A multi-nephron model of whole-kidney function for simulation of renal pathologies and blood pressure regulation

Robert G. MOSS[1,2], Thibault GROSSE[1,2], and S. Randall THOMAS[1,2]

[1]*IR4M UMR8081 CNRS, Orsay & Villejuif, FRANCE;*
[2] *University Paris Sud XI, Orsay, FRANCE*

Correspondence: stephen-randall.thomas@u-psud.fr ; +33 142114826; IR4M Equipe 3, Institute Gustave-Roussy, Service Imagerie, 1er sous/sol, 114 rue Edouard Vaillant, 94805 Villejuif, FRANCE

Introduction

Mathematical modeling has contributed much to our understanding of many aspects of kidney function [1,2,3]. However, to date, there has been very little effort to develop a model that faithfully represents whole-kidney function and dysfunction. We present the first multi-nephron model of whole-kidney function targeting physiopathology applications both at the level of intra-kidney defects and of systemic problems due to altered kidney function (i.e., hypertension). The model allows simulation/prediction of the consequences of defects in transport within individual nephron segments and of progressive failure of nephrons, as in chronic kidney disease.

The model is complete in itself for exploration of kidney function, but it is also "interoperable" in the sense that the source code is open source, the model can be used as a brick in multi-organ systems models (think of Guyton-type models [4,5,6]), and its variables and parameters are tagged with the VPH reference ontologies from the RICORDO project[1].

Model description and Numerical methods

The model represents the kidney as six lumped nephrons, representing six populations of nephrons of different lengths and with glomeruli situated at a different depths in the cortex. Extension of the model to include many more families of nephrons, using the same solution method, would be straightforward (with a corresponding increase in computational cost). The relative numbers of each population are scaled here to the rat kidney, but can easily be scaled to other species having a different ratio of short to long nephrons, different proportion of long loops reaching to the papilla, etc. The blood supply reflects the main features that are specific to the kidney, namely, all blood enters and leaves the kidney via the renal artery and renal vein, resp., and there is independent irrigation of the three kidney zones (cortex, outer medulla (OM), and inner medulla (IM)). Since there is no experimental evidence for heterogeneity of permeabilities of the vasa recta (the blood vessels carrying blood to and from the renal medulla), we represent the vasa recta as a shunted structure, thus treating the reduction of the number of vessels towards the papillary tip without needlessly increasing the number of tubes (which would considerably increase computation time).

Treatment of the corticopapillary osmotic gradient in the IM presented a special problem, since it is still not known how this gradient is really produced and maintained [7]. This osmotic gradient is nonetheless essential for maintenance of water balance, since it serves to concentrate (or dilute) the urine, so we adopted a strategy known to work in theory but not yet proven experimentally, namely, we assumed production of metabolically produced external osmoles (lactate produced from glucose in the hypoxic IM) [8,9]. This leads to realistic corticopapillary osmotic gradients of NaCl and urea and thus serves the purpose here.

The model also explicitly includes a the regulation of renal blood blow (RBF) and glomerular filtration rate (GFR) by TGF (tubuloglomerular feedback) and the myogenic response, and includes relevant aspects of the renin-angiotensin system (RAS).

[1] http://www.ricordo.eu/

Results and Discussion

The parameters for separate sections of the model have been "calibrated" based on available published experimental results for the various parts of the system, and overall behavior is compatible with a variety of experimental studies on animal models (especially in rats and dogs). Furthermore, the model has been incorporated into an extended version of the classic Guyton model of blood pressure regulation, in place of the over-simplistic renal module of that model. The result is a more robust model that allows exploration of a wider variety of pharmacological interventions and genetic polymorphisms that result in renal transport defects.

Conclusion

The model presented here is the first multi-nephron model to treat the main aspects of whole-kidney function at a level of detail appropriate not only to reproduce such global features as pressure-natriuresis (central to blood pressure regulation), but also to serve as a platform for exploration of hypotheses about the consequences of alterations of glomerular filtration, of TGF, or of transporters specific to individual nephron segments. Although the level of detail is not at the individual nephron level, the inclusion of several families of nephrons of different lengths allows exploration of certain types of progressive kidney failure.

Nonetheless, this is still far from a "definitive" model of the kidney — future models will undoubtedly include detailed transporter kinetics along the nephrons at the cellular membrane level, will treat additional solutes in order to deal with, e.g., acid-base regulation, and will move in the direction of true structure-function 3-D models with thousands of single-nephrons and blood vessels, based on anatomical reconstructions of actual kidneys.

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