

33rd Annual Scientific Meeting of the European Society for Magnetic Resonance in Medicine and Biology, Vienna/AT - Teaching Session, Sept 29th 2016 08:00-09

Measurement of Renal Perfusion and Filtration

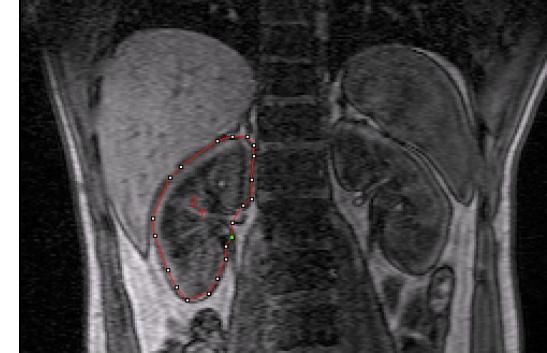
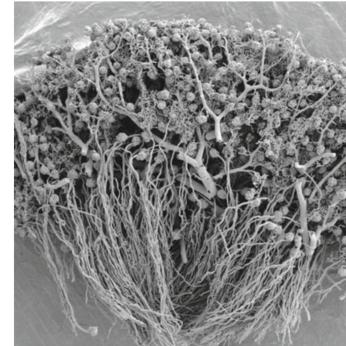
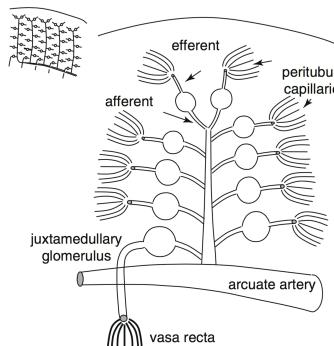
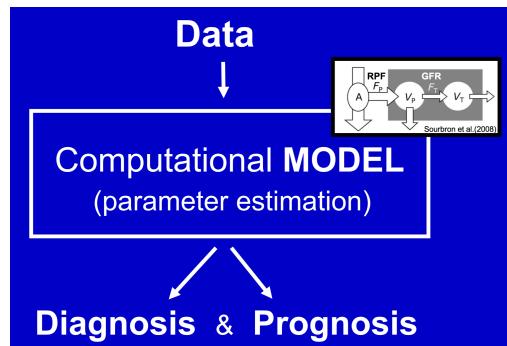
www.esmrmb.org

Syllabus: <https://github.com/arvidl/functional-kidney-imaging> E-poster: esmrmb2016.0010002

Prof. Arvid Lundervold BSc, MD, PhD

Neuroinformatics and Image Analysis Laboratory, Department of Biomedicine
Department of Radiology, Haukeland University Hospital

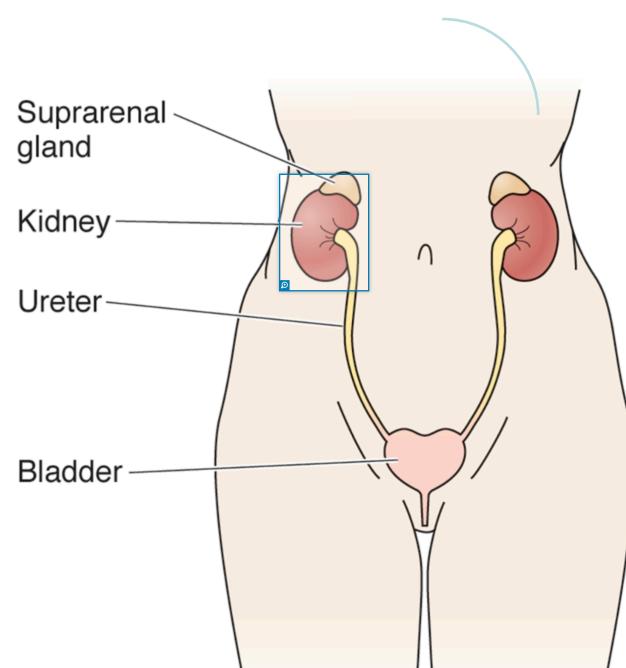
University of Bergen
Norway



Measurement of renal perfusion and filtration

- Kidney **structure and function** – physiological parameters **RPF** and **GFR**
- **Multiscale analysis – systems medicine – radiomics**
- “**Mass balance**” and **compartment models**
- **DCE-MRI** for measuring perfusion and filtration
- **Tracer kinetics and parameter estimation** (down to single voxels)
- **Motion correction and kidney segmentation**
- **Software for DCE-MRI and estimation of renal perfusion and filtration**
 (“open science” & “reproducible research”)

The kidney



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

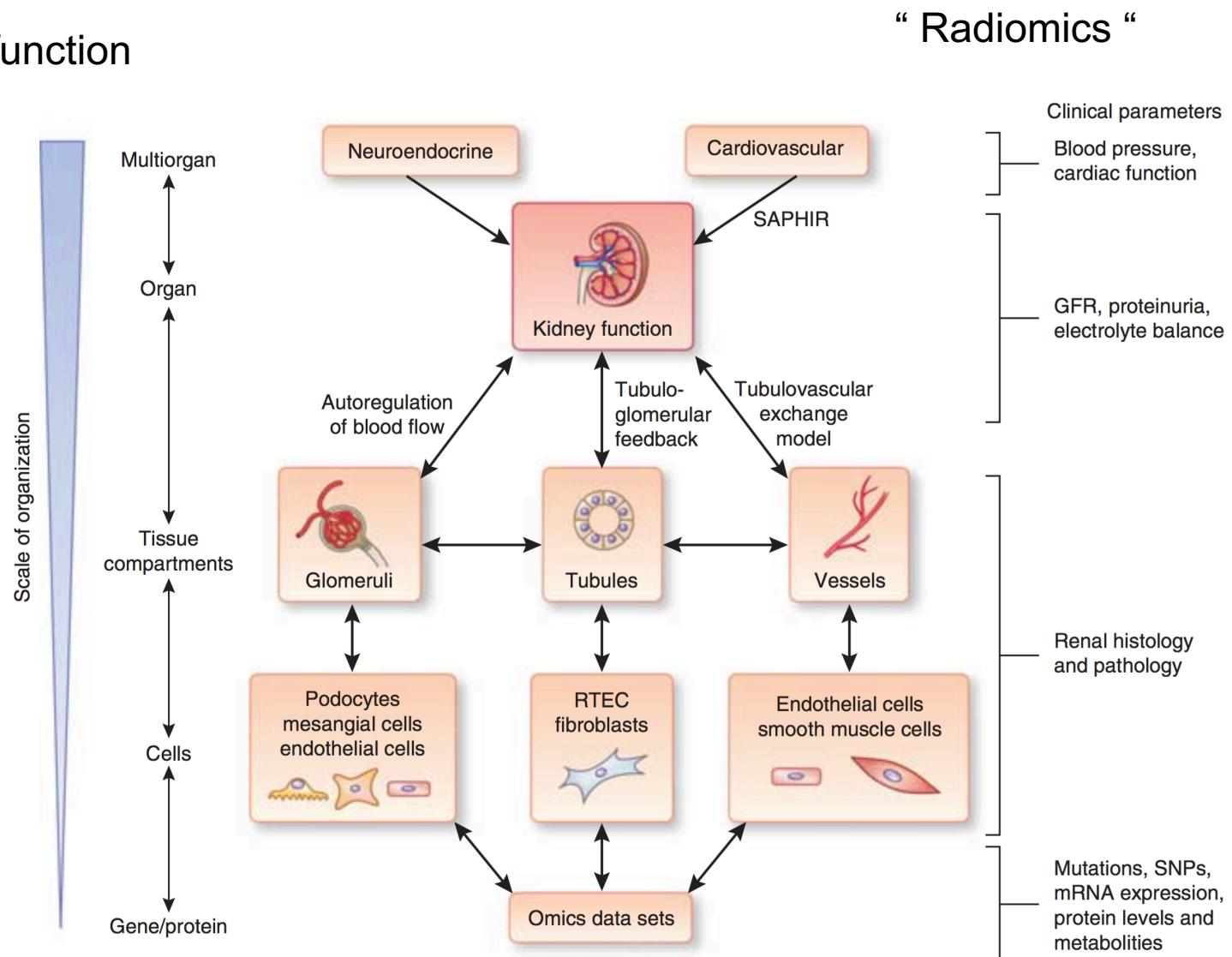
Boron & Boulpaep, Medical Physiology, 3rd ed. Elsevier, 2017

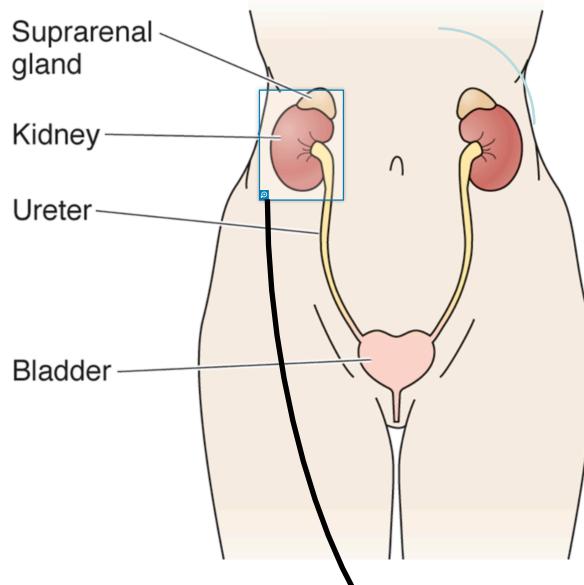
Multiscale analysis of kidney function

- Normal kidney function

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

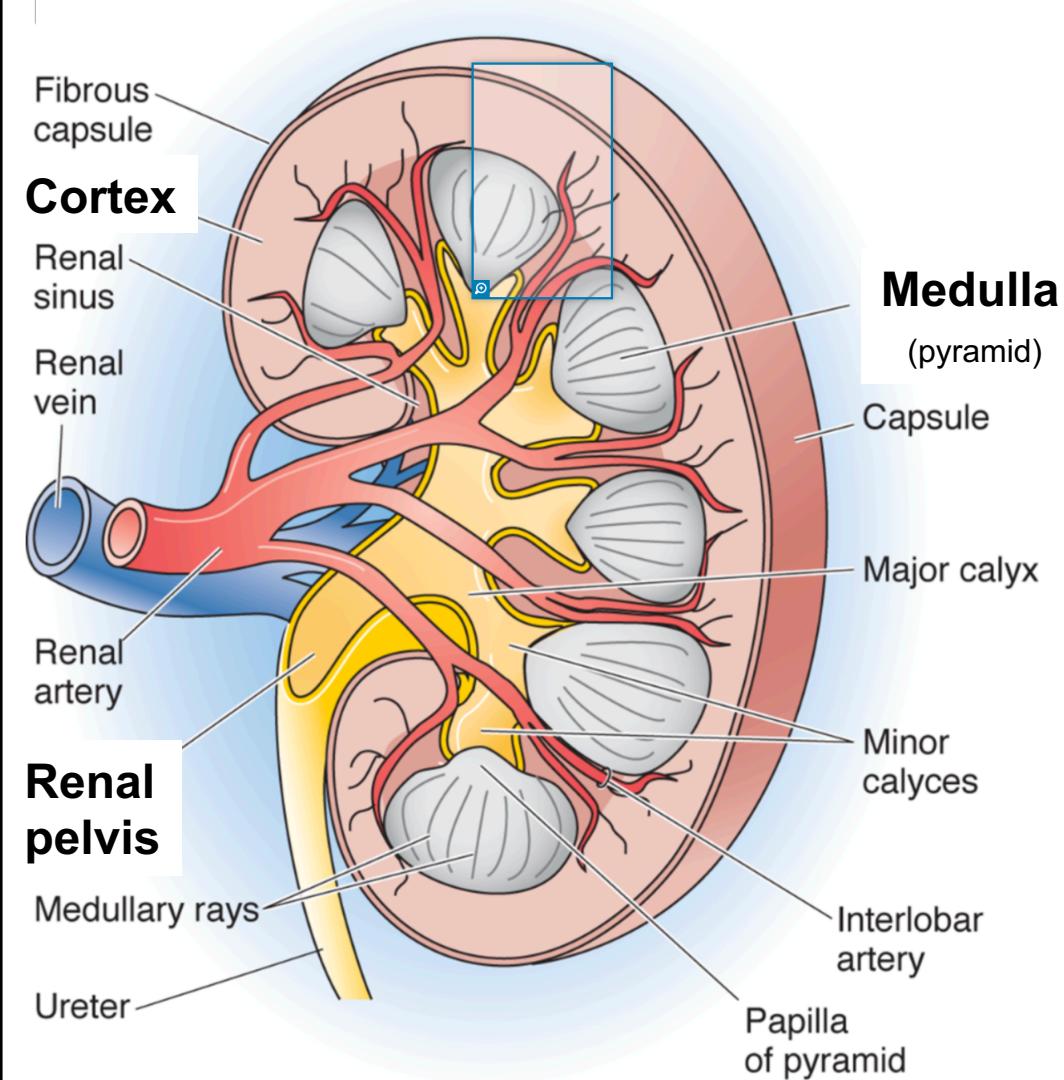
maintained by coordinated regulation at different levels of organization



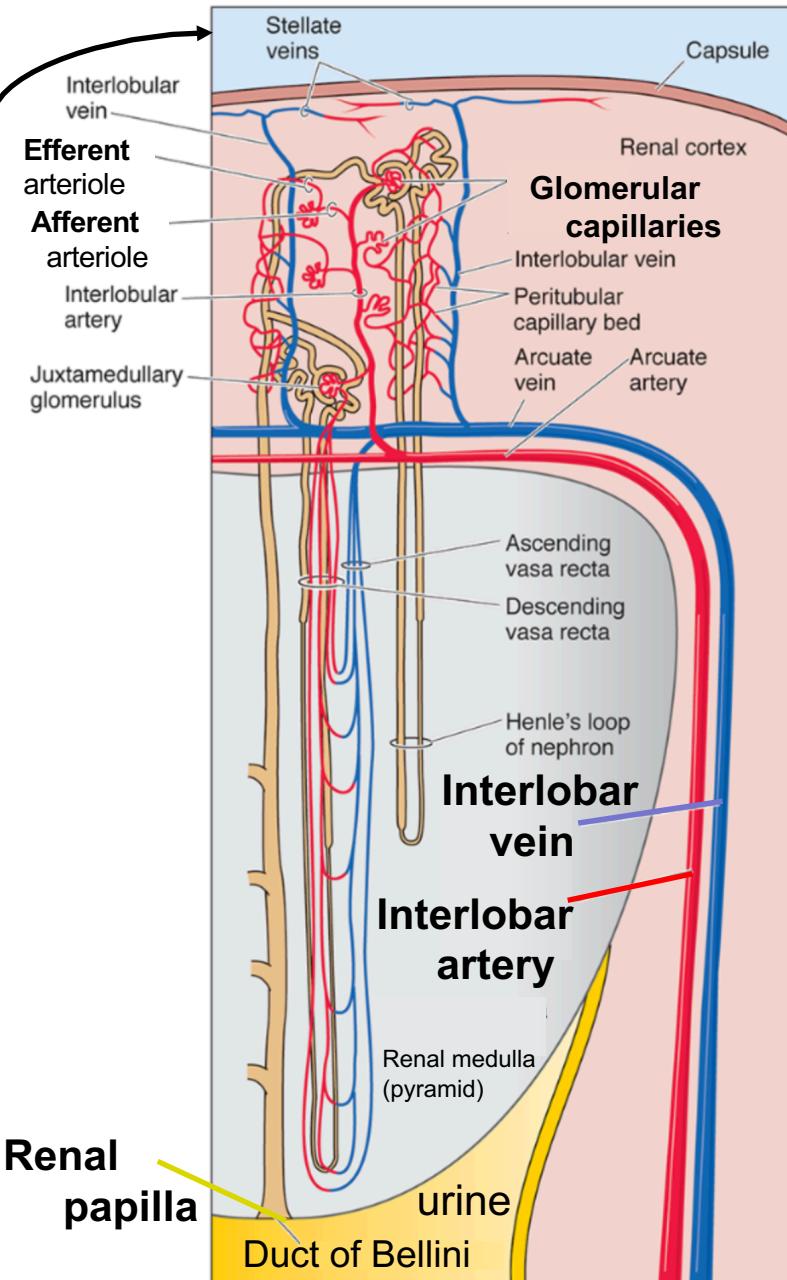
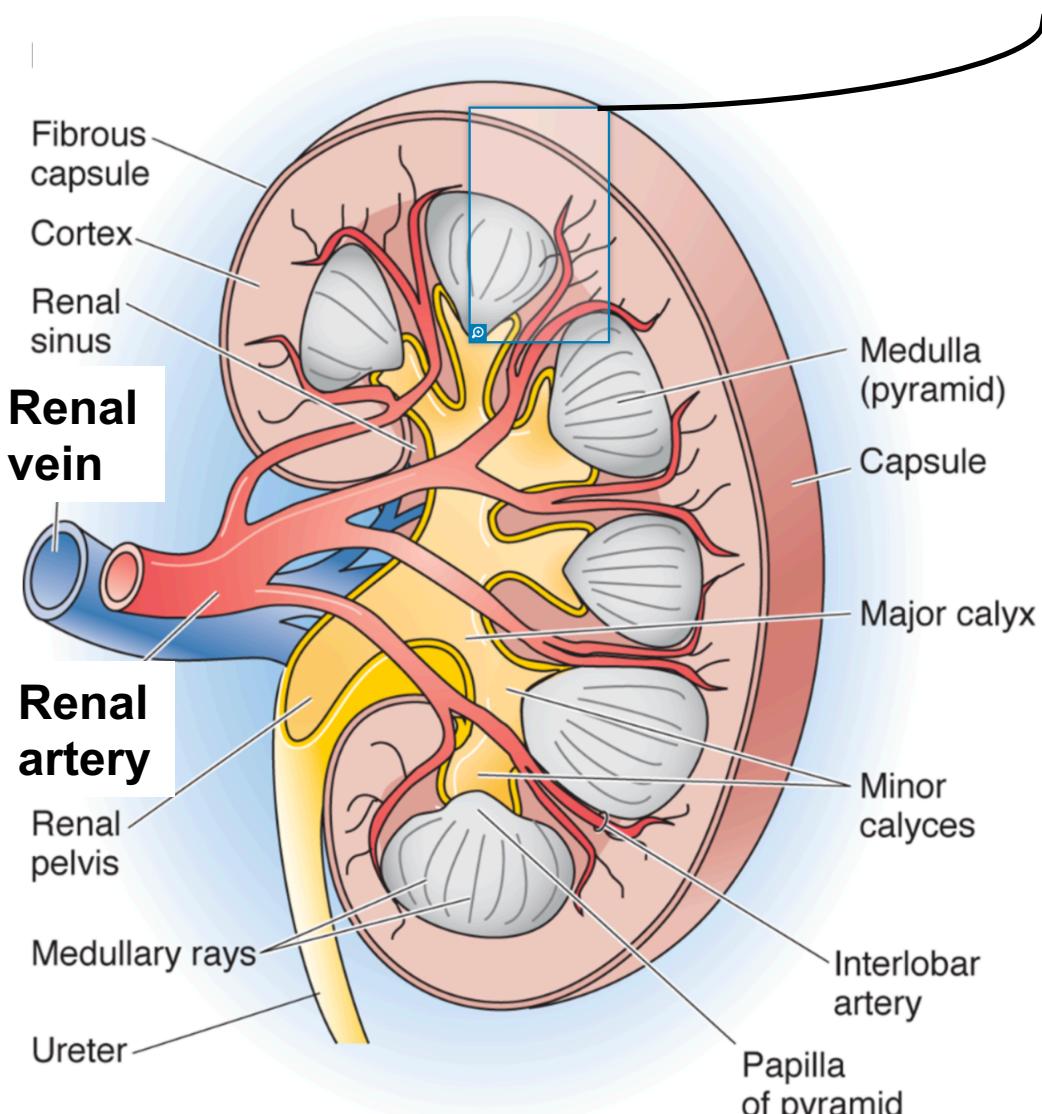


- act as filters
- body homeostasis
(fluid status, pH, electrolytes)
- hormone production
- <0.5% of body weight
- ~20% of cardiac output

Kidney morphology

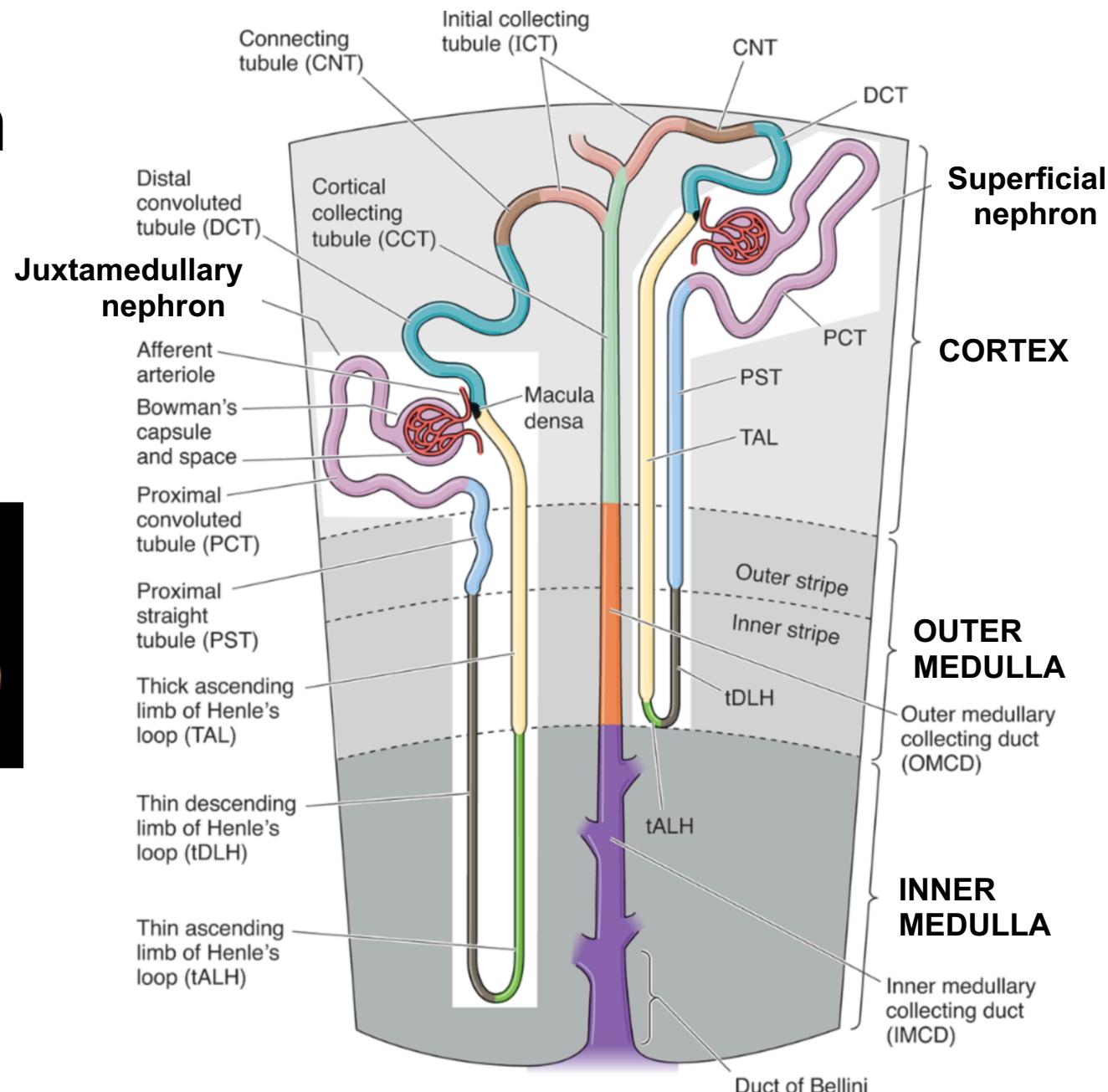
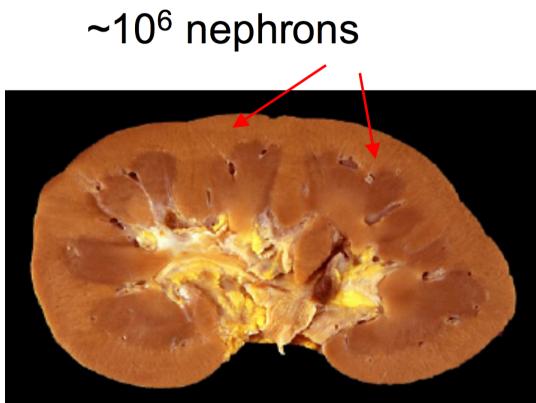


Major blood vessels



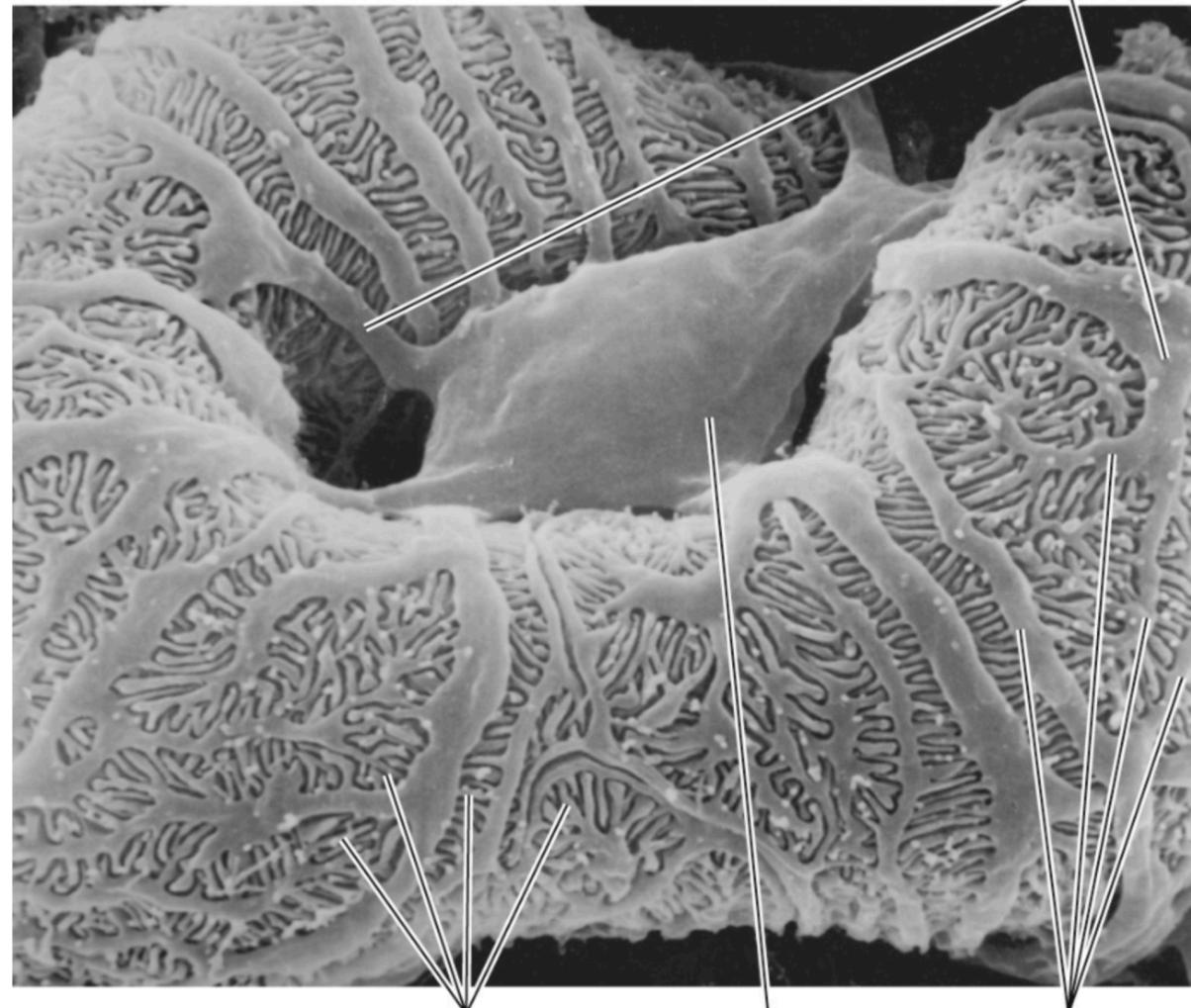
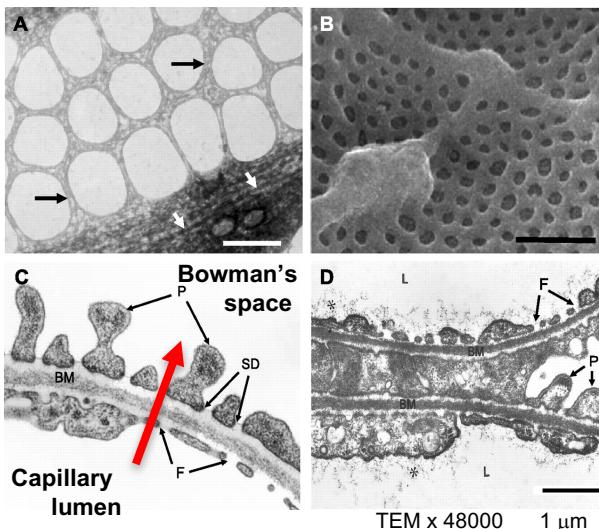
Boron & Boulpaep, Medical Physiology, 3rd ed. Elsevier, 2017

The nephron



Where the filtration (GFR) takes place

Glomerular capillary covered by the foot processes of podocytes →



“ 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

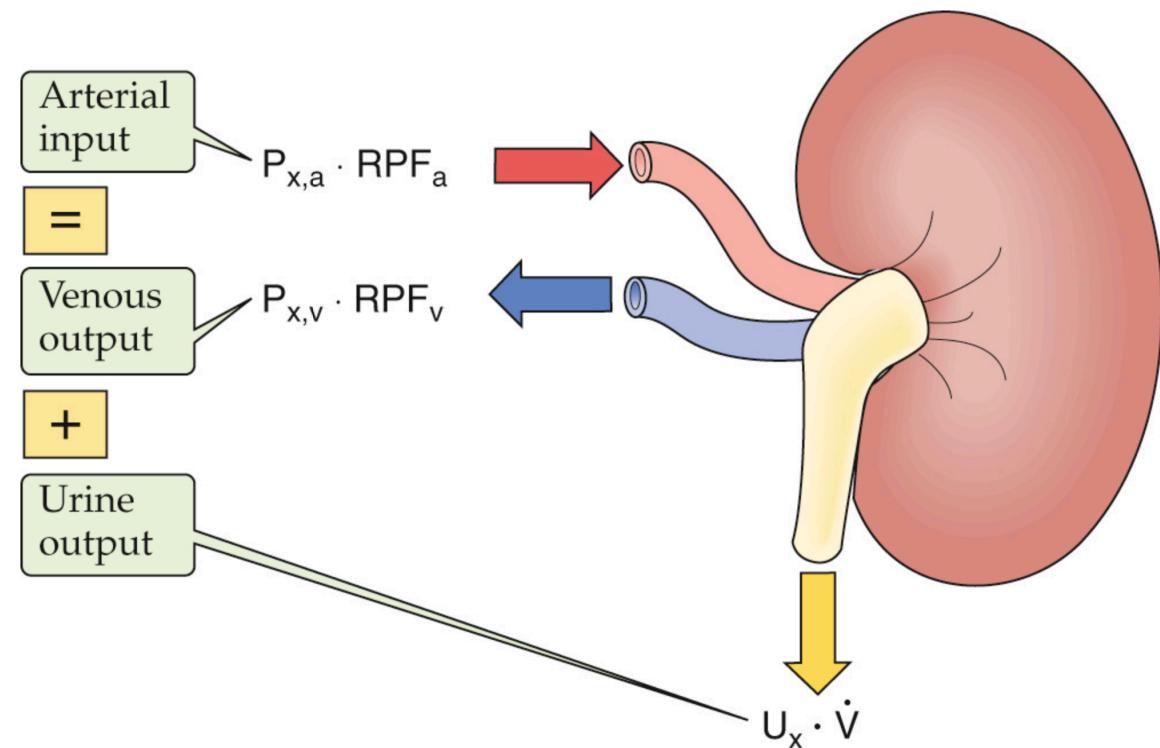
renal plasma flow in renal vein

U_X

concentration of X in urine

\dot{V}

urine flow (volume urine per time unit)



Arterial input of X

$$\underbrace{P_{X,a}}_{\frac{\text{mmole}}{\text{mL}}} \cdot \underbrace{RPF_a}_{\frac{\text{mL}}{\text{min}}}$$

Venous output of X

$$\underbrace{P_{X,v}}_{\frac{\text{mmole}}{\text{mL}}} \cdot \underbrace{RPF_v}_{\frac{\text{mL}}{\text{min}}}$$

Urine output of X

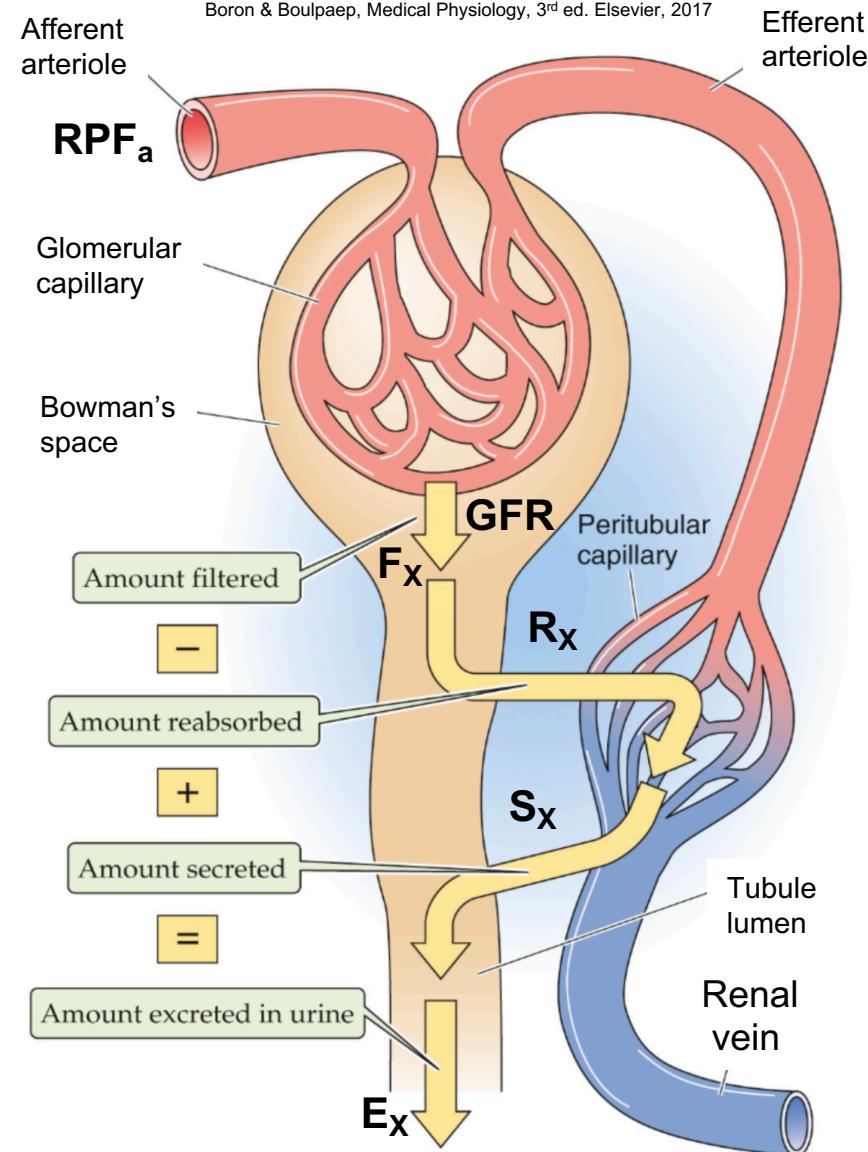
$$\underbrace{U_X}_{\frac{\text{mmole}}{\text{mL}}} \cdot \underbrace{\dot{V}}_{\frac{\text{mL}}{\text{min}}}$$

“ 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
---	---	---	---

$$\overbrace{E_x} = \overbrace{F_x} - \overbrace{R_x} + \overbrace{S_x}$$



“ 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).

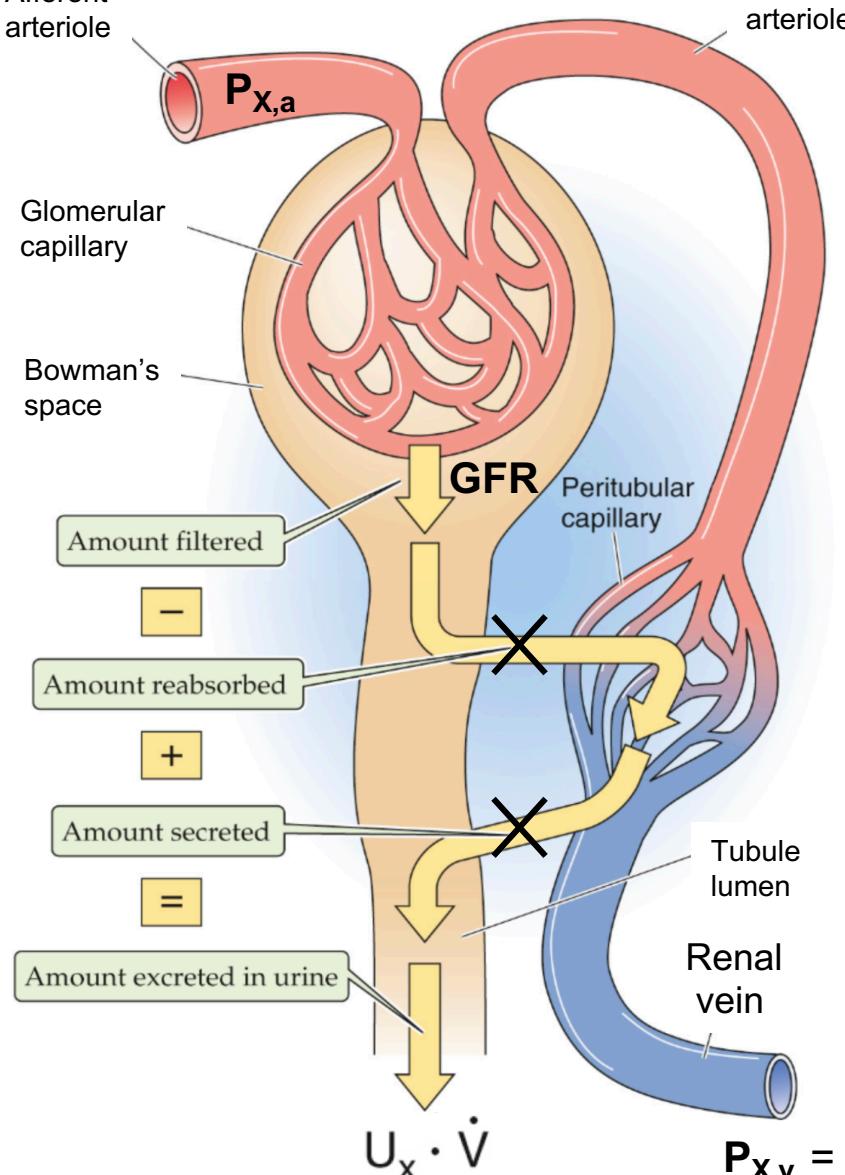
Input into
Bowman's space

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

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

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

Afferent
arteriole



“ Mass balance “

clearance of a substance X

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



Clearance of X, C_x

$$\text{Virtual arterial input } \overbrace{P_{X,a} \cdot C_X}^{} = \overbrace{0}^{\text{Virtual venous output}} + \overbrace{(\dot{U}_X \cdot \dot{V})}^{\text{Actual urine output}}$$

GFR

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

$$\overbrace{\frac{P_X \cdot GFR}{\text{mL}}}^{} = \overbrace{\frac{\dot{U}_X \cdot \dot{V}}{\text{mL}}}^{} \quad \begin{aligned} GFR &= \frac{\dot{U}_X \times \dot{V}}{P_X} \\ &\frac{\text{mL}}{\text{min}} = \frac{(\text{mg/mL}) \times (\text{mL/min})}{(\text{mg/mL})} \end{aligned}$$

Afferent
arteriole

RPF_a

Glomerular
capillary

Bowman's
space

F_x

R_x

S_x

E_x

Peritubular
capillary

Tubule
lumen

Renal
vein

Amount filtered

-

Amount reabsorbed

+

Amount secreted

=

Amount excreted in urine

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

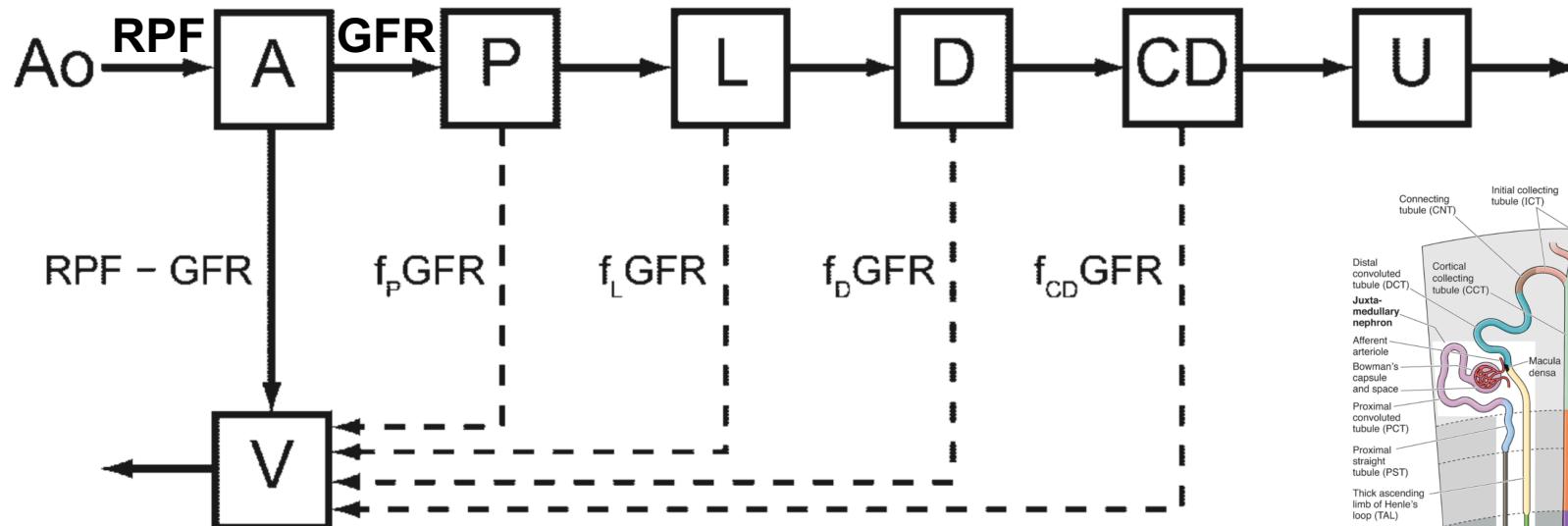
$$C_{\text{PAH}} = RPF_a \sim 600 \text{ mL/min}$$

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

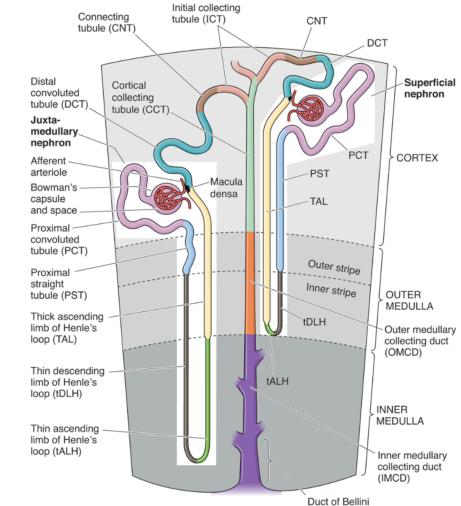
$$\text{Filtration fraction, FF} = GFR / RPF \sim 0.2$$

Multi-compartment modeling of renal perfusion and filtration

(A model for determination of single-kidney GFR)



Dashed lines represent tracer-free fluid resorption,
in terms of fractions of GFR: $f_P, f_L, f_D, f_{\text{CD}}$



Ao - aorta

A - intrarenal arteries and glomerular vessels

P - proximal convoluted tubule

L - loop of Henle

D - distal convoluted tubule

CD - collecting duct

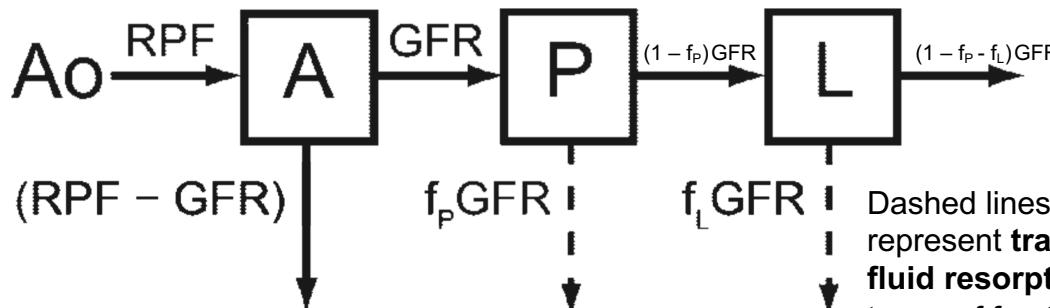
V - vasa recta and veins

U - ureter

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 (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

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

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

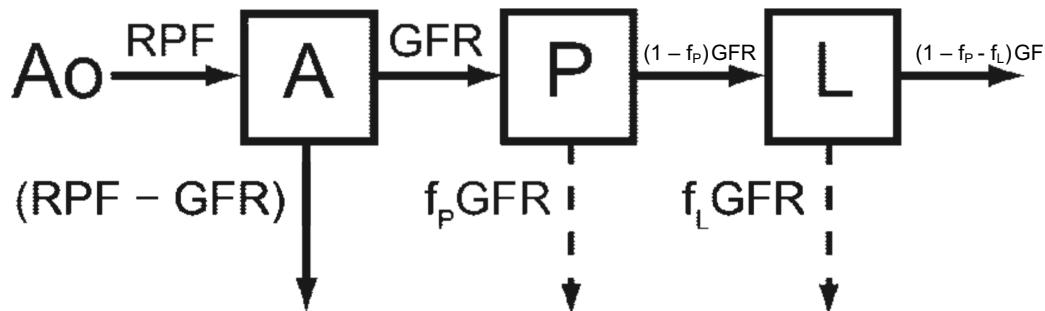
$$\frac{dL}{dt} = \frac{GFR}{V_L} [(1 - f_P)P - (1 - f_P - f_L)L]$$

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

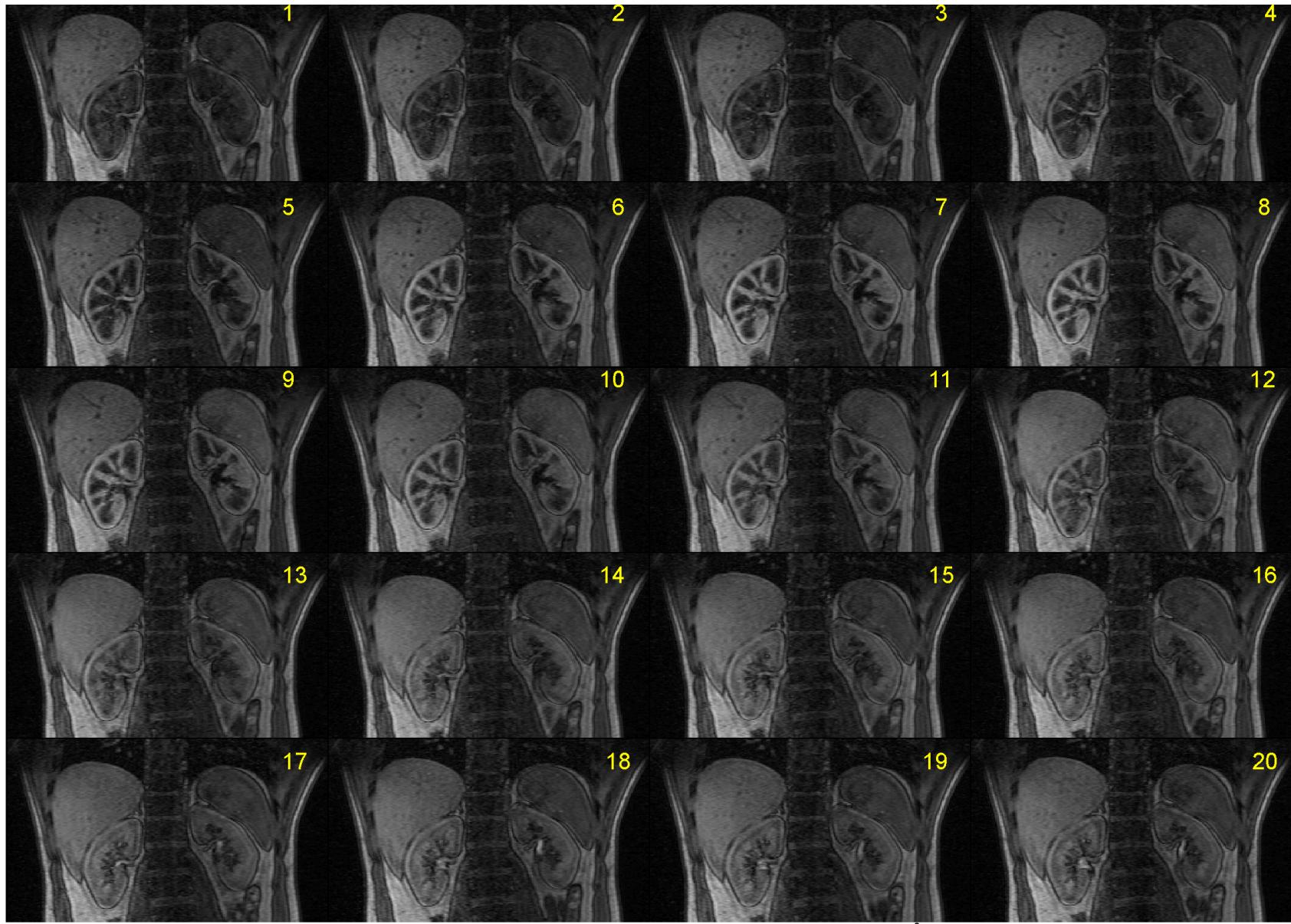
f_P

f_L

V_{A,Cx}

V_{A,Med}

DCE-MRI of the moving kidney

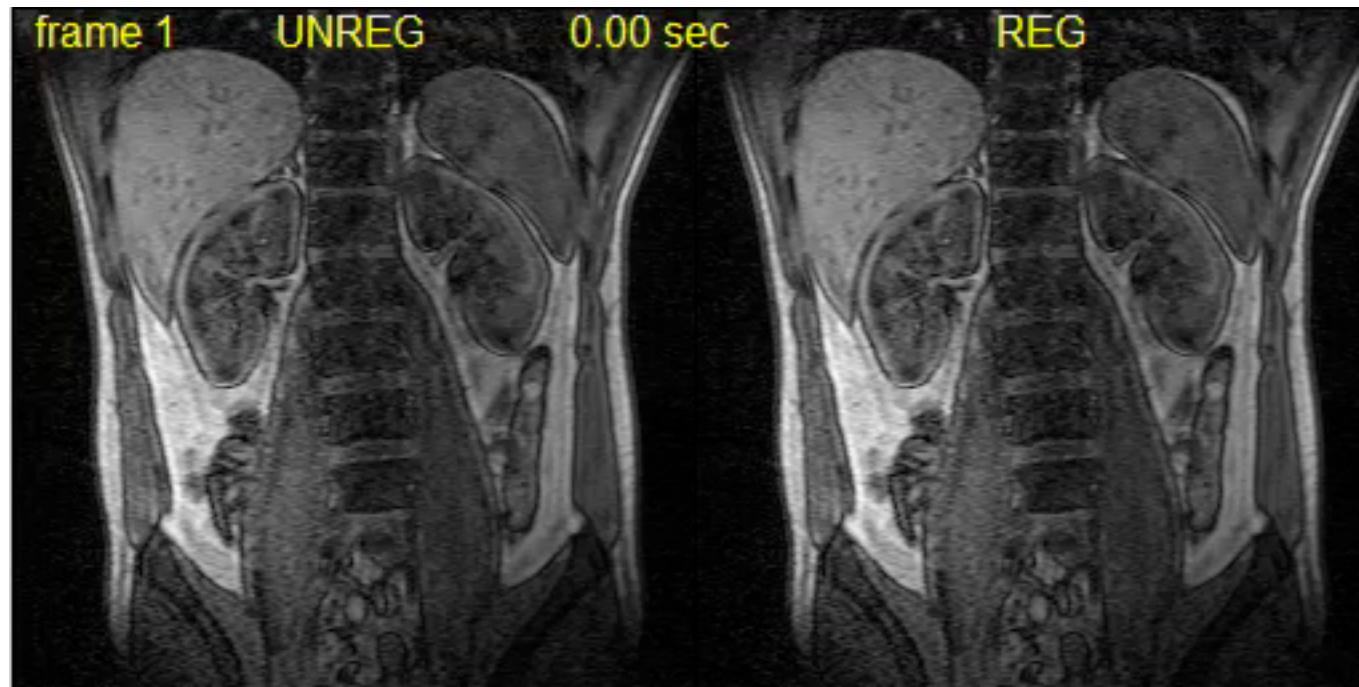


bergen_capio_20050419_kidney_volume_timeseries.mat 20 slices, 20 time frames, voxel-size: 1.48 x 1.48 x 3 mm³

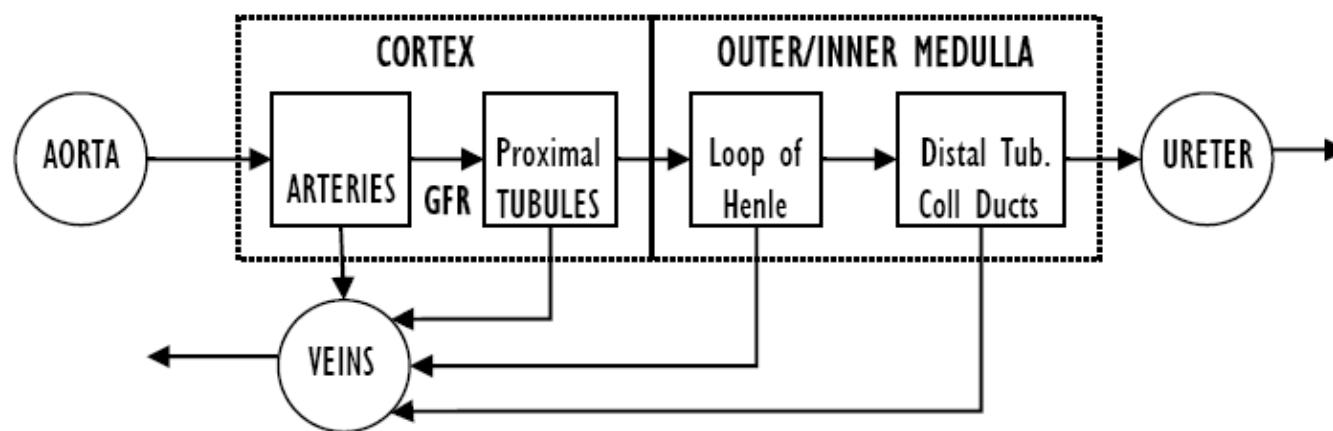
with Prof. Jarle Rørvik et al.

Pharmacokinetic modeling of perfusion and filtration using DCE-MRI

The
moving
kidney



R. Sance et al., ISPA 2006

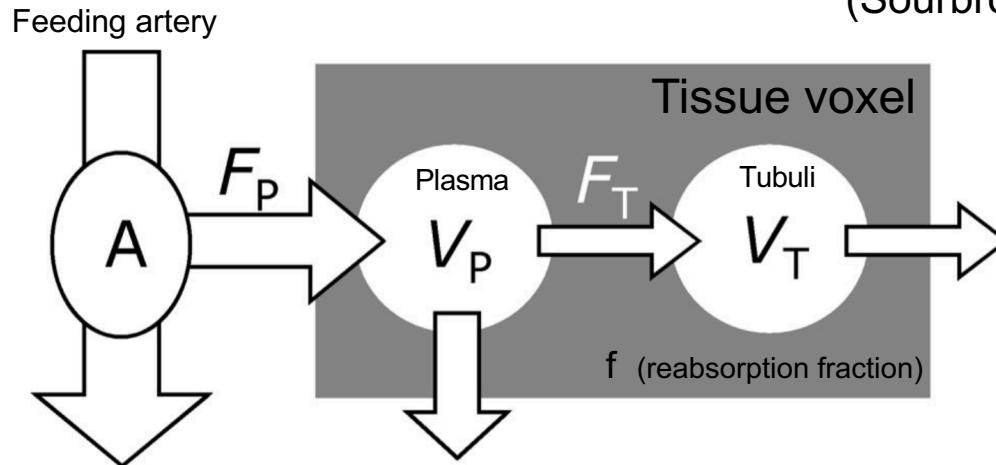


Lee VS et al. Renal function measurements from MR renography and a simplified multicompartmental model. Am J Physiol Renal Physiol 2007;292:F1548–F1559.

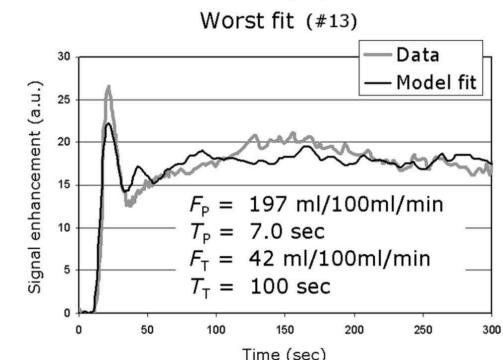
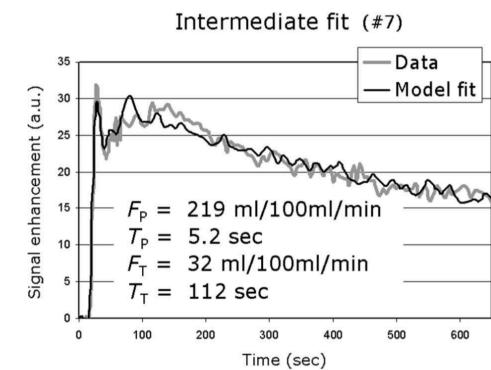
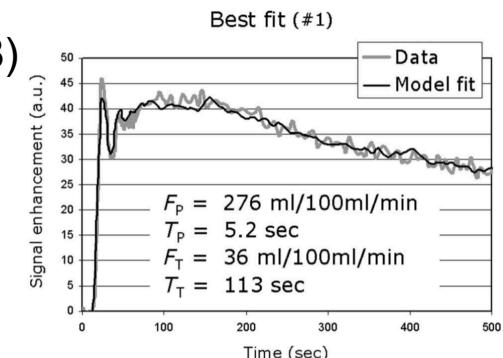
The
motion-
corrected
kidney

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

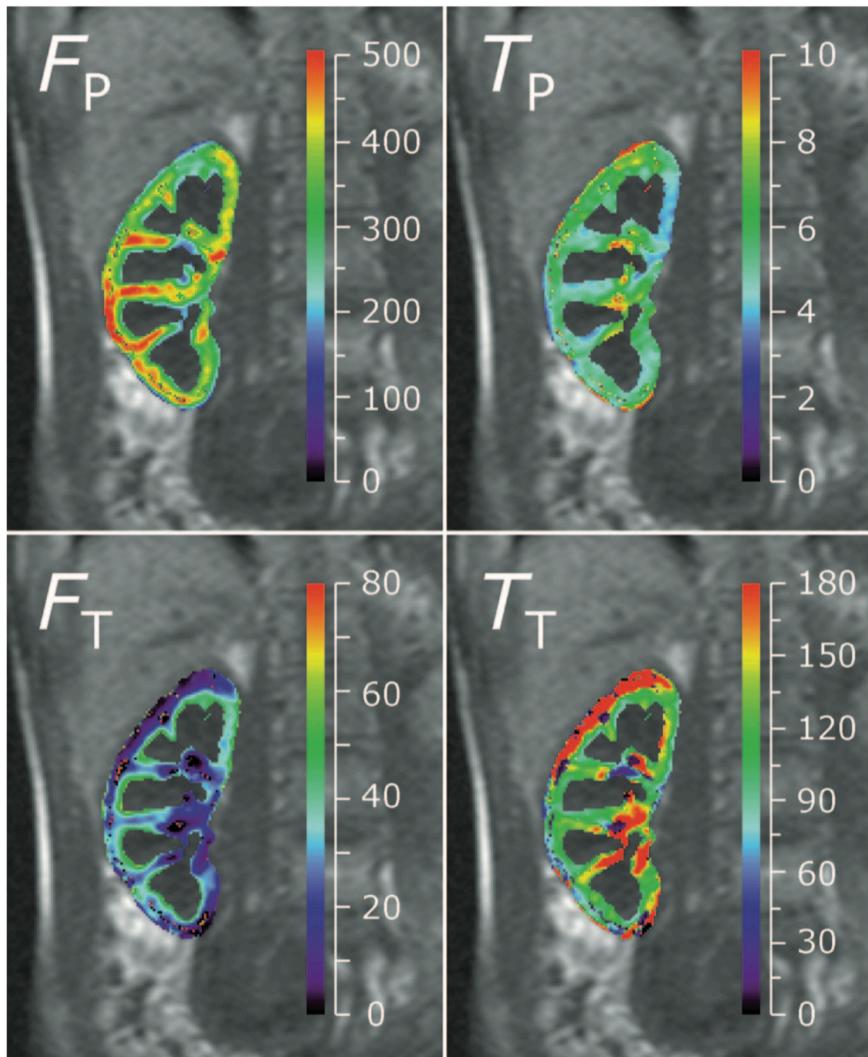
(Sourbron et al., 2008)



- (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



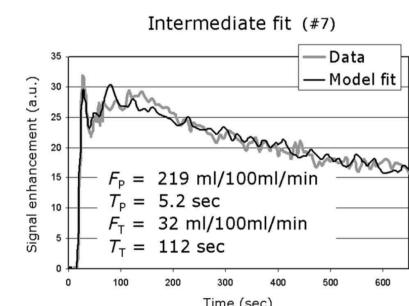
The four independent model parameters

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

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

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

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

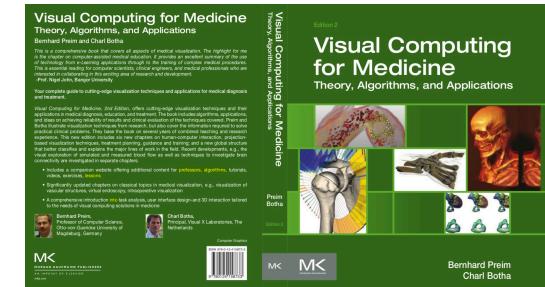
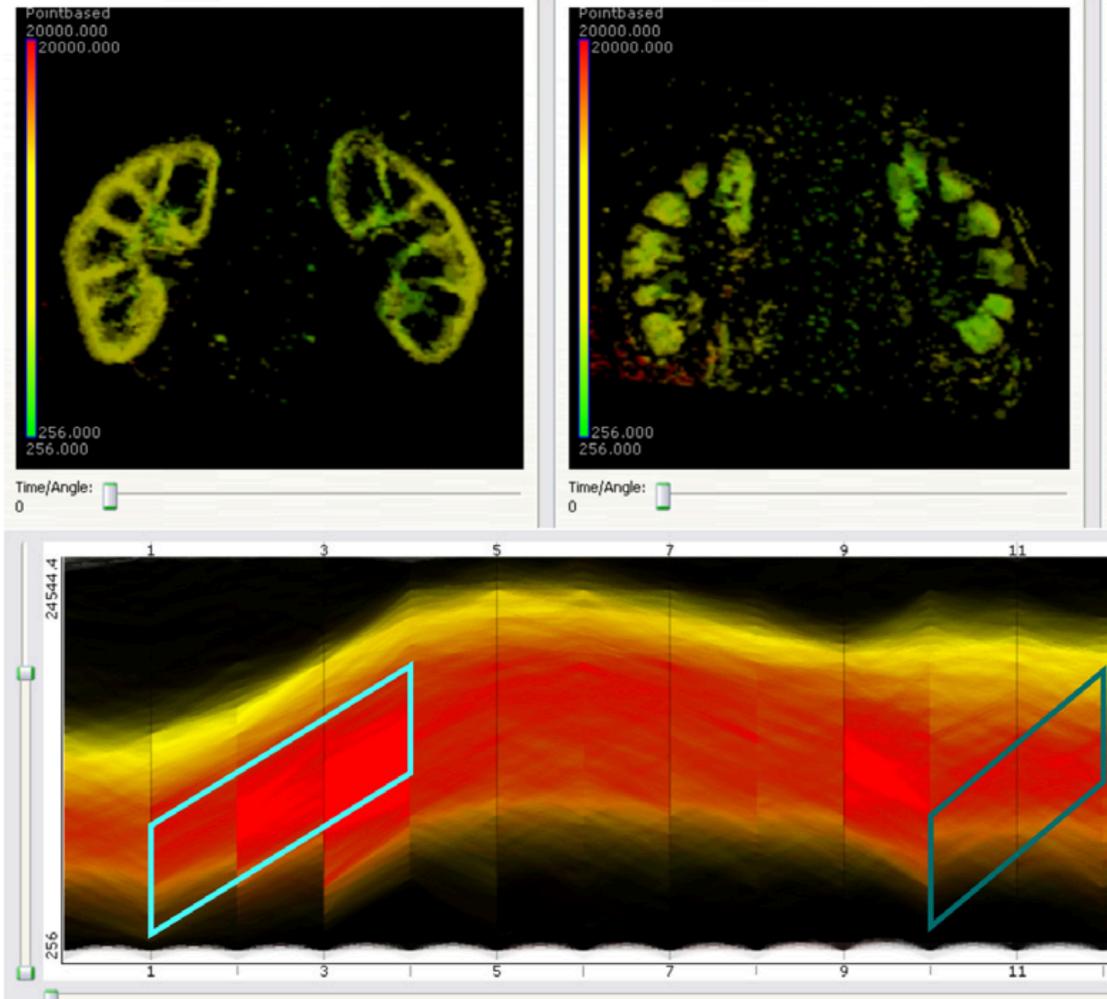


for the data with the intermediate fit accuracy

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

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

Visual Exploration and Analysis of Perfusion Data



Preim B, Botha C. Visual Computing for Medicine, Second Edition.
<http://dx.doi.org/10.1016/B978-0-12-415873-3.00016-X>

The lower image depicts all time-intensity curves of a renal perfusion study.

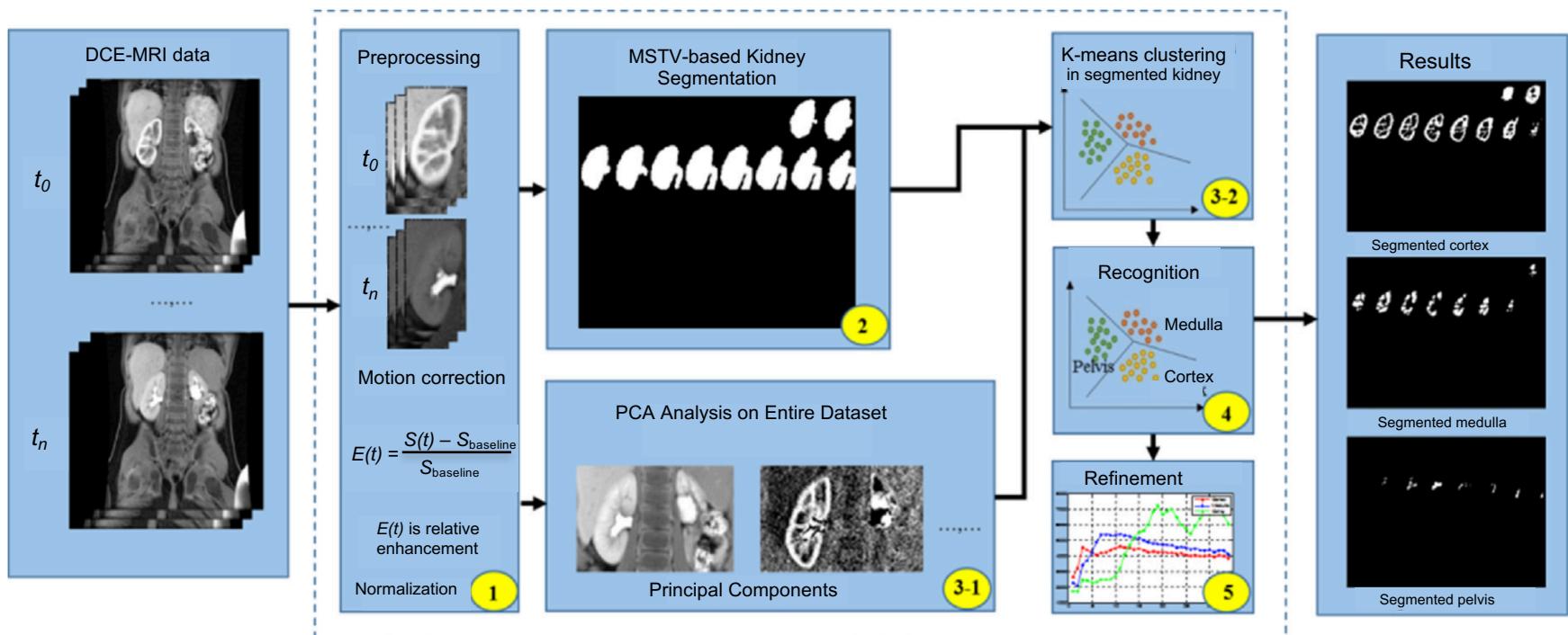
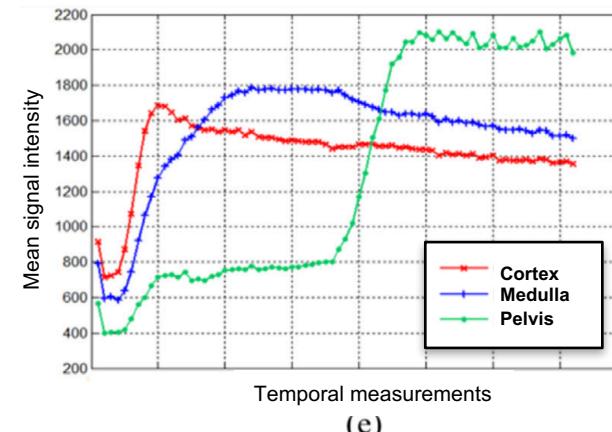
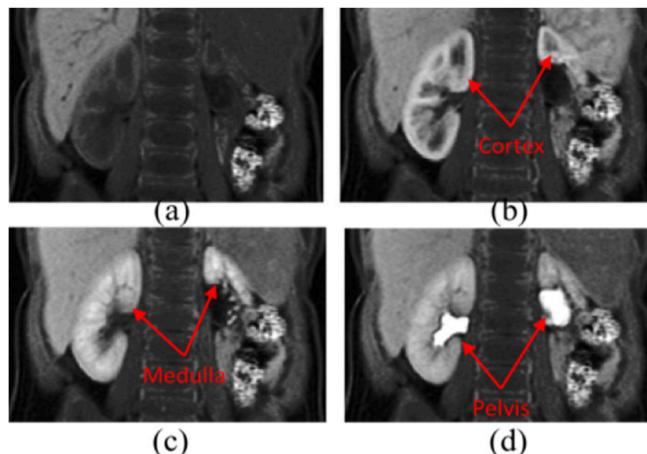
Gradient sum brushes are employed to select regions with similar perfusion characteristics.

In the top left image, the renal cortex is shown based on the selection with left brush.

The right image shows the renal medulla where contrast enhancement occurs later.

(Courtesy of Steffen Oeltze, University of Magdeburg)

Renal compartment segmentation from DCE-MRI



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

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

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.

The R language
www.r-project.org

dcemriS4

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

Ferl GZ.

DATforDCEMRI: An R Package for Deconvolution Analysis and Visualization of DCE-MRI Data

Journal of Statistical Software 2011;44(3):1-18.

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

The R language
www.r-project.org

DATforDCEMRI

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

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

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

DCEMRI.jl

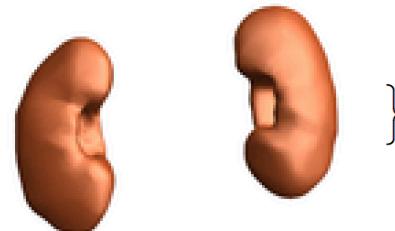
Python module : <https://github.com/welcheb/pydcemri>

The Python language
www.python.org

Software - the kidney & computational anatomy

```
In[6]:= AnatomyData[Entity["AnatomicalStructure", "Kidney"], {"Mass", "Density", "Image"}]
```

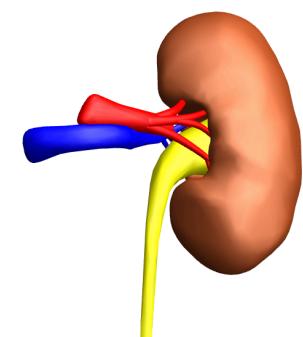
```
Out[6]= {Interval[{120., 160.}] g, 1.05 g/cm3, }
```



```
In[7]:= AnatomyData[Entity["AnatomicalStructure", "Kidney"], {"Function", "ArterialSupply"}]
```

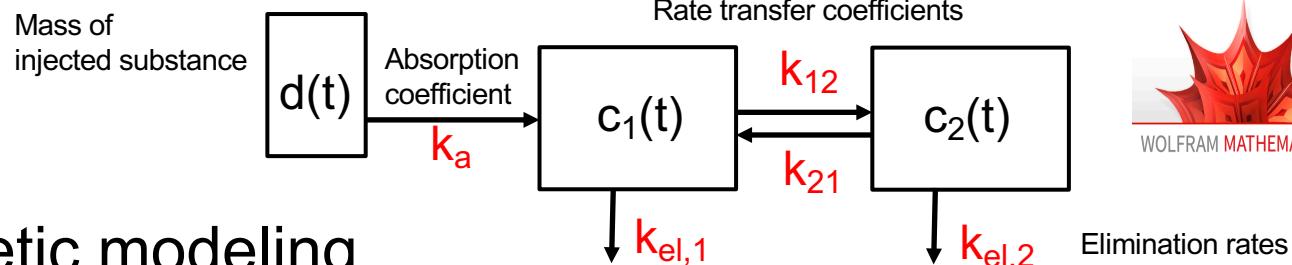
```
Out[7]= {functions in blood filtration and urine production; controls water-salt balance, pH balance, and blood pressure; secretes erythropoietin to stimulate production of red blood cells; and produces calcitriol to promote bone growth, { renal artery }}
```

```
In[11]:= AnatomyPlot3D[{Entity["AnatomicalStructure", "LeftKidney"], Red,
Entity["AnatomicalStructure", "LeftRenalArtery"], Blue,
Entity["AnatomicalStructure", "LeftRenalVein"], Yellow,
Entity["AnatomicalStructure", "LeftUreter"]}]
```



DIDACTIC Software

Pharmacokinetic modeling



The main assumption here is that both compartments are well mixed. When the drug does not absorb, it is assumed to be administered in a rapid dose (i.e. bolus injection). The constants k_{12} and k_{21} represent the rate transfer coefficients from compartment 1 to compartment 2 and vice versa, assuming a first-order transfer between them. Each compartment has its own elimination rate $k_{el,1}$ and $k_{el,2}$. The absorption coefficient k_a determines the rate at which the drug absorbs into the first compartment, assuming absorption to be first order. The concentrations and time are intentionally left unit-less but the whole system is dimensionally consistent. The drug elimination reaction order is ro.

Injected dose:

$$\frac{\delta d(t)}{\delta t} = -k_a d(t) \quad ro = 1$$

The first dose is at time zero, and the same mass is then injected for each subsequent dose.

Compartment one:

$$\frac{\delta c_1(t)}{\delta t} = k_a \frac{d(t)}{V_1} - k_{12} c_1(t) - k_{el,1} c_1(t)^{ro} + k_{21} c_2(t)$$

The initial condition for compartment one is that the drug concentration there is zero when absorption occurs, and it is the mass of the drug divided by the volume of compartment one when absorption does not occur.

Compartment two:

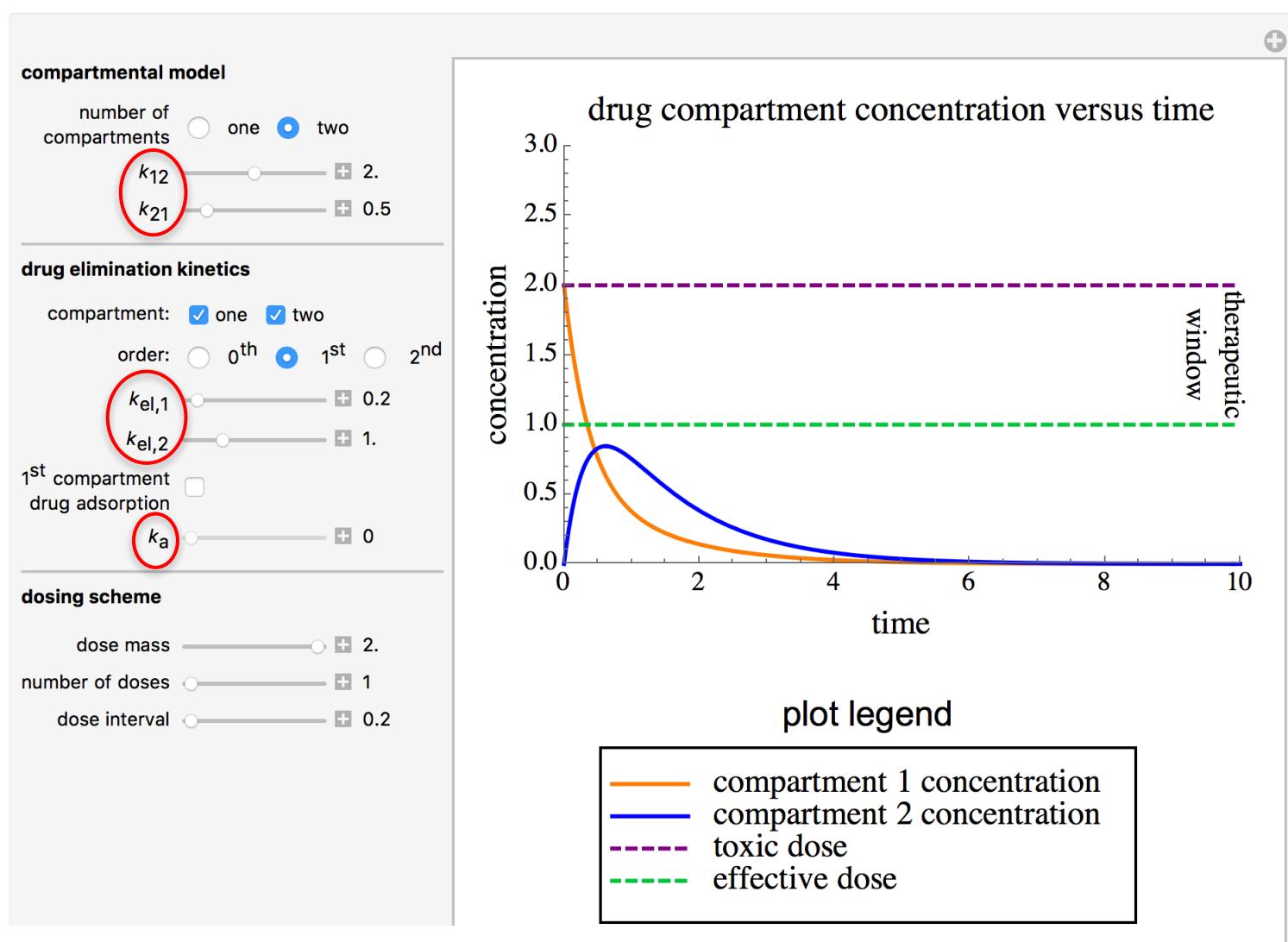
$$\frac{\delta c_2(t)}{\delta t} = k_{12} c_1(t) - k_{21} c_2(t) - k_{el,2} c_2(t)^{ro}$$

The initial condition for compartment two is that the concentration there is zero at time zero.

DIDACTIC Software - Pharmacokinetic Modeling

In DCE-MRI
we are
solving the
inverse
problem:

Estimate the
parameters
(e.g. GFR, RPF)
by fitting
the measured
data to
the model
(in the least
squares sense,
using an
optimization
scheme)

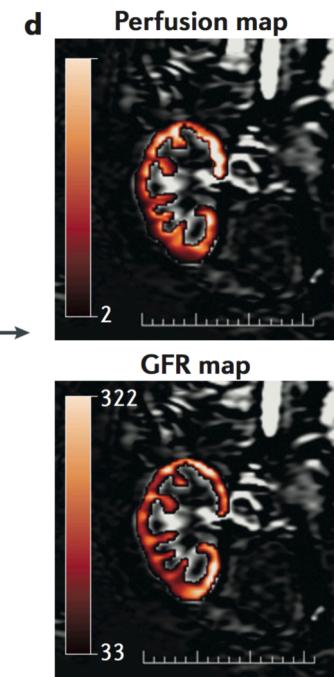
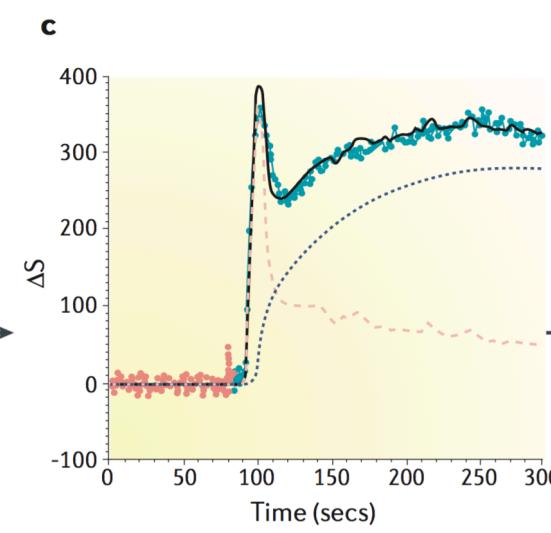
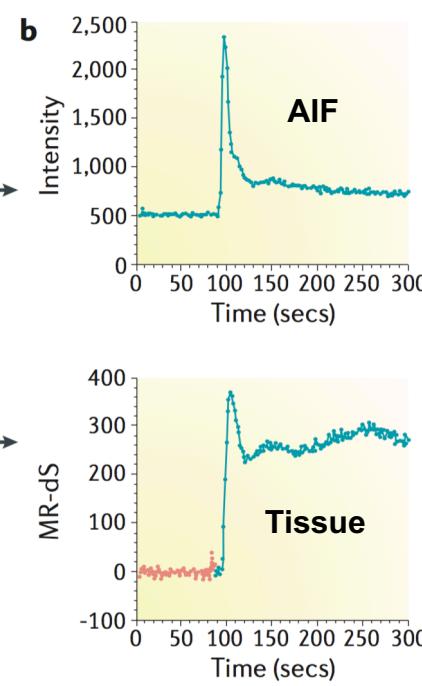
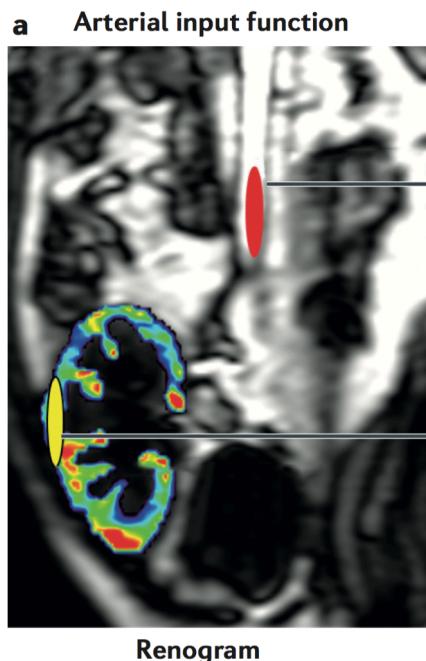


```
/. First@NDSolve[{
  d'[t] == -ka*d[t],
  c1'[t] == ka*d[t]/V1 - (k12*c1[t]) - (kel1)*(c1[t])^(ro) + k21*c2[t],
  c2'[t] == k12*c1[t] - k21*c2[t] - (kel2)*(c2[t])^(ro),
```

Contributed by: Nicholas R. Larson

With additional contributions by: John L. Falconer and Rachael L. Baumann

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a) The **renogram** is a map of the maximal signal intensity that can be obtained after injection of a gadolinium-based tracer bolus.

b) By placing a region of interest on the aorta (**red**) and on the cortex (**yellow**), signal intensity time curves (kinetic curves) can be produced. The aortic kinetic curve enables characterization of the shape of the bolus (arterial input function, AIF).

c) A two-compartment model is applied to these kinetic data to extract the perfusion component and the extraction component.

d) Quantitative maps of perfusion and glomerular filtration rate (GFR; in ml/min/g of tissue) can be generated from these data, respectively.

Summary

- Kidney **structure and function** – the core parameters: **RPF** and **GFR**
- “**Mass balance**” - **compartment models** and **tracer kinetic principles**
- **DCE-MRI** - the most established measuring technique for renal perfusion and filtration (but also: **Arterial Spin Labeling, ASL** - non-contrast perfusion imaging, and **BOLD fMRI**)
- **Parameter estimation (GFR and RPF)** - possible down to single voxels
- The importance of **motion correction** and **kidney segmentation**
- The value of model-free **visual exploration and analysis**
- **Software** for model-based estimation of renal perfusion and filtration in the context of “**open science**” & “**reproducible research**”

Not covered: (see Syllabus @ <https://github.com/arvidl/functional-kidney-imaging>)

- Mapping: **SI time courses** → **[Gd] time courses** (MR sequence dependent)
- **AIF and deconvolution**
- **Validation** (e.g. MR-GFR vs. iohexol-GFR w/blood sampling) and **test-retest reliability**

e.g. Eikefjord et al. AJR 2015, 2106

Thanks !