# Implementing in vivo perfusion measurements using DCE MRI

Yue Cao, Ph.D.
Departments of Radiation Oncology and Radiology
University of Michigan

## Learning objectives

- To understand practical issues to extract quantitative imaging metrics
- To understand how to increase robustness and objectiveness in the analysis
- To understand limitations of derived quantitative imaging metrics



## Quantitative imaging as a biomarker

- Various physiological, metabolic and molecular parameters of tissue may serve as both prognostic as well as evaluative methods for disease and therapeutic response/outcome
- Imaging systems have significant power to aid *in vivo* estimation of these parameters



## What is the relevance of perfusion analysis?

- Blood supply is critical to the sustainability of tissue
  - Nutrients and oxygen are supplied by vessels
- Vasculature and blood supply to tissue may be a highly relevant biomarker in cancer therapy
  - Neovasculature → Tumor aggressiveness
  - Changes in neovascualture →Tumor response
  - Changes in normal vasculature →Normal tissue damage

## Quantitative metrics related to perfusion

- Metrics include blood flow, transit time, transfer rates to tissue, blood volume
- These metrics are estimated using parametric and/or compartmental models
- The proper model selection depends upon the organ of interest as well as the physiological condition
- There is no single model that can be applied to all systems and physiological conditions
- It is important to understand
  - What problem is to be addressed
  - What assumptions are used in the models
  - What physiological parameters are derived from the model
  - How parameters are related to each other



## Examples of perfusion related models

- Brain perfusion model
  - Brain perfusion (Ostergaard MRM 1999)

$$C_t(t) = \int_0^t C_{AIF}(\tau) R(t-\tau) d\tau$$

- Kety model (Toft JMRI 1999)
  - Transfer constant to tissue and blood volume

$$C_t(t) = K^{trans} \int_0^t e^{-k_{ep}(t-\tau)} C_p(\tau) d\tau + v_p C_p(t)$$

- Dual-input and single compartment liver perfusion model
  - Arterial and portal venous perfusion

$$C_t(t) = \frac{1}{(1-Hct)} \int_0^t [k_a C_a(\tau-\tau_a) + k_p C_p(\tau-\tau_p)] e^{-k_2(t-\tau)} d\tau$$



## Comments

- Models approximate problems and have their limitations
- Different physiological parameters can be estimated from different models
- Interpretation of extracted parameters depends upon the model, organ, image acquisition, and biological conditions
- Models will be discussed in detail in CE-Imaging: MRI III (WE-A-303A-1 7:30 AM)

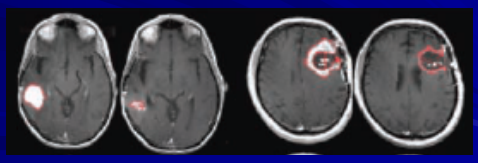


## Imaging methods for perfusion estimation

- PET and SPECT
- Dynamic contrast enhanced CT and MR imaging
  - High spatial resolution
    - Tumor size, structures, partial volume, input function
  - High temporal resolution
    - input function, model stability
  - Artery input functions estimated directly from images
  - High signal to noise ratio
  - Short acquisition time
    - A few min vs 30-60 min in PET/SPECT
  - Respiratory motion management paradigm during acquisition
    - Single or multiple breath holds vs free breathing in PET/SPECT
  - Anatomic images generated in the same imaging session

## Choose acquisition sequence, parameters and models

- What is targeted in the clinical trial
  - Anti-VEGF therapy in recurrent GBM
- choose right acquisition, parameters and a model
  - $K^{trans}$ and blood volume
    - Toft (Key) and CBV models



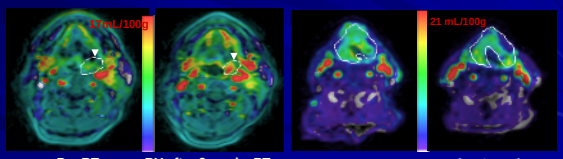
Sorensen et al, Cancer Research 2009

Cao AAPM2009

## Choose acquisition sequence, parameters and models

- What is targeted in the clinical trial
  - Chemo + RT In HN Cancer
- choose right acquisition, parameters and a model
  - Blood volume and flow
    - Toft and blood flow models

**Local control** **Local failure**



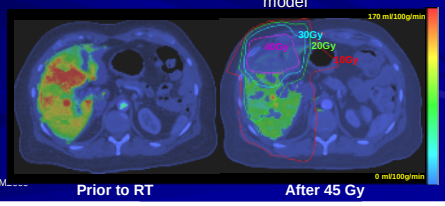

Pre RT BV after 2 weeks RT BV pre RT BV after 2 weeks RT

Cao, et al Red Journal 2008

Cao AAPM2009

## Choose acquisition sequence, parameters and models

- What is targeted in the clinical trial
  - Radiation effect on liver function
- choose right acquisition, parameters and a model
  - Portal venous perfusion
    - Dual-input and single compartment liver perfusion model




Prior to RT After 45 Gy

Cao AAPM2009

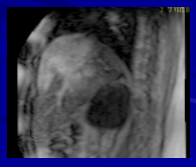
## DCE MRI acquisition paradigm

- Imaging sequence and parameters
  - 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
      - Blood volume and blood flow → short
      - transfer constant from intravasculature space to tissue → long
      - transfer constant rate from tissue back to intravasculature space → longer
  - Temporal resolution
    - Blood flow → high temporal resolution
    - Trade-off with spatial resolution

Cao AAPM2009

## Example: liver DCE protocol

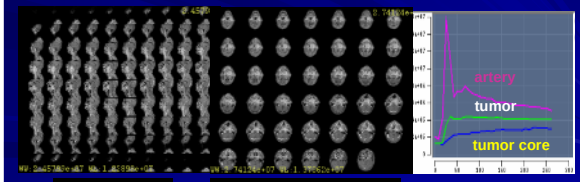
- 3D gradient-echo pulse sequence on Philips 3T scanner
  - FOV of 330 mm
  - 75% of FOV in the phase encoding direction
  - ~60 slices in the oblique sagittal coronal orientation
  - voxel size of 1.3x3x3 $mm^3$
  - TFE of 200, TE/TR of 2.1/4.5 ms
  - flip angle of 20 degree
  - sense factor of 2 in 2 directions
  - Temporal 2.5 s per volume



Cao AAPM2009

## Example: DCE Data for HN cancer

**Image Acquisition:**
Sagittal Plane → reduce the in-flow effect
3D Volumetric → cover the primary tumor and involved node
Voxel size 2x2x2 mm → reformat images as axial




**Sagittal images** **Reformatted axial images**

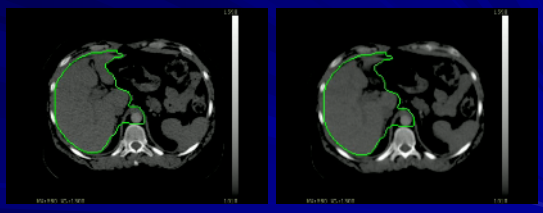
Cao AAPM2009

## Extraction of perfusion parameters from DCE MRI via post-processing

- General paradigm for data analysis
  - Re-align dynamic image volumes within series
  - Correct baseline signal intensities
  - Determine artery input function
  - Choose a physiological model
- Process dynamic images

Cao AAPM2009

## Realignment of dynamic volumes within series



**Before registration** **After registration**

Cao AAPM2009

## Extraction of perfusion parameters from DCE MRI via post-processing

- General paradigm for data analysis
  - Re-align dynamic image volumes within series
  - Correct baseline signal intensities
  - Determine artery input function
  - Choose a physiological model
  - Process dynamic images



## Baseline correction

- T1 weighted signal intensity

$$S = S_o \sin\alpha \frac{1 - e^{-TR \times R_1}}{1 - \cos\alpha \times e^{-TR \times R_1}}$$

- If TR x T1 << 1,

$$S = S_o \frac{\sin\alpha}{1 - \cos\alpha} TR \times R_1 [1 + O(10^{-2})]$$

- Signal intensity difference after and before contrast

$$\Delta S = S_a - S_b = S_o \frac{\sin\alpha}{1 - \cos\alpha} TR \times \Delta R_1 \Rightarrow \Delta R_1 \propto \Delta C \ ?$$



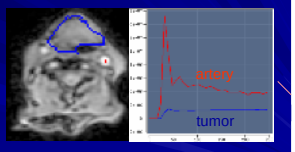
## Extraction of perfusion parameters from DCE MRI via post-processing

- General paradigm for data analysis
  - Re-align dynamic image volumes within series
  - Correct baseline signal intensities
  - Determine artery input function
  - Choose a physiological model
  - Process dynamic images



## Determine artery input function

- Artery input function
  - Threshold intensities to find the most rapid contrast uptake voxels in artery
- Large artery vs small artery
  - Small artery
    - Close to tissue of interest
    - Suffers from partial volume averaging
  - Large artery
    - Less partial volume effect
    - Distant from tissue of interest
    - Time delay




$$C_t(t) = K^{trans} \int_0^t e^{-k_{ep}(t-\tau)} C_p(\tau - t_0) d\tau + v_p C_p(t - t_0)$$

## Extraction of perfusion parameters from DCE MRI via post-processing

- General paradigm for data analysis
  - Re-align dynamic image volumes within series
  - Correct baseline signal intensities
  - Determine artery input function
  - Choose a method of analysis
  - Process dynamic images



## Choose a method for analysis

- Most people use available (commercial) software
  - This may or may NOT be adequate for the problem being addressed
- Understand the underlying model
- Test the software (model) with a set of simulated dynamic data (with known truth)
- Understand performance of tested software



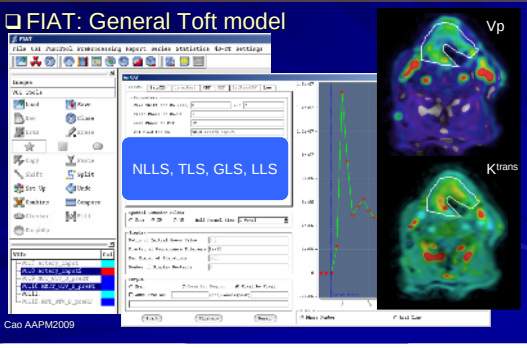
## Extraction of perfusion parameters from DCE MRI via post-processing

- General paradigm for data analysis
  - Re-align dynamic image volumes within series
  - Correct baseline signal intensities
  - Determine artery input function
  - Choose a physiological model
  - Process dynamic images



## Process dynamic Images

- FIAT: General Toft model



## Potential sources of error

- Performance of the scanner and coil
  - T1 Phantom → QA
    - homogeneity of $B_0$ and $B_1$ fields, artifacts, noise, R1 vs C, stability
  - Flow phantom → QA of flow assessment
- Human study
  - Image quality
    - noise, distortion, motion artifacts
  - Temporal resolution
  - Length of dynamic acquisition
  - T1 change over time interval of assessment
    - Quantify native T1
    - Allow us to correct T1 effect if there is any change
  - Artery input function
    - Errors and inconsistency



## Other concerns

- Quantitative image consistency – need for test-retest to determine a minimum change that can be detected reliably
- OVER-ANALYSIS – extracting information that exceeds the limits of the measurement method
  - How many parameters can be fitted in a model given SNR of dynamic DCE MRI
  - A balance between complexity and reliability



## Develop and test Software tools

- Implementation of perfusion-related measurement and model application is not standard for all image acquisition methods or applications
- Robust and flexible software tools are needed to ensure proper data management
- Test performance of software tools
  - Simulated phantom data sets with known "truth"



## A Concern !

- Toft models

$$C_t(t) = K^{trans}\int_0^t e^{-k_{ep}(t-\tau)}C_p(\tau)d\tau + v_p C_p(t)$$

Extravascular contribution  intravascular contribution

$$C_t(t) = K^{trans}\int_0^t e^{-k_{ep}(t-\tau)}C_p(\tau)d\tau$$

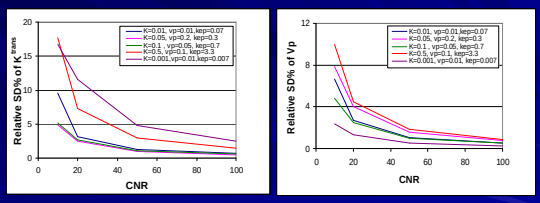
**Values of the two $K^{trans}$s are not comparable!**

## Test Software Tools

- We have developed a simulated DCE phantom for testing the standard DCE model (general Toft model)
- Parameters have been considered
  - CNR, temporal resolution, dynamic acquisition time, $K^{trans}$, $V_p$, $k_{ep}$, input function temporal jitter, …
  - >1 million simulations to cover a large range of variations of parameters
  - 2500 simulations for each combination of the parameters → statistics



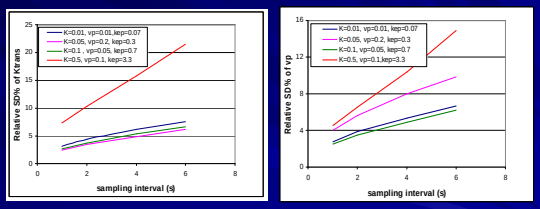
## Contrast to Noise Ratio




**$K^{trans}$ and Vp do not have same sensitivity to noise!**



## Sample Interval




Stability of large Ktrans values depends upon the sample interval



## Test Software Tools

- We form a TG to evaluate software tools for quantification of DCE MRI
  - Validate data, test tools, report results
  - Make data available for public via CaBIG, QIN, QIBA and possible professional society, e.g., AAPM
  - publish the test results
- This test will provide
  - a common ground to communicate between investigators
  - Guidance for image acquisition design
  - QA for multi-center clinical trials
- We call for participants to test their software tools using the same data sets
  - Please send email to yuecao@umich.edu

## Resources are still needed to aid in DCE-based perfusion as a biomarker

- Standards for acquisition, models, and terminologies
- Criteria for reproducible imaging
- Validation methodologies
  - Phantoms: T1, flow, and simulated phantoms
  - "Gold standard", "standard" or validated data
- Multiple efforts are underway to provide such resources
  - QIBA
  - NIH PAR 08-225 – Quantitative Imaging Network



## Acknowledgements


- NIH/NCI 3 P01 CA59827
- NIH/NINDS/NCI RO1 NS064973
- NIH/NCI R21 CA113699
- NIH/NCI R21 CA126137


- Open positions for Post-Doctoral fellows
  - Send CV to yuecao@umich.edu