Probing biological systems with ultrasound

S. Lori Bridal, Pascal Dargent

Sorbonne University, UMR CNRS 7371 –U1146 INSERM, Laboratoire d’Imagerie Biomédicale, France
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

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

Agrawal et al. Cancer, 2009

Structural and functional heterogeneity of vascularization associated with progression and malignancy
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
Can evaluate functional flow and its heterogeneity

Multiple advantages:

- Contrast-enhanced ultrasound
- Intravenous Injection
- Specific acoustic signature
Quantification can be achieved from image-based data

\[ \text{CHIQ} = 9.46 \text{ dB/dec} \]
\[ \text{VB} = 9.50 \text{ dB/dec} \]
\[ \text{PxP} = 9.51 \text{ dB/dec} \]

[Payen et al., Ultra Med Biol 2013]
Contrast agent (CA)

Injection

Injected CA

Vascular recirculation network

Circulating CA

Tissue of interest

Transit time distribution

$T_{r_x}(t)$

$C_x(t) = I \otimes (1 - T_{r_{x,cdf}})(t)$

System settings, acquisition protocol and conditions, acoustic propagation

DCE-US acquisition

Acquired sequence

$G_x(t)$

Linearisation

Quantitative flow parameters

Compensated echo-power

$f_x(t)$

Motion and attenuation compensation

Nature of motion, out of plane movements

Flow model, model of signal, input modulation, analysis region

Compensated echo-power

Contrast echo-power

$f_{x,moving}(t)$

Quantification

取得对比回声功率

$Post\ processing$

No modulation (bolus), destruction, CODIM

Acoustic modulation

系统设置，采集协议和条件，声波传播

DCE-US 采集

获取序列

$G_x(t)$

线性化

定量流参数

补偿声功率

$f_x(t)$

运动和衰减补偿

运动，非平面运动

流模型，信号模型，输入调制，分析区域

补偿声功率

对比声功率

$f_{x,moving}(t)$

量化

更正后的回声功率
Clinically accessible use of CEUS to assess tumor status

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

• 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 heterogeneity

• 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

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 heterogeneity

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 FIR values for different zones

WP : FRI = 0.3545
LP : FRI = 0.7146
NP : FRI = 0.8658

$T_N = 0.733$

$T_P = 0.309$

100% WP tumors

all tumors

Accounting for flow heterogeneity

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 FIR values for different zones

WP : FRI = 0.3545
LP : FRI = 0.7146
NP : FRI = 0.8658

$T_N = 0.733$

$T_P = 0.309$

100% WP tumors

all tumors
Example of zone evolution over time

Day 13
FIR map
Well Perfused
Low Perfused
Not Perfused

Day 15

Day 21

Relative sizes of functional territories during growth
Microbubbles enable many imaging advances

Voxels > microvasculature
   – Flow tracer kinetics
   – Diffusion model
   – Fluid dynamic model

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

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

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.
Theranostics, 2017

Opacic et al.
Nat Comm, 2018
Enticing capacities to visualize new aspects of tumor microvasculature with subresolution blood dynamics
Acknowledgements

Imaging and Therapy Development
Laboratoire d’Imagerie Biomédicale
Modeling the contrast response

\[ f(t) = u(t) + v(t) \]

\[ f(t) = u(t) \cdot v(t) \]

Hypothesis: Multiplicative model of signal

\[ \text{dose ranging data} \]

\[ 2 \times 10^5 \text{ mb/mL} \]

\[ 8 \times 10^4 \text{ mb/mL} \]