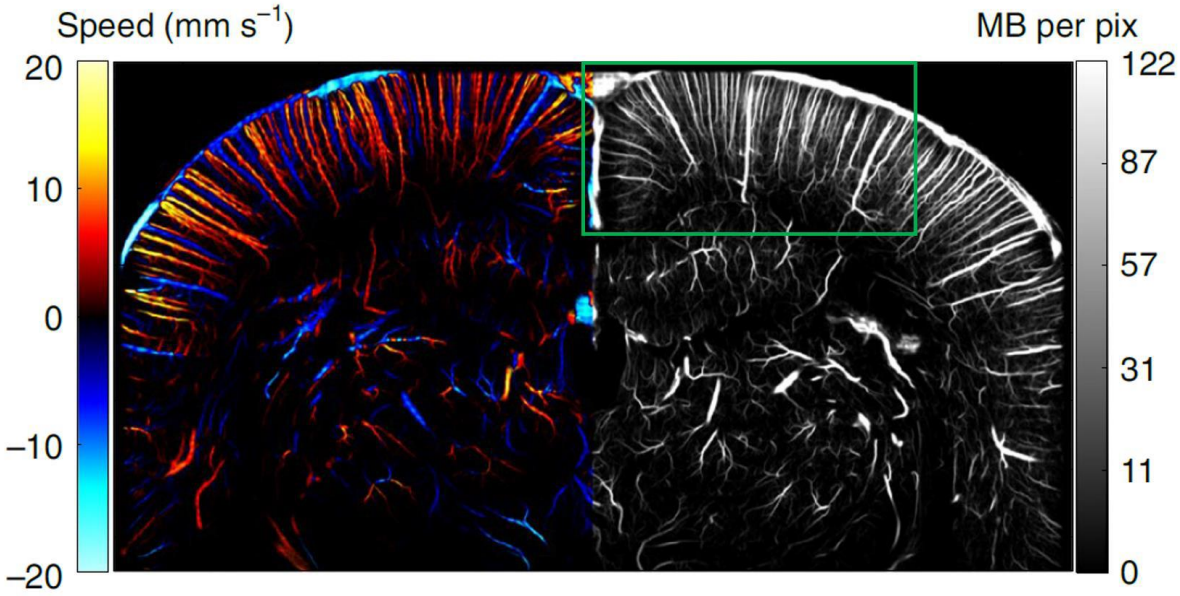

Figure 1: Microbubble density and speed in a rat brain, from [2]. Green rectangle shows the ROI you will be working on

I. EXPERIMENT DESCRIPTION

You will be working on real ULM data of a rat's brain acquired for the publication of a research paper [2]. Here is a summary of the methods section describing the experiment:

Ultrasound imaging acquisition. US imaging was performed using rapid acquisition of coronal section images of the rat brain using a linear ultrasound probe operating at 15.625 MHz (128 piezoelectric elements, 110 µm pitch, 8 mm elevation focus, Vermon) connected to an ultrafast ultrasound scanner (Iconeus, 128 channels, 62.5 MHz sampling rate) driven with Neuroscan live acquisition software (v.1.3, Iconeus and INSERM Accelerator of Technological Research in Biomedical Ultrasound). […]

Over the entire acquisition, 3600 blocks of 400 compounded frames at a 1,000-Hz frame rate were acquired, each frame being a compound frame acquired via 11 tilted plane wave emissions (−10° to 10° with 2° steps). The pulse shape corresponds to two periods of sinusoids, the transmit voltage is 5 V and the mechanical index is 0.09. Blocks were continuously acquired (no temporal gap between two successive blocks). Each frame corresponds to 1016 time samples acquired from each of the 128 channels, at a sampling rate of 62.5 MHz.

Note: the original data is subdivided into many blocks of 400 frames for technical reasons only, mostly data size and saving time.

In this project, you will have 2 objectives:

1) Reconstruct high quality images from raw "RF" data
2) From the images, localize and track the microbubbles to build super-resolved microbubble density and velocity maps

Because the original dataset is huge, and because image reconstruction is computationally intensive, you will work on small data subsets, and I will not ask you to reconstruct all the frames needed to make a nice ULM image. You thus have access to 2 different datasets:

- **Raw_data_10_frames** contains 10 frames of raw "RF" data as collected on the ultrasound scanner, as well as the relevant acquisition parameters you will need to reconstruct the images. You will use this file for the 1st part of the project, and will be evaluated on the quality of the image you obtain.
- **BF_IQ_cropped_bloc001 to BF_IQ_cropped_bloc1000**, contain 1000 blocks of high quality reconstructed images. As opposed to the original images from the paper, is limited to a small part of the brain, as displayed in the green rectangle on Fig. 1, so that we can have a maximum of temporal frames with a limited data size.

Data are available here:
Take only Raw_data_10_frames https://filesender.renater.fr/?s=download&token=feae3390-4573-40e1-8cbe-5a67acf2d4fc
For the 2nd part of the project, take BF_IQ_cropped_bloc001, etc here:
https://filesender.renater.fr/?s=download&token=17b0834c-32b9-43c5-bf38-c8530a170a00

Side Note: There is actually a filtering step needed to separate bubble signal from higher intensity tissue (brain, skull, etc…) signal. This step will not be covered at all in this project, so the data you will be working on are already filtered. If interested, you can find more information on this here [3].

Points to consider before moving forward:

1) *How long was the entire imaging experiment described in introduction? Why do we need such a long acquisition?*

2) *Load the raw data and take a look at the AcqParameters structure. It contains several acquisition parameters you will need to reconstruct an image, given in Internation System Units. The raw data are in the rf_data variable. Can you describe its different dimensions? What is the maximum depth we can reconstruct?*
3) *Display (in log scale) 1 frame of the raw data obtained with a 0° plane wave. Explain what you observe in the data.*

II. FROM RAW ULTRASOUND DATA TO HIGH QUALITY IMAGES OF THE BRAIN

In ultrasound imaging, the images are usually reconstructed with what is called Delay-and-Sum (DAS) Beamforming [4]. It consists of the following steps (see Figure 2):

1) Define a reconstruction grid covering the field of view (pixel number and size),
2) For a given ultrasound emission (e.g. plane wave at 0°), calculate the time of flight of the wave from the transducer to the pixel of interest and back to each transducer element. Usually this is done by considering a homogeneous speed of sound in the medium (e.g. 1540 m/s, as in water).
3) Sum the echos along this delay law to reconstruct every pixel of the image.

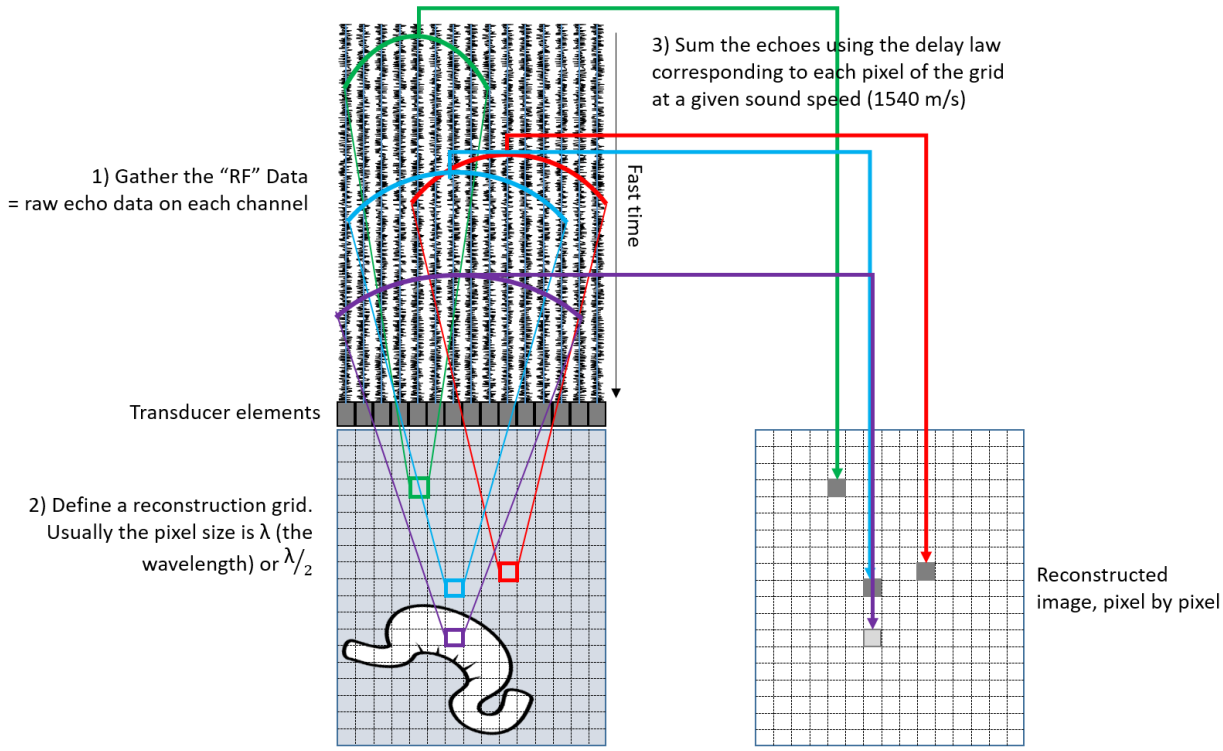

Figure 2: Schematic of the Delay-and-Sum Beamforming process

This is a linear and computationally efficient way of solving the image reconstruction inverse problem and it works very well in most soft tissue imaging applications. Indeed, when the sound speed of the imaging medium is homogeneous, the wave propagation is well known, and it is fairly straightforward to compute the time-of-flights corresponding to each pixel of the reconstruction grid. In the particular case of transcranial imaging however, the ultrasound wave has to go through the skull, in which the sound speed is much higher (~3000m/s) than in the surrounding soft tissues (~1540 m/s). This

difference in sound speed will distort the wavefronts, and the homogeneous model will no longer hold to compute the time-of-flights (see Figure 3).

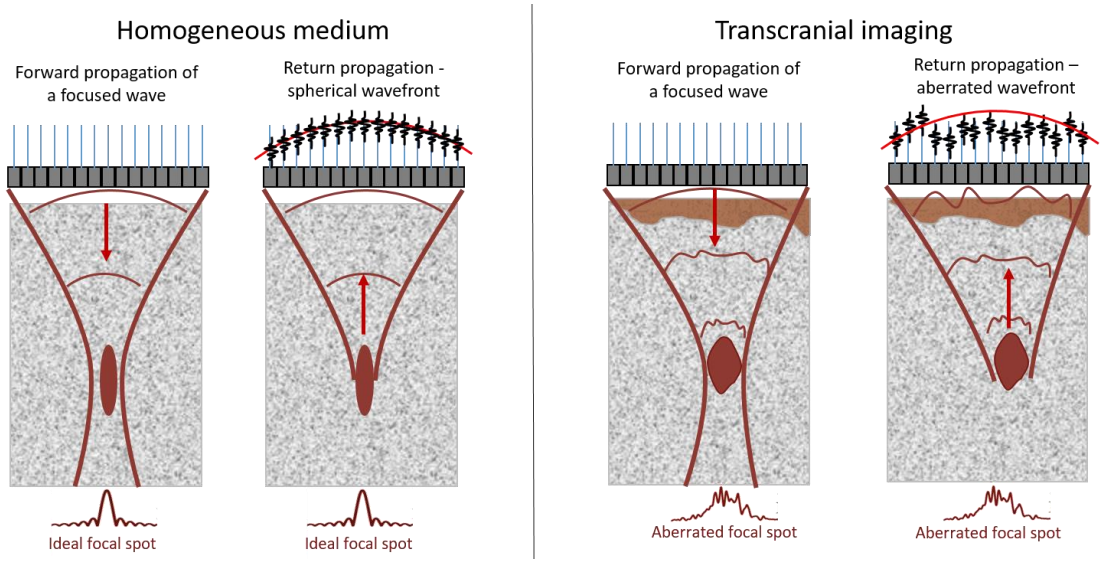

Figure 3: Schematic of the skull induced aberrations.

If we use a standard DAS Beamforming, the images will be of poor quality, as described in [2]: "The images in transcranial experiments present some shadowed areas caused by a well-known stripe artifact: the curvature in the internal surface of the skull where major pial vessels run introduce aberration of the ultrasound waves, producing shadowed areas underneath." (see Figure 4).

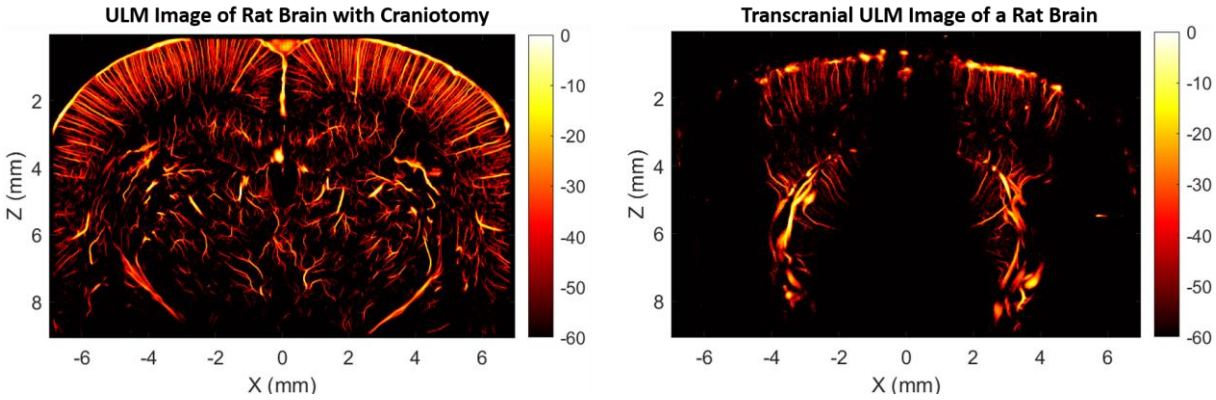

Figure 4: Example of the effect of skull aberration in ULM images of a rat's brain

Your first objective will be to improve the DAS beamforming process to take into account the skull induced aberrations. This is usually called "adaptive beamforming". You can start from the DAS beamforming template code provided. Several parameters are readily set, don't hesitate to ask if you want more details on what they represent.

Write and test a standard DAS algorithm:

1) *Fill the gaps in the DAS beamforming template:*
    a. *What is the wavelength of this acquisition? Set the pixel size accordingly*

b. *What is the approximate size of a mouse brain? Set the reconstruction grid limits accordingly*
c. *Under the hypothesis of a constant sound speed (1540 m/s), what is the "return" delay law from a given pixel to the transducer elements? Fill the corresponding gap in the template*

2) *Reconstruct 1 frame of your data, and display it with the proper dimensions. What do you see on the image? Is the image quality the same in the entire field of view?*

Find the skull induced aberration law:

Microbubbles are point-like scatterers, located beneath the skull, and their echos are highly coherent wavefronts. They can thus be used to retrieve the aberration law induced by the skull [5]. The echo wavefronts indeed reach the transducer piezo-elements with a delay that can be decomposed in (1) a geometrical delay due to propagation in free space (at a sound speed of 1540 m/s) and (2) an aberration delay law du to propagation in the skull. If we compensate for the geometrical delays, the bubble wavefront will appear as almost flat, and the variation around a flat line will correspond to the skull aberration delay (see Figure 5). This delay law can then be used to correct the standard DAS beamformer, and adapt it to any given acquisition to obtain high quality images.

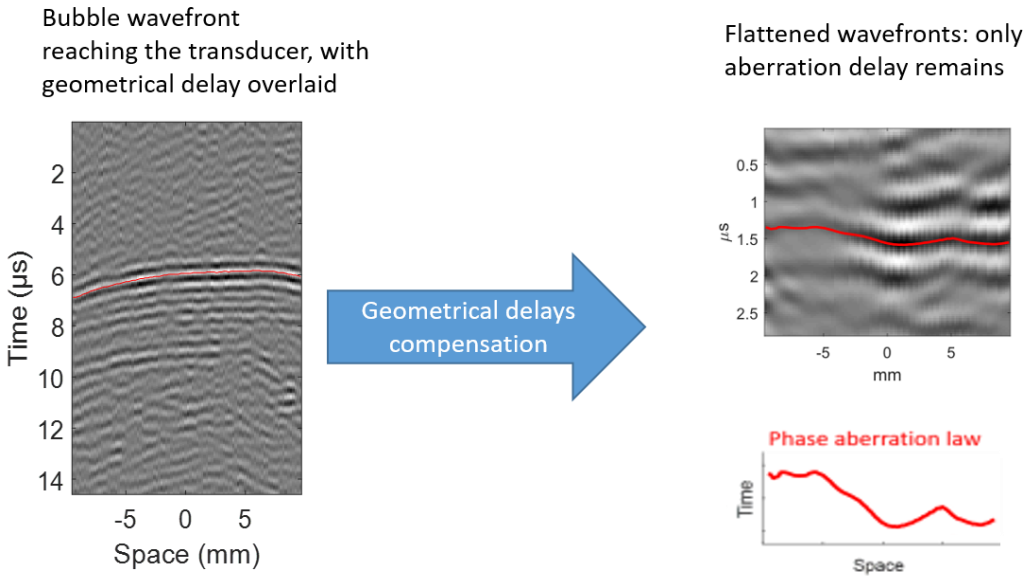

Figure 5: Bubble wavefront flattening and calculation of aberration dealy law.

1) *Locate a bubble on the image you have reconstructed with the classical DAS beamformer. Try to find a bubble that is more or less in the centre of your image, and as deep as possible. Do you see why? You can use the ginput function of Matlab.*
2) *Using the geometrical delay corresponding to this bubble position, extract the flattened wavefront from the raw rf signals. As in the beamforming algorithm, you can sum coherently the different emission angle to enhance the bubble signal. You should keep enough temporal sample points to see the entire wavefront.*
3) *Interpolate this data (for e.g. 10 times), to have a higher temporal resolution. Keep track of your new sampling frequency. You can use the interp1 function of Matlab.*
4) *To compute the aberration delay law, a solution is to use a cross-correlation between a signal of reference, and the signal received on each of the transducer elements. The delay to apply to each transducer element will correspond to the lag of maximum correlation. What can you*

use as a reference signal? Note 1: you can compute the cross-correlation in the time domain (xcorr function) but it can be faster in the Fourier domain where it reduces to a multiplication by the conjugate. Note 2: The delay law you will find may exhibit phase jumps. You can use the unwrap matlab function to fix this.

Reconstruct a high quality image by correcting the DAS beamformer

1) *Add the aberration delay law to your initial beamformer. Should you add it to the forward or the return delay law?*
2) *Reconstruct a new image with this correction, and compare it to your original image. What metrics can you use to measure image quality?*

At the end of this section, you are capable of reconstructing high quality images even in the case of a complex propagation medium, like the skull. For your evaluation, please hand in a .mat file with the aberration law you found, as well as the final image you reconstructed. In your paper, you should include the comparison of the uncorrected and corrected images (as quantitative as possible), as well as any explanation that you find relevant on the correction process.

III. BUBBLE LOCALIZATION

The objective of this section is to obtain a bubble localization map from the beamformed images.

The image reconstruction process is quite computationally intensive. To save you a long calculation time, I already reconstructed high quality images of the same acquisition (from [2]), you will thus be working on what we call "beamformed IQ" data. In ultrasound imaging, we usually display images in dB, which corresponds to 20*log10(abs(IQ)), with the proper normalization.
As a reminder, the images were acquired on an ultrafast ultrasound scanner with an imaging probe operating at 15.625 MHz, placed to image a coronal section of a rat's brain. You will work on 80 seconds of acquisition, acquired at a frame rate of 1000 Hz. Those images are grouped in 3600 blocks of 400 frames each for technical reasons (there is no temporal gap between blocks).
In this project, you will work with a subset of images (to reduce data to a size that you can handle on your computer). BF_IQ_cropped_bloc001 to BF_IQ_cropped_bloc1000, contain 1000 blocks of cropped images. It is limited to a small part of the brain, as displayed in the green rectangle on Fig. 1, so that we have more temporal frames with a limited data size. You are encouraged to write and test your codes using 1 or 2 blocks. Once you are happy with your algorithm, run it on the entire dataset, to produce your final localisation images.
You can find important meta-information (pixel size, frame rate, etc…) in DataParameters. All parameters are given in International System Unit.
Points to consider before moving forward:

1) *Load data, and display a mean image with correct dimensions, etc... This is called a Power Doppler (PD) image.*
2) *What are the reconstruction grid dimensions in mm and λ?*
3) *What is the temporal step between 2 frames?*

Microbubbles are very small (< system resolution) and very intense scatterers for ultrasound. It means that they appear as bright dots on the image. More precisely, they appear as the PSF of the imaging system. The two first steps of the bubble localization algorithm are: (1) locating all maxima in the image, because bubbles are bright, and (2) for each of these spots determine whether or not it is an actual bubble, based on the local intensity and shape: it must have a high intensity and look like the PSF to be a bubble.
Points to consider before moving forward:

1) Take 1 frame of IQF, and find all local intensity maxima. Display those maxima on your PD image. What do you observe?

2) From the data you have, try to find the PSF of the imaging system, and display it.

3) For each local maximum, find the intensity value and the local correlation coefficient with the PSF.

4) Use this to determine which of the maxima are real bubbles and which are not.

5) Display the bubble density map you obtain. What is the resolution, is it "super-resolution"?

This is the end of the guided questions. From here on, we will set general goals, with a few leads of how to tackle the problem. You can see this as a small research project, so feel free to use any resource you can find to help (existing articles, open source code, matlab help, Wikipedia, whatever!). You can of course discuss among yourselves or ask me questions, but each group has to hand in its own solution and article.

IV. IMPROVING THE RESOLUTION

The objective of this section is to build a bubble density map with a resolution of $\lambda/10$.

Think of how you can refine the localization of the intensity maximum, based on surrounding pixel value. Be careful that interpolation can dramatically increase data size, and introduce noise.

V. BUBBLE TRACKING

The objective of this section is to obtain a bubble velocity map with a resolution of $\lambda/10$.

You can use the bubble positions across temporal frames to determine their velocity. Be careful of units (pixel size, frame rate, etc…). A difficulty will be to identify a given bubble in consecutive frames. You can search for open source code that performs a similar task of tracking dots, maybe in other fields of science: tracking fluorophores in biology, tracking planets in astronomy, tracking particles in fluid mechanics, etc…

VI. DISPLAY

Medical imaging is about displaying rich information in a compact and readable manner. You will be evaluated on the quality of your displays as well as on the quantitative data you obtain.

Once your algorithm is working on the 1st dataset, try to run it on the larger one. You may have to adapt some parameters, but working on many more frames means that you will localize many more bubbles and obtain much nicer images.

Your paper should have at least 3 figures: the initial PD image, the high resolution bubble density map and the high resolution velocity map. You will have to think of how to deal with pixel size and inter pixel bubble positions. Any other figure is welcome but try to stick to the 4 page limit.

VII. MATLAB FUNCTION LIBRARY (NON EXHAUSTIVE)

Svd, eig, reshape, simpletracker, imregionalmax, conv, interp2, imresize, corr2, findpeaks, matchpairs, filter, filter2, ginput

VIII. BIBLIOGRAPHY

There is a large literature on ULM, and this selection is by no mean exhaustive, but only a few potentially useful examples.

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