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The Virtual Kidney: an eScience interface and Grid portal

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The Virtual Kidney uses a web interface and distributed computing to provide experimental scientists and analysts with access to computational simulations and knowledge databases hosted in geographically separated laboratories. Users can explore a variety of complex models without requiring the specific programming environment in which applications have been developed.

This initiative exploits high-bandwidth communication networks for collaborative research and for shared access to knowledge resources. The Virtual Kidney has been developed within a specialist community of renal scientists but is transferable to other areas of research requiring interaction between published literature and databases, theoretical models and simulations and the formulation of effective experimental designs.

A web-based three-dimensional interface provides access to experimental data, a parameter database and mathematical models. A multi-scale kidney reconstruction includes blood vessels and serially sectioned nephrons. Selection of structures provides links to the database, returning parameter values and extracts from the literature.

Models are run locally or remotely with a Grid resource broker managing scheduling, monitoring and visualization of simulation results and application, credential and resource allocation. Simulation results are viewed graphically or as scaled colour gradients on the Virtual Kidney structures, allowing visual and quantitative appreciation of the effects of simulated parameter changes.

Keywords: kidney modelling; computational biology; three-dimensional anatomical visualization; Grid computing; Physiome; cyberinfrastructure

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One contribution of 15 to a Theme Issue 'The virtual physiological human: tools and applications II'.

1. Background

(a) The Physiome and virtual physiological human

The Kidneyome project, also known as the 'Virtual Kidney', is part of the larger International Union of Physiological Sciences Physiome Project, an internationally collaborative open source project to provide a public domain framework for computational physiology, including the development of modelling standards, computational tools and web-accessible databases of models of structure and function at all spatial scales: interactions; protein pathways; integrative cell function; tissue and whole-organ structure–function relationships (Thomas *et al.* 2008; Thomas in press); and finally the integrative function of the whole organism (Bassingthwaighte 2000; Hunter & Borg 2003). A key initiative for promoting and supporting development of the Physiome in the European Seventh Framework Programme is the virtual physiological human (VPH), which has been defined as 'a methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system'. VPH is *not* 'the supermodel' that will explain all possible aspects of human physiology or pathology. It is a way to share observations, derive predictive hypotheses from them and integrate them into a constantly improving understanding of human physiology/pathology, by regarding it as a single system (Fenner *et al.* 2008).

The Virtual Kidney represents an information management model that can be implemented for other organ systems within the Physiome Project or the VPH (or, indeed, for non-biological systems). It provides access to facilities for computational modelling where geographically separated scientists require access to computational models, specialized parameter databases, management of distributed computing power and visualization of experimental data. Information architectures included in the Virtual Kidney provide integration of parameter and evidence-based databases, computational models, text-mining tools and distributed computing solutions with flexible and intuitive real-world interfaces and visualization options. These features will support developments in virtual experimental design and are likely to be of significant value in the development of clinical decision support environments.

The Virtual Kidney project is concerned with the development of an interactive distributed web-based repository of models of the mammalian kidney. An interactive portal incorporates a three-dimensional anatomical image of a generic kidney with a multi-scale representation that provides a tool for browsing and access to a collection of distributed published models at all levels of renal physiology. This enables researchers to integrate and combine existing and new models, and non-modellers to interact with the models, altering key parameters according to their own hypotheses and visualizing the simulation results in a variety of formats. The portal will include the existing types of models relevant to renal physiology, including kinetic models of transporters and channels, transport models of individual cell types, flat model epithelia (such as bladder and cultured epithelia) and tubular segments along the nephron, models of the microcirculation, of tubuloglomerular feedback and of inner and outer medulla at various levels of detail. Importantly, the portal will provide access to alternative models for various mechanisms, which may be based on different

interpretations of the experimental data. To date, it has been more usual for an experimenter or modeller to select a single preferred model because it has been difficult to interact with alternative versions that have been developed in other laboratories using different programming environments.

Further development of the functional and structural kidney models will take into account the variety of scales, numerical methods and programming languages used in kidney modelling studies, and implementation of the resource will be facilitated by translation of the models into established biological system markup languages such as CellML and FieldML (Lloyd *et al.* 2004). For proof of concept, we have implemented a simulation of a particular kidney function, namely regulation of fluid and electrolyte transport, by modelling transport within a specific cell type (distal tubule cells of the early distal convoluted tubule (DCT)). The implemented model concerns only distal tubule cells of the early DCT; later models, to be added during planned enhancements, add principal and intercalated cells and integrate the cell model into a length of distal tubules. Further extensions will include implementation of cellular transport models in all segments in a single nephron, and then as a parallel system representing the whole kidney.

The major resources and connectivity associated with the current implementation of the Virtual Kidney are shown in figure 1.

(*b*) *eScience portals*

An eScience portal is simply a website or desktop tool for accessing and running scientific applications and data, or linking together such applications into tool chains. Such portals have several different flavours, which are as follows.

— *Desktop utilities*. Graphical user interfaces (GUIs) for wrapping command-line applications, which allow users to launch and run applications on a remote supercomputer using a 'drag and drop' style GUI that hides complexity and platform dependencies. Many of these have been developed, e.g. as part of the USA 'Science Portals' initiative, but adoption has been limited as they do not offer significant productivity gains and often hide or limit access to applications.
— *Workflow wrappers*. Building a 'wrapper' around a chain or collection of tools to automate common operations (e.g. Kepler, or more recently in the bioinformatics domain, Bioconductor or GenePattern). These tools are becoming more common or popular in cutting-edge bioinformatics research, as they automate or simplify the process of running chains of tools (e.g. a mass spectrometry tool for proteomics, followed by a statistical analysis tool followed by a link to a database tool for genetic information).
— *Integrative research platforms*. Tools that allow users to combine and/or explore several tools, data observations and research. Such tools are far less mature and are open research areas. The Kidneyome portal described in this paper is such a tool.

Research can be classified as experimental/observational, modelling/simulation or integrative, where integrative means combining multiple observations/experiments and models developed by different research teams. It is clear that integrative research is becoming increasingly important as new

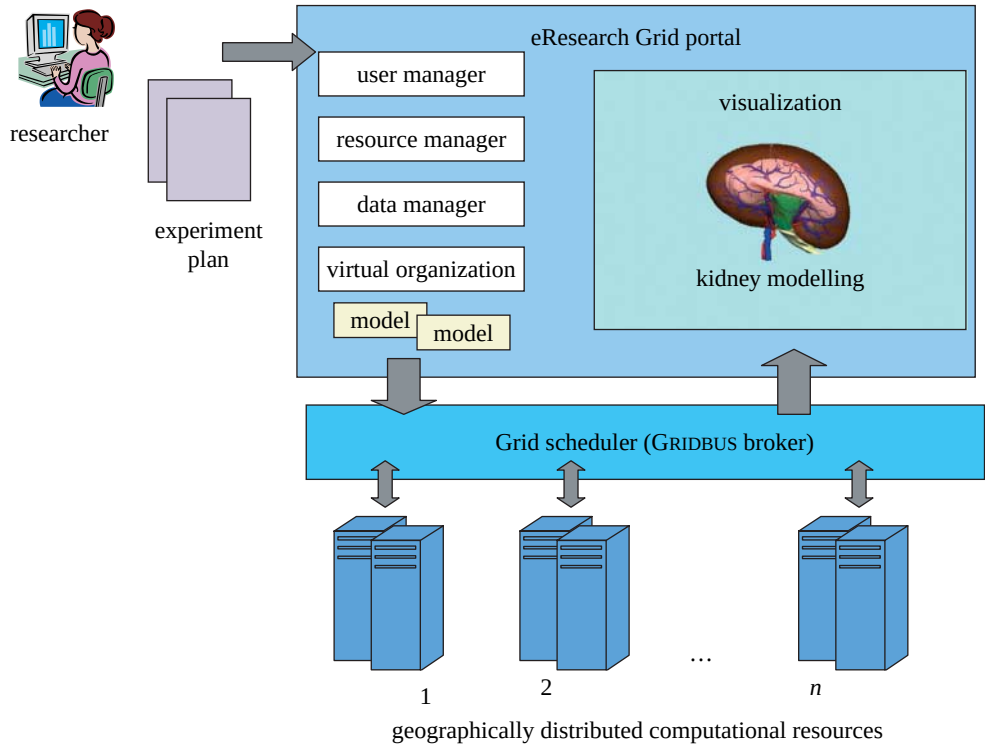

Figure 1. Overview of the resources and connectivity involved with operation of the Virtual Kidney (Kidneyome). A three-dimensional interactive interface allows users to explore the anatomy of the kidney and provides access to the quantitative kidney database (QKDB). A Grid portal presents a user interface to distributed kidney models enabling researchers to integrate and combine existing and new models, and non-modellers to alter key parameters and visualize simulation results.

insights and knowledge build on the increasing wealth of observational data and legacy models (Stein 2008). Integrative research is highly dependent on software platforms and it is important to distinguish between software platforms and conventional software tools, such as spreadsheets or toolkits such as Matlab. Software platforms are designed to seamlessly integrate the existing tools together, and are specifically designed to meet the needs of a research community, unlike general purpose tools such as Matlab.

The high-level generic architecture of an eResearch platform to support integrative Physiome research is illustrated in figure 2.

The 'front end' or user interface to an eResearch platform for Physiome research is typically a web portal: a website that provides information from diverse sources in a unified way. A generic eResearch portal can provide the following range of services and middleware.

— A 'user manager' for authentication, and managing a user's environment and preferences (often integrated into the portal).
— A 'virtual organization (VO) manager' to allow users to form and join projects to share resources such as observational data or models on a per-project basis (Alfieri *et al.* 2003).

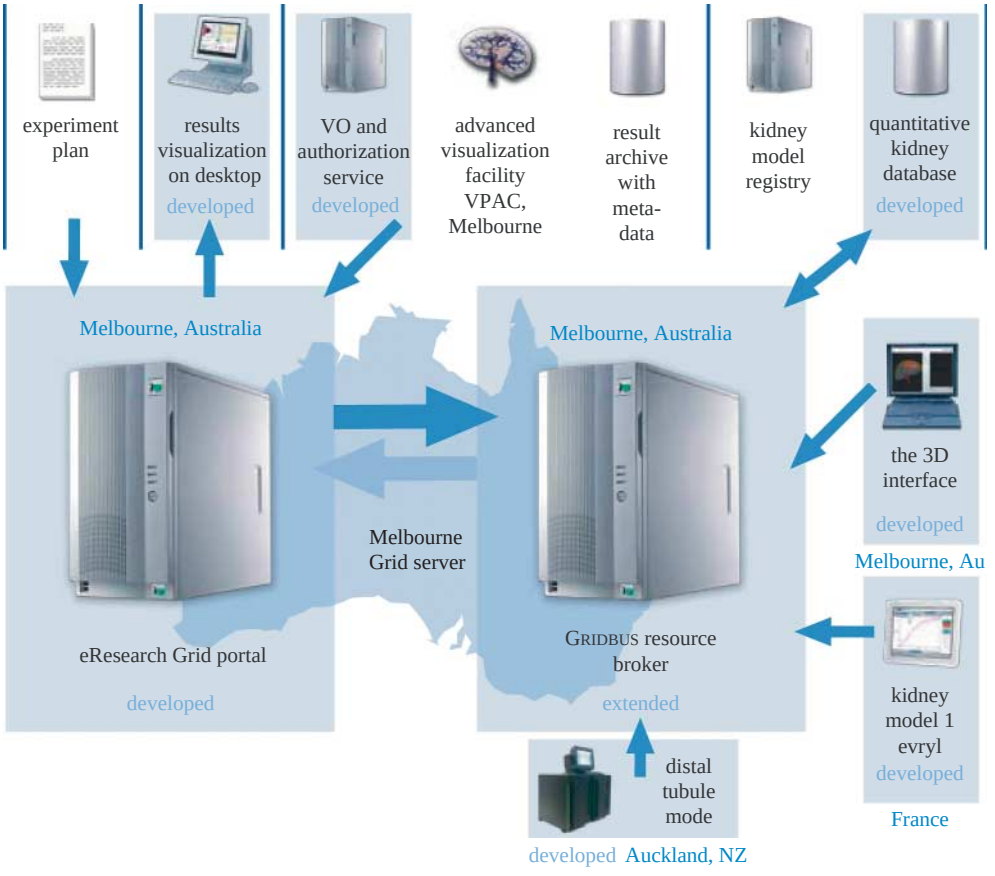

Figure 2. The high-level generic architecture of a Grid-based eResearch platform to support integrative Physiome research.

— A 'resource manager' managing the top-level resources available to a user, including resource discovery processes such as 'metadata services' and providing wrappers to legacy services.
— A 'data manager' to provide access to Grid data sources through interface standards such as STORAGE RESOURCE MANAGER (http://sdm.lbl.gov/srm-wg/) or brokers such as STORAGE RESOURCE BROKER (Baru *et al.* 1998).
— A 'Grid scheduler' running remote computational models and assembling the results. An example relevant to this paper is GRIDBUS (Venugopal *et al.* 2004).

Underlying most current eResearch projects is the notion of a 'Grid' (Foster & Kesselman 1999), or underlying infrastructure and middleware that connect together compute and data infrastructure across a wide area network, for example the Globus TOOLKIT and middleware (Foster & Kesselman 1998).

More recently, the concept of a Grid has been superseded by 'cloud computing', which is a Grid in which the physical connections are hidden from the user and a user can assemble a cloud of resources and tools. Cloud computing

simply means that the integrative research platform must hide Grid tool details and dependencies from users, and conversely that the Grid tools, such as PBS and Condor in figure 1, must support interoperation better.

(c) *Mathematical modelling for the kidney*

Mathematical modelling has been used for many years in analysing the operation and function of complex biological systems and, in particular, the approach has been very successful in modelling heart physiology ranging from the molecular level to the whole organ (Noble 2002; Hunter & Nielsen 2005). Computational modelling has long played a key role in research on kidney physiology, and research groups around the world have constructed a wide variety of mathematical models in different formats and simulation environments. These models have been useful tools for their developers but have often been proprietary with limited interoperability, restricting access to other users and providing barriers to the integration of models derived from different sources.

The World Wide Web coupled with distributed computing resources provides opportunities to integrate and explore renal models in a distributed model repository, allowing researchers a ready and interactive access to a collection of models and resources that minimize the requirement for specialist programming or computational modelling expertise on the part of the experimenter. Such knowledge systems or 'cyberinfrastructures' are becoming available in many areas of eScience (Stein 2008), and it is timely to consider their development and deployment in the areas of physiology and related life sciences.

The direction of mathematical modelling in research on the physiology of renal transport systems has been determined by the complex interactions among coupled flows, kidney metabolism and detailed anatomy at all levels of kidney organization, and also by the inaccessibility of the inner kidney structures to *in vivo* intervention. The behaviour *in vivo* of nephron segments and blood vessels 'hidden' within the kidney interior must be inferred from micropuncture samples taken at accessible surface sites, from measurements performed *in vitro* by such techniques as microperfusion, vesicle studies, patch clamp, immunofluorescence imaging and from the anatomical/architectural features of the kidney. Theoretical analyses have been crucial to quantitative formulation of working hypotheses, interpretation of experimental results and development of new experimental techniques required for the measurement of crucial parameters whose importance was appreciated during modelling studies. For example, modelling studies have helped our understanding of glomerular filtration, (quasi)isotonic reabsorption in the proximal tubule, the roles of several nephron segments in acid–base regulation and the mechanisms involved in autoregulation and tubuloglomerular feedback. The importance of countercurrent flows in proximal tubule fluid reabsorption and in the many 'cycles and separations' relationships among medullary nephron segments, collecting ducts and medullary blood vessels, and details of medullary microcirculation in relation to solute and water recycling have also been the subjects of extensive modelling where measurements have been difficult or impossible.

The models targeted for implementation in the core collection cover a wide range of scales and represent some of the classic studies in the field. The initial implementation of three example models is reported in this paper and it is

planned to revise the range of interaction options and the interface in response to feedback from users. Authors of other models will be encouraged to assist with the preparation of their models for inclusion in the Virtual Kidney. The current list of examples includes (but will not be limited to) the following:

(i) proximal tubule reabsorption (Weinstein 1986, 1994, 1998*a*,*b*; Thomas & Dagher 1994);
(ii) distal tubule reabsorption (Chang & Fujita 1999);
(iii) tubuloglomerular feedback (Holstein-Rathlou & Marsh 1990; Holstein-Rathlou *et al.* 1991; Layton *et al.* 1991);
(iv) glomerular filtration (Deen *et al.* 1972);
(v) medullary models of the urine-concentrating mechanism
— simple central core model (Stephenson *et al.* 1976, 1987; Foster & Jacquez 1978);
— multi-individual-nephron flat model (Lory 1987; Thomas 1991);
— shunted-multi-nephron flat model (Hervy & Thomas 2003);
— inner medullary collecting duct acid–base transport (Weinstein 1998*a*,*b*); and
(vi) a library of channel and transporter kinetics models.

2. The Virtual Kidney: an eScience portal

A web-based eScience portal has been developed for access to experimental data and parameter values abstracted within a quantitative kidney database (QKDB) and to a repository of mathematical models of kidney function.

There are three specific aims for the project.

(i) *Workflow automation.* To implement the infrastructure necessary for interacting with the core set of remote modelling resources on diverse computing platforms, and managing this Grid-based collaborative online resource in terms of communication protocols, user management, session management, authentication, resource registration, etc.
(ii) *Visualization and data fusion.* To develop software for converting and rendering diverse result sets from the core set of legacy models in a common web-based three-dimensional interface.
(iii) *Model integration.* To adapt the development-intensive interface tools to the particular problems posed by kidney modelling so that we can proceed with integration of many more models at all scales with only minimal changes in the interface software. The 'workflow' is not rigid or fixed and new models can be readily added and/or adapted. This is the emerging trend in bioinformatics and is a feature of tools, such as GenePattern, which allows a flexible integration of genetic and proteomic analysis.

(*a*) *Three-dimensional portal*

The portal presents a cross-disciplinary approach to providing researchers with access to computational models developed in laboratories around the world and uses global distributed computing to manage workflow and deliver solutions to the user's desktop.

The user is presented with a three-dimensional 'Virtual Kidney' interface, based on a translucent multi-scale reconstruction of a rat kidney showing major anatomical structures as well as renal arteries and veins to several levels of branching derived from synchrotron images (Nordsletten *et al.* 2006). Within the kidney are examples of reconstructed serially sectioned nephrons. The user can rotate the kidney, display or hide individual structures and zoom in on any portion. The selection of a structure provides a link to the search facility of a specialized database, the QKDB, which contains a comprehensive catalogue of parameter values, extracts from the literature and other relevant resources, such as collections of anatomical and histological images.

The basic principle is to create a web page that presents the user (i.e. the visitor to the website; also called the 'client') with an annotated list or a visual interface for selection of one of the available models. Once this choice has been made, the user is presented with a more detailed description of the chosen model, including literature references, and is given the opportunity either to look at the results of some pre-configured simulations to 'get the feel' of the model, or to alter particular parameter values (within a constrained range representing physiologically reasonable values) in order to customize the model as required. Upon submitting the new parameter values, the user will be served, after a wait that depends on the execution time of the model calculations, with the results and may choose among several styles of presentation. These include simple tables or graphical output, or in some cases more visually appropriate presentations, or the user may request to download the results as a table for post-treatment in a spreadsheet or graphing program of their own. An important feature of the portal is the ability to save 'session state', such that users can return to an interactive session and take up where they left off.

The screenshots shown in figure 3 are derived from an early version of the Virtual Kidney interface (Lonie *et al.* 2004). This preliminary model was constructed from micro-CT scans of a rat kidney and serially sectioned casts of mouse kidney tubules. The model is designed not only for exploring kidney anatomy but also for allowing a selection of structures with linked access to QKDB and for the collection of curated, interactive models at various scales. When running some simulation models, spatial distributions of quantitative output data derived from calculations from models can be mapped onto the anatomical representation in various ways. For instance, solute concentrations derived from a nephron flow model can be mapped back to the nephron graphically using look-up tables to colour code ranges of concentration and assigning the relevant colour to voxels representing the location of solutions of this concentration (figure 3, right side). This GUI is built on the XML User Interface Language environment of the Mozilla open source browser. It is effectively a web-based version of a stable and proven three-dimensional visualization environment developed by the Bioengineering Institute in Auckland, which has been used extensively for cardiac physiology simulation and cardiac anatomy navigation (Christie *et al.* 2002). The Melbourne-based members of our group have been working closely over the past few years with the Bioengineering Institute to develop the web-based version of this environment, and enhance the environment with the specific functionality required for rendering renal modelling results. This work has also addressed the need to develop the software tools required for converting and rendering diverse sets of kidney modelling results

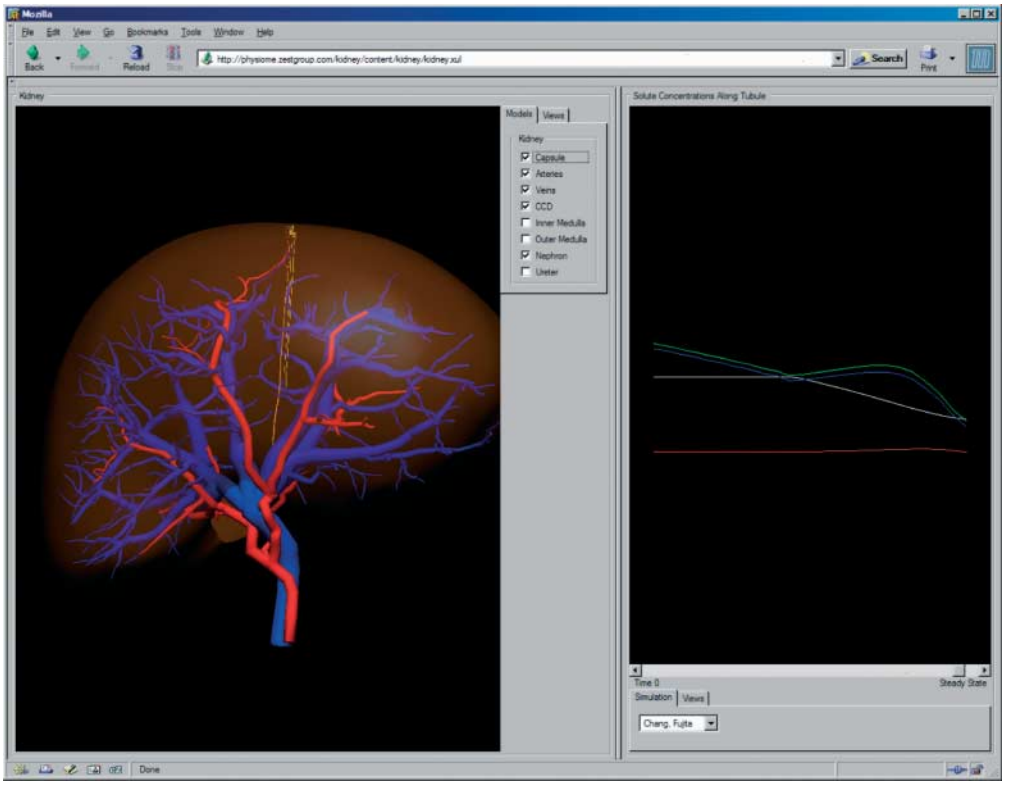

Figure 3. Screenshot of the Virtual Kidney interface showing (left side of screen) the three-dimensional anatomical representation of a kidney with vasculature and example nephrons, derived from reconstructed serial sections and (right side of screen) graphical output of a distal tubule simulation (Chang & Fujita 1999) in which selected solutes (shown in colour) are plotted as concentrations against distance along tubule segment.

in this common three-dimensional interface—for instance, converting and rendering the results depicted in the kidney simulation (KSIM) interface depicted in figure 3. The Virtual Kidney interface is intended both as a means of navigating the model databases and as a means of running model simulations and viewing simulation results, with the only requirement being a Mozilla-based browser.

(*b*) *Quantitative kidney database*

Our QKDB (Dzodic *et al.* 2004; Ribba *et al.* 2006) is open via a web GUI (http://physiome.ibisc.fr/qkdb/) and is in use among a small group of collaborating laboratories. It is built on a flexible, extensible and generic data model (entity-relationship model) implemented under MYSQL/PHP/APACHE. This database has been seeded from the bibliography resources of the present project participants and presently includes experimental data from some 300 research publications. QKDB is open not only for consultation but, equally importantly, for (password-protected) contributions from the renal research community. This resource thus puts 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 includes the following types of information, for human kidneys where known, but especially in experimentally studied species (mammalian, amphibian and avian) and in model epithelia such as cultured cells and amphibian skin and urinary bladder:

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

Importantly, the experts who enter the data via the web interface are encouraged to include annotations concerning experimental conditions, relevance and 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 are entered only by authenticated researchers, under password control. Finally, a board of experts oversees new entries before they become accessible to web queries.

(*c*) *Model repository and links*

The portal provides an interactive user interface to a collection of distributed published models at all levels of renal physiology, enabling researchers to integrate and combine existing and new models, and non-modellers to interact with the models, altering key parameters according to hypotheses of their own and visualizing the simulation results. The portal will include all existing types of models relevant to renal physiology, including kinetic models of transporters and channels, transport models of individual cell types, of flat model epithelia (such as bladder and cultured epithelia) and of tubular segments along the nephron, models of the microcirculation, of tubuloglomerular feedback and of inner and outer medulla at various levels of detail. Importantly, the portal will provide access to alternative models for various mechanisms, which may be based on different interpretations of the experimental data. To date, it has been more usual for an experimenter or modeller to select a single preferred model since it has been difficult to interact with alternative versions that have been developed in other laboratories using different programming environments.

The underlying models are implemented via XML markup descriptions (e.g. CellML, see www.cellml.org) or as executable program files stored locally on the server or remotely (e.g. on the model author's server). We have sought approaches that are consistent, as far as possible, with standards and ontologies being developed for other organs under the Physiome initiative.

A menu lists the repository of mathematical models, such as segmental (e.g. proximal or distal tubule), regional (e.g. medullary transport) or multi-nephron complex systems models, which may be run on the local machine or, via a Grid portal (KidneyGrid), simultaneously on several remote machines. The simulation results (e.g. solute concentrations or local flow rates) are visible on the Virtual Kidney structures as scaled colour gradients, thus allowing a visual and quantitative appreciation of the effects of simulated parameter changes. Figure 4*b* shows x–y plots of the results. The selection of a progressive set of parameter changes allows systematic evaluation of the effects of changes in one or more elements of a model and can be used to predict the probable outcomes of experimental interventions. This approach is likely to become an increasingly important aspect of experimental design testing and could have significant benefits in determining the cost-effectiveness of experimental programs.

The portal allows scientists to explore from their desktop a variety of computational models that have previously been accessible only within the laboratory in which they were developed. It is important to note that the listed legacy kidney models and resources represent a number of different implementation techniques (different modes of interaction—command line, graphical interface and command file driven—running on different platforms). An interoperability problem arises during attempts to integrate or co-locate such legacy models because standards have not been available or adopted for data representation, interaction or communication.

There are several ways of addressing this issue, the best of which might be to recode all the models in a common representation format as discussed above. However, this is obviously a long-term and resource-intensive solution, and probably not feasible without a direct and substantial input from each of the model developers.

We have adopted a reasonable alternative approach, namely to develop interaction 'wrappers' around the current model implementations and convert the output in the central portal so that diverse result sets can be rendered on a common interface. This approach requires infrastructure 'middleware' to manage the communication channels, data transfer channels, user session state, user authentication, etc., within the context of a central portal.

(*d*) *Model examples*

(i) *Distal tubule reabsorption and secretion*

The implementation is based on the model of Chang & Fujita (1999); currently, we have two cell types working with advection–diffusion spatial modelling and have demonstrated agreement of the numerical output with that in the published work. This has been implemented and currently provides the luminal output results. The intracellular and other output results documented in the original publication have not been included as yet. In the longer term, the aim of the Kidneyome project is to develop a platform for 'plug and play' modelling, where there is a standard basis of representation for all models (preferably an XML-based open modelling markup language such as CellML; see www.cellml.org) and data representation is similarly standardized. We have made initial proof-of-concept moves towards this goal by developing a CellML-based

implementation of the Chang and Fujita model (although the input and output data formats are still 'proprietary' to some extent) and rendering the results in an open standards-based three-dimensional interface. The next stage will involve integrating the transport characteristics of the various distal tubule cell types to model fluid dynamics and ionic fluxes along this tubule segment in the context of an accurate structural nephron model. Detailed models of distal tubule transport are of interest because gain-of-function mutations in distal tubule transporters (e.g. the thiazide-sensitive NaCl cotransporter) or ion channels (e.g. epithelial Na channel) involved in reabsorption of sodium chloride are implicated in several forms of hereditary hypertension (Lifton *et al.* 2001; Tripodi *et al.* 2004).

Future extensions will include a library of kinetic models of the different channels and transporters (and their various isoforms) expressed in all cell types along the nephron and implementation of cellular transport models in all segments in a single nephron, and then as a parallel system representing the whole kidney.

(ii) *Medullary models of the urine-concentrating mechanism*

Shunted multi-nephron flat model (Hervy & Thomas 2003) KSim present state. A prototype Java applet (http://www.ibisc.univ-evry.fr/~srthomas/kidneysim/) has been used to display simulation results, and its use is demonstrated for one of the models of the renal medulla (Hervy & Thomas 2003). On this website, separate web pages present: the history leading up to the development of this particular model; a description of the model itself, including a table of the basic parameter values; and finally a window giving entry into a Java applet for presentation of simulation results. The visitor may choose among a small set of previous simulations (typical of those presented in the published paper) or may launch a new simulation (server-side execution) based on their modifications of a selected set of model parameter values. The applet loads the chosen set of simulation results in the form of an XML file and permits the web visitor to display them as x–y plots or as a colour gradient diagram of the medullary structures (figure 4).

Development of this demonstration provides valuable experience concerning the possibilities and limitations of existing graphics packages for Java applets and reveals key development features for development of a more flexible and generic approach for use with the variety of models projected for the Kidneyome site.

(iii) *Multi-nephron model*

In addition to segmental and medullary transport models, the portal currently supports a multi-nephron model as demonstrated by the inclusion of a dynamical network model (Moss *et al.* 2009). The modelling approach combines network automata, graphs in which each node has a state and a set of rules for changing the state, into a single model. The structure of the model is explicitly represented as a network of graph automata, which captures the hierarchy, interactions and couplings in the system. The model captures the dynamics of a system of nephrons by maintaining a *system state* at each node of the network, and through a set of *update rules* that operate on the state at each node. This approach is well suited to studying emergent dynamics—dynamics that arise from the

interactions and couplings between nephrons—at different levels of hierarchy. The purpose of this model is to explore the ways in which the stability of whole-kidney function arises from the dynamics of individual nephrons.

The nephron tubule is modelled as one-dimensional graph automata, consisting of one node for each functionally distinct nephron segment and one node for each layer of interstitial medullary fluid in which the nephron is situated. Larger systems of nephrons are built up by connecting with edges multiple nephron models to the same interstitial fluid nodes. Whole-kidney models can be constructed by mimicking the renal pyramid structure of the kidney and collecting duct systems and relating regions of interstitial fluid to an *arterial tree*. The arterial tree is modelled as a hierarchical network, which distributes blood to each nephron automatum in proportion to the resistances of the pre-glomerular blood vessels including the afferent arterioles.

Interactions between nephron segments and between nephrons and the interstitial environment are achieved via the edges of the network and the update rules that operate on the nodes of the graph. Nephron dynamics are captured by discrete time and difference equations. Solutions are obtained for new inputs or disturbances by combining multiple equations to reach a shared equilibrium; for example, as in the diffusion of water within multiple descending limbs of Henle. Equations are solved simultaneously using Gaussian elimination.

The model has been used to study emergent dynamics, and the interactions that arise between haemodynamic coupling and vascular signalling, in the context of two-, eight- and 72-nephron systems. The experiments performed to date have focused on the dynamics of systems of nephrons, rather than individual nephrons or nephron segments. Specifically, the experiments have explored changes in the filtration rates of entire columns of nephrons, and the filtration rate of the system as a whole and exploring the power spectral densities to determine the dominant frequencies present in these filtration rate values. The experiments demonstrated that the degree of vascular signalling present between nephrons in the system affects both the magnitude of their filtration rates and also which frequencies are dominant.

Further experiments using this model have studied the emergent effects of localized perturbations of selected input parameters on whole-system behaviour. In a typical analysis, the reabsorption of water in the descending limb of Henle was impaired for a fraction of the nephrons in the system, and the effects on the whole-system filtration rate were observed. These experiments consistently demonstrated that the system dynamics were highly stable and were only slightly affected by the impairments. These experiments were the first study of the emergent dynamics produced by impaired nephron function, and serve to illustrate how the model may be used to predict emergent dynamics induced by localized renal disease. An example of the use of the portal to select input parameter data and to display the output from the model is shown in figure 5.

This modelling approach has been demonstrated to scale up to much larger systems than existing multi-nephron models (Marsh *et al.* 2007). Based on timing measurements and a performance analysis of the model implementation, the simulation of whole-kidney function based on the dynamics of individual nephrons is feasible for the first time. A simulation can also be distributed over multiple computers, resulting in a performance gain of up to a 10-fold speed up when compared with a single computer simulation. In order to simulate

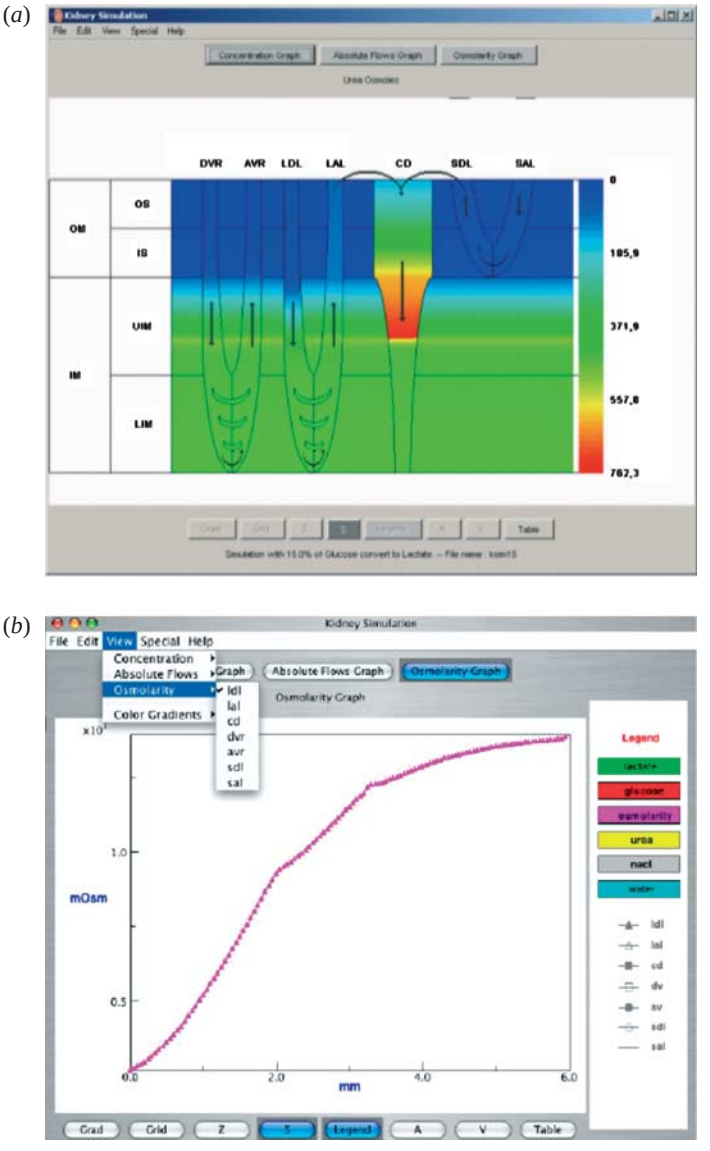

Figure 4. Medullary model of the urine-concentrating mechanism. (*a*) Example result showing distribution of urea concentration within the medulla, displayed using a colour gradient to represent concentration values. (*b*) Graphical output from the model representing changes in osmolarity along the length of the long descending limb of the loop of Henle (ldl).

whole-kidney function, a model of an entire kidney (e.g. the human kidney contains approx. 1 million nephrons) is required and since the network model is compositional, it is possible to grow a whole-kidney model.

Using the network model, experimenters can also explore the emergent dynamics of multi-nephron or whole-kidney models. Various parameters can be controlled by the experimenter, such as the degree of haemodynamic coupling and vascular signalling in the system, the filtration rates of the individual nephrons and various parameters governing fluid and solute transport. More

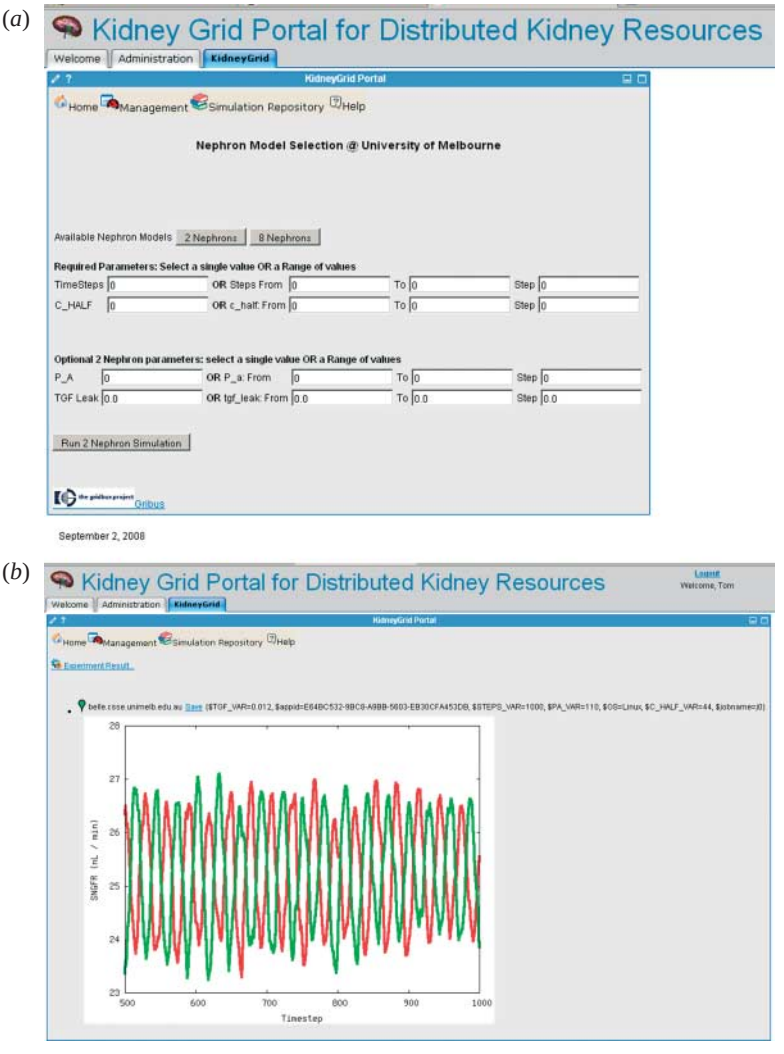

Figure 5. Example of the use of the portal to run the multi-nephron model. (*a*) Input parameters screen allows the choice of two-nephron or eight-nephron model and provides for selection of parameter scan within a range or over a series of designated time steps with single values for each parameter under investigation. (*b*) Example results from two-nephron model (red or green representing each nephron in the pair). When plotted against time, single nephron glomerular filtration rate in each nephron is shown to oscillate out of phase with the other.

importantly, the network allows us to replace any of the currently used update rules with equations from other models. The systems that are available for experimentation through the portal are currently limited to two-nephron and eight-nephron models but models of up to 512 nephrons have been executed.

(*e*) *Grid portal*

The use of a Grid resource broker demonstrates the ability to compose, schedule, monitor and visualize the results of simulations and simplifies the development of application, credential and resource management, while

decoupling the launch platform from the underlying Grid middleware. The development, architecture, features and performance of the KidneyGrid platform included within the Virtual Kidney have been described by Chu *et al.* (2008). The steps involved in running a Grid-enabled session are the following.

(i) User initiates session with portal by selecting modelling resources required and 'planning' experiment with the resources available.
(ii) User completes authorization through Globus middleware infrastructure.
(iii) Portal contacts Grid broker to request resources (Remote/Local Kidney Database or remote simulations).
(iv) Grid broker queries registry to provide reference to resource. Registry returns references to resources required and broker returns reference plus any important control data to the portal.
(v) Broker opens communication channel to remote resource and sets up. Note that resources may be locally based (e.g. in the local mirror of the Kidney database) or hosted on remote servers.
(vi) More commonly, simulations will be hosted on remote sites, running on proprietary systems. The Grid broker will manage communications with the remote resource through a combination of tailored communications and/or implementation of service-based wrappers at the remote resource. It is preferable that as few resources as possible are required to be implemented on the remote resource, and communication brokering will therefore most probably be tailored to individual model resources with most processing of result datasets occurring at the eResearch portal.
(vii) User session state, including the current state of experiment, is saved to local database.
(viii) Results are visualized on the user's desktop in their browser that is running the three-dimensional Virtual Kidney portal.
(ix) Alternatively, for complex datasets, it may be preferable to use advanced visualization resources, such as the Victorian Partnership for Advanced Computing Advanced Visualization Facility in Melbourne.

3. Future developments

A long-term challenge for the Physiome initiative is to build a modelling framework in which the effect of a gene mutation can be modelled all the way from its effect on protein structure and function to how the altered properties of the protein affect a cellular process such as signal transduction, and how the changed properties of that process alter the function of tissues and organs. It will also help to clarify the way in which environmental influences, along with genetic expression, influence physiological function. There will be many other benefits from this integrative framework. Understanding how model parameters are affected by individual variation, embryological growth, ageing and disease, for example, will have enormous potential benefits for the design of medical devices, the diagnosis and treatment of disease and the development of new drugs. Extension of such models to explore the effects of pathology and genetic disorders is now possible with the growth of computing power and Internet connectivity and ready access to such resources through eScience portals will be a central pillar of the VPH endeavour.

The Kidneyome or Virtual Kidney will contribute to the overall generation of a set of computational resources relevant to all aspects of human physiology and pathology. In the short term, it is expected that the portal will accumulate relevant curated data from the literature and provide experimental scientists with access to a wide variety of models with which they can simulate effects of changes in their chosen renal system, and thus inform the process of experimental design. At this stage, we have included only a few long-standing 'legacy' models, some of which are now outdated. We plan to add more current models including a reimplementation of some distal tubule models (Weinstein 1994, 1998*a*,*b*). The concentrating mechanism is more problematic as there are simply not any 'successful' models since there is no satisfactory explanation of all aspects of the mechanism. More value will be added to the portal by including a library of channel and transporter kinetic models as they become available and, we anticipate, models of the various cell types along the nephron.

In the longer term, the integration of various low-level models with systems or network approaches is likely to allow the development of interactive multi-scale representations of the kidney that can be placed within the other body systems to explore quantitatively the activity of control systems involved in the regulation of the cardiovascular system and fluid and electrolyte balance.

The Physiome Project relies on software tools to facilitate constructing and exploring models, but such tools are unlikely to ever be a single unified model; instead, our view is that the Physiome will be enabled by a range of eScience portals, such as the Virtual Kidney, customized for the researchers and research issues for specific organs and systems, ranging from kidneys to the respiratory or lymphatic systems.

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References

Alfieri, R., Cecchini, R., Ciaschini, V., dell'Agnello, L., Frohner, Á. & Gianoli, A. 2003 VOMS: an authorization system for virtual organizations. In *First European Across Grids Conference, Santiago de Compostela*.

Baru, C., Moore, R., Rajasekar, A. & Wan, M. 1998 The SDSC storage resource broker. In *Proc. CASCON'98, Toronto, Canada*.

Bassingthwaighte, J. B. 2000 Strategies for the Physiome Project. *Ann. Biomed. Eng.* **28**, 1043–1058. (doi:10.1114/1.1313771)

Chang, H. & Fujita, T. 1999 A numerical model of the renal distal tubule. *Am. J. Physiol.* **276**, F931–F951.

Christie, R., Bullivant, D., Blackett, S. & Hunter, P. J. 2002 Modelling and visualising the heart. *Comput. Vis. Sci.* **4**, 227–235. (doi:10.1007/s00791-002-0079-3)

Chu, X.-C., Lonie, A., Harris, P. J., Thomas, S. R. & Buyya, R. 2008 A service-oriented Grid environment for integration of distributed kidney models and resources. *Concurrency Comput. Pract. Exp.* **20**, 1095–1111. (doi:10.1002/cpe.1285)

Deen, W. M., Robertson, C. R. & Brenner, B. M. 1972 A model of glomerular ultrafiltration in the rat. *Am. J. Physiol.* **223**, 1178–1183.

Dzodic, V., Hervy, S., Fritsch, D., Khalfallah, H., Thereau, M. & Thomas, S. R. 2004 Web-based tools for quantitative renal physiology. *Cell. Mol. Biol.* **50**, 795–800.

Fenner, J. W. *et al.* 2008 The EuroPhysiome, STEP and a roadmap for the virtual physiological human. *Phil. Trans. R. Soc. A* **366**, 2979–2999. (doi:10.1098/rsta.2008.0089)

Foster, D. M. & Jacquez, J. A. 1978 Comparison using central core model of renal medulla of the rabbit and rat. *Am. J. Physiol.* **234**, F402–F414.

Foster, I. & Kesselman, C. 1998 The Globus Project: a status report. In *Proc. IPPS/SPDP'98 Heterogeneous Computing Workshop*, pp. 4–18.

Foster, I. & Kesselman, C. 1999 *The Grid: blueprint for a future computing infrastructure*. San Francisco, CA: Morgan Kaufmann Publishers.

Hervy, S. & Thomas, S. R. 2003 Inner medullary lactate production and urine-concentrating mechanism: a flat medullary model. *Am. J. Physiol. Renal Physiol.* **284**, F65–F81.

Holstein-Rathlou, N. H. & Marsh, D. J. 1990 A dynamic model of the tubuloglomerular feedback mechanism. *Am. J. Physiol.* **258**, F1448–F1459.

Holstein-Rathlou, N. H., Wagner, A. J. & Marsh, D. J. 1991 Tubuloglomerular feedback dynamics and renal blood flow autoregulation in rats. *Am. J. Physiol.* **260**, F53–F68.

Hunter, P. J. & Borg, T. K. 2003 Integration from proteins to organs: the Physiome Project. *Nat. Rev. Mol. Cell Biol.* **4**, 237–243. (doi:10.1038/nrm1054)

Hunter, P. J. & Nielsen, P. M. F. 2005 A strategy for integrative computational physiology. *Physiology* **20**, 316–325. (doi:10.1152/physiol.00022.2005)

Layton, H. E., Pitman, E. B. & Moore, L. C. 1991 Bifurcation analysis of TGF-mediated oscillations in SNGFR. *Am. J. Physiol.* **261**, F904–F919.

Lifton, R. P., Gharavi, A. G. & Geller, D. S. 2001 Molecular mechanisms of human hypertension. *Cell* **104**, 545–556. (doi:10.1016/S0092-8674(01)00241-0)

Lloyd, C. M., Halstead, M. D. B. & Nielsen, P. M. F. 2004 CellML: its future, present and past. *Prog. Biophys. Mol. Biol.* **85**, 433–450. (doi:10.1016/j.pbiomolbio.2004.01.004)

Lonie, A. J., Stevens, C. & Harris, P. J. 2004 Computer modeling of kidney function. In *Proc. Exp. Biol.* LB520, Washington, DC.

Lory, P. 1987 Effectiveness of a salt transport cascade in the renal medulla: computer simulations. *Am. J. Physiol.* **252**, F1095–F1102.

Marsh, D. J., Sosnovtseva, O. V., Mosekilde, E. & Holstein-Rathlou, N.-H. 2007 Vascular coupling induces synchronization, quasiperiodicity, and chaos in a nephron tree. *Chaos* **17**, 015 114. (doi:10.1063/1.2404774)

Moss, R., Kazmierczak, E., Kirley, M. & Harris, P. 2009 A computational model for emergent dynamics in the kidney. *Phil. Trans. R. Soc. A* **367**, 2125–2140. (doi:10.1098/rsta.2008.0313)

Noble, D. 2002 The rise of computational biology. *Nat. Rev. Mol. Cell Biol.* **3**, 459–463. (doi:10.1038/nrm810)

Nordsletten, D., Blacket, S., Bentley, M., Ritman, E. & Smith, N. P. 2006 Structural morphology of renal vasculature. *Am. J. Physiol.* **291**, H296–H309. (doi:10.1152/ajpheart.00814.2005)

Ribba, B., Tracqui, P., Boix, J. L., Boissel, J. P. & Thomas, S. R. 2006 QxDB: a generic database to support mathematical modelling in biology. *Phil. Trans. R. Soc. A* **364**, 1517–1532. (doi:10.1098/rsta.2006.1784)

Stein, L. D. 2008 Towards a cyberinfrastructure for the biological sciences: progress, visions and challenges. *Nat. Rev. (Genet.)* **9**, 678–688. (doi:10.1038/nrg2414)

Stephenson, J. L., Mejia, R. & Tewarson, R. P. 1976 Model of solute and water movement in the kidney. *Proc. Natl Acad. Sci. USA* **73**, 252–256. (doi:10.1073/pnas.73.1.252)

Stephenson, J., Zhang, Y., Eftekhari, A. & Tewarson, R. 1987 Electrolyte transport in a central-core model of the renal medulla. *Am. J. Physiol.* **253**, F982–F997.

Thomas, S. R. 1991 Effect of varying salt and urea permeabilities along descending limbs of Henle in a model of the renal medullary urine concentrating mechanism. *Bull. Math. Biol.* **53**, 825–843. (doi:10.1016/S0092-8240(05)80409-4)

Thomas, S. R. In press. *Kidney modeling and systems physiology*. Wiley Interdisciplinary Reviews: Systems Biology and Medicine.

Thomas, S. R. & Dagher, G. 1994 A kinetic model of rat proximal tubule transport—load-dependent bicarbonate reabsorption along the tubule. *Bull. Math. Biol.* **56**, 431–458.

Thomas, S. R. *et al.* 2008 SAPHIR: a Physiome core model of body fluid homeostasis and blood pressure regulation. *Phil. Trans. R. Soc. A* **366**, 3175–3197. (doi:10.1098/rsta.2008.0079)

Tripodi, G., Florio, M., Ferrandi, M., Modica, R., Zimdahl, H., Hubner, N., Ferrari, P. & Bianchi, G. 2004 Effect of *Add1* gene transfer on blood pressure in reciprocal congenic strains of Milan rats. *Biochem. Biophys. Res. Commun.* **324**, 562–568. (doi:10.1016/j.bbrc.2004.09.079)

Venugopal, S., Buyya, R. & Winton, L. 2004 A Grid service broker for scheduling distributed data-oriented applications on global grids. In *Proc. 2nd Int. Workshop on Middleware for Grid Computing*. New York, NY: ACM Press.

Weinstein, A. M. 1986 A mathematical model of the rat proximal tubule. *Am. J. Physiol.* **250**, F860–F873.

Weinstein, A. M. 1994 Mathematical models of tubular transport. *Annu. Rev. Physiol.* **56**, 691–709. (doi:10.1146/annurev.ph.56.030194.003355)

Weinstein, A. M. 1998*a* Insights from mathematical modeling of renal tubular function. *Exp. Nephrol.* **6**, 462–468. (doi:10.1159/000020556)

Weinstein, A. M. 1998*b* A mathematical model of the inner medullary collecting duct of the rat—acid/base transport. *Am. J. Physiol.* **43**, F856–F867.