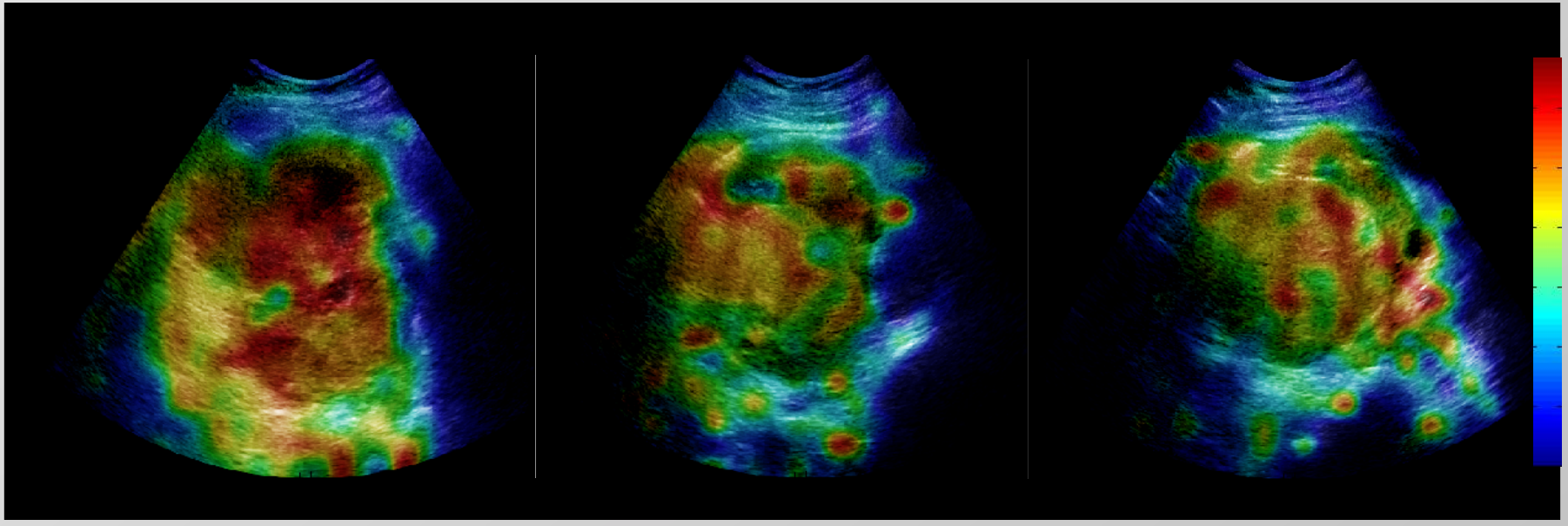
Functional Imaging of Cancer Using Contrast-Enhanced Ultrasound

JOHN M. HUDSON



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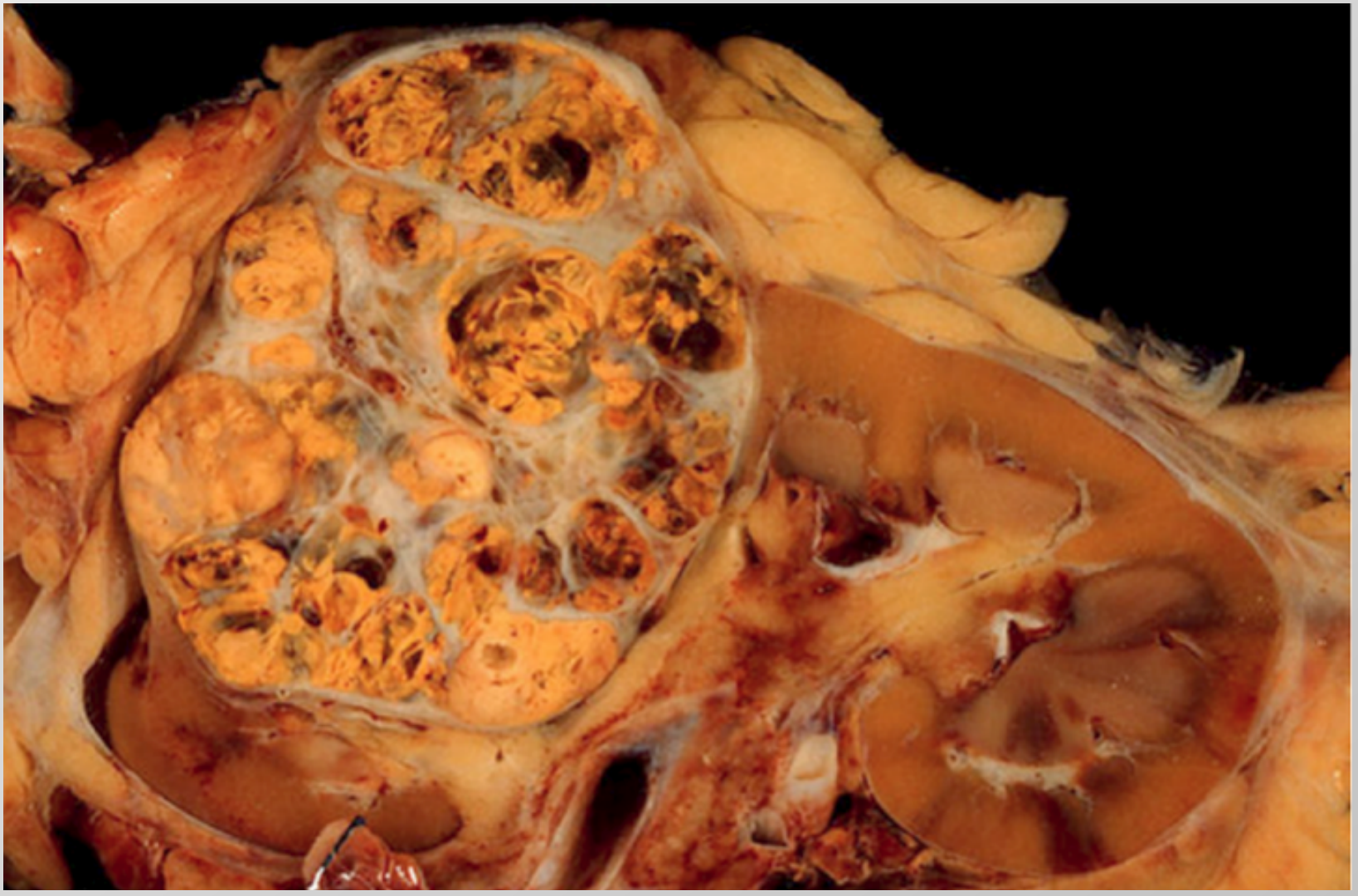
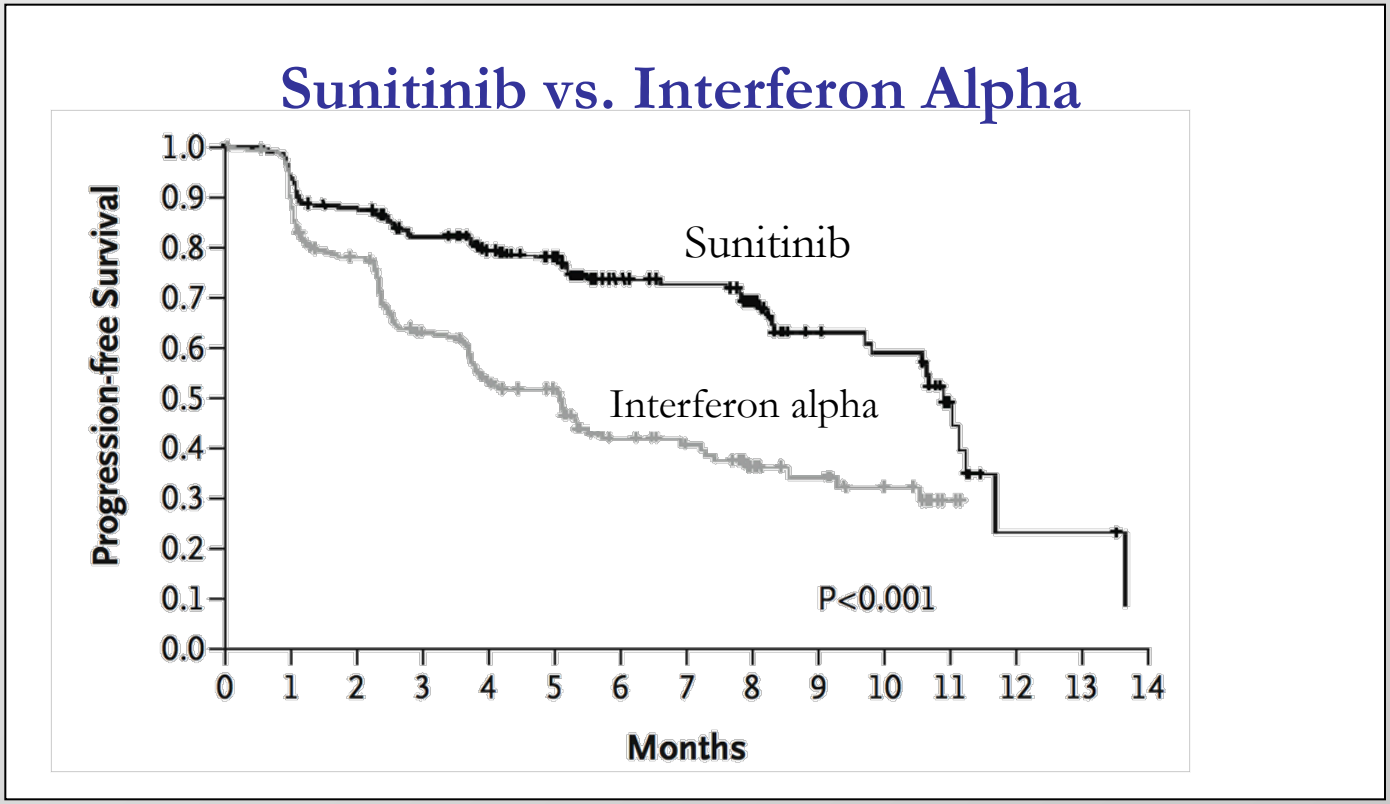
Renal Cell Carcinoma (RCC)



Anti-angiogenic Treatments for Metastatic Renal Cell Carcinoma (RCC)

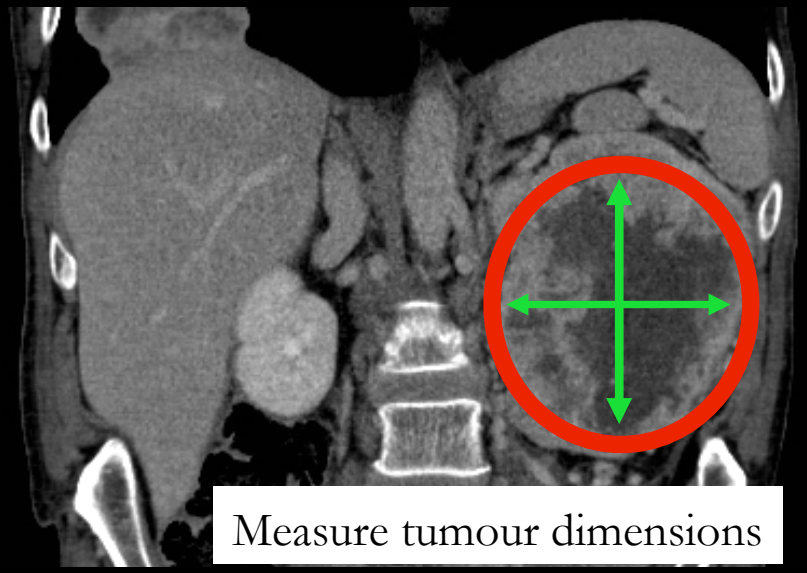


- Anti-angiogenic drugs have increased the progression free survival time for patients with RCC.
- Response is patient-specific - optimal schedule for treatment unknown

RJ Motzer *et al.*, NEJM, v356(2), 2007

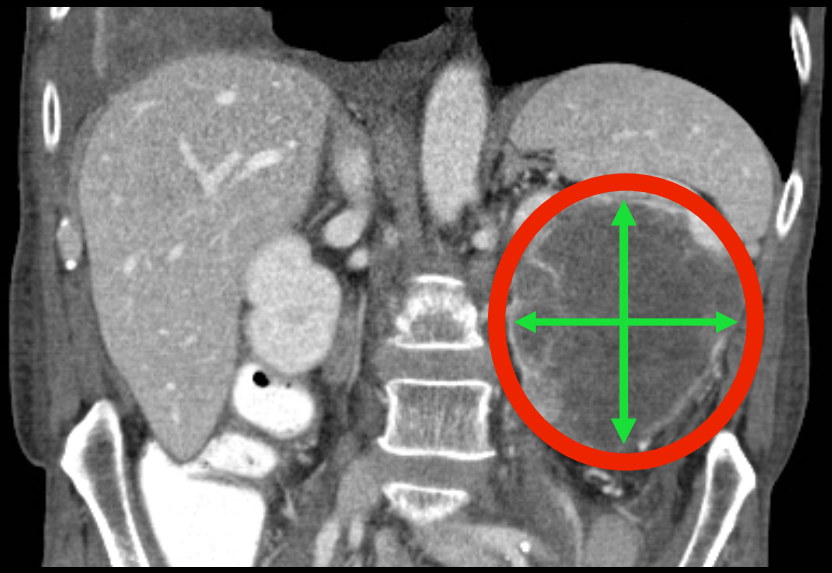
Standard Measures of Tumour Response

Before Sunitinib Treatment



Measure tumour dimensions

After 2 Weeks of Sunitinib Treatment



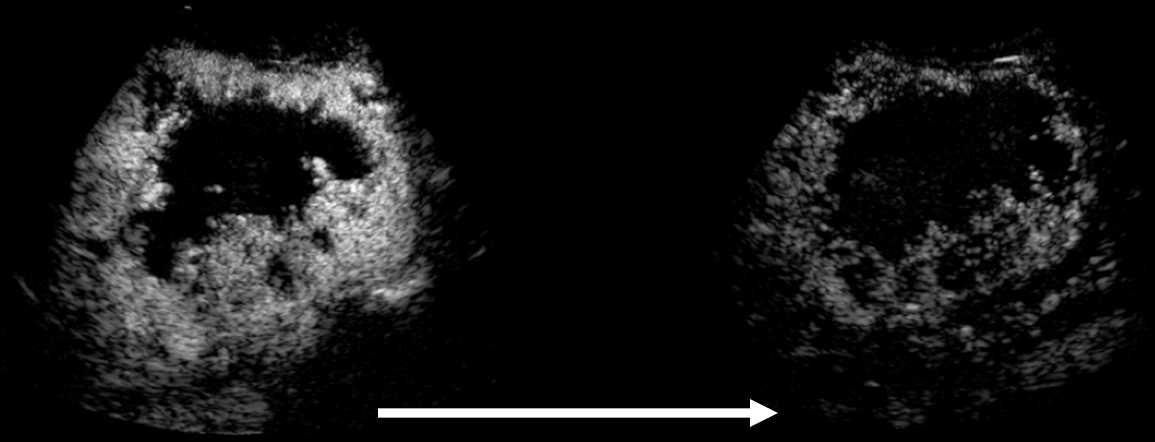
The Challenge

- Current measures of therapeutic response (RECIST) rely on anatomical size
- Tumour size does not always change in response to treatment

Functional Measures of Tumour Response

Before Sunitinib Treatment

After 2 Weeks of Sunitinib Treatment



Decrease in blood perfusion

The Trend

– Shift from anatomical to functional measurements that target the parameters that are affected by therapy (e.g. blood volume, blood perfusion, permeability etc.)

Objectives and Motivation:

– Medical imaging as a biomarker for tumour response

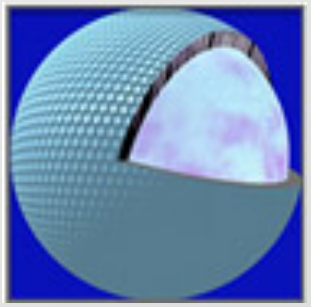
- Dynamic contrast enhanced ultrasound

Functional Imaging of Cancer Using Contrast-Enhanced Ultrasound

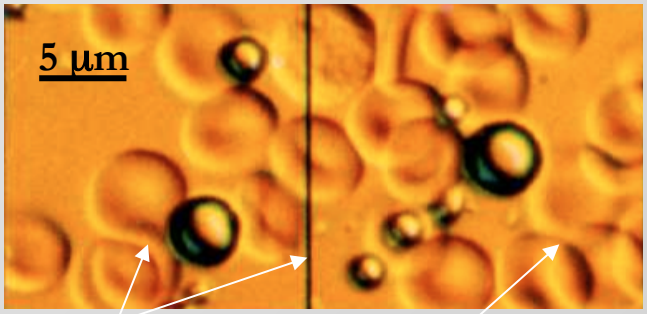
Overview of today's talk:

- Introduce ultrasound contrast agents and highlight their unique properties
- Describe how microbubble dynamics can be used to quantify properties of the microvasculature
- Demonstrate how contrast-enhanced ultrasound can be used to monitor the response of the tumour vasculature to anti-angiogenic therapy.

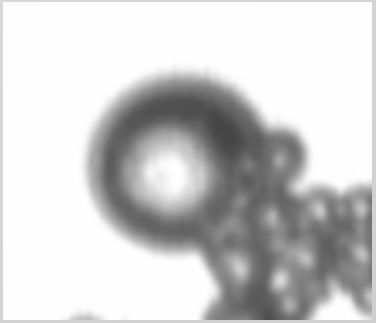
Ultrasound Contrast Agents



Definity™:
- perfluorocarbon gas
- lipid shell



Microbubble Red blood cell



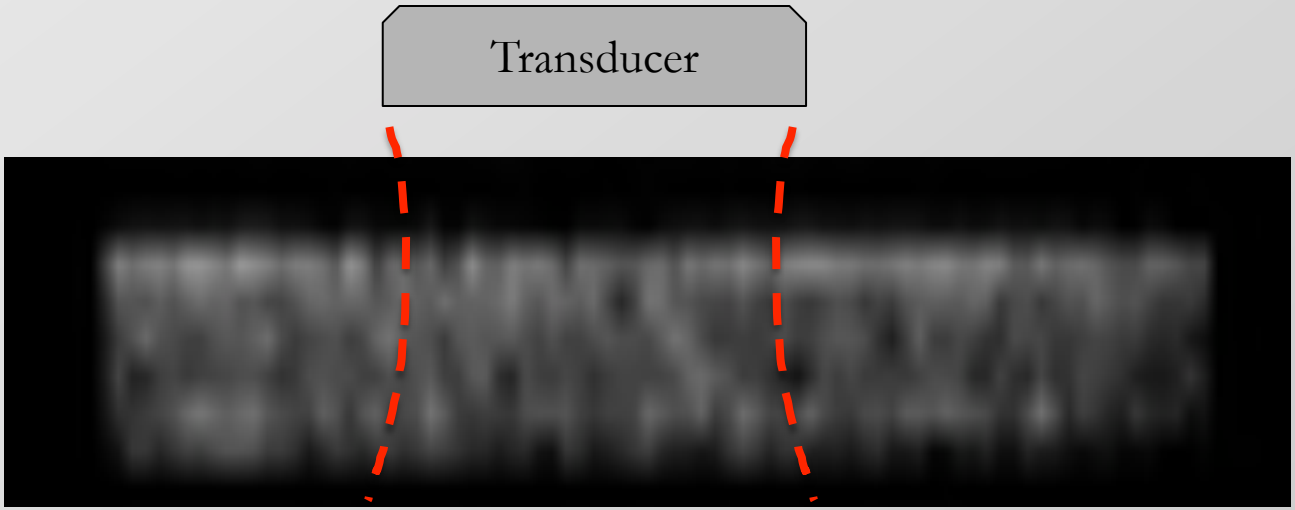
Bubble responding to ultrasound

Univ. Twente

Microbubble Tracer Properties

- Same size as red blood cells = Intravascular = a blood pool agent
- Bubbles can be discriminated from tissue using bubble specific imaging (e.g. Harmonic Imaging, Pulse Inversion)
- Measured signal is proportional to number of bubbles (concentration)
- Bubbles can be disrupted

Acoustic Microbubble Disruption



Measuring Flow Using Microbubble Disruption

Procedure of Disruption-Replenishment

1) Performed during a constant infusion of microbubbles
2) High pressure disrupts the agent within the imaging plane (negative bolus)
3) The scan plane is replenished with new bubbles at a rate determined by blood flow

Wei *et al.* BSR, 1997

Disruption-Replenishment: Clinical Example

Contrast Specific Imaging

Conventional Imaging

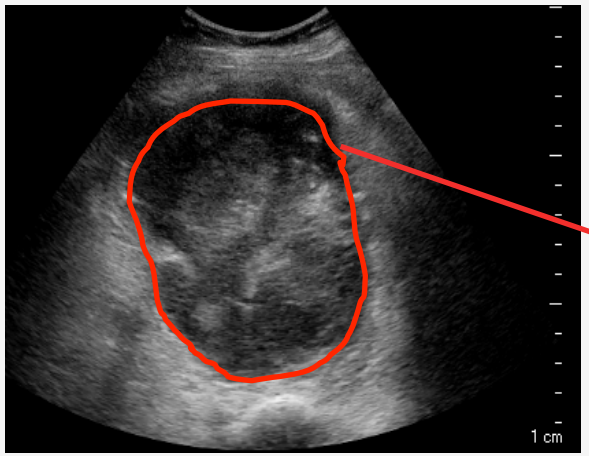
Human renal cell carcinoma

1 cm

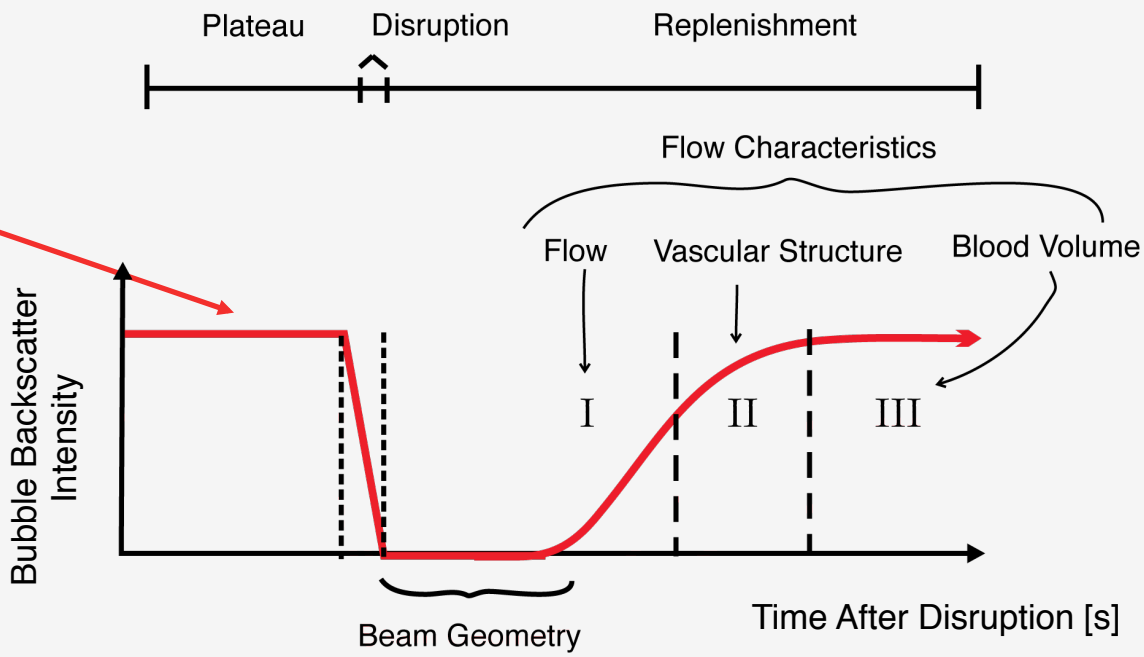
- Rate of enhancement is related to the local flow velocity
- Relative intensity of a region is related to the local blood volume

Quantification: Time Intensity Curve

Region of Interest **Replenishment Time Intensity Curve**



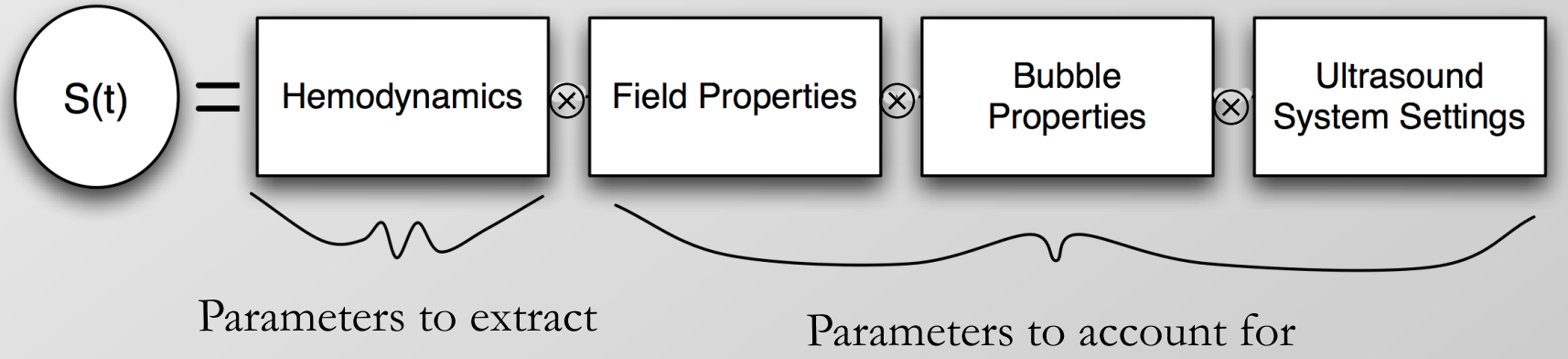
Region of interest (ROI) quantification performed on linearized image data



Microvascular determinants of the replenishment time-intensity curve:

- Plateau intensity ∝ Blood volume
- Rate of replenishment ∝ Flow velocity
- Transition region ∝ Vascular organization

A Model of Disruption Replenishment



Generalized Replenishment Model

$$S(t) = \int_{z_o}^{z_1} B(y,z) \cdot F(z,t) \cdot dz$$

Time Intensity

Beam Function

Flow Function

JM Hudson, R. Karshafian, PN Burns, Ultrasound in Medicine and Biology, 2009

Modeling the Replenishment Measurement

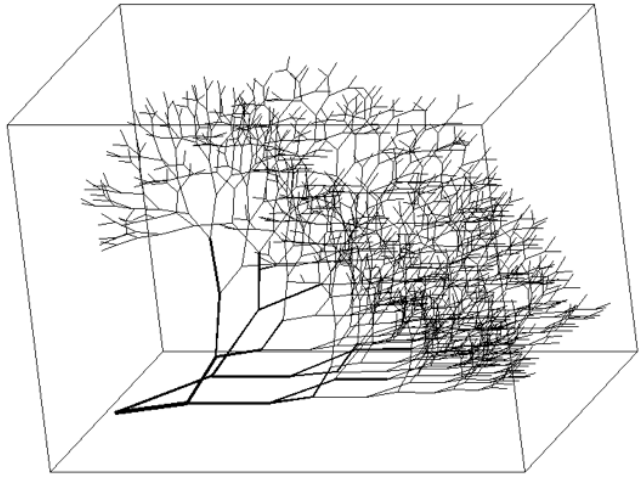
Flow through a Vascular Network

Structural Characteristics of the Microvasculature

- Bifurcating network
- Self similar construction with scale

- Lognormally distributed:
  - Flow transit times/velocities
  - Vessel diameters/ flow rates

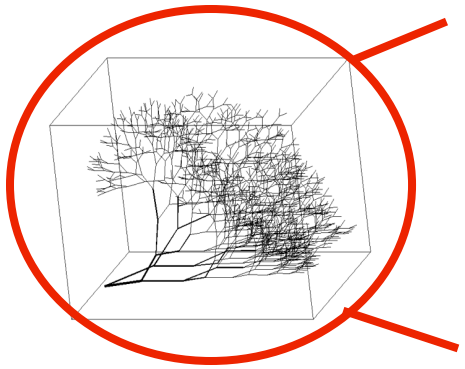
Fractal Model of the Vasculature



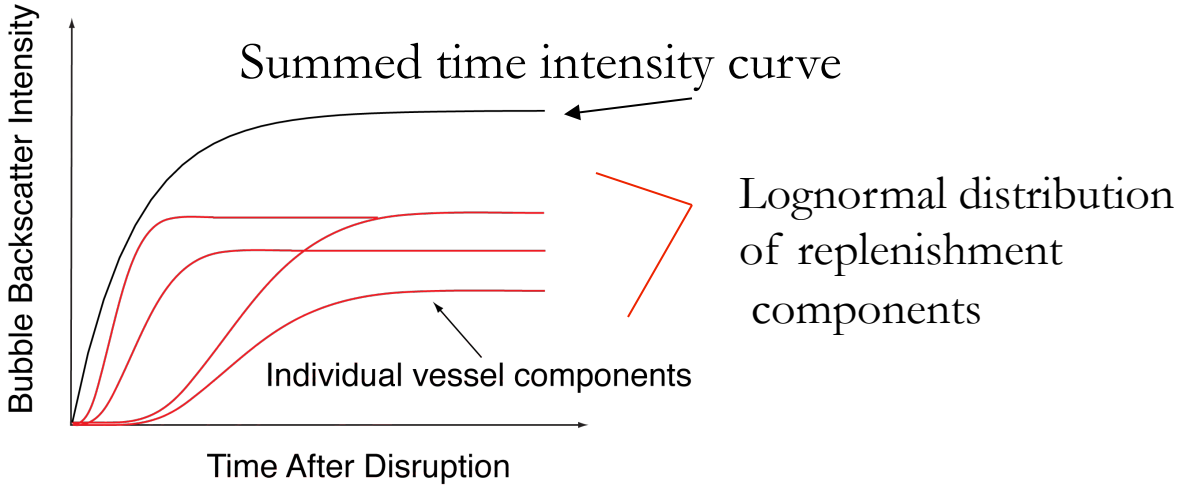
(Image provided by Raffi Karshafian)

Modeling the Replenishment Measurement

Flow through a Vascular Network



Region of interest



The Lognormal Perfusion Model

$$F_{lognorm}(z,t) = \frac{A}{2} \cdot erfc\left(\frac{\ln\left(\frac{z}{t}\right) - \mu_f}{\sigma_f \sqrt{2}} \right)$$

A is related to the total vascular cross section

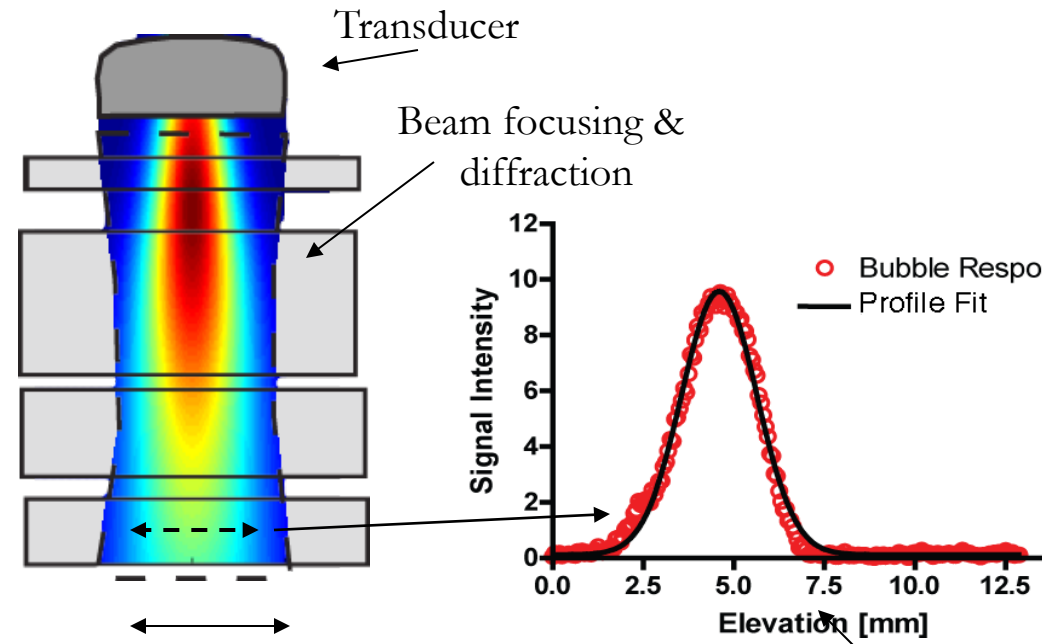
μ_f is related to the mean flow velocity

σ_f is related to vascular morphology

Modeling the Replenishment Measurement

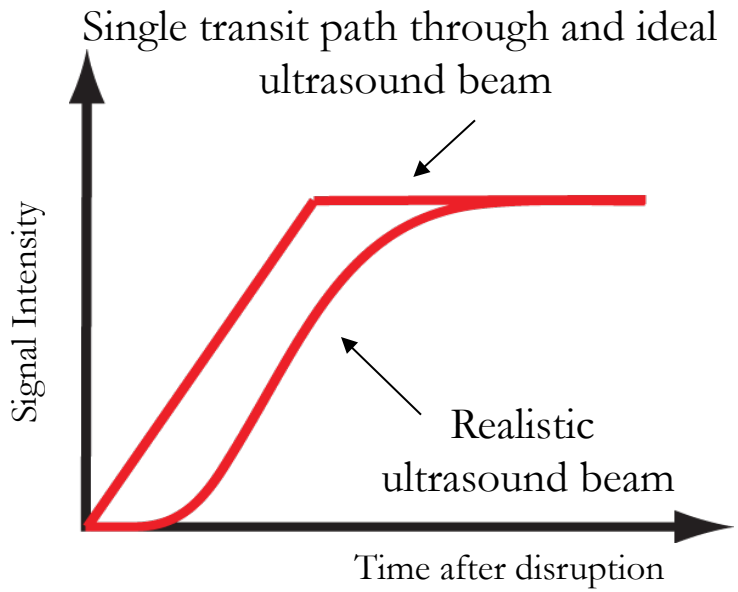
Influence of the Ultrasound Beam

- **Microbubbles are detected with different sensitivity within the image slice**



$$S(t) = \int_{z_o}^{z_1} B(y,z) \cdot F(z,t) \cdot dz$$

- **Beam shape influences the replenishment curve**



Clinical Protocol:
Monitoring Anti-angiogenic Therapy

Lead Principal Investigator: Dr. Georg Bjarnason (Odette Cancer Centre)

Study Population:

- Patients with metastatic renal cell carcinoma treated with an anti-angiogenic drug Sutent (Pfizer).

Scanning Schedule:

- Pre-treatment: Week 0; On-Treatment: Weeks 1 & 2; Off-treatment: Week 6
- Radiologists: Dr. Mostafa Atri & Dr. Laurent Milot

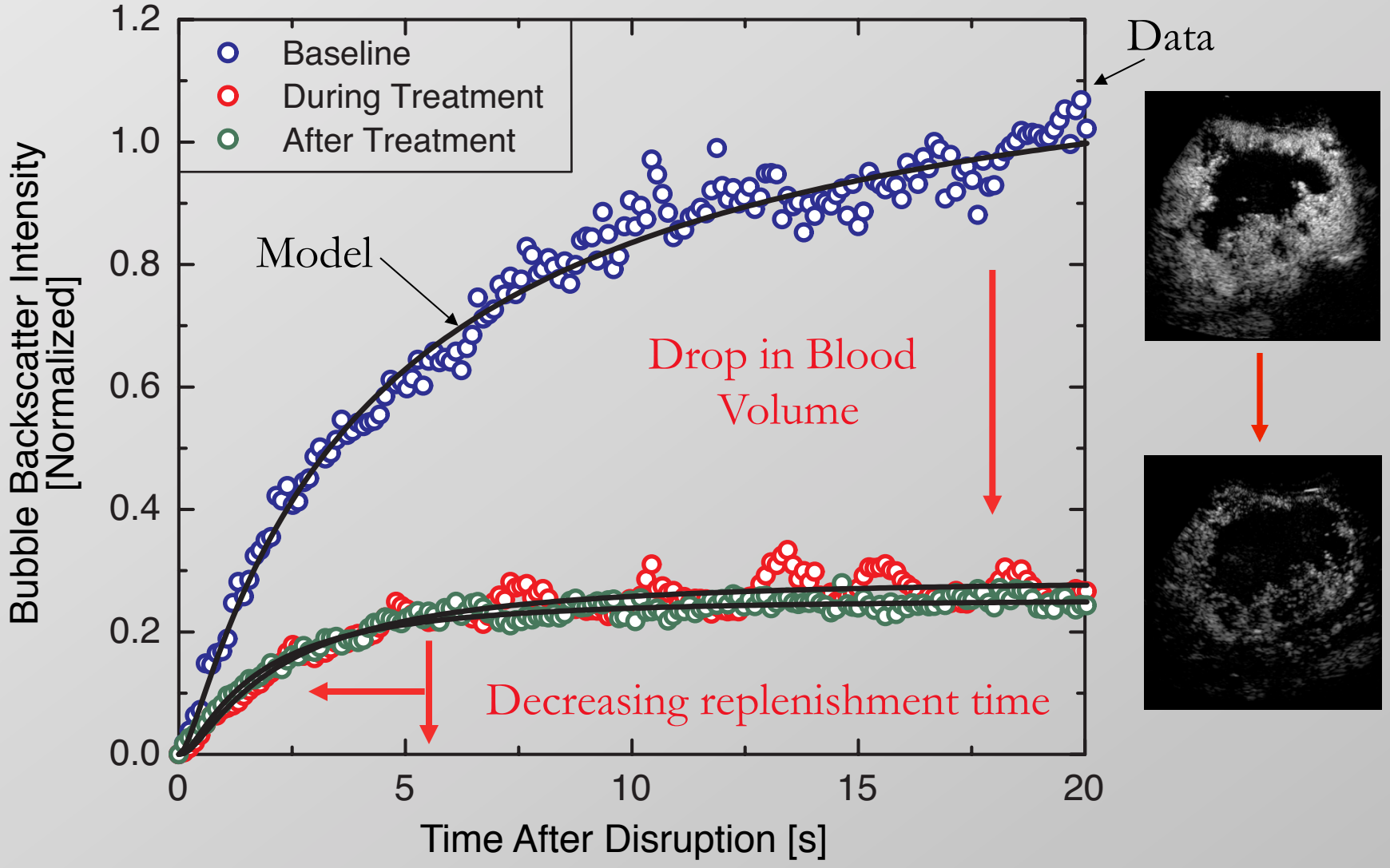
Contrast Agent:

- Clinical microbubble contrast agent - Definity (Lantheus Medical Imaging)
- Infused at a constant rate for 12 minutes.

Scanner Settings:

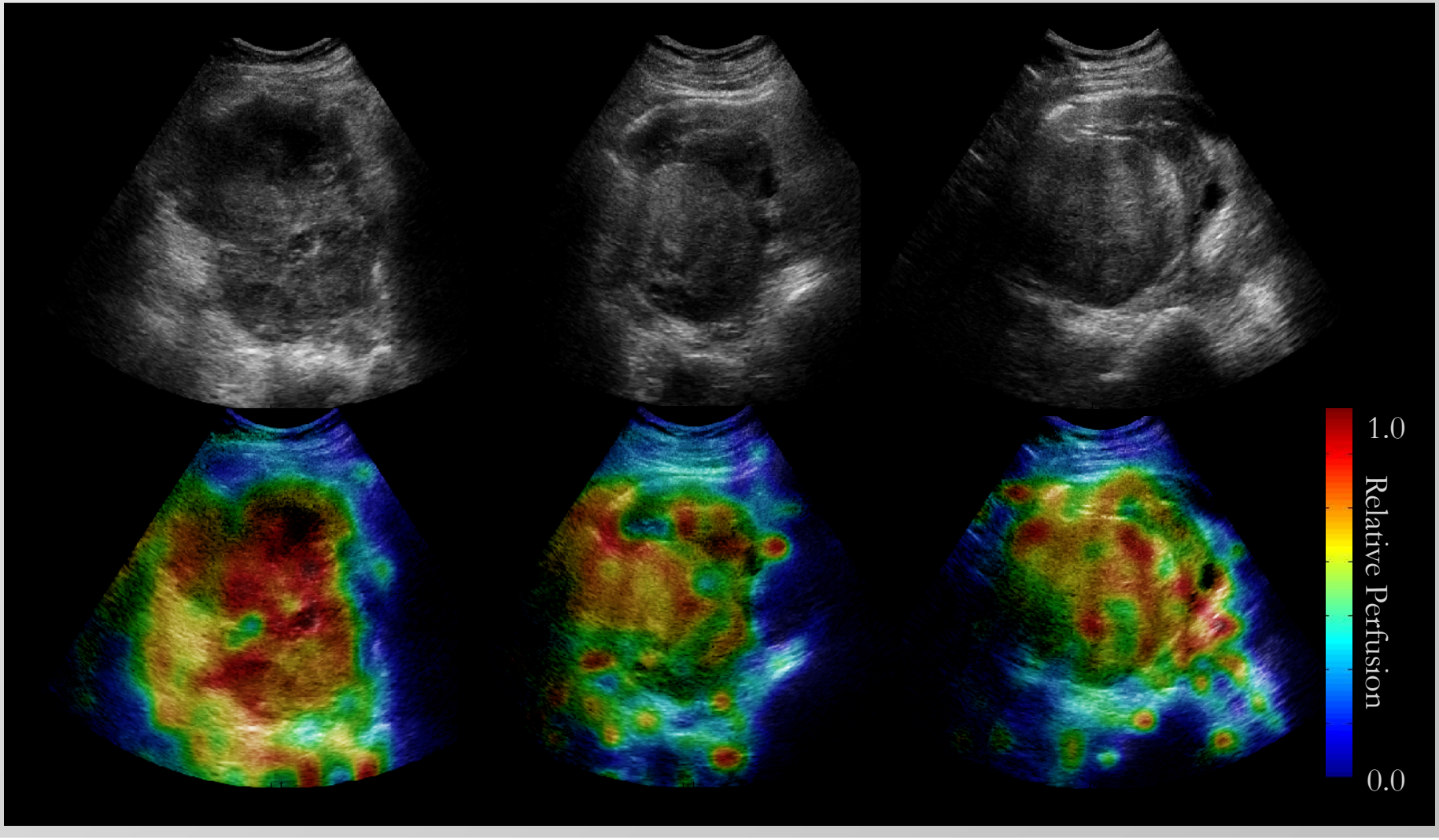
- Clinical ultrasound scanner (iU22) with C5-1 probe (Philips Ultrasound).
- Ultrasound settings are optimized during baseline scan and kept constant throughout the study.

Quantifying Anti-angiogenic Response with Microbubbles



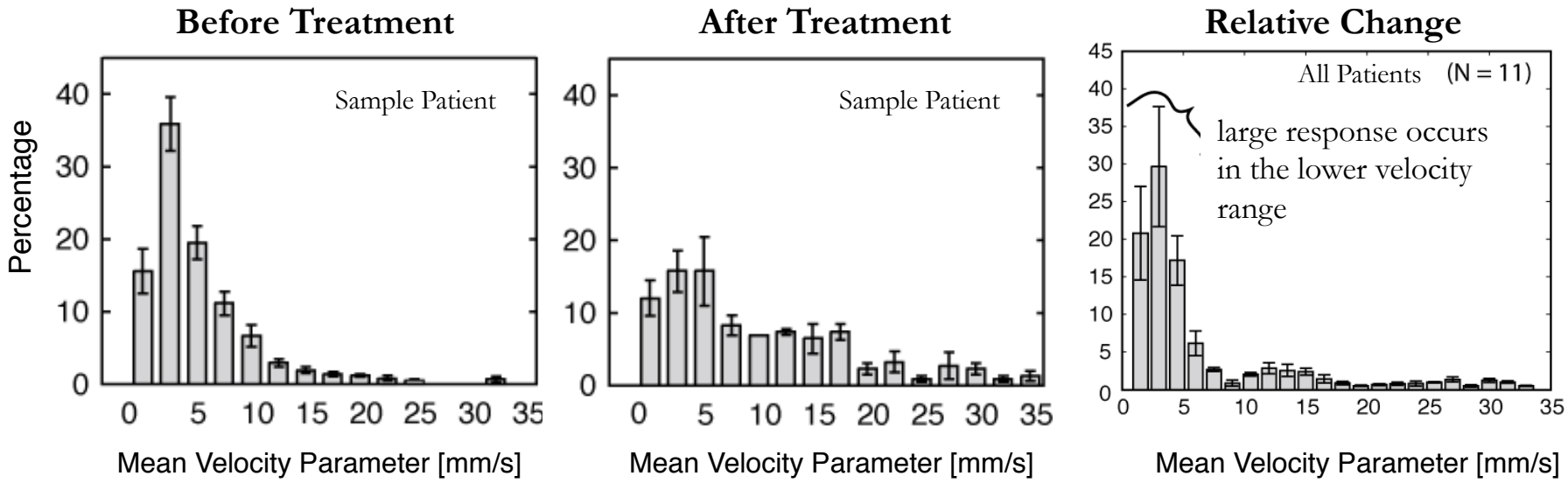
Parametric Image Maps:
Spatial Distribution of Blood Perfusion

Before Treatment | During Treatment | After Treatment



Anti-angiogenic Therapies Target Small Blood Vessels

Average Histograms of the Velocity Distribution Throughout the Tumour



- Response is most prominent in the lower velocity range (small vessels).
- Supports clinical findings that anti-angiogenic drugs target small vessels.

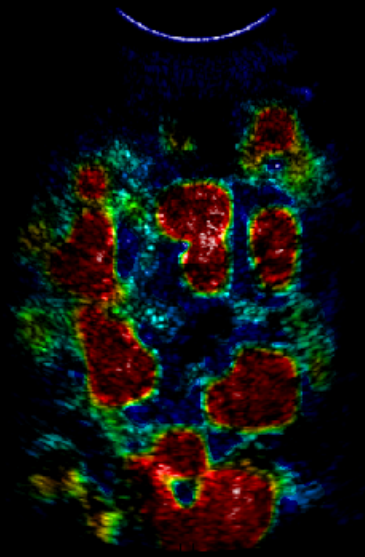
Implications:

- Can quantify the portion of the vasculature that is responding to treatment by filtering large vessel flow.

Parametric Images of Relative Blood Perfusion

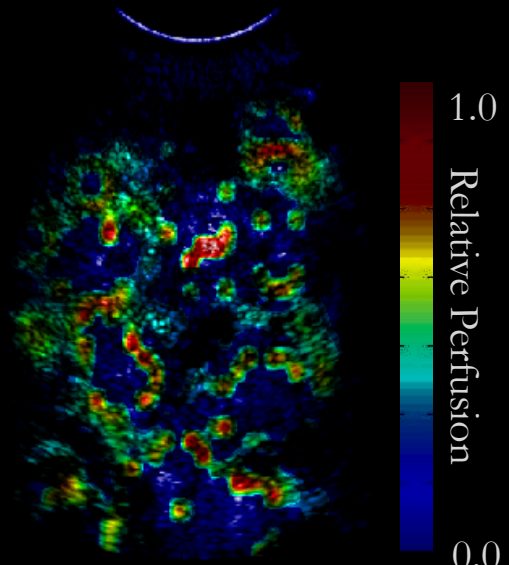
B-mode

Overlaid Perfusion Map



Large and small vessel flow

Filtered Perfusion Map

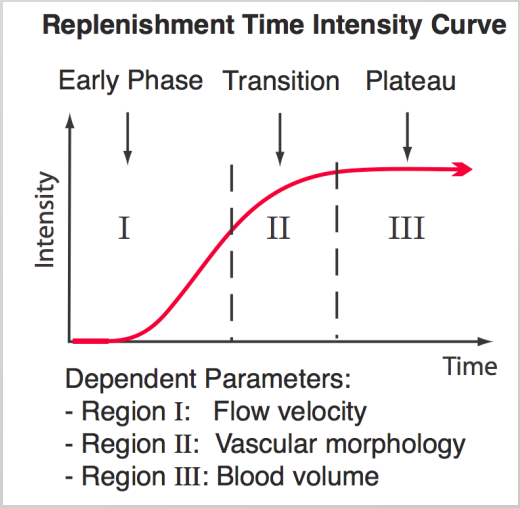


Small vessel flow

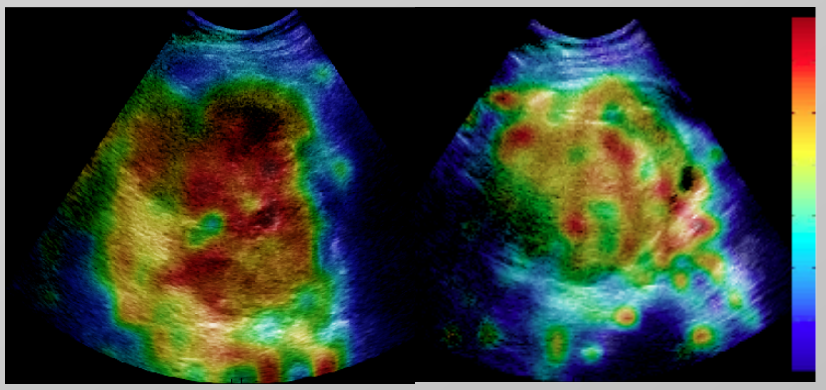
Summary

Ultrasound contrast agents are composed of small microbubbles that travel with similar haemodynamics to red blood cells.

Microbubble dynamics are used to probe the vascular properties of tissues



Microbubble dynamics can be used to monitor the response of cancers to anti-angiogenic therapy.



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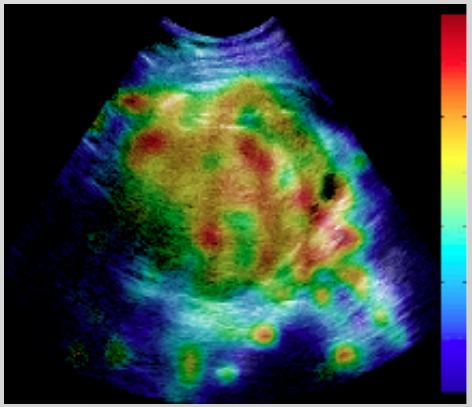

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