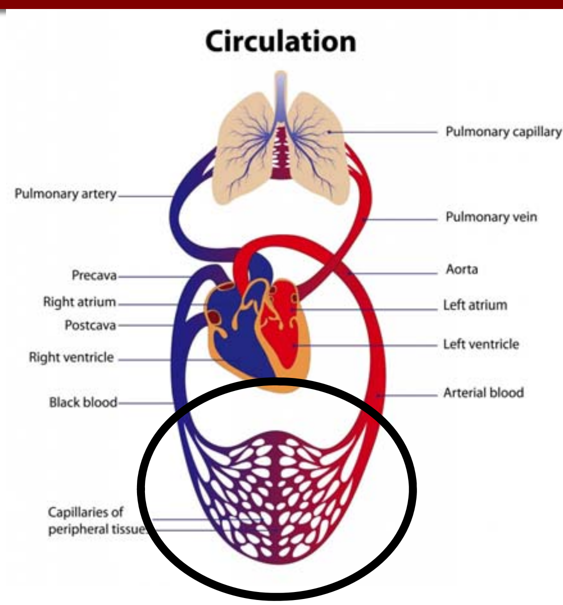
# 3D Dynamic Contrast Enhanced Ultrasound: Potential Tool for Treatment Response Evaluation

**Dimitre Hristov**

Radiation Oncology, Stanford University

Stanford Radiation Oncology Seed Grant
Stanford Cancer Institute Translational Award
NIH R01 CA195443-02
Philips Healthcare

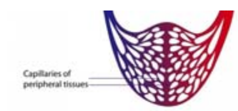
## The vascular system




http://www.alearningfamily.com/main/wp-content/uploads/CirculatorySystemcpMarynaMelnyk.jpg

## The vascular system

| | Aorta | Arteries | Arterioles | Capillaries | Venules | Veins | Vena Cava |
|---|---|---|---|---|---|---|---|
| Internal Diameter (um) | $2.5 \times 10^4$ | $3 \times 10^3$ – $1 \times 10^4$ | 30 | 5 | 70 | $5 \times 10^3$ | $1.2 \times 10^4$ |
| Total Area ($cm^2$) | 5 | 20 | 40 | 2500 | 250 | 80 | 250 |
| Pressure (mmHg) | 100 | 90 | 60 | 17 | 10 | 5 | < 5 |
| Mean Flow Velocity (mm/s) | 300 | 20 | 20-0.3 | 0.3 | 3 | 3 | 10 |
| Vessel Class | Feeding | Feeding | Feeding | Exchange | Draining | Draining | Draining |



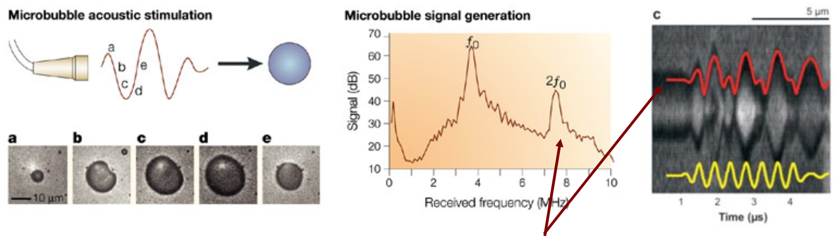

http://www.alearningfamily.com/main/wp-content/uploads/CirculatorySystemcpMarynaMelnyk.jpg

## Microbubbles: Contrast Agents

| Name | Manufacturer | Gas | Shell | Mean Size (um) | Concentration (#/ml) | Year |
|---|---|---|---|---|---|---|
| Levovist | Bayer Schering/Pharma AG | Air | Galactose, trace palmitin | 2-4 | $1.2\text{-}2.0 \times 10^8$ | 1996 |
| Optison | GE Healthcare AS | C3F8 | Human Albumin | 2-4.5 | $5.0\text{-}8.0 \times 10^8$ | 1997 |
| Definity | Lantheus Medical Imaging | C3F8 | Phospholipid | 1.1-3.3 | $1.2 \times 10^8$ | 2001 |
| Sonovue | Bracco | SF6 | Phospholipid | 2-3 | $5.0 \times 10^8$ | 2001 |
| Sonazoid | Amersham Health | C4F10 | Lipids | | $0.3 \times 10^9$ | 2006 |

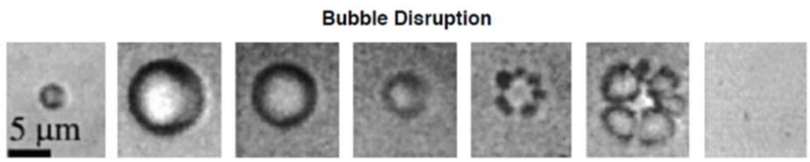
**Microbubbles are purely intravascular agents**

## Microbubbles




Jonathan R. Lindner Nature Reviews Drug Discovery 3, 527-533 (June 2004)

Nonlinear response





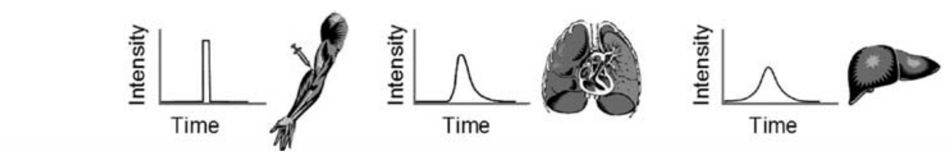

## Microbubble non-destructive imaging

| Method | Transmitted Sequence (**red** have inverted phase) | Algebra to combine | Summed Tissue Echo | Summed Bubble Echo |
|---|---|---|---|---|
| B-mode | | N/A | | |
| Pulse Inversion | | $Echo_1 + Echo_2$ | | |
| Contrast pulse sequencing (CPS) | | $Echo_1 + Echo_2 + Echo_3$ | | **Amplitude proportional to microbubble concentration** |
| Power | | $Echo_1 - 2*Echo_2$ | | |

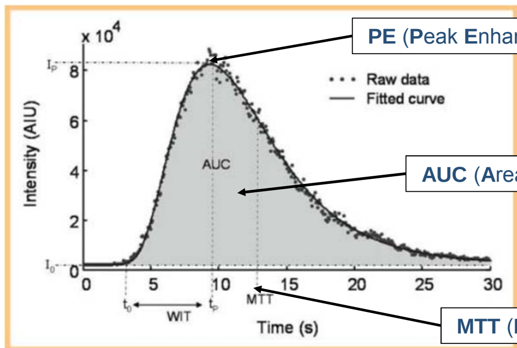
C.F. Caskey, et al., **Leveraging the power of ultrasound for therapeutic design and optimization**, J. Control. Release (2011),doi:10.1016/j.jconrel.2011.07.032

## Injection method 1: Bolus Injection

STROUTHOS *ET AL.*: INDICATOR DILUTION MODELS FOR THE QUANTIFICATION OF BLOOD FLOW




**Bolus injection**



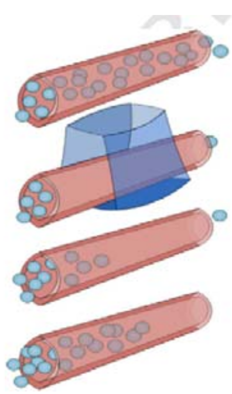

**PE** (**P**eak **E**nhancement)

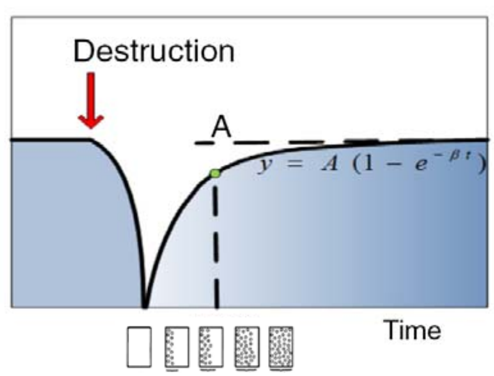
**AUC** (**A**rea **U**nder the **C**urve)

**MTT** (**M**ean **T**ransit the **T**ime)



## Injection method 2: Destruction-replenishment






**Constant infusion with destruction-replenishment**

A = **rBV** (**r**elative **B**lood **V**olume)
β x A = **rBF** (**r**elative **B**lood **F**low)



C.F. Caskey, et al., **Leveraging the power of ultrasound for therapeutic design and optimization**, J. Control. Release (2011),doi:10.1016/j.jconrel.2011.07.032

## Biomarker for treatment response

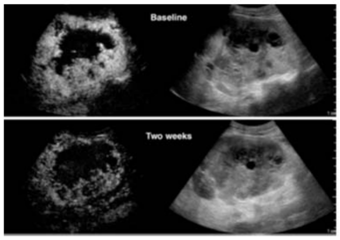
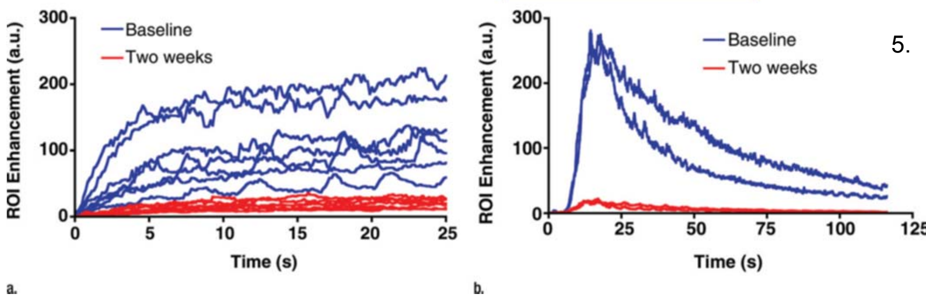



**Table 2**

**Correlation of Changes in DCE US Parameters after 2 Weeks of Treatment with PFS**

| DCE US Parameter | PFS Spearman *r* | PFS *P* Value |
|---|---|---|
| $INF_{BV}$ | −0.26 | .4 |
| $INF_{VM}$ | −0.33 | .28 |
| $BOL_{PK}$ | 0.13 | .67 |
| $BOL_{AUC}$ | 0.18 | .55 |
| $BOL_{TTP}$ | 0.55 | .053 |
| $BOL_{MTT}$ | 0.12 | .71 |




**Advantages:**
1. Available worldwide at bedside
2. Inexpensive
3. No ionizing radiation/contrast toxicity
4. Versatile and easy transport
5. Good temporal/spatial resolution

**Main Limitation: 2D Sampling Errors**

**Dynamic Microbubble Contrast enhanced US to Measure Tumor Response to Targeted Therapy: A Proposed Clinical Protocol with Results from Renal Cell Carcinoma Patients Receiving Antiangiogenic Therapy**, Williams et al, *Radiology:* Volume 260: Number 2—August 2011

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## Tracked 4D contrast enhanced US imaging

- **Potential**
  - Elimination of sampling artifacts (3D vs 2D)
  - Comprehensive motion correction
  - 3D fusion with B-mode US or other imaging modality
    - Enabler for follow up studies
  - Parametric (but likely low resolution) maps of heterogeneity of vascular parameters

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## 3D DCE-US (3D *Dynamic* *Contrast* *Enhanced* *UltraSound*)

### Power Modulation (PM) Contrast Imaging Mode

- MI = 0.09
- Destruction (“Flash”) MI = 0.77

- Elevation resolution: ~3 mm
- Azimuth resolution: 2-4 mm
- Axial resolution 0.5-2 mm

- Acquisition rates (<1 volume/sec, with 4 firings per line)

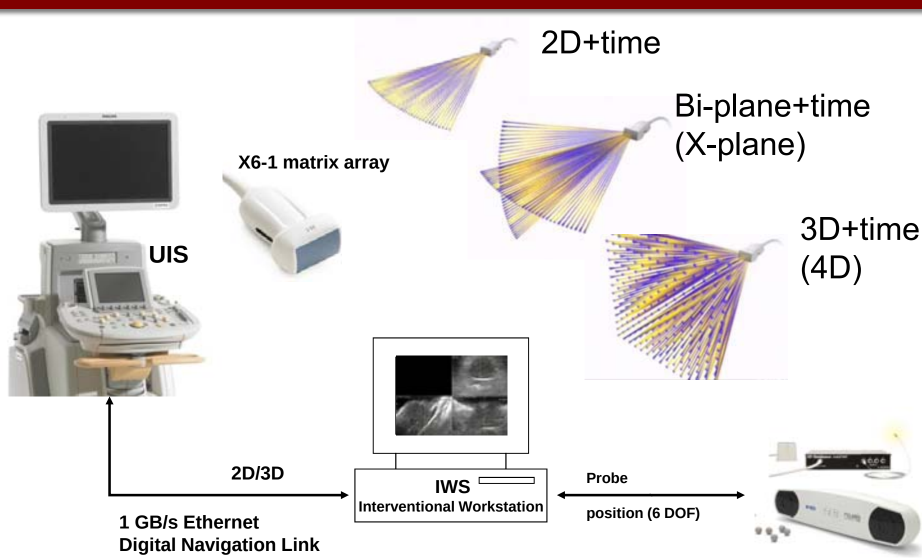
Parameters evaluated in phantom, 6-12 cm depth

**X6-1 matrix array**

- ~250um pitch, 9212 elements 2D array
- ~40 mm x 20 mm
- Central frequency: 3.2 MHz (1-6 MHz)
- 100 x 90 degree virtual apex scan format

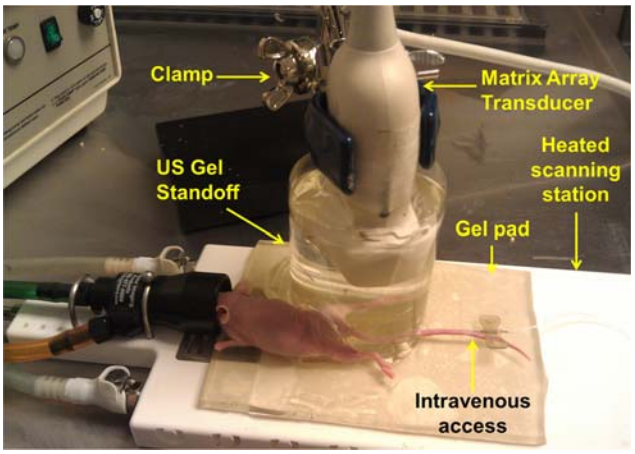
**Microbeamforming for Large-Aperture Ultrasound Transducers**, Freeman , S., Ultrasound Imaging Symposium, 2011 AAPM/COMP Meeting, 7/31-8/4, Vancouver, CA

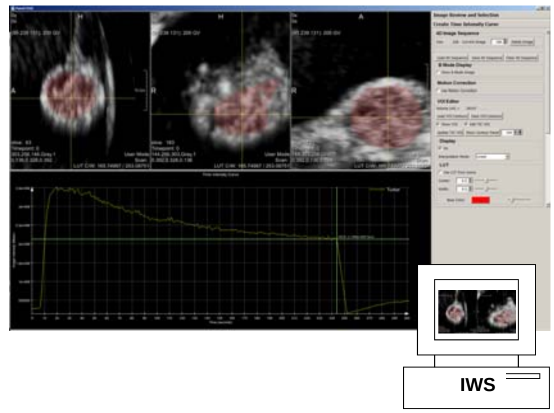
## Tracked 4D Ultrasound




**Automatic 3D ultrasound calibration for image guided therapy using intramodality image registration**. Schlosser J, Kirmizibayrak C, Shamdasani V, Metz S, Hristov D. *Phys Med Biol* 2013;58:7481-7496.

## 3D DCE-US in mouse colon cancer model




**Three-dimensional Dynamic Contrast-enhanced US Imaging for Early Antiangiogenic Treatment Assessment in a Mouse Colon Cancer Model,**
Huaijun Wang, Dimitre Hristov, Jiale Qin, Lu Tian, and Jürgen K. Willmann, Radiology 2015 277:2, 424-434

**Three-dimensional ultrasound molecular imaging of angiogenesis in colon cancer using a clinical matrix array ultrasound transducer.**
Wang H, Kaneko OF, Tian L, Hristov D, Willmann JK. *Invest Radiol.* 50(5):322-9, 2015.

## 3D DCE-US for monitoring treatment response

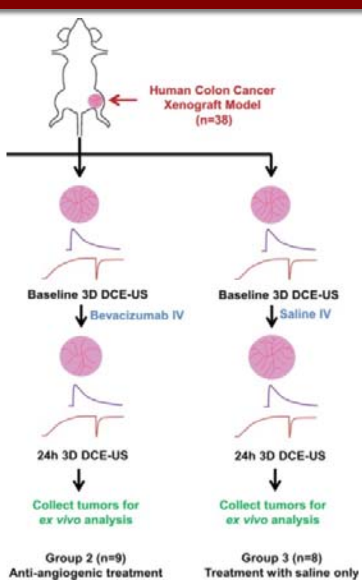



**Table 2**

**Percentage Change of Quantitative Values of Different Perfusion Parameters after Antiangiogenic and Saline-Only Treatment in Human Colon Cancer Xenografts**

| | Antiangiogenic Treatment ($n$ = 9) | | Saline-Only Treatment ($n$ = 8) | |
|---|---|---|---|---|
| Parameter | Percentage Change | *P* Value | Percentage Change | *P* Value |
| PE (au) | −63 ± 23 | .004 | 15 ± 47 | .94 |
| AUC (au) | −55 ± 28 | .04 | 12 ± 19 | .81 |
| TTP (sec) | 7 ± 42 | .92 | 11 ± 75 | .60 |
| rBV (au) | −61 ± 26 | .007 | 31 ± 87 | .47 |
| rBF (au) | −64 ± 23 | .001 | 69 ± 119 | .38 |
| Blood flow velocity ($sec^{-1}$) | −4.5 ± 52 | .58 | 9 ± 29 | .81 |

Note.—Values are percentage changes from baseline to 24 hours after treatment. *P* values were calculated between baseline and 24 hours after treatment.

**Some parameters change significantly with treatment**

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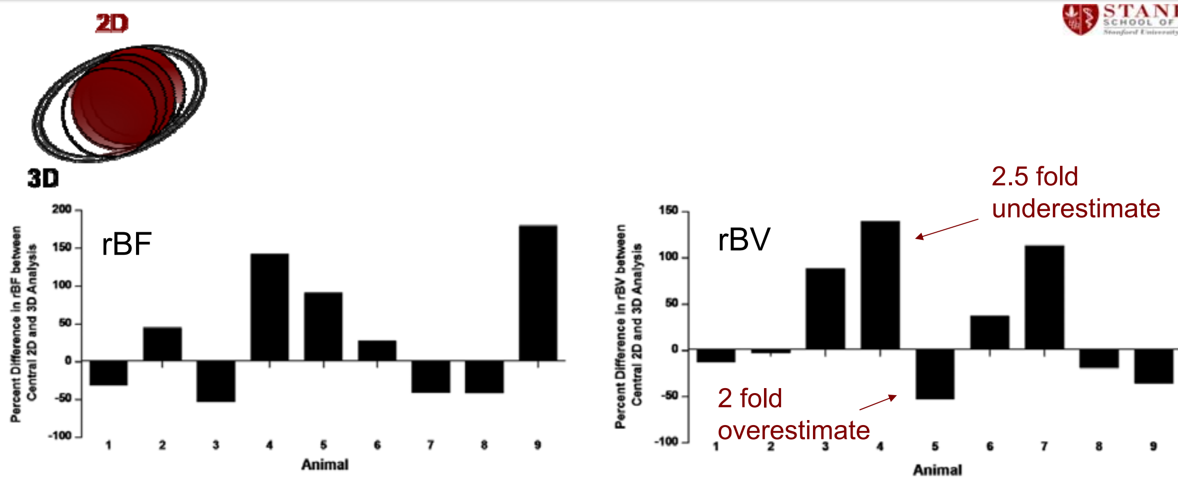
## Significant differences between 2D and 3D measured response




**Three-dimensional Dynamic Contrast-enhanced US Imaging for Early Antiangiogenic Treatment Assessment in a Mouse Colon Cancer Model,** Huaijun Wang, Dimitre Hristov, Jiale Qin, Lu Tian, and Jürgen K. Willmann, Radiology 2015 277:2, 424-434

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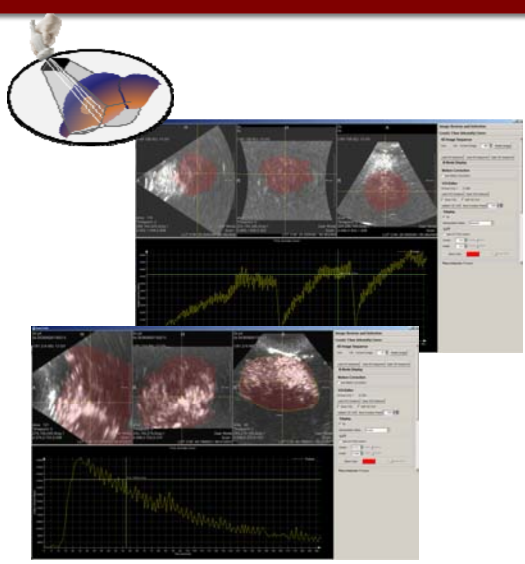
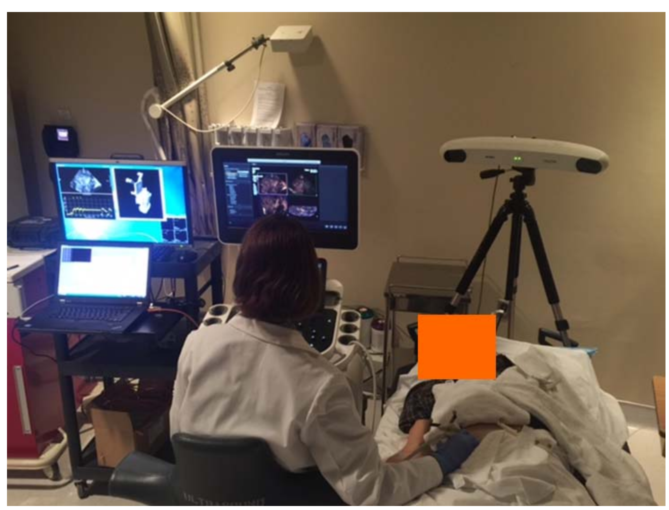
## 3D DCE-US: feasibility and repeatability in patients with liver metastases





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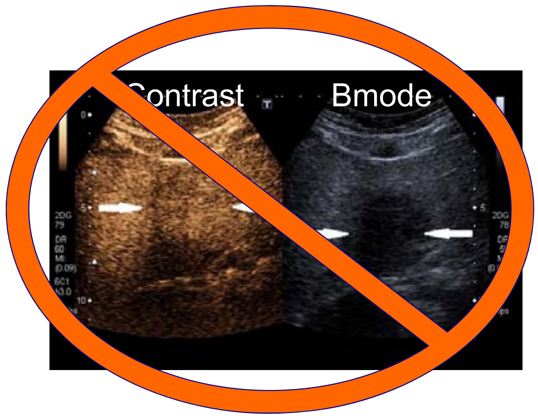
## 3D DCE-US Technical Limitations

Philips X6-1

Philips Epiq 7 and iU22
X6-1 3D transducer




Ahmed El Kaffas*, Renhui Gong, Rosa M. Sigrist, Juergen K Willmann, Dimitre Hristov, **Clinical Evaluation of Real-Time Optical Tracking to Provide Feedback During Blinded Contrast-Enhanced Ultrasound Imaging**, Beyond Imaging RSNA, Chicago, IL, November 27- December 2, 2016.

## Problem Statement

**Limitation:**

- Current commercial 3D DCE-US does not display side-by-side B-mode & contrast-mode.
- Leaves operator with no positioning feedback during acquisition.
- Challenging during long acquisition sessions (i.e. disruption-replenishment) and can affect quantification.

**Solution:**

- Use an optical-tracking and guidance system to assist operators during 3D DCE-US data acquisition.

**Aim:**

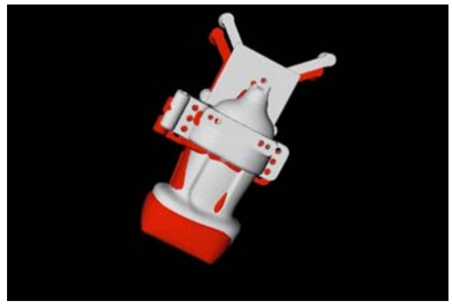
- Evaluate the use of optical-tracking to maintain a set position during lengthy acquisition, and to compare performance to Bmode and current 3D DCE-US implementation.

## Assessment of Set Up

**Can a tracked virtual transducer help sonographers remain in the same position?**

1. Place transducer on saved reference position

2. Remain at that location using
   I. Bmode,
   II. Virtual Probe,
   III. Memory



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## Methods

- 5 experienced operators with > 1 year of experience
- 1 volunteer healthy patient
- Operators were asked to maintain the same position for 4 minutes with:
  - View of Bmode
  - View of live virtual probe
  - Memory
- Optical tracking was used to determine extent of motion of probe relative to original position over the scan time
- Magnitude of displacement of a selected voxel was computed over the whole 4D cine was computed relative to a reference position.

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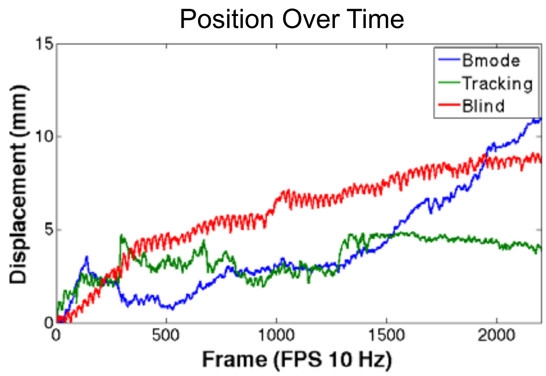
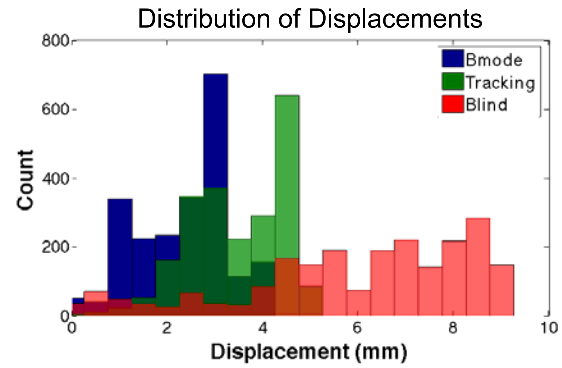
## Results on Operator 1

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## Results

| | B mode (mm) | | | Track (mm) | | | Memory (mm) | | |
|---|---|---|---|---|---|---|---|---|---|
| **Operator** | **mean** | **std** | **skw** | **mean** | **std** | **skw** | **mean** | **std** | **skw** |
| **1** | 2.11 | 1.26 | 0.03 | 3.67 | 2.03 | -0.07 | 0.94 | 0.58 | 0.54 |
| **2** | 9.64 | 12.00 | 0.48 | 3.22 | 2.06 | 0.17 | 8.01 | 63.06 | 16.96 |
| **3** | 2.34 | 0.96 | -0.38 | 3.47 | 0.98 | -0.43 | 5.96 | 2.37 | -0.82 |
| **4** | 2.78 | 1.62 | -0.02 | 2.41 | 1.54 | 0.31 | 3.57 | 0.44 | 7.13 |
| **5** | 1.91 | 0.56 | -1.03 | 4.62 | 3.42 | 0.46 | 4.43 | 22.56 | 7.15 |
| **Average** | **3.75** | **3.28** | **-0.18** | **3.48** | **2.01** | **0.09** | **4.58** | **17.80** | **6.19** |

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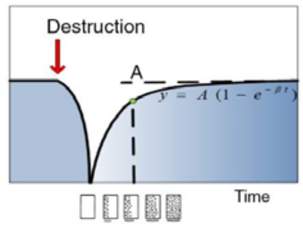
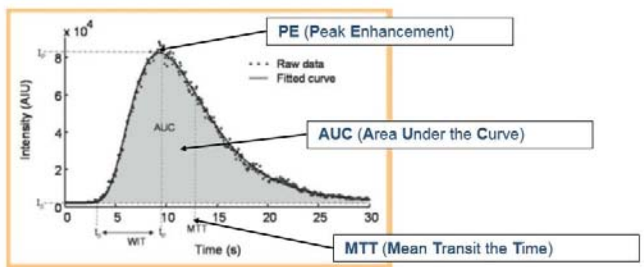
## Feasibility and Repeatability in Patients with Liver Metastases: Objective 1

### Repeatability

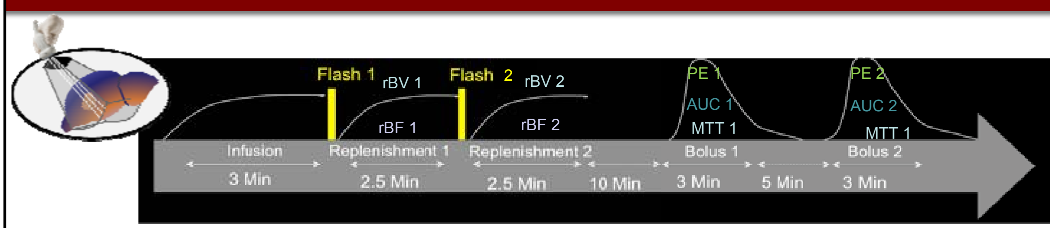
- Injection Method 1: Destruction replenishment
  - Relative blood volume (**rBV**)
  - Relative blood flow (**rBF**)
- Injection Method 2: Bolus Injection
  - Peak Enhancement (**PE**)
  - Area under the curve (**AUC**)
  - Mean transit the time (**MTT**)



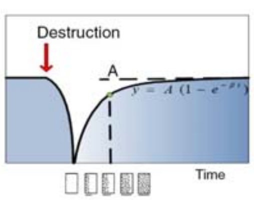

A = **rBV** (relative **B**lood **V**olume)
β x A = **rBF** (relative **B**lood **F**low)




## Analysis of Repeatability

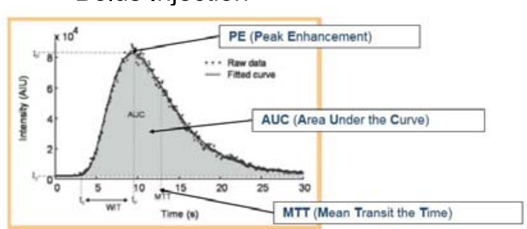



### Destruction Replenishment



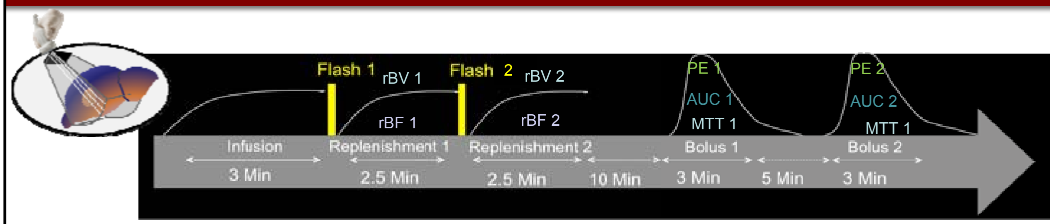

A = **rBV** (relative **B**lood **V**olume)
β x A = **rBF** (relative **B**lood **F**low)

### Bolus Injection




A. El Kaffas*, R. M. Sigrist, G. Fisher, S. Bachawal, J. Liau, A. Karanany, J. Rosenberg, H. Wang, D. Hristov, J. K. Willmann, **3D Dynamic Contrast-Enhanced Ultrasound of Liver Metastases from Gastrointestinal Tumors: First-in-Human Assessment of Feasibility and Reproducibility**, RSNA Annual Meeting, Chicago, IL, November 27-December 2, 2016.

## Analysis of Repeatability




Destruction Replenishment

Bolus Injection

For analysis, calculate the interclass correlation coefficient for the 1st and 2nd measurements

| | 3D ICC |
|---|---|
| rBV | 0.97 (0.89,0.99) |
| rBF | 0.96 (0.85,0.99) |
| PE | 0.92 (0.78,0.98) |
| AUC | 0.92 (0.77,0 .98) |
| TP | 0.84 (0.58,0.95) |
| MTT | 0.63 (0.27,0.89) |

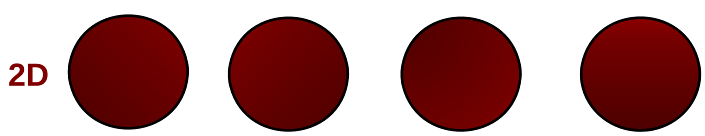
**ICC >0.90**
**Good 3D Repeatability**

A. El Kaffas*, R. M. Sigrist, G. Fisher, S. Bachawal, J. Liau, A. Karanany, J. Rosenberg, H. Wang, D. Hristov, J. K. Willmann, **3D Dynamic Contrast-Enhanced Ultrasound of Liver Metastases from Gastrointestinal Tumors: First-in-Human Assessment of Feasibility and Reproducibility**, RSNA Annual Meeting, Chicago, IL, November 27-December 2, 2016.

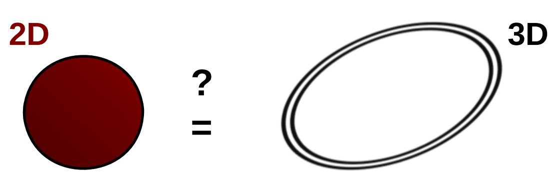
## Feasibility and Repeatability in Patients with Liver Metastases : Objective 2

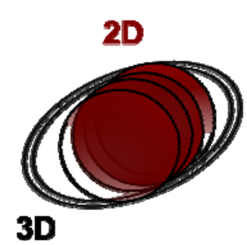
### Analysis of 2D and 3D measurements of 3D DCE-US

- Heterogeneity measured across 4 2D planes




- Comparison of 2D vs 3D measurements

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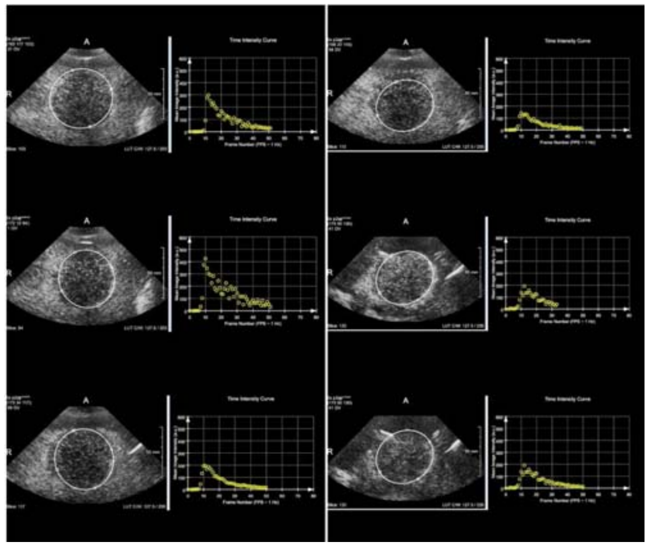
## Heterogeneity of 2D measurements

| | Average COV |
|---|---|
| rBV | 0.43 (0.34,0.42) |
| rBF | 0.51 (0.40,0.62) |
| PE | 0.33 (0.24,0.42) |
| AUC | 0.32 (0.25,0.42) |
| TP | 0.17 (0.13,0.21) |
| MTT | 0.29 (0.21,0.39) |

Large 2D sampling errors

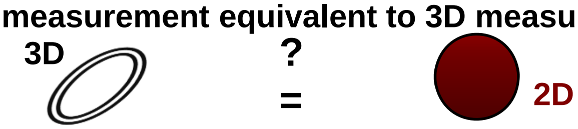
**2D Planes show Heterogeneity**



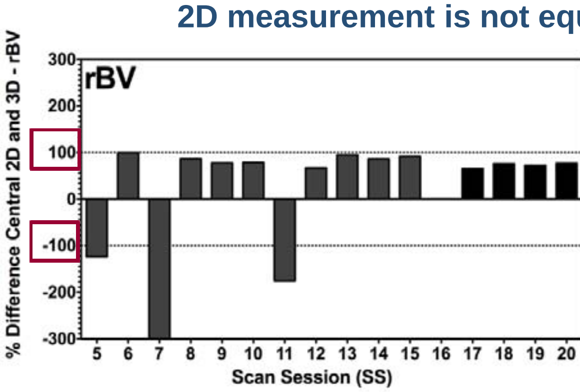
Comparing different 2D Planes

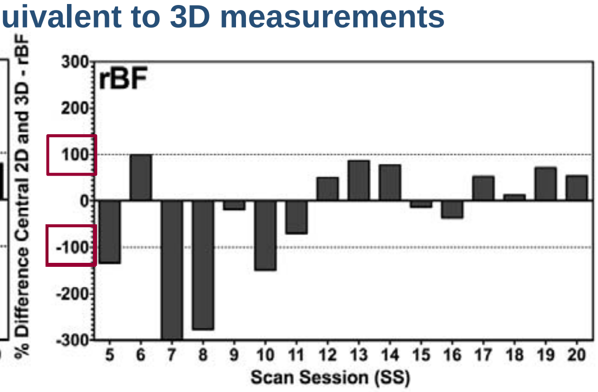
## Comparison of 2D vs 3D Measurements

**Is 2D measurement equivalent to 3D measurement?**




**2D measurement is not equivalent to 3D measurements**




**Quantitative Three-Dimensional Dynamic Contrast-Enhanced Ultrasound Imaging: Feasibility and Repeatability in Patients with Liver Metastases**, Ahmed El Kaffas, *, Rosa Maria Silveira Sigrist, *, George Fisher, Sunitha Bachawal, Joy Liau, Huaijun Wang, Alexander Karanany, Isabelle Durot, Jarrett Rosenberg, Dimitre Hristov, Jürgen K. Willmann (accepted for publication in Theranostics)

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## Significance of vascular damage

RADIATION RESEARCH 177, 311–327 (2012)
0033-7587/12 $15.00

DOI: 10.1667/RR2773.1

REVIEW

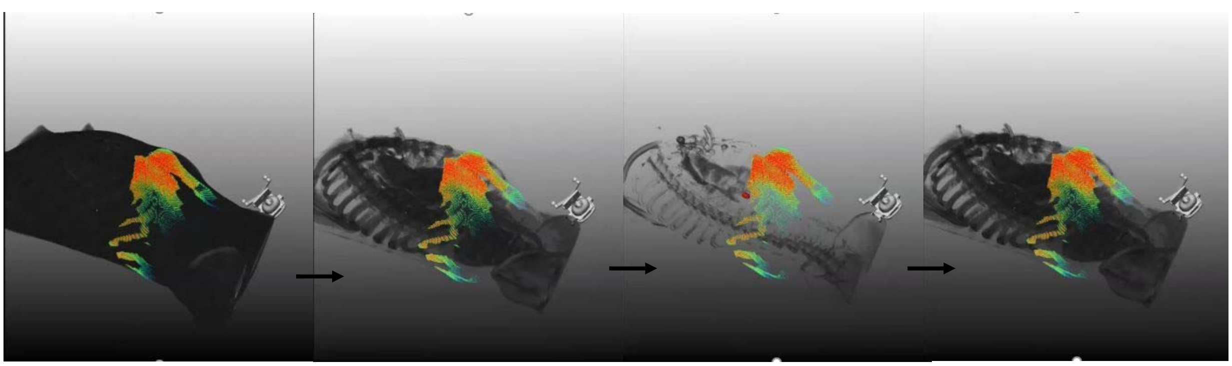
Radiation-Induced Vascular Damage in Tumors: Implications of Vascular Damage in Ablative Hypofractionated Radiotherapy (SBRT and SRS)

Heon Joo Park,[a,b] Robert J. Griffin,[c] Susanta Hui,[a] Seymour H. Levitt[a,d] and Chang W. Song[a,1]

[a] Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota Medical School, Minneapolis, Minnesota; [b] Department of Microbiology, Center for Advanced Medical Education by BK21 Project, College of Medicine, Inha University, Inchon, Korea; [c] Department of Radiation Oncology, University of Arkansas for Medical Sciences, Little Rock, Arkansas; and [d] Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden

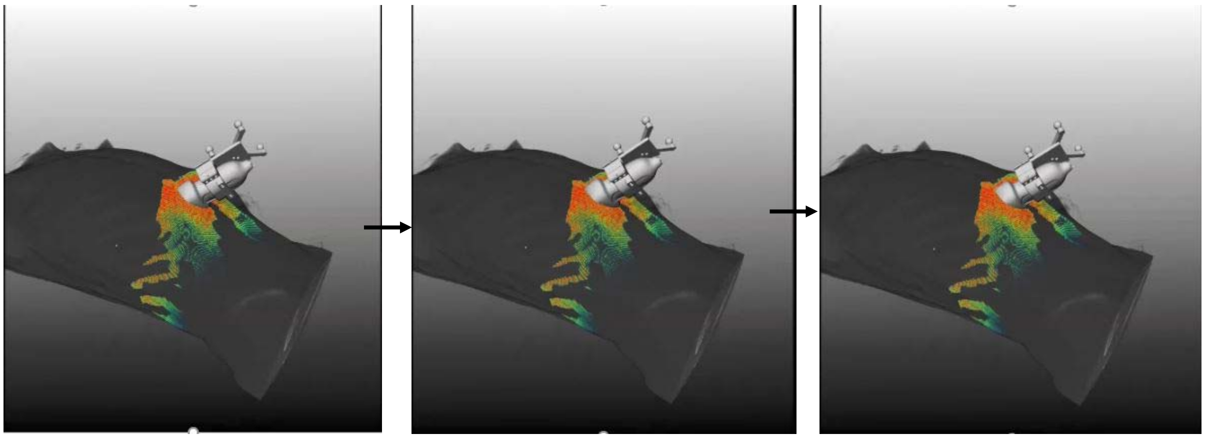
**"Little is known about the vascular changes in human tumors treated with high-dose hypo-fractionated radiation such as stereotactic body radiotherapy or stereotactic radiosurgery"**

## Probe placement map generation



***Define target and map attenuation to target from surface***

## Probe placement map confirmation



***Visualize probe in virtual space during actual imaging.***

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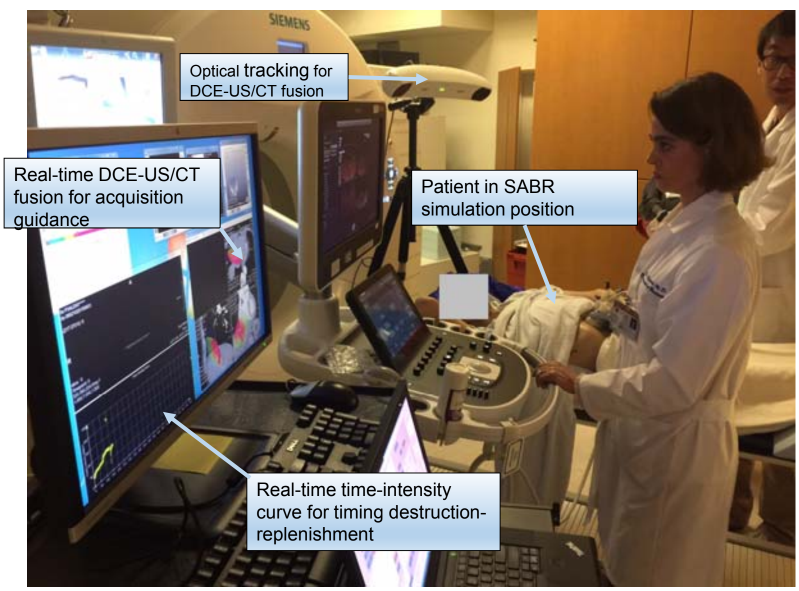
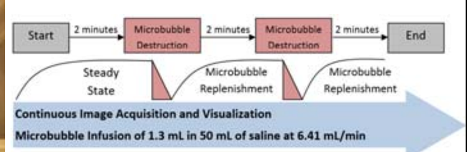
## 3D DCE-US for RT planning and response evaluation



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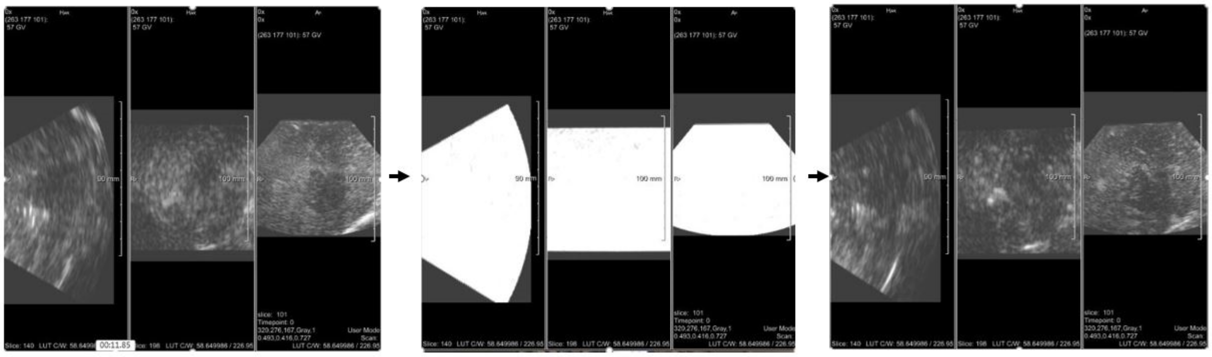

***Video: 3D DCE-US for RT planning and response evaluation***

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## 3D DCE-US fusion with CT and planned dose distribution

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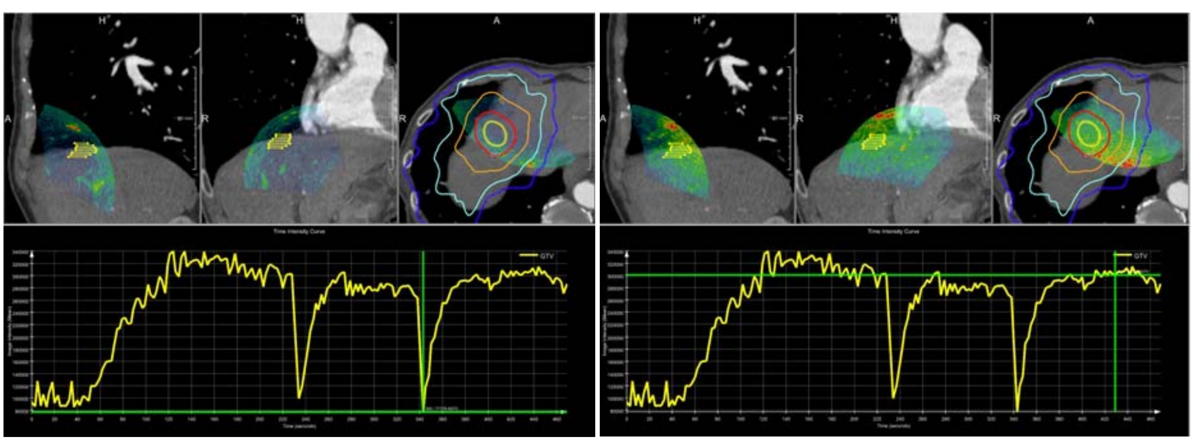


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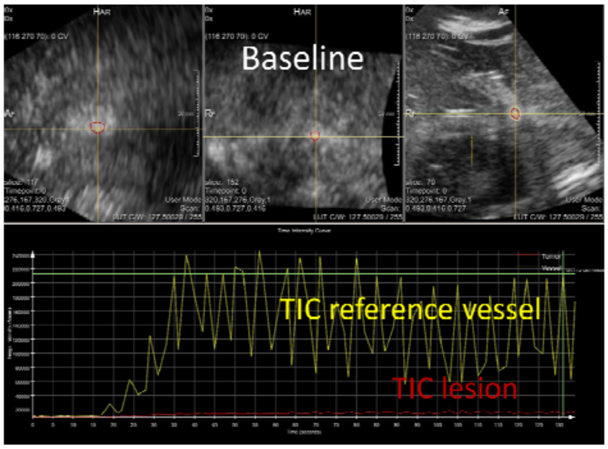
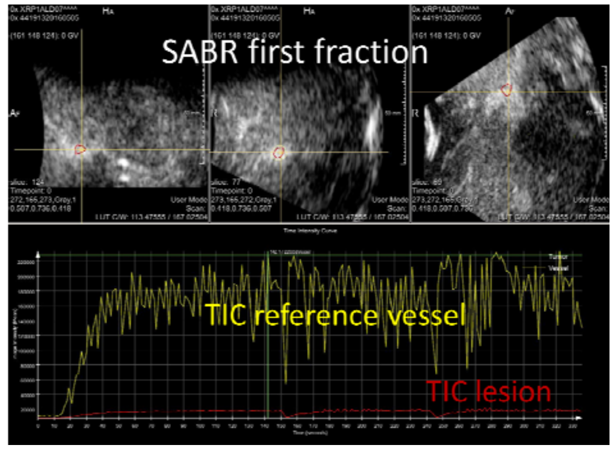
## 3D DCE-US quantification

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## DCE-US: challenges in acquisition and quantification

Interface Focus


*Interface Focus* (2011) **1**, 520–539
doi:10.1098/rsfs.2011.0026
*Published online* 18 May 2011

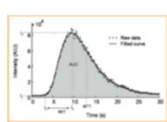

Review

Quantitative contrast-enhanced ultrasound imaging: a review of sources of variability


M.-X. Tang[1,*], H. Mulvana[2], T. Gauthier[3], A. K. P. Lim[4], D. O. Cosgrove[2], R. J. Eckersley[2] and E. Stride[5]


**DCE-US is inherently an off-line modality.**

- Do we really need real time processing?
- Are we discarding useful data?



- **Scanner**
  - Output power
  - Focal depth
  - Dynamic range and gain
  - Frequency
- **Patient**
  - Blood pressure
  - Physiological Interactions
  - Tissue motion
  - Tissue attenuation
- **Bubbles**
  - Stability
  - Injection and handling
  - Dosage
  - Concentration effects

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## 3D DCE-US: rethink acquisition and quantification

- **Lack of concurrent low-MI 3D B-mode data**
  - No anatomical guidance for prolonged acquisitions
  - Precludes comprehensive motion correction based on anatomy
  - Precludes 3D fusion with B-mode US or other imaging modality for follow up studies

- **Potential Solution**
  - Reconstruct only low-MI B-mode guidance mode in real time
  - Save all RF channel data for offline reconstruction of DCE-US and corresponding B-mode
  - Additional benefits: linear signal, attenuation corrections

**Data management**

- **~23.6 MB/s** per channel, sampling at 4
- x central frequency (X6-1 transducer)
- **~6 GB/s** for a 256 channel system
- **~2 TB** (6 min acquisition)

- **6.6 GB/s**, 8 lane PCIe 3.0
- **~3 GB/s**, sequential write, Intel DC P3608 Solid State Drive, **4 TB**

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## 3D DCE-US: rethink acquisition and quantification

- **Low volume rates: ~1 volume every 2 sec**
  - large respiratory-induced variations from volume-to-volume is a challenge for motion tracking
  - Fast 2D DCE-US allows 7-130 samples with distinct intensity values during a replenishment of a 4 mm thick slice (~10 frames/sec, 0.3 mm/s - 6 mm/s velocities)
  - Slow 3D DCE-US only 1-6 samples for the same conditions

- **Potential Solution: ultrafast plane wave imaging**
  - For a 10 cm deep lesion, fundamental physics limits number of transmits to 7700/s
  - Line-by-line 3D DCE-US imaging over large FOV: too slow yet low resolution (48x80 lines, 4 transmits per line)
  - Need alternative beamforming and data processing with fewer transmits per image

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## 3D DCE-US: rethink acquisition and quantification

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- **Ultrafast plane wave imaging**

Phys. Med. Biol. 59 (2014) L1–L13 doi:10.1088/0031-9155/59/19/L1

Fast Track Communication

### 3D ultrafast ultrasound imaging *in vivo*

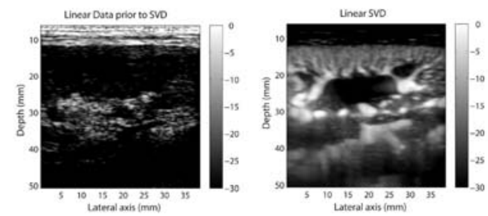
Jean Provost, Clement Papadacci, Juan Esteban Arango, Marion Imbault, Mathias Fink, Jean-Luc Gennisson, Mickael Tanter[1] and Mathieu Pernot[1]

1906 IEEE TRANSACTIONS ON ULTRASONICS, FERROELECTRICS, AND FREQUENCY CONTROL, VOL. 61, NO. 12, DECEMBER 2014

### Combined Perfusion and Doppler Imaging Using Plane-Wave Nonlinear Detection and Microbubble Contrast Agents

Charles Tremblay-Darveau, Ross Williams, Laurent Milot, Matthew Bruce, *Member, IEEE*, and Peter N. Burns, *Member, IEEE*

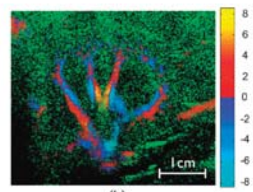
Phys. Med. Biol. 62 (2017) 31 Y Desailly *et al*




### Contrast enhanced ultrasound by real-time spatiotemporal filtering of ultrafast images

Yann Desailly[1], Anne-Marie Tissier[2], Jean-Michel Correas[1,2], Frédéric Wintzenrieth[3], Mickaël Tanter[1,4] and Olivier Couture[1,4]

[1] CNRS, INSERM, ESPCI Paris, PSL Research University, Institut Langevin, 1 rue Jussieu, F-75005, Paris, France
[2] Ultrasound Department, Department of Adult Radiology, Necker University Hospital, 149 Rue de Sèvres, 75015 Paris, France
[3] Supersonic Imagine, 510 rue René Descartes, F-13857 Aix-en-Provence, France




(b)