Renal Filtration Models
Sunrise Course ISMRM 2010
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1. **Basics of kidney anatomy and physiology.** The kidney consists of an outer layer (cortex), inner layer (medulla), and collecting system, which drains into the renal pelvis. The functional unit of the kidney is a nephron, which spans cortex and medulla (Fig. 1). The renal filtration occurs at the glomerulus, a sieve which separates the ultrafiltrate, which passes into the renal tubules, and larger components, such as blood cells and proteins, which stay in the bloodstream. The efficiency of filtration is characterized by the glomerular filtration rate (GFR). In healthy people GFR is about 50-60 ml/min per kidney. GFR is an important clinical parameter. In practice it is often assessed by approximate population-based formulas, e.g., by measuring the creatinine level in blood, clearance methods, such as inulin clearance, or by nuclear medicine methods (combined clearance and imaging methods). These methods have considerable drawbacks, and measuring GFR in the course of an MRI examination is desirable.
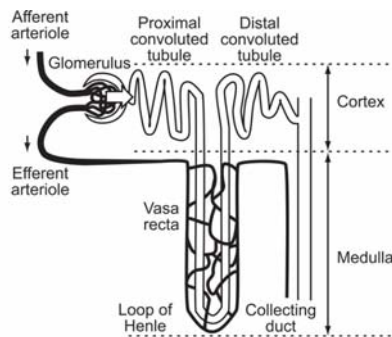
Figure 1: Schematic of a nephron. The nephron receives blood supply from arterioles and consists of the glomerulus, proximal convoluted tubules, loops of Henle, distal convoluted tubules and collecting ducts. The renal filtration occurs at the glomerulus. The majority of the glomeruli are located in the cortex.

2. **A brief overview of methods and tools for measuring renal perfusion and filtration parameters with MRI** [1]. All of the usual "good practices" in dynamic contrast-enhanced (DCE) imaging are valid for kidney examinations. Acquisition: Fast GRE sequence (2D or 3D, temporal resolution of few seconds (below 5 s), preferably coronal slice through the abdominal aorta for measuring arterial input function (AIF). T1-mapping is desirable for conversion of signal to concentration, especially in medulla, where T1 can vary greatly. Tools for image registration are critical, because kidney images suffer from respiratory motion, and software for image segmentation is also very helpful.

3. **Overview of renal models** [2]. General assumptions. Kidney is viewed as a combination of vascular and one or more tubular compartments. Compartmental models: Instantaneous mixing, fixed volumes, constant parameters, venous compartment is ignored, leakage into interstitial space is also neglected. Distributed

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models: no instant mixing assumption. Required data: Concentrations of contrast in aorta or renal artery and renal tissue (cortex and/or medulla, or combined renal parenchyma).
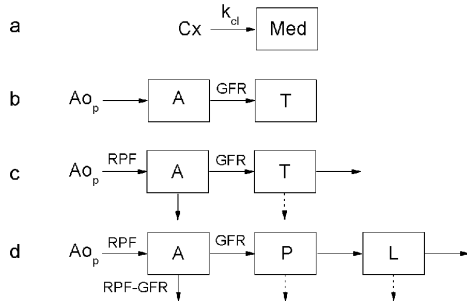
Figure 2: Schematics of renal models. a) Baumann-Rudin model, b) Patlak-Rutland model, c) Two-compartment models, d) Three-compartment models. Cx, Med – cortex and medulla; Ao_p – plasma concentration in aorta; A, T – vascular and tubular compartments, P and L – proximal tubules and loops of Henle; RPF – renal plasma flow, k_{cl} – clearance index.

a. Baumann-Rudin (BR) model [3,4]. Data: Cortex [serves as input function] and medulla. Assumptions: No outflow from tubular compartment. Result: clearance index that correlates with GFR. No input function is required. BR model does not yield absolute GFR and requires selection of inflow interval, which may be subjective.
b. Patlak-Rutland (PR) model: Two-compartment (2C) inflow-only model [5-8]. Data: AIF and renal tissue (cortex and undifferentiated (cortex+medulla) renal parenchyma have been used). Compartments: Vascular and tubular. Assumptions: No outflow from renal tubules, the concentration in vascular compartment is the same as in AIF. PR yields GFR, but requires selection of inflow interval; inflow-only interval in kidney is short, so validity can be compromised.
c. Two-compartment models with tubular outflow. Data: Same as for PR. Compartments: Vascular and tubular.
    i. 2C without dispersion (2C) [8]. Assumptions: Concentration in vascular compartment is the same as in AIF.
    ii. 2C with dispersion (2CD) [6,7]. Assumptions: Concentration in vascular compartment is broadened by dispersion over the volume of the vascular compartment.
d. Three-compartment models [9,10]. Data: AIF, cortex, medulla.
    i. 3C compartmental model with dispersion (3CD) [9]. Compartments: Serially connected vascular compartment (in both cortex and medulla), proximal tubules (in cortex only), and loops of Henle (in medulla only). Assumptions: vascular compartment contributes in proportion to vascular volume fractions in cortex and medulla; contrast from proximal tubules flows into the loops of Henle.
    ii. 3C distributed parameter model based on impulse-response function (IRF) (3C-IRF) [10]. Assumptions: Same as for 3CD, apart from

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instant mixing. Contrast takes a minimum transit time to traverse each compartment before appearing in the next compartment.

1. Note: A similar 2C-IRF model has been implemented (Zhang J et al. (unpublished)).

4. **GFR determined with renal models** [2]**.** What is "the best" model? Models that provide the highest precision and accuracy of parameters may not necessarily provide the best fit quality, as it often occurs in model fitting.

    a. Precision and accuracy of renal models studied by simulations. In functioning kidneys, 3C-IRF model seems to offer superior precision of GFR (about 15% at 10% noise). In dysfunctional kidneys, 2C models perform better than 3C. 2CD model yields the worst precision in both cases.

    b. Performance of models with real experimental data:

        i. GFR agreement with reference: All models yield high correlation (Pearson R~0.74 and higher) of fitted GFR with the nuclear medicine reference GFR, but seem to be differently biased. Both strong under- and over-estimation of GFR has been reported. PR method and models applied to cortical data provide the most heavily biased results.

        ii. Fit quality: As expected, among 2C models, the more flexible 2CD model provides lower residuals. 3C-IRF model produces lower residuals than 3CD.

    c. Can GFR bias be explained by the structure of the models and data?

        i. Pure inflow models are expected to yield lower GFRs than similar models with outflow. For example, PR is expected to provide lower GFRs than 2C or 2CD.

        ii. Models without dispersion provide higher GFR than models with dispersion applied to the same data, i.e., GFR from 2C is expected to be higher than GFR from 2CD.

        iii. GFR obtained from cortical data tend to be lower than GFR obtained with the same model applied to the renal parenchyma data from the same kidney.

        iv. Cortical data are more difficult to fit with two-compartment models because of the strong overlap between vascular and tubular features in cortical curves. Medullary data are easier to fit because of the more pronounced loop of Henle peak; however, parameters obtained from medullary data are indirect measures of glomerular filtration.

        v. Models with no AIF can be more robust because errors in AIF can translate into large errors in GFR.

5. Conclusions

   a. GFR can be measured as a part of a clinical DCE MRI examination of the kidney. The accuracy and precision of GFR estimates depend on the quality of data, patient population, available methods of analysis, and the choice of renal model.

   b. All models provide estimates that correlate strongly with the reference measurements of GFR, but GFR values appear to be biased in different degrees. The magnitude of the bias depends on the assumptions of the model (e.g., inflow versus inflow+outflow) and the data used (e.g., cortex versus parenchyma). These biases must be taken into account when comparing GFR results from different models.

   c. More flexible models (2CD, 3CD, 3C-IRF) do not perform well in severely dysfunctional kidneys, in which concentration curves contain less information than in functioning kidneys. However, due to concerns over nephrogenic systemic fibrosis (NSF), patients with severely compromised renal function are unlikely to receive gadolinium-enhanced DCE MRI.

   d. Accurate measurements of AIF are crucial for fully quantitative models. Some errors in AIF data, such as distortions incurred during conversion to concentration due to errors in baseline single, can be corrected in postprocessing [11].

   e. The choice of model is dictated by the quality of data, required parameters and computational efficiency.

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