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Part 1 Summary of ULM processing step

This chapter details the ULM processing and localisation algorithms with graphical illustrations, and analytical formulas for weighted average and radial symmetry algorithms.



Supplementary figure 1-1 ULM processing steps

power law compression)

All this process has been implemented in this article and is provided in the supplementary online scripts.

Supplementary figure 1-2 Example of density rendering of the in vivo rat brain perfusion dataset



The density rendering represents the number of trajectories passing through a single pixel. Here, the square pixel's size has been defined to $\frac{\lambda}{10} = 10 \mu m$. A power compression factor of 1/4 is applied to magnify the rendering. This example image has been processed with the radial symmetry algorithm. The associated code is provided in the online code package. Scale bar: 1 mm

Supplementary figure 1-3 Example of density rendering with axial velocity encoding of the *in vivo* rat brain perfusion dataset



As ULM provides hemodynamic information, the axial direction of flow can be encoding in colors on the density image.

Upward and backward flow can be distinguished. In this image, the blue color encodes the upward flows and the red color encodes the backward flows. This color encoding helps to differentiate arteries from veins in the neocortex. A power compression factor of 1/4 is applied on the density. Scale bar: 1 mm

Supplementary figure 1-4 Example of velocity rendering of the in vivo rat brain perfusion dataset



In this image, the mean velocity is encoded with color. Slowest velocities appear blue, and high velocity regions are red with a max velocity of 70 mm/s. The velocity display range can be modified by users. A velocity power compression factor of 1/1.5 is applied to increase the dynamics of the rendering. Pixel's saturation is defined by the density image, with a power compression of 1/4, in order to shadow low density regions.

Scale bar: 1 mm

Supplementary figure 1-5 Illustrations localisation algorithms on a centered and cropped image of a simulated microbubble of *in silico* dataset



Supplementary method 1-6 Analytical solution for the weighted average method

Let's assume you have an image of a microbubble composed of a grid of $[N_z, N_x]$ pixels. To recover the position of the centroid, the interpolation schemes will upsample that image on a grid of $[N_z * res, N_x * res]$ pixels, with *res* the upscaling resolution factor and then either find the maximum intensity or the centroid of the intensity distribution. The intensity I_{sr} coming out of the interpolation will be expressed as a linear combination of original intensities:

$$I_{sr}(i,j) = \sum_{(k_i,k_j)\in Z_q} I_k \phi_{int}(i-k_i,j-k_j)$$

where (i, j) belong to the interpolated space Z_{sr} and (k_i, k_j) belong to the original space Z_q .

The function φ_{int} is called the synthesis function and can take many forms as long as it satisfies the interpolation property: it must vanish for all already known samples of the intensity except for the origin where it must take the value 1 - more simply put, if the intensity is known at the pixel in the departure grid, interpolation can not change its value in the arrival grid. This is the classical approach to interpolation, there is a more general approach where the synthesis function does not satisfy the interpolation property and is not necessarily finite support and where the coefficients are calculated based on the original intensity values but are not necessarily equal to them. The operation defined above is a discrete convolution equation.

Our assumption under the weighted average localisation scheme is that one does not need to calculate all of the intensities on the refined grid to perform localisation, but we can calculate the position of the maximum intensity based on centroids.

Mathematically speaking, our problem becomes: $z_c = \left\{z \in Z_{sr}/I_{sr}(z) = \max_{z \in Z_{or}}I\right\}$; $x_c = \left\{z \in Z_{sr}/I_{sr}(z) = \max_{z \in Z_{or}}I\right\}$; $x_c = \left\{z \in Z_{sr}/I_{sr}(z) = \max_{z \in Z_{or}}I\right\}$

$$\left\{ x \in X_{sr}/I_{sr}(x) = \max_{x \in X_{sr}} I \right\}$$

with (z_c, x_c) the coordinates of the centroid, (Z_{sr}, X_{sr}) the subset of coordinates in the superresolved basis, and *I* the intensity of the image.

We assume that we have centered our subset space Z_k on the maximum known value of I_k at z_{ck} a and a Gaussian distribution of the intensity in our subset. The sub-pixel location of the peak can be estimated by calculating the centroid of the intensities²⁹. In an image with intensities I(i, j), we can define the image moments as: $M_{pq} = \sum_i \sum_j i^p j^q I(i, j)$,

and the centroid is defined by :

$$(z_c, x_c) = \left\{ \frac{M_{10}}{M_{00}}, \frac{M_{01}}{M_{00}} \right\}$$

This centroid is equal to the location of the peak only if the intensity is Gaussian and in our discrete case, it can be written as:

$$z_{c} = z_{ck} + \frac{\sum_{i=-\lfloor \frac{f_{z}}{2} \rfloor}^{\lfloor \frac{f_{z}}{2} \rfloor} \sum_{j=-\lfloor \frac{f_{x}}{2} \rfloor}^{\lfloor \frac{f_{x}}{2} \rfloor} I(i,j) w_{z}(i,j)}{\sum_{i=-\lfloor \frac{f_{z}}{2} \rfloor}^{\lfloor \frac{f_{z}}{2} \rfloor} \sum_{j=-\lfloor \frac{f_{x}}{2} \rfloor}^{\lfloor \frac{f_{x}}{2} \rfloor} I(i,j)} ; \quad x_{c} = x_{ck} + \frac{\sum_{i=-\lfloor \frac{f_{z}}{2} \rfloor}^{\lfloor \frac{f_{z}}{2} \rfloor} \sum_{j=-\lfloor \frac{f_{x}}{2} \rfloor}^{\lfloor \frac{f_{x}}{2} \rfloor} I(i,j) w_{x}(i,j)}{\sum_{i=-\lfloor \frac{f_{z}}{2} \rfloor}^{\lfloor \frac{f_{z}}{2} \rfloor} \sum_{j=-\lfloor \frac{f_{x}}{2} \rfloor}^{\lfloor \frac{f_{x}}{2} \rfloor} I(i,j)} I(i,j)}$$

with the weights defined as: $w_z(i,j) = i$; $w_x(i,j) = j$; and $(z_{ck}, x_{ck}) = \{I(z,x) > I(i,j), \forall (i,j)\}$

And $f_z = FWHM_z$, $f_x = FWHM_x$ the Full Width at Half Maximum of the intensity profile in the *z*, *x* direction respectively.

Supplementary method 1-7 Analytical solution for the radial symmetry algorithm

$$Let \ I \ be \ a \ 5x5 \ matrix \ containing \ a \ microbubble: \ I = \begin{bmatrix} I_{11} & I_{12} & I_{13} & I_{14} & I_{15} \\ I_{21} & I_{22} & I_{23} & I_{24} & I_{25} \\ I_{31} & I_{32} & I_{33} & I_{34} & I_{35} \\ I_{41} & I_{42} & I_{43} & I_{44} & I_{45} \\ I_{51} & I_{52} & I_{53} & I_{54} & I_{55} \end{bmatrix}$$

We define (\vec{u}, \vec{v}) the basis as the rotation of the original basis (\vec{z}, \vec{x}) , rotated by $\theta = +\frac{3\pi}{4}$, and the rotation matrix $R_{(\vec{u},\vec{v})}$:

$$R_{(\vec{x},\vec{z})\rightarrow(\vec{u},\vec{v})} = \begin{bmatrix} \cos(\theta) & -\sin(\theta) \\ \sin(\theta) & \cos(\theta) \end{bmatrix} = -\frac{\sqrt{2}}{2} \begin{bmatrix} 1 & 1 \\ -1 & 1 \end{bmatrix}$$

and
$$R^{-1} = R_{(\vec{u},\vec{v})\rightarrow(\vec{x},\vec{z})} \begin{bmatrix} \cos(\theta) & \sin(\theta) \\ -\sin(\theta) & \cos(\theta) \end{bmatrix} = -\frac{\sqrt{2}}{2} \begin{bmatrix} 1 & -1 \\ 1 & 1 \end{bmatrix}$$

We set: dIdv = I(1: N_z - 1, 1: N_x - 1) - I(2: N_z, 2: N_x), and dIdu = I(1: N_z - 1, 2: N_x) - I(2: N_z, 1: N_x - 1)

The line given by the equation $dIdu. \vec{u} + dIdv. \vec{v}$ is the line that defines the gradient of intensity according to the basis (\vec{u}, \vec{v}) . The line given by the equation:

 $(u.\vec{u} + v.\vec{v})(dIdu.\vec{u} + dIdv.\vec{v}) = \vec{0}$

will define the subset (u, v) of coordinates defining an orthogonal to the intensity gradient and we can write it as:

$$\begin{bmatrix} u \\ v \end{bmatrix}^{T} \begin{bmatrix} dIdu \\ dIdv \end{bmatrix} = 0 \Leftrightarrow \begin{bmatrix} u \\ v \end{bmatrix}^{T} \cdot R_{(\vec{u},\vec{v})\to(\vec{z},\vec{x})} \begin{bmatrix} dIdu \\ dIdv \end{bmatrix} = 0$$

$$\Leftrightarrow \begin{bmatrix} u \\ v \end{bmatrix}^{T} \cdot -\frac{\sqrt{2}}{2} \begin{bmatrix} 1 & -1 \\ 1 & 1 \end{bmatrix} \begin{bmatrix} dIdu \\ dIdv \end{bmatrix} = 0$$

$$\Leftrightarrow \begin{bmatrix} u \\ v \end{bmatrix} \cdot \begin{bmatrix} dIdu - dIdv \\ dIdu + dIdv \end{bmatrix} = 0$$

$$\Leftrightarrow u \cdot (dIdu - dIdv) + v \cdot (dIdu + dIdv) = 0$$

Let $(u_k, v_k) = (z_k, x_k)$ be the coordinates belonging to the orthogonal to the gradient, we need to find the center (z_c, x_c) minimizing the distance to the orthogonal of the gradient. If we want our basis to be centered around (z_c, x_c) , the equation above becomes: $(z_k - z_c) - m(x_k - x_c) = 0$

with $m = \frac{dIdu + dIdv}{dIdv - dIdu}$.

The distance from the point $C(z_c, x_c)$ to the point $K(z_k, x_k)$ belonging to the line directed by the vector $\overrightarrow{u_d}$ orthogonal to the gradient in *K* is

$$d(c, K \in \overrightarrow{u_d}) = \frac{||\overrightarrow{KC} \land \overrightarrow{u_d}||}{||\overrightarrow{u_d}||}$$

thus: $d(c, K \in \overrightarrow{u_d}) = d_k = \frac{|(z_k - z_c) - m(x_k - x_c)|}{1 + m^2}$

Let $\chi^2 = \sum_k d_k^2 w_k$ with w_k a weight given to each pixel. The goal of this is to compensate for low SNR in areas where the gradient is low, and:

$$w_k = \frac{dImag^2}{\sqrt{(z_k - z_c)^2 + (x_k - x_c)^2}}$$

and $dImag^2 = dIdu^2 + dIdv^2$

As w_k , is defined with respect to (z_c, x_c) , we will use the classical weighted average method as an initial guess of (z_c, x_c) to calculate each w_k . To find the maximum intensity point, one must

minimize all of the distance d_k , for example, minimize the sum of all distances d_k . We will thus differentiate χ^2 with respect to (z_c, x_c) and solve for (z_c, x_c) .

$$\frac{\partial \chi^2}{\partial x_c} = \frac{\partial \sum_k d_k^2 w_k}{\partial x_c} = \sum_k \frac{\partial \left(\frac{\left((z_k - z_c) - m_k (x_k - x_c) \right)^2 w_k}{m_k^2 + 1} \right)}{\partial x_c} = \sum_k \frac{2((z_k - z_c) - m_k (x_k - x_c)) m_k w_k}{m_k^2 + 1}$$

solving for $\frac{\partial \chi^2}{\partial x_c} = 0$ leads to:

$$\sum_{k} \frac{m_k w_k}{m_k^2 + 1} \left((z_k - z_c) - m_k (x_k - x_c) \right) = 0$$
$$\sum_{k} \frac{m_k w_k}{m_k^2 + 1} * z_c - \sum_{k} \frac{m_k^2 w_k}{m_k^2 + 1} * x_c = \sum_{k} \frac{m_k w_k}{m_k^2 + 1} * (z_k - m_k x_k)$$

and for $\frac{\partial \chi^2}{\partial z_c}=0$

$$\sum_{k} \frac{w_{k}}{m_{k}^{2} + 1} * z_{c} - \sum_{k} \frac{m_{k}w_{k}}{m_{k}^{2} + 1} * x_{c} = \sum_{k} \frac{w_{k}}{m_{k}^{2} + 1} * (z_{k} - m_{k}x_{k})$$

If we write this with matrices, it becomes:

$$\begin{bmatrix} \sum_{k} \frac{m_{k}w_{k}}{m_{k}^{2}+1} & \sum_{k} \frac{m_{k}^{2}w_{k}}{m_{k}^{2}+1} \\ \sum_{k} \frac{w_{k}}{m_{k}^{2}+1} & \sum_{k} \frac{m_{k}w_{k}}{m_{k}^{2}+1} \end{bmatrix} = \begin{bmatrix} \sum_{k} \frac{m_{k}w_{k}}{m_{k}^{2}+1} * (z_{k}-m_{k}-x_{k}) \\ \sum_{k} \frac{w_{k}}{m_{k}^{2}+1} * (z_{k}-m_{k}x_{k}) \end{bmatrix}$$

Calculating the values of (z_c, x_c) , is straightforward from the expression above:

$$\text{Let } \Omega = \begin{bmatrix} \sum_{k} \frac{m_{k}w_{k}}{m_{k}^{2}+1} & \sum_{k} \frac{m_{k}^{2}w_{k}}{m_{k}^{2}+1} \\ \sum_{k} \frac{w_{k}}{m_{k}^{2}+1} & \sum_{k} \frac{m_{k}w_{k}}{m_{k}^{2}+1} \end{bmatrix}$$

$$\begin{bmatrix} z_c \\ x_c \end{bmatrix} = \Omega^{-1} \begin{bmatrix} \sum_k \frac{m_k w_k}{m_k^2 + 1} * (z_k - m_k x_k) \\ \sum_k \frac{w_k}{m_k^2 + 1} * (z_k - m_k x_k) \end{bmatrix}$$

Part 2 : Point Spread Function In Silico Data

We will present supplementary figures related to the dataset containing simulated scatterers designed to investigate the PSF inhomogeneity in space and its effect on localisation. The goal of these few figures is to help us understanding how the algorithms are affected by sub-wavelength displacements and how well they can recover one scatterers position with different SNR but without any motion and without trying to reconstruct canals. No tracking is performed in this chapter.





In an empty medium of size $5\lambda \times 5\lambda$, a scatterer was placed in the center and was moved in a $(\lambda \times \lambda)$ space with $\frac{\lambda}{21}$ steps. Above, the points simulated are represented with black filled dots. The grid has a step of $\frac{\lambda}{21} \times \frac{\lambda}{21}$, and inside each one of the 441 squares, 3 random positions are chosen for the scatterer. With all these positions, maps with $\frac{\lambda}{21}$ increments can be estimated by averaging results from the 3 positions of each square, avoiding gridding due to the $\frac{\lambda}{21} \times \frac{\lambda}{21}$ grid.

Supplementary figure 2-2 Beamformed image of scatterer moved in a $(\lambda \times \lambda)$ space



The response to an ultrasound wave of the scatterer positions depicted in figure 1-1 was simulated with the Verasonics Research Ultrasound Simulator (3 tilted plane wave, 15MHz, linear probe with 128 elements, pitch $1,116 \times \lambda$). The speed of sound was set to 1540 m/s. Radiofrequency data were beamformed by the provided beamformer in square pixels of λ . The beamformed image is presented above and was limited to a $5\lambda \times 5\lambda$ space. The Signal to Noise Ratio of the final beamformed image was clutter noise modeled by a Gaussian filtered white Gaussian noise. We used the wgn Matlab function to generate a 0.2 ohm impedance noise, with a +/-10dB amplitude. The resulting noise was then smoothed using a 2D Gaussian kernel of size 0.7 pixel. Finally, the noise was added to beamformed image by choosing an amplitude in dB between the maximum intensity value of the beamformed image and the average intensity of the generated noise. This process results in noised images, with a user-selected SNR, and a pseudo clutter with 20dB of amplitude (more details in figure 2-3). 7 different SNR values were tested.



Supplementary figure 2-3 Simulated clutter noise explanation

Simulated beamformed images have been noised using a custom method to generate a clutter like noise.

First, a white noise is generated using the wgn Matlab function with power of -2dBW and an impedance of 0.2 Ohms. The amplitude of this noise is set to 10dB, which is the clutter amplitude. The mean clutter amplitude is set to adjust the SNR wanted in dB related to the maximal intensity of the raw image. A gaussian filter is finally applied with a standard deviation of 1.5 pixel.





Lanczos, Sp-Inter for spline) are almost constant as these schemes have a high average error and standard deviation. The No-Shift has the maximum error in all cases as it is reporting the scatterer to be exactly centered regardless of its intensity. The Gaussian fitting (Gauss-Fit) and radial symmetry (RS) scheme are more affected by SNR than the other schemes but have considerably lower lateral errors and standard deviations. Finally, it is important to note that the weighted average (WA) scheme has similar standard deviations to the best localisation algorithms until SNR drops below 40dB making it a very good candidate for high SNR applications such as in harmonic imaging in both directions. For the axial direction, it continues being a good candidate up until SNR drops below 25dB. This is very useful for vascularisation aligned in a preferential axis (i.e. the brain or the kidney).

Supplementary figure 2-5 Distributions of directional errors for PSF at various SNR levels

For each of the position simulated, the lateral and axial error distributions are plotted.

No Shift	14/ 4	Cub Intern	l a Intorn	Sn Intorn	Gausa Eit	Pe	Distributions are not always centered for
	-0.07	Cub-Interp		Sp-interp	Gauss-Fit	 	the interpolation scheme
ο Ξ	σ=0.27	σ=0.15	σ=0.09	σ=0.09	σ=0.17	σ=0.25	At 10dB all algorithms seem to have
ara		L L	<u>n</u>		4		At IUUD , all algorithms seent to have
June 111 - Late	distanting to	. 14 4				AL.	poor localisation precision except for the
-\lambda/2 +\lambda/2 -	$\lambda/2$ + $\lambda/2$	-λ/2 +λ/2	-λ/2 +λ/2	-λ/2 +λ/2	-λ/2 +λ/2	-\/2 +\/2	Lanczos and Spline interpolation. The
σ=0.29	σ=0.27	σ=0.22	σ=0.19	<i>σ</i> =0.19	<i>σ</i> =0.18	<i>σ</i> =0.31	Gaussian fitting seems to perform a bit
De la							better than the radial symmetry.
a							
AX AVERATION AND A	بالاستعال	L. P.	a la la	(so II		. all all a	
-\/2 +\/2	$\lambda/2$ $+\lambda/2$	$-\lambda/2$ $+\lambda/2$	-\/2 +\/2	$-\lambda/2$ $+\lambda/2$	- \/2 + \/2	- \/2 + \/2	
15dB No Shift	WA	Cub-Intorn	l z-Intorn	Sp.Intorp	Gauss-Eit		At 15dB the Gaussian fitting takes the
	0.24		-=0.00			0.14	lead for lateral error localisation. The
Ωσ=0.29	σ=0.24	σ=0.15	σ=0.09	σ=0.08	σ=0.09	σ=0.14	Langzag and anling interpolation perform
aral o		1.6	- 1 1			<u> </u>	Lanczos and spine interpolation perform
	and the second	11					very well, only surpassing the radial
-\lambda/2 +\lambda/2 -\	$\lambda/2$ + $\lambda/2$	$-\lambda/2$ $+\lambda/2$	-λ/2 +λ/2	-λ/2 +λ/2	-λ/2 +λ/2	-λ/2 +λ/2	symmetry-based algorithm moderately.
σ=0.29	σ=0.25	σ=0.22	<i>σ</i> =0.19	<i>σ</i> =0.19	<i>σ</i> =0.15	<i>σ</i> =0.19	
ale							
A magneticated	dist. also	June 1	111	T IV			
-\lambda/2 +\lambda/2	$\lambda/2$ $+\lambda/2$	$-\lambda/2$ $+\lambda/2$	-λ/2 +λ/2	-λ/2 +λ/2	-λ/2 +λ/2	-λ/2 +λ/2	
20dB No Shift	WA	Cub-Interp	Lz-Interp	Sp-Interp	Gauss-Fit	RS	At 20dB . The Gaussian fitting and radial
a=0.29	σ=0.2	g=0.15	σ=0.09	g=0.08	a=0.06	a=0.08	symmetry surpass all other algorithms for
	0.2						the first time. Their result for the lateral
era							error are similar. For the axial error, the
and the Lat							representation along the diagonals of the
-λ/2 +λ/2	-λ/2 +λ/2	-λ/2 +λ/2	-λ/2 +λ/2	= \/2 + \/2	-1/2 +1/2	-λ/2 +λ/2	reprojection along the diagonals of the
-0.00				70L	-702 -702		redial average two achieves an ables its
σ=0.29	σ=0.21	σ=0.22	σ = 0.19	σ=0.19	σ=0.13	σ=0.14	radial symmetry scheme enables its
σ=0.29	<i>σ</i> =0.21	σ=0.22	σ=0.19	σ=0.19	σ=0.13	σ=0.14	radial symmetry scheme enables its distribution to be centered around 0. The
	σ=0.21	σ=0.22	σ=0.19	σ=0.19	σ=0.13	σ=0.14	radial symmetry scheme enables its distribution to be centered around 0. The Lanczos and Spline Interpolation come
	σ=0.21	σ=0.22	σ=0.19	σ=0.19	σ=0.13	σ=0.14	radial symmetry scheme enables its distribution to be centered around 0. The Lanczos and Spline Interpolation come second.
	σ =0.21	-λ/2 +λ/2	σ=0.19 -λ/2 +λ/2	σ=0.19 -λ/2 +λ/2	-λ/2 +λ/2	σ=0.14 -λ/2 +λ/2	radial symmetry scheme enables its distribution to be centered around 0. The Lanczos and Spline Interpolation come second.
	σ=0.21	σ=0.22 -λ/2 +λ/2 Cub-Interp	σ=0.19 //2 +.//2 Lz-Interp	σ=0.19 	→ <i>N</i> 2 → <i>N</i> 2 → <i>N</i> 2 + <i>N</i> 2 Gauss-Fit	σ=0.14 -λ/2 +λ/2 RS	radial symmetry scheme enables its distribution to be centered around 0. The Lanczos and Spline Interpolation come second. At 25dB , the Gaussian fitting and radial
σ=0.29 σ=0.29 σ=0.29 σ=0.29 σ=0.29 σ=0.29 σ=0.29	$\sigma=0.21$ ψ w $\sigma=0.16$	σ=0.22 -λ/2 +λ/2 Cub-Interp σ=0.15	σ=0.19 - _{M2} + _{M2} Lz-Interp σ=0.09	σ=0.19 	-λ/2 +λ/2 Gauss-Fit σ=0.13	σ=0.14 \/2 +.\/2 RS p=0.05	radial symmetry scheme enables its distribution to be centered around 0. The Lanczos and Spline Interpolation come second. At 25dB , the Gaussian fitting and radial symmetry alleviate all other algorithms
σ=0.29 σ=0.2	σ=0.21 • · · · · · · · · · · · · · · · · · · ·	σ=0.22 -M2 +M2 -M2 -0.15	σ=0.19 	σ=0.19 //2 +.//2 Sp-Interp σ=0.08	$-\frac{1}{\sqrt{2}}$ $\frac{1}{\sqrt{2}}$ $$	σ=0.14 	radial symmetry scheme enables its distribution to be centered around 0. The Lanczos and Spline Interpolation come second. At 25dB , the Gaussian fitting and radial symmetry alleviate all other algorithms chances to perform as well. This confirms
$\begin{array}{c c} & \sigma = 0.29 \\ \hline \\ $	σ=0.21 	σ=0.22 -λ/2 +λ/2 Cub-Interp σ=0.15	σ=0.19 	σ=0.19 /2 +.//2 Sp-Interp σ=0.08	$\sigma = 0.13$ $\sigma = 0.13$ $-\lambda/2 + \lambda/2$ Gauss-Fit $\sigma = 0.03$	σ=0.14 σ=0.14 κχ κχ σ=0.05	radial symmetry scheme enables its distribution to be centered around 0. The Lanczos and Spline Interpolation come second. At 25dB , the Gaussian fitting and radial symmetry alleviate all other algorithms chances to perform as well. This confirms the pivotal point observed at 15dB. The
σ=0.29 σ=0.29 ν.ν2 +ν2 - 25dB No Shift σ=0.29 σ=0.	σ=0.21 	σ=0.22 -λ/2 +λ/2 Cub-Interp σ=0.15	σ=0.19 -λ/2 +λ/2 Lz-Interp σ=0.09	σ=0.19 -\/2 +\/2 Sp-Interp σ=0.08	σ=0.13 σ=0.13 σ=0.13 σ=0.03	σ=0.14 -λ/2 +λ/2 RS σ=0.05	radial symmetry scheme enables its distribution to be centered around 0. The Lanczos and Spline Interpolation come second. At 25dB , the Gaussian fitting and radial symmetry alleviate all other algorithms chances to perform as well. This confirms the pivotal point observed at 15dB. The weighted average outperforms the
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Supplementary figure 2-6 Error maps for a scatterer moved in a λ space at various SNR levels

For each of the position simulated, the lateral, axial error and RMSE are rendered with respect to their location.



30dB No Shift	МА	Cub-Interp	Sp-Interp	Gauss-Fit	RS 8. IV June entrestry 8. June entrestry 8. IV June entrestry 0.	At 30dB , the Gaussian fitting and radial symmetry-based algorithm adopt their specific droplet shaped distribution on the lateral error for the first time. They possess two peaks of error at approximately $\frac{\lambda}{4}$ in the axial direction. This case is specific to localisation schemes relying on the shifts along the diagonal (so-called reprojection) and explains the very low value of lateral error for Gaussian fitting and radial symmetry. The errors for the weighted average schemes decrease and concentrate on the furthest positions from the center. The cubic interpolation RMSE continues to adopt a ring shape distribution.
40dB No Shift	WA	Cub-Interp	Sp-Interp	Gauss-Fit	RS 0.3 (1) Jule approximation of the second	The trends observed at 30dB continue at 40dB . The weighted average error exhibits a large advantage over the interpolation-based schemes. The radial symmetry confirms its advantage over the Gaussian fitting for the lateral error.
60dB No Shift	WA	Cub-Interp	Sp-Interp	Gauss-Fit	RS 1 Jule approach	The weighted average exhibits the smallest axial error but retains a symmetrical distribution at 60dB . The advantage of the radial symmetry-based algorithm over the Gaussian fitting is clear for the axial error.

Part 3 : In silico canal simulation

We will present here the dataset comprised of simulated canals. We have produced additional figures to explain how the dataset was devised, how well the different algorithms perform on this dataset with the addition of tracking. The idea behind this set is to be able to perform the complete ULM process and to have access to the ground truth to calculate statistical indices and look at complicated structures designed by our team. The errors of each algorithm are presented, as well as our separation index which was used to calculated the maximum attainable resolution.

In the next 7 figures, the density renderings are obtained by counting the number of trajectories passing through each pixel of size $\frac{\lambda}{10} \times \frac{\lambda}{10}$. These trajectories are obtained by applying the 7 different localisation algorithms and then Kuhn-Munkres assignment-based tracking with a custom defined interpolation of microbubbles' trajectories. This will smooth the trajectories and restore a more natural curvature.



Supplementary figure 3-1 Simulated canals in silico with Verasonics Vantage Research Simulator

Rendering of the simulated canals devised for the second in silico dataset. It comprises of complex 3D tubes in the imaging plane mimicking an actual 2D imaging situation. Inside, point-like scatterers are placed at random in each of the tubes section and then are propagated through 20,000 frames according to a Poiseuille flow model assuming continuity on streamlines. The concentration, speeds and noise level can all be adjusted by the user. We studied the localisation errors and the effect of different signal to noise ratio using this dataset. The point-like scatterer's ultrasound response is simulated using the Verasonics Research Ultrasound Simulator using a 128 elements linear probe, with elements' pitch of 1.116 λ , and with $\lambda \times \lambda$ beamformed pixels. The top white line represents a length of 10 pixels (i.e. 10 wavelengths).

Supplementary figure 3-2 Density based rendering of localisation algorithms and tracking algorithm



No-shift algorithm

The errors in the lateral and axial direction are corrected by the tracking algorithm. However, for the two bifurcating canals, the errors have a clear effect: the separation is not well resolved and pinpointing its location would be largely erroneous. It is interesting to note that even without sub-pixel localisation, the large vessels are well resolved. To evaluate the quality of ULM, one should then really look at subwavelength vessels. The top white line represents a length of 10 pixels (i.e. 10 wavelengths).





Supplementary figure 3-3 Distribution of errors for *in silico* canal simulation for localisation and tracking schemes for various SNR levels









Supplementary figure 3-5 Measured gap for separation estimation

Measured gap for separation estimation. The gap value measured, as presented in Supplementary figure 3-4, is reported here for all localisation algorithms and plotted against the simulated canal to canal distance. As soon as its value stays above zero, the simulated canal-to-canal distance is registered as the separation criteria index. This gives us the minimal distance between two close structures. The radial symmetry (RS) outperforms all algorithms with a significant margin of 19% over the Gaussian fitting algorithm (Gauss-Fit). Interestingly, the weighted average localisation (WA) yields better separation than the interpolation-based algorithms. The no-shift algorithm has a separation index of 0.77, the maximum of that index being 1. Even the poorest localisation algorithms can yield better than expected result with an adequate post-processing tracking algorithm.

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Supplementary figure 3-6 Definition of statistical classification and results for different localisation and tracking schemes



right plot. For the three indices, the Gaussian fitting and radial symmetry come out on top with as much as 85.9% simulated scatterers being picked up by the best localisation algorithm. The sensitivity of weighted average and the best interpolation-based algorithms are quite low at around 40%, while the precision is higher for the latter at 71.8%. The no-shift algorithm has the lowest values albeit not as low as one would expect given that no localisation is involved. The Jaccard index which represents a detection rate is at most 63.2% and can be as low as 11.8% for the no-shift scheme. Gaussian fitting and radial symmetry are more precise than others. This is due to a low localisation error, and as such a high cardinality of true positives.

Part 4 : In vivo ULM datasets

In this chapter, we will present the *in vivo* rat brain perfusion dataset. The ULM rendering was applied with and without track interpolation. Non-interpolated tracks reveal the behavior of localisation methods. The aim of this chapter is to present real-life images and to better understand the different steps of the ULM process. It also helps us to illustrate the gridding effect on in vivo data and calculate a gridding index.

At the end of this chapter, we present the ULM redering for the three *in vivo* additional datasets: *"in vivo* rat brain bolus", *"in vivo* rat kidney", and *"in vivo* mouse tumor".



Supplementary figure 4-1 Power Doppler rendering of in vivo rat brain dataset

In the next 7 figures, the density renderings are obtained by counting the number of trajectories passing through each pixel of size $\frac{\lambda}{10} \times \frac{\lambda}{10}$. These trajectories are obtained by applying the 7 different localisation algorithms and then Kuhn-Munkres assignment-based tracking without interpolation of microbubbles' trajectories.

Supplementary figure 4-2 Positions localized by all algorithms





Supplementary figure 4-3 Density rendering localisation algorithms with track interpolation

In the next 7 figures, the density renderings are obtained by counting the number of trajectories passing through each pixel of size $\frac{\lambda}{10} \times \frac{\lambda}{10}$. These trajectories are obtained by applying the 7 different localisation algorithms and then Kuhn-Munkres assignment-based tracking with a custom defined interpolation of microbubbles' trajectories. This will smooth the trajectories and restore a more natural curvature. A compression factor of 1/3 is applied.





The radial symmetry yields the best image of the set if we don't consider the artifacts caused by the acquisition mask. It seems to have more of the smaller vessels compared to the Gaussian fitting-based algorithm, which we hypothesize to be vessels because of its high sensitivity index.



Supplementary figure 4-4 Peak to peak Power Spectral Density analysis to devise a gridding index

These graphs represent the Power Spectral Density of the signal present in the *in vivo* images postlocalisation and tracking, but before track interpolation. The PSD is averaged along the z direction, leading to a lateral frequency dependency.

Two of the main peaks are chosen to calculate the value of the peak to baseline (the fundamental frequency and its first harmonic). By summing these two values, we obtain an index that will characterize the amount of gridding present in the images. We can see that both the Gaussian fitting (Gauss-Fit) and radial symmetry (RS) based algorithm do not present large peaks. The No-Shift on the other hand has a periodic Power Spectral density at frequency corresponding to the reconstruction grid scale. These values are calculated and presented in the main article.





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Supplementary figure 4-6 Density renderings for dataset "in vivo rat kidney"

Radial symmetry-based algorithm



Supplementary figure 4-7 Density renderings for dataset "in vivo mouse tumor"

Part 5 : Global Scoring

In this chapter, we present the PALA global score devised with our study and explain additional information such as how we simulated noise in the two first datasets, classical ULM rendering.



Supplementary figure 5-1 PALA global score obtained for all the 7 algorithms tested

The PALA global score is obtained by summing 7 of the different indices chosen with user specified weights. The weights are inscribed in the legend of the figure in parenthesis.

The radial symmetry (RS) comes out as the clear winner of our tests with an index 14% higher than the second-best algorithm: the weighted average (WA). It is important to note that the weighted average surpasses the Gaussian fitting (Gauss-Fit) based algorithm thanks to it amazingly low time of calculation and not because it produces the highest quality images. The Spline (Sp-Inter), Lanczos (Lz-Interp) interpolations are tightly packed with a similar global score. Depending on your application, the weighted average method might be better than the radial symmetry method, for example if you want to have real-time reconstruction of ULM.

		No-Shift	WA	Cub- Interp	Lz-Interp	Sp-Interp	Gauss-Fit	RS
DMGE	λ	0.38	0.17	0.25	0.19	0.19	0.11	0.10
RWISE	Score	23.5	65.4	50.3	61.2	62.0	77.2	80.8
Processin	S	1563	1598	8429	7627	5531	75640	1984
g Time	Score	100.0	99.5	63.4	65.6	72.6	15.8	94.8
Gan	λ	0.77	0.50	0.68	0.58	0.59	0.46	0.36
Gap	Score	22.9	50.1	32.1	41.6	40.6	53.9	64.1
Gridding	[AU]	21.7	12.2	16.2	8.2	12.0	6.6	7.3
Gridding	Score	27.7	59.4	45.9	72.5	60.1	78.1	75.8
Jaccard	Score	11.8	27.4	28.1	43.5	44.9	63.2	55.7
Precision	Score	24.0	48.6	51.7	71.1	71.8	85.9	79.0
Saturation	%	35.1%	46.3%	37.6%	37.8%	38.6%	45.1%	48.2%
Saturation	Score	35.1	46.3	37.6	37.8	38.6	45.1	48.2
This table p	resents	the highest	values in gr	een and th	e lowest in	red. One c	an note that	t the radial
symmetry (R	lS) base	d algorithm (comes first oi	close seco	ond for all inc	lices.		

Supplementary table 5-2 rable with an the index values and score conversion

	RMSE	Pro Time	Gap	Gridding	Jaccard	Precision	Saturation
Non- Weighted	1	1	1	1	1	1	1
3D ULM	2	3	1	2	1	1	2
2D Scanning	1	2	1	1	1	1	2
Real-time	1	3	1	1	1	1	1
Low SNR	2	0.5	2	2	2	2	1
PALA global Score	2	2	1	1	2	1	1

Supplementary table 5-3 Table of weights for different scoring scenarii

This table presents weighting scenarii to reflect experimental requirements: e.g. for real-time imaging, the processing time is primordial.

The final scores are then computed by a weighted average of indices presented in the next table.

Supplementary table 5-4 Table weighted average scores for the 6 scenarii

	No-Shift	WA	Cub- Interp	Lz-Interp	Sp-Interp	Gauss-Fit	RS
Non- Weighted	35.0	56.7	44.2	56.2	55.8	59.9	71.2
3D ULM	44.3	63.9	47.5	58.0	58.0	54.2	74.4
2D Scanning	42.2	60.3	45.6	55.2	55.7	53.3	71.3
Real-time	49.4	66.2	48.4	58.3	59.5	50.1	76.5
Low SNR	26.5	52.0	42.2	56.6	55.1	66.9	70.1
PALA global Score	38.0	58.9	45.1	56.4	57.0	57.5	73.0
This table pres	This table presents the weighted average scores for each scenarii over 100.						

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Part 6 : Tables

Localisation method	Related articles	Comments		
Gaussian fitting	(Ackermann and Schmitz, 2016; Luke et al., 2016; O'Reilly and Hynynen, 2013; Song et al., 2018b) ^{19–22}	Usually, these works use a Gaussian convolved PSF rather than a Gaussian fitting with an optimizer.		
Weighted average based	(Christensen-Jeffries et al., 2015; Hansen et al., 2016; Heiles et al., 2019; Lin et al., 2017; Song et al., 2018a; Soulioti et al., 2018; Viessmann et al., 2013; Zhang et al., 2018; Zhu et al., 2019) ^{10,13,15,23–28}	Except for Heiles et al 2019, these work on data beamformed with pixels of sizes below the wavelength or data beamformed with commercial scanners which might affect PSF shape and full width at half maximum.		
LanczosbasedinterpolationandGaussian fitting	(Errico et al, 2015) ⁹			
Spline based interpolation	(Huang et al., 2020; Song et al., 2018b) ^{22,29}			
Linear based interpolation	(Song et al., 2018a) ¹⁵	On top of the linear-based interpolation, this paper convolves with a Gaussian profile.		
Cubic based interpolation	(Song et al., 2018b) ²²	This paper is a comparison of algorithms		
Radial symmetry	(Parthasarathy, 2012) ³⁰ (optic super-resolution only)			
RF-based	(Brown et al., 2019; Christensen- Jeffries et al., 2017a, 2017b; Desailly et al., 2013, 2015) ^{16,17,31–33}	These papers are based on radiofrequency data before beamforming. In particular, the papers from the team at Imperial College/Kings College London use the onset of the Hilbert transform of the RF signals.		

Supplementary figure 6-1state of the art of localisation methods for ULM

Supplementary figure 6-2 Summary of the media simulated

Structure	Diameters	Maximal velocities
A pseudo double belix	3λ	$v_{max} = 3 \lambda / frame$
	2λ	$v_{max} = 2 \lambda / frame$
A curved tube with a constant diameter and a horseshoe pattern	0.5 λ	$v_{max} = 0.5 \lambda / frame$
	0.2 λ	$v_{max} = 0.2 \lambda / frame$
3 curved tubes with 3 different diameters	0.1 λ	$v_{max} = 0.1 \lambda/frame$
	0.05λ	$v_{max} = 0.05 \lambda/frame$
4 spreading tubes with a constant diameter	0.1 λ	$v_{max} = 0.9 \lambda/frame$
A watermark comprised of the word ULM that does not serve other purposes but identification	0.1 λ	$v_{max} = 0.4 \lambda / frame$

Supplementary figure 6-3 Summary of the metrics

		Dataset		
Number	Measurement	In silico PSF	In silico flow	In vivo
1	Lateral error	Х	Х	

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2	Axial error	Х	Х	
3	RMSE	Х	Х	
4	True Positive		Х	
5	False Negative		Х	
6	False Positive		Х	
7	Gap		Х	
8	Number of detections			Х
9	Saturation			Х
10	Gridding Index			Х
11	Processing time			Х

Supplementary figure 6-4 Conversion of metrics to score

Metric	Unit	Conversion	Score Range
RMSE	Wavelengths	$Score(x_i) = 100 * (1 - \frac{x_i}{0.5\lambda})$	0 λ : 100/100 0.5 λ : 0/100
Processing Time	Seconds	$Score(x_i) = 100 * (1 - 0.5) * log10 \left(\frac{x_i}{min(x)}\right)$	<i>min</i> (<i>x</i>): 100/100 100 * <i>min</i> (<i>x</i>) : 0/100
Separation Index	Wavelengths	$Score(x_i) = 100 * (1 - \frac{x_i}{1\lambda})$	0 λ : 100/100 1 λ : 0/100
Gridding Index	dB	$Score(x_i) = 100 * (1 - \frac{x_i}{30})$	0 <i>dB</i> : 100/100 30 <i>dB</i> : 0/100
Jaccard	[%]	$Score(x_i) = x_i$	100 % : 100/100 0 % : 0/100
Precision	[%]	$Score(x_i) = x_i$	100 % : 100/100 0 % : 0/100
Saturation	[%]	$Score(x_i) = x_i$	100 % : 100/100 0 % : 0/100