MEFANET 2012
Brno

The Virtual Physiological Human (VPH) project, with focus on an integrated core model of blood pressure regulation

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(Imagerie par Résonance Magnétique Médicale et Multi-Modalités)
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Équipe 5: Imagerie fonctionnelle de la micro-vascularisation tumorale
IGR, Villejuif

Plan

Part 1: VPH: Network of Excellence etc.

- **what it is (and what it's not?)**

Part 2: SAPHIR & Renal Physiome

- **one small item in the VPH effort…**

Part 1: VPH: Network of Excellence etc.

The VPH NoE

http://www.vph-noe.eu

- VPH/Physiome: some history…
  - roots in the IUPS Physiome
- VPH: framework for computational representation of the human body as an integrated, complex and dynamic system
- NoE: coordination of efforts, identification of user needs, standards, ontologies, toolkit, application, training, dissemination
- Community building and Training
- Long-term sustainability (VPH Institute)

VPH-I: First call

1 NoE

3 IPs

9 STREPs

2 CAs

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

VPH NoE Consortium Overview

http://www.vph-noe.eu

- 13 Core Partners

  4 UK (UCL, UOXF, UNOTT, USFD)
  3 France (CNRS, INRIA, ~~ERCIM~~)
  2 Spain (UPF, IMIM)
  1 Germany (EMBL [EBI])
  1 Sweden (KI)
  1 Belgium (ULB)
  1 New Zealand (UOA)
  1 Italy (IOR)

- Associate / General Membership

  50 General & Associate Members

- VPH-Institute

  recently founded and now operating

The VPH ToolKit

- Open markup language (XML) standards for describing data and models at spatial scales that range from proteins to the human organ
- Application programming interfaces (APIs) for implementing these VPH standards
- Workflows that use existing middleware for facilitating grid-enabled VPH research
- Web-accessible repositories for data, models and workflows based on the VPH standards and including annotation and tutorials for non-expert biologist users
- A library of open source computational routines and graphical user interfaces that, via the APIs, can access the data and model repositories

WP2 – the Exemplar Projects

- Exemplar Projects (EPs), as conceived in DoW:
  - existing projects, with 'external' funding (not EU VPH projects)
  - "solid examples of horizontal and vertical model/data integration"
  - direct commitment to link up with and reinforce VPH ToolKit development, for which they are granted **6-12 PersonMonths of support** from the NoE
- EPs maintain a two-way give-and-take with the VPH Toolkit
  - adopt and give feedback on appropriate toolkit items
  - identify/point out unsatisfied needs in the WP3 ToolKit development
  - provide high quality content
  - provide showcase demonstrators/workflows for the the ToolKit
- Five "seedEPs" at start, then three open calls (one per year) for new EPs

VPH NoE Exemplar Projects

	Name
seedEP1	SAPHIR: A multi-organ Core Model of arterial pressure and body fluids homeostasis (CNRS, Evry)
seedEP2	IMUS: integrated multi-level modeling of the musculoskeletal system (ULB, IOR)
seedEP3	WHAM: "Modeling human disease in the presence of model and parameter uncertainty" (KI)
seedEP4	Towards quantitative assessment of drug safety by multiscale and molecular simulation tools (IMIM/GRIB)
seedEP5	Modeling and visualizing brain function and pathophysiology (ERCIM/ICS-Forth)
EP6 (Call 1)	Establishing ontology-based methods to improve interoperability between data and models for the VPH ToolKit: the Guyton case study (EBI, CNRS, UoA, Univ. Wash.)
EP7 (Call 2)	CIGENE: Integrating genetic theory and genomic data with multiscale models in a population context
EP8 (Call 2)	The NoE, Infrastructure and the Challenge of Call6
EP9 (Call 2)	VIP for VPH : Execution of medical image simulation workflows on DEISA through workflow interoperability between the Virtual Imaging Platform and the VPH toolkit
EP10 (Call 3)	Environment for Sexually Transmitted Infection Modelling
EP11 (Call 3)	Vascular Tissue Modelling Environment (VTME)

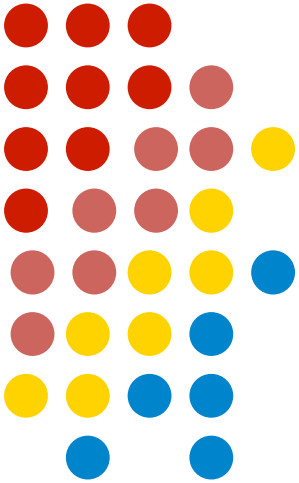
VPH Training activities

VPH-MIP Overview

Multi-Institutional Graduate Programme for Virtual Physiological Human Scientists

Industry-Academia Meeting

Barcelona, 29th September 2011



Education and Culture DG
Lifelong Learning Programme

EACEA
Education, Audiovisual & Culture Executive Agency

UNIVERSITAT POMPEU FABRA

UCL

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POLITECNICO DI MILANO

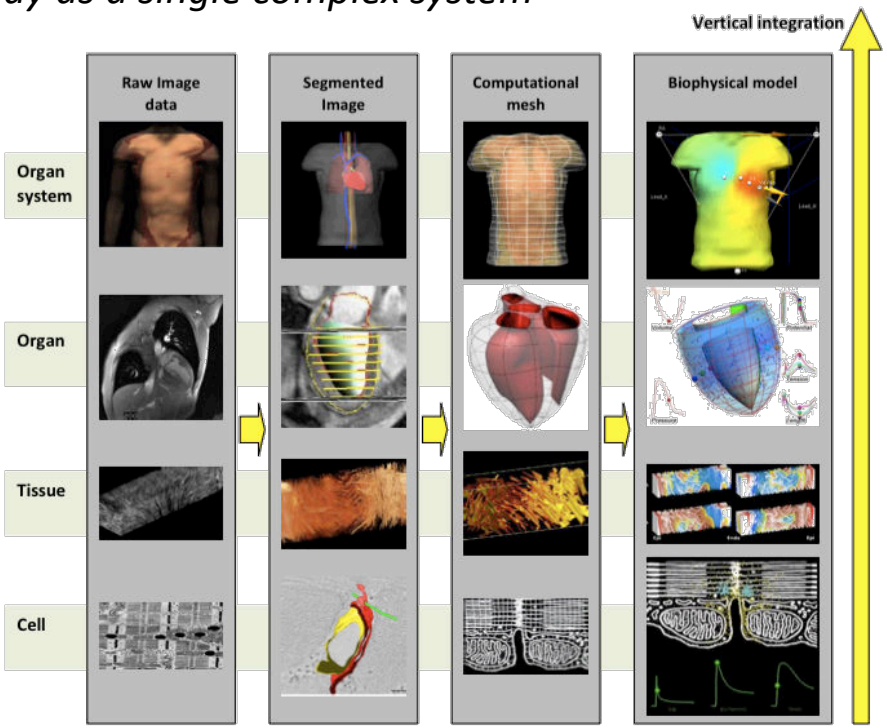
ULB Université Libre de Bruxelles

The University Of Sheffield.

VPH-MIP: Motivations

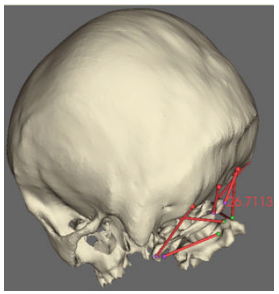
- *Virtual Physiological Human* (VPH) is an emerging discipline which aims at:
  - *Creating a methodological and technological framework which will allow the collaborative investigation of the human body as a single complex system*

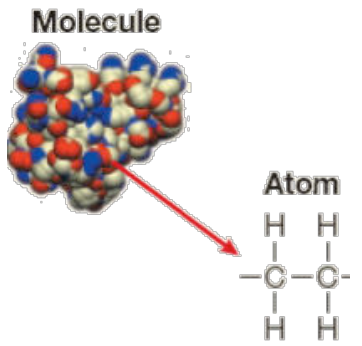
- There is no VPH-specific training available in Europe, focused on the differentiating characteristics of VPH:
  - Heterogeneous data fusion
  - Multi-scale and multi-physics modelling of human physiopathology
  - Simulation of complex clinical workflows



VPH-MIP: Rationale

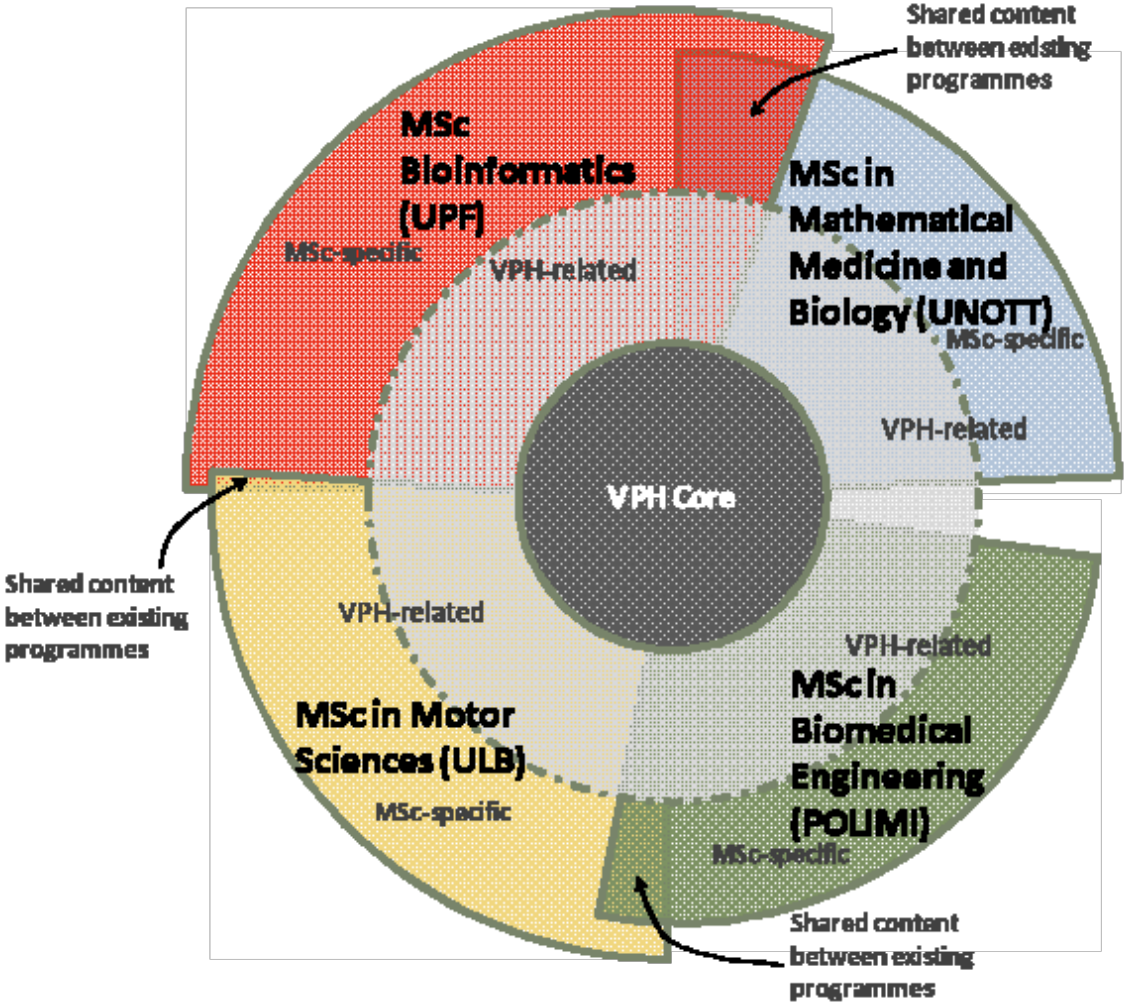
- In such a multidisciplinary field, students must receive a solid scientific background if they are to make future contributions
- Thus, training should be based on existing Masters programmes in related disciplines
  - Eg. Bioinformatics, biomedical engineering, mathematical modeling
- Existing programmes must be <u>combined</u> to <u>complement</u> <u>each other</u>, and extended to address VPH-specific training needs





VPH-MIP: Current Scenario

- Masters programmes being integrated into the framework
- Identify share content
- Identify existing VPH-related modules
- Identify essential gaps in training
- *VPH-Core*: on-line modules essential for VPH training

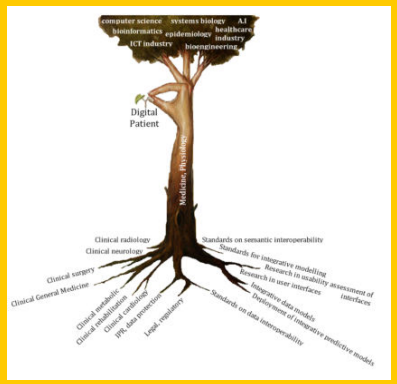


VPH-MIP: Expected Outcomes

- A framework where different Masters programmes related to the VPH can be
  - Integrated, Combined, and Exploited
- Understanding on how new Masters programmes could become part of such framework
  - Legal and Quality concerns

- **Understanding the industry expectations on new graduates in the field**
- Set of *Core VPH* on-line training modules
  - Contents designed and available on an e-learning platform

EC FP7 Project 'DISCIPULUS': Objectives & Cooperation



2. *To capture and quantify the needs from:*
   - *Clinicians*
   - *Regulatory agencies*
   - *Healthcare providers*
   - *Educators*
   - *Patient consultative groups*

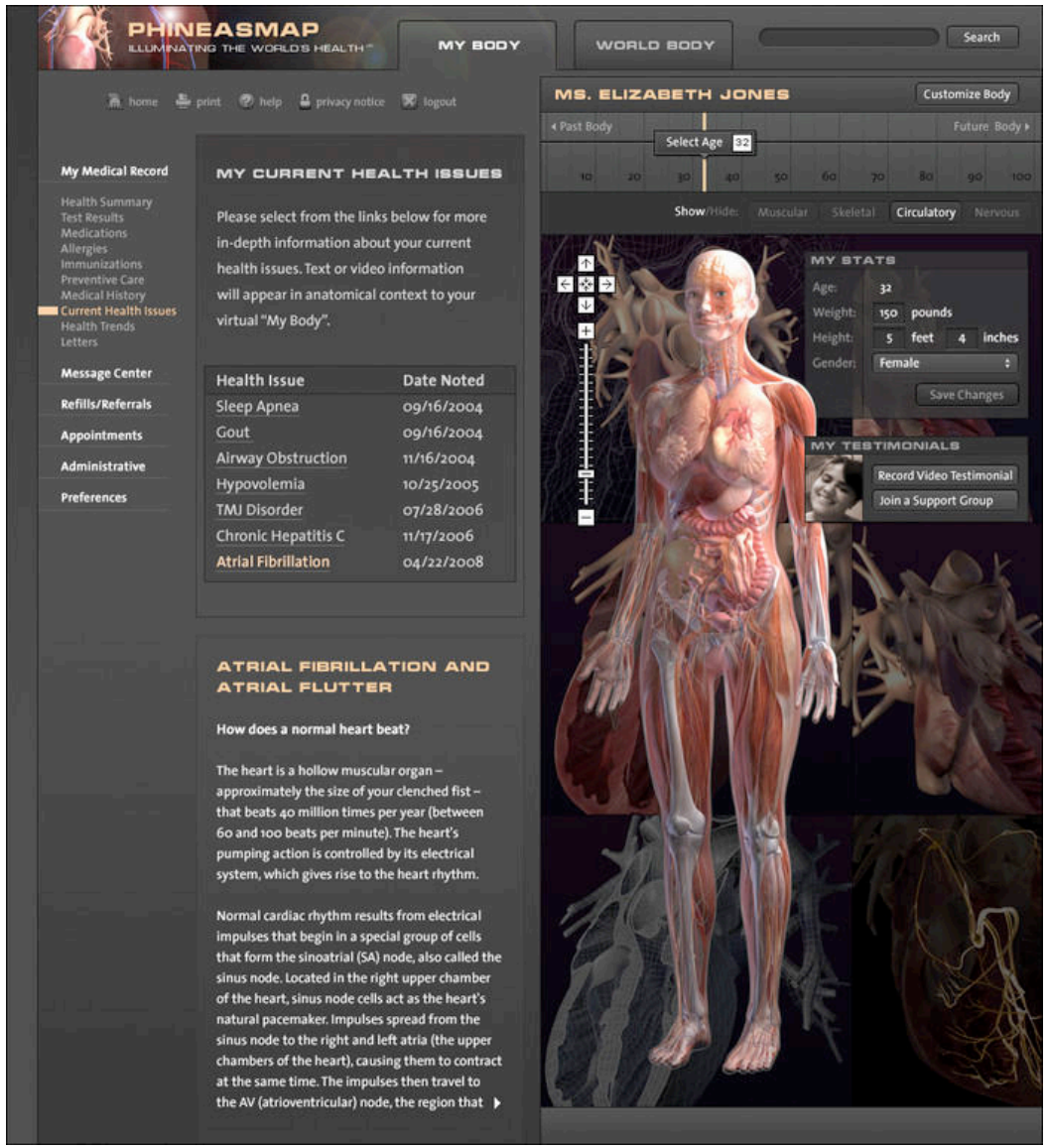
   … to tackle adoption and uptake issues

- 18-month project
- Begins October 2011
- Consulting as widely as possible
- Opportunity for AMEE engagement from the outset
- Please get in touch if you're interested
- k.m.mccormack@sheffield.ac.uk

Key Facts: VPH & Digital Patient

- VPH: a grand plan to make all human physiology computable
- The computer models represent an integration of…
  - Small and large
  - Fast and slow
  - All organs, all systems, all disciplines
- All models personalised, can be interconnected
- Outputs are enhanced diagnostic & treatment options
  - Example: should we treat an aneurysm?
    - Currently: What size is it?
    - VPH: How strong are the walls? (+ many others)
- VPH requires patient data – store it in an Avatar
- Help? How do we design, control, explain this Digital Patient?

The Digital Patient
Towards a Future of Medical Avatars



Avatars: A reminder…

1. Hindu mythology: The descent of a deity to the earth incarnate.

2. From which: An embodiment or personification, as of a principle, attitude, or view of life.

3. And in Digital Technology: A graphical representation of a person.

What should be stored in the Avatar?

- **Blood pressure etc.**
- **Medical images**
- **Laboratory tests**
- **Diagnoses**
- **Interventions**
- **Data from simulations**
- **Lifestyle choices, partners…**

Anything we should NOT store?

VPH: Summary of Part 1

- A major European and international effort for collaboration and interoperability
  - VPH NoE, VPH-I projects, VPH Institute, IUPS Physiome
- Models, databases, repositories, markup languages, reference ontologies
- Training
  - VPH-MIP
  - VPH Textbook
- …

Part 2: SAPHIR & Renal Physiome

SAPHIR: Scientific Context

- SAPHIR: French ANR and an Exemplar Project in the VPH Network of Excellence
- Develop a collaborative "core modelling environment" for multi-organ integrated physiology
  - target problem: regulation of blood pressure and fluids homeostasis
- Collateral needs:
  - multi-resolution, multi-formalism numerical package
  - common language for model description/translation
  - database to underpin parameter estimation and model validation
  - ontology development
    - to standardize nomenclature
    - to enable adoption of reference identifiers across scales/models/ DBs...

Towards a modular core model environment

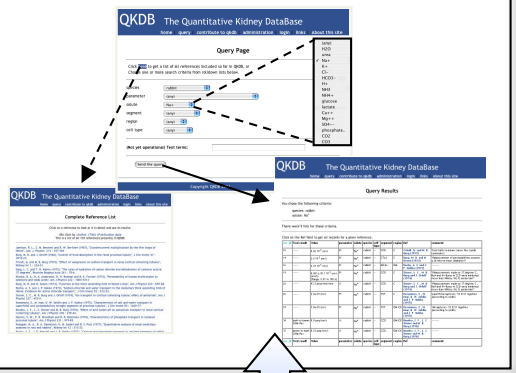
Detailed replacement modules

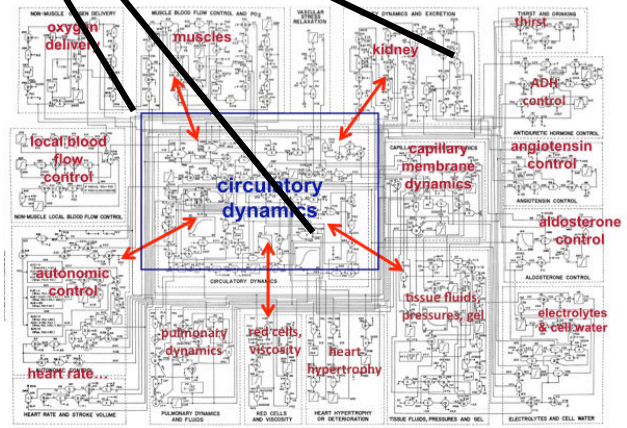
DAEML (& CellML)

XSLT converters

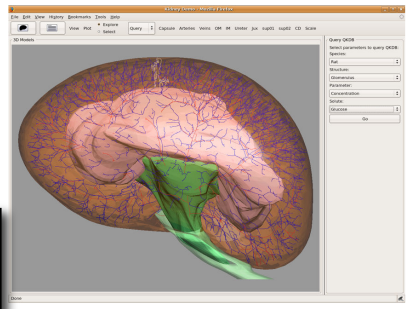
Robust multi-formalism solver: M2SL

Parameter DB: QKDB/ QSDB





Interactive Model repository: Virtual Kidney/ KidneyGrid Portal



Ontology tools

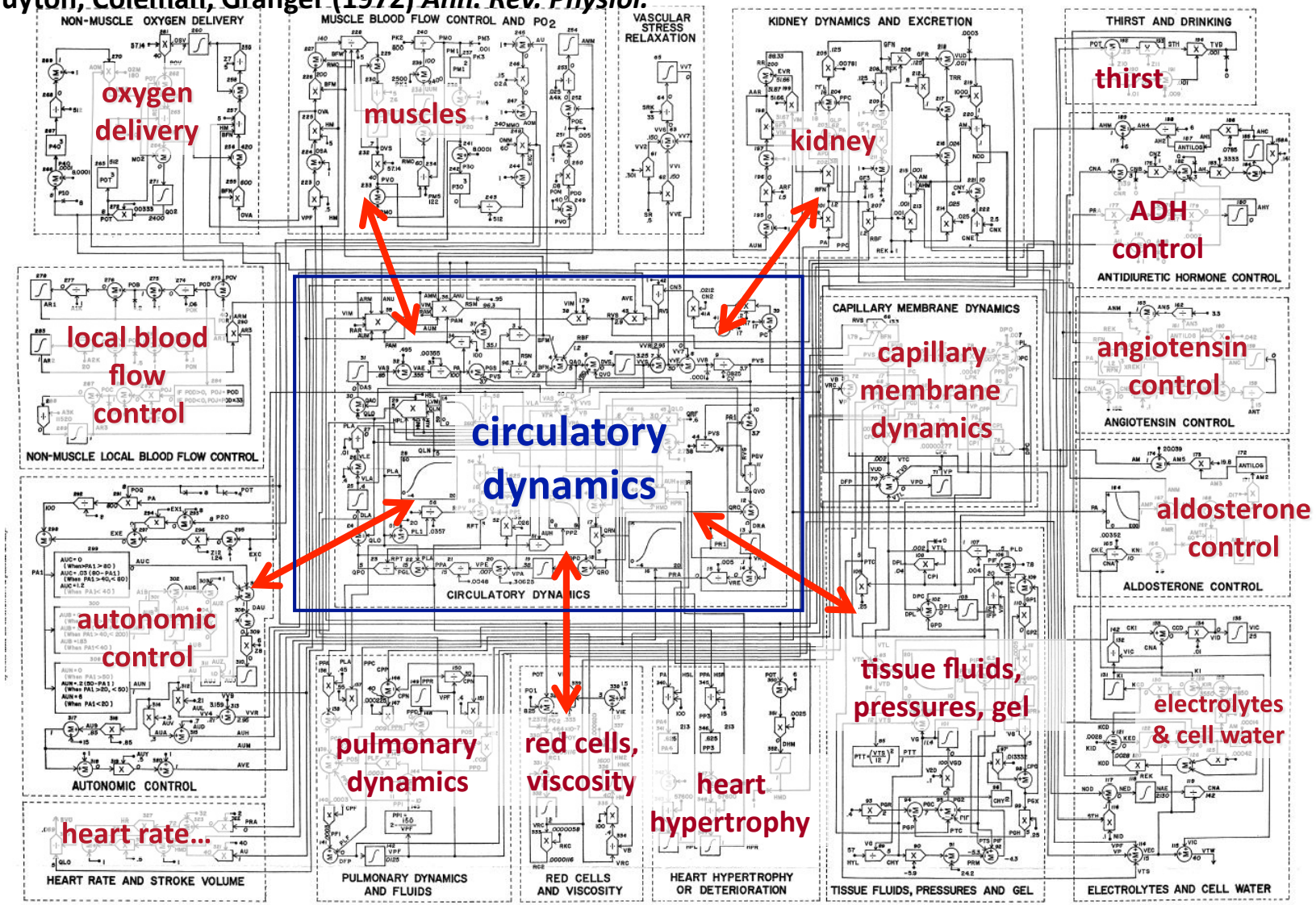
OMIE:
Ontology Mapping within an Interactive and Extensible environment

"Guyton" ontology

Auto-Information extraction from PDF files

SAPHIR: a core model inspired by the Guyton models

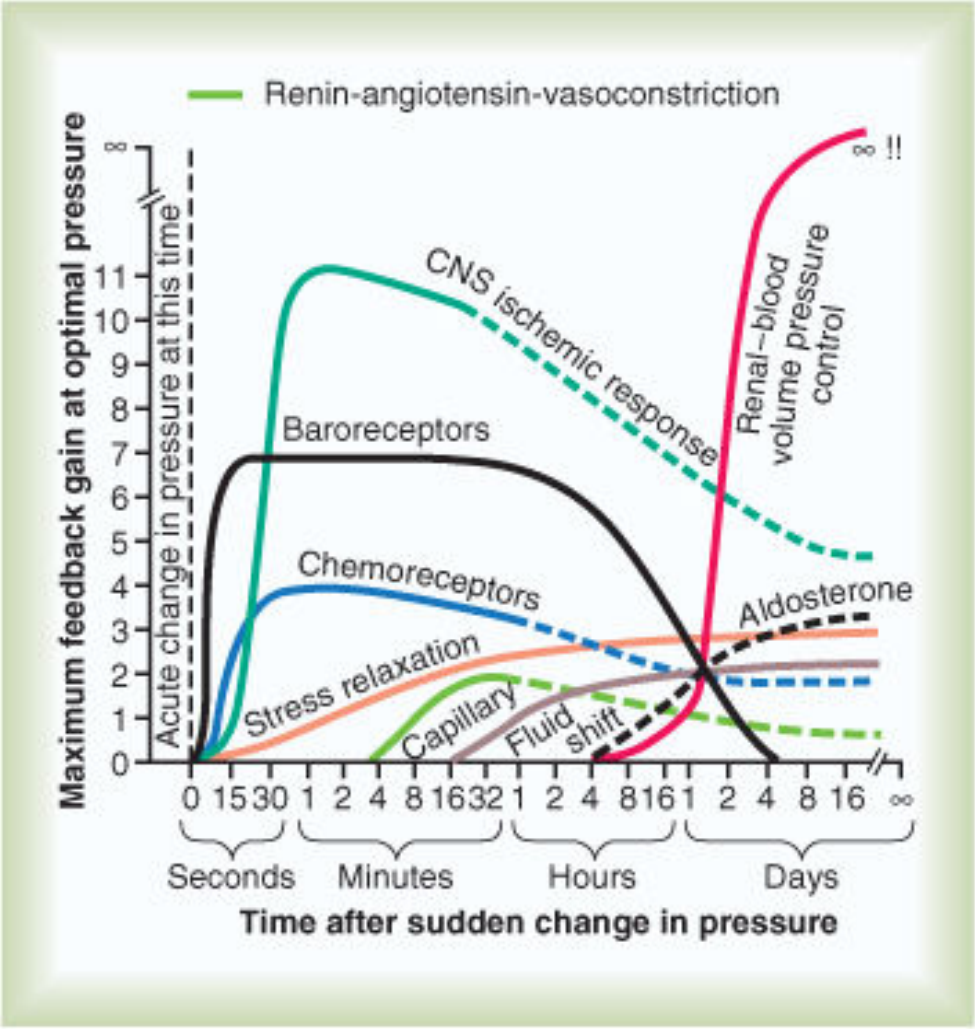
Guyton, Coleman, Granger (1972) *Ann. Rev. Physiol.*



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

Blood pressure regulation: multi-organ integration - many systems are involved, at many scales

- **regulatory systems act over different time scales**

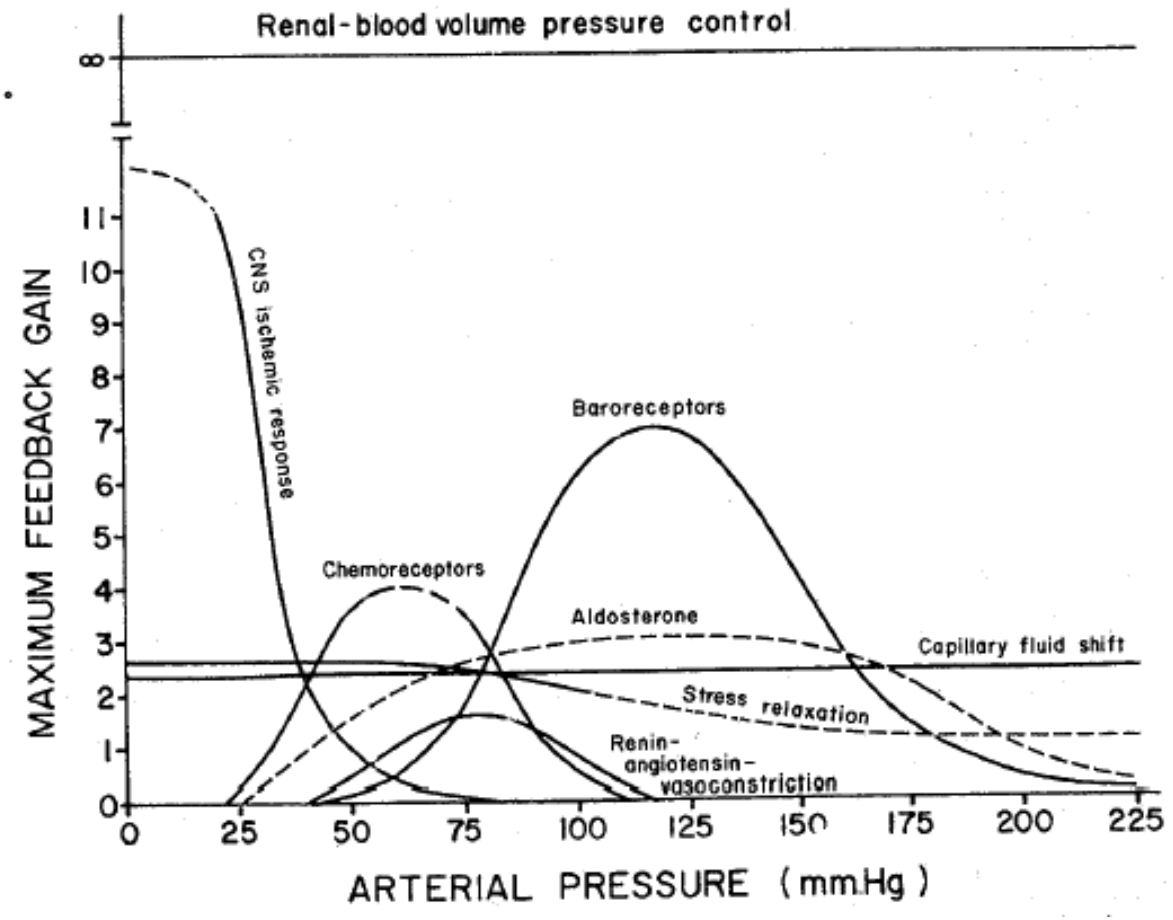


from Guyton, A. C. (1980). Circulatory Physiology III. Arterial Pressure and Hypertension. Philadelphia, W.B. Saunders.

Blood pressure regulation: multi-organ integration - many systems are involved, at many scales

- regulatory systems act over different time scales

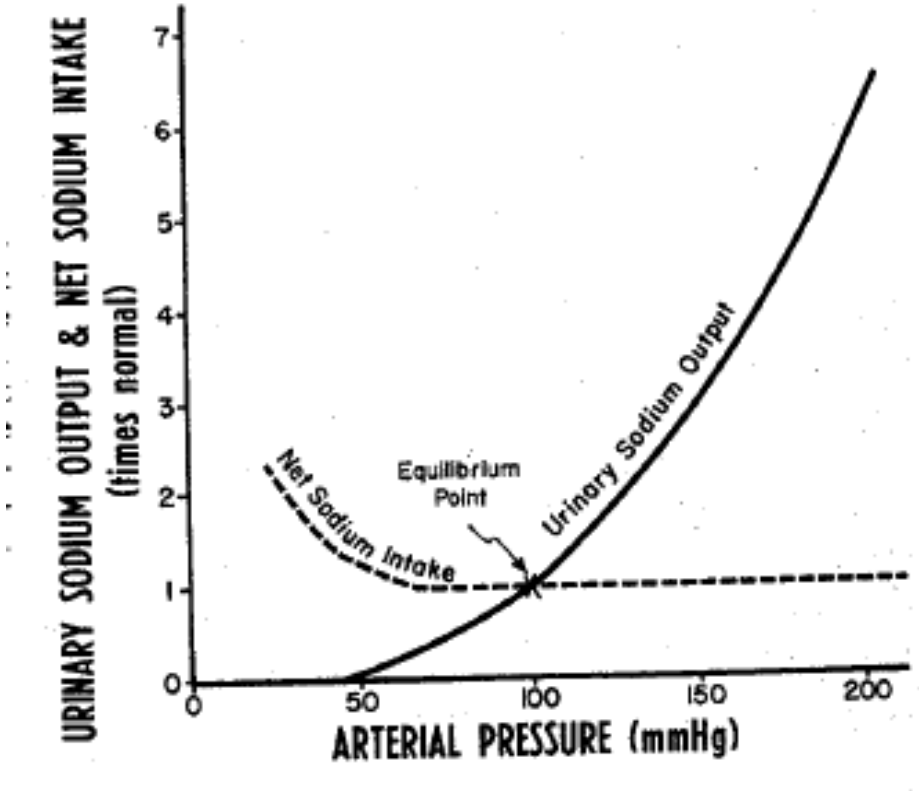
- **and over different pressure ranges**



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:

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.

In the long-term, we must be in water and salt balance,

i.e., INPUT must equal OUTPUT

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

Shifting the Renal Function Curve…

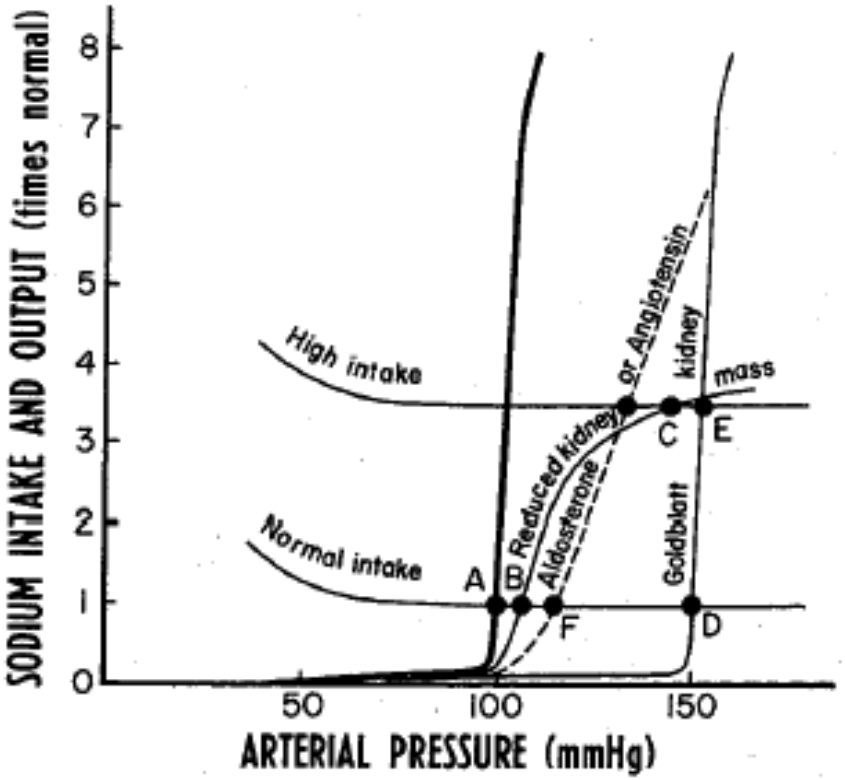
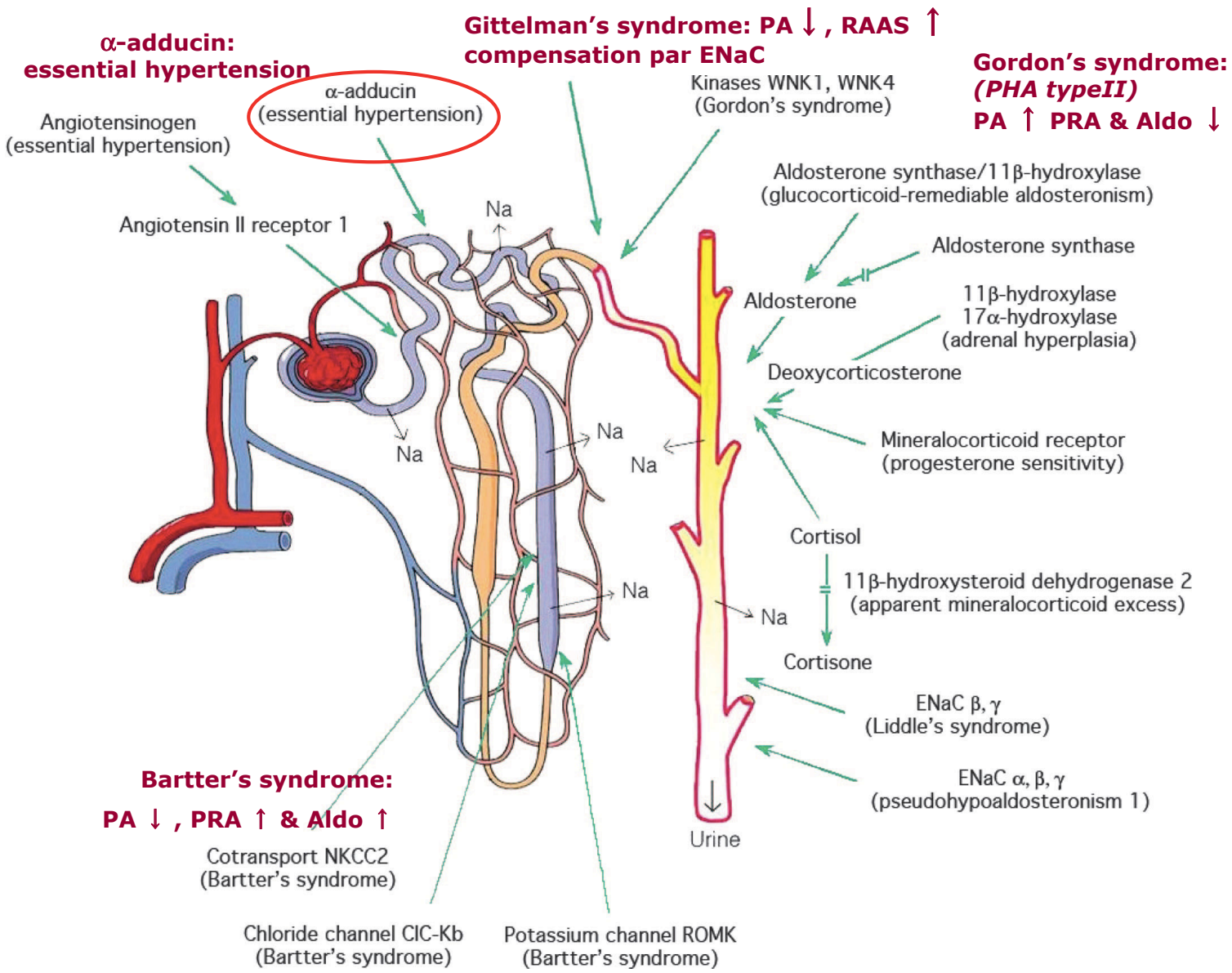


Figure 7–9. Analysis of arterial pressure regulation in several altered functional or pathological states of the kidneys: (1) reduced kidney mass, (2) Goldblatt kidneys, and (3) increase in aldosterone or angiotensin.

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

Defects of renal transporters are implicated in health problems. These are pharmacological targets with inter-connected relationships.



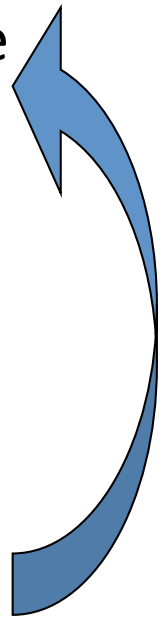
(Meneton, P. et al. (2005). Physiol Rev 85(2): 679-715.)

Target scenario: Hypertension—Defects of Distal Tubule NaCl reabsorption.

How to model the gene-to-organism relationship?

We must account for:

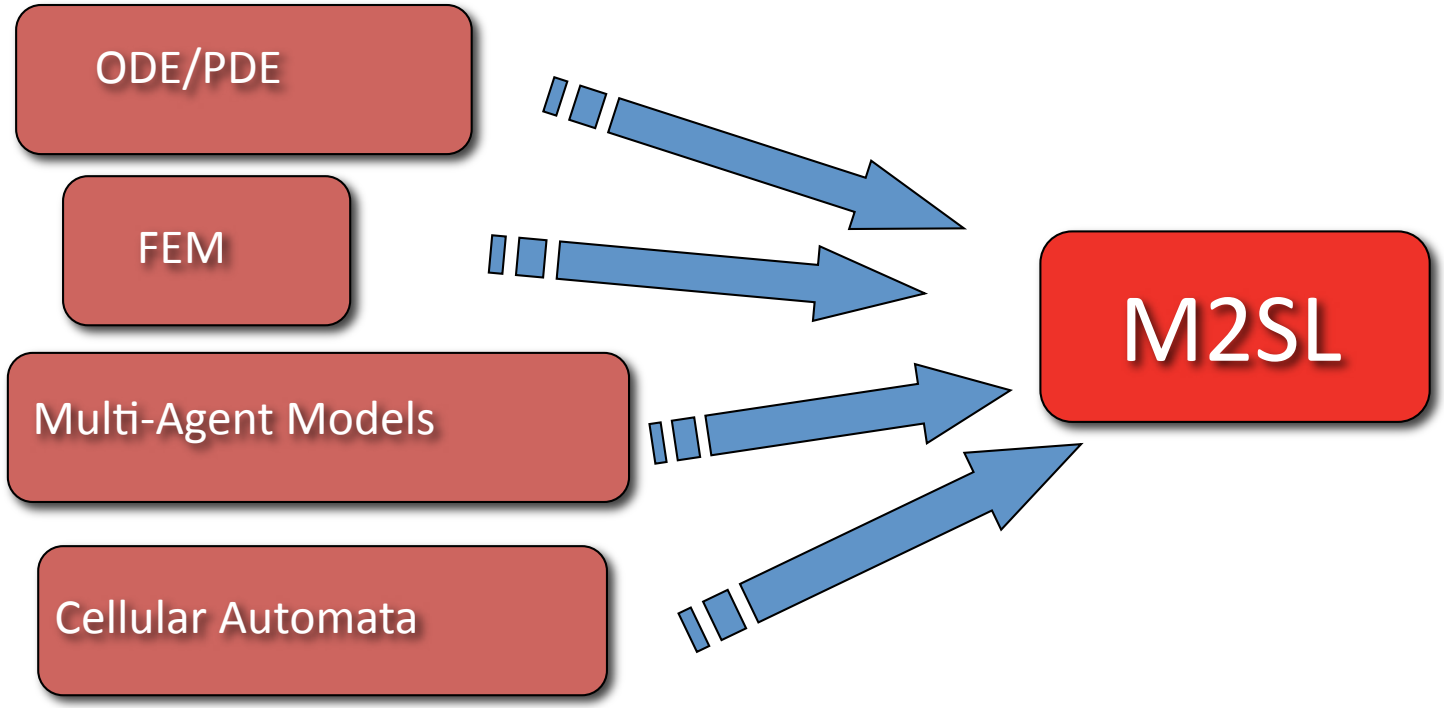
- the change of function at the molecular/ cell membrane level
  - therapeutic target
- the impact on blood volume, via NaCl reabsorption
- the resulting effect on blood pressure
- hormonal and nervous system feedbacks
  - (including possible effects on expression of the target gene!)



BUT keep execution time manageable!

M2SL: *Multiformalism Multilevels Simulation Library®*

A. Hernandez(Rennes)



Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

UNIVERSITÉ DE RENNES 1

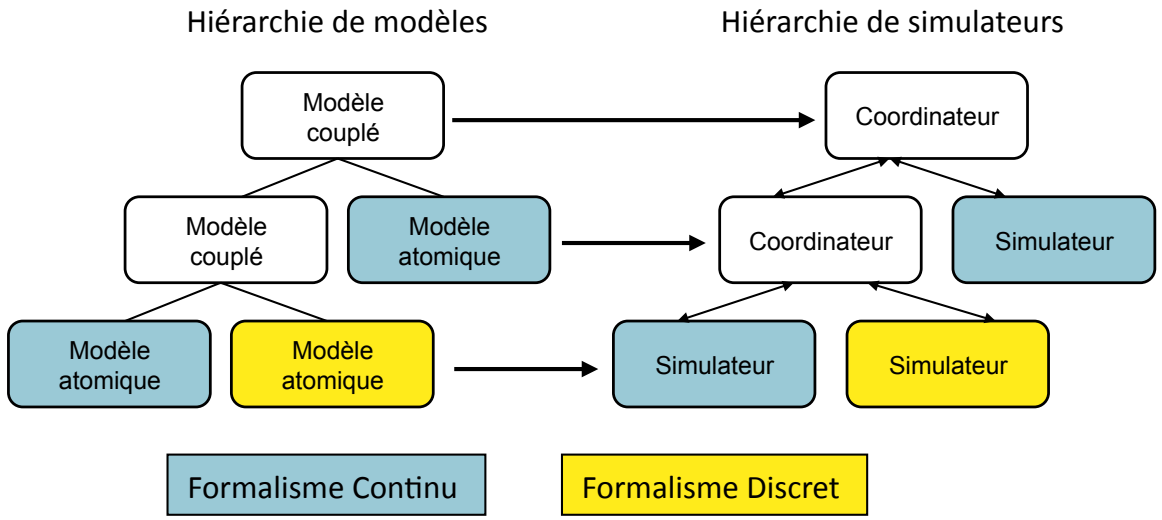
LTSI

M2SL: *Multiformalism Multilevels Simulation Library®*

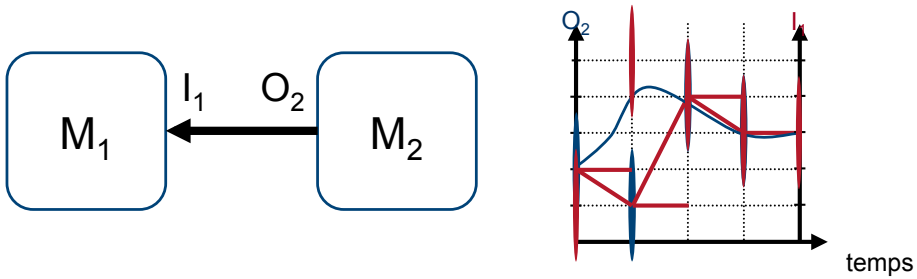
A. Hernandez(Rennes)

Multi-formalism modeling by co-simulation

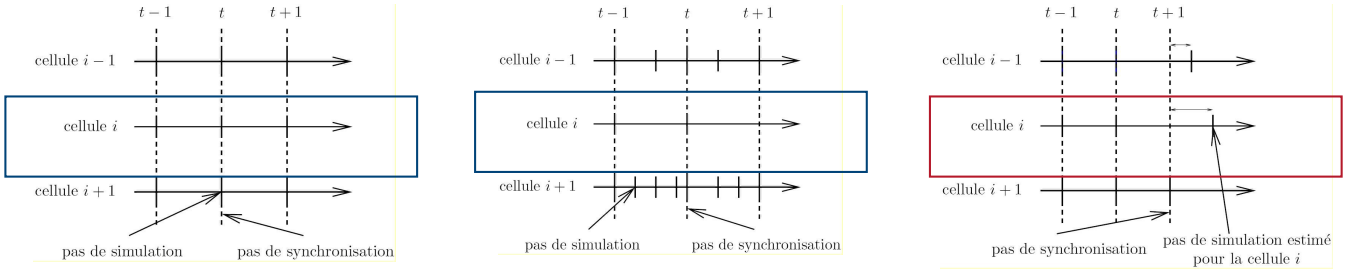
- Hierarchical structure
- Object-oriented
- Distributed approach



Input/output coupling



Temporal Synchronization



Synchronisation & simulation à pas fixe

Synchronisation à pas fixe & simulation adaptative

Synchronisation & simulation adaptatives

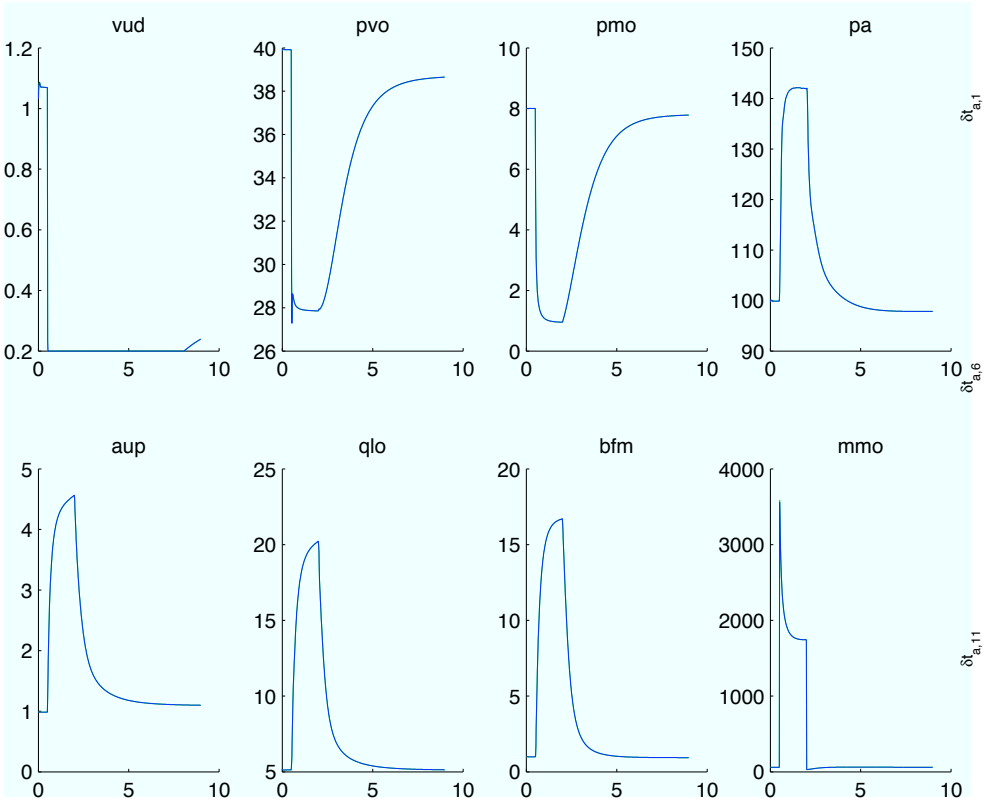
Benchmark – Adaptive with fixed coupling

Simulation of 2 min. of intense exercise

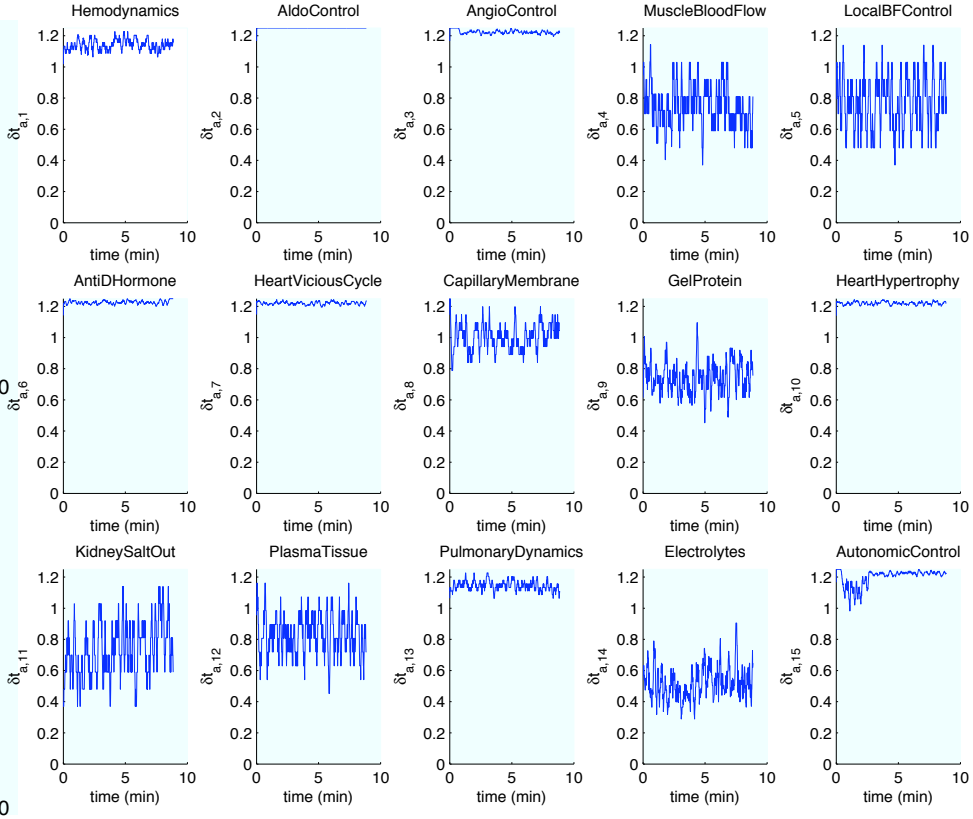
DT initialized to 1e-4, coupling = 2.5e-4, max abs. Err = 5e-13

Execution time **3.2 secs : ~ 3 times faster than a standard fixed-step**

Outputs with reference (FIXED) in green

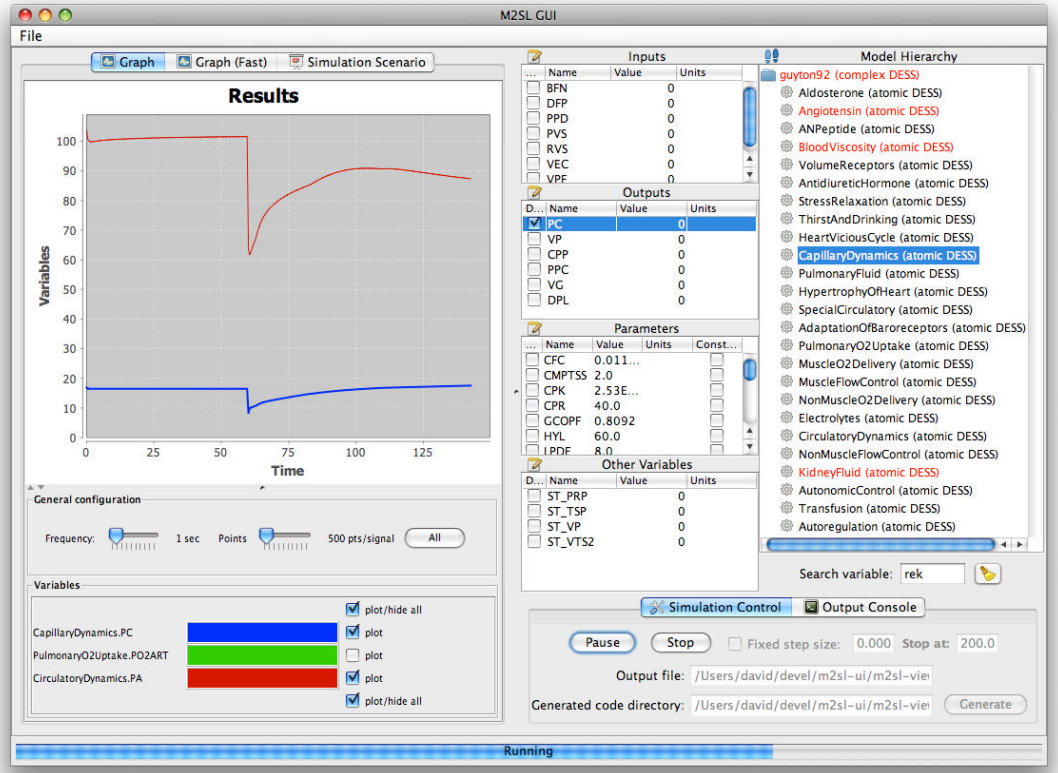


DT of each sub-model

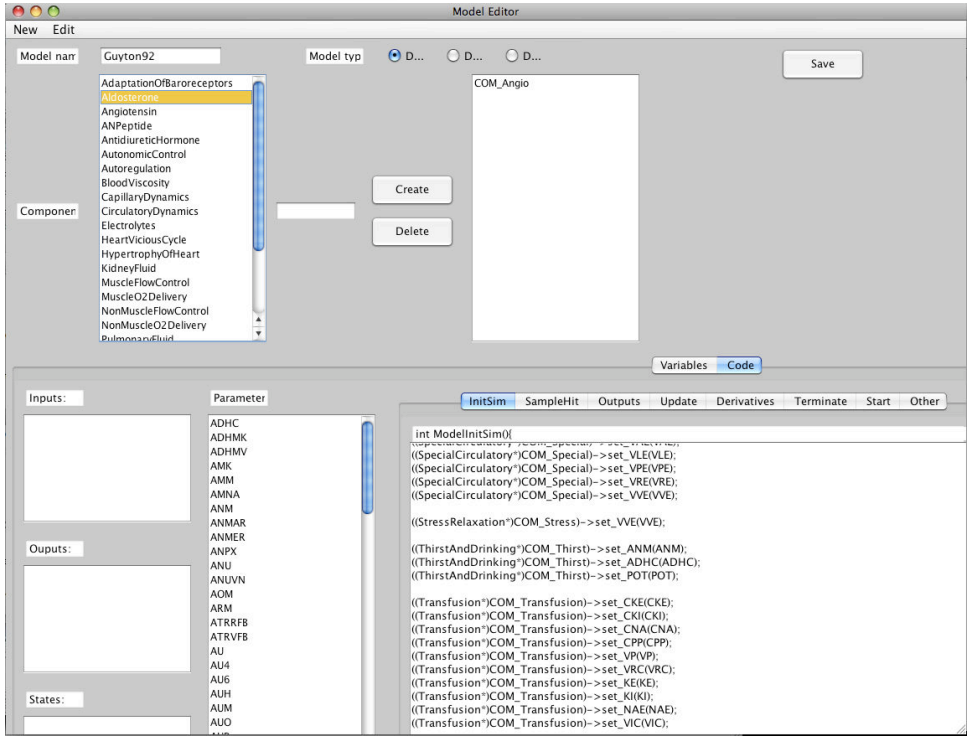


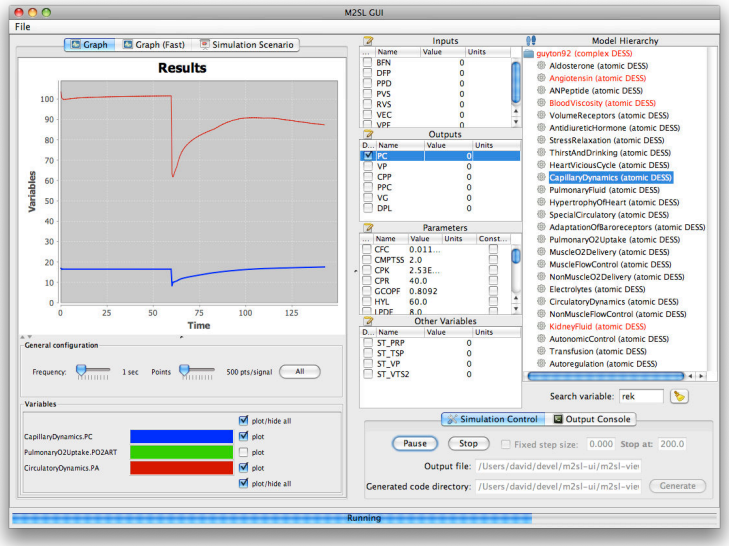
M2SL User Interface

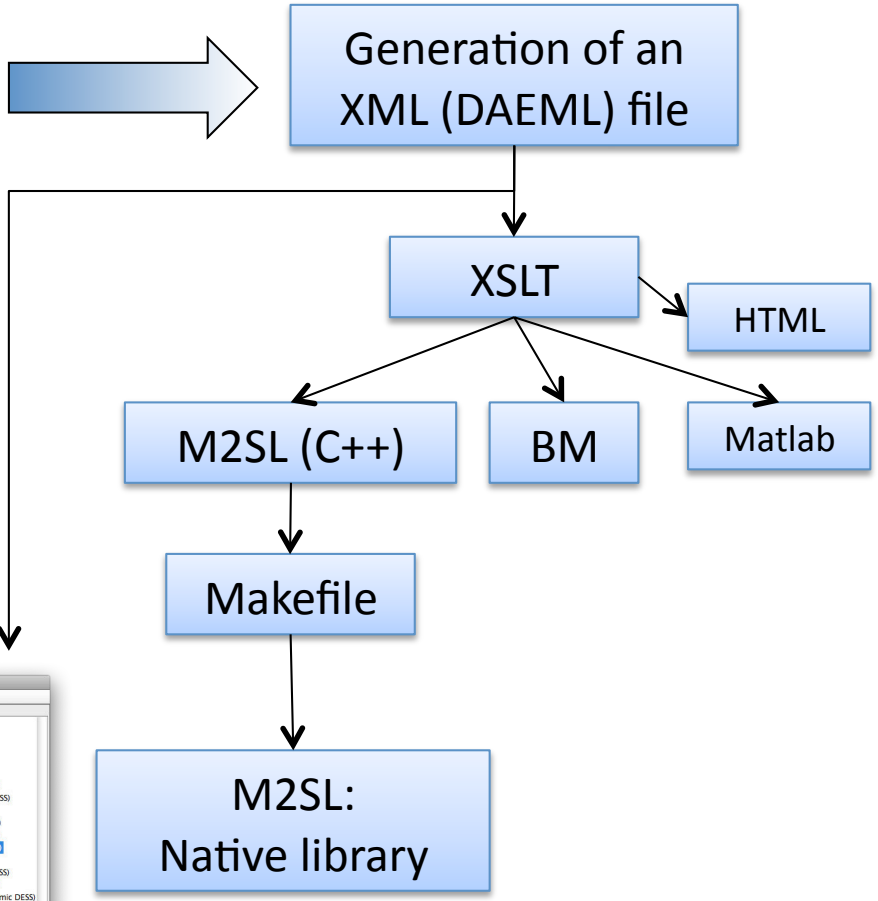
- **Control M2SL simulation.**
- Manipulate M2SL simulation parameters.
- Change model parameters before and during simulation.
- Observe model hierarchy and variables (inputs, outputs, parameters) in real-time.
- Search variables by name.
- **Load model from a XML file (DAEML).**
- **Generate and compile C/C++ code from DAEML files.**
- **Load compiled models without DAEML files.**
- Create and manipulate simulation scenarios: automatically modify parameter values during simulation.
- All changes and configuration are saved in a DAEML file.



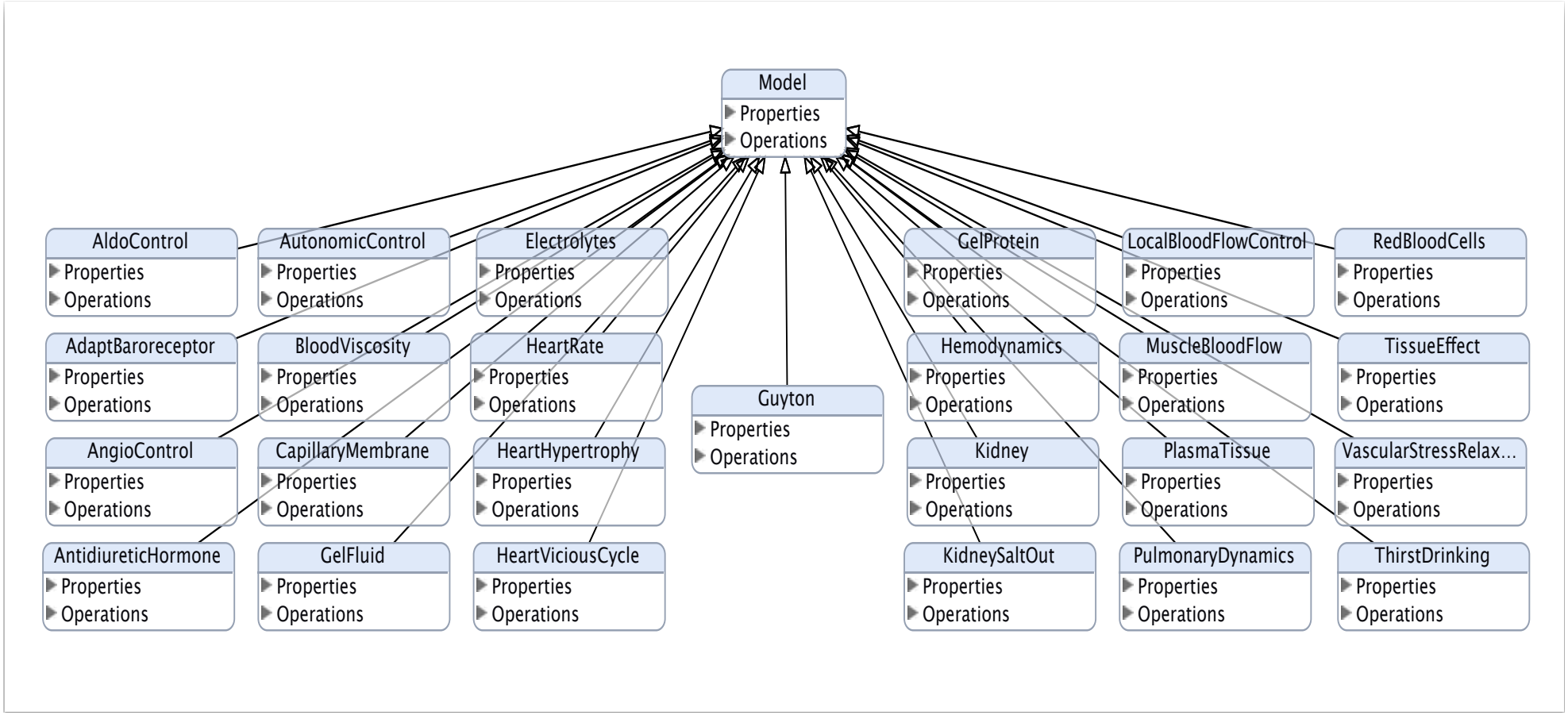
GUIs for DAEML & M2SL







Modular systems-model of blood pressure: breakdown for M2SL



plus detailed replacement models for individual modules:

- CVS, lung, kidney

Detailed multi-scale extensions and replacement modules

Modular systems-model of blood pressure:

Kidney module

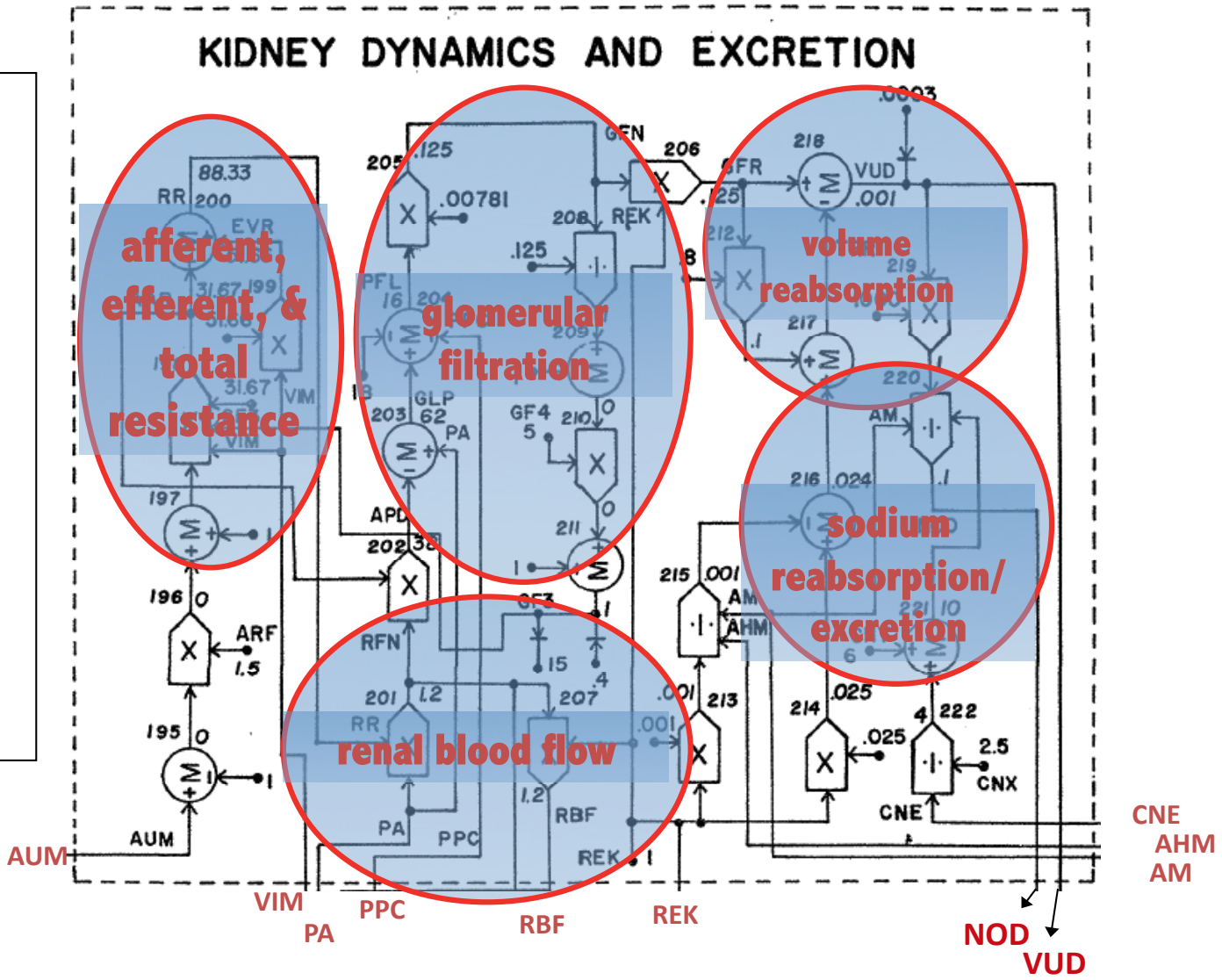
INPUTS

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

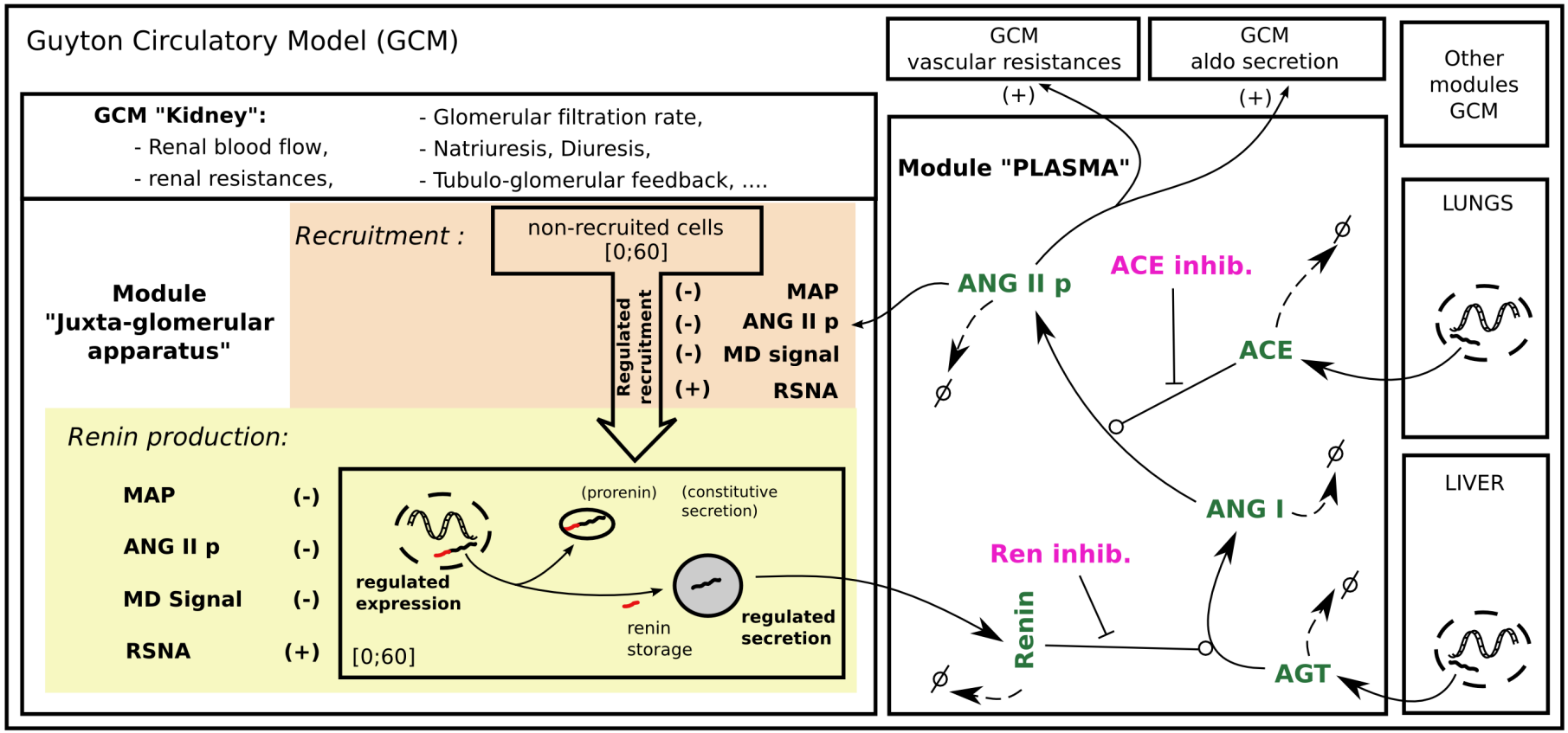


Guyton, A.C., T.G. Coleman, and H.J. Granger, "Circulation: Overall regulation." Annual Reviews of Physiology, 1972. 34:13-44.

Module RAAS

(Renin-Angiotensin-Aldosterone-System)

F. Guillaud & P. Hannaert (Poitiers)



Principal Sources: BRENDA ; Schweda *et al., 2007 ; Brown, 2007 ; Karaalsan et al., 2005 ; Geary et al., 1992 ; Yao et al., 2003 ; Leyssac et al., 2000 ; Kim et al., 2005 ; Corvol et al., 1995 ; Boddi et al., 1997 ; Wagner et al., 2007 ; Skøtt, 1986 ; DiBona, 1985 ; Holmer et al., 1997 ; Kopp et DiBona, 1993 ; Blumenfeld et al., 1999 ; Persson et al., 2004 ; Bader et Ganten, 2000 ; Grünberger et al., 2006 ; Ortiz-Capisano et al., 2006 ; Ortiz-Capisano et al., 2007 ; Peti-Peterdi et al., 2004 ; Taugner et al., 1981 ; Taugner et al., 1984 ; Sequeira López et al., 2004 ; Pentz et al., 2007...*

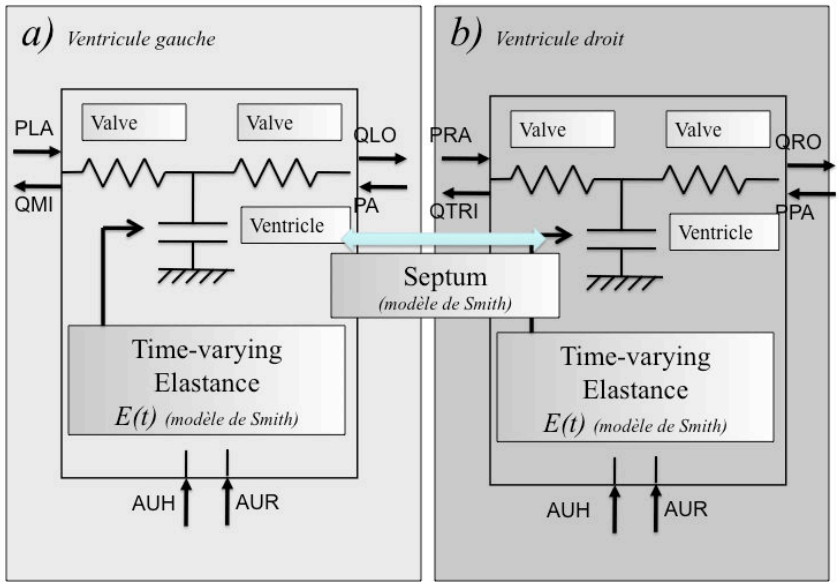
from **Guillaud, F. and P. Hannaert** (2010). "A computational model of the circulating renin-angiotensin system and blood pressure regulation." Acta Biotheor 58(2-3): 143-170.

G72 vs. G92 vs. RAAS model

			GUYTON 72	GUYTON 92	MODELE
Sécrétion/production de rénine	signaux régulateurs	signal MD	non	~oui – flux tubulaire	Oui – TGF
		signal RSNA	non	non	Oui – AUM
		signal ang II	non	non	oui
		signal PA	~oui – renal blood flow	non	oui
	expression génique		non	non	oui
	sécrétion dans le plasma		Non – calcul de facteur	Non – calcul de facteur	Oui + calcul de facteur
	recrutement cellulaire		non	Oui, non explicite – flux tubulaire	Oui – 2 pools, 4 signaux régulateurs
SRA endocrine	Bilans de matière		non	non	oui
	Équations enzymatiques		non	non	oui
	Concentrations explicites		non	non	oui
	Compartiment plasmatique		non	non	oui

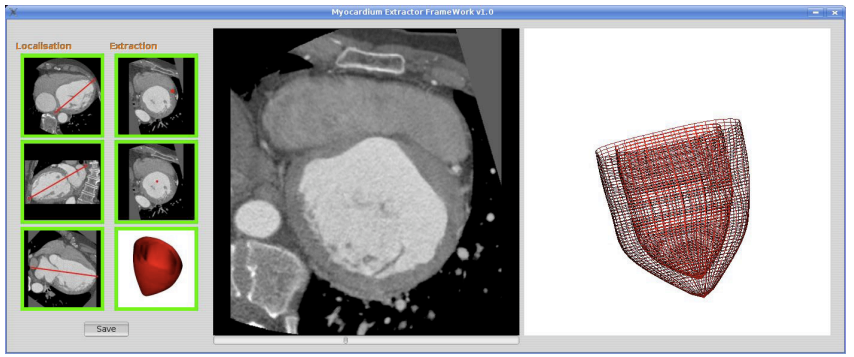
Higher-Resolution models: Pulsatile models of the heart (LTSI)

- Each ventricle is represented as a single contractile element, by means of a variable elastance model
  - Using moving average interface components for input-output coupling with the G72 model
  - Direct coupling for a full-pulsatile version (requiring re-identification of the G72 parameters)



A higher-resolution FEM model of the LV integrating:

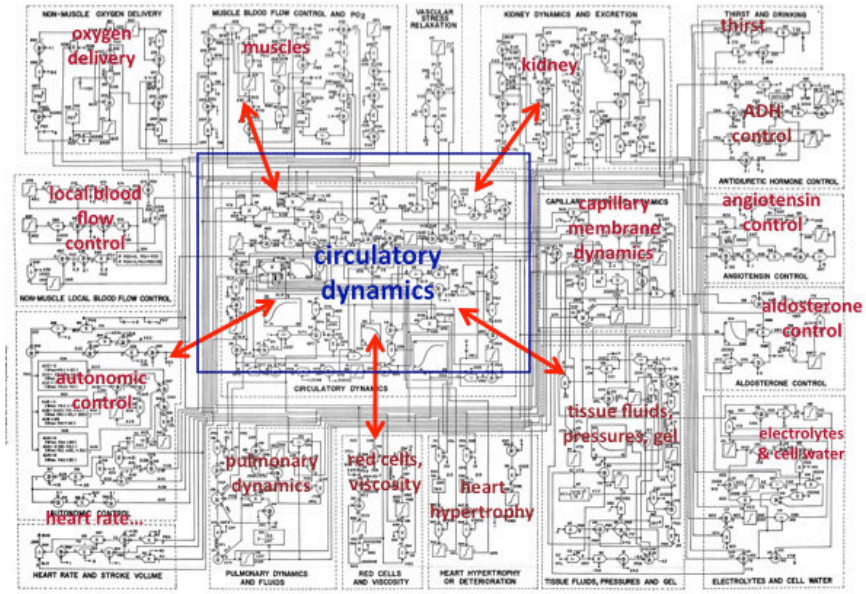
A patient-specific geometry obtained from CT images
A more detailed electro-mécano-hydraulic model
Moving average interface with the G72 model
New finite element method simulator for M2SL



(Hernandez et al. (2011). "Integration of detailed modules in a core model of body fluid homeostasis and blood pressure regulation." Prog Biophys Mol Biol 107(1): 169-182.)

G92 Sensitivity analysis and generation of a Virtual Population

- To enable comparison of alternative or more detailed modules
- As a guide for *in silico* exploration of drug effects, genetic polymorphisms, etc.



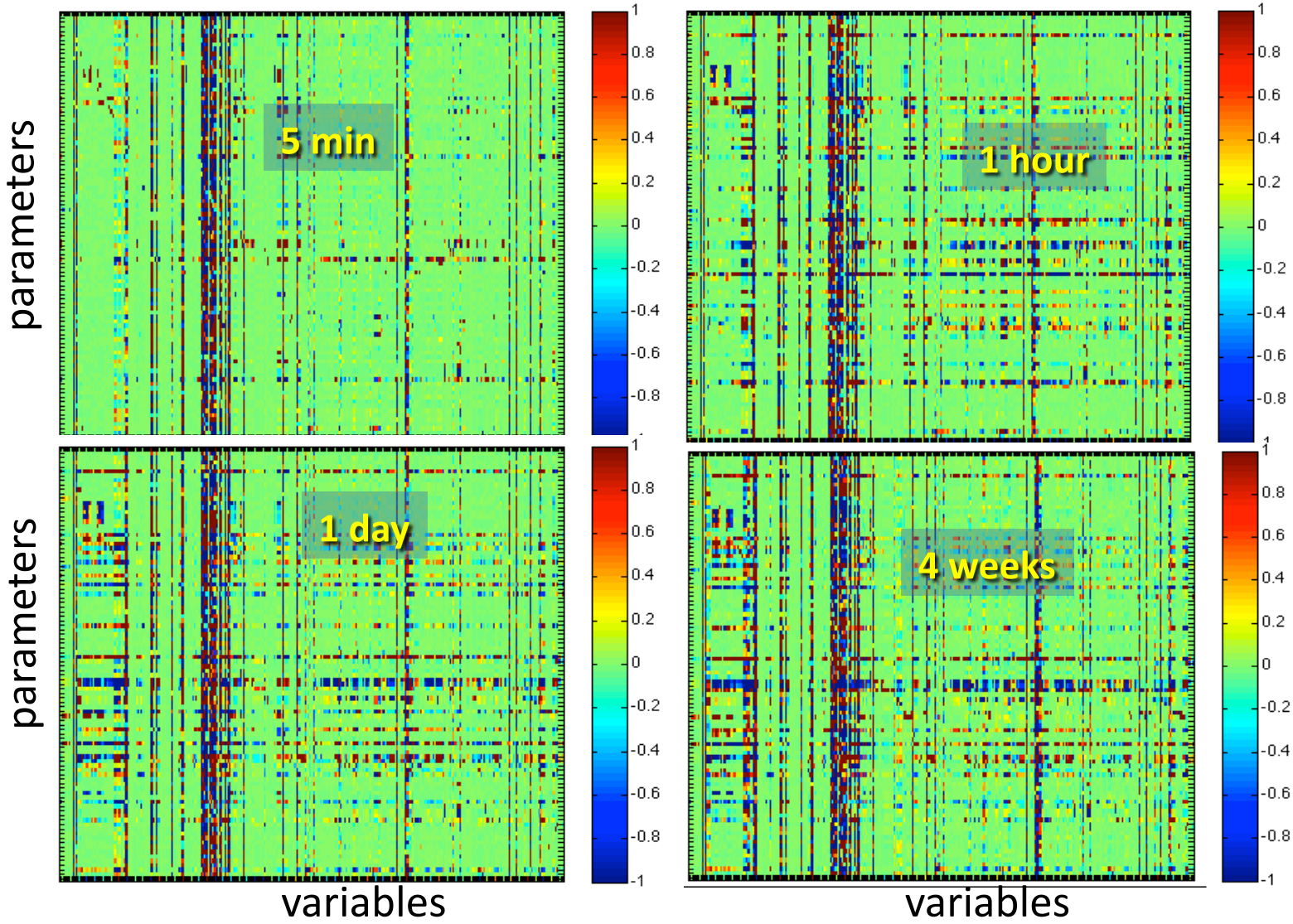
Guyton (G92): Comprehensive Sensitivity analysis...

- **I/O maps of the 25 modules** (all SAPHIR teams)
  - For each module: plots of all output variables as function of each input, over a relevant physiological range of values

- **Comprehensive sensitivity analysis** (IBISC team)
  - Sensitivity of 297 system variables to each of 96 selected parameters at 5 min., 1h, 1day, and 4 weeks (steady-state) are calculated
  - This is done for *normal* steady state and also (twice) for >1000 x 96 randomized "individuals" (Morris. 1991. "Factorial Sampling Plans for Preliminary Computational Experiments." *Technometrics*, 33(2): 161-174)
  - We have thus:
    - virtual population of env. 500 000 randomized individuals, and
    - mean ± SD of the effect of each parameter on each variable, and also estimates interactions among the parameter effects (covariance analysis provides details)

G92 global sensitivity analysis

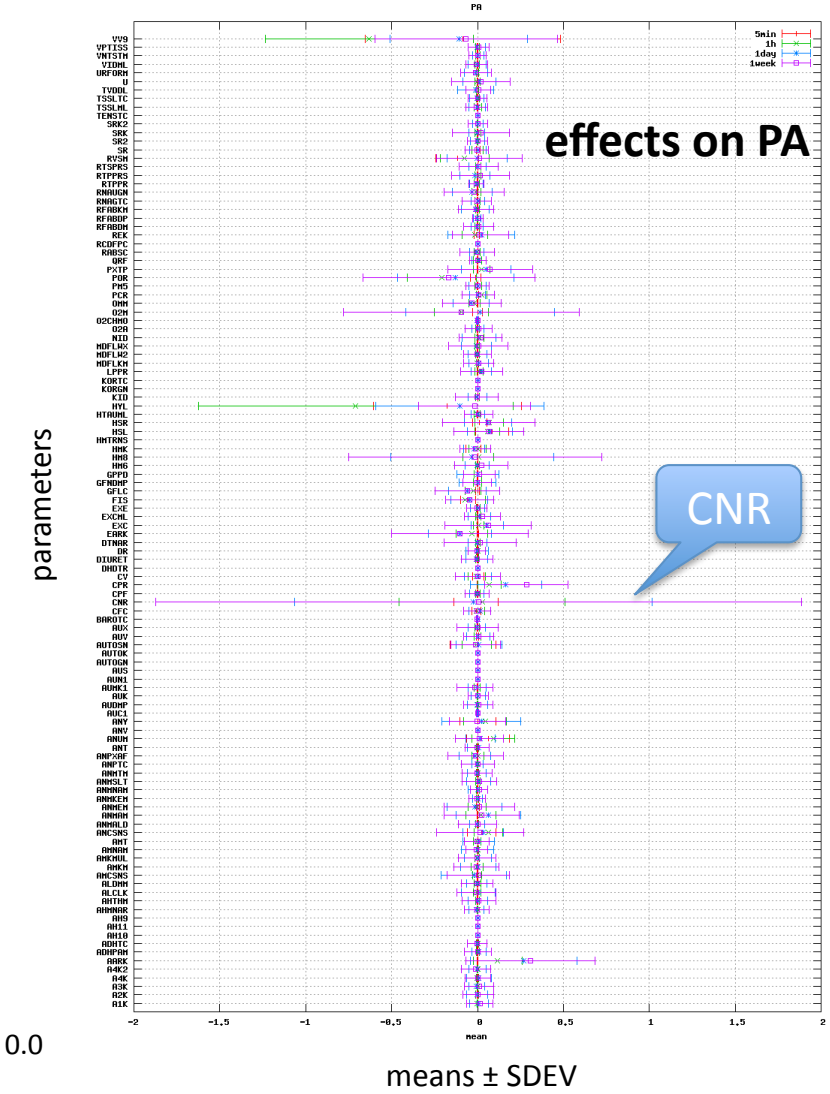
"heatplots" of means of elementary effects



Mean values of the normalized effect, (% change of v_j wrt its steady state value), of a small change of each parameter (one-at-a-time, 10% of allowed range) on all variables. Effects are shown at four times after the parameter change, as marked. The graph is truncated at ± 1%.

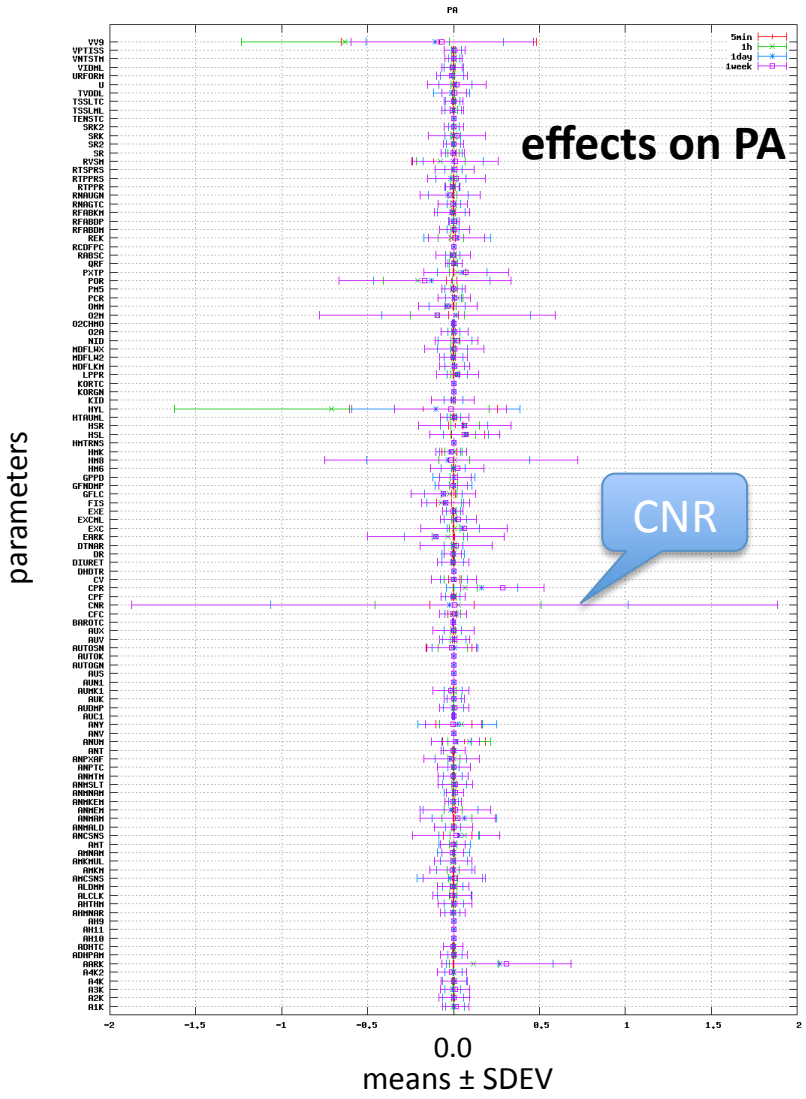
Clearly, the patterns change with time after the parameter perturbations.

Example of sensitivity results for the variable "PA" (arterial blood pressure) as a function of all 96 model parameters



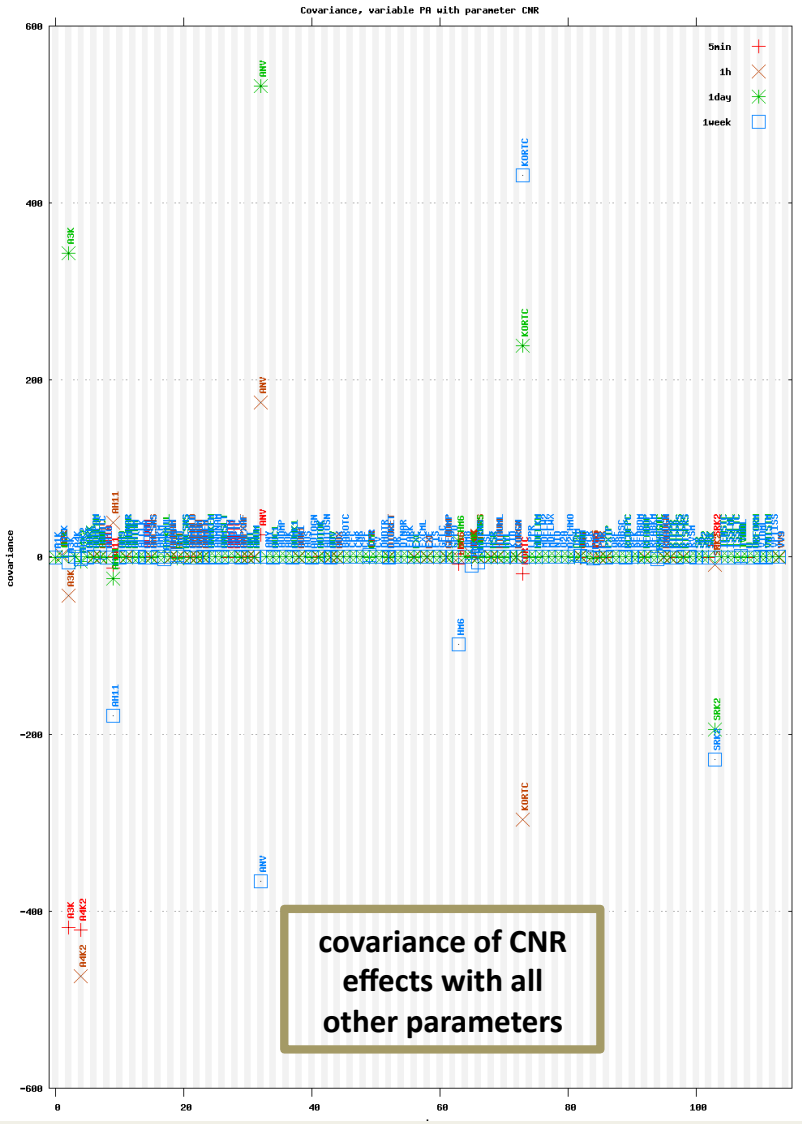
"Morris plots" of means and standard deviations (SDEV) of normalized effects of all parameters on the variable "PA" **at four times after perturbation**

Example of sensitivity results for the variable "PA" (arterial blood pressure) as a function of all 96 model parameters



"Morris plots" of means and standard deviations (SDEV) of normalized effects of all parameters on the variable "PA" **at four times after perturbation**

(CNR: reference sodium concentration to determine ADH secretion rate)



Effect of CNR on PA

Covariance analysis reveals interactions with other parameters

In addition to the sensitivity analysis: Large Population of "Virtual (Guyton) Individuals"

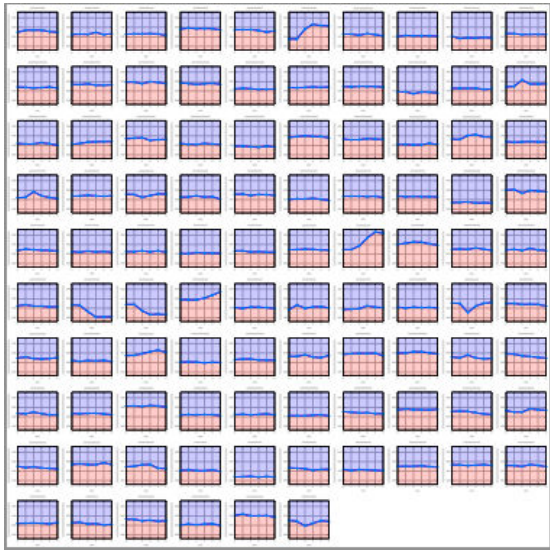
Randomized parameters → analogous to "*genotype*"

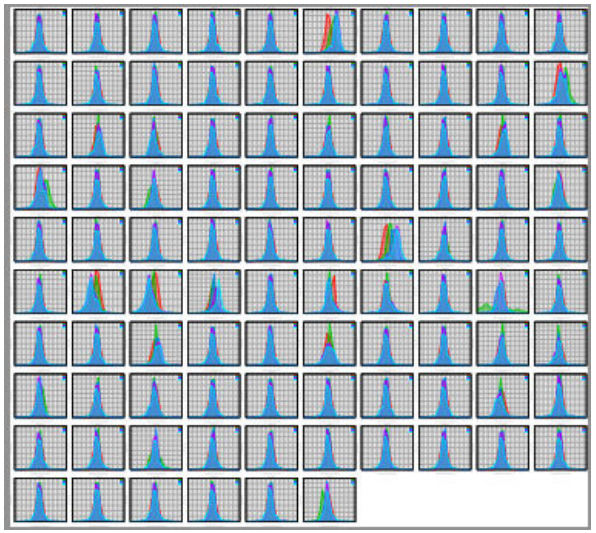
This results in a variety of virtual "*phenotypes"*

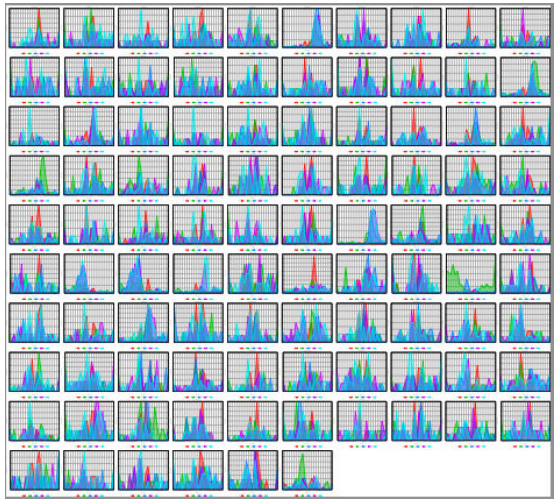
Not surprisingly, a large proportion of the virtual population is "*hypertensive*"

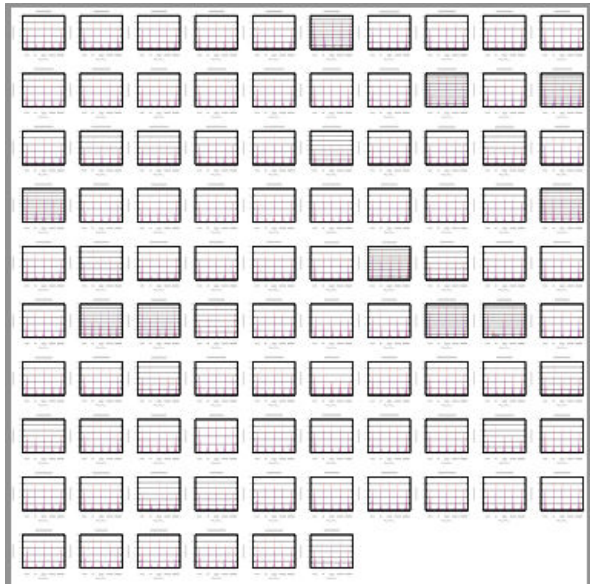
The differences between parameter values of the normotensive vs. hypertensive subpopulations may be interesting…

Multiplots to visualize sensitivity results







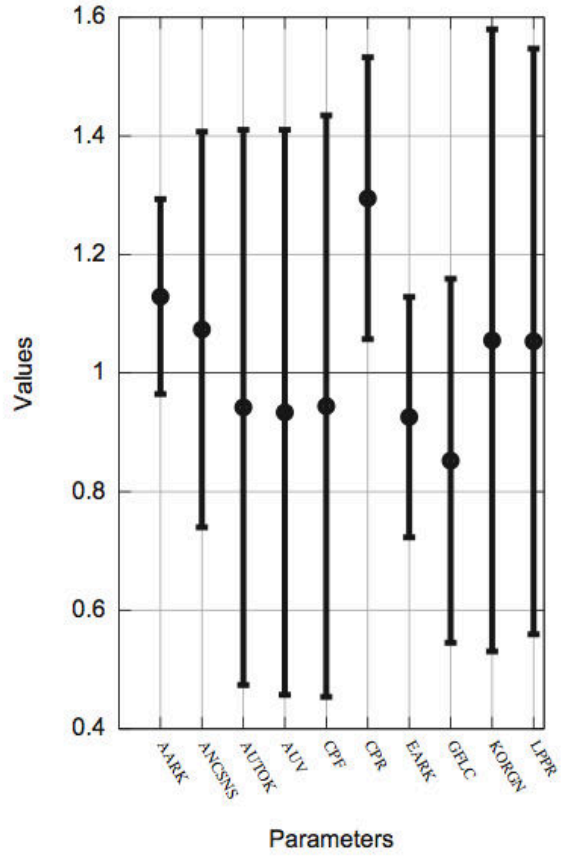


Virtual "Guyton-population":

Parameters most implicated in high BP in the virtual population

192 000 "virtual individuals" with randomized parameter values:
• 109,266 were Hypertensive (MAP above 106 mmHg)

Parameters whose means increased or decreased by at least 5% in pre-hypertensive or hypertensive subpopulations compared to normotensive subpopulation



Increased by >5% in hypertensives:

AARK basic afferent arteriolar resistance
ANCSN sensitivity controller of AngII effect
CPR critical plasma protein concentration for protein destruction
KORGN gain of positive feedback Korner concept
LPPR rate of liver protein production).

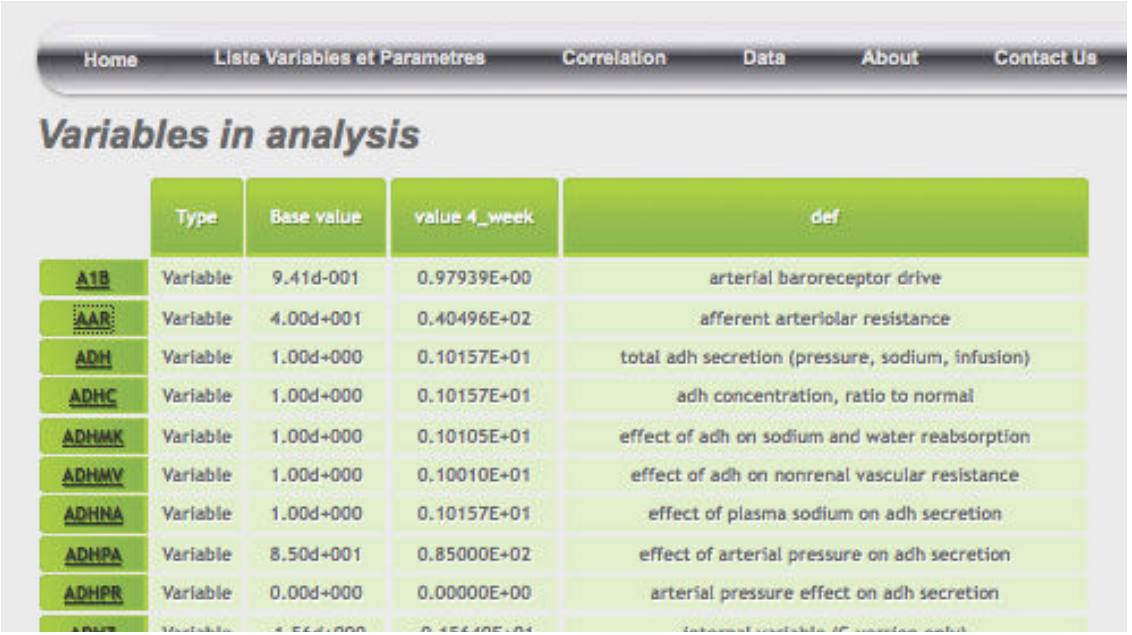
Decreased by >5% in hypertensives:

AUTOK rate of development of very rapid autoregulation
AUV blood volume shifted from unstressed to stressed
CPF pulmonary capillary filtration coefficient
EARK basic efferent arteriolar resistance
GFLC glomerular filtration coefficient)

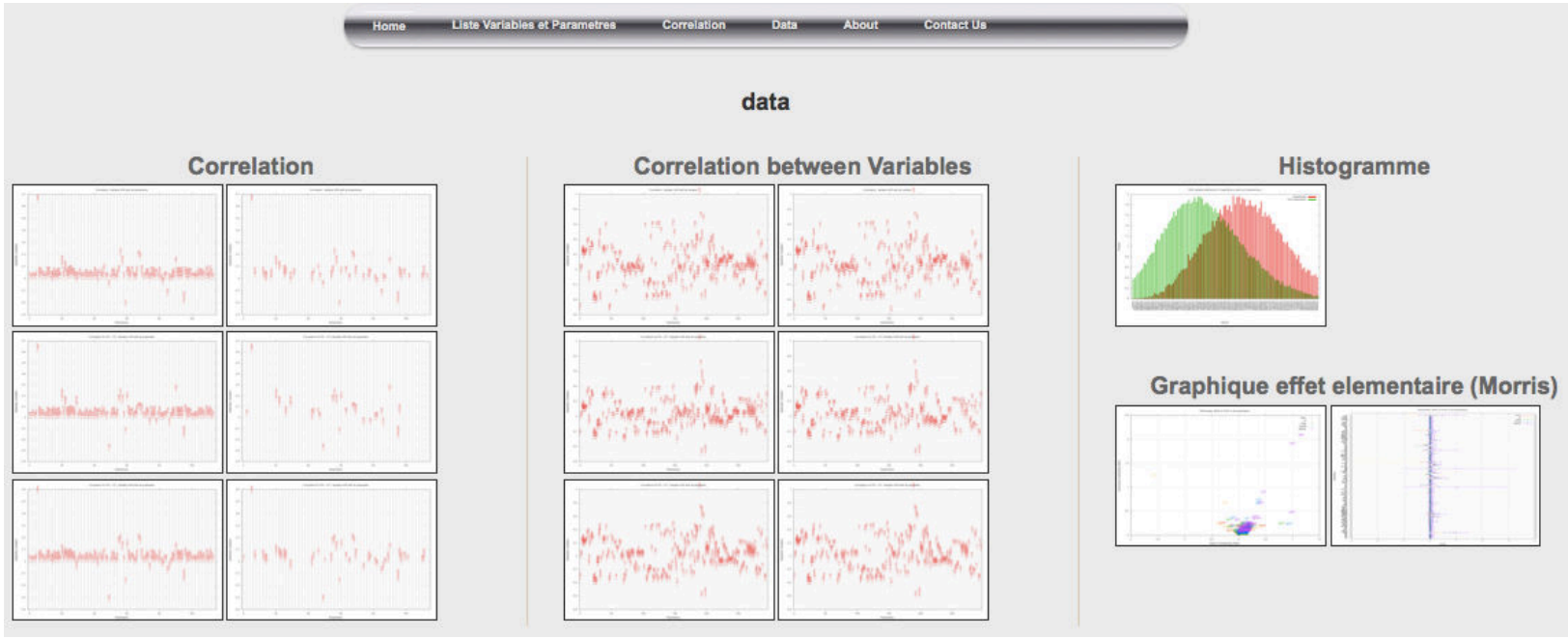
from: Hernandez, A. I., V. Le Rolle, D. Ojeda, P. Baconnier, J. Fontecave-Jallon, F. Guillaud, T. Grosse, R. G. Moss, P. Hannaert and S. R. Thomas (2011). "Integration of detailed modules in a core model of body fluid homeostasis and blood pressure regulation." Prog Biophys Mol Biol 107(1): 169-182

Web interface for database of sensitivity results

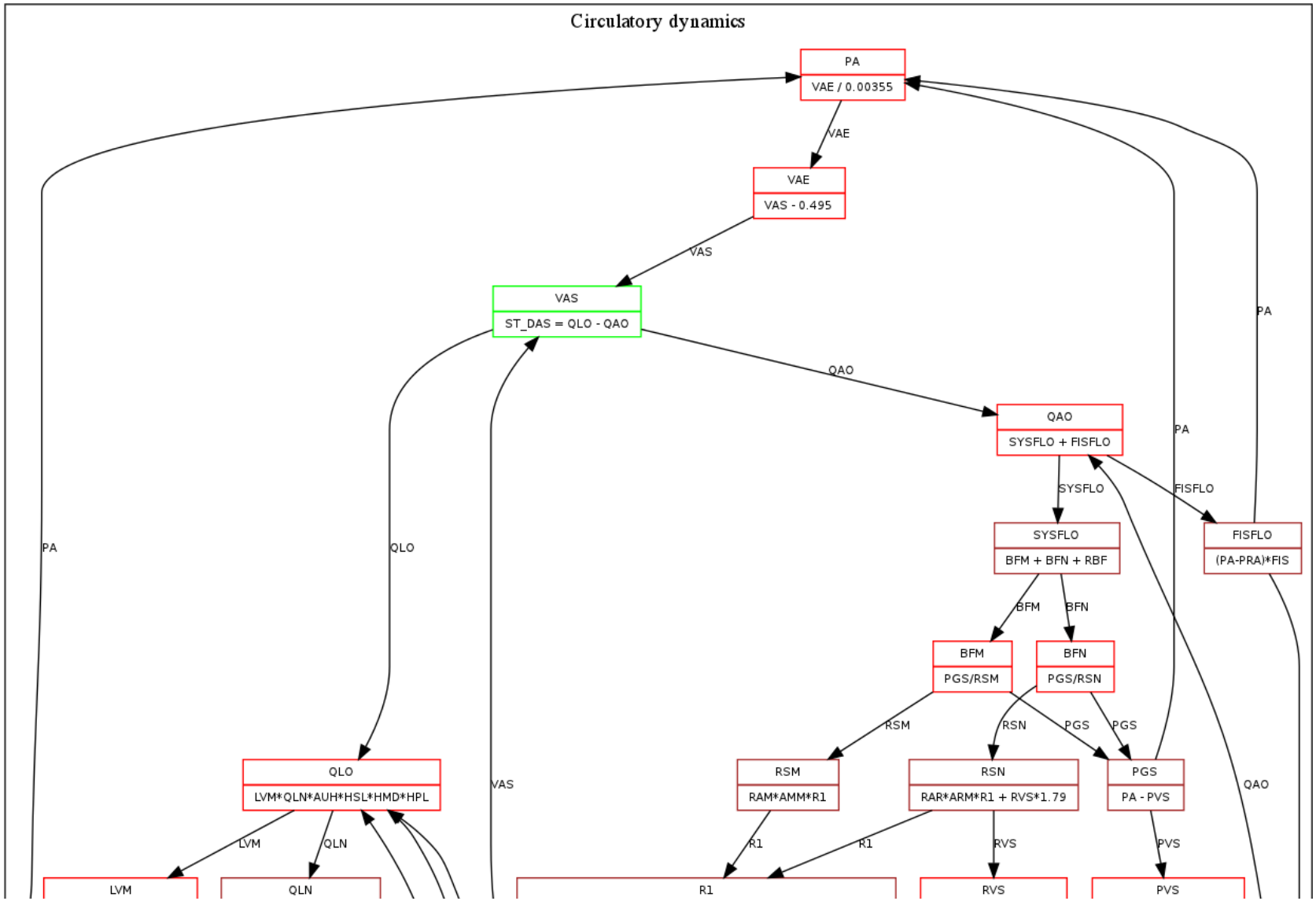
- virtual population of >200 000 virtual individuals → exploration of novel relationships among the plethora of parameters & variables



	Type	Base value	value 4_week	def
A1B	Variable	9.41d-001	0.97939E+00	arterial baroreceptor drive
AAR	Variable	4.00d+001	0.40496E+02	afferent arteriolar resistance
ADH	Variable	1.00d+000	0.10157E+01	total adh secretion (pressure, sodium, infusion)
ADHC	Variable	1.00d+000	0.10157E+01	adh concentration, ratio to normal
ADHMK	Variable	1.00d+000	0.10105E+01	effect of adh on sodium and water reabsorption
ADHMV	Variable	1.00d+000	0.10010E+01	effect of adh on nonrenal vascular resistance
ADHNA	Variable	1.00d+000	0.10157E+01	effect of plasma sodium on adh secretion
ADHPA	Variable	8.50d+001	0.85000E+02	effect of arterial pressure on adh secretion
ADHPR	Variable	0.00d+000	0.00000E+00	arterial pressure effect on adh secretion

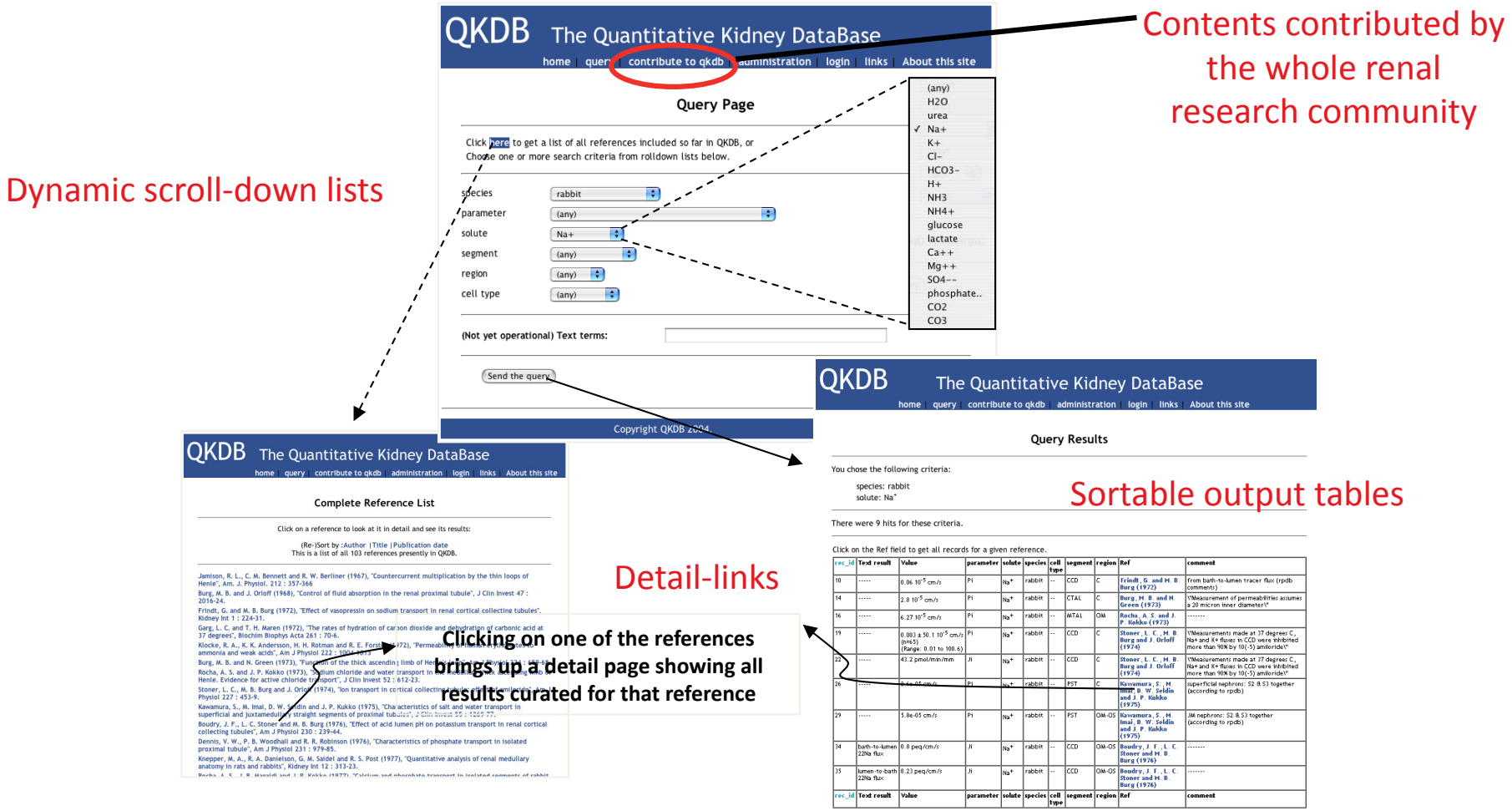


Automated construction of a graph of model-structure



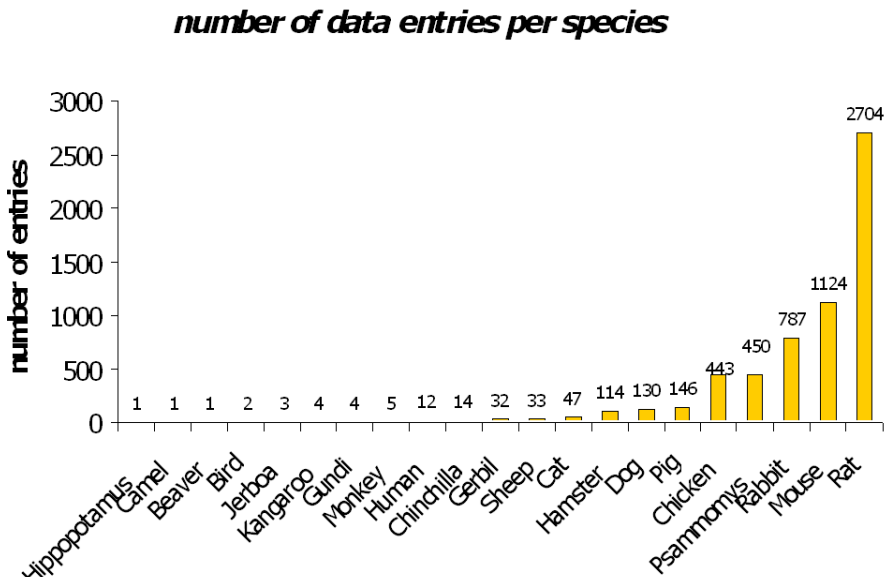
with live links to sensitivity results

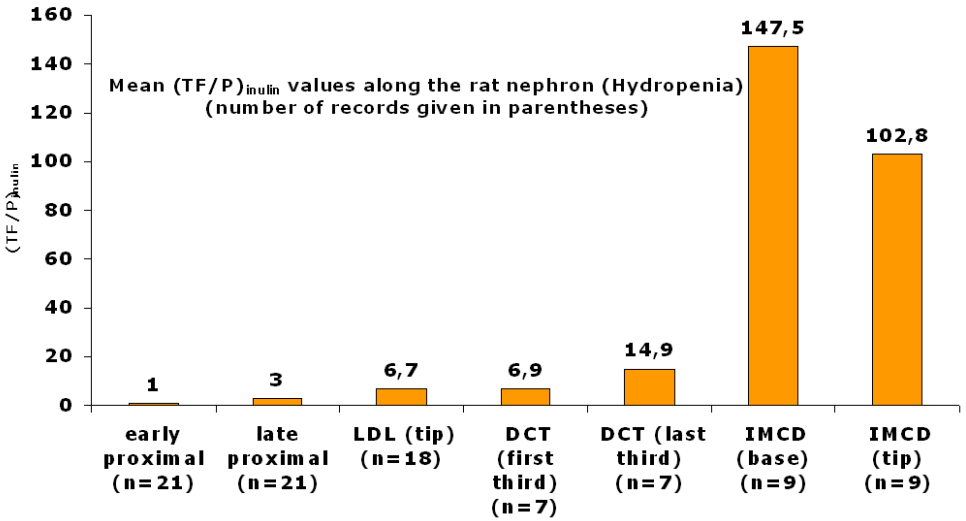
QKDB (Quantitative Kidney DataBase)
<http://physiome.ibisc.fr/qkdb>

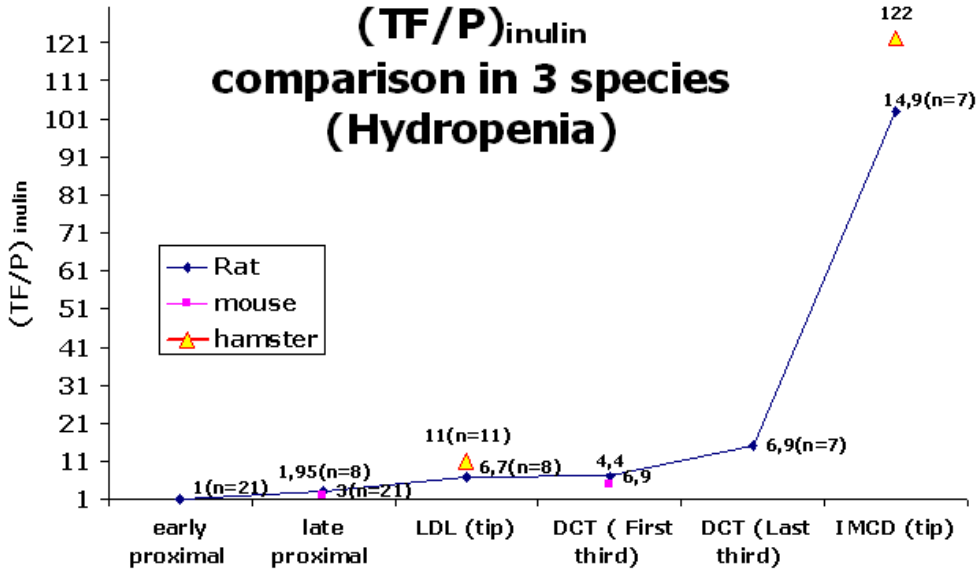


One-stop shopping for all quantitative measurements relative to kidney physiology, including anatomical features, transport parameters, flows and concentrations, transporter kinetics, etc.

QKDB : what's there?







QKDB (Quantitative Kidney DataBase)
<http://physiome.ibisc.fr/qkdb

- New version soon to be released:
  - Drupal CMS interface
    - better user management
    - easier updating and editing of the interface
    - better integration into other resources
    - new features:
      - download search results as csv files
      - automatically generate graphs of search results
  - Incorporation of new knowledge-management tool for semi-automatic data entry from original articles

Automatic information extraction based on QKDB descriptors

Anne-Lise Minard, Rémi Delorme, Brigitte Grau, Anne-Laure Ligozat (ENSIIE)

PMID	Fichier
Insertion d'un PDF	
	Parcourir...
Valider le nouveau PDF :	Envoyer
Effacer le PDF actuel	
10589704	Cervenka1999JASN10_2631
9457649	deJesusFerreira1997jphysio505_749
13679473	Hartner2003Nephro_dial_transp18_1999
14679186	Hoenderop2003jci112_1906
15339977	Loffing2004JASN15_2276
12122007	Lorenz2002jbc277_37871
9468475	Ma1998jbc273_4296
12963802	Marks2003j_physiol553_137
11832428	Nagami2002ajp282_F472
15902302	Nijenhuis2005jci115_1651
9507206	Okubo1998kid_int53_617
9530261	Rivers1998ajp274_F453
9689137	Schnermann1998PNAS95_9660
9786924	Schultheis1998JBC273_29150
11352847	Weinstein2001ajp280_F1072
15855658	Weinstein2005ajp289_F6

	Reconstitution
Mode d'Affichage	Visionnage du découpage

o	SPECIES
o	ORGAN, TISSUES, CELL LINE
o	STRUCTURE TYPE
o	TUBE SEGMENT
o	EPITHELIAL COMPARTMENT OR MEMBR
o	CELL TYPE
o	REGION
o	MEMBRANE PROTEIN
o	PARAMETER
o	SOLUTE
o	Others

Impaired Renal NaCl Absorption in Mice Lacking the ROMK Potassium Channel, a Model for Type II Bartterâ€™s Syndrome*

John N. Lorenzâ€¡, Nancy R. BairdÂ§, Louise M. Judd Â¶, William T. Noonanâ€¡, Anastasia Andringa * , Thomas Doetschman Â¶ , Patrice A. Manning Â¶ , Lynne H. Liu Â¶ , Marian L. Miller * , and Gary E. Shull Â¶ **

ROMK is an apical K * channel expressed in the thick ascending limb of Henle (TALH) and throughout the distal nephron of the kidney . Null mutations in the ROMK gene cause type II Bartterâ€™s syndrome , in which abnormalities of electrolyte , acid-base , and fluid-volume homeostasis occur because of defective NaCl reabsorption in the TALH . To understand better the pathogenesis of type II Bartterâ€™s syndrome , we developed a mouse lacking ROMK and examined its phenotype . Young null mutants had hydronephrosis , were severely dehydrated , and *95 % died before 3 weeks of age . ROMKdeficient mice that survived beyond weaning grew to adulthood ; however , they had metabolic acidosis , elevated blood concentrations of Na * and Cl * , reduced blood pressure , polydipsia , polyuria , and poor urinary concentrating ability . Whole kidney glomerular filtration rate was sharply reduced , apparently as a result of hydronephrosis , and fractional excretion of electrolytes was elevated . Micropuncture analysis revealed that the single nephron glomerular filtration rate was relatively normal , absorption of NaCl in the TALH was reduced but not eliminated , and tubuloglomerular feedback was severely impaired . These data show that the loss of ROMK in the mouse causes perturbations of electrolyte , acid-base , and fluid-volume homeostasis , reduced absorption of NaCl in the TALH , and impaired tubuloglomerular feedback .

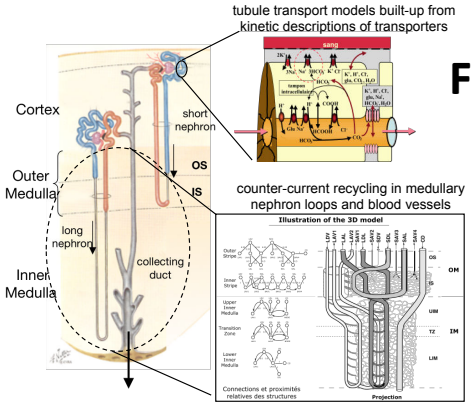
Bartterâ€™s syndrome , a hypokalemic alkalosis with dehydration , hypotension , and severe polyuria which develops before birth or during infancy (1) , is caused by null mutations in any of four genes encoding proteins involved in NaCl absorption in the renal thick ascending limb of Henle (TALH) . 1 These are the NKCC2 Na * -K * -2Cl * cotransporter (2) , the ROMK potassium channel (3) , the CLC-KB chloride channel (4) , and barttin (5) , a *-subunit of the chloride channel (6) . Na * and Cl * , in a 1:2 ratio , are absorbed across the apical membrane of TALH cells by the coupled activities of NKCC2 and ROMK and extruded via the basolateral Na * , K * -ATPase and chloride channel (6 , 7) ; additional Na * is absorbed via the paracellular pathway . Although NKCC2 directly mediates uptake of Na * , K * , and Cl * , the activity of ROMK is critical because the K * concentration in the luminal fluid is much lower than that of Na * and Cl * . Thus , the continuous electroneutral uptake of Na * , K * , and Cl * requires that K * be recycled to the lumen of the tubule . Apical K * secretion via ROMK replenishes luminal K * and also contributes , in concert with basolateral Cl * efflux via CLC-KB/ barttin (5 , 6) , to the transcellular electrical potential that is the driving force for Na * absorption via the paracellular pathway (8) .

The different types of Bartterâ€™s syndrome , caused by null mutations in NKCC2 , ROMK , CLC-KB , and barttin , are referred to as types Iâ€“IV , respectively . The syndrome is thus heterogeneous , consistent with the variety in genetic mechanisms , and the physiological phenotypes overlap to some degree with those of Gitelmanâ€™s syndrome , a milder hypokalemic alkalosis caused by null mutations in the thiazide-sensitive NaCl cotransporter of the distal convoluted tubule (9 , 10) . Detailed analysis of the physiological functions and relative importance of the transporters involved in each type of Bartterâ€™s syndrome would be facilitated by the development of knockout mouse models . A mouse model for Bartterâ€™s syndrome type I , involving NKCC2 , has already been developed (11) ; null mutants exhibit severe hydronephrosis , dehydration , polydipsia , polyuria , and an inability to concentrate the urine , and they usually die before weaning .

There are multiple N-terminal variants of ROMK (gene locus Kcnj1) (12â€“14) . One or more of these variants is expressed in the TALH , distal convoluted tubule , connecting tubule , collecting duct , and macula densa (15 , 16) , consistent with functions in K * recycling to facilitate Na * reabsorption in the TALH , K * secretion in the distal nephron , and tubuloglomerular feedback (17 , 18) . The broad distribution of ROMK in the renal nephron , in contrast to the restricted distribution of NKCC2 , and the possibility that other apical K * channels (17) or K * -independent modes of NaCl transport for NKCC2 (19) might provide some compensation for its absence , suggested that the loss of ROMK might lead to a different phenotype than that of the Nkcc2 knockout

o	SPECIES	o	REGION
o	ORGAN, TISSUES, CELL LINE	o	MEMBRANE PROTEIN
o	STRUCTURE TYPE	o	PARAMETER
o	TUBE SEGMENT	o	SOLUTE
o	EPITHELIAL COMPARTMENT OR MEMBRANE	o	Autres (identifiés mais non associables)
o	CELL TYPE	o	Autres (non identifiés comme pertinent)

Towards a whole-kidney model, integrated into a global Cardiovascular system (à la Guyton)



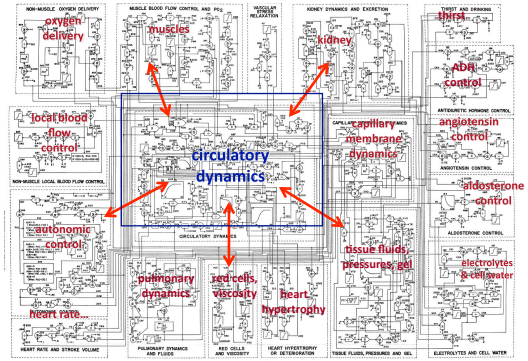
kidney models at many scales

Objectives:

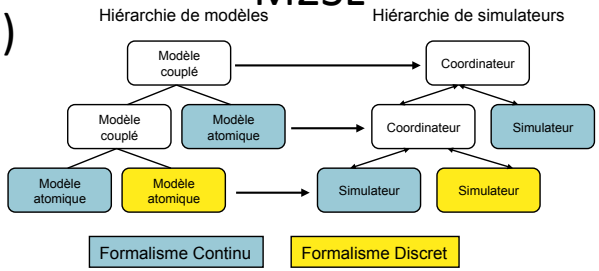
From many good components:

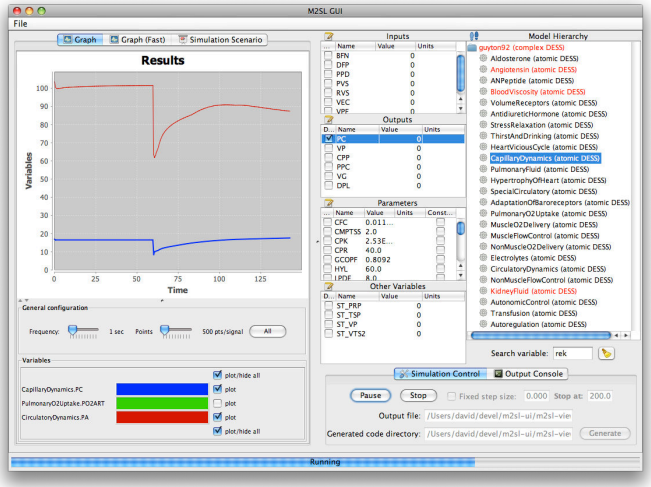
- "local" models of kidney function
- Guyton models of BP regulation
- Ikeda model of acid-base regulation
- data from clinical trials and population studies
- functional data from experimental models
- powerful numerical tools (… M2SL…)
- talented collaborators
- …

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



M2SL





Interactive GUI for M2SL models

Build an integrated, interactive tool

- pharmacological and, eventually, clinical relevance
- scalable for specific patients (or different species of experimental models)
- "re-useable", well-documented, standards-based, etc., for the Physiome/VPH

SAPHIR & BIMBO collaborators

IBISC (FRE 3190) & IR4M UMR8081

- **SR Thomas**
  - Thibault Grosse (CDD VPH)
  - Rob Moss (postdoc BIMBO)
  - Stana Agnes (Ing IGR)
  - Pierre Mazière (postdoc SAPHIR)
  - Jérôme Bazin (CDD VPH NoE)

MC ENSIIE : Brigitte Grau, **Anne-Laure Ligozat**, Amel Bouzeghoub, Anne-Lise Minard

MC IBISC : Fariza Tahi, Farida Zehraoui, Nadia Abchiche, Tarek Melliti

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U. Paris VI
Jean-Pierre Françoise

NASA
Ron White

BIMBO team (Lyon)
François Gueyffier
Ivanny Marchand, Alexandra Laugerotte, Thierry Dumont

Virtual Physiological Human
network of excellence

http://saphir.ibisc.fr/

ANR AGENCE NATIONALE DE LA RECHERCHE