

¹ 3DQLayers: Volumetric Layer Based Analysis for Quantitative Renal MRI

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⁷ Summary

⁸ Informative measurements of the kidneys structure and function can be performed using quantitative Magnetic Resonance Imaging (MRI) where each voxel of the image is a measurement of the physical properties of the tissue being imaged. Traditionally, analysis of these images is performed by segmenting the kidney into its constituent tissue types and calculating the average of each measurement for each tissue type. The process of segmenting renal tissue types is time consuming and inaccurate. An alternative to tissue segmentation proposed by Pruijm *et al* involves dividing the kidney into layers based on the distance of each voxel between the outer and inner surface of the kidney, a method known as Twelve Layer Concentric Objects (TLCO) (Li *et al.*, 2020; Milani *et al.*, 2017; Piskunowicz *et al.*, 2015). Layer based analysis only requires segmenting the whole kidney rather than the tissues within and is therefore quicker and more repeatable. The TLCO method does however have some limitation, it can only be performed on a single slice image, requires the image to be acquired at a specific angle to the kidneys, requires manual delineation of the outside and inside surface of the kidney, divides the kidney into the same number of layers irrespective of the size of the kidney and the software itself is closed source. These limitations are addressed by 3DQLayers, an open source Python package to automatically define 3D, multi-slice, renal layers of known thickness.

²⁴ Statement of need

²⁵ Background

²⁶ The kidneys are a pair of structurally and functionally complex organs in the lower abdomen that participate in the control of bodily fluids by regulating the balance of electrolytes, excreting waste products of metabolism and excess water from blood to urine (Lote, 2012). The each kidney is separated into two tissue types; cortical tissue located towards the outside of each organ, and medullary tissue arranged in small pyramids towards the centre of the organ (Hall, 2015), as shown in Figure 1. Quantitative MRI is the process of taking measurements where the value of each voxel has numerical significance, in physical units, based on the tissues underlying properties rather than simply representing signal intensity in arbitrary units. Example quantitative measurements include how readily water can diffuse through the tissue and the rate at which blood perfuses into the tissue. To help interpret quantitative images, regions of interest (ROI) are defined and statistical measures taken of the voxels within each region.

³⁷ Segmenting ROI for the renal cortex and medulla manually is time consuming, difficult and prone to intra- and inter-reader variation thus decreasing the repeatability of measurements. ³⁸ Pruijm *et al* proposed an alternative to tissue ROI based analysis in the Twelve Layer Concentric Object (TLCO) method (Li *et al.*, 2020; Milani *et al.*, 2017; Piskunowicz *et al.*, 2015) where users delineate the inner and outer boundaries of the kidney to generate twelve equidistant

42 layers between the renal pelvis and the surface of the kidney. The outer layers are analogous to
43 the cortex; inner layers, the medulla; and gradient of the central layers, the cortico-medullary
44 ratio.

45 TLCO requires the MR image to be a single slice cutting through the kidneys on their
46 longest axis (coronal-oblique) however, this is not always desirable (Bane et al., 2020). Often
47 researchers prefer to acquire multi-slice images to increase the number of voxels in the image
48 and gain a better understanding of the heterogeneity of the kidney. Additionally flexibility in
49 the orientation images are acquired at is highly desirable. These limitations of TLCO were the
50 motivation for the development of 3DQLayers, a volumetric, quantitative-depth based analysis
51 method for renal MRI data.

52 Methods

53 3DQLayers is an open-source Python package that aims to build upon the premise of TLCO
54 and allow layer based analysis to be fully automated for use in large studies. 3DQLayers
55 fundamentally differs from TLCO in that layers are defined based on each voxels distance from
56 the surface of the kidney in millimetres rather than the proportion through the kidney. As
57 such, the input to 3DQLayers is a whole kidney ROI; this can be automatically generated from
58 a structural image (Daniel et al., 2021; Daniel, 2024).

59 The pipeline by which layers are defined is outlined in Figure 2. Pre-processing steps fill in
60 holes in the ROI caused by cysts as the surface of a cyst is not representative of the surface
61 of the kidney. Next the voxel-based representation of the ROI is converted to a smoothed
62 mesh-based representation of the kidneys, the distance from the centre of each voxel to the
63 surface of the mesh can then be calculated producing a depth map (Dawson-Haggerty, 2023).
64 As tissue adjacent to the renal pelvis is not representative of the medulla, it is excluded from
65 layer-based analysis. This is achieved by automatically segmenting the pelvis then calculating
66 the distance from each voxel to the pelvis as above. Voxels closer than a specified threshold,
67 typically 10 mm, are excluded from the depth map. Finally, a layer image is generated by
68 quantising the depth map to a desired layer thickness, typically 1 mm.

69 The layer image and quantitative images are resampled to the same resolution using NiBabel
70 (Brett et al., 2023), this allows each layer to be used as an ROI with statistical measures of
71 the quantitative image e.g. median, standard deviation and kurtosis, calculated as a function
72 of depth through the kidney. The gradient of the central layers can be calculated, additionally,
73 if tissue ROI are available the distribution of tissue types with depth can be explored. As the
74 layers are generated from a structural image rather than the quantitative map, using 3DQLayers
75 stipulates no requirements on quantitative map acquisition, unlike TLCO.

76 An object oriented interface makes it easy for users to generate layers and use them to
77 analyse quantitative images. Documentation is provided to guide users through installation via
78 PyPI, conda or from source code on GitHub and includes tutorials and an API reference. An
79 automated test suite with high coverage gives users confidence in the stability of 3DQLayers
80 and that there will be no unexpected changes to results unless highlighted in the change-log.

81 Usage Examples

82 An estimated glomerular filtration rate (eGFR) above 90 ml/min/1.73m² is considered healthy.
83 Figure 3 shows 3DQLayers being used to measure different gradients of R₂^{*} in volunteers
84 with normal and impaired renal function. This replicates results shown using TLCO however
85 3DQLayers controls for kidneys size and as such the gradients are measured in quantitative
86 units of Hz/mm rather than Hz/layer as in TLCO.

87 3DQLayers can also be used to analyse kidneys outside the body. Figure 4 shows example
88 quantitative maps acquired from a kidney removed for transplant and associated layer profiles.
89 Figure 5 compares results of ROI-based analysis and layer-based analysis in fifteen transplant

90 kidneys. A significant correlation between outer layers and the cortex, and inner layers
 91 and the medulla was shown across all quantitative mapping techniques and a significant
 92 correlation between cortico-medullary ratio and layer gradient was shown for T_1 , T_2 , T_2^* and
 93 Magnetisation Transfer Ratio (MTR) mapping.

94 ?? shows how 3DQLayers can be used in combination with tissue ROI to analyse the distribution
 95 of tissues within the kidney. Average cortical thickness can be defined as the depth at which
 96 most voxels are medulla rather than cortex. Cortical thickness has been hypothesised as a
 97 potential biomarker (Yamashita et al., 2015).

98 Figures

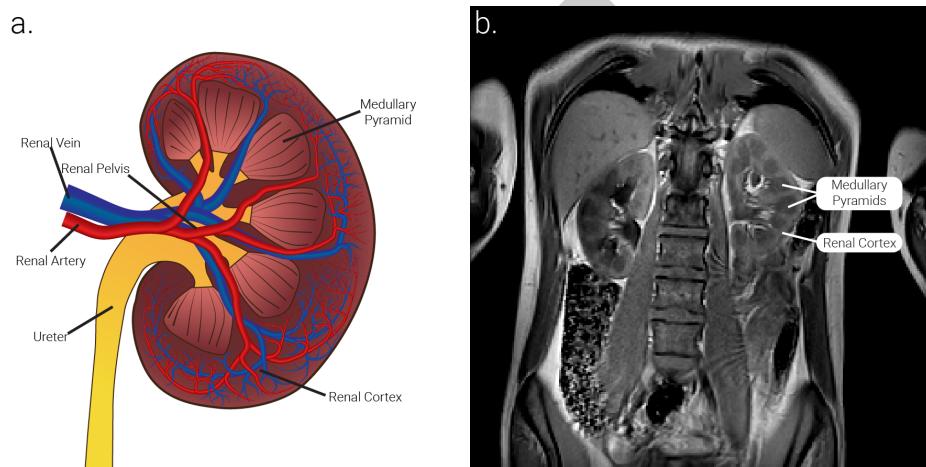


Figure 1: a) A schematic of the kidneys showing the renal cortex and medullary pyramids. b) An anatomical MR Image of the abdomen showing the kidneys with the renal cortex appearing as a light band towards the outside of the kidneys and medullary pyramids as darker patches towards the centre of the kidneys.

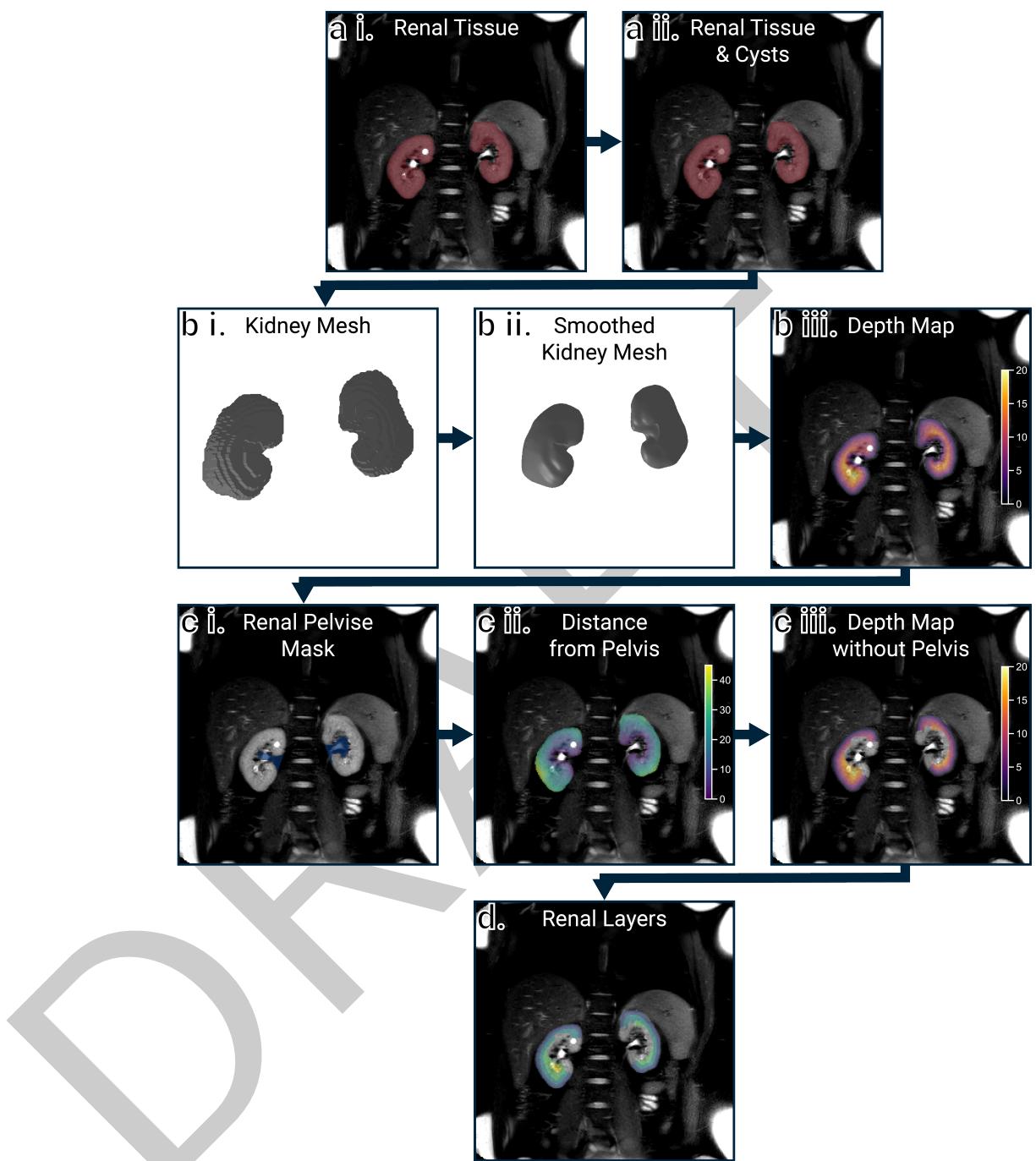


Figure 2: The mask from the T2-weighted structural scan (a i) has any cysts filled (a ii) and is converted into a smooth mesh representing the renal surface (b i and ii). The distance (in mm) from each voxel to the surface of the mesh is calculated (b iii). The renal pelvis is segmented (c i) and any tissue within 10 mm (c ii) of the pelvis is excluded from the depth map (c iii). The tissue is then grouped into layers of a desired thickness, here shown as 5 mm layers for illustrative purposes (d).

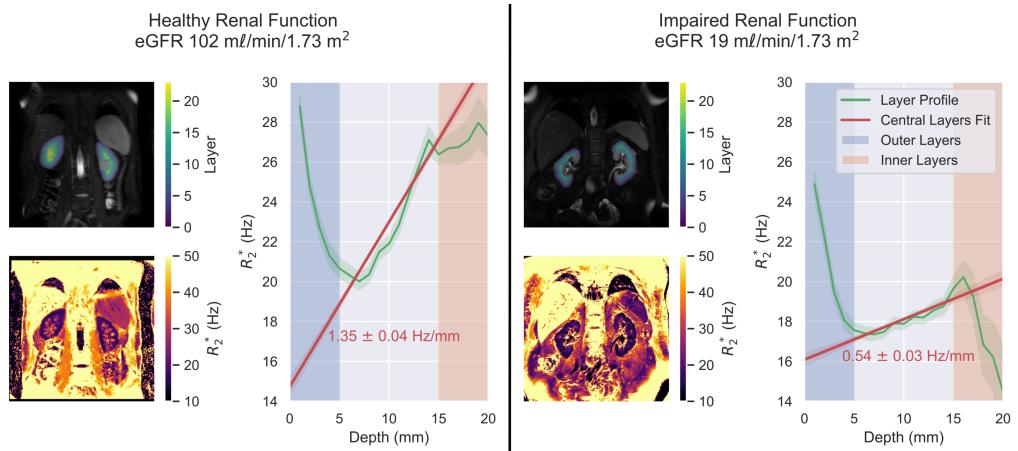


Figure 3: Layers, R_2^* maps and layer profiles measured using 3DQLayers for a subject with healthy renal function and a subject with impaired renal function. Shading around lines shows the 95% confidence interval.

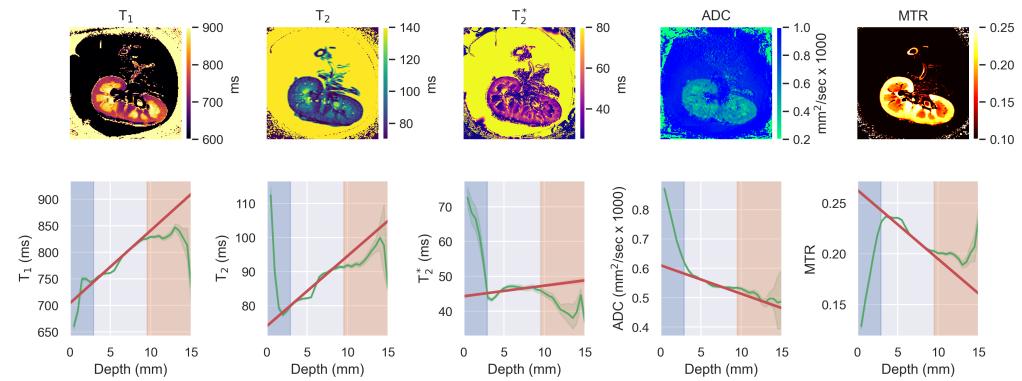


Figure 4: Example quantitative maps and associated depth profiles when 3DQLayers is applied to transplant kidneys. Uncertainty shading shows the 95% confidence interval of each layer.

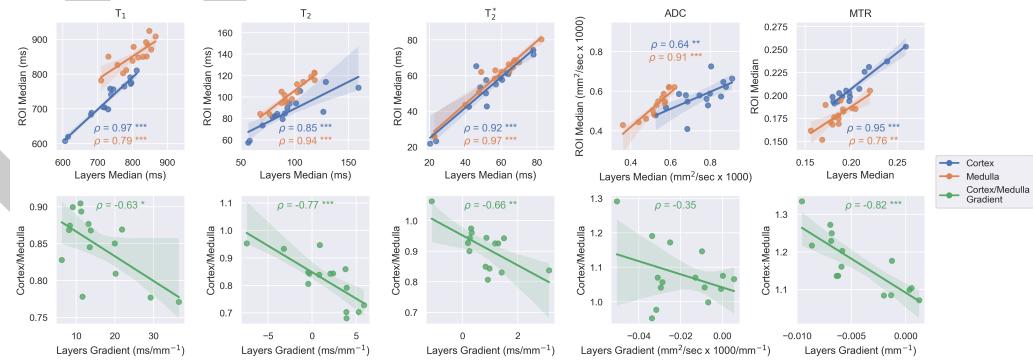
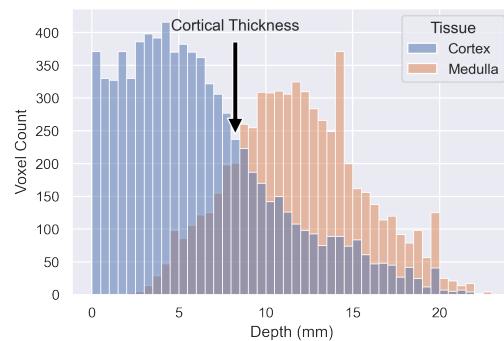


Figure 5: Agreement between tissue label-based analysis methods and layer-based analysis methods and the Pearson's correlation coefficient (\$ \$). * represents a p -value between 0.05 and 0.1, ** between 0.01 and 0.001, and *** < 0.001.



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Acknowledgements

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