Probing biological systems with ultrasound

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Ultrasound and biological systems

Safely probe living systems in real-time

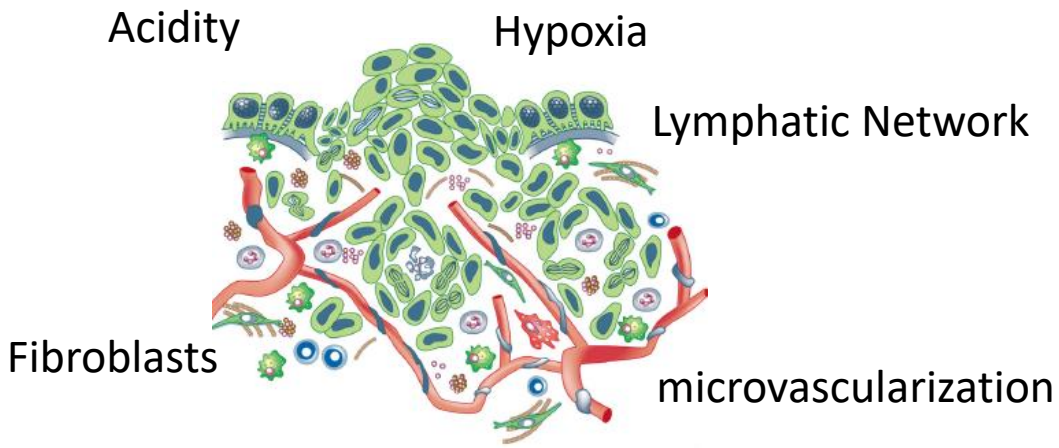
- Characterization of low-level blood flow

Precisely evaluate physical properties of biological materials

- Resonant ultrasound spectroscopy

Characterization of low-level blood flow

Tumor microenvironment



- Molecular reactions
- Cell-cell interactions
- Pysiological relationships

Structural and functional heterogeneity of vascularization associated with progression and malignancy

Agrawal et al. Cancer, 2009

Features and processes

- patient/tumor-dependent
- present heterogeneity within a tumor
- evolve both with time and treatment

Need longitudinal imaging biomarkers

That meaningfully probe a tumor's

- functional, molecular and heterogeneity profile.

1) Discovery

   Advances in imaging (engineering, modeling, chemistry …) enable response to unmet medical needs

2) Technical validation

   Accessibility, repeatability and reproducibility (devices, contrast agents, software…)

3) Link to tumor biology and outcome

   Key to developing measurement value in guiding decision-making

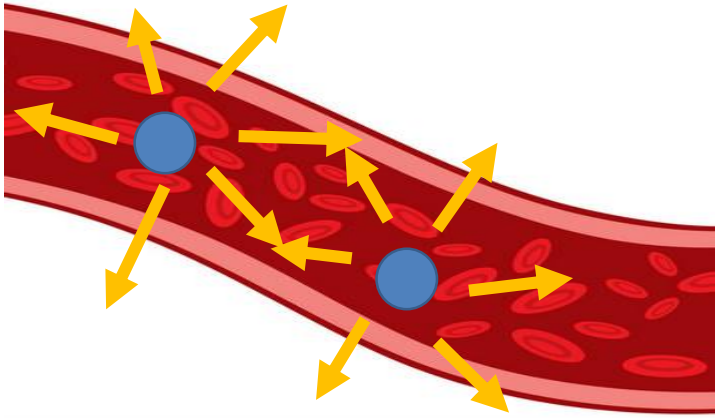
4) Clinical validation and cost-effectiveness

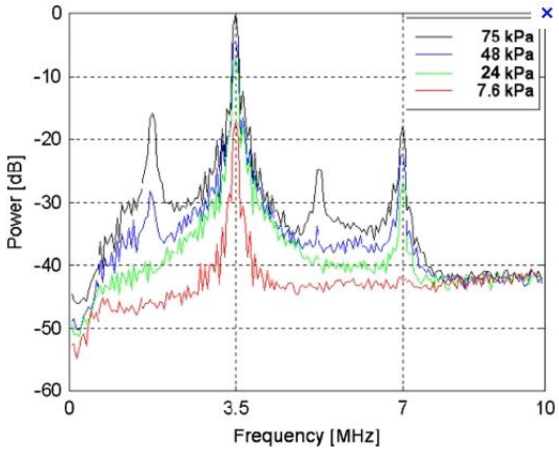
   Advantage of cost per quality adjusted life year with respect to current standard of care

Contrast-enhanced ultrasound

Intravenous Injection

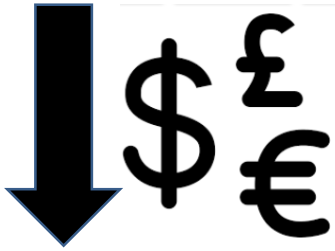
Specific acoustic signature

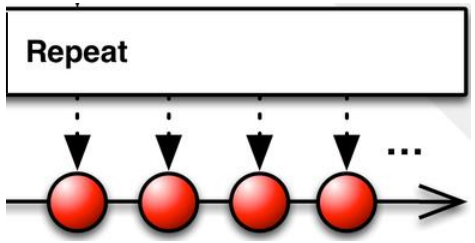




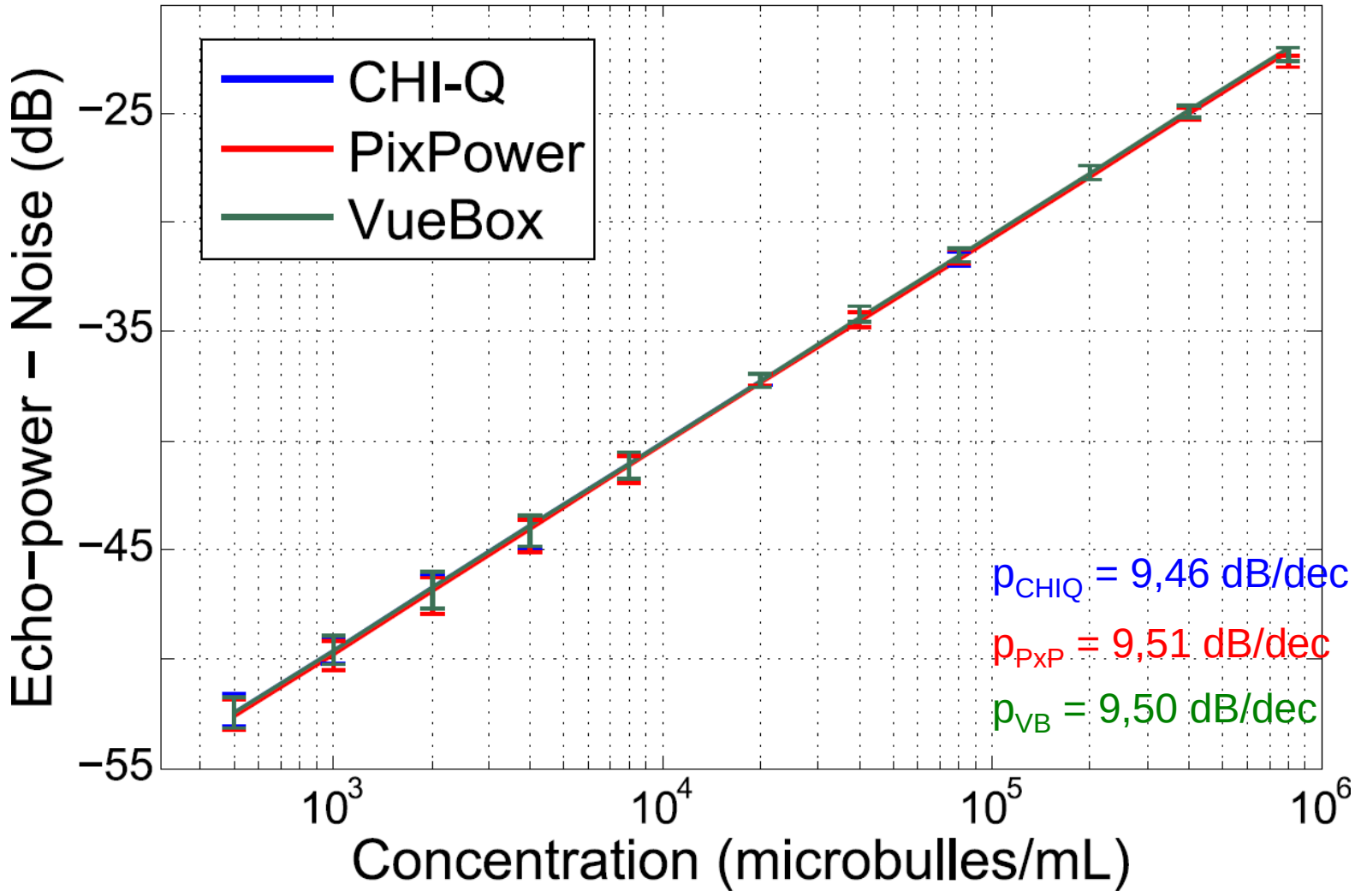
Can evaluate functional flow and its heterogeneity

Multiple advantages:

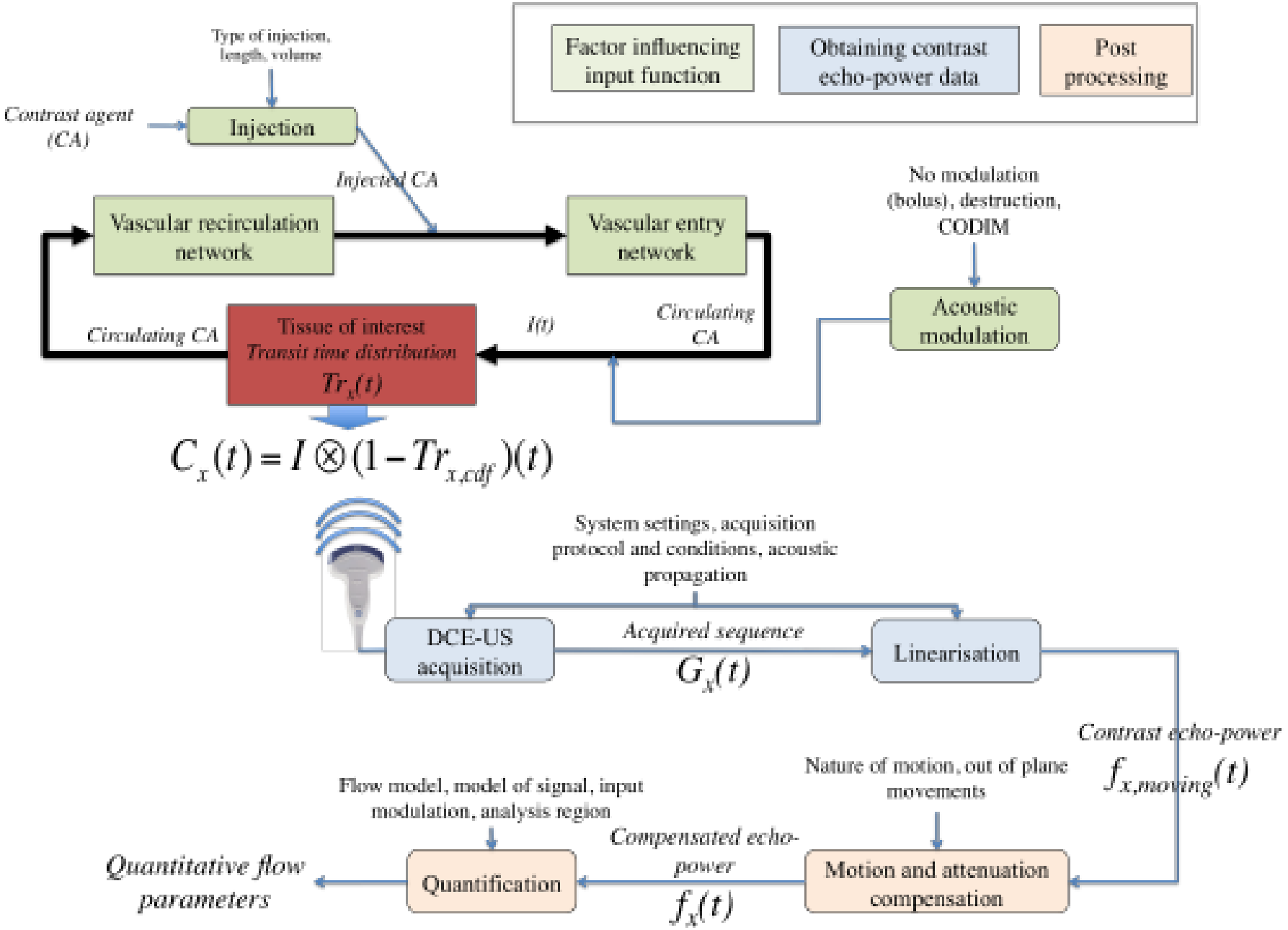




Quantification can be achieved from image-based data



*[**Payen** et al., Ultra Med Biol 2013]*

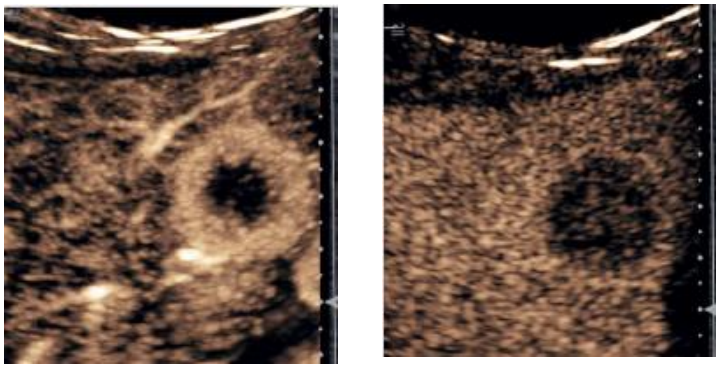

Factor influencing input function
Obtaining contrast echo-power data
Post processing
Type of injection, length, volume
Contrast agent (CA)
Injection
Injected CA
Vascular recirculation network
Vascular entry network
No modulation (bolus), destruction, CODIM
Acoustic modulation
Circulating CA
Tissue of interest
Transit time distribution
$Tr_x(t)$
I(t)
Circulating CA
$C_x(t) = I \otimes (1 - Tr_{x,cdf})(t)$
System settings, acquisition protocol and conditions, acoustic propagation
DCE-US acquisition
Acquired sequence
$G_x(t)$
Linearisation
Contrast echo-power
$f_{x,moving}(t)$
Nature of motion, out of plane movements
Flow model, model of signal, input modulation, analysis region
Compensated echo-power
$f_x(t)$
Motion and attenuation compensation
Quantification
Quantitative flow parameters

Clinically accessible use of CEUS to assess tumor status

- Qualitative

  Vascular distribution and enhancement patterns to characterize focal liver lesions as malignant or benign

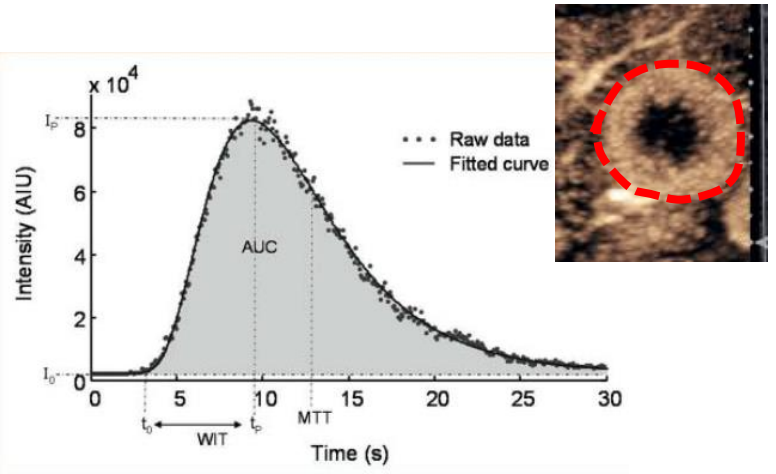
Malignant Lesion : arterial and portal phases



Dietrich, Ultrasound Int Open 2017

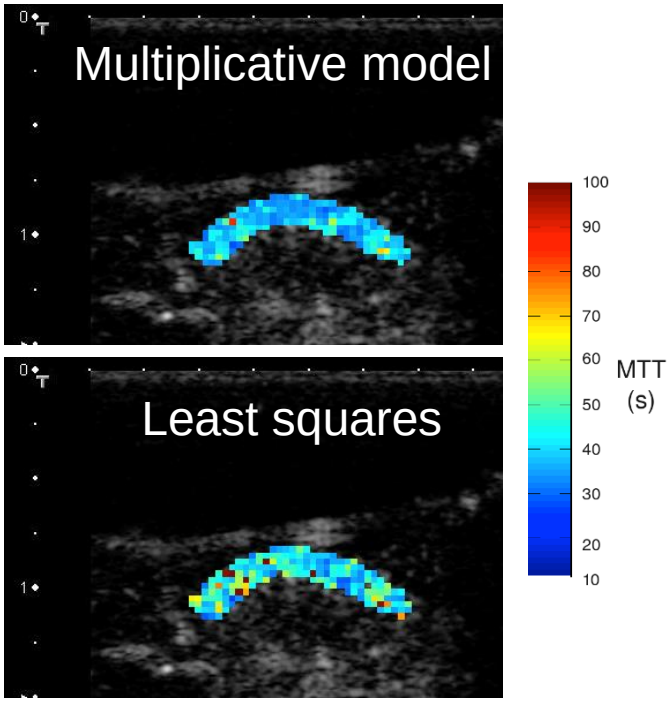
- Quantitative:

  Δ AUC for contrast time intensity curves (TIC) for prediction of solid-tumor response to anti-angiogenic therapy *Lassau, Invest Radiol, 2014*



Improved capacity to map heterogenity

- **Identified that the gamma distribution is consistent with the nature of DCE-US signal**
  - ➢ Flexible choice for mathematical analysis
- **Definition of a multiplicative noise model to describe DCE-US signal**

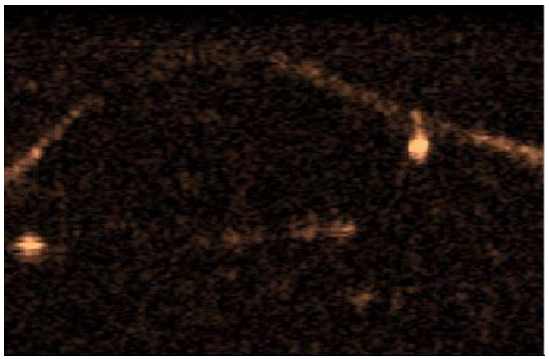


Mean transit time mapped from small ROA in mice renal cortex

➔ Significantly lower variability from small ROA because algorithm is better adapted to the nature of the signal

*[**Barrois** et al. IEEE Trans UFFC, 2013]*

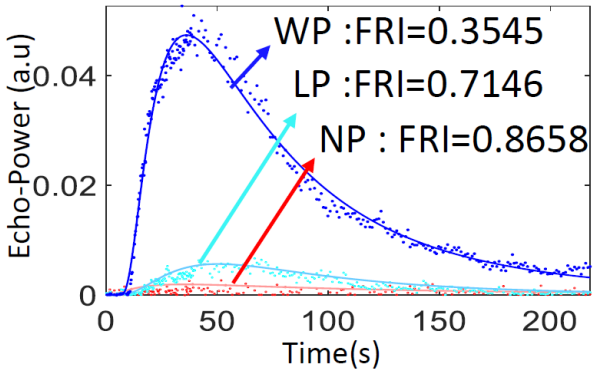
Accounting for flow heterogenity



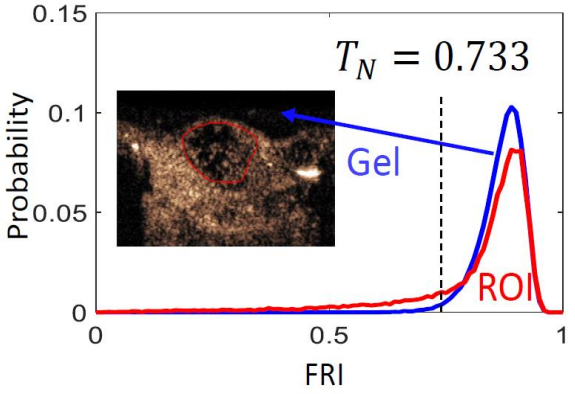
Visually different areas:
→ Well Perfused area (WP)
→ Low Perfused area (LP)
→ Not Perfused area (NP)

Time Intensity Curve used to differentiate the zone based on a goodness of fit parameter (FIR)

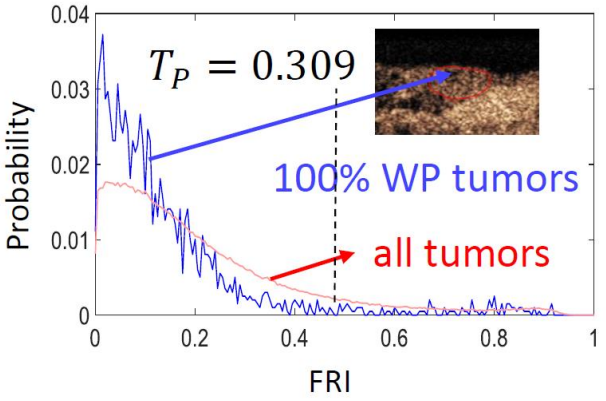
Example of FIR values for different zones



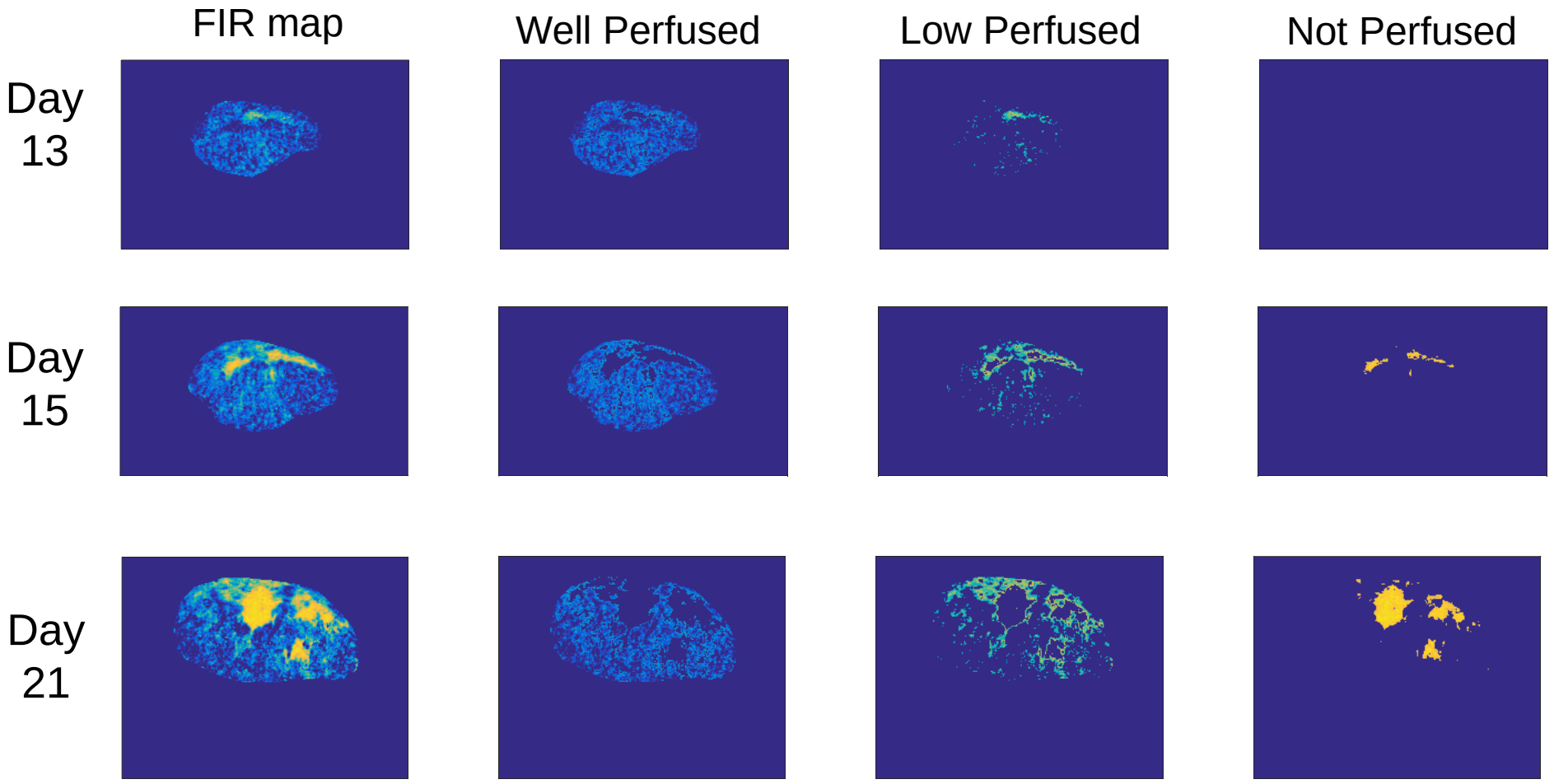
Estimation threshold for NP zones



Estimation threshold for WP zones



Example of zone evolution over time



Relative sizes of functional territories during growth

Microbubbles enable many imaging advances

Voxels > microvasculature

- Flow tracer kinetics
- Diffusion model
- Fluid dynamic model

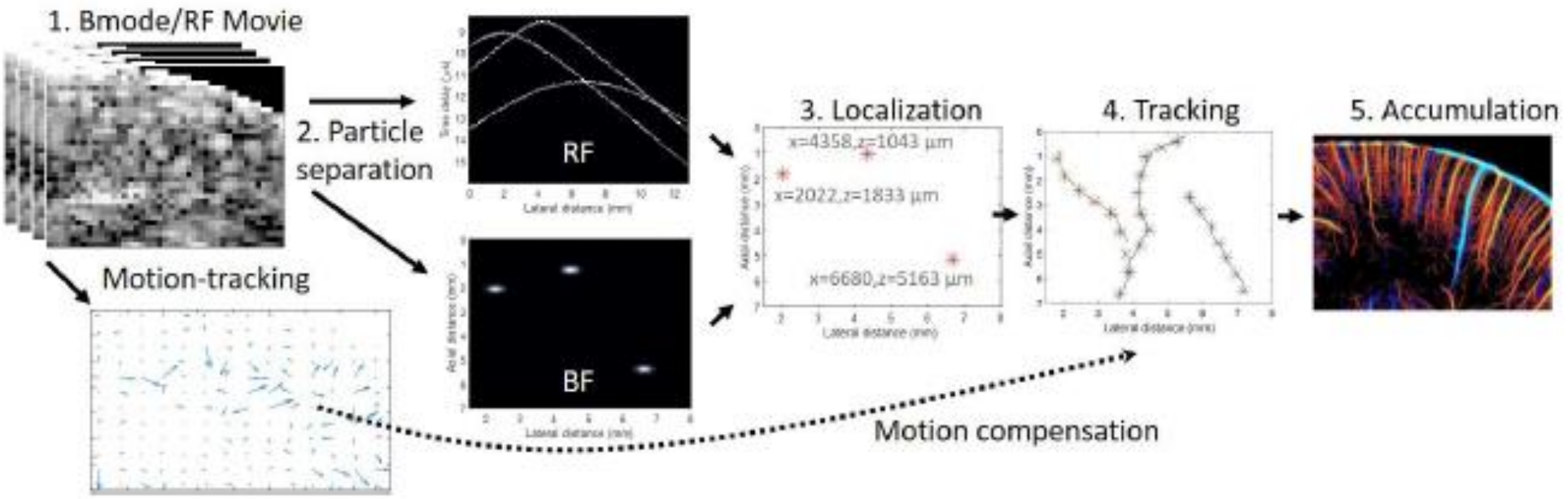
Georges Seurat: Un dimanche après-midi à l'île de la Grande Jatte

Traces out microvessels

- Acoustic angiography
- Spatiotemporal filtering of ultrafast images
- Motion model ultrasound localization microscope

Claude Monet: Les Nymphéas

Key: plane-wave ultrarapid ultrasound



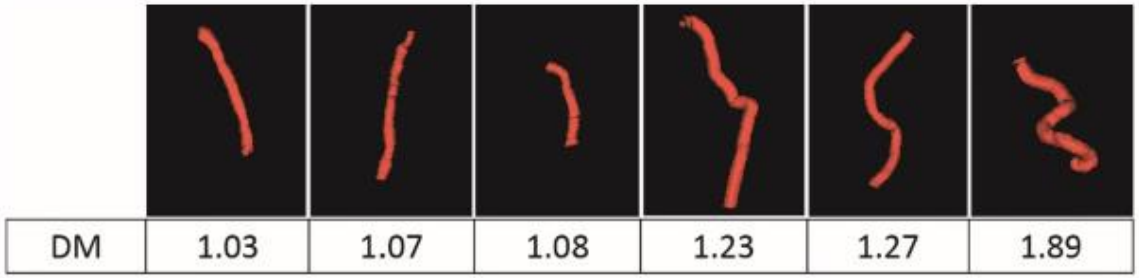
Identify and track individual microbubbles

*[**Couture** et al. IEEE Trans UFFC, 2018]*

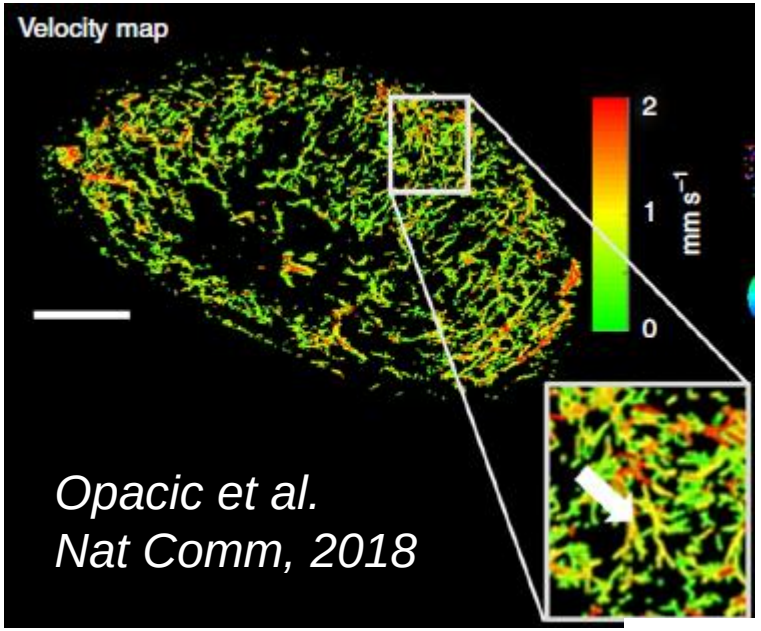
Subresolution mapping of vessels and flow

- Relative blood volume
- Arrival time
- Spatiotemporal correlation
- Mean transit time

- Distance to closest vessel
- Tortuosity/branching
- Vessel flow velocity



Lin et al.
Theranositcs, 2017



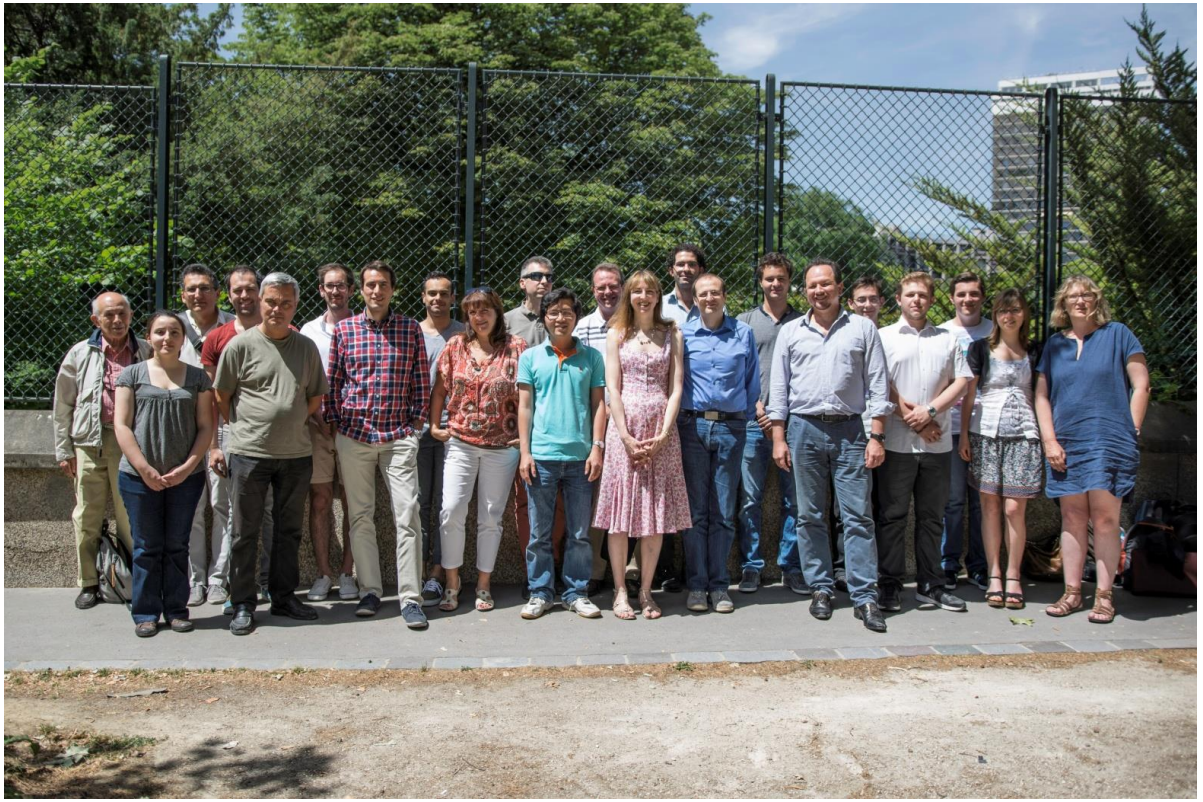
Opacic et al.
Nat Comm, 2018

Summary

- Sensitive to physiological motion
- Need precise localization of microbubble center-points
- Without volumetric information tracking and characterization are incomplete

Enticing capacities to visualize new aspects of tumor microvasculature with subresolution blood dynamics

Acknowledgements



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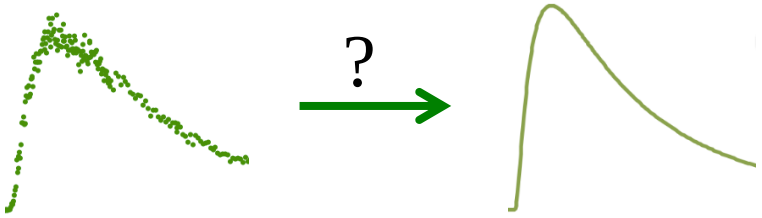
FLI
France Life Imaging

Plan cancer 2009 2013

Modeling the contrast response



f(t) *u(t)*

$$f(t) = u(t) + v(t)$$
$$f(t) = u(t).v(t)$$

Hypothesis : Multiplicative model of signal