

What DCE MRI can(not) tell us about renal pathophysiology

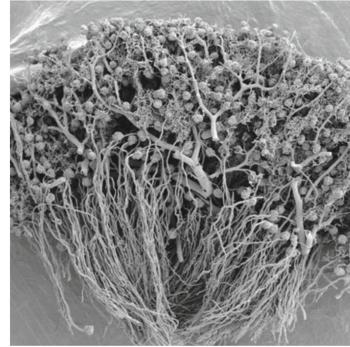
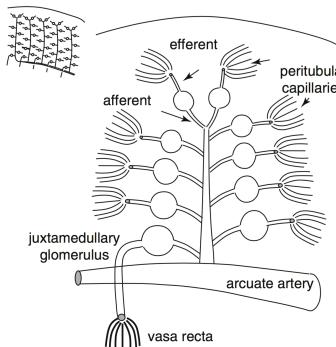
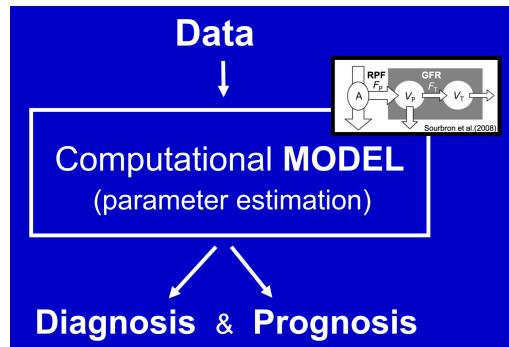
http://www.cost.eu/COST_Actions/ca/CA16103

Syllabus: <https://github.com/arvidl/dce-mri-renal-pathophysiology>

Prof. Arvid Lundervold BSc, MD, PhD

Neuroinformatics and Image Analysis Laboratory, Neural Networks Research Group
Department of Biomedicine

University of Bergen
Norway



Renal pathophysiology and DCE-MRI

- Kidney **structure and function**
- Kidney **diseases & Bayes theorem**
- Renal **pathophysiology** – multiscale approach – systems medicine
- What renal **DCE-MRI**
 - can tell us
 - can not tell us
- **Software** for DCE-MRI - estimation of renal perfusion and filtration
 - (“open science” & “reproducible research”)

Other measurement techniques

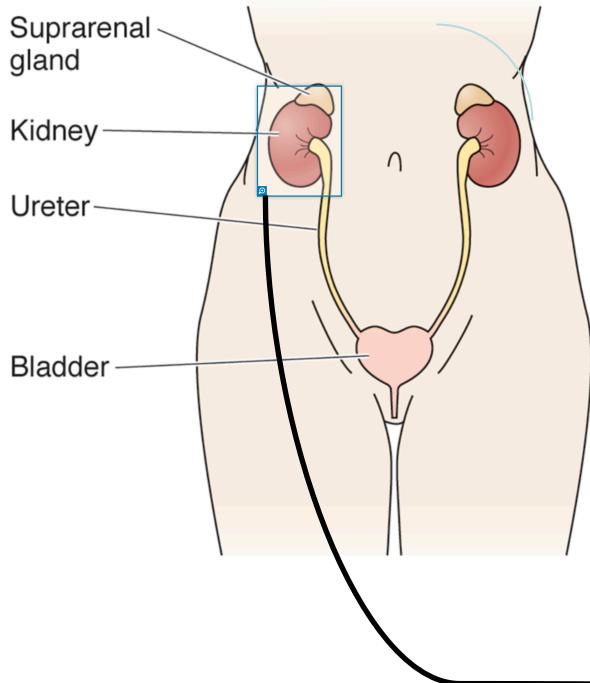
What **DCE MRI** can(not) tell us about renal pathophysiology (Lundervold, Thu 12 Oct 09:00)

What **ASL MRI** can(not) tell us about renal pathophysiology (Buchanan, 09:40)

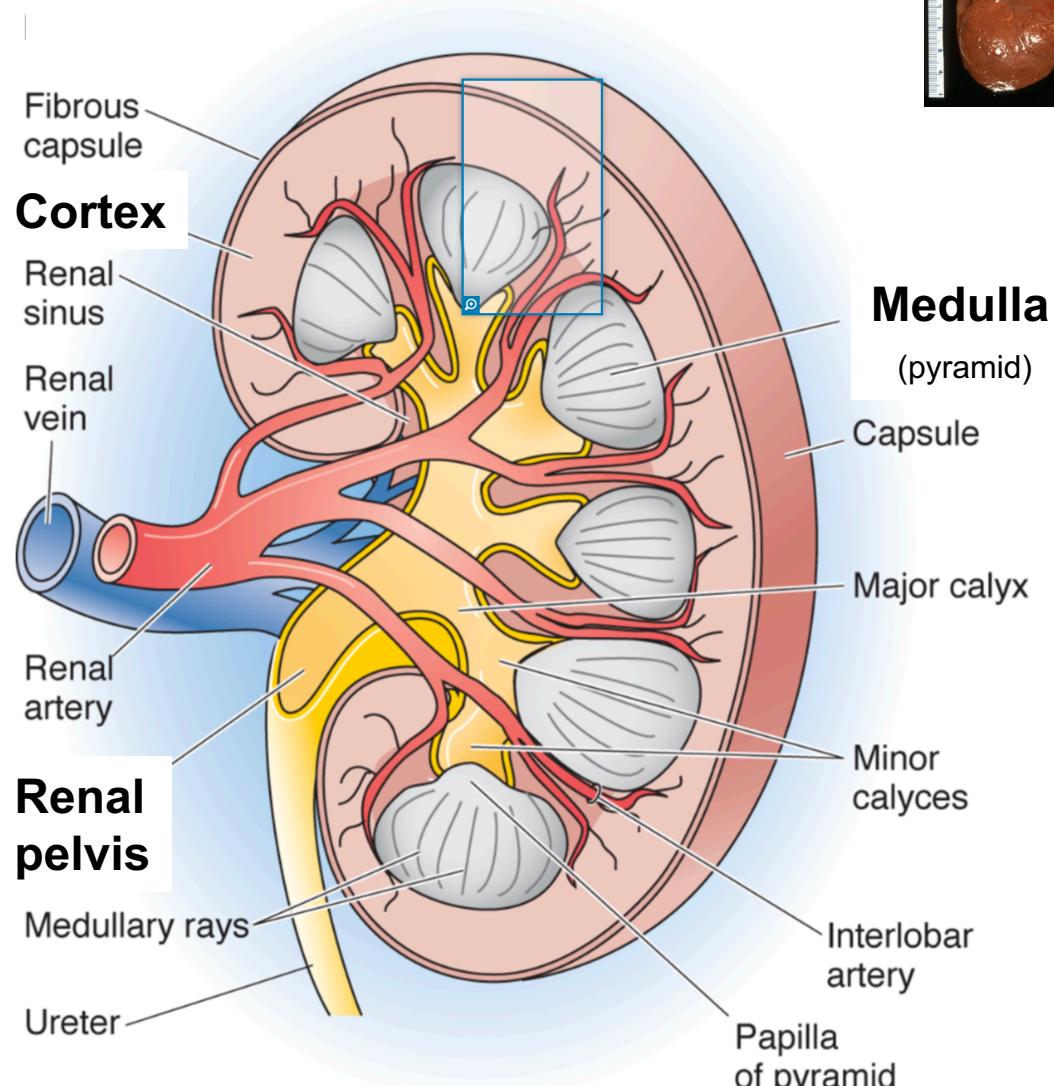
What **oxygen sensitive MRI** can(not) tell us about renal pathophysiology (Prasad, 14:10)

What **diffusion MRI** can(not) tell us about renal pathophysiology (Vallee, 16:50)

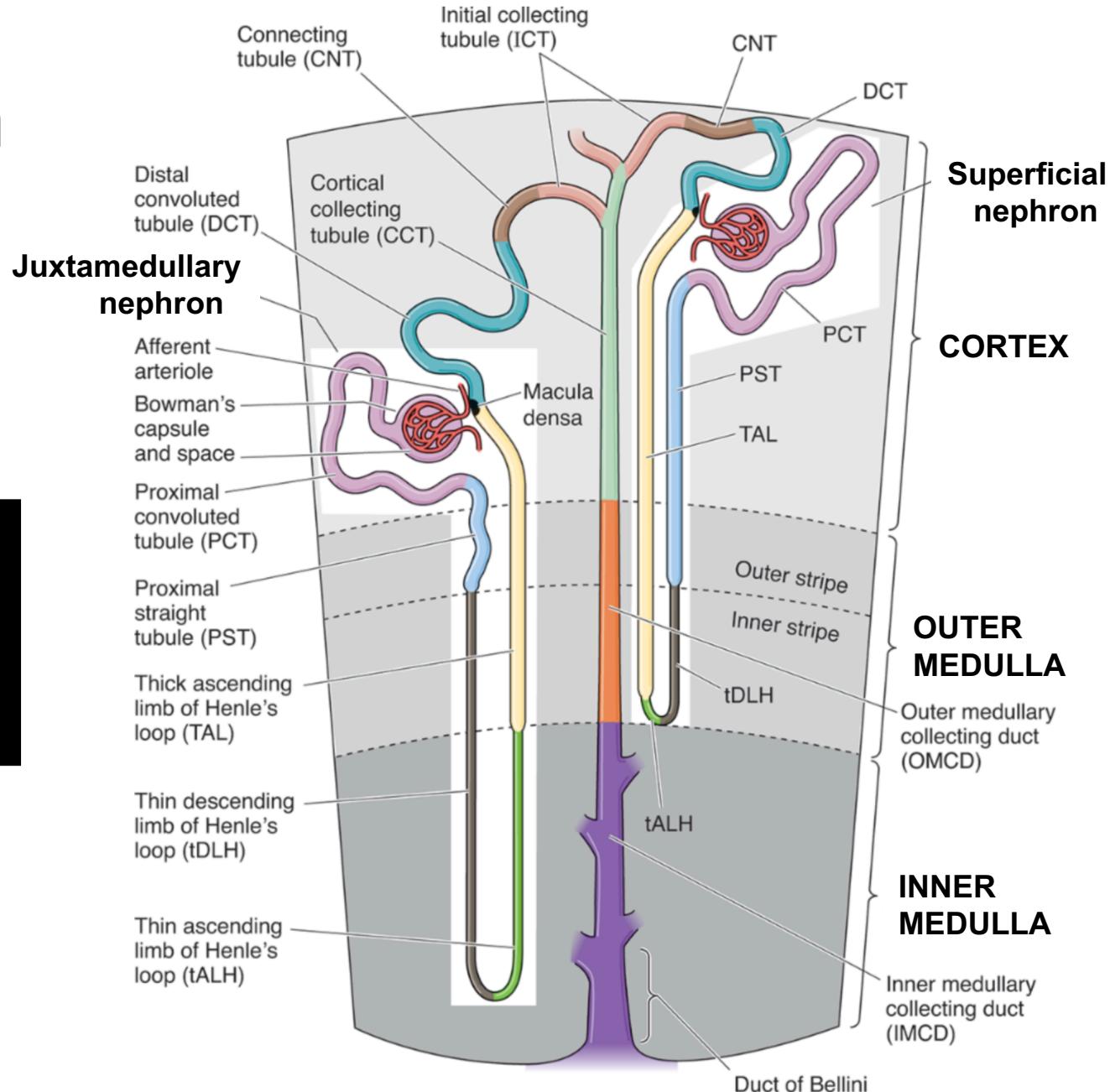
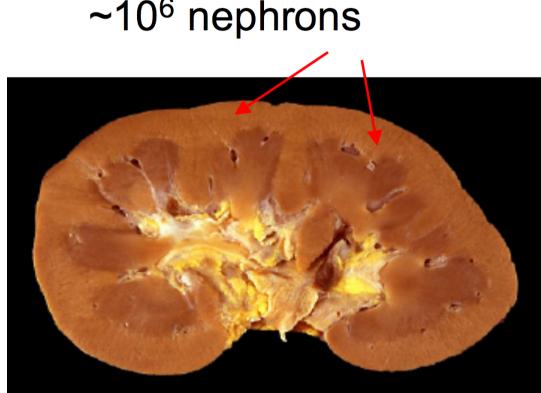
Kidney morphology



- act as filters
- body homeostasis
(fluid status, pH, electrolytes)
- hormone production
- <0.5% of body weight
- ~20% of cardiac output



The nephron

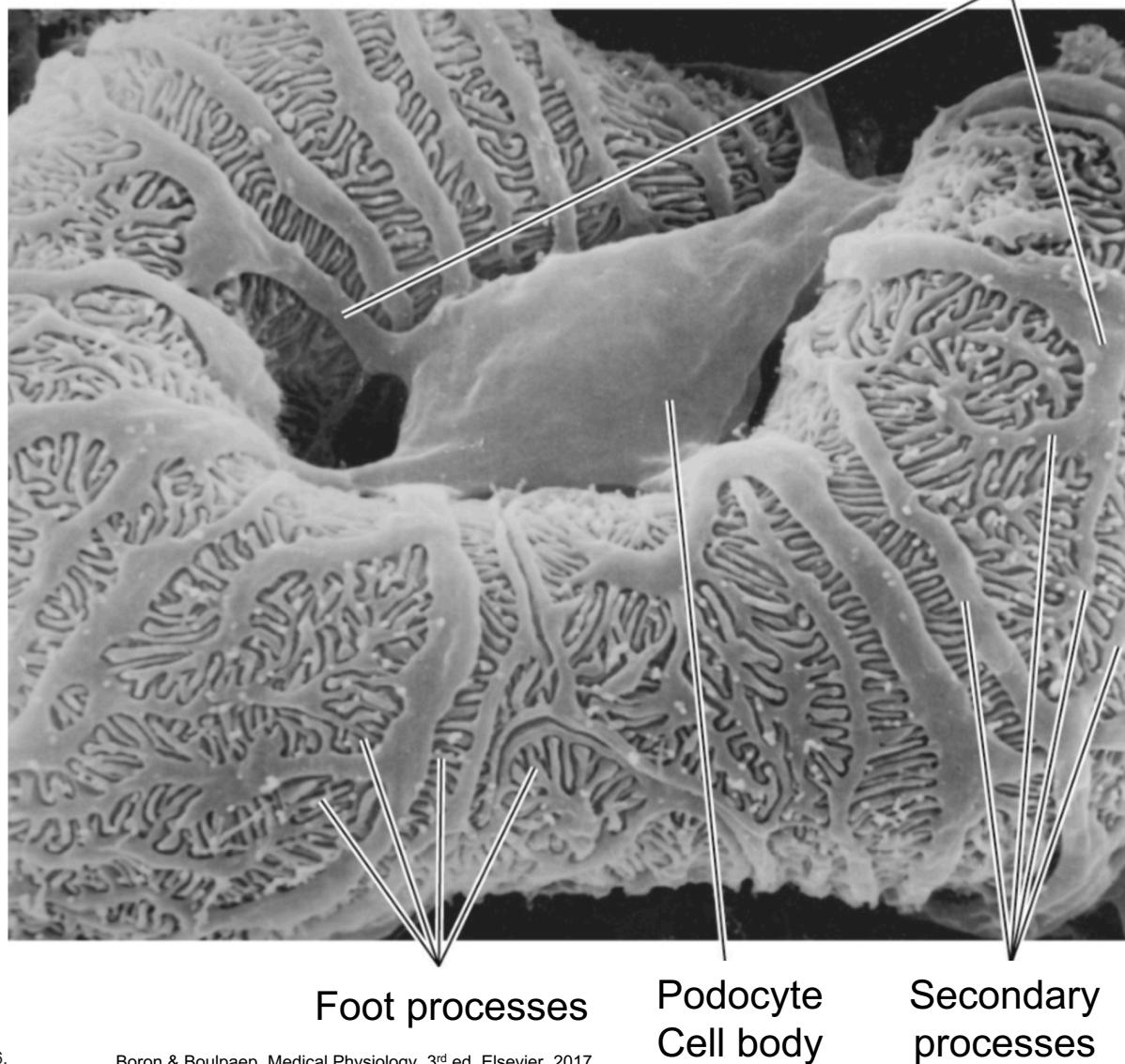
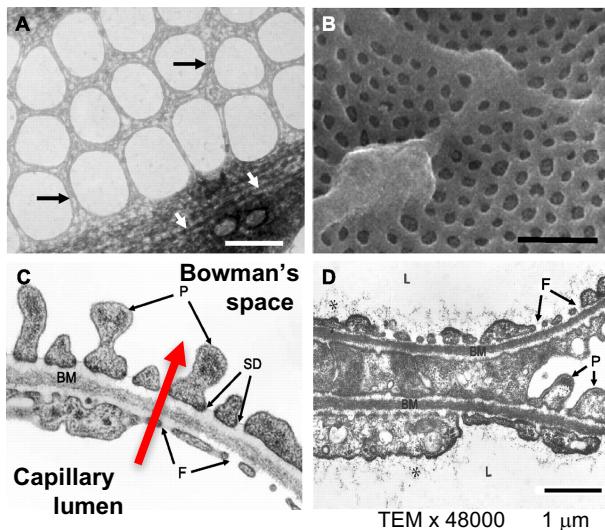


measureable by DCE-MRI

Where the filtration (GFR) takes place

Primary
processes

Glomerular
capillary
covered by the
foot processes
of podocytes →



Pathophysiology

observed condition
during a disease state

operating
mechanism

Diseases of the genitourinary system N00-N99



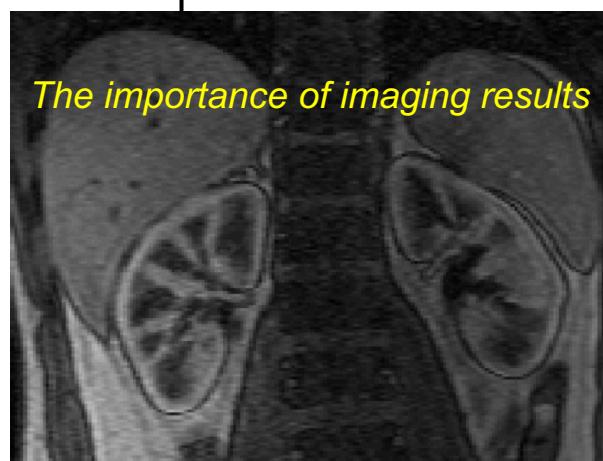
- N00-N08 Glomerular diseases
- N10-N16 Renal tubulo-interstitial diseases
- N17-N19 Acute kidney failure and chronic kidney disease

- N17 Acute kidney failure
- N18 Chronic kidney disease (CKD)
- N19 Unspecified kidney failure

- N00 Acute nephritic syndrome
 - N01 Rapidly progressive nephritic syndrome
 - N02 Recurrent and persistent hematuria
 - N03 Chronic nephritic syndrome
 - N04 Nephrotic syndrome
 - N05 Unspecified nephritic syndrome
 - N06 Isolated proteinuria with specified morphological lesion
 - N07 Hereditary nephropathy, not elsewhere classified
 - N08 Glomerular disorders in diseases classified elsewhere
 - N10 Acute pyelonephritis
 - N11 Chronic tubulo-interstitial nephritis
 - N12 Tubulo-interstitial nephritis, not specified as acute or chronic
 - N13 Obstructive and reflux uropathy
 - N14 Drug- and heavy-metal-induced tubulo-interstitial and tubular conditions
 - N15 Other renal tubulo-interstitial diseases
 - N16 Renal tubulo-interstitial disorders in diseases classified elsewhere
- N17 Acute kidney failure
- N17.0 Acute kidney failure with tubular necrosis
 - N17.1 Acute kidney failure with acute cortical necrosis
 - N17.2 Acute kidney failure with medullary necrosis
 - N17.8 Other acute kidney failure
 - N17.9 Acute kidney failure, unspecified
- N18 Chronic kidney disease (CKD)
- N18.1 Chronic kidney disease, stage 1
 - N18.2 Chronic kidney disease, stage 2 (mild)
 - N18.3 Chronic kidney disease, stage 3 (moderate)
 - N18.4 Chronic kidney disease, stage 4 (severe)
 - N18.5 Chronic kidney disease, stage 5
 - N18.6 End stage renal disease
 - N18.9 Chronic kidney disease, unspecified

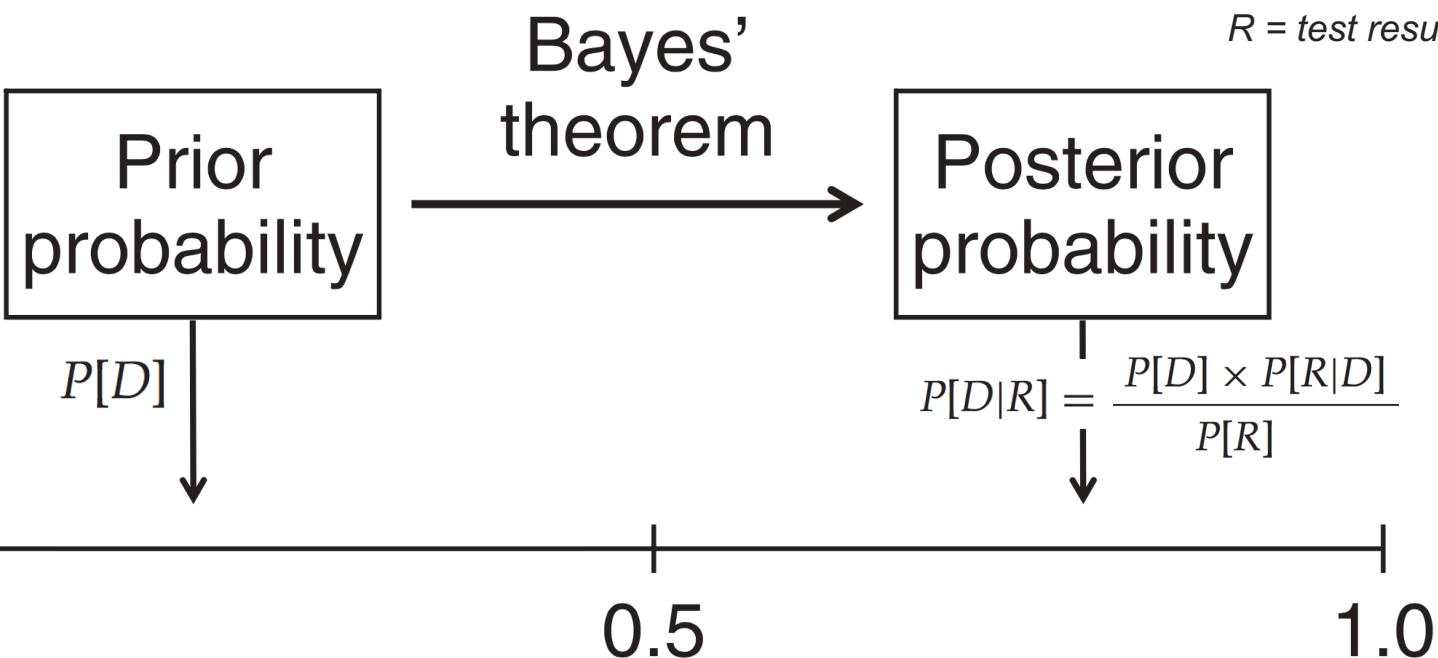


- N00–N08 G
- N10–N16 R
- N17–N19 A



The pre-test probability and the post-test probability of disease

D = disease
R = test result



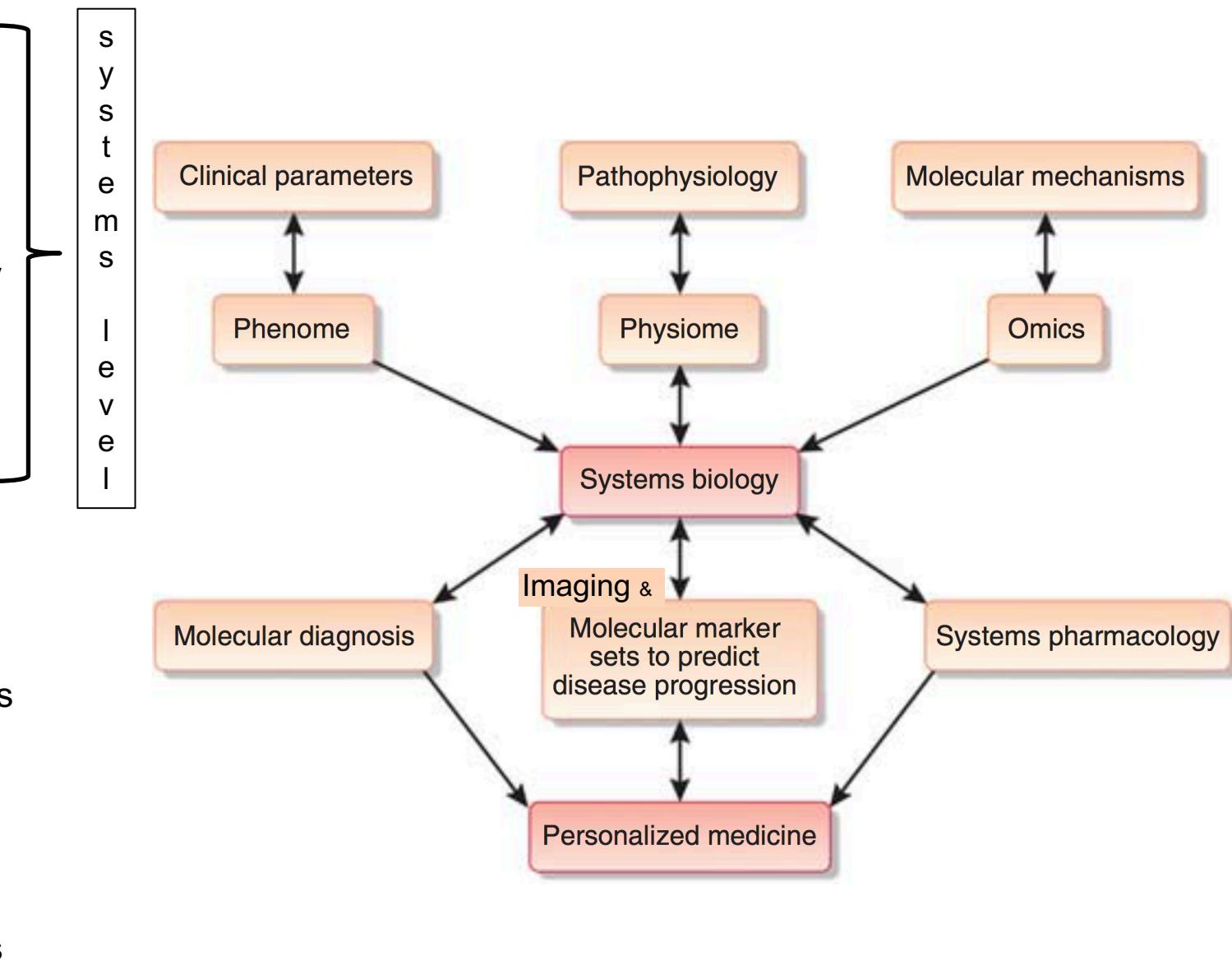
Probability of disease

Sox et al. Medical Decision Making 2nd ed., 2013

- ▶ N18.1 Chronic kidney disease, stage 1
- ▶ N18.2 Chronic kidney disease, stage 2 (mild)
- ▶ N18.3 Chronic kidney disease, stage 3 (moderate)
- ▶ N18.4 Chronic kidney disease, stage 4 (severe)
- ▶ N18.5 Chronic kidney disease, stage 5
- ▶ N18.6 End stage renal disease
- ▶ N18.9 Chronic kidney disease, unspecified

Systems biomedicine of kidney diseases

- Integrate clinical parameters
- Assess disease pathophysiology
- Reveal molecular mechanisms of diseases

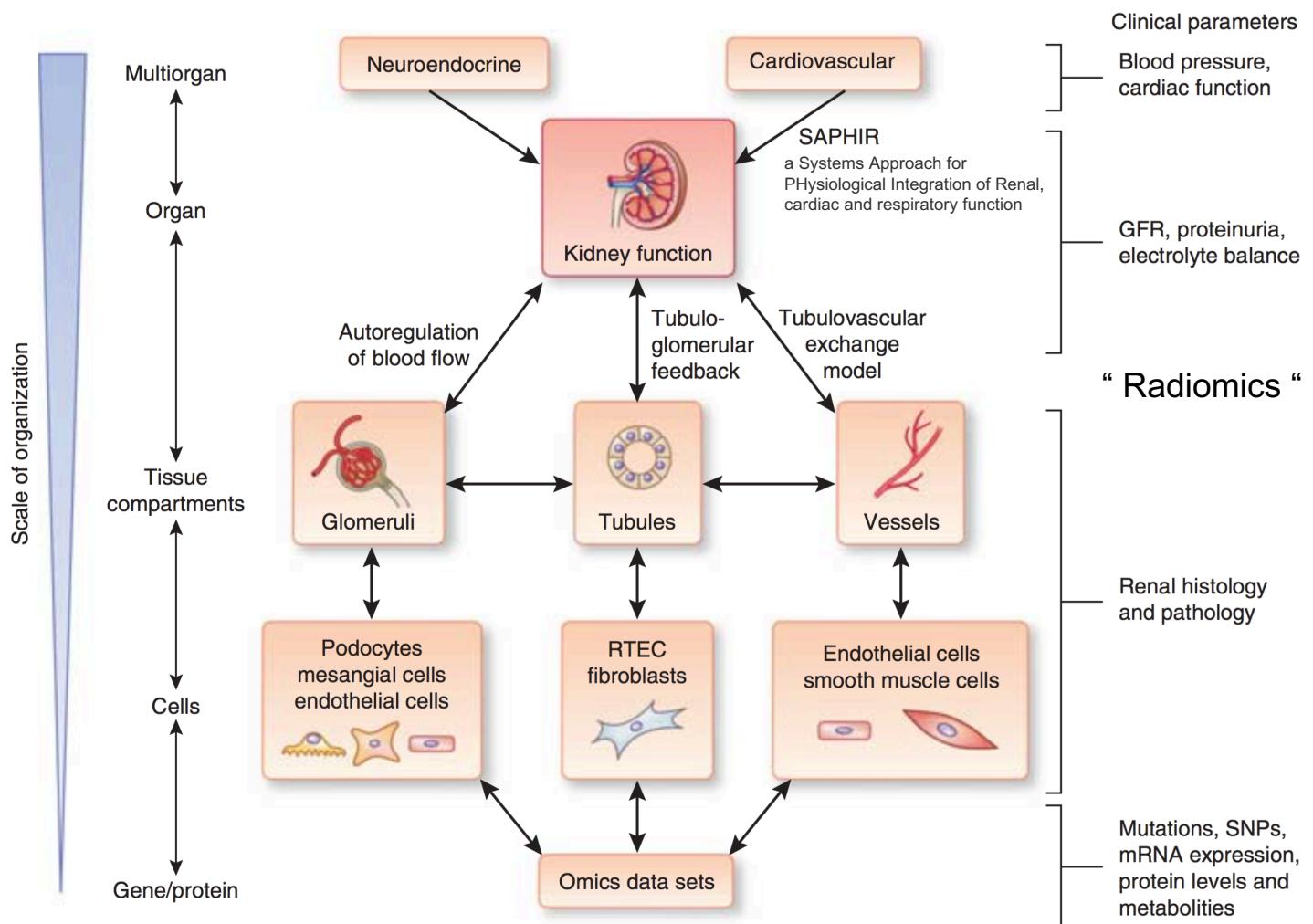


Multiscale analysis of kidney function

Normal kidney function

e.g. maintenance of fluids, electrolytes, and acid–base balance and clearance of toxins

maintained by coordinated regulation at different levels of organization



DCE-MRI
basic principle

“ Mass balance “ of a solute or tracer X

(X is not synthesized, degraded, or accumulated in the kidney)

$P_{X,a}$

plasma concentration of X in renal artery

$P_{X,v}$

plasma concentration of X in renal vein

RPF_a

renal plasma flow in renal artery

RPF_v

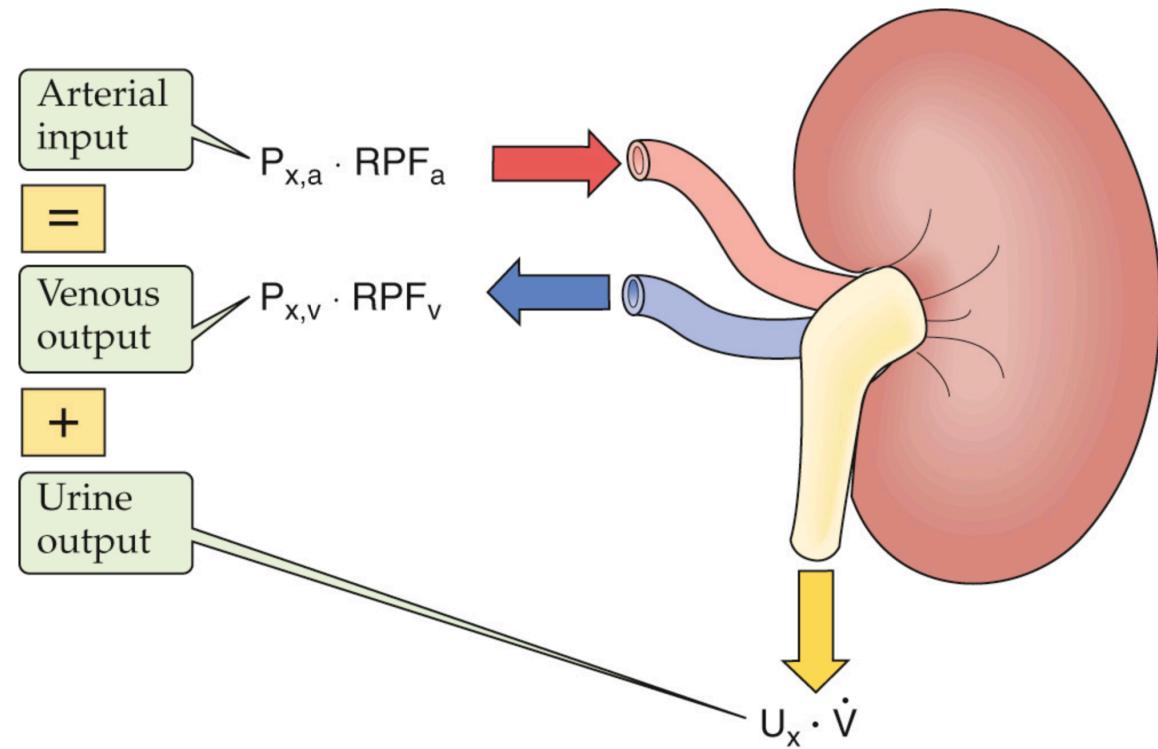
renal plasma flow in renal vein

U_X

concentration of X in urine

\dot{V}

urine flow (volume urine per time unit)



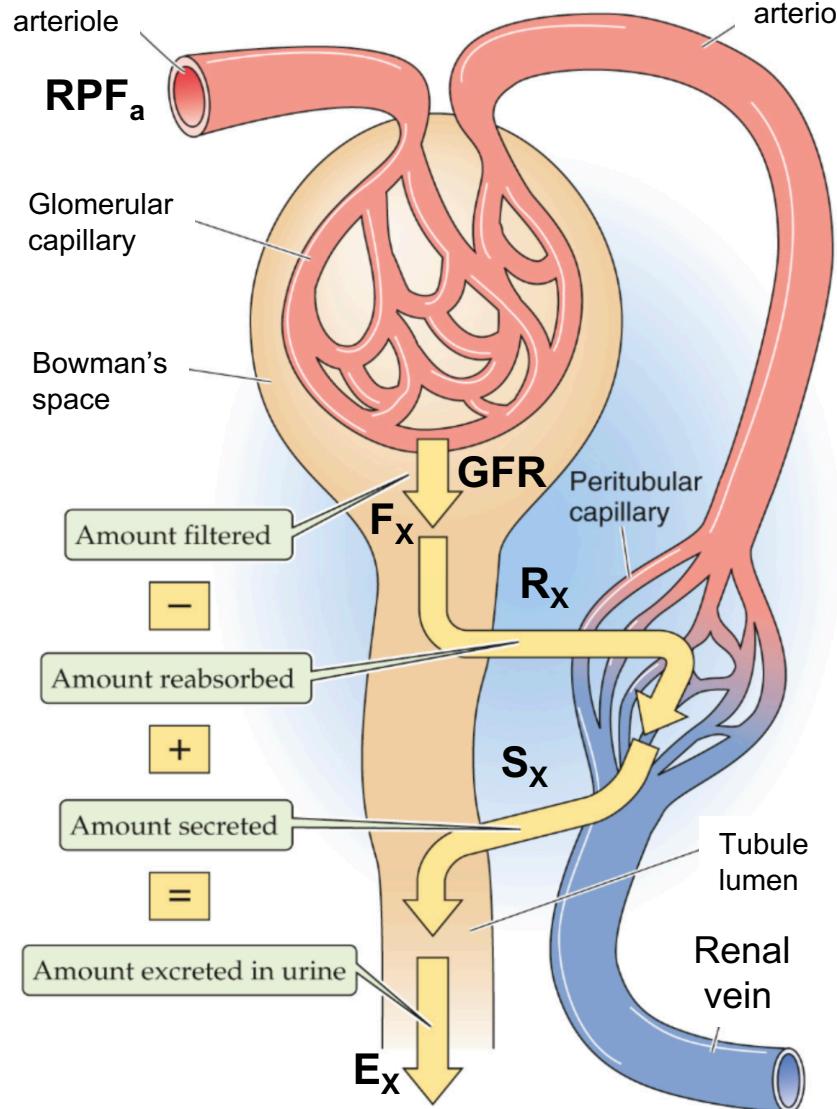
$$\underbrace{P_{X,a} \cdot RPF_a}_{\frac{\text{mmole}}{\text{mL}}} + \underbrace{U_X \cdot \dot{V}}_{\frac{\text{mmole}}{\text{mL}}} = \underbrace{P_{X,v} \cdot RPF_v}_{\frac{\text{mmole}}{\text{mL}}} + \underbrace{U_X \cdot \dot{V}}_{\frac{\text{mmole}}{\text{mL}}}$$

“ Mass balance “

clearance of a substance X

Amount excreted per unit time	Amount filtered per unit time	Amount reabsorbed per unit time	Amount secreted per unit time
\dot{E}_x	\dot{F}_x	\dot{R}_x	\dot{S}_x

$$\dot{E}_x = \dot{F}_x - \dot{R}_x + \dot{S}_x$$



“ Mass balance “

clearance of a substance X

Clearance of X, C_x

$$\underbrace{P_{X,a} \cdot C_x}_{\text{Virtual arterial input}} = \underbrace{0}_{\text{Virtual venous output}} + \underbrace{(U_x \cdot \dot{V})}_{\text{Actual urine output}}$$

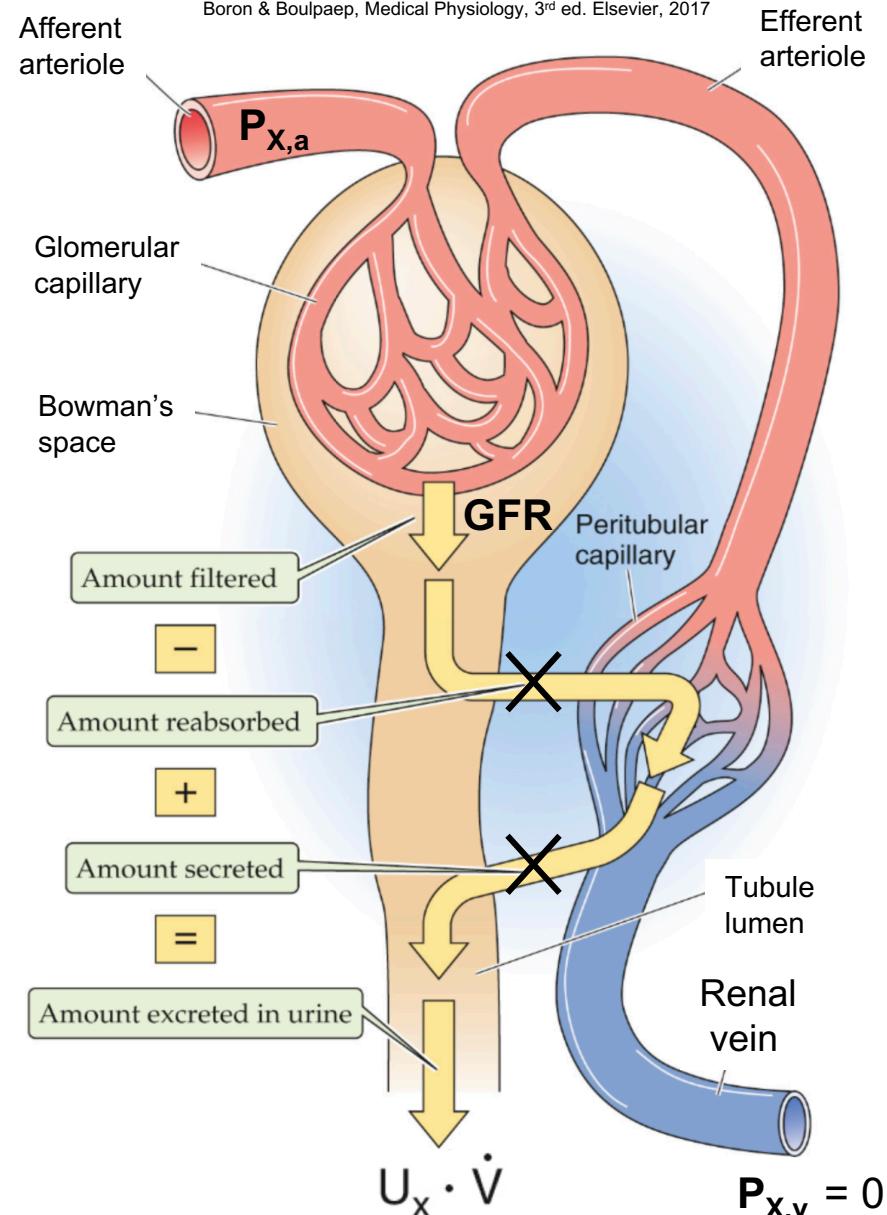
1. Substance must be freely filterable in the glomeruli.
2. Substance must be neither reabsorbed nor secreted by the renal tubules.
3. Substance must not be synthesized, broken down, or accumulated by the kidney.
4. Substance must be physiologically inert (not toxic and without effect on renal function).

Input into
Bowman's space Output into
urine

$$\frac{\overbrace{P_x \cdot GFR}^{\text{mg}}}{\text{mL min}} = \frac{\overbrace{U_x \cdot \dot{V}}^{\text{mg mL}}}{\text{mL min}}$$

$$GFR = \frac{U_x \times \dot{V}}{P_x}$$

$$\frac{\text{mL}}{\text{min}} = \frac{(\text{mg/mL}) \times (\text{mL/min})}{(\text{mg/mL})}$$



$$P_{X,v} = 0$$

“ Mass balance “

clearance of a substance X

$$\text{Amount excreted per unit time} = \text{Amount filtered per unit time} - \text{Amount reabsorbed per unit time} + \text{Amount secreted per unit time}$$

$$\dot{E}_X = \dot{F}_X - \dot{R}_X + \dot{S}_X$$



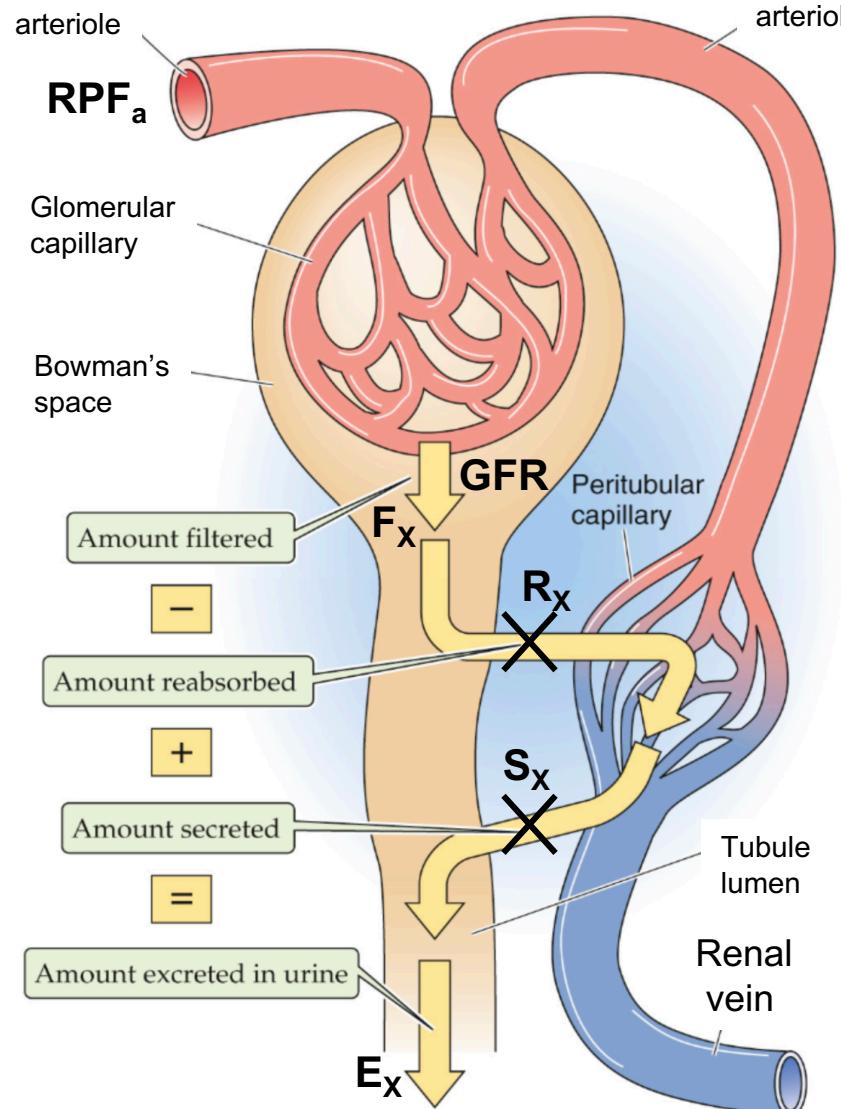
Clearance of X, C_X

$$\text{Virtual arterial input} \quad \text{Virtual venous output} \quad \text{Actual urine output}$$

$$\dot{P}_{X,a} \cdot C_X = 0 + (\dot{U}_X \cdot \dot{V})$$

1. Substance must be freely filterable in the glomeruli.
2. Substance must be neither reabsorbed nor secreted by the renal tubules.
3. Substance must not be synthesized, broken down, or accumulated by the kidney.
4. Substance must be physiologically inert (not toxic and without effect on renal function).

GFR



Input into
Bowman's space Output into
urine

$$\frac{\dot{P}_X \cdot \dot{GFR}}{\frac{\text{mg}}{\text{mL}} \cdot \frac{\text{mL}}{\text{min}}} = \frac{\dot{U}_X \cdot \dot{V}}{\frac{\text{mg}}{\text{mL}} \cdot \frac{\text{mL}}{\text{min}}}$$

$$\text{GFR} = \frac{\dot{U}_X \times \dot{V}}{\dot{P}_X}$$

$$\frac{\text{mL}}{\text{min}} = \frac{(\text{mg/mL}) \times (\text{mL/min})}{(\text{mg/mL})}$$

$$C_{\text{inulin}} = GFR \sim 125 \text{ mL/min}$$

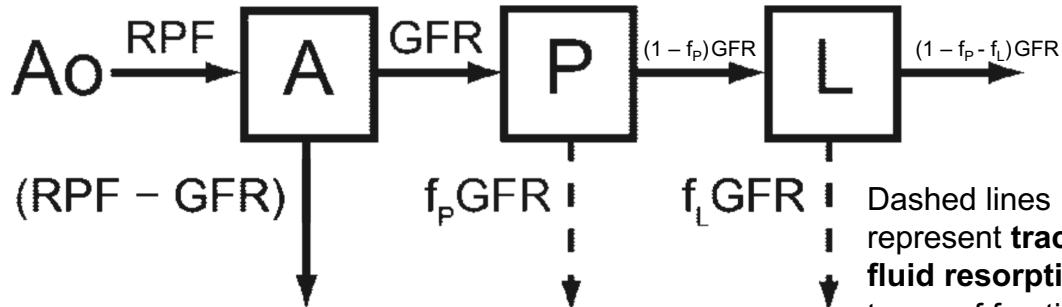
$$C_{\text{PAH}} = RPF_a \sim 600 \text{ mL/min}$$

$$C_{\text{glucose}} = 0$$

$$\text{Filtration fraction, FF} = GFR / RPF \sim 0.2$$

Three-compartment modeling of renal perfusion and filtration

Simplified three-compartment model for determination of single-kidney GFR:



Conservation of mass (simplified model):

X = tracer substance (e.g. Gd)

$$V_A = V_{A,Cx} + V_{A,Med} \quad [\text{mL}]$$

V_P - volume of P [mL]

V_L - volume of L [mL]

$Ao(t)$ - aorta (AIF) [mM X/ mL whole blood]

$A(t)$ - intrarenal arteries and glomerular vessels
[mM X / mL plasma]

$P(t)$ - proximal convoluted tubule [mM X / mL tubular fluid]

$L(t)$ - loop of Henle [mM X / mL tubular fluid]

RPF = Renal plasma flow [mL/min]

GFR = Glomerular filtration rate [mL/min]

Hct = hematocrit, $(1 - Hct)$ = plasma fraction

$$\frac{dA}{dt} = \frac{RPF}{V_{A,Cx} + V_{A,Med}} \left[\frac{Ao}{(1 - Hct)} - A \right]$$

$$\frac{dP}{dt} = \frac{GFR}{V_P} [A - (1 - f_P)P]$$

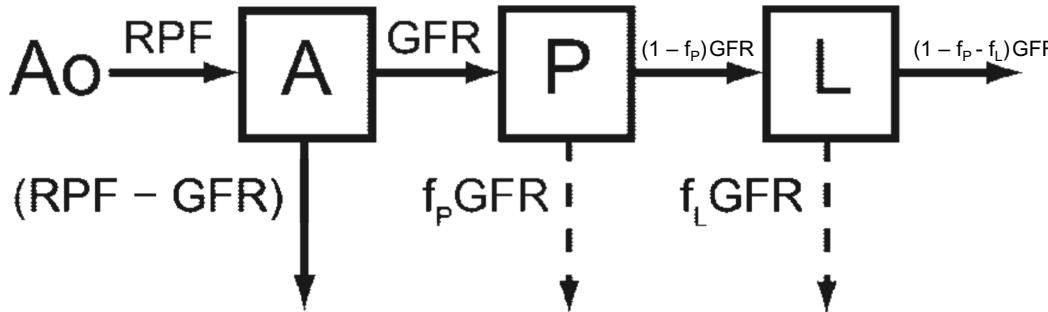
$$\frac{dL}{dt} = \frac{GFR}{V_L} [(1 - f_P)P - (1 - f_P - f_L)L]$$

System of 3 coupled ordinary differential equations, ODEs

Lee VS et al. Renal function measurements from MR renography and a simplified multicompartmental model. Am J Physiol Renal Physiol 2007;292:F1548–F1559.

Three-compartment modeling of renal perfusion and filtration

Simplified three-compartment model for determination of single-kidney GFR:



Conservation of mass

MR measurements:

The AIF, $Ao(t)$ from **MR renography (DCE-MRI)**

$$Cx(t) = \frac{V_{A,Cx}}{V_{Cx}} A(t) + \frac{V_P}{V_{Cx}} P(t) \quad \text{from MR renography}$$

$$Med(t) = \frac{V_{A,Med}}{V_{Med}} A(t) + \frac{V_L}{V_{Med}} L(t) \quad \text{MR renography}$$

The volumes V_{Cx} and V_{Med} from **segmented 3D MRI**

Parameters estimated:

(with some simplifying assumptions)

RPF

GFR

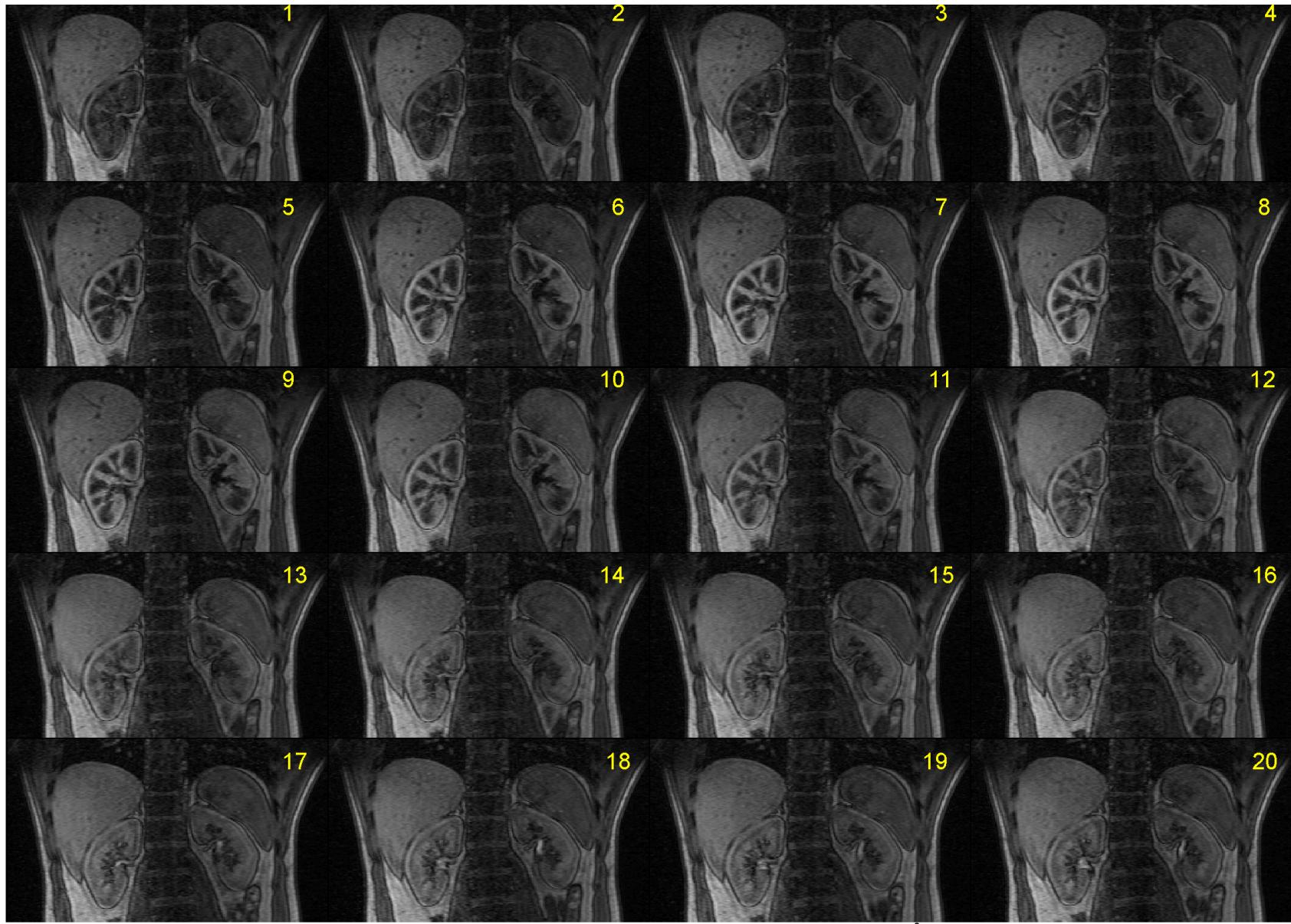
f_p

f_L

$V_{A,Cx}$

$V_{A,Med}$

DCE-MRI of the moving kidney

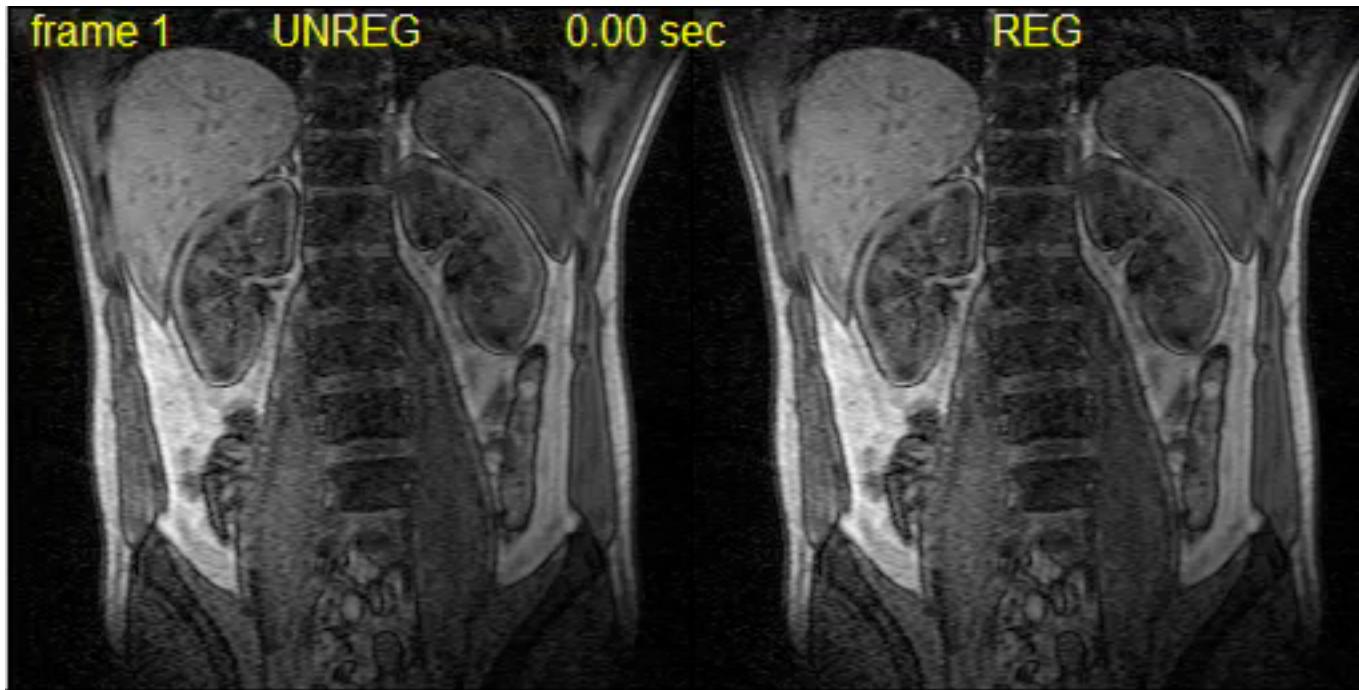


bergen_capio_20050419_kidney_volume_timeseries.mat 20 slices, 20 time frames, voxel-size: 1.48 x 1.48 x 3 mm³

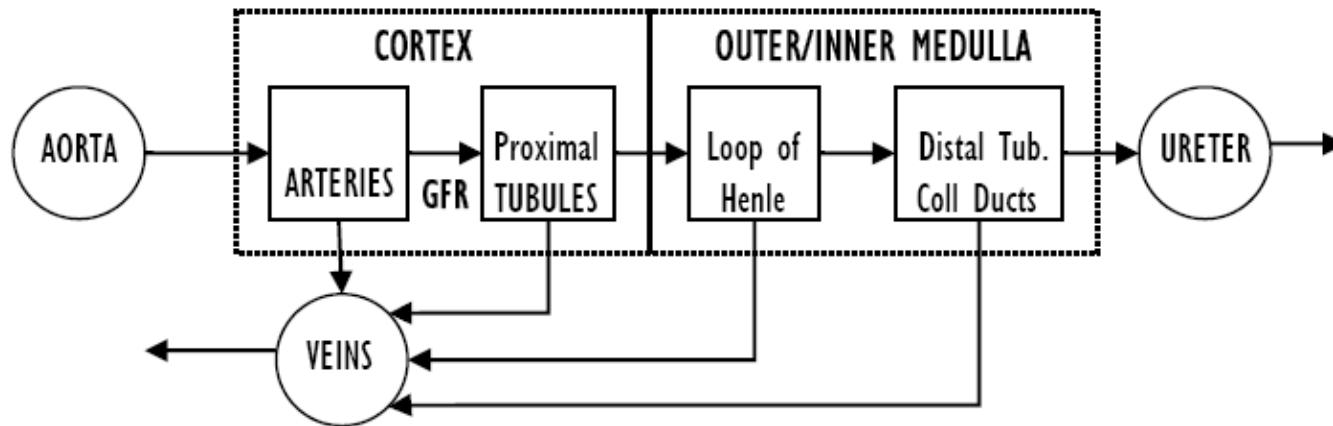
with Prof. Jarle Rørvik et al.

Pharmacokinetic modeling of perfusion and filtration using DCE-MRI

The
moving
kidney



R. Sance et al., ISPA 2006

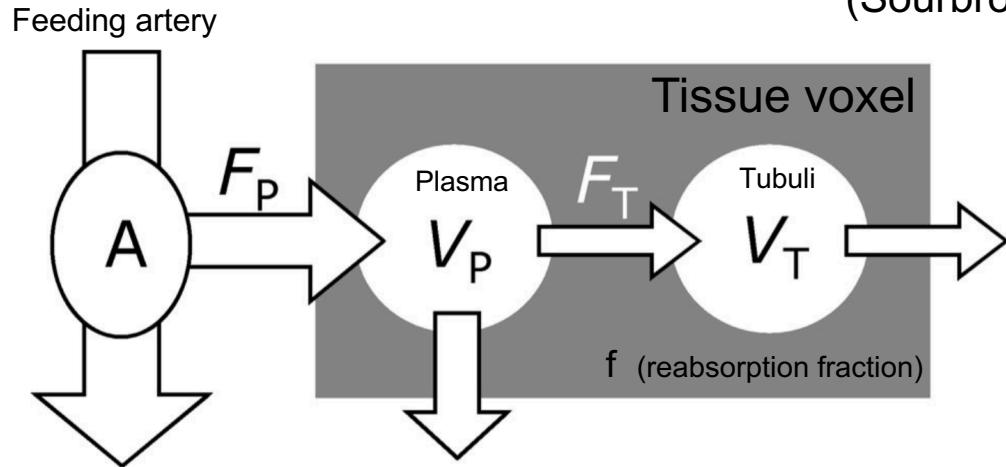


Lee VS et al. Renal function measurements from MR renography and a simplified multicompartmental model. Am J Physiol Renal Physiol 2007;292:F1548–F1559.

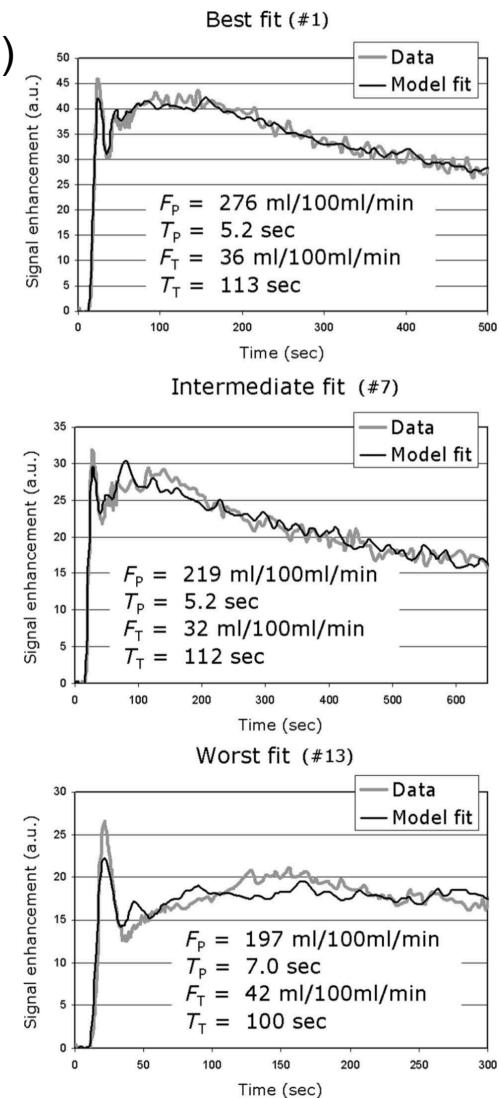
The
motion-
corrected
kidney

MRI-measurement of perfusion and glomerular filtration in the human kidney with a separable compartment model

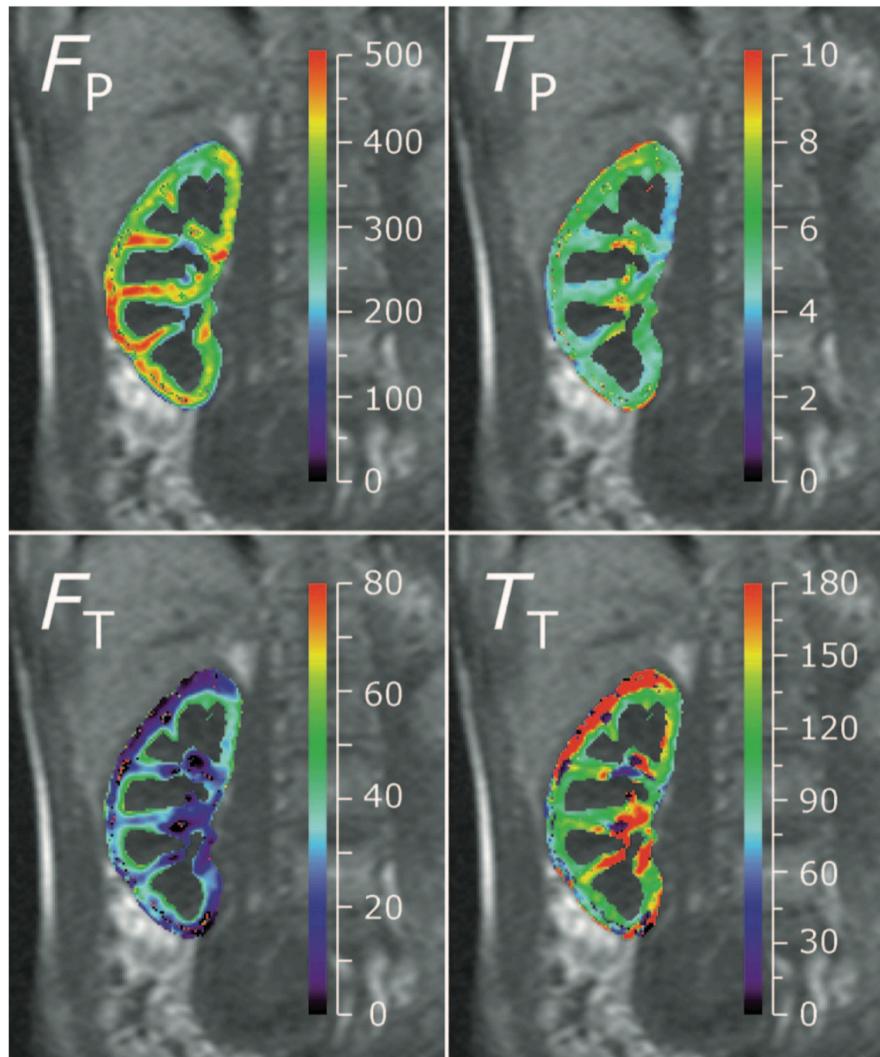
(Sourbron et al., 2008)



- (i) The plasma flow F_P carries the contrast agent from an arterial region (A) into the tissue (gray rectangle)
- (ii) It first enters the tissue plasma, where it distributes over the plasma volume V_P
- (iii) A fraction of the entering contrast agent is filtered out of the vascular space and is carried by the tubular flow F_T into the tubular system where it distributes over the tubular volume V_T . In the tubuli a fraction f of the filtrate is reabsorbed.
- (iv) The contrast agent leaves the tissue carried by the outflow out of the vascular and tubular spaces.



MRI-measurement of perfusion and glomerular filtration in the human kidney with a separable compartment model



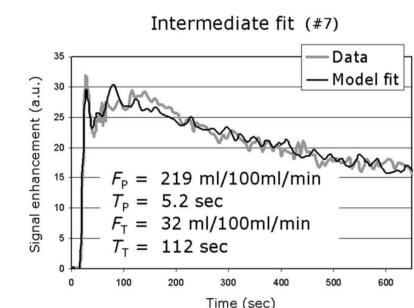
The four independent model parameters

$$F_P \text{ (mL/100 mL/Min)}$$

$$T_P = \text{MTT}_P \text{ (sec)}$$

$$F_T \text{ (mL/100 mL/Min)}$$

$$T_T = \text{MTT}_T \text{ (sec)}$$

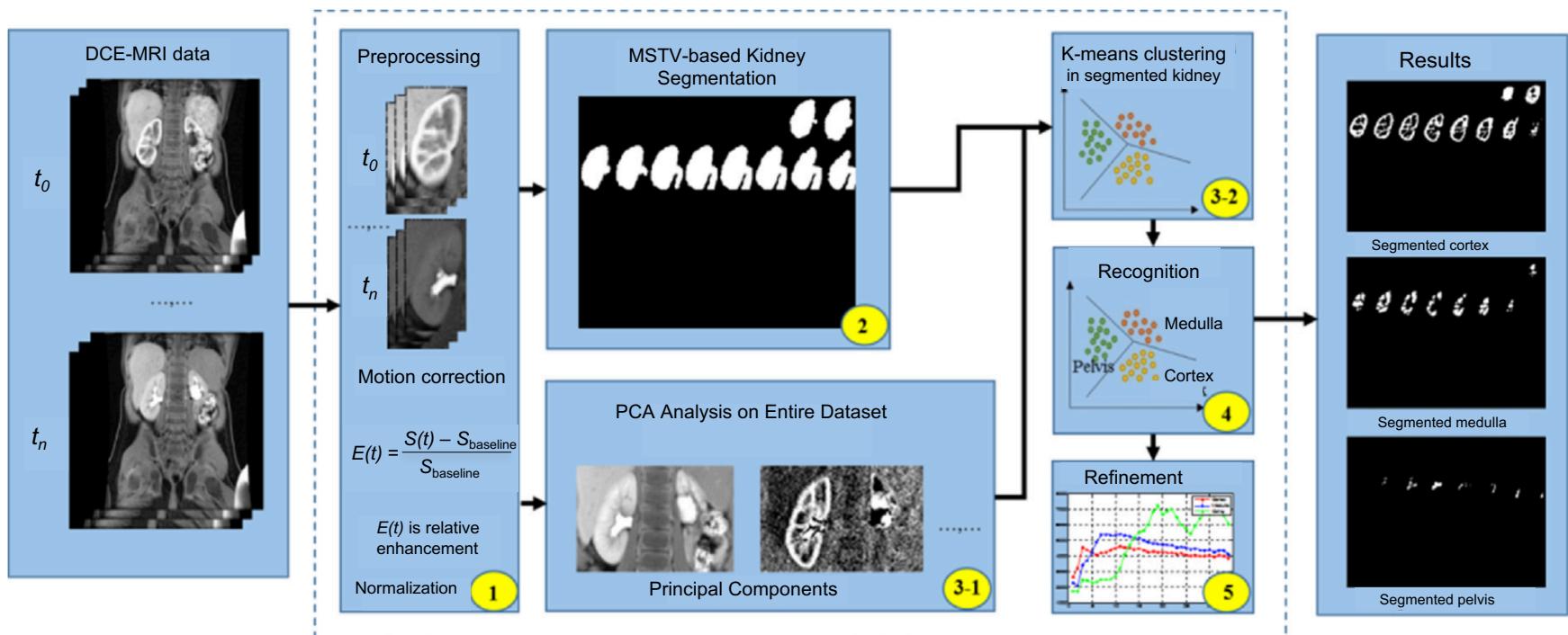
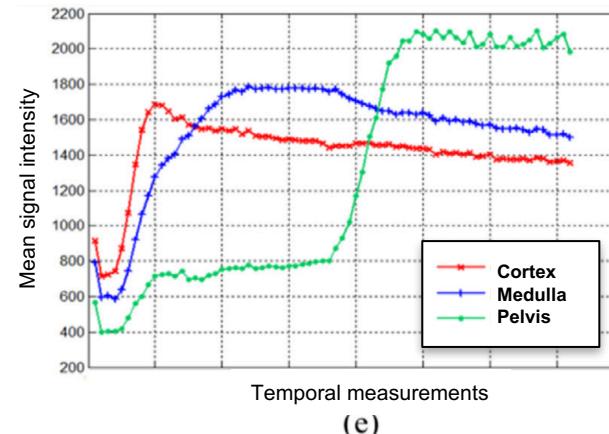
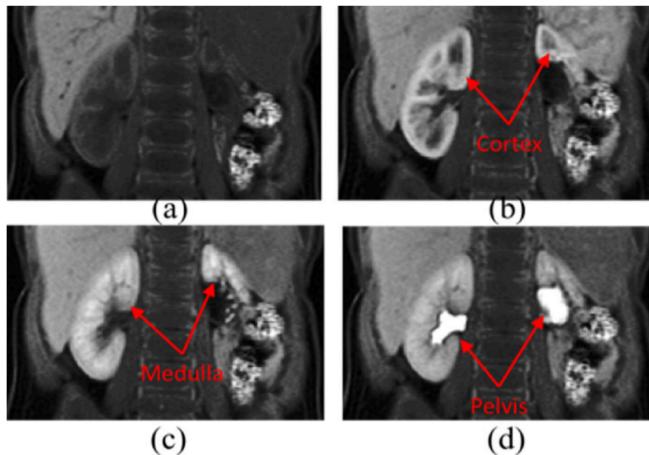


for the data with the intermediate fit accuracy

The cortex region was defined retrospectively as those pixels with $V_P > 20 \text{ mL/100 mL}$.

The parametric maps (colored) are superposed on a precontrast image (gray) for anatomic reference.

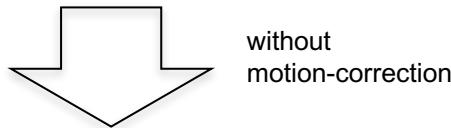
Renal compartment segmentation from DCE-MRI



MSTV = Maximally Stable Temporal Volume

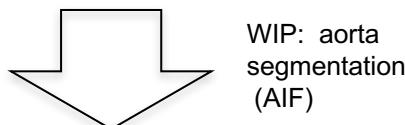
Yang X et al. Renal compartment segmentation in DCE-MRI images. Medical Image Analysis 2016;32:269-280.

Fast semi-supervised segmentation of the kidneys in DCE-MRI using convolutional neural networks (CNN) and transfer learning



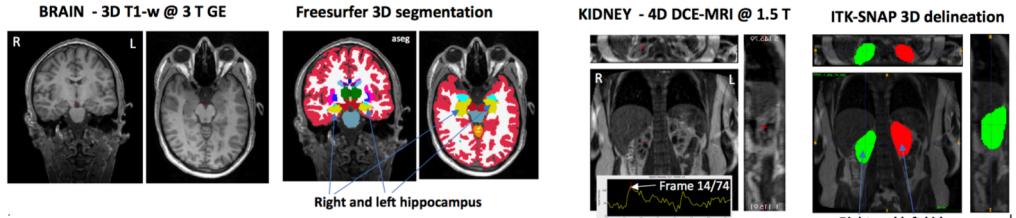
Left & right kidney volumes

Mean SI time courses

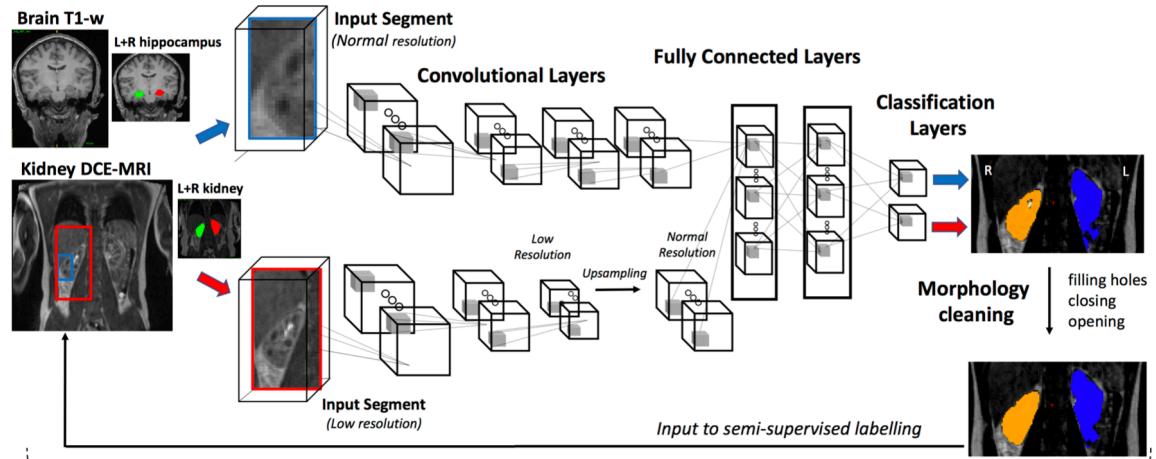


~ GFR, ~ RPF

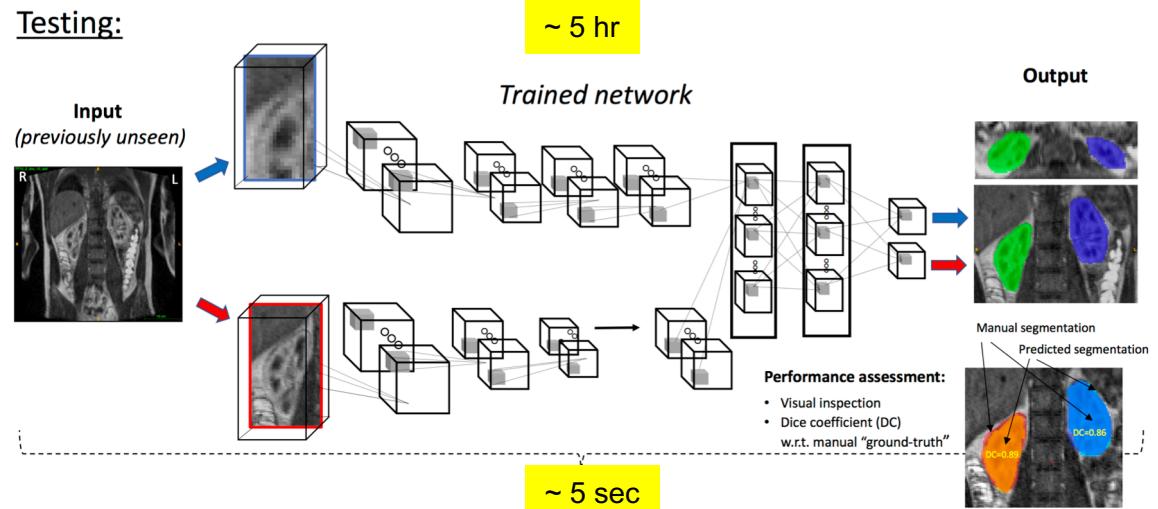
Labelling:



Training:



Testing:

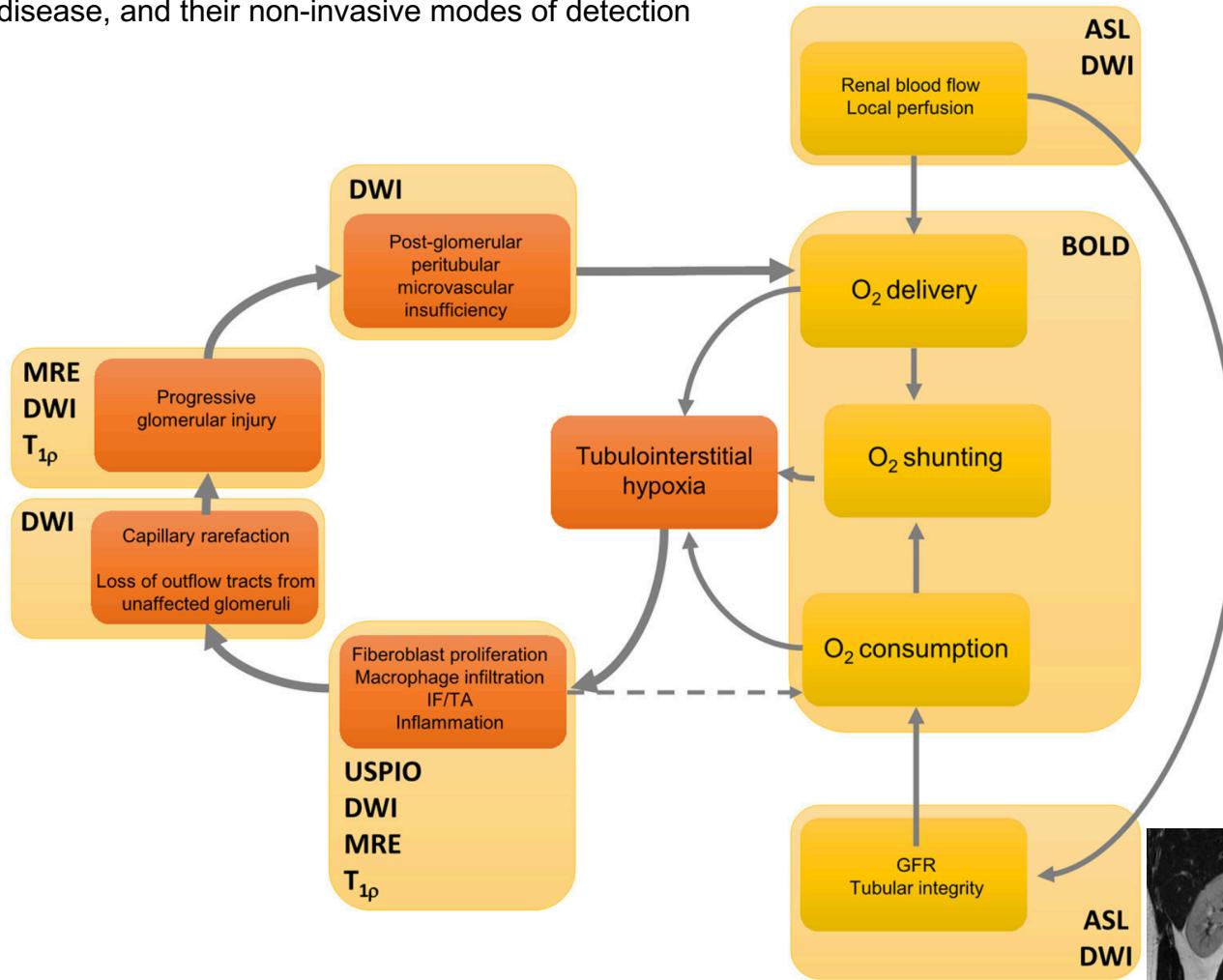


What DCE-MRI can **not** tell us

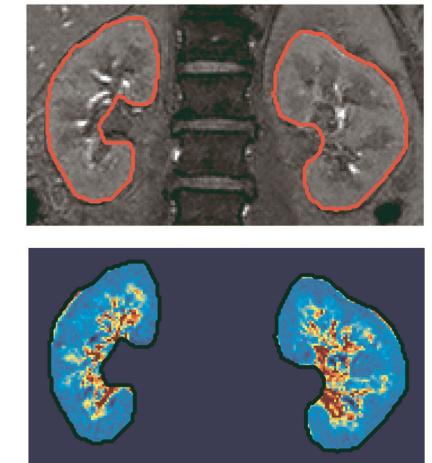
(Patho)physiological process	Imaging technique
➤ Oxygenation	Blood oxygen level dependent (<u>BOLD</u>) imaging
➤ Water diffusion and tubular flow	Diffusion weighted imaging (<u>DWI</u>)/Diffusion tensor imaging (<u>DTI</u>)
(Arterial) blood supply	Arterial spin labeling (ASL)
➤ Scarring	T_1 in the rotating frame ($T_{1\rho}$)
	Magnetic resonance elastography (<u>MRE</u>)
	Diffusion weighted imaging (DWI)/Diffusion tensor imaging (DTI)
➤ Inflammation	Ultrasmall superparamagnetic particles of iron oxide (USPIO) enhanced imaging
➤ Vascular reactivity	Hemodynamic response imaging (HRI)
➤ Maintenance of corticomedullary sodium gradient	<u>^{23}Na-MRI</u>

What DCE-MRI can not tell us

A feedforward loop in the hypothesized processes of the development of fibrosis in chronic kidney disease, and their non-invasive modes of detection

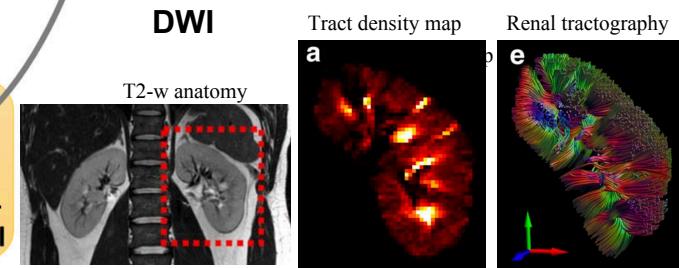


BOLD



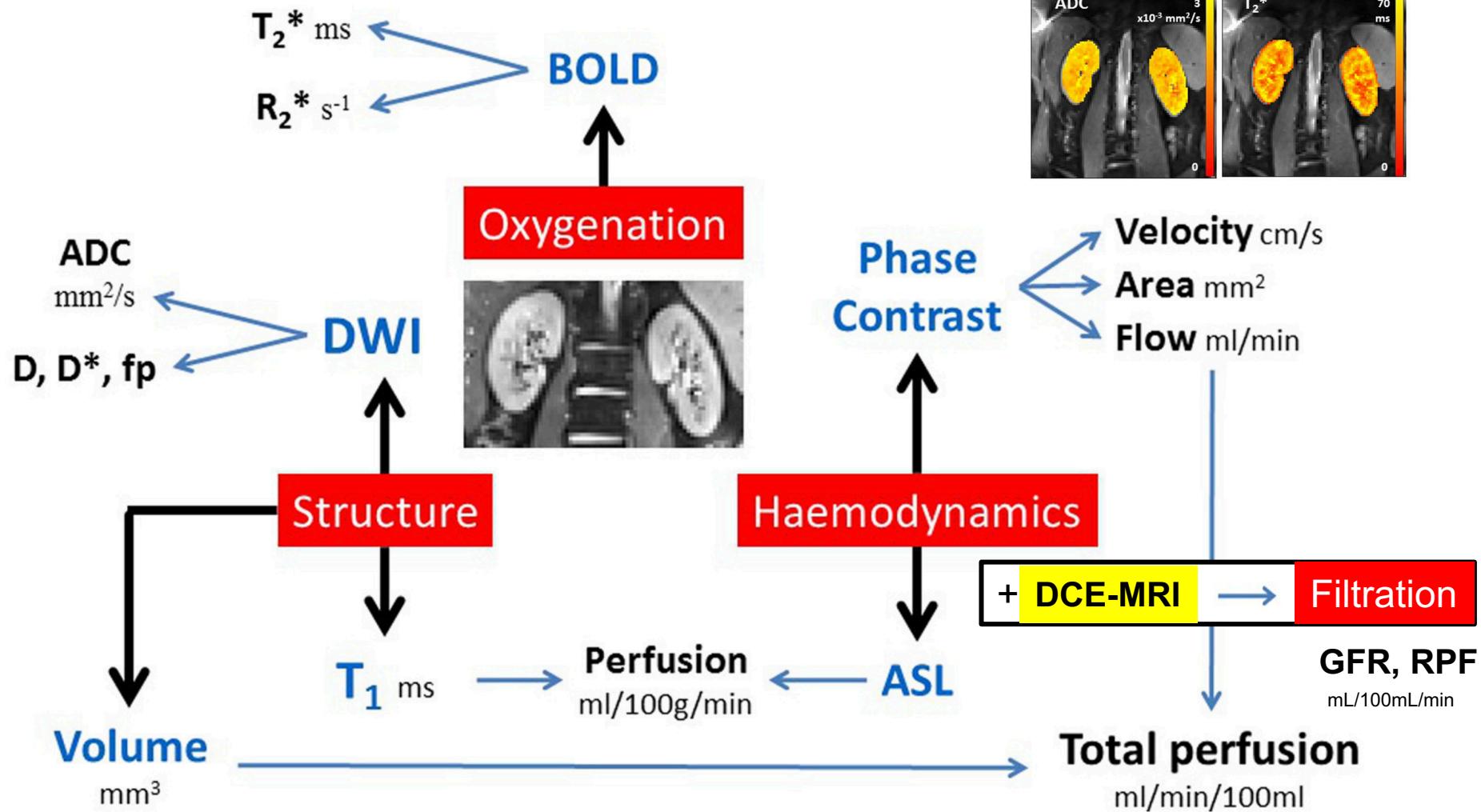
R₂* map. The scale denotes R₂* values in s⁻¹
a low R₂* indicates higher oxygenation

DWI



van Baalen et al. JMRI 2017

Multiparametric renal MRI !



DCE-MRI: numerical analysis software

Interactive Data Language (IDL)

<http://www.harrisgeospatial.com/ProductsandSolutions/GeospatialProducts/IDL.aspx>

Sourbron S, Biffar A, Ingrisch M, Fierens Y, Luypaert R.

PMI: platform for research in medical imaging.

Magn Reson Mater Phys. 2009 Oct 1;22(1):539.

PMI

<https://github.com/plaresmedima/PMI-0.4>

<https://sites.google.com/site/plaresmedima>

OsiriX (C/C++) on MacOS

www.osirix-viewer.com

Zöllner FG, Daab M, Sourbron SP, Schad LR, Schoenberg SO, Weisser G.

An open source software for analysis of dynamic contrast enhanced magnetic resonance images: UMMPerfusion revisited.

BMC Med Imaging. 2016;16:7. doi:10.1186/s12880-016-0109-0.

UMMPerfusion

<http://ikrsrv1.medma.uni-heidelberg.de/redmine/projects/ummperfusion>

MATLAB

www.mathworks.com

Schmid VJ, Whitcher B, Padhani AR, Yang GZ.

Quantitative analysis of dynamic contrast-enhanced MR images based on Bayesian P-splines.

IEEE Trans Med Imaging. 2009;28(6):789-798. doi:10.1109/TMI.2008.2007326

<https://github.com/petmri/ROCKETSHIP>

ROCKETSHIP

DCE-MRI: numerical analysis software

The R language
www.r-project.org

Schmid VJ, Whitcher B, Padhani AR, Taylor NJ, Yang GZ.

Bayesian methods for pharmacokinetic models in dynamic contrast-enhanced magnetic resonance imaging.
IEEE Transactions on Medical Imaging 2006;25(2):1627-1636.

dcemriS4

<http://dcemri.sourceforge.net> <https://cran.r-project.org/web/packages/dcemriS4>

The R language
www.r-project.org

Ferl GZ.
DATforDCEMRI: An R Package for Deconvolution Analysis and Visualization of DCE-MRI Data
Journal of Statistical Software 2011;44(3):1-18.

DATforDCEMRI

<https://cran.r-project.org/web/packages/DATforDCEMRI>

The Julia language
<http://julialang.org>

Smith DS, Li X, Arlinghaus LR, Yankeelov TE, Welch EB.
DCEMRI.jl: a fast, validated, open source toolkit for dynamic contrast enhanced MRI analysis.
PeerJ. 2015;3:e909. doi:10.7717/peerj.909

DCEMRI.jl

<https://github.com/davidssmith/DCEMRI.jl> <https://www.ncbi.nlm.nih.gov/pubmed/25922795>

Python module : <https://github.com/welcheb/pydcmri>

The Python language
www.python.org

Thanks !