THE RENAL PHYSIOME PROJECT

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ABSTRACT

We discuss current progress towards two complementary web resources being developed for the Renal Physiome: (1) a database (QKDB) for quantitative and anatomical data at all levels of kidney organization, including molecular-level information on membrane channels and transporters, structural and functional parameter values at the epithelial level, measured flows and concentrations along vessels and nephron segments, anatomical data (including imaging studies) at all scales, etc.; and (2) an interactive interface to mathematical models of kidney structure and function, built around a zoomable 3D virtual unilobed kidney. These resources will facilitate interaction among renal modelers, experimental laboratories, and clinical researchers.

1. INTRODUCTION

Present understanding of renal physiology has been achieved using a wide variety of experimental techniques and also owes much to hypothesis-based mathematical modeling studies. Both have been used at every scale from the molecular to the whole organ level, but there is a felt need for better integration across these scales, both for the experimental results and for the legacy of mathematical models of transport and flows at all scales. Furthermore, new advances in non-invasive imaging techniques show promise for questions traditionally difficult to approach because of the kidney’s particular problem of internal access (i.e., introduction of probes perturbs the very processes under study).

In the interest of developing a holistic approach to biomedical data integration and interpretation, the Renal Physiome effort is exploring possibilities for multiscale modeling and simulation explicitly targeting questions of physiopathology and has initiated a quantitative kidney database (QKDB)† to provide centralized access to measured parameter values, anatomical features, and functional characteristics at all scales from membrane transporters to the whole organ, both in human, when available, and in animal models. An interactive World Wide Web interface to legacy mathematical models at all levels of kidney physiology is also underway. Integral to the project is the development of ontologies, necessary to resolve issues of semantic ambiguity, consistency of descriptions, relational descriptions, and the like, and to enable integration with related resources in other fields.

2. RENAL IMAGING TECHNIQUES

Investigation of renal physiology depended largely on in vivo and in vitro tubule micropuncture and microperfusion in, especially, small animals with uni-lobed kidneys (rabbit, rat, hamster, chinchilla, etc.), on vesicle studies of channel and transporter properties in apical and basolateral cell membranes of the various nephron segments, and on biochemical studies, e.g., microdetermination of cAMP production or Na,K-ATPase in individual micro-dissected nephron segments [1][2].

Complementary to these, and sometimes playing an integral part, renal imaging techniques of many kinds have been essential, as reviewed by Hierholzer & Hierholzer [3]. In addition to the invasive techniques necessary in studies of tubular function and renal anatomy, the inspection and visualization of renal structure and function were revolutionized by non-invasive techniques such as ultrasound, use of radioisotopes, computer tomography, NMR, and X-ray imaging.

Dantzler and Pannabecker [4][5] have published results using immunohistochemical localization and computerized three-dimensional reconstruction to provide surprising new insights into the heterogeneous transport properties along the long loops of Henle in the rat inner medulla.

More recently, multiphoton techniques [6, 7] show great potential for applications that require deep optical sectioning

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1http://www.lami.univ-evry.fr/~srthomas/qkdb
of living tissue samples (such as the glomerulus and the inner medulla).

3. CONTRIBUTIONS OF RENAL MODELING

Mathematical models have contributed to our understanding of kidney function on many issues and at virtually every scale from molecular (transporter and channel function) to epithelial and whole kidney levels (for a recent review, see [8]). Of note very recently: (1) two modeling studies addressing issues of transport along the distal tubule [9], [10], incorporating new experimental findings (e.g., the presence of a peritubular KCl cotransporter) and treating variable cell volume in response to solute concentrations. These papers investigate, among other things, the response of cell volume to changes in solute delivery or peritubular composition, and the homeostatic effect of those volume changes; and (2) a timely modeling study [11] of the new and interesting results of Dantzler and Pannabecker [4,5], in which the authors identified two hypothetical modes that appear to be capable of expaining a significant IM osmolality gradient, based on the heterogeneous permeability values, while maintaining reasonable urine flow. Both modes are similar to the passive hypothesis previously described by Kokko and Rector [12] and by Stephenson [13].

4. RENAL PHYSIOME RESOURCES

Despite the important contributions of mathematical models mentioned above, they are often not consulted by the vast majority of renal physiologists because of their mathematical difficulty, and their development usually requires weeks or months of literature research to unearth measured values of relevant parameter values.

Two web resources are currently under development with the aim of helping with these two problems. First, a quantitative kidney database (QKDB) is intended to house accumulated published measurements (across all studied animal species). This will not only streamline the development of future models, but will also provide a valuable central source for easy cross-species comparisons. Second, a web interface for interactive access to the collection of legacy mathematical models of kidney structure and function, with particular attention to creating a convivial interface for modification of model parameters, launch of custom simulations, and presentation of the results.

The glue that binds these two resources is a common renal ontology, currently under development.

4.1. QKDB: a quantitative kidney database

Our Quantitative Kidney Database, QKDB [14] is already in use among a small group of collaborating laboratories. We have established a flexible, extensible, and generic data model (entity-relationship model) for the database, have implemented this under MySQL, and have built (using PHP) a web GUI with basic functionality. This database is being seeded from the bibliography resources of the present project participants and is open not only for consultation but, equally importantly, for (password protected) contributions from the renal research community. This resource will thus put legacy measurements, as well as recent and new data, at the ready disposal of renal researchers, thereby facilitating comparisons of results obtained in different species and under various experimental conditions. It will especially include the following types of information, for human kidneys where known, but especially in experimentally studied species (mammalian, amphibian, avian, ...) and in model epithelia such as cultured cells and amphibian skin and urinary bladder:

- transport parameters, such as permeabilities to water and various solutes, kinetics of transporters and channels, in all nephron and vessel segments and kidney regions,
- tubular concentrations and flow rates along the various segments of the nephron and vessels,
- qualitative and quantitative anatomical details, such as: tubule diameters and epithelial and cellular dimensions for the various nephron and vessel segments; relative placement of structures in each kidney region; typical kidney sizes and weights for different species; dimensions of cortical and medullary regions and subregions; and of course anatomical images, etc.
- and the list can be extended as needed.

Importantly, the experts who enter the data via the web interface are encouraged to include annotations concerning experimental conditions, relevance & limitations of experimental techniques, etc. Quality control of the curated data is assured at several levels. In addition to syntax checking on entry form contents and the use of pull-down menus built dynamically from the contents of the database (thus avoiding duplication and multiple spellings of field names), the data will be entered only by authenticated researchers, under password control. Finally, a board of experts will oversee new entries before they become accessible to web queries.

4.2. Interactive web interface to kidney models

We are developing a modeling resource consisting of an interactive web interface to a collection of legacy models at all levels of kidney physiology, with, for each curated model: documentation, physiological context, easily interpreted output, a statement of model limitations, interactive exploration, and user-customization of selected parameter values. Within a 3D-virtual-kidney graphical user interface (GUI), development will proceed in two phases: – initially, inclusion of a
core collection of models: glomerular filtration; several simple tubular models (PCT, DCT); simple TGF model; simple medullary models (basic central core; six-tube, ‘flat’ medulla); – in a second phase: work toward a comprehensive collection of renal models and their translation into a common markup language.

At present, we have developed two prototypes on which we will build: a Java applet\(^2\) to display simulation results, and an initial "virtual kidney" interface [15][16][17]. To ground the development in a realistic context, we used one of our own models of the renal medulla [18] as a test case for both interfaces.

In the Java applet prototype, separate web-pages present: the history and description of the model itself and a window giving entry into a Java applet. The visitor may choose among a small set of previous simulations or may launch a new simulation based on his/her modifications of a selected set of model parameter values. The applet loads the simulation results as an XML file and displays them as x-y plots or as a color-gradient diagram of the medullary structures.

The present version (Figure 1) of the “virtual kidney” interface was constructed from casts of a rat kidney, but is still incomplete. For exploration of kidney anatomy, the model can be zoomed, rotated and even disassembled using the mouse and its buttons. For example, the capsule (cortex), outer medulla and blood vessels can be removed, revealing anatomically correct superficial and juxtamedullary nephrons whose paths through the outer and inner medulla can be examined by rotating and zooming. We will use this interface not only for exploring kidney anatomy but also as an interface to a collection of curated, interactive models at various scales. At present, we have begun by implementing one of our own models of the renal medulla [18] and a model of transport along the distal nephron [19]. The latter model was coded into CellML and FieldML (a collaborative effort with the teams in Auckland and Melbourne) [20] as a test study towards which we intend to evolve. This GUI (graphical user interface) is being built using the XUL environment of the Mozilla group (open source development tools) to provide a web front-end for the 3D visualization environment (CMISS/CMGUI) developed by the group of Peter Hunter in Auckland.

5. CONCLUSIONS

The long-term goal of the Renal Physiome project is to take structural and physiological data at the molecular, cell, tissue, and organ levels, and combine them with advanced modeling techniques to produce a multi-level, structurally and functionally integrated, quantitative, computer based hierarchical model (or nested set of models) of the mammalian kidney [21]. The more immediate goal is to develop progressively more integrated models spanning several levels of organiza-

![Fig. 1. 3D-Virtual Kidney interface. The model can be zoomed, rotated, and even disassembled using the mouse and its buttons.](http://www.lami.univ-evry.fr/∼srthomas/kidneysim/)

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7. REFERENCES


