Breast dispersion imaging using undersampled DCE MRI

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Introduction
Dynamic Contrast-enhanced (DCE) Breast MRI

Pre

Dynamic

Post-contrast

0.5 x 1.2 x 2.0 mm
13 seconds
14 images

0.5 x 0.6 x 1.0 mm
120 seconds
4 images

Pre

Post

Pre

Post

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The pattern of enhancement matters

Malignant tumors

• Signal intensity increased to 100% within the first 2 minutes\(^1\).

• Aorta is enhanced within 11.5 seconds\(^2\).

• Rapid uptake and washout of the contrast agent\(^3\).

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Semi-quantitative analysis

• Compromises are made between spatial and temporal resolution.
• High spatial resolution imaging is increasingly being used.
• Three time-point acquisition
  • microvascular permeability (K)
  • extracellular fraction(ν)
• ACR recommend
  • Spatial resolution: 1mm in-plane, 3 mm slice thickness
  • Temporal resolution: 120 s or less

Image Acquisition for quantitative analysis

Differential subsampling with Cartesian ordering (DISCO) DCE-MRI

Quantitative Analysis: Pharmacokinetic model

Tofts et al., JMRI 1999

- $C_t \ (t)$: Tissue Concentration (mMol/l)
- $C_p \ (t)$: Plasma Concentration (mMol/l)
- $K_{trans}$: Transfer Constant (min$^{-1}$)
- $k_{ep}$: Flux rate (min$^{-1}$)
- $v_e$: Fractional volume of EES
- $v_p$: Fractional volume of plasma

Two Compartment Model (2CXM):

$$C_t(t) = \frac{C_p(t)}{1 + K_{trans} t} + k_{ep} v_e C_t(t)$$

Extended Tofts Model (2CXM):

$$C_t(t) = \frac{C_p(t)}{1 + k_{ep} v_e} + K_{trans} t$$

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AN TRANSIT TIME (MTT) IS CONSIDERED

\[ C_t(t) = F_p C_p(t) \times \left[ A e^{-\alpha t} + (1 - A) e^{-\beta t} \right]; \]

\[ k_{01} = A \cdot (\alpha - \beta) + \beta; \]

\[ k_{12} = \frac{\alpha \beta}{k_{01}}; \]

\[ k_{21} = \alpha + \beta - k_{12}; \]

\[ v_p = F_p / k_{01} \]

\[ PS = k_{21} \cdot v_p \]

\[ MTT = v_p / (PS + F_p) \]

- \( F_p \) : plasma perfusion
- \( PS \) : permeability and surface area of the capillary walls
- \( MTT \) : the ratio of the volume of distribution in the plasma space (\( v_p \)) to the total plasma inflow (\( PS + F_p \)).
Determination of $C_p(t)$

- $C_p(t)$: Arterial Input Function (AIF)
  - Subject-specific AIF (sAIF)
  - Gaussian and exponential model

\[
C_p(t) = \sum_{n=1}^{N} \frac{A_n}{\sigma_n \sqrt{2\pi}} \exp \left( -\frac{(t-T_n)^2}{2\sigma_n^2} \right) + \frac{\alpha \exp(-\beta t)}{1 + \exp(-s(t-\tau))}
\]
Determination of $C_p(t)$

- $C_p(t)$: Arterial Input Function (AIF)
  - Population AIF (pAIF):
  - Modified Fritz Hansen bi-exponential model

$$C_p(t) = D(a_1 e^{-m_1 t} + a_2 e^{-m_2 t})$$

Walker-Samuel et al., PMB, 2006
Parker et al., MRM, 2006
Pharmacokinetic Mapping

$S_t$

$C_t$

$C_{t-fit}$

$K_{trans}$

$K_{ep}$

Courtesy: Dr. Subashini Vedanthm

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Limitations

Fitting with 2CXMs with global uniform $C_p(t)$

- Improved fitting with sAIF in the first 2-3 very early enhancement time points
- All models have limited accuracy in catching up the rapid enhancement
- Hard to obtain correct AIF
- A uniform AIF might not be ideal
Objective

• Inspired by the intravascular dispersion concept, we replace the global AIF with a local AIF in order to account for local variations in contrast delivery.

• Compare the goodness-of-fit of the dispersion and non-dispersion models

• Compare diagnostic performance of the dispersion and non-dispersion models
Methods
Dispersion model: mLDRW model

• The intravascular transport of a bolus of contrast agent is driven by a combination of dispersion and convection effects

\[
\frac{\partial}{\partial t} C_p (x, t) = D \frac{\partial^2}{\partial x^2} C_p (x, t) - v \frac{\partial}{\partial x} C_p (x, t)
\]

• Assuming a Gaussian distribution of the traveling contrast bolus \( C_p (t) \), it can be solved using a modified local density random walk (mLDRW) model

\[
C_p (t) = \alpha \sqrt{\frac{\kappa}{2\pi t}} e^{-\frac{\kappa(t-MTT)^2}{2t}} ; \kappa = \frac{\nu^2}{D}
\]

• mLDRW model:

\[
C_t (t) = \alpha \sqrt{\frac{\kappa}{2\pi t}} e^{-\frac{\kappa(t-MTT)^2}{2t}} * K_{\text{trans}} e^{-k_{\text{ep}} t}
\]
mLDRW model

\[ C_p(t) = \alpha \sqrt{\frac{\kappa}{2\pi t}} e^{-\frac{\kappa(t-MTT)^2}{2t}} \]

- \( \kappa \): dispersion term [min\(^{-1}\)]
- \( MTT \): mean transit time [min]
- \( \kappa \propto (1/\text{Dispersion coefficient}) \)

Courtesy: Dr. Subashini Vedanthm
Mischi et al., IEEE EMBS 2013, Carr et al., ISMRM 2014
Comparison

• The standard Tofts model

\[
C_t (t) = C_p (t) * K^{\text{trans}} e^{-\frac{K^{\text{trans}}}{v_e} t} = C_p (t) * K^{\text{trans}} e^{-k_{ep} t}
\]

• The extended Tofts model

\[
C_t (t) = v_p C_p (t) + C_p (t) * K^{\text{trans}} e^{-k_{ep} t}
\]

• The comprehensive 2CXM

\[
C_t (t) = F_p C_p (t) * [A e^{-\alpha t} + (1 - A) e^{-\beta t}]
\]

• mLDRW model

\[
C_t (t) = \alpha \sqrt{\frac{\kappa}{2\pi t}} e^{-\frac{\kappa(t-MTT)^2}{2t}} * K^{\text{trans}} e^{-k_{ep} t}
\]

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Data Acquisition

- 37 patients (24 to 73 yrs) with 60 known masses
  - 43 malignant tumors (32 IDC, 3 ILC, 2 Mucinous Carcinoma, 6 DCIS)
  - 17 benign lesions

- A 0.1 mmol/kg dose of Gadobutrol (Gadovist) was injected at the rate of 2 ml/sec followed by a 20ml saline flush

- Imaging acquisition
  - Differential subsampling with Cartesian ordering (DISCO) DCE-MRI
  - 3D RF-spoiled gradient recalled echo (SPGR) sequence with Dixon fat-water separation
Evaluation

• Goodness-of-fit:
  • \[ MSE = \frac{SSE}{n-m} \]
  • F test: evaluate if the mLDRW model generates a significant better fitting to other models

• Diagnostic performance
  • ROC curve is built over the ROI voxels representing the class of malignant and benign tissue for each model
  • The ROC generation is performed via a 5-fold cross validation process on 60 tumors.
Result
Goodness-of-fit

- Population AIF used in non-dispersion models
## Goodness-of-fit

- Fitting errors over the entire dataset

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Model</th>
<th>MSE</th>
<th>p (F-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population AIF (pAIF, 60 tumors)</td>
<td>Tofts</td>
<td>0.0058±0.0106</td>
<td>&lt;&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Ext. Tofts</td>
<td>0.0057±0.0105</td>
<td>&lt;&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>2CXM</td>
<td>0.0035±0.0066</td>
<td>&lt;&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>mLDRW</td>
<td>0.0013±0.0026</td>
<td></td>
</tr>
<tr>
<td>Patient-Specific AIF (sAIF, 18 tumors)</td>
<td>Tofts</td>
<td>0.0051±0.0079</td>
<td>0.0095</td>
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<tr>
<td></td>
<td>Ext. Tofts</td>
<td>0.0045±0.0067</td>
<td>0.0245</td>
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<td></td>
<td>2CXM</td>
<td>0.0037±0.0064</td>
<td>0.0254</td>
</tr>
<tr>
<td></td>
<td>mLDRW</td>
<td>0.0023±0.0041</td>
<td></td>
</tr>
</tbody>
</table>
Pharmacokinetic mapping (voxel-by-voxel)

Benign

mLRDW $\kappa [\text{min}^{-1}]$

Standard Tofts $k^{\text{trans}} [\text{min}^{-1}]$

Ext. Tofts $k^{\text{trans}} [\text{min}^{-1}]$

2CXM $F_p [\text{ml/(ml/min)}]$

$\kappa [\text{min}^{-1}]$

$k^{\text{trans}} [\text{min}^{-1}]$

$k^{\text{trans}} [\text{min}^{-1}]$

PS [ml/(ml/min)]

$M_T [\text{min}]$

$\nu_p [\text{ml/(ml/min)}]$

$M_T [\text{min}]$

IDC

mLRDW $\kappa [\text{min}^{-1}]$

Standard Tofts $k^{\text{trans}} [\text{min}^{-1}]$

Ext. Tofts $k^{\text{trans}} [\text{min}^{-1}]$

2CXM $F_p [\text{ml/(ml/min)}]$

$\kappa [\text{min}^{-1}]$

$k^{\text{trans}} [\text{min}^{-1}]$

$k^{\text{trans}} [\text{min}^{-1}]$

PS [ml/(ml/min)]

$M_T [\text{min}]$

$\nu_p [\text{ml/(ml/min)}]$

$M_T [\text{min}]$
Diagnostic Performance

- AUC for $\kappa$ is 0.96, the highest among all the compared parameters.
  - Sensitivity of 87.1% ± 3.9%
  - Specificity of 93.1% ± 2.8%
Discussion and Limitations

• The malignant tissue is highly correlated with the ‘hot spots’ in the dispersion map $\kappa$ (i.e., $\kappa = \nu^2/D$)
  • Vascular endothelial growth factor (VEGF)
  • Vascular tortuosity mechanism has a counter effect on dispersion

• A constant $T_{10}$ value to convert the DCE signal-time curves to tissue concentration-time curves without acquiring the $T_{10}$ maps and $B_1$ maps that account for the spatially varying signal changes
Conclusion

- A new window is proposed to investigate the physiology of breast tumor microcirculation through the estimation of an intravascular dispersion property.
- The mLDRW dispersion no longer requires the measurement of AIF.
- The goodness-of-fit is greatly improved with mLDRW model.
- The dispersion related parameter, $\kappa$, demonstrates superior performance in discriminating benign and malignant tumor.
Future work: Abbreviated DCE

ABBREVIATED DCE

Joint Annual Meeting ISMRM / ESMRMB, May 11-16, 2019, Montreal, CA
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