Detection of change in cancer breast tissues from fractal indicators:

A brief introduction

ANR MISTIC

Journées Textures à Vannes

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* Computational Modeling, Analysis of Imagery and Numerical Experiments

Tissue density fluctuations in normal vs. cancerous breasts

Overall mammographic density:

$\Longrightarrow$ important risk factor for breast cancer radiological assessment

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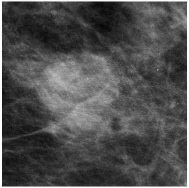
Local fluctuations: self-similar textures $\Longrightarrow$ fractal analysis for

- classification of mammogram density (Caldwell et al., 1990, *Phys. Med. Biol.*)
- lesion detectability in mammograms (Burgess et al., 2001, *Med. Biol.*)
- assessment of breast cancer risk (Heine et al., 2002, *Acad. Radiol.*)

Mammogram



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Fractional Brownian fields: characterized by their local roughness

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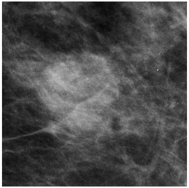
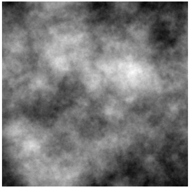
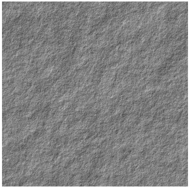


fractional Brownian field



stationary increments



Breast **microenvironment** plays a crucial role in tumorigenesis:

- structure integrity preserved $\Longrightarrow$ lesions are suppressed
- structure lost by tissue disruption $\Longrightarrow$ tumor is promoted

Tumor vs. healthy not only in the tumor but also in its surrounding tissue

Motivations and goals

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Main idea: quantify density fluctuations through the Hust exponent estimated in

multifractal formalism based on 2D Wavelet Transform Modulus Maxima

$\Longrightarrow$ risk assessment and tumorous breasts detection without seeing a tumor

fBf of Hurst exponent $H \in [0,1]$ denoted $\{B_H(\boldsymbol{x}),\, \boldsymbol{x} \in \mathbb{R}^2\}$

- Gaussian field with zero-mean
- and for some $\sigma^2 > 0$, correlation function writing

$$\mathbb{E}\left[B_H(\boldsymbol{x})B_H(\boldsymbol{y})\right] = \frac{\sigma^2}{2}\left(\|\boldsymbol{x}\|^{2H} + \|\boldsymbol{y}\|^{2H} - \|\boldsymbol{x}-\boldsymbol{y}\|^{2H}\right)$$

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$$= \|\boldsymbol{x}-\boldsymbol{y}\|^{2(H-1)} 2H(2H-1)\|\boldsymbol{h}\|^2 + o\left(\|\boldsymbol{h}\|^2\right)$$

A very short reminder about fractional Brownian fields

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- $H < 1/2$: anti-correlated
- $H = 1/2$: uncorrelated $\Longrightarrow$ disruption
- $H > 1/2$: long-range correlated

A very short reminder about fractional Brownian fields

Self-similarity

$$\forall \boldsymbol{h} \in \mathbb{R}^2, \lambda > 0, \quad B_H(\boldsymbol{x} + \lambda \boldsymbol{h}) - B_H(\boldsymbol{x}) \overset{\text{(law)}}{\simeq} \lambda^H (B_H(\boldsymbol{x} + \boldsymbol{h}) - B_H(\boldsymbol{x}))$$

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Local regularity: same roughness everywhere $h(\boldsymbol{x}) \equiv H \implies$ monofractal signature

The larger the Hurst exponent H, the smoother the texture.

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Singularity spectrum: $\mathcal{D}(h)$ Haussdorff dimension of $\{\boldsymbol{x} \in \mathbb{R}^2,\ h(\boldsymbol{x}) = h\}$

$$\mathcal{D}(h) = \begin{cases} 2 & h = H \\ -\infty & h \neq H \end{cases}$$

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$\Longrightarrow$ estimation of $h, \mathcal{D}(h)$: multifractal formalism based on wavelet transform

Local fractal analysis of mammographic breast tissue

CompuMAINE local mammogram analysis (Marin et al., 2017, Phys. Med. Biol.)

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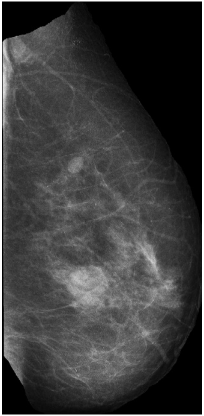
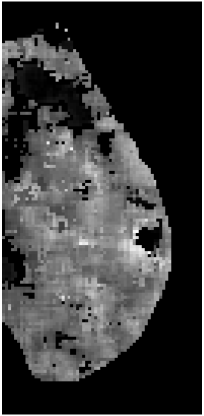
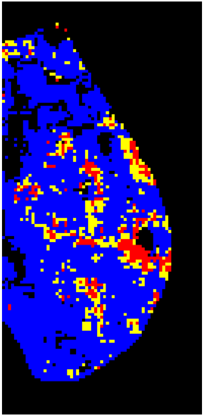

Dataset: *University of South Florida*, Digital Database for Screening Mammography

- Mediolateral oblique views only;
- 43 normal, 49 cancer, 35 benign;
- for benign and cancer microcalcification only, masses excluded;

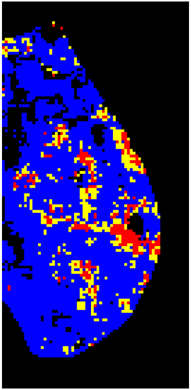

Image sliding-window analysis:

- squared 360×360-pixel window
- with 32-pixel horizontal and vertical shifts

$\Longrightarrow$ analysis of all 360×360-pixel overlapping patches

Example: mammogram of size 4459×2155 pixels

4457 patches $\Longleftrightarrow$ 4457 measures of the roughness H

Metric: number of yellow patches

$H \sim 1/2 \Longrightarrow$ disrupted tissues

Assessment of the role of disruption in tumor promotion

Q.: Is the quantity of disrupted tissues, $H \simeq 1/2$, indicative of a tumorous breast?

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Wilcoxon rank test a.k.a. Wilcoxon-Mann-Whitney

Independent sets of real numbers X and Y, of cardinalities n_x and n_y respectively

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If at least 20 samples, law of S_x well approximated by a Gaussian with

$$\mu = n_x n_y/2; \quad \sigma^2 = n_x n_y(n_x + n_y + 1)/2.$$

If $|S_x - \mu|/\sigma > 1.96$, **H0** is rejected with confidence level $\alpha = 0.05$.

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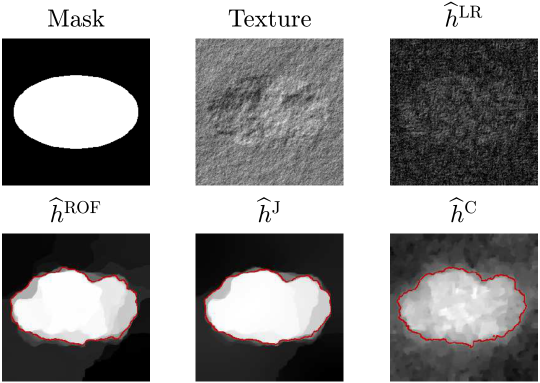
Tumorous breasts have **more disrupted tissues** compared to normal breasts:

normal vs. cancer: $P \sim 0.0423$, normal vs. benign: $P \sim 0.0009$.

Pascal et al., 2020, *Ann. Telecommun.*; Pascal et al., 2021, *Appl. Comput. Harmon. Anal.*; Pascal et al., 2021, *J. Math. Imaging Vis.* $\Longrightarrow$ *Journées ANR Mistic, April 2023*

$$\left(\widehat{\boldsymbol{h}}, \widehat{\boldsymbol{v}}\right)(\boldsymbol{\mathcal{L}}; \lambda, \alpha) = \underset{\boldsymbol{h},\boldsymbol{v}}{\operatorname{argmin}} \sum_{a} \|\log \boldsymbol{\mathcal{L}}_{a,\cdot} - \log(a)\boldsymbol{h} - \boldsymbol{v}\|^2 + \lambda \mathcal{Q}(\mathbf{D}\boldsymbol{h}, \mathbf{D}\boldsymbol{v}; \alpha)$$



$\Longrightarrow$ estimation of the local regularity, i.e., roughness, at the **pixel** level

But first: assess that the wavelet leaders formalism agrees with WTMM on patches

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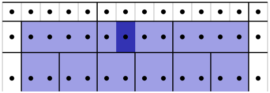
Wavelet leaders: $\mathcal{L}_{a,\underline{n}}$ at scale a and pixel $\underline{n}$ supremum of wavelet coefficients

- at all finer scales $a' \leq a$
- in a spatial neighborhood



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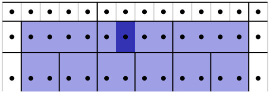

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homogeneous monofractal texture of Hurst exponent $H \Longrightarrow \tau(q) = qH$

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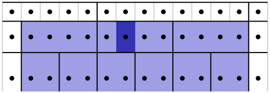

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linear regression to estimate H for all 360×360-pixel overlapping patches

Wavelet leader coefficients (Wendt et al., 2009, Sig. Process.)

- $H < 1/2$ monofractal anti-correlated: fatty tissues (healthy)
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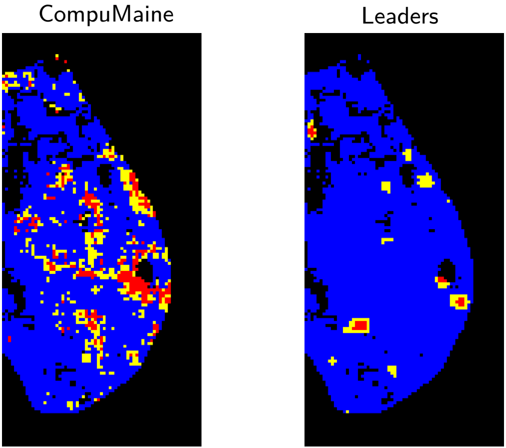

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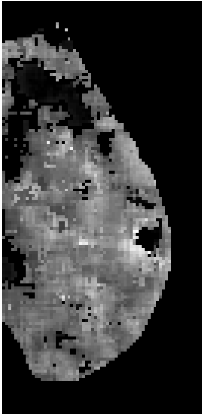
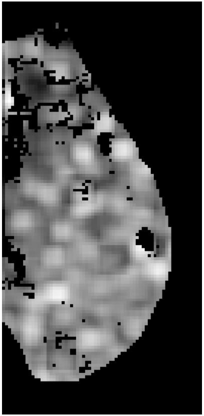
CompuMaine



Leaders



Multifractal analysis of mamographic microenvironment

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2D Wavelet Transform: $\{f(\boldsymbol{x}),\ \boldsymbol{x} \in \mathbb{R}^2\}$ 2D-field

Smoothing function $\varphi(\boldsymbol{x}) \Longrightarrow$ wavelets $\psi_1(\boldsymbol{x}) = \partial_{x_1}\varphi(x_1, x_2)$, $\psi_2(\boldsymbol{x}) = \partial_{x_2}\varphi(x_1, x_2)$

$$\mathbf{T}_\psi[f](\boldsymbol{b}, a) = \begin{pmatrix} a^{-2}\int \psi_1\left(a^{-1}(\boldsymbol{x}-\boldsymbol{b})\right) f(\boldsymbol{x})\,\mathrm{d}\boldsymbol{x} \\ a^{-2}\int \psi_2\left(a^{-1}(\boldsymbol{x}-\boldsymbol{b})\right) f(\boldsymbol{x})\,\mathrm{d}\boldsymbol{x} \end{pmatrix} \overset{\text{(complex)}}{=} \mathbf{M}_\psi[f](\boldsymbol{b}, a) \exp\left(\mathrm{i}\mathbf{A}_\psi[f](\boldsymbol{b}, a)\right)$$

Example: Gaussian and Mexican hat smoothing functions

$$\varphi_{\text{Gauss}}(\boldsymbol{x}) = \exp(-\|\boldsymbol{x}\|^2/2); \quad \varphi_{\text{Mex}}(\boldsymbol{x}) = (2 - \|\boldsymbol{x}\|^2)\exp(-\|\boldsymbol{x}\|^2/2)$$

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Wavelet Transform Modulus Maxima

$$\{(\boldsymbol{b}, a) \in \mathbb{R}^2, \times\mathbb{R}_+^* \quad \mathbf{M}_\psi[f](\boldsymbol{b}, a) \text{ locally maximal in direction } \mathbf{A}_\psi[f](\boldsymbol{b}, a)\}$$

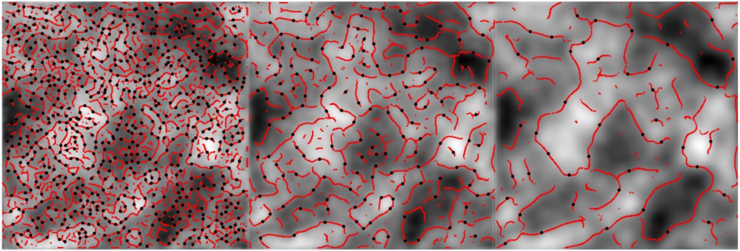
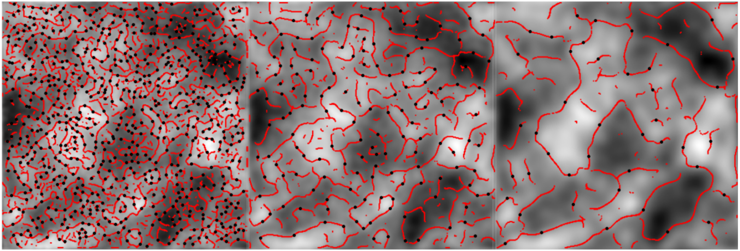


Figure 4.2: The maxima chains are shown for scales $a = 2^1\sigma_w$ (left), $a = 2^2\sigma_w$ (middle), and $a = 2^3\sigma_w$ (right) (where $\sigma_w = 7$ pixels) overlaid onto a 2D fBm image with $H = 0.5$. The local maxima along $\mathcal{M}_\psi$ (WTMMM) are shown through small filled black dots.

Source: Basel G. White



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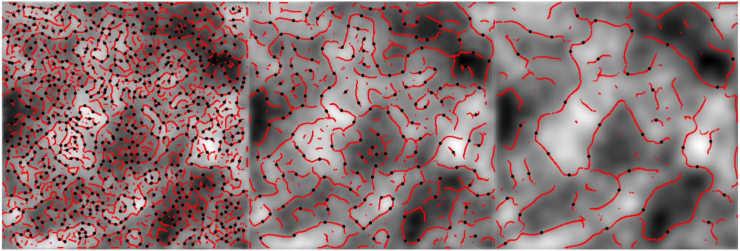
Wavelet Transform space-scale skeleton: $\mathcal{L}(a)$

lines formed by WTMM maxima across scales



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If a maxima line $\mathcal{L}_{\boldsymbol{x}_0}(a)$ is pointing toward a singularity $\boldsymbol{x}_0$ as $a \to 0^+$, then

$$\mathbf{M}_\psi[f](\mathcal{L}_{\boldsymbol{x}_0}(a)) \sim a^{h(\boldsymbol{x}_0)}, \quad a \to 0^+$$

provided that the wavelet has $n_\psi > h(\boldsymbol{x}_0)$ vanishing moments.

Partition function: for a set $\mathfrak{L}(a)$ of maxima lines

$$\mathcal{Z}(q,a) = \sum_{\ell \in \mathfrak{L}(a)} \left(\sup_{(\boldsymbol{b},a') \in \ell, a' \leq a} \mathbf{M}_\psi[f](\boldsymbol{b},a') \right)^q$$

q: statistical order moment

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Roughness, quantified by Hölder exponent, characterized by $\tau(q)$ spectrum

$$Z(q,a) \sim a^{\tau(q)}, \quad a \to 0^+$$

For 2D fractional Brownian field: $\tau(q) = qH - 2$ is **linear**.

Multifractal framework: Wavelet Transform Modulus Maxima

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Singularity spectrum: $\mathcal{D}(h)$ Haussdorff dimension of $\{\boldsymbol{x} \in \mathbb{R}^2, \, h(\boldsymbol{x}) = h\}$

$$\mathcal{D}(h) = \min_q \left(qh - \tau(q) \right) \quad \text{(Legendre transform of } \tau\text{)}$$

Numerically: unstable estimation of $\tau(q)$ and $\mathcal{D}(q)$

$\Longrightarrow$ Mean quantities in a canonical ensemble with Boltzmann weights

$$\mathrm{W}_\psi[f](q, \ell, a) = \frac{\left| \sup_{(\boldsymbol{b}, a') \in \ell, a' \leq a} \mathbf{M}_\psi[f](\boldsymbol{b}, a') \right|^q}{\mathcal{Z}(q, a)}$$

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Roughness: robust local regularity estimation

$$h(q,a) = \sum_{\ell\in\mathfrak{L}(a)} \ln\left(\mathrm{W}_\psi[f](q,\ell,a)\right) \mathrm{W}_\psi[f](q,\ell,a),$$

$$h(q) = \frac{\mathrm{d}\tau}{\mathrm{d}q} = \lim_{a\to 0^+} \frac{h(q,a)}{\ln a}$$

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- The larger the patch, the larger the range of q values, the better the estimate;
- but risk of confusing average of several monofractal signatures and multifractal.

$\Longrightarrow$ estimation on overlapping patches of size 360×360 pixels with 32-pixel shift

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Image sliding window analysis

1. Check that the central 256×256 pixels are contained in the mask;
2. if so, compute the Wavelet Transform for 50 scales, from $a = 7$ to 120 pixels;
3. extract the space-scale skeleton from the central 256×256 pixels;
4. compute $h(q,a)$ and $\mathcal{D}(q,a)$ from the partition function $\mathcal{Z}(q,a)$;
5. linear regressions $h(q,a)$ vs. $\log_2(a)$ and $\mathcal{D}(q,a)$ vs. $\log_2(a)$:

how to choose the range of scales $[a_{\min}, a_{\max}]$?

For **each** patch of 360×360 pixels, i.e., 15.5×15.5 mm

roughness: $h(q) = \lim_{a \to 0^+} \frac{h(q,a)}{\ln a}$; singularity spectrum: $\mathcal{D}(q,a) = \lim_{a \to 0^+} \frac{\mathcal{D}(q,a)}{\ln a}$

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The Autofit Methodology: imposing $\log_2 a_{\max} - \log_2 a_{\min} \geq 1$ explore

$$\log_2 \frac{a_{\min}}{\sigma_w} = 0.0, 0.1, \ldots, 2.1, \;, \;\; \log_2 \frac{a_{\max}}{\sigma_w} = 2.0, 2.1, \ldots, 4.1, \;\; \text{with} \;\; \sigma_w = 7 \text{ pixels}$$

and select $[a_{\min}, a_{\max}]$ if and only if

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- linear regression on $h(q=0,a)$ from $a_{\min}$ to $a_{\max}$ yields

$$-0.2 < \widehat{h}(q=0) = \widehat{H} < 1$$

  - $H \leq -0.2$: high roughness $\Longrightarrow$ abnormally high noise
  - $H \geq 1$: low roughness, differentiable field $\Longrightarrow$ artificially smooth

For **each** patch of 360×360 pixels, i.e., 15.5×15.5 mm

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- linear regression on $\mathcal{D}(q=0,a)$ from $a_{\min}$ to $a_{\max}$ yields

$$1.7 < \widehat{\mathcal{D}}(h(q=0)) < 2.5$$

for a monofractal field of Hurst exponent H, expected to be $\mathcal{D}(H) = 2$

but finite size effect affect the maxima lines as $a \to 0^+$

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and select $[a_{\min}, a_{\max}]$ if and only if

- coefficient of determination of linear regression on $h(q=0,a)$ from $a_{\min}$ to $a_{\max}$

$$R^2 > 0.96$$

sufficiently linear to extract the Hurst exponent H

For **each** patch of 360×360 pixels, i.e., 15.5×15.5 mm

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and select $[a_{\min}, a_{\max}]$ if and only if

- weighted standard deviation across q of the $\widehat{h}(q)$ estimated from $a_{\min}$ to $a_{\max}$

$$\mathrm{sd}_w < 0.06$$

$\Longrightarrow$ excludes multifractal scaling

q	-2	-1.5	-1	-0.5	-0.3	-0.2	-0.1	0	0.1	0.2	0.3	0.5	1	1.5	2	2.5	3
w	0.1	0.5	1	3	5	7	9	10	9	8	7	5	3	2	1	0.5	0.2

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and select $[a_{\min}, a_{\max}]$ if and only if

- weighted average of goodness of fit of $\widehat{h}(q)$ estimated from $a_{\min}$ to $a_{\max}$

$$\langle R_w^2 \rangle > 0.96$$

$\Longrightarrow$ ensures self-similarity

q	-2	-1.5	-1	-0.5	-0.3	-0.2	-0.1	0	0.1	0.2	0.3	0.5	1	1.5	2	2.5	3
w	0.1	0.5	1	3	5	7	9	10	9	8	7	5	3	2	1	0.5	0.2

For **each** patch of 360×360 pixels:

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The Autofit Methodology: imposing $\log_2 a_{\max} - \log_2 a_{\min} \geq 1$ explore 418 couples

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and select $[a_{\min}, a_{\max}]$ if and only if

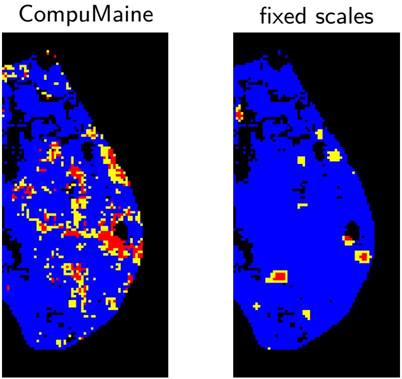
- $-0.2 < h(q=0) < 1$: expected roughness
- $1.7 < \widehat{D} < 2.5$: expect 2
- $R^2 > 0.96$: accurate estimation of H
- $sd_w < 0.06$: monofractal scaling
- $\langle R_w^2 \rangle > 0.96$: $h(q,a)$ sufficiently linear

$\Longrightarrow$ If no scale range $[a_{\min}, a_{\max}]$ for which all conditions are satisfied: **no scaling**.

Local fractal analysis of mammographic breast tissue

Wavelet leader coefficients (Wendt et al., 2009, Sig. Process.)

- $H < 1/2$ monofractal anti-correlated: fatty tissues (healthy)
- $H > 1/2$ monofractal long-range correlated: dense tissues (healthy)
- $H \simeq 1/2$ monofractal uncorrelated: disrupted tissues (tumorous)



$$[a_{\min}, a_{\max}] = [2^3, 2^5]$$

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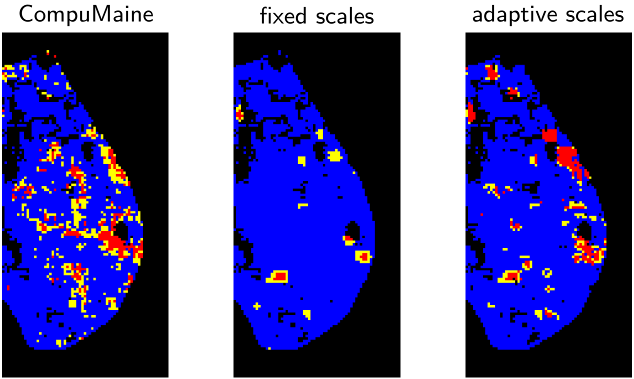

$[a_{\min}, a_{\max}] = [2^3, 2^5]$ $[a_{\min}, a_{\max}] \subset [2^2, 2^8]$

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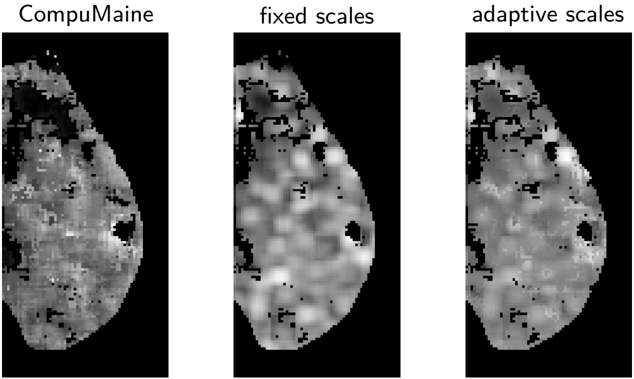

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Marin et al., 2017, *Phys. Med. Biol.*

DDSM: *University of South Florida*, Digital Database for Screening Mammography

43 normal vs. 49 cancer, 35 benign

$\Longrightarrow$ digitized films: lossless LJPEG 12-bit images (pixel values: integers in $[0, 4095]$)

Tumorous breasts have more disrupted tissues compared to normal breasts:

normal vs. cancer: $P \sim 0.0423$, normal vs. benign: $P \sim 0.0009$.

Mammogram datasets

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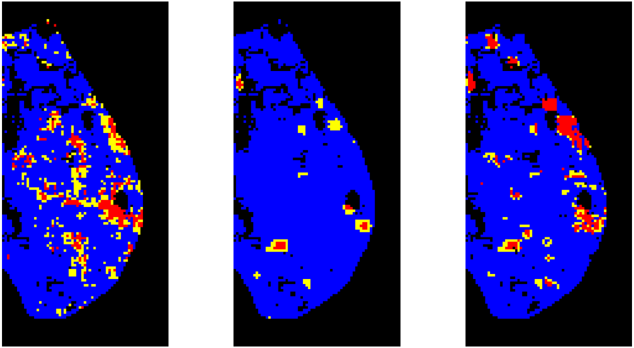
CompuMaine | fixed scales | adaptive scales



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Wavelet leaders with

- Daubechies wavelets with $n_\Psi = 2$ vanishing moments
- $\sim$ scales selected by the CompuMaine autofit method, up to rounding errors

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$\underline{\text{cancer vs. benign:}}$ $P \sim 0.074$

Patch-wise fractal analysis of mammograms with WT modulus maxima method

- disrupted tissues, characterized by $H \sim 1/2$, indicate loss of homeostasis
- quantity of disrupted tissues discriminates between

  (Marin et al., 2017) tumorous vs. normal $P \sim 0.0006$

  (Gerasimova-Chechkina et al., 2021) cancer vs. benign $P \sim 0.0030$

$\Longrightarrow$ exploration of 418 couples of $(a_{\min}, a_{\max})$ for each patch and strict conditions

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$\Longrightarrow$ exploration of 418 couples of $(a_{\min}, a_{\max})$ for each patch and strict conditions

Reproduction with wavelet leaders formalism on Russian dataset

- range of scales for each patch extracted from CompuMaine analyses,
- remains less informative: $P \sim 0.0740$

From patch-wise to pixel-wise fractal analysis

- using wavelet leaders framework,
- combined with variational methods,
- with PyTorch implementation to benefit from fast GPU computing,
- reduced number of hyperparameters & fine-tuned automatically

$\Longrightarrow$ increase the sensibility in the measurement of the quantity of disrupted tissues

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Asymmetry in tissue disruption in cancerous cases

- assessed both in Marin et al., 2017 and Gerasimova-Chechkina et al., 2021,
- to be evaluated with (pixel-wise) wavelet leader fractal analysis

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Anisotropic Gaussian fields for mammogram modeling

- observed in Richard & Biermé, 2010
- many tools that have never been applied to mammogram yet!