Multi-scale modeling of the kidney to understand both its internal mechanisms and its role in the body

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VPH call projects

- 1 NoE
- 3 IPs
- 10 STREPs
- 2 CSAs

Acronym	Topic	Project type
VPH NoE	Networking	NoE
VPHOP	Osteoporosis	IP
euHeart	Heart/CV disease	IP
ARTreat	CV/Atheroschlerosis	IP
preDiCT	Heart/CV disease	STREP
ContraCancrum	Cancer	STREP
ARCH	Vascular/AVF & haemodialysis	STREP
PASSPORT	Liver/surgery	STREP
PredictAD	Alzheimers/BM & diagnosis	STREP
NeoMARK	Oral cancer/BM, D & T	STREP
VPH2	Heart/LVD surgery	STREP
IMPPACT	Liver cancer/RFA therapy	STREP
HAMAM	Breast cancer/diagnosis	STREP
Action-Grid	Grid access EU – LA & Balkans	CA
RADICAL	Security and privacy in VPH	CA

Plan for the talk

- Kidney modeling: to what purpose?
  - To understand how the kidney works ("hypothesis -based")
  - Quantitative representation of current knowledge
  - Health-directed (diagnosis, therapy…)
- Integrated, multi-scale modeling (Physiome related): a gene-to-organism example related to hypertension
- Tools (parameter databases, interactive model repositories…)

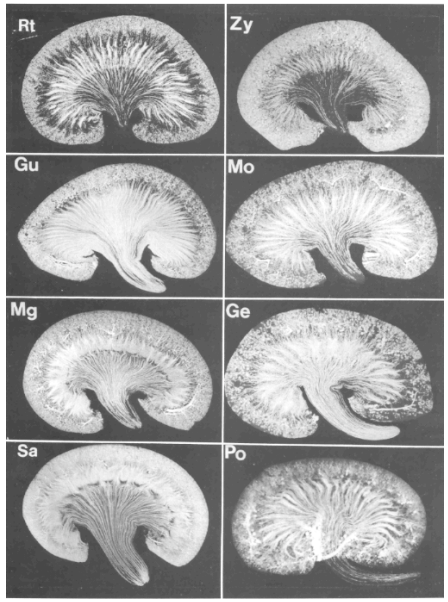
Introduction/ What's a kidney?

Rat
omnivore
150-300g

Gundi
vegetarian
150-300g

Mongolian gerbil
vegetarian
100-200g

Sand rat
(*Psammomys obesus*)
vegetarian
100-200g



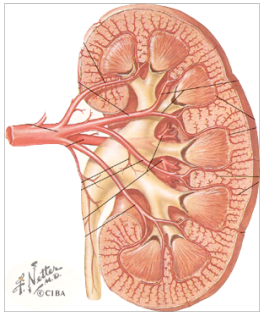
Zygodontomys
tropical rain forest
30-60g

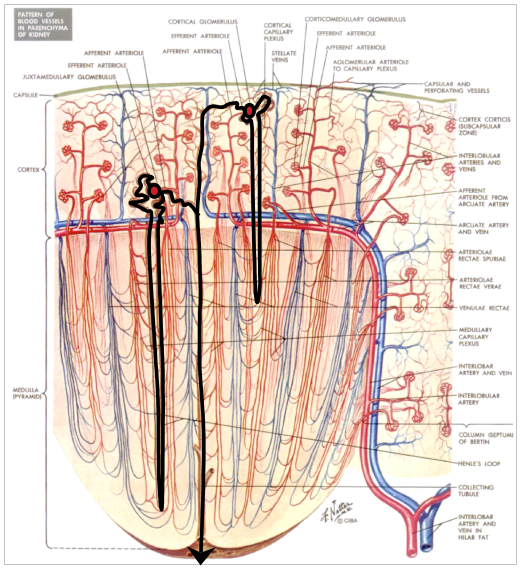
Mouse
vegetarian
35-50g

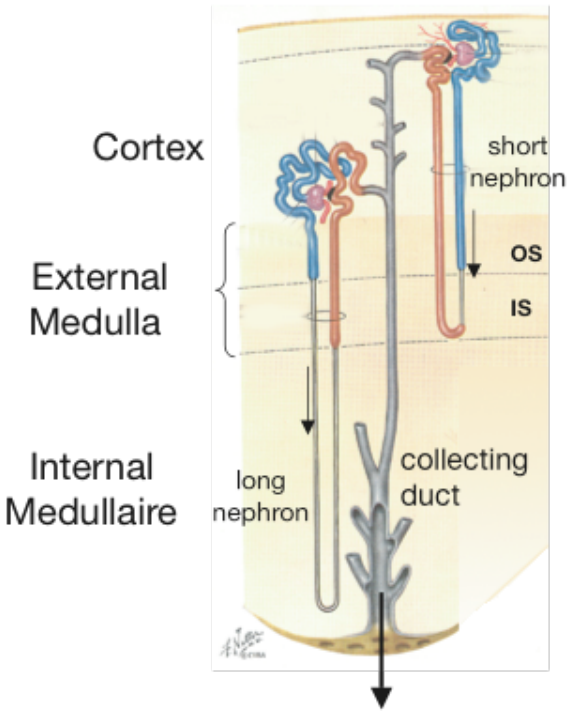
Gerbil
vegetarian
20-40g

Pocket mouse
vegetarian
20-40g

HUMAN KIDNEY







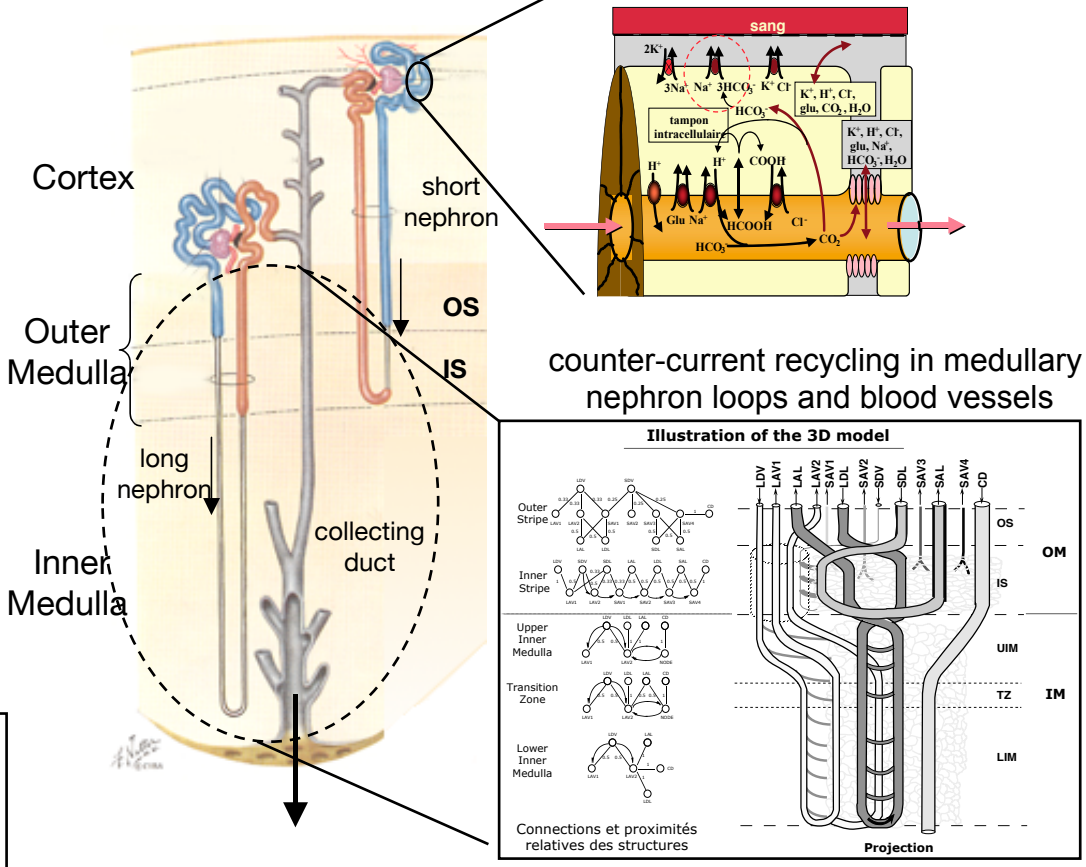
Modeling the Kidney at various scales

Existing models address questions of kidney function at many levels, including:

- metabolism
- kinetics of membrane channels and transporters,
- tubular transport of solutes and water by individual nephron segments,
- tubulo-glomerular feedback,
- medullary microcirculation
- full medullary models (urine concentrating mechanism)

The Future:
Integrated whole-kidney models to address clinical questions

tubule transport models built-up from kinetic descriptions of transporters



Web tools to *streamline model development* and *provide universal access*

- QKDB: Quantitative Kidney Database (and generic version: QxDB)
- Interactive model repositories

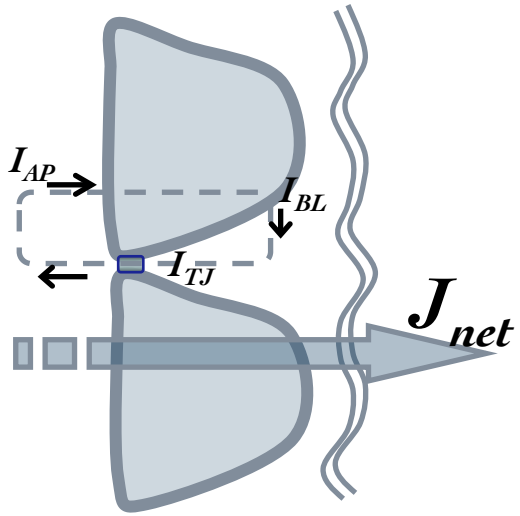
Epithelial transport: Dynamical system description

ODEs describe changes of flows and concentrations

- Conservation of matter (reflects system topology)

$$\frac{dV}{dt} = A^a J_v^a - A^b J_v^b \qquad V\frac{dC_i^c}{dt} = A^a J_i^a - A^b J_i^b - C_i^c \frac{dV}{dt}$$

- Electroneutrality
  - in symmetrical/isolated cells: $\sum I_i = 0$
  - in epithelia: $\sum I_{tot} = \sum I_{cell} + \sum I_{TJ} = 0$
- Details of flow kinetics
  - phenomenological rate equations, or
  - deterministic kinetic descriptions



vectorial transport thanks to symmetry breaking

Kinetic Equation for the basolateral Na-3(HCO_3) transporter

$$J_{NaBic} = \frac{V_{max}^{NaBic} \frac{2\mathcal{F}\psi_{bl}}{RT}((Na^+)_c(HCO_3^-)_c^3 exp(\frac{-2\mathcal{F}\psi_{bl}}{RT}) - (Na^+)_b(HCO_3^-)_b^3)}{(1 - exp(\frac{-2\mathcal{F}\psi_{bl}}{RT})(1 + \frac{(Na^+)_c}{k_{Na}})(1 + \frac{(HCO_3^-)_c^3}{k_{Bic}})(1 + \frac{(Na^+)_b}{k_{Na}})(1 + \frac{(HCO_3^-)_b^3}{k_{Bic}})}.$$

Each of the transporters, channels, and pumps in such epithelial transport models has a kinetic description based on *in vitro* studies (vesicles, patch clamp, heterologous expression in oocytes,…).

What have we learned using epithelial/tubule models?

Proximal Convoluted Tubule (PCT)

-mechanism of (quasi-)isosmotic fluid reabsorption

-load-dependent HCO_3^- reabsorption (LDBR)

-flow-dependent vs. load-dependent fluid reabsorption

-weak-acid cotransport contribution to acid secretion

-detailed model of brush-border & its role in flow-dep. solute & water uptake (rigidity of microvilli and their attachment to cytoskeleton)

-standing gradient in inter-cellular space

-cell-cell coupling by cable analysis of multi-electrode experiments

-contribution of intra-epithelial circular current to PCT reabsorption

-role of peritubular oncotic pressure in autoregulation of PCT reabsorption

-AP-BL cross-talk issues

-leaky vs. tight and AP-BL coupling

-effective intermediates/signals

-maintenance of cellular homeostasis in the face of massive vectorial transport

-role of variable stoichiometry of BL $Na^+/(n)$ HCO_3^- in PCT acid-base regulation

-route of Cl^- transport (trans- or para-cellular?)

-adequacy of AQP to explain trans-cellular Jv

-Na/K pump

  -dependence on ATP, V_{BL}, and ion concentrations

  -intra-membrane coupling with K^+ transporters and channels

-…

What have we learned? (cont.)

Thick ascending limb of Henle (MTAL & CTAL)

-AP & BL routes for transport of Na^+, K^+, Cl^-, HCO_3^-

-apical K^+ recycling

-mechanism of action of furosemide

-dependence of paracellular Ca^{++} & Mg^{++} uptake on kinetics of AP & BL channels and transporters

-origin and crucial role of the lumen-positive membrane potential paracellular ion reabsorption

-Bartter's syndrome (mutation of NKCC2 or ROMK --> hypokalemia & metabolic alkalosis)

Early Distal Tubule (DCT)

-role of thiazides and amiloride in DCT ion transport

-role of thiazide-sensitive Na-Cl cotransporter in salt uptake

-open: *role of adducin's pump-effect on TSC in hypertension

-lack of a role for early DCT in recovery from Cl^- depletion alkalosis

-participation of bicarbonate, ammonium, and phosphate buffer systems in acid-base transport

Late Distal Tubule/Cortical Connecting Duct (LDT/CCD)

-ADH-dependent osmotic equilibration

-ENaC and sodium reabsorption (-->role in hypertension awaits explanation at higher level of integration)

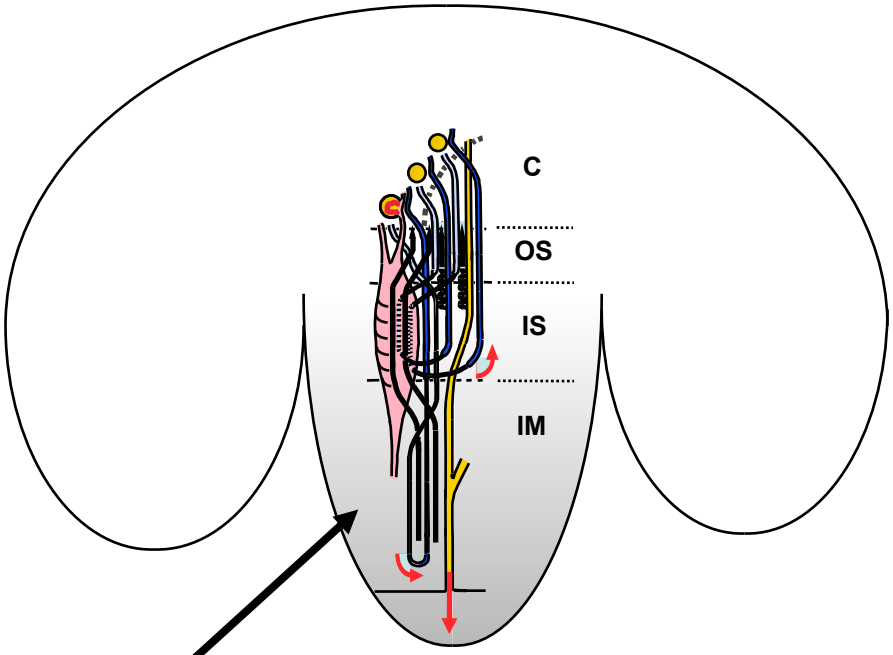
-separate/complementary/coupled roles of principal and intercalated cells in Na^+-abs./K^+-secretion vs. acid secretion

-open: *mechanism of divalent ion reabsorption and PTH/calcitonin effects

Collecting Duct (OMCD & IMCD)

-**recent series of detailed models addressing many issues…**

Anaerobic glycolysis in the IM: an osmotic motor?



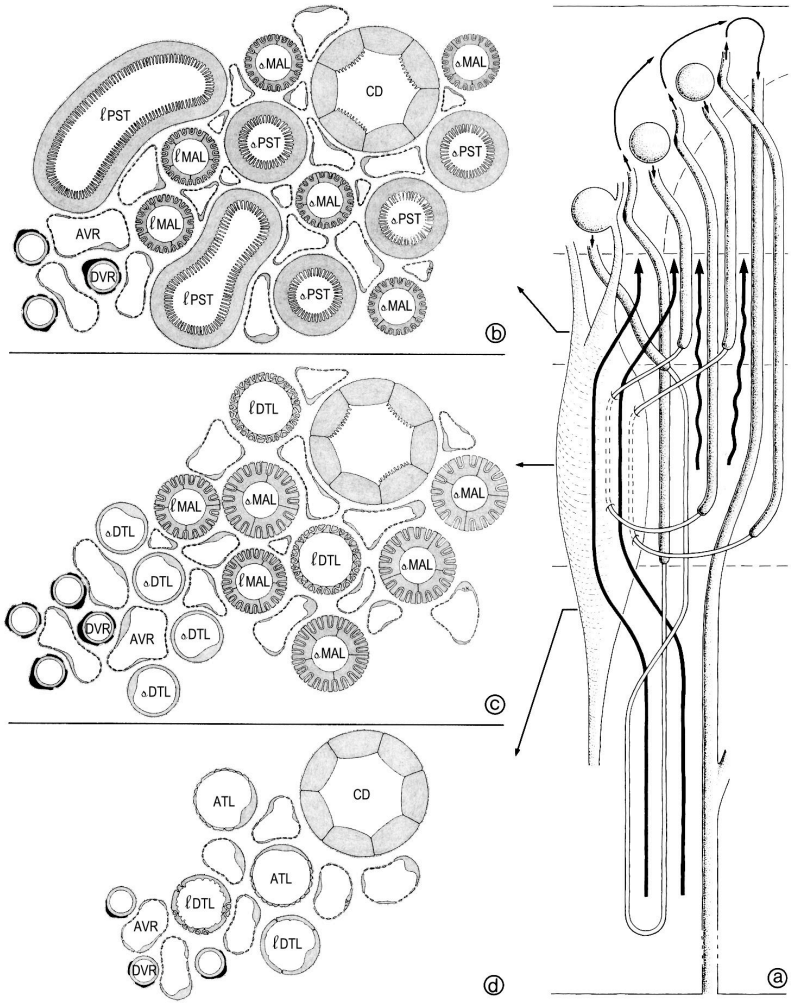
Inner medullary hypoxia ⇨ anaerobic glycolysis

1 glucose ➔ 2 lactates + 2 H^+

i.e., Net osmole production !

(Thomas, Am.J.Physiol. 2000, 2003,2004)

Lemley & Kriz: Cycles and separations…



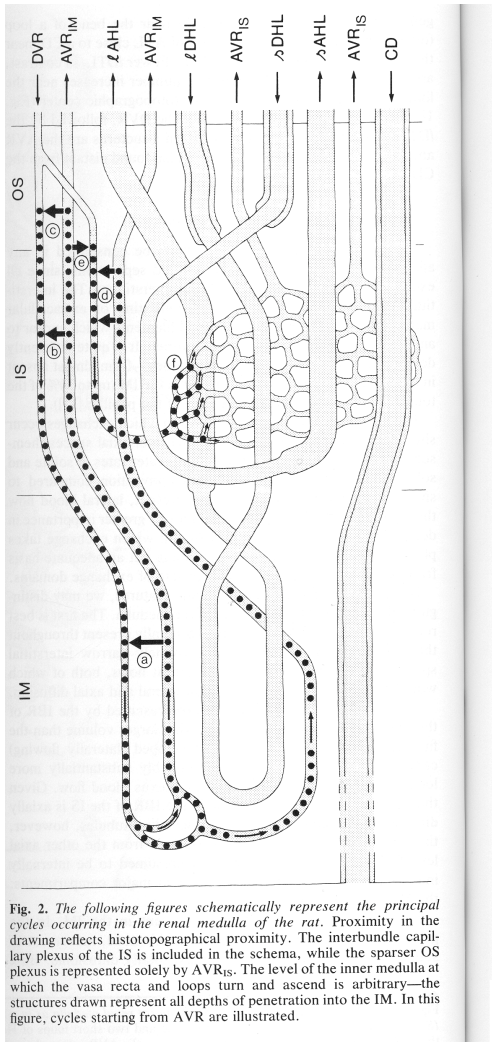


Fig. 2. *The following figures schematically represent the principal cycles occurring in the renal medulla of the rat.* Proximity in the drawing reflects histotopographical proximity. The interbundle capillary plexus of the IS is included in the schema, while the sparser OS plexus is represented solely by AVR_{IS}. The level of the inner medulla at which the vasa recta and loops turn and ascend is arbitrary—the structures drawn represent all depths of penetration into the IM. In this figure, cycles starting from AVR are illustrated.

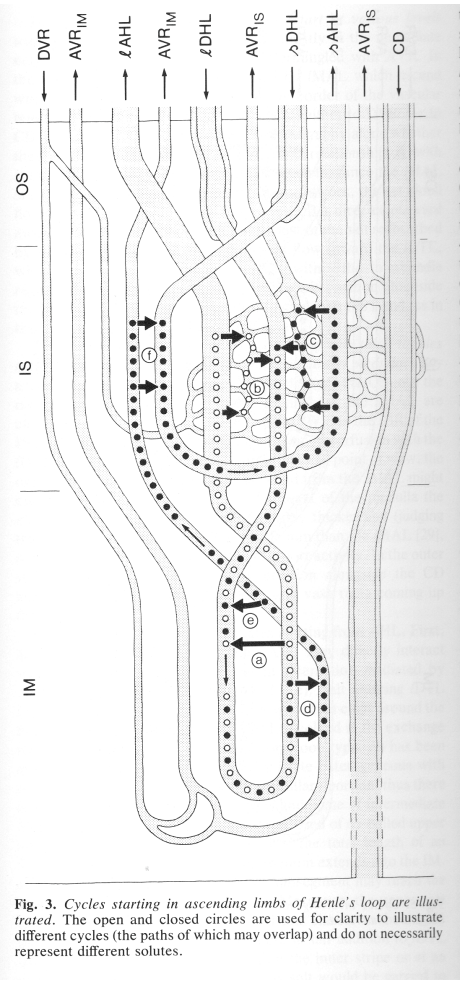
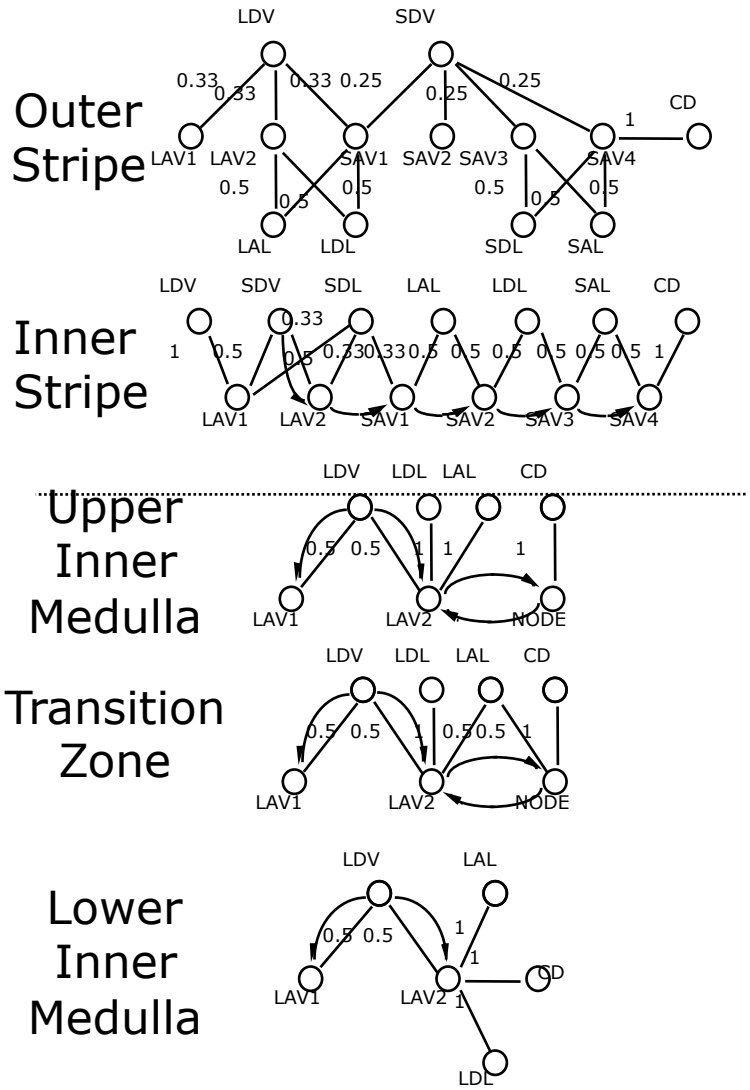


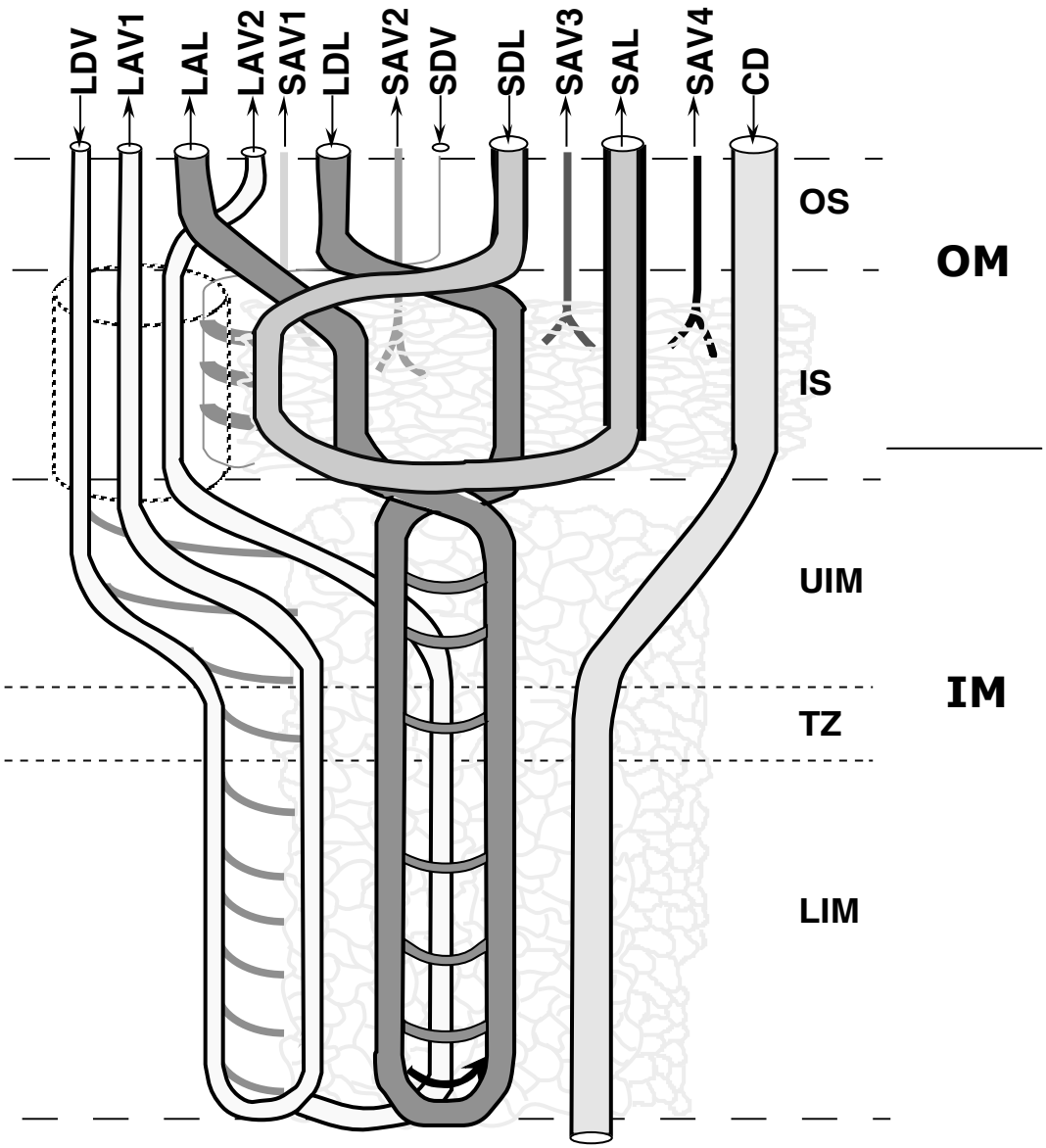
Fig. 3. *Cycles starting in ascending limbs of Henle's loop are illustrated.* The open and closed circles are used for clarity to illustrate different cycles (the paths of which may overlap) and do not necessarily represent different solutes.

Lemley, K. V. and W. Kriz (1987). "*Cycles and separations: The histotopography of the urinary concentrating process.*" Kidney International **30**: 538-548.

Illustration of the 3D "WKM" model

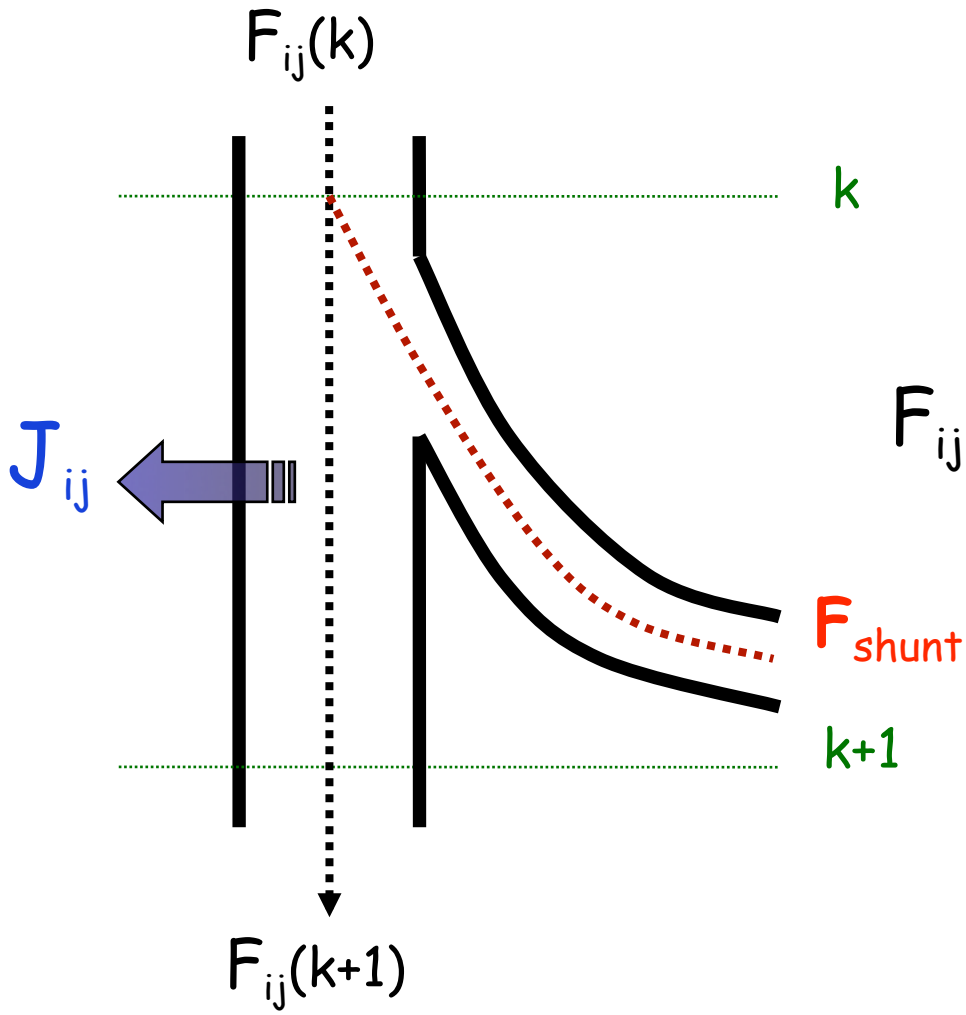


Connections et proximités relatives des structures



Thomas (1998) Am.J.Physiol. 275:F671–F690

The ODEs for tubular flows of solutes and water are discretized (centered) in space



$$F_{ij}(k+1) = F_{ij}(k) - J_{ij} - F_{shunt}$$

System Equations

Mass balance and KEDEM-KATCHALSKY flux coupling

5 flows (4 solutes + volume flow) in each of 13 tubular structures:
a system of 65 ODEs with multiple boundary conditions

volume flow: $\frac{dF_{iv}}{dx} = -J_{iv}$ solute flows: $\frac{dF_{iv}c_{ij}}{dx} = -J_{ij}$

Transepithelial flux equations:

volume: $$J_{iv} = A_i Lp_{iv} \sum_{j=1}^{4} RT\sigma_{ij}\left(c_{AVR,j} - c_{ij}\right)$$

solute: $$J_{ij} = A_i\left(\underbrace{P_{ij}\left(c_{ij} - c_{AVR,j}\right)}_{\text{diffusion}} + \underbrace{\left(1-\sigma_{ij}\right)J_{iv}\frac{\left(c_{ij} + c_{AVR,j}\right)}{2}}_{\text{solvent drag}} + \underbrace{\frac{Vmax_{ij}\,c_{ij}}{\left(Km_{ij} + c_{ij}\right)}}_{\text{active transport}} \right)$$

subject to Global Mass Balance

In collaboration with Alan Hegarty

(Maths Dept., Univ. of Limerick),

this model is currently being extended to treat dynamic transients

(Maria Gonzalez, Ph.D. thesis)

The kidney's role in the body

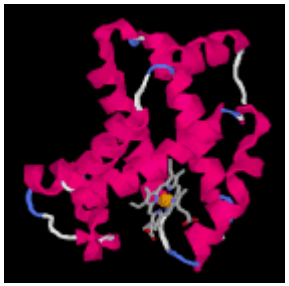
So, there is a significant legacy of work on "local" models of renal function at many scales

But, what about integrated kidney models, or whole organism models where the kidney plays its part?

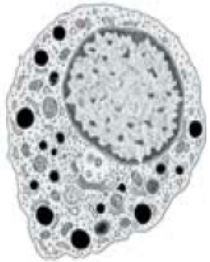
The International Physiome Project

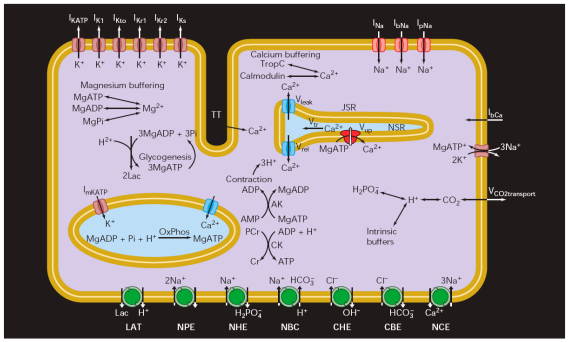
Illustration of various scales considered, from genome to organism

Genes and genomes



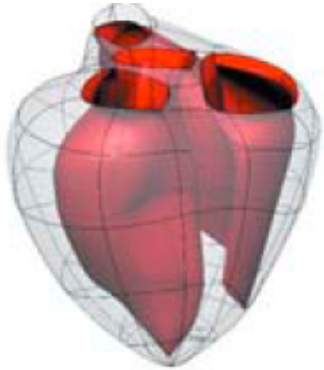
Protein structures



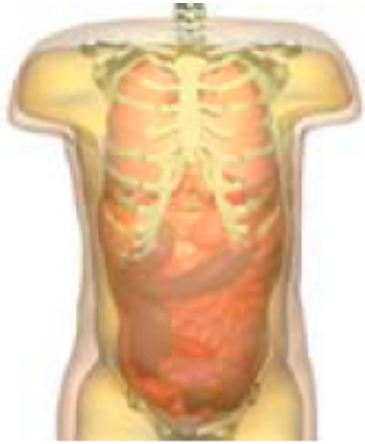


Cellular Functions

Tissues : muscles, epithelia, ….



Organs : heart, kidney, lung, ….



Organ Systems with interactions and regulations

Hunter, P. and P. Nielsen (2005). "A strategy for integrative computational physiology." Physiology (Bethesda) 20: 316-25.

Integrative multi-resolution models?

The challenge: supplying enough, but not too much, detail…

An example problem involving the kidney:

Hypertension: BP regulation involves multiple systems

Our proposal: Develop a core model of the whole system at low resolution, as a set of standardized I/O n-ports, and also open, flexible, available, validated, compatible…

Integrative multi-resolution models?

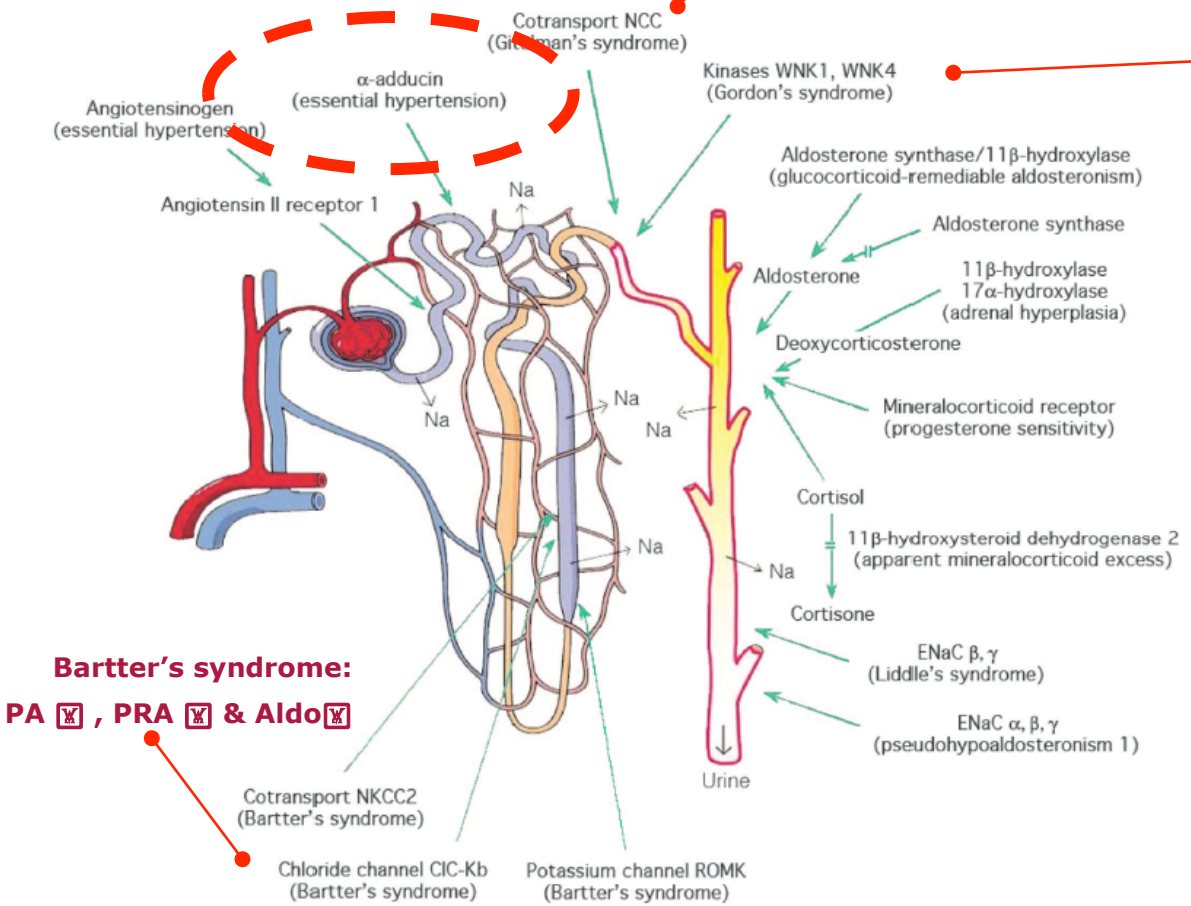
The role of kidney channelopathies in long-term control of blood pressure.

Kidney & Na^+ : polymorphisms & mutations

Gittelman's syndrome: PA ↓, RAAS ↑
compensation par ENaC

Gordon's syndrome:
(PHA typeII)

PA ↑
PRA & Aldo ↓

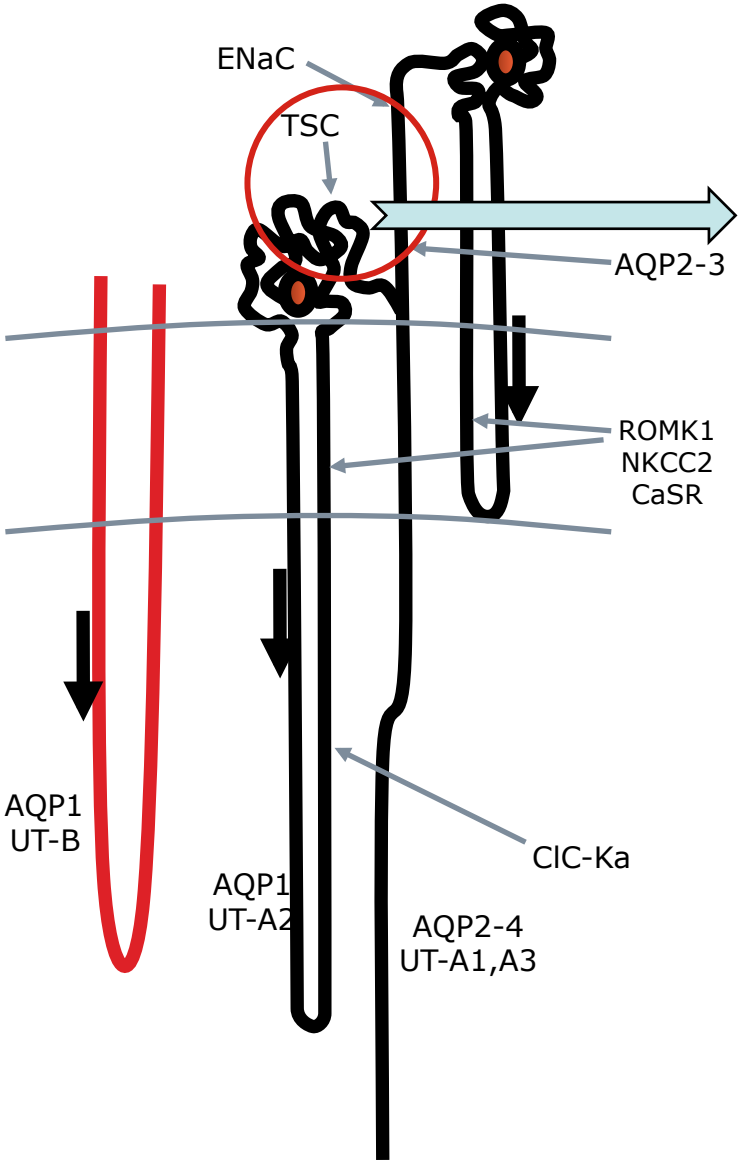


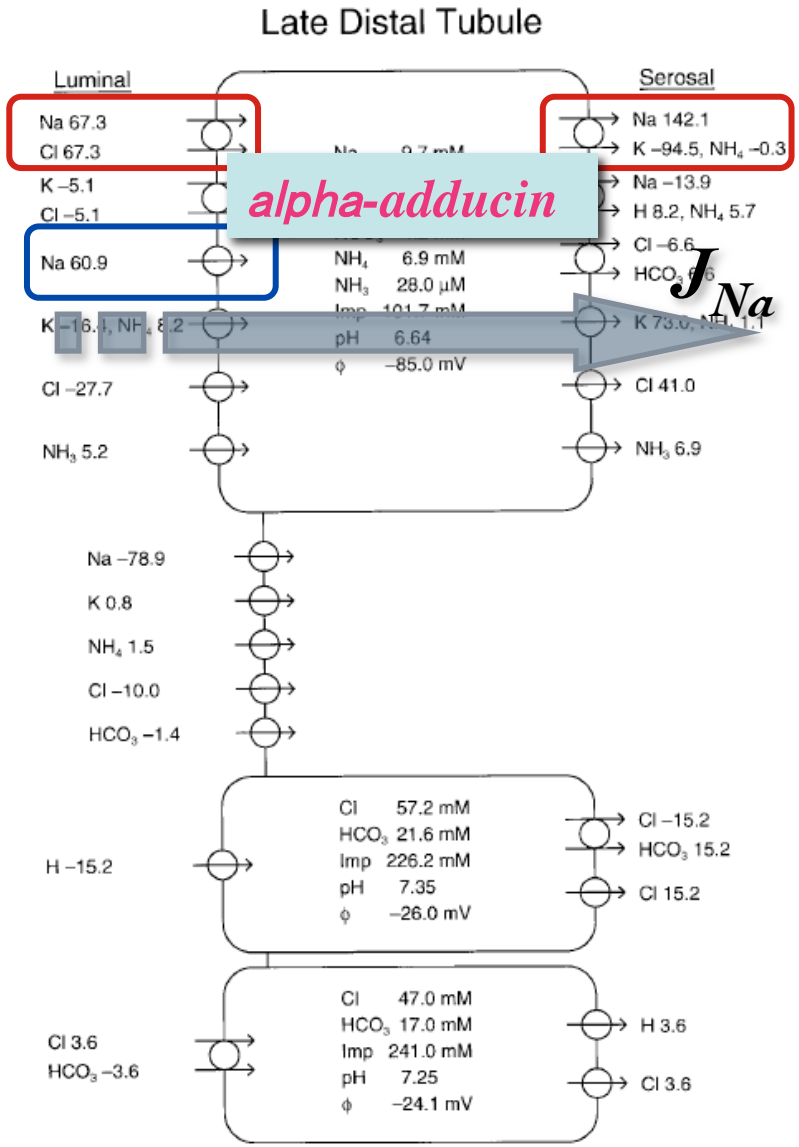
Bartter's syndrome:
PA ↓ , PRA ↑ & Aldo ↓

FIG. 4. Mutations and polymorphisms altering blood pressure levels in humans. They have been identified in rare Mendelian forms of hypertension or hypotension or have been linked to essential hypertension. Most of them are present in genes involved directly or indirectly in renal sodium handling, i.e., genes coding for tubular sodium transport systems or for proteins belonging to regulatory pathways. [Adapted from Lifton et al. (213).]

Meneton et al., 2005

Distal Tubule J_{Na} too high ➡…➡ Hypertension

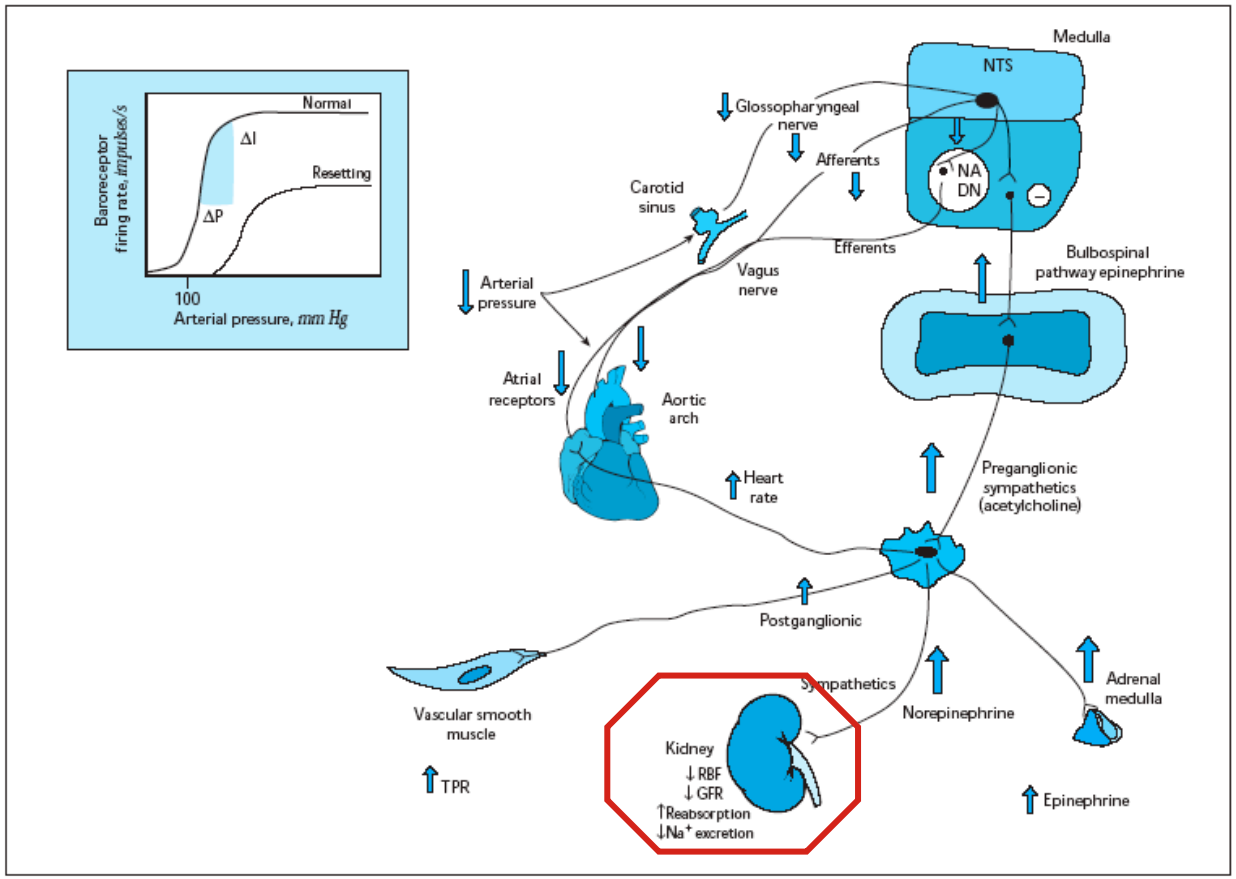




Hypertension involves many regulatory influences

1.12 Hypertension and the Kidney

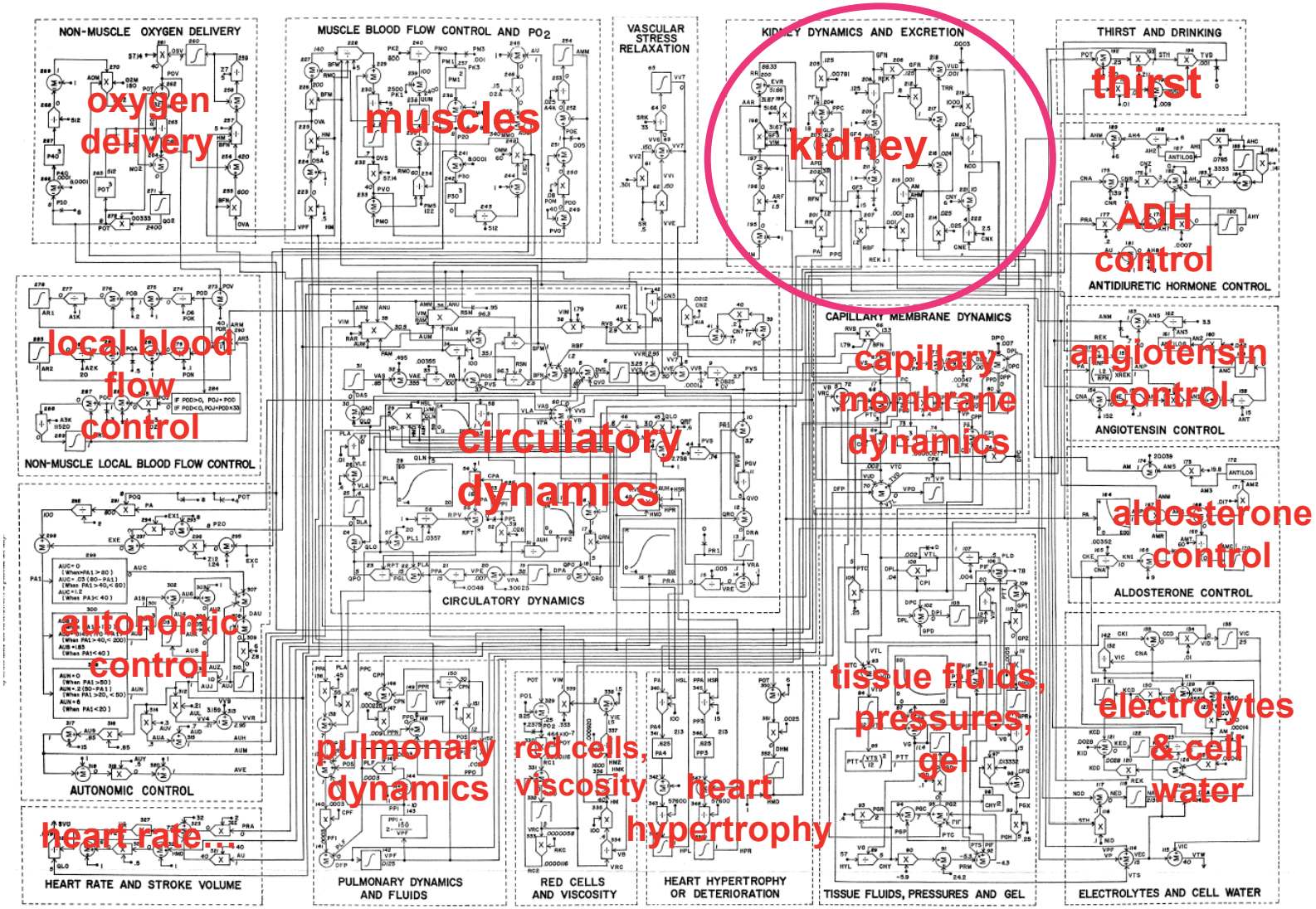
Systemic Factors Regulating Arterial Pressure and Sodium Excretion



from Schrier: *Atlas of Diseases of the Kidney*

Project ANR-Biosys 2006-2009 — SAPHIR:

"a Systems Approach for PHysiological Integration of Renal, cardiac, and respiratory functions"



Guyton, Coleman, Granger (1972) *Ann. Rev. Physiol.*

Towards a multi-organ, multi-resolution, multi-mode modeling environment for the Physiome

Modular systems-model of blood pressure: Kidney module

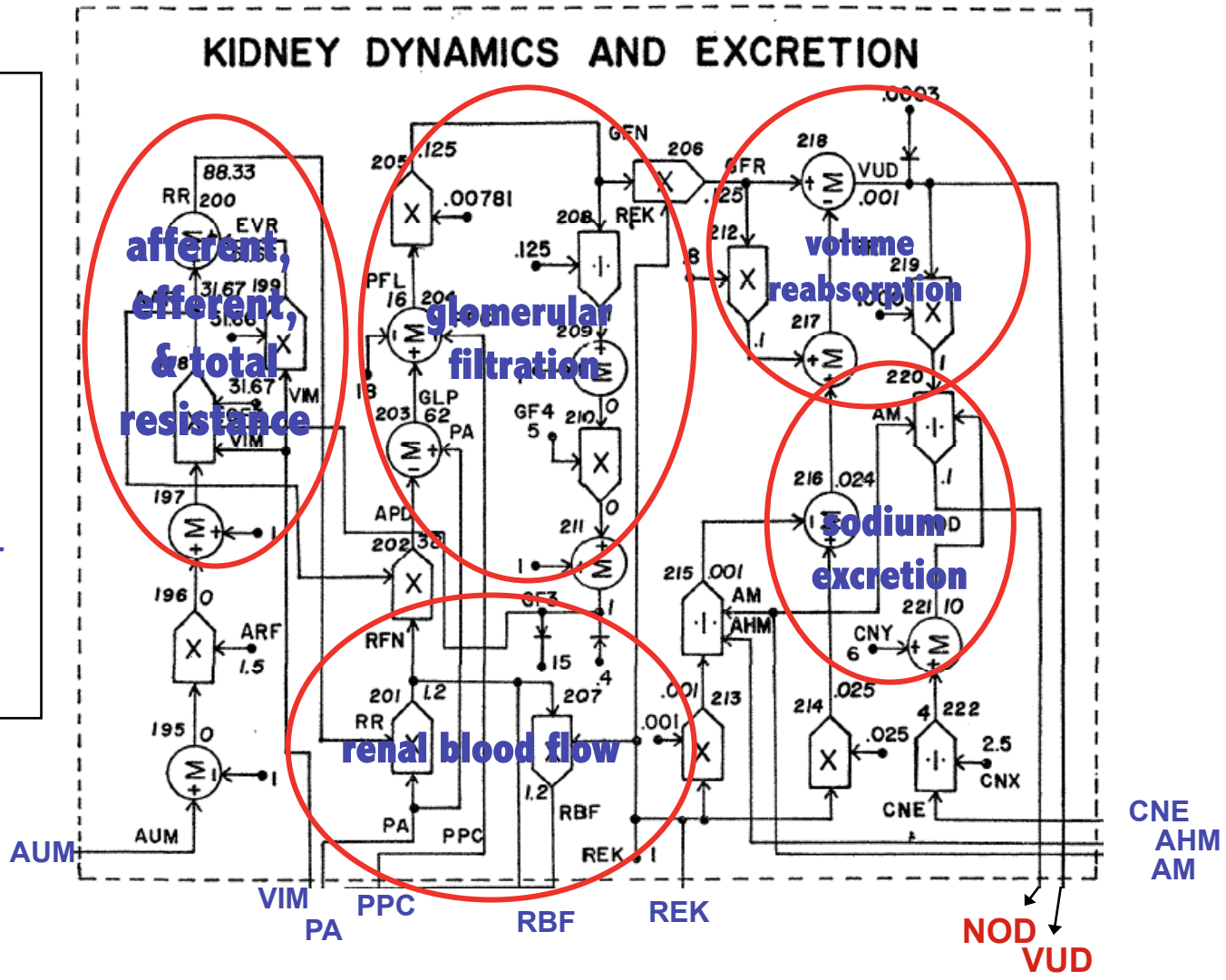
INPUTS

AUM: sympathetic vasoconstrictor effect on arteries

VIM: Blood viscosity
PA: aortic pressure
PPC: plasma COP
RBF: Renal Blood Flow
REK: percent of normal renal function
CNE: third factor effect
AHM: ADH multiplier
AM: aldosterone multiplier

OUTPUTS

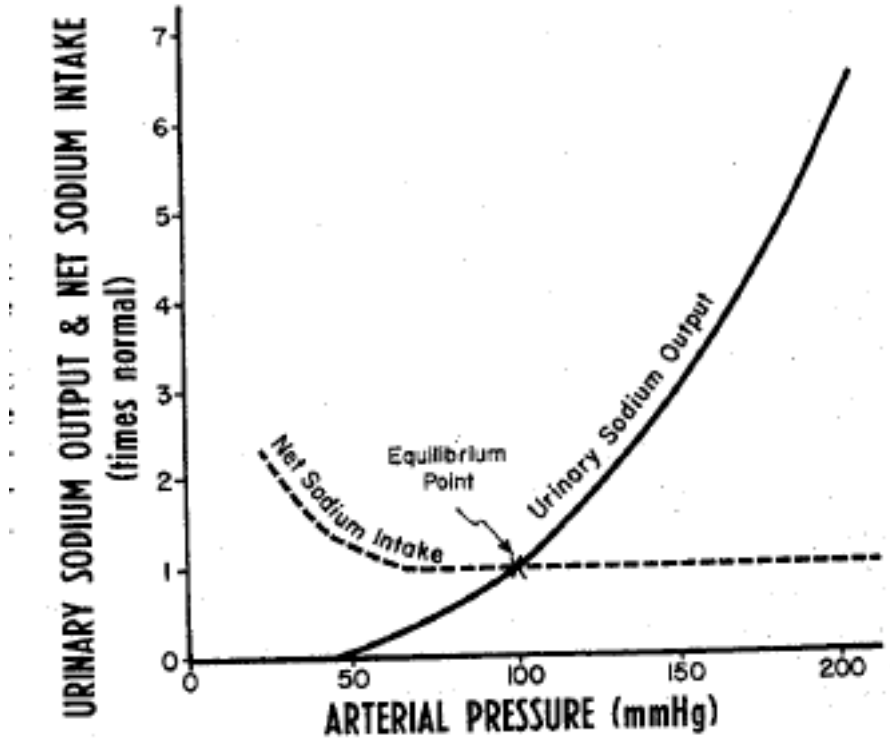
NOD: rate of renal Na+ excretion
VUD: rate of urine output



Guyton, A.C., T.G. Coleman, and H.J. Granger, "Circulation: Overall regulation." Annual Reviews of Physiology, 1972. 34:13-44.

The Infinite-Gain feature of the
kidney - blood volume - pressure regulator:

The (acute) renal function curve and Net sodium intake



from Guyton, A. C. (1980). Circulatory Physiology III. Arterial Pressure and Hypertension. Philadelphia, W.B. Saunders.

The Infinite-Gain feature of the kidney – blood volume – pressure regulator:

Shifting the Renal Function Curve…

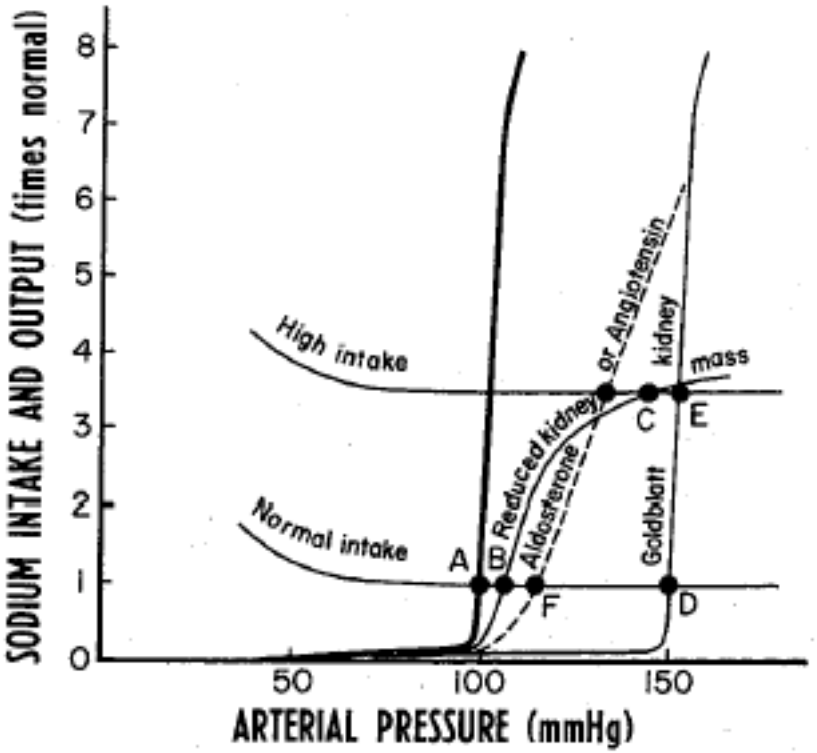


Figure 7–9. Analysis of arterial pressure regulation in several altered functional or pathological states of the kidneys: (1) reduced kidney mass, (2) Goldblatt kidneys, and (3) increase in aldosterone or angiotensin.

from Guyton, A. C. (1980). Circulatory Physiology III. Arterial Pressure and Hypertension. Philadelphia, W.B. Saunders.

SAPHIR (cont.)

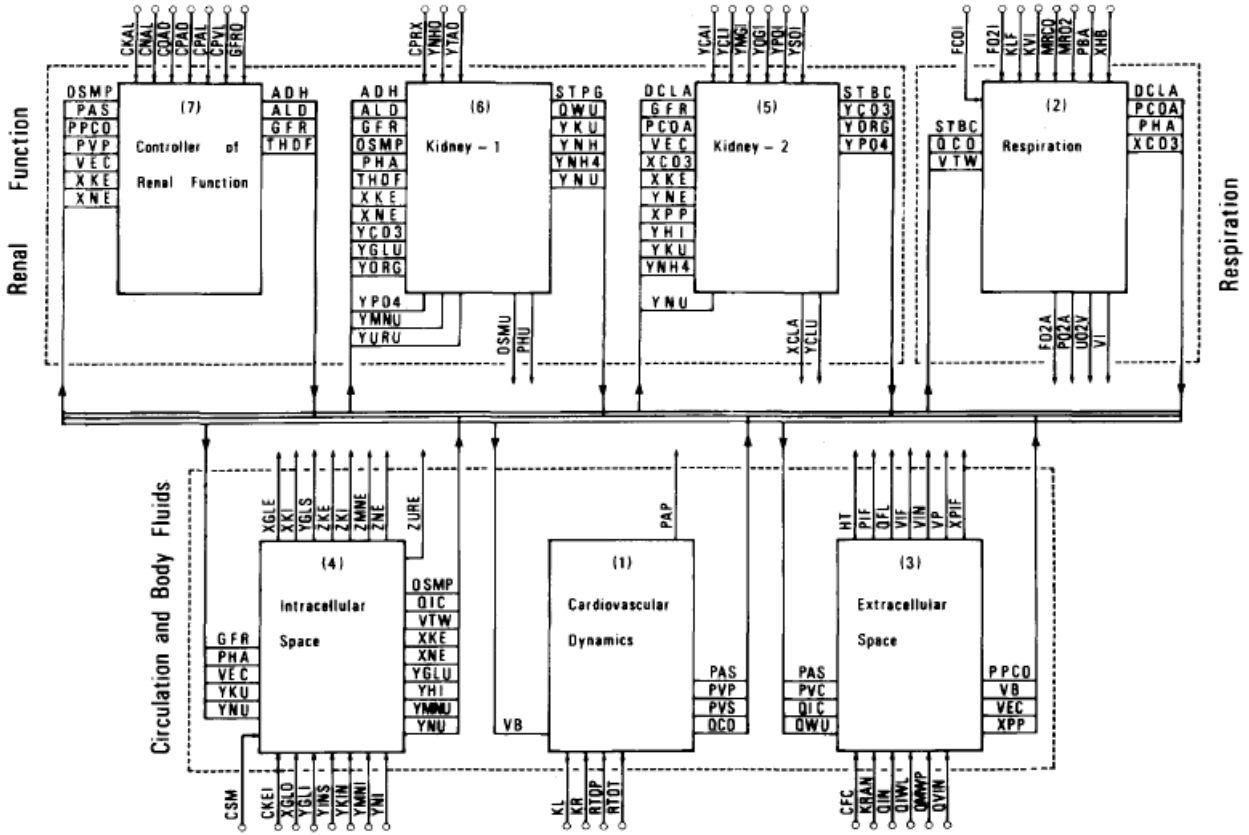


FIGURE 1. Block diagram of the model. Variables on the right side of each block indicate the outputs to the other blocks, and on the left, inputs from the other blocks. On the top and bottom of each block are fixed inputs or constant parameters (⟶) and the outputs which do not affect the other blocks (⟶). Explanations of the variables and their normal values are given in Appendix I.

Na, K, Cl,
glucose,
urea,
blood pH,
HCO3,
CO2, O2,
Ca++, Mg
++,
mannitol,
blood
hemoglobin,
COP,
phosphate,
sulfate,
NH4+

Ikeda, N., et al., "**A model of overall regulation of body fluids**".
Annals of Biomedical Engineering, 1979. 7:135-166.

SAPHIR : Implementation

Build a modular, extensible, open source systems modeling environment

- Multi-scale, multi-mode, multi-resolution simulation toolbox
  - based on one developed for cardiac modeling (A. Hernandez, Rennes)
- Multiple alternative/complementary modules for each sub-system, at various scales and various granularities
  - kidney, cardiac, pulmonary, red blood cells, vascular…
- Quantitative parameter database
  - based on generic version of QKDB
- Markup language(s)
- Ontologies
- Grid-portal web interface with systems mediation

This will serve as a candidate prototype for other Physiome "core models"

SAPHIR as a prototype physiology "core model"

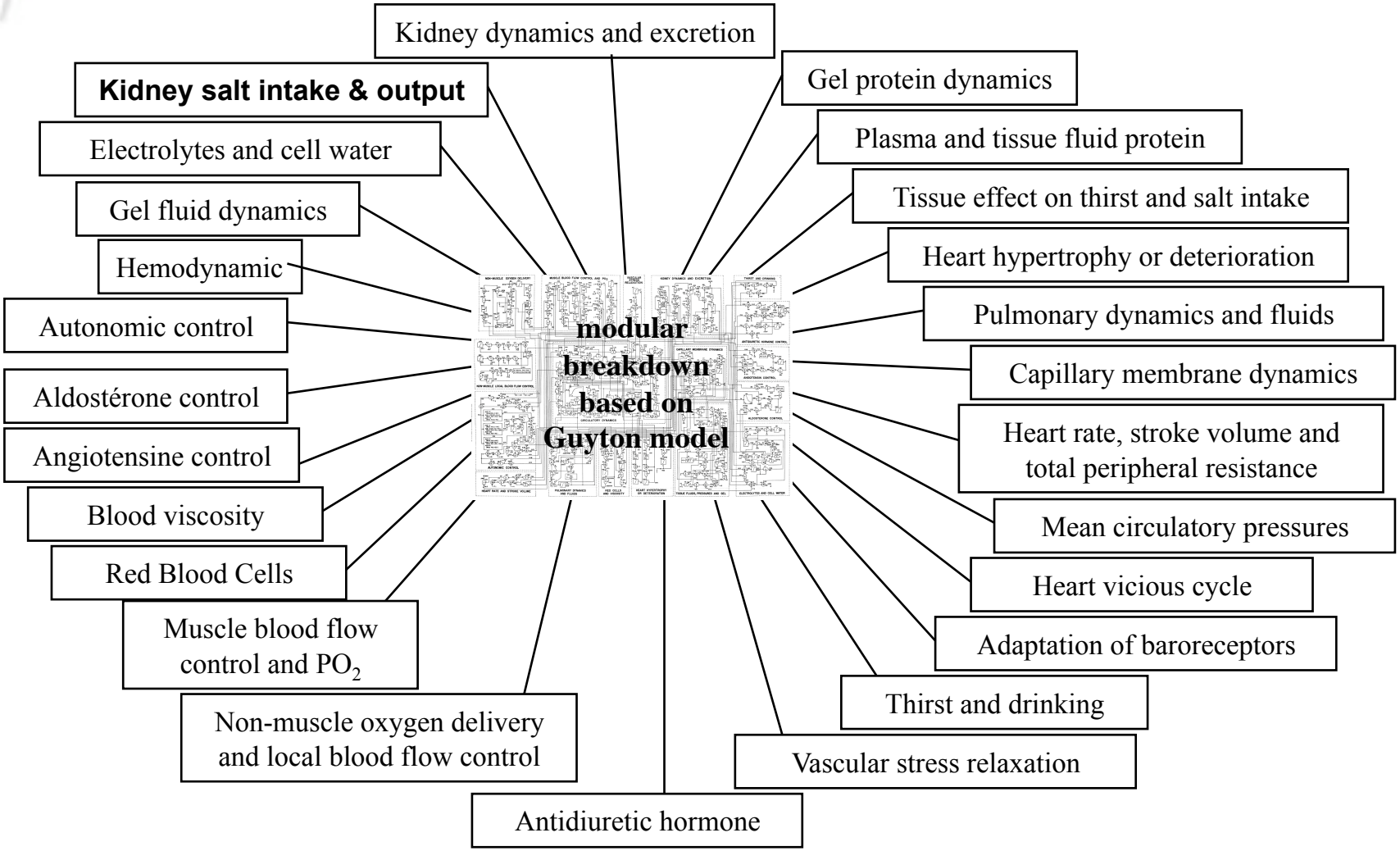
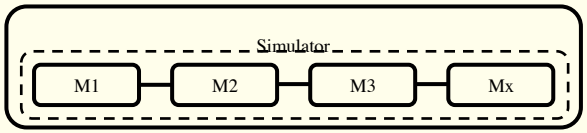


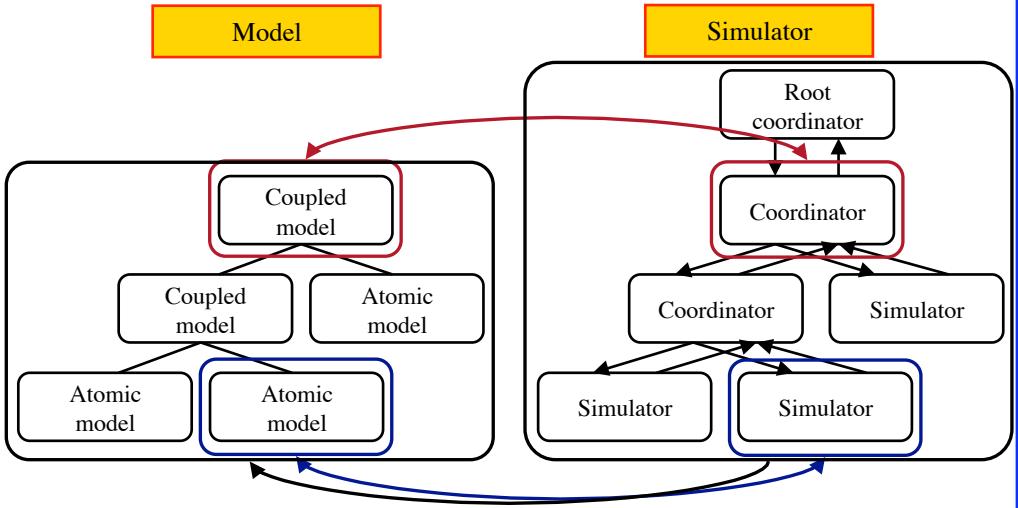
Figure 1. Modular multi-scale modeling environment. Using the Guyton model as starting point, we defined a number of object-oriented sub-modules. The whole collection is solved using the M2SL toolbox (Rennes lab), which automatically finds optimum step-size for individual modules and distributes the calculation over a number of parallel processors, when available.

M2SL: Multiformalism Multilevels Simulation Library®

M2SL (OO, C++), developed by A Hernandez, LTSI, Rennes
Based on *Distributed Architecture (Zeigler et al., 2000)*

- Generic simulators -> centralized approach
  - Single simulation loop for all elements
  - Changes => whole system redefinition
  - Unadapted to multiformalism modeling
  - Computer/time consuming





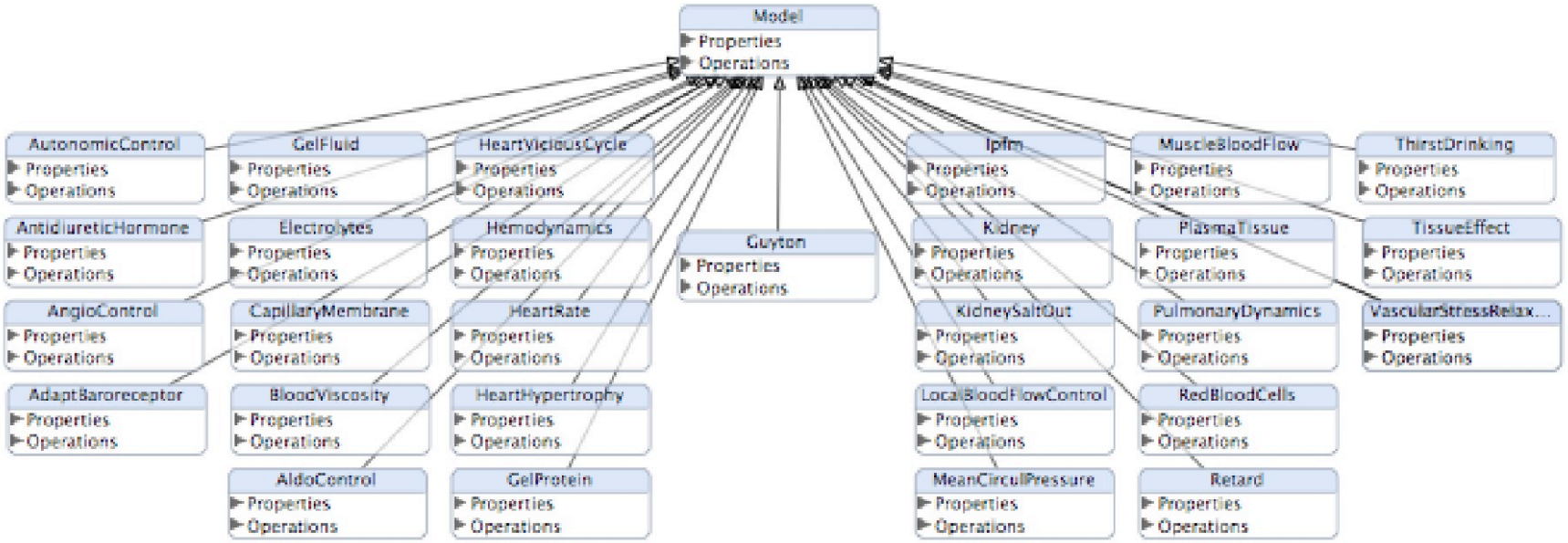
- Object Oriented programing ⇨ 2 main classes
  - Model
  - Simulator
- Association [Model – Simulator]
  - Simulator ⇔ Atomic model
  - Coordinator ⇔ Coupled model
  - Root coordinator ⇔ Simulation (whole)

- Simulation procedure(s) handled by « coordinator(s) »
  - Message exchanges (eg. for coupling)
  - Concurrent evolution of the elements
  - Calls to simulation methods
  - Adaptative simulation step & adaptative coordination step

✍ *M2SL well-adapted to multiformalism & co-simulation*

✍ *Fast execution*

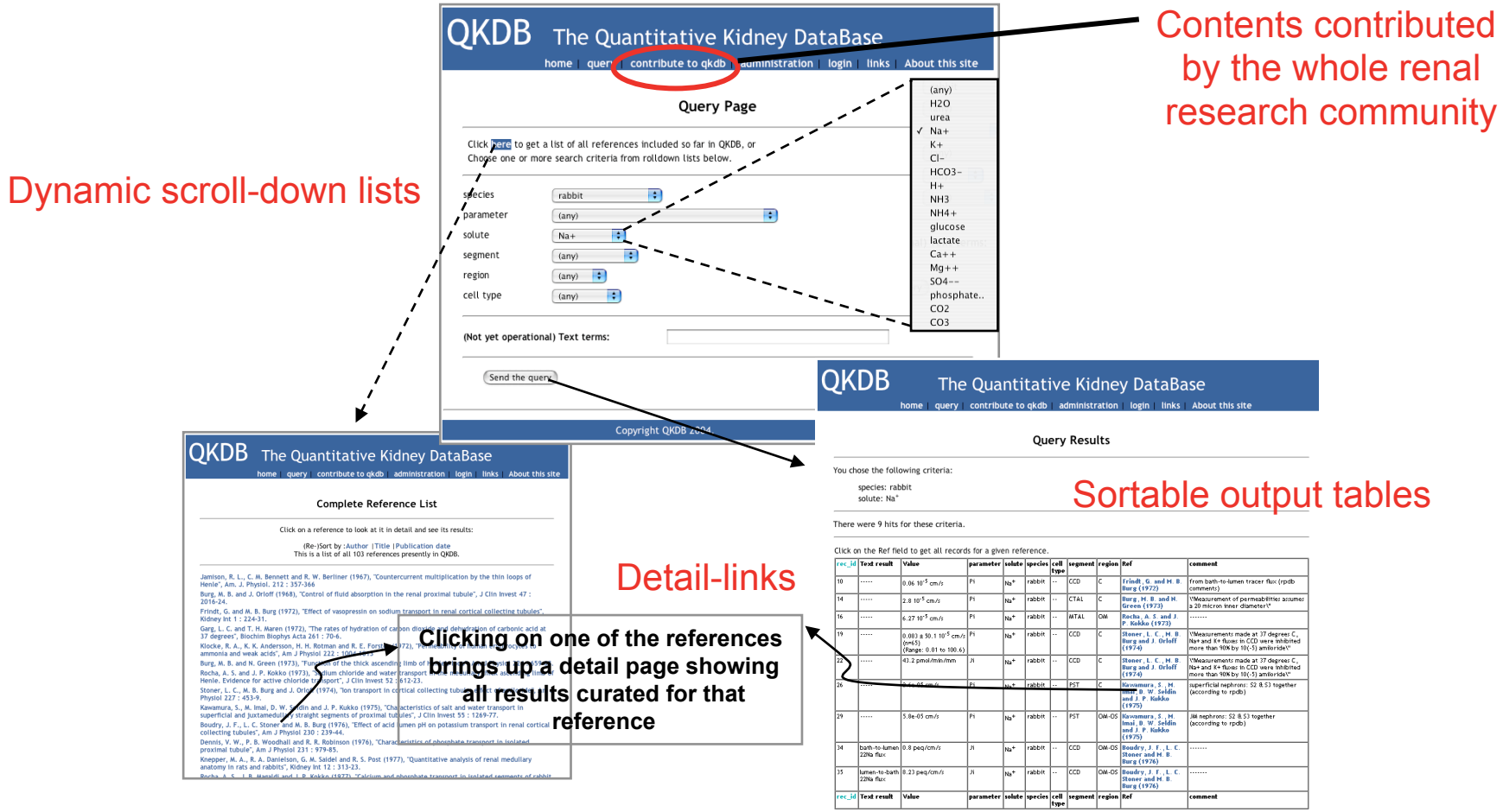
M2SL: Multiformalism Multilevels Simulation Library®



Modularisation of the Guyton model in M2SL

QKDB **(Quantitative Kidney DataBase)**

http://lami.univ-evry.fr/~srthomas/qkdb

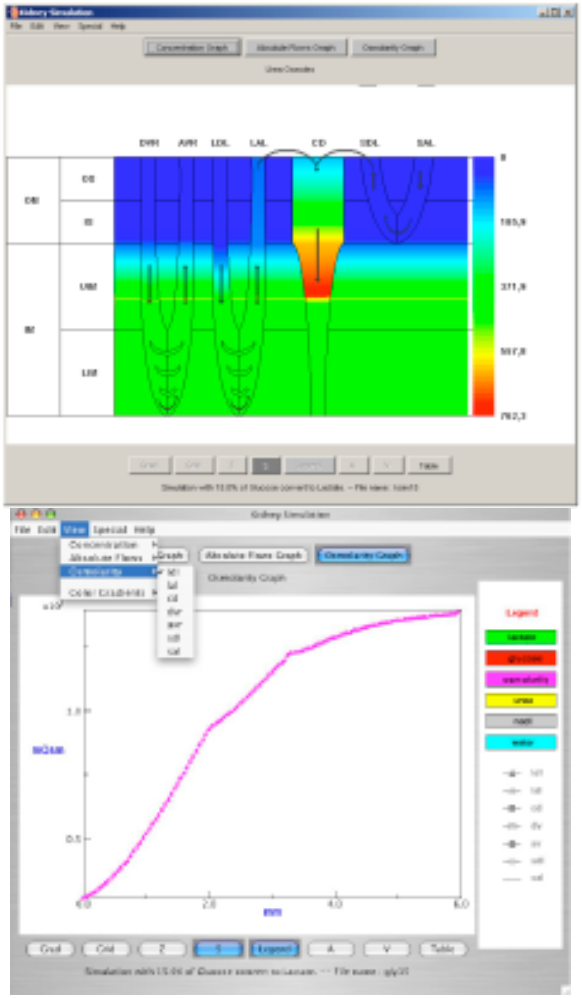


One-stop shopping for all quantitative measurements relative to kidney physiology, including anatomical features, transport parameters, flows and concentrations, transporter kinetics, etc.

Web-based model repository & interactive modelling tools

Java Applet

display results of customized legacy models

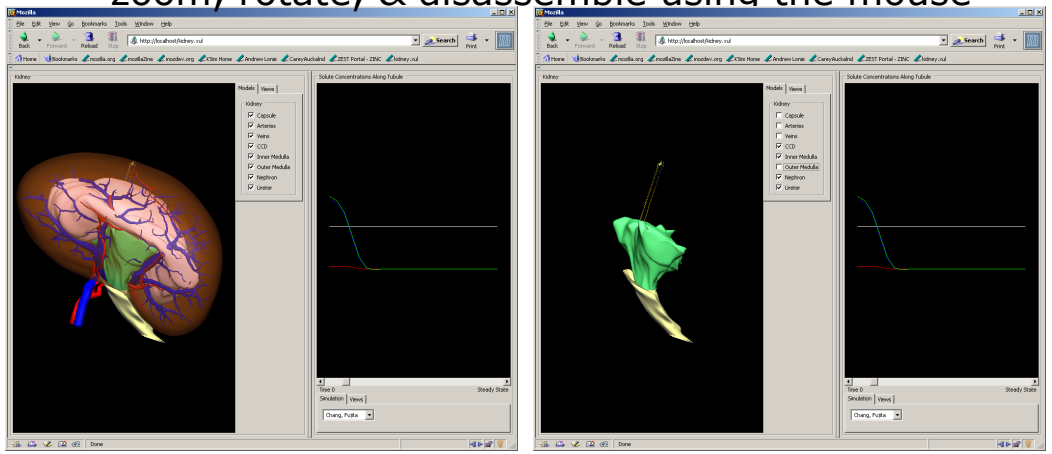


http://lami.univ-evry.fr/~srthomas/kidneysim

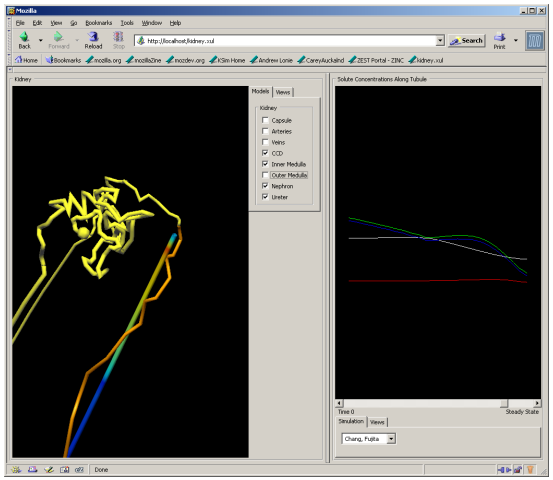
SR Thomas et co. (France)

3D Virtual kidney

zoom, rotate, & disassemble using the mouse

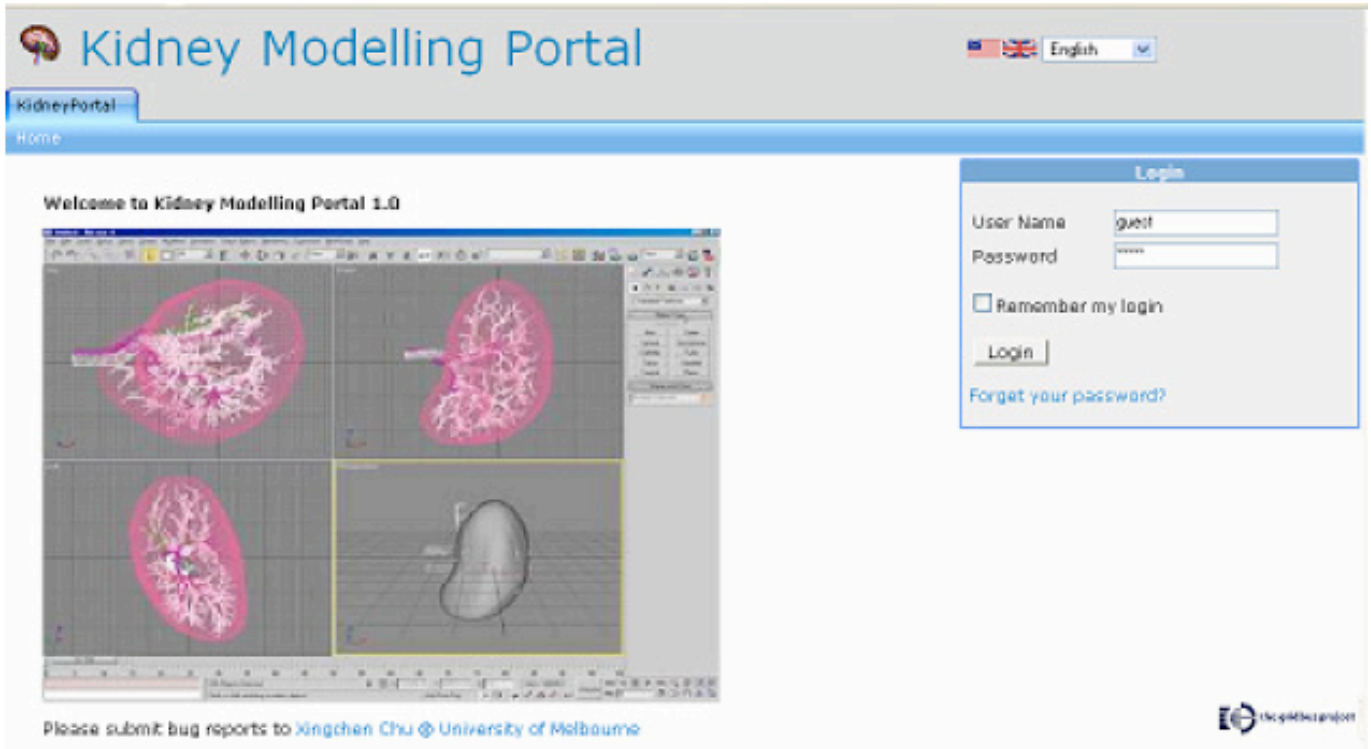


As proof of concept, a model of transport along the distal tubule (Chang & Fujita 1999), coded in CellML, is displayed on the virtual kidney



Lonie & P. Harris (Melbourne),
Carey Stevens (Auckland), SR Thomas (France)

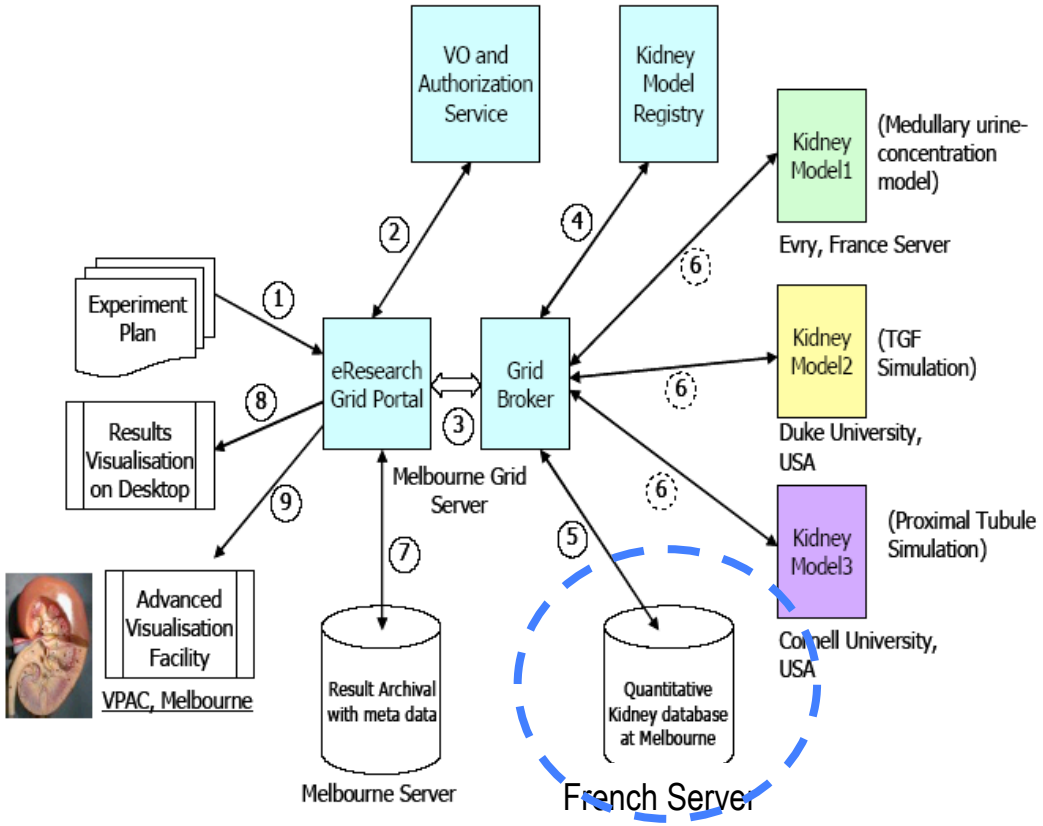
KidneyGrid:
A Grid Platform for Integration of Distributed Kidney Models and Resources



Access page to KidneyGrid

KidneyGrid: A Grid Platform for Integration of Distributed Kidney Models and Resources (2006), X. Chu, A. Lonie, P. Harris, S.R. Thomas, and R. Buyya. Technical Report, GRIDS-TR-2006-13, Grid Computing and Distributed Systems Laboratory, Univ. Melbourne, Australia. (4th International Workshop on Middleware for Grid Computing - MGC 2006 Melbourne. http://mgc2006.lncc.br/)

KidneyGrid (cont.)



A Grid-based eResearch Architecture for Integration of Distributed Kidney Models

KidneyGrid: A Grid Platform for Integration of Distributed Kidney Models and Resources (2006), X. Chu, A. Lonie, P. Harris, S.R. Thomas, and R. Buyya. Technical Report, GRIDS-TR-2006-13, Grid Computing and Distributed Systems Laboratory, Univ. Melbourne, Australia. (4th International Workshop on Middleware for Grid Computing - MGC 2006 Melbourne. http://mgc2006.lncc.br/)

Collaborators

(partial list)

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