DCE MRI for Quantitative Assessment of Therapy Response

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Open positions for Post-Doctoral fellows
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Learning Objectives

- Understand the strengths and weaknesses of commonly used pharmacokinetic models
- Understand the influence of image acquisition parameters and image quality on derived quantitative metrics
- Provide examples of clinical applications in therapy assessment

Imaging For Assessment of Tx Response

- Rapid growth field
- Driven by the needs of fast development in therapeutic modalities
  - Targeted tx, concurrent or sequential multi-modality tx,
  - organ-reserved tx,
  - aggressive, complex, risk vs benefit, individualized
- Challenging conventional paradigms for therapy assessment
  - Endpoints, e.g., TV reduction
  - Time, e.g., months after completion of Tx
- Changing in Tx assessment paradigms
  - Early, e.g., during the course of and early after therapy
  - Biomarkers as surrogate endpoints
DCE MRI for Tx Assessment

- Early prediction of chemoradiation treatment response of GBM (Cao 2006a, 2006b)
- Early prediction of outcomes of chemo and radiation therapy in advanced HN cancers (Cao 2008, Dirix 2009)
- Early assessment of liver function during radiation therapy (Cao 2007, 2008)
- Early assessment and prediction for neurotoxicity after brain irradiation (Cao CCR, 2008)

Overview

- Sequences
  - Dynamic susceptibility contrast (DSC) T2* (or T2)-weighted imaging
  - Dynamic contrast enhanced (DCE) T1-weighted imaging
- Vascular and perfusion parameters
  - Blood flow, blood volume, vascular permeability, extravascular extracellular space
- Trade-offs
  - Sequences, parameters, pharmacokinetic models
  - Complexity, robustness, accuracy, reliability, reproducibility, ..., surrogacy (application)

Outline

- Typical protocols
- Physiological origins of DCE and DSC imaging
- Image processing and modeling
- Limitations
- Clinical values of perfusion and vascular permeability imaging for therapy assessment

DSC Imaging

- Imaging Sequence
  - 2D GE or SE EPI sequence to acquire dynamic T2*- or T2-weighted images during a bolus of Gd-DTPA injection
  - TR/TE (ms): 1500/40-60 (GE) or 60-100(SE)
  - Flip angle: 30-60°, slice thickness: 4-6 mm
  - Dynamic repetition: 35-120
  - # slices: ~14-19
  - Single dose of Gd-DTPA (0.1 mM/kg) w an injection rate 2-4 cc/s
Dynamic Contrast Uptake Curve

- Signal intensities decrease during the bolus arrival

Estimation of Relative CBV

\[ CBV = \mu \int \frac{S_0}{S(t)} dt \]

Over the first pass

Rosen MRM 1991

Tradeoffs of MRI parameters

- Gradient echo (GE) vs spin echo (SE)
  - SE:
    - sensitive to microvasculature
    - suitable for ischemic stroke, cognitive function, etc
    - Less sensitive to contrast, double doses
  - GE:
    - sensitive to both micro- and macro-vasculature
    - suitable for brain tumor due to neovascularization
    - More sensitive to contrast, single dose

Mis-estimation of CBV

- Vascular leakage, contrast effects on T1, or both
- T1 effect is more problematic for SE than GE
- Underestimation for SE and overestimation for GE

Minimize mis-estimation

- Reduce T1 effects
  - longer TR, smaller flip angle, and GE, single dose of contrast
- Integrate only the area under the first pass of the Gd bolus
- Correct the effect of vascular leakage numerically (Weisskoff 1994, Johnson 2003, Cao 2006b)
Application Questions

- In your setting, do you see any overshooting or undershooting in the tail of dynamic signal intensities?
- If yes, in what region(s), normal tissue, tumor, or ischemic stroke tissue, do you see overshooting or undershooting?
- Do you use the integral under the area of the first pass of contrast bolus to estimate relative CBF?
- If not, what are the tradeoffs of your method compared to the area under the first pass?

Estimation of Relative CBF

- Imaging sequence
  - Same as one for CBV
  - TR: 1500ms or shorter
- Estimation of relative CBF
  - Determine the artery input function (AIF), \( R_{2}^{*} \) usually from middle cerebral artery
  - Calculate \( R_{2}^{*} \) in every voxel of tissue
  - The residual function \( R \) is determined by deconvolution computation, which can be done by SVD (Ostergaard 1999, MRM)
  - The amplitude of the residual function \( R \) is proportional to blood flow

Concerns of Estimation of CBF

- Assumptions in the model
  - Intravascular contrast agent
  - Artery input function: a delta function or a short bolus
- Reality
  - Leaky vasculature in both brain tumor and ischemic stroke
  - Gd-DTPA is not an intravascular contrast agent with leaky vasculature
  - Artery input function is not a delta function
- Trade-offs in MRI parameters
  - Fast injection rate for a short bolus of contrast vs patient tolerance and safety
  - Shorter RT (<1.5s) for more reliable estimation of CBF vs smaller number of slices (less spatial coverage)

Sources of Error

- Artery input function
  - Partial volume average in the middle cerebral artery → large uncertainty in the amplitude of AIF
  - Disperse and delay in AIF → distorted R
- Vascular leakage
- Susceptibility artifacts
- Sense artifacts
- Inadequate temporal resolution
**SENSE Artifact During Dynamic Scans**

With SENSE

"SENSE" artifacts

Without SENSE

All other parameters were the same!
SENSE: 19 slices within 1.5 s
No SENSE: 14 slices within 1.5 s

**Application Questions**

- In your setting, do you think you can determine artery input function reliably and consistently?
- What percentage errors do you think the variation in artery input function will propagate into the variation in the estimation of CBF?
- Do you use SENSE in dynamic scans? If yes, what fraction of scans do you have "SENSE" artifacts?
- What are the limitations in your application due to the relative nature of CBF?

**DCE Imaging**

- Imaging sequence
  - 2D or 3D flash or SPGR sequence to acquire dynamic T1-weighted images during a bolus of GD-DTPA injection
  - TR/TE (ms): min/min
  - Flip angle: 10°-30°
  - Plane: sagittal or axial
    - Sagittal plane to avoid the in-flow effect due to unsaturated blood spins
    - Isotropic voxel size to permit reformatting images in the axial plane
  - Dynamic acquisition
    - Long enough to be sensitive to contrast uptake in tissue
    - Long enough to cover contrast wash-out in tissue

**Example in HN DCE MRI**

Imaging Acquisition:
Sagittal Plane
Isotropic voxel size: 2x2x2 mm³
reformatted in axial
3D Volumetric coverage
Pharmacokinetic Models

- Pharmacokinetic models
  - Parameters can be concerned in a PK model
    - Intravascular space (plasma plus blood cell)
    - Transfer constant from vasculature to tissue
    - Back-flux rate from tissue to vascular space
    - Extravascular extracellular space
    - Blood flow
  - Main differences among the models are what parameters have been considered for a particular physiological or pathological condition

Two compartmental model

- Two compartmental model – standard model (Kety or Toft model 1999 in JMRI)
  - Contrast concentration in a voxel due to intra (blood volume) and extra vascular (leakage or contrast uptake) contributions
  - Inputs:
    - contrast concentrations in artery
    - contrast concentrations in tissue
  - Fitted parameters:
    - $K_{trans}$, plasma volume ($v_p$) and $k_{ep}$

DCE Data Modeling

- T1 weighted signal intensities
  - $S = S_0 \sin \left[ \frac{1}{1 - \cos (\frac{TR}{T1})} \right]$ for $TR \ll T1$
- Signal intensity difference after and before contrast injection
  - $S = S_o \sin \left[ \frac{1}{1 - \cos (TR / T1)} \right] R_1 (1 + O(10^{-3}))$

Concerns of $K_{trans}$ and $V_p$ (I)

- Interpretation of $K_{trans}$ (Toft 1999)
  - Blood flow limited condition:
    - permeability surface area product (PS) $\gg$ perfusion (F) $→$ $K_{trans} = Fp (1-Hct)$ represents blood flow
  - Permeability limited condition:
    - P >> PS $→$ $K_{trans} = P_{sp}$ depicts transfer constant of contrast from intravascularure to extravascularure space
  - Mixed condition:
    - $F-PS → K_{trans} = EFP (1-Hct)$ represents both blood flow and transfer constant
Concerns of $K_{\text{trans}}$ and $V_p$ (II)

- $V_p$ is more reproducible than $K_{\text{trans}}$
- What is a better method to estimate blood volume, DCE vs DSC, depends upon the organ
  - Brain $\rightarrow$ DSC
  - Other body sites $\rightarrow$ DCE
- The DSC method may have high sensitivity than the DCE method but blood volume estimated from DSC is a relative measure

Application Questions

- In your setting, do you use a TR that is short enough to satisfy the first order approximation of $TR*R_1$ being negligible?
- Do you think you can use more complex models in a clinical trial setting given the quality of DCE data that you are getting? Why?

Variation: Patlak Model

- Multiple time-graphic method (Patlak 1983)
  - The back flux of contrast from interstitial space to intravascular space is omitted if it is small enough
  \[ C_p(t) = K_{\text{trans}} \int_0^t C_p(t) \, \text{d}t + v_p C_p(t) \]
  \[ C(t)/C_p(t) = K_{\text{trans}} \int_0^t C_p(t) \, \text{d}t + v_p + y = K_{\text{trans}} + v_p \]

Variation: Toft model

- Toft models with and without the intravascular term
  \[ C_p(t) = K_{\text{trans}} \int_0^t e^{\lambda_p(t)} \, C_p(t) \, \text{d}t + v_p C_p(t) \]
  \[ C(t) = K_{\text{trans}} \int_0^t e^{\lambda_p(t)} \, C_p(t) \, \text{d}t \]

Values of the two $K_{\text{trans}}$s are not comparable! If the intravascular contribution is not small enough compared to the extravascular contribution, the second model results in a large error.
**Application Questions**

- In your setting, do you include the intravascular contribution into your model?
- If not, do you estimate the percentage discrepancy in the estimation of $k_{trans}$ with and without considering the intravascular contribution?
- How do they change over the longitudinal study of a clinical trial?

**Blood Flow from DCE Data**

- Derivative form vs integral form

\[
\left(\frac{dC}{dt}\right)_{\text{max}} = F \cdot C_p(t)_{\text{max}} \\
C_v(t) = F \int_0^t C_p(\tau) d\tau, \quad < T
\]

The derivative form is easier to compute than the integral form!

**Vascular Permeability from DSC Data**

- Estimation of vascular permeability from DSC images (Weisskoff 1994, Johnson 2003, Cao 2006)

**CBV and Vascular Leakage**

- CBV and vascular leakage

Cao, JMRI 2006
**Imaging for Therapy Assessment**
- Longitudinal study
  - Repeated measures
  - Reproducibility of measures, robustness of the model → reliability of quantitative metrics
- Sensitive indicator (biomarker)
  - Sensitive to therapy-induced changes
- Predictive value
  - Early changes associated with Tx responses and outcomes
- Surrogate endpoint

**Pre-RT CBV in High-Grade Gliomas**
- Small rTV w High-CBV
- Large rTV w High-CBV
- P = 0.002

**Early CBV Changes During RT**
- Pt A: Decrease → Better OS
- Pt B: Little Change → Worse OS

**Prediction of PFS in Glioma**
- 198 pts with low or high grade glioma
  - 136 pts w high-grade gliomas
- Mean relative CBV in gliomas
  - Predict median time for progression
  - Independent histological grade
- Age and mean relative CBV were independent predictors for clinical outcomes
- P < 0.001

**Law, Radiology 2008**

**Cao, IJROPB, 2006**
Quantitative Vascular Leakage in High-Grade Gliomas

The extent of Vascular Leakage

Predictors for OS

Early Assessment for Outcomes in Advanced HNC
**Early Assessment for Local Control in Advanced HNC**

<table>
<thead>
<tr>
<th>Primary Disease</th>
<th>TBV (mL/100g)</th>
<th>TBF (mL/100g min)</th>
<th>GTV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference wk2-pre</td>
<td>Difference wk2-pre</td>
<td>% Difference wk2-pre</td>
</tr>
<tr>
<td>LC</td>
<td>5.1 (-0.6 – 13.2)</td>
<td>20.1 (-3.9 – 54.6)</td>
<td>-28%</td>
</tr>
<tr>
<td>LF</td>
<td>1.0 (-1.7 – 1.6)</td>
<td>15.0 (-22.1 – 41.1)</td>
<td>-21%</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.03 n.s.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Changes in TBV after 2 weeks of FRT have better sensitivity and specificity than TV changes for prediction of local failure.

**Identify Poorly Perfused Sub-Tumor Volumes**

TBV 2 weeks after the start of RT

Wang, poster SU-DD-A3-2

**ROC Analysis**
Perfusion and vascular parameters estimated from DCE and DSC MRI have been demonstrated to have the potential to be biomarkers for therapy assessment, including targeted therapy (e.g., anti-angiogenesis drugs), multi-modality treatment (e.g., chemo and radiation therapy), and individualized therapy (risk vs benefit).

It has been demonstrated that BV and BF could be more sensitive indicators of response/outcome to Tx than tumor volume reduction.

They are generally available but standards for acquisition, and quantification are important for multi-center clinical trials.