

A Multi-formalism solver (M2SL) and XML model markup (DAEML): Application to the Guyton models

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OpenModelica Workshop

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Linköping

Overview

- The Guyton CVS (CardioVascular System) model: foundation for a collaborative “core model” for the VPH (Virtual Physiological Human)
 - Quick description of its underpinnings
 - Our modularization, extensions, and
 - Global sensitivity analysis and Virtual Population
- A brief introduction to M2SL: Multiformalism Multilevels Simulation Library
 - Objectives
 - Structure
 - User interface

SAPHIR & BIMBO collaborators

IR4M UMR8081 (CNRS Orsay & Villejuif)

Randy Thomas

Rob Moss
Thibault Grosse
Stana Agnes
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Pierre Baconnier

Julie Fontecave-Jallon
Pascale Calabrese
Enas Abdulhay

NASA

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Collaborators from BIMBO project (Lyon)

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Alexandra Laugerotte
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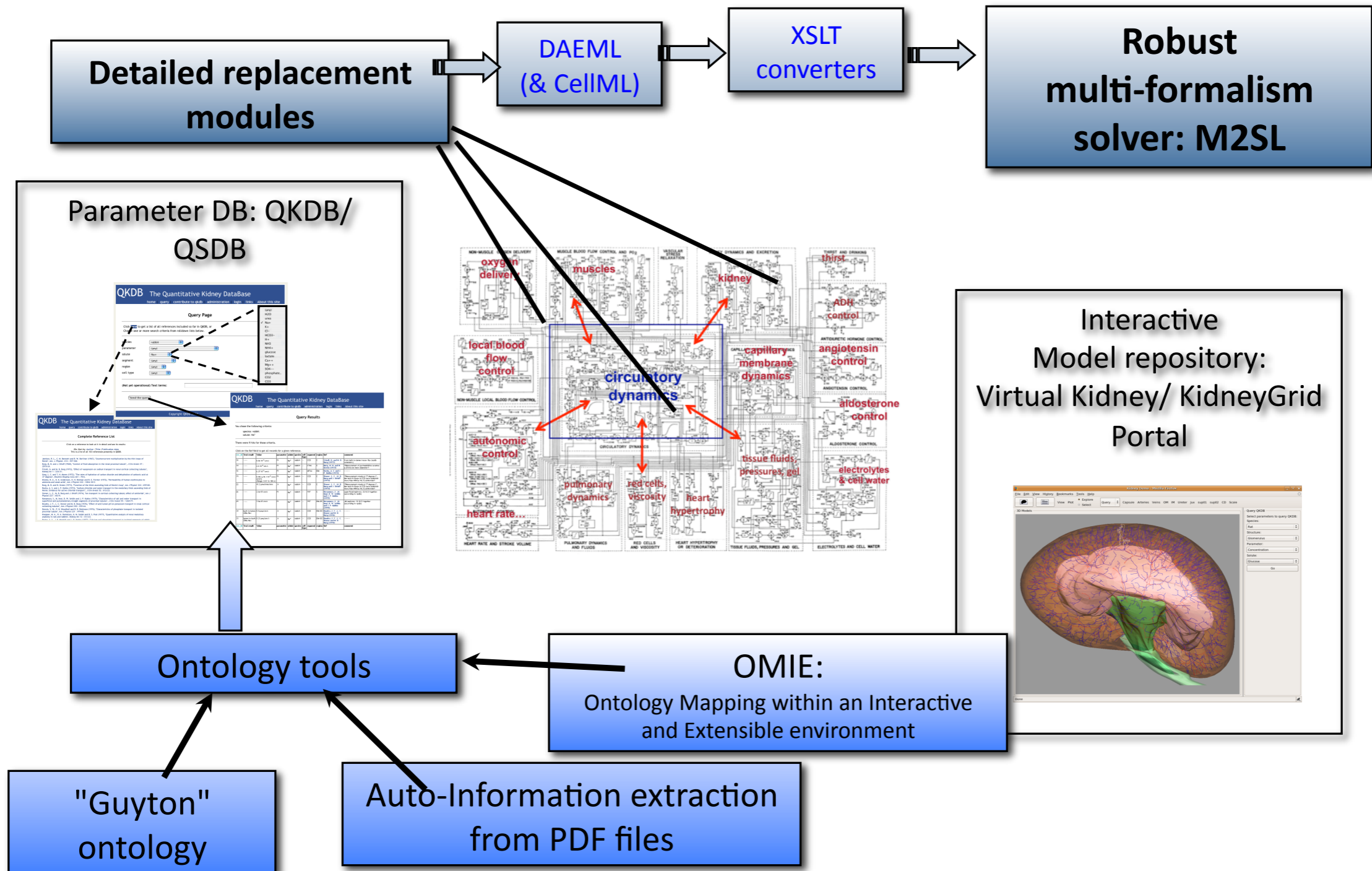
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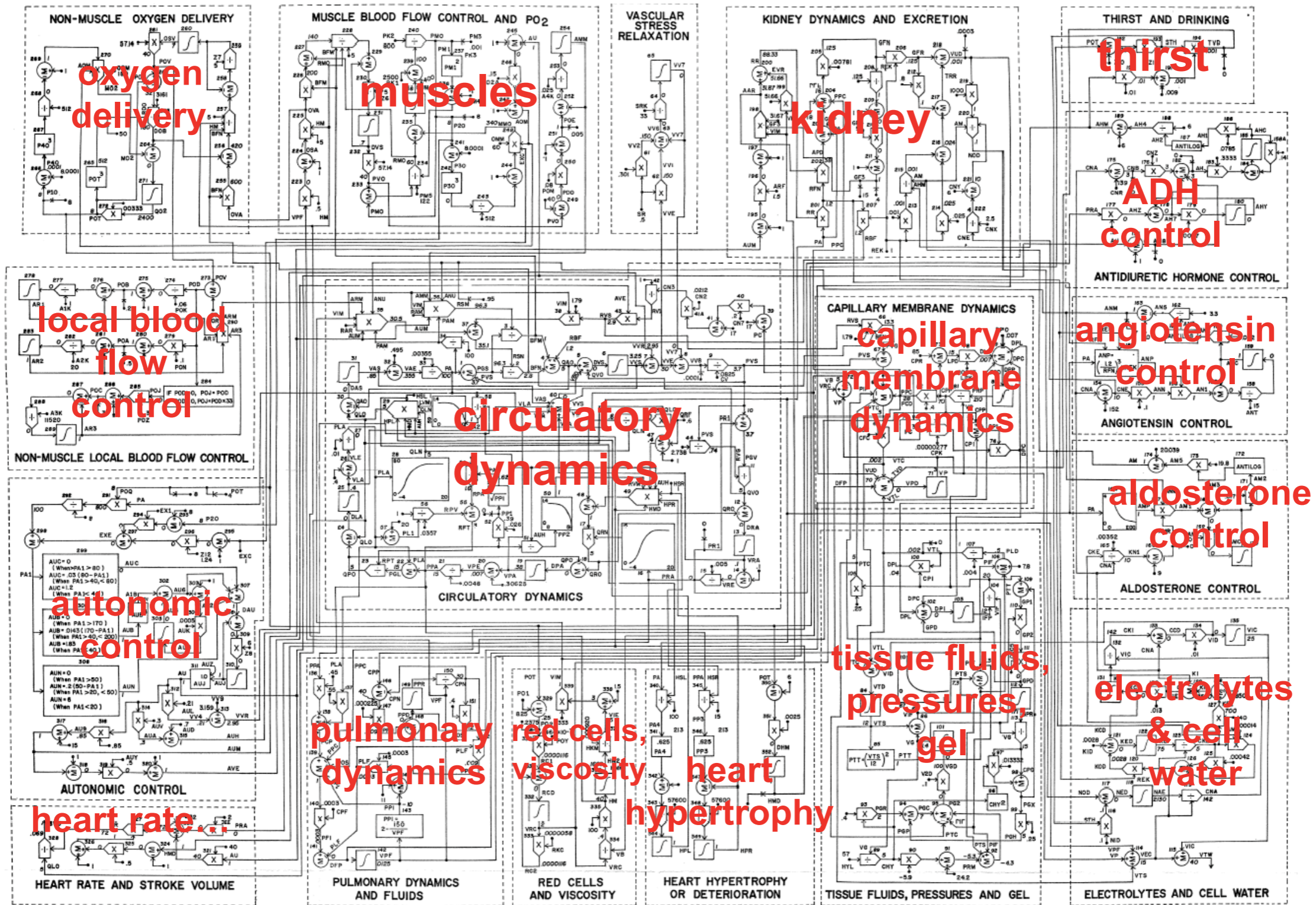
Collaborations
(HumMod, G92) with
the group of
Jiri Kofranek,
Charles University,
Prague

SAPHIR: Towards a modular “core model” environment

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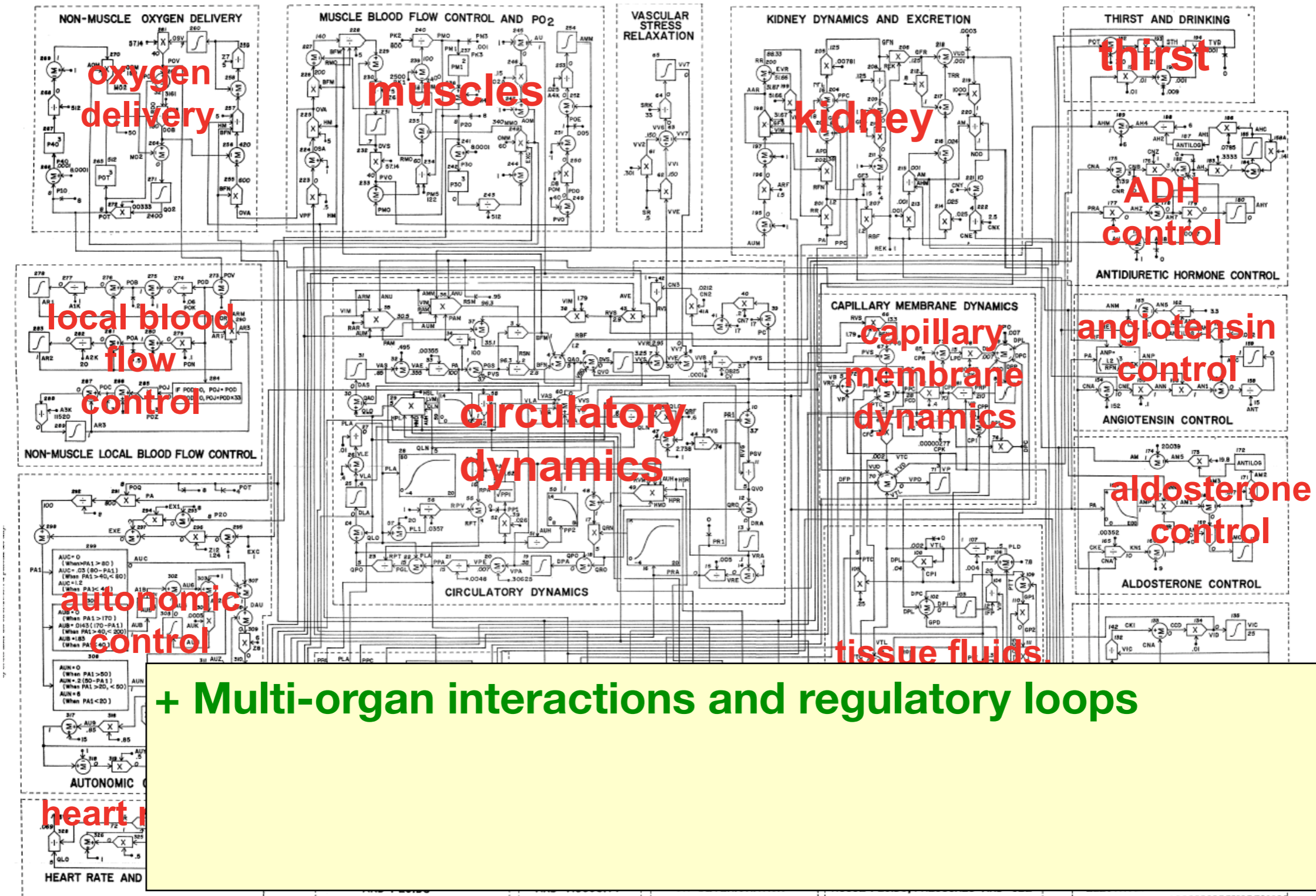


Core-model environment: Guyton CVS models



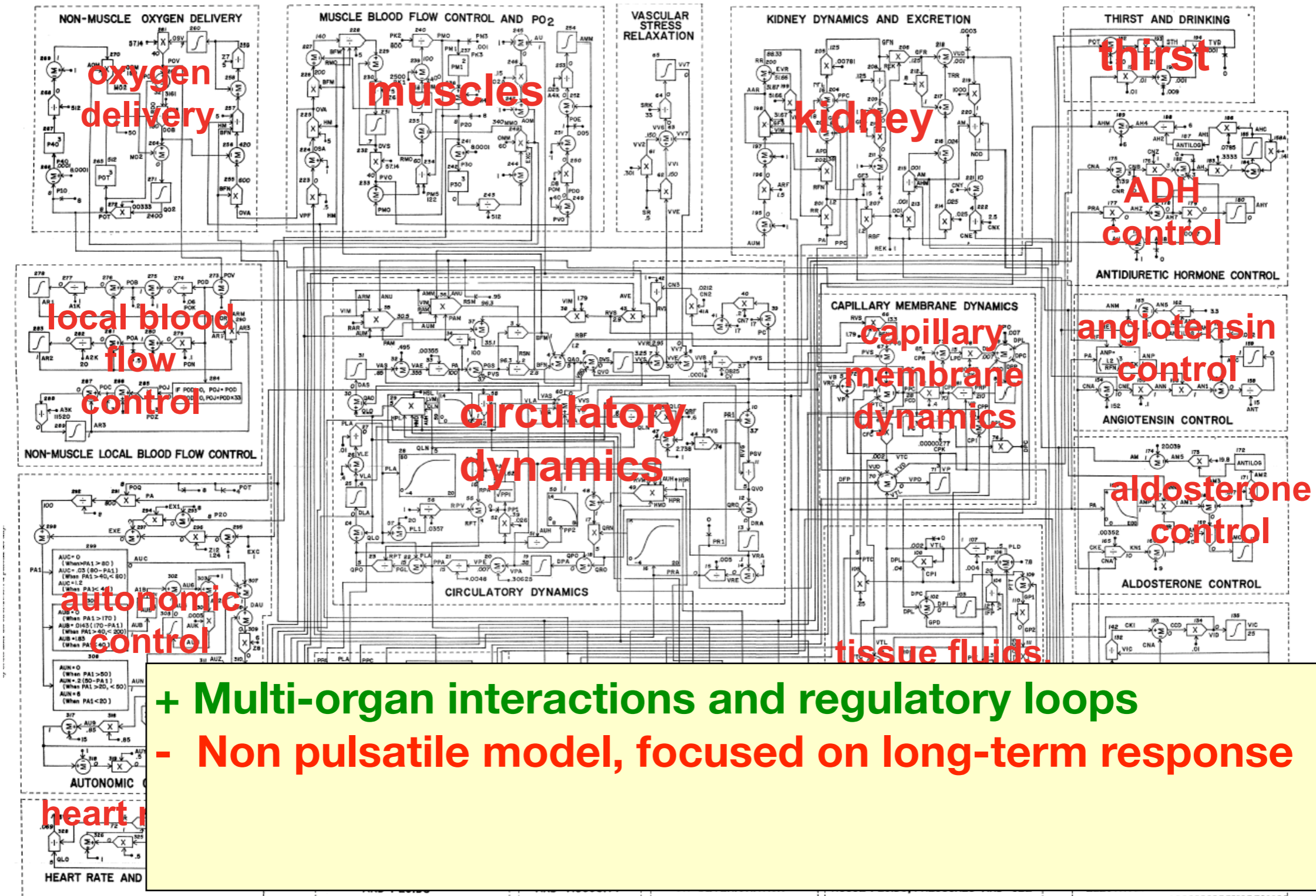
Guyton, Coleman, Granger (1972) *Ann. Rev. Physiol.*

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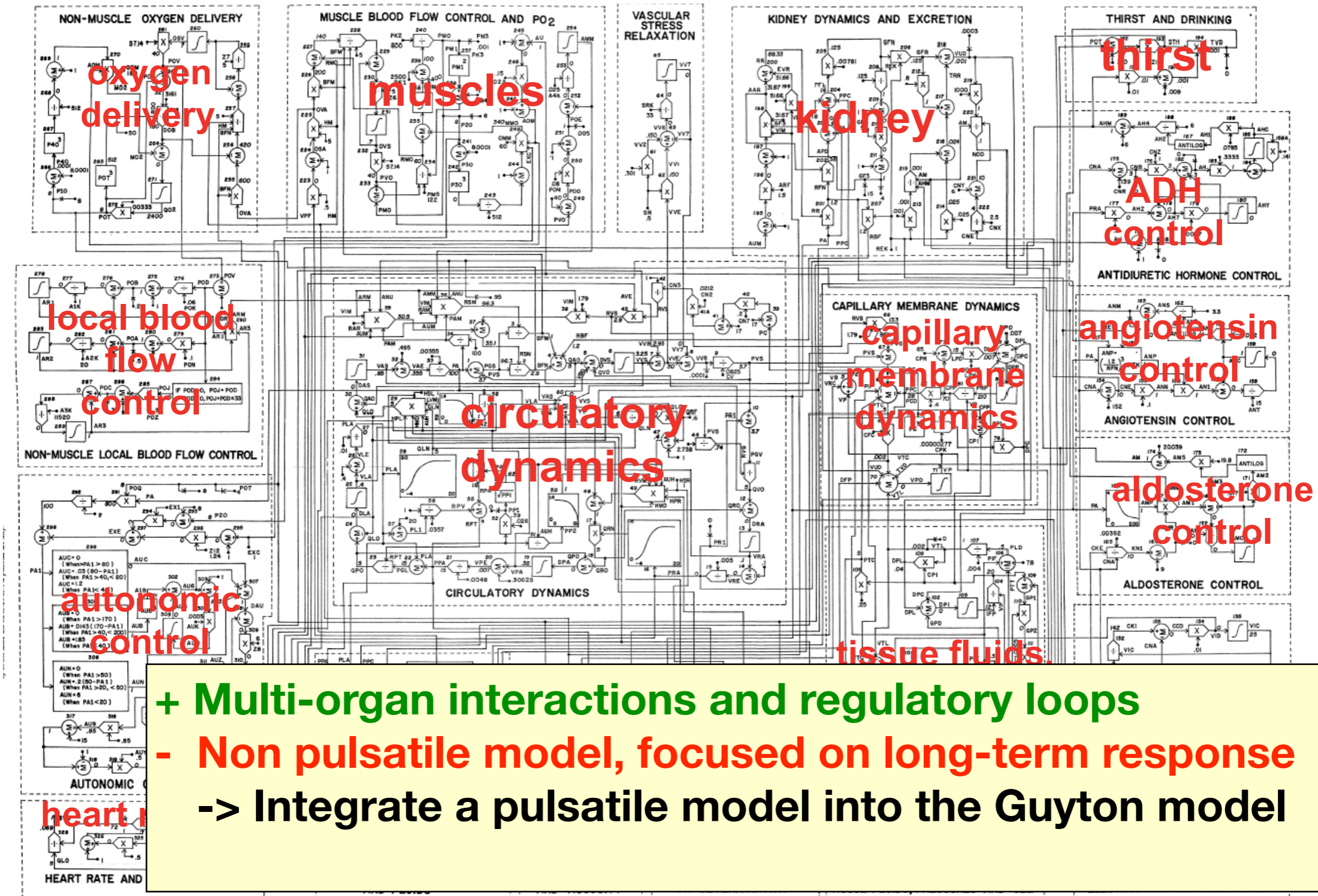
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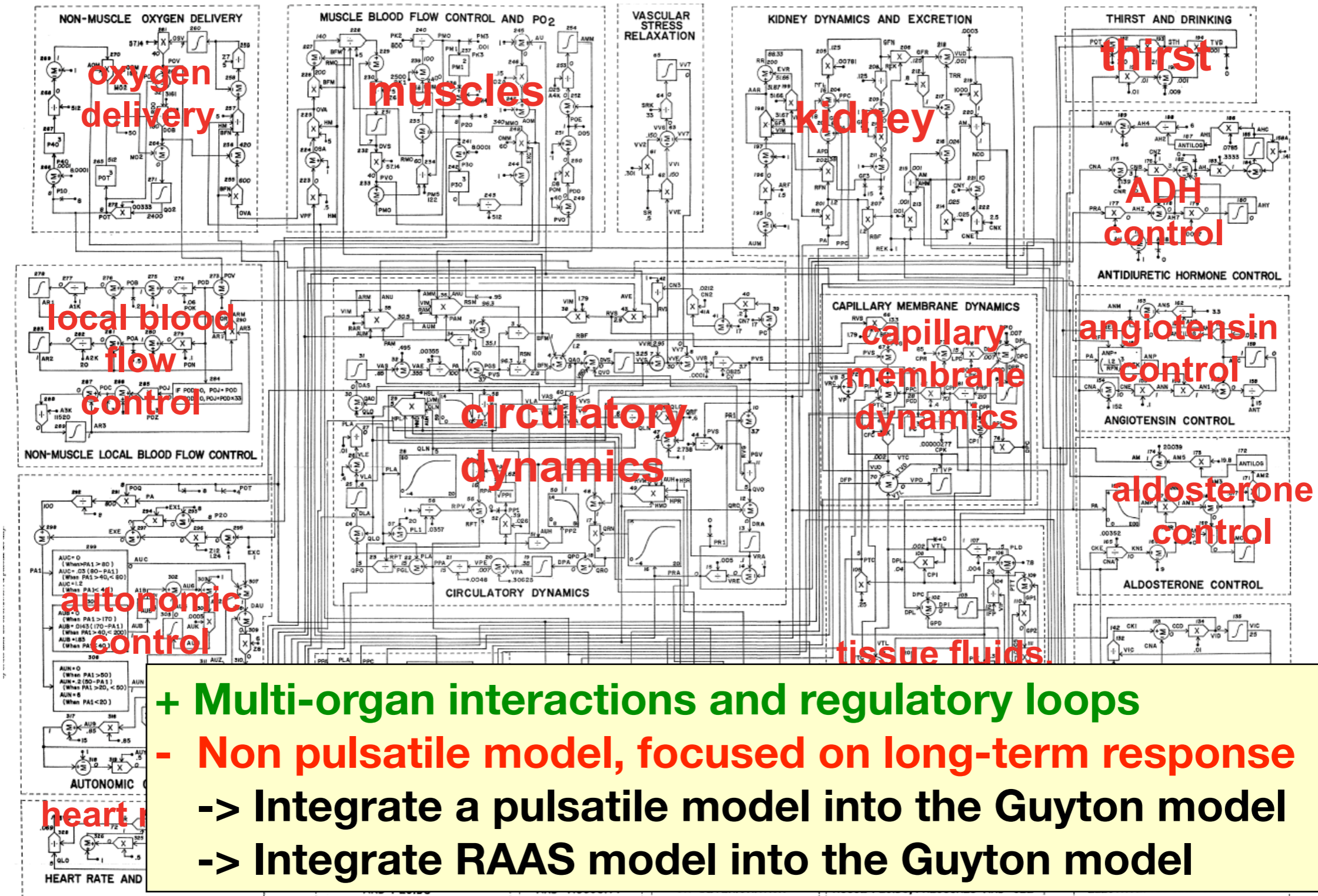
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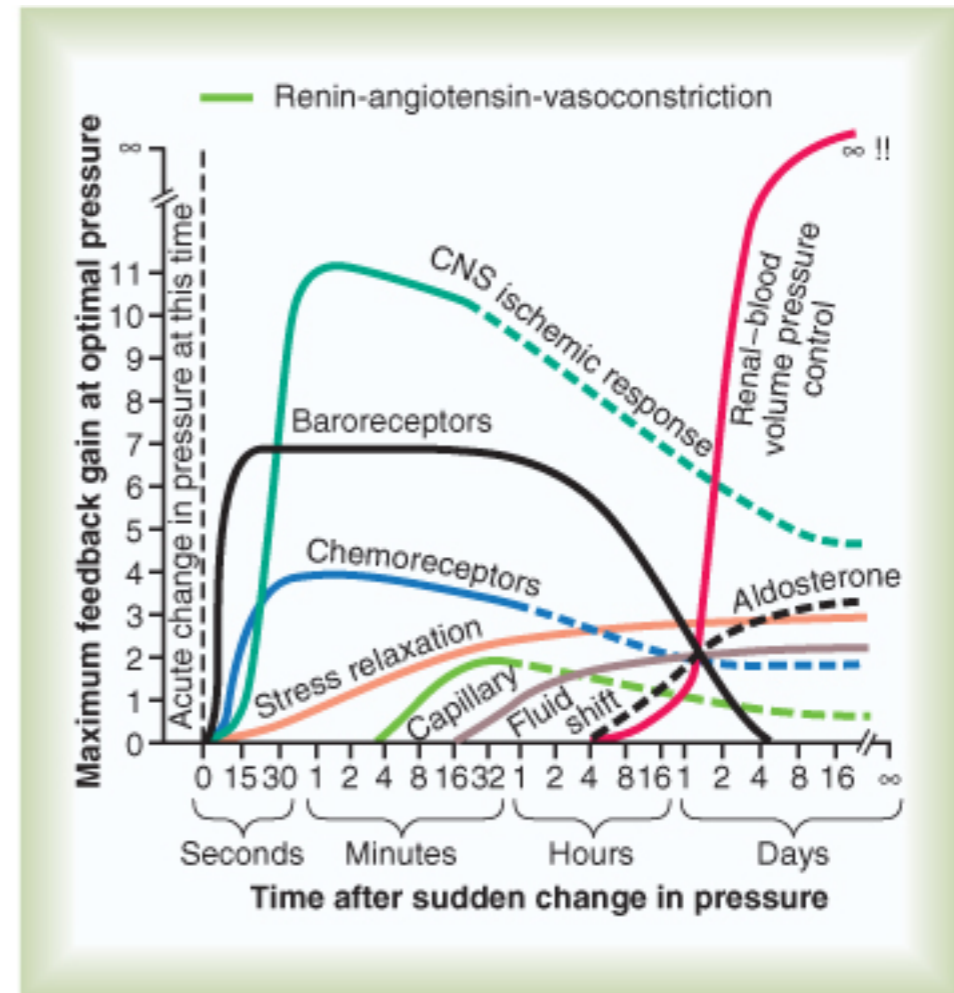


Guyton, Coleman, Granger (1972) *Ann. Rev. Physiol.*

Blood pressure regulation: multi-organ integration

many systems are involved, at many scales

regulatory systems act over different time scales



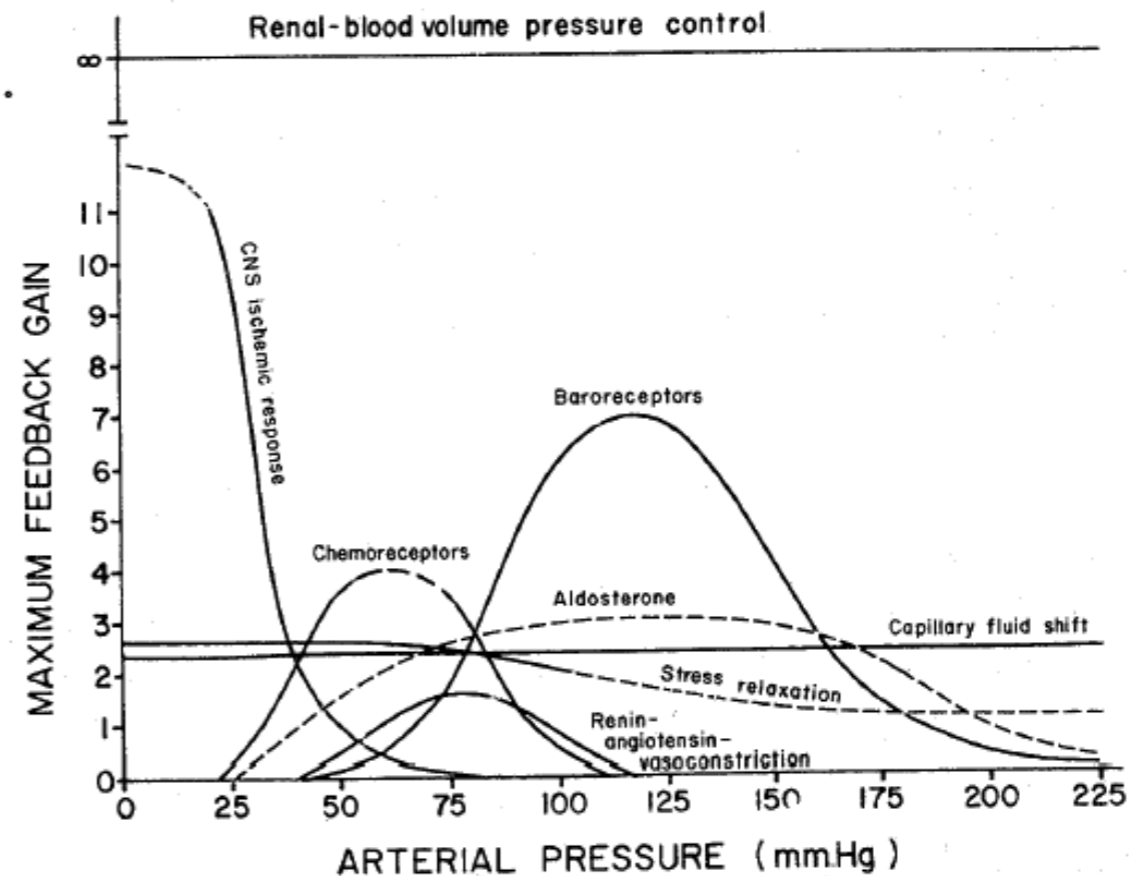
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Blood pressure regulation: multi-organ integration

many systems are involved, at many scales

regulatory systems act
over different time scales

and over different
pressure ranges



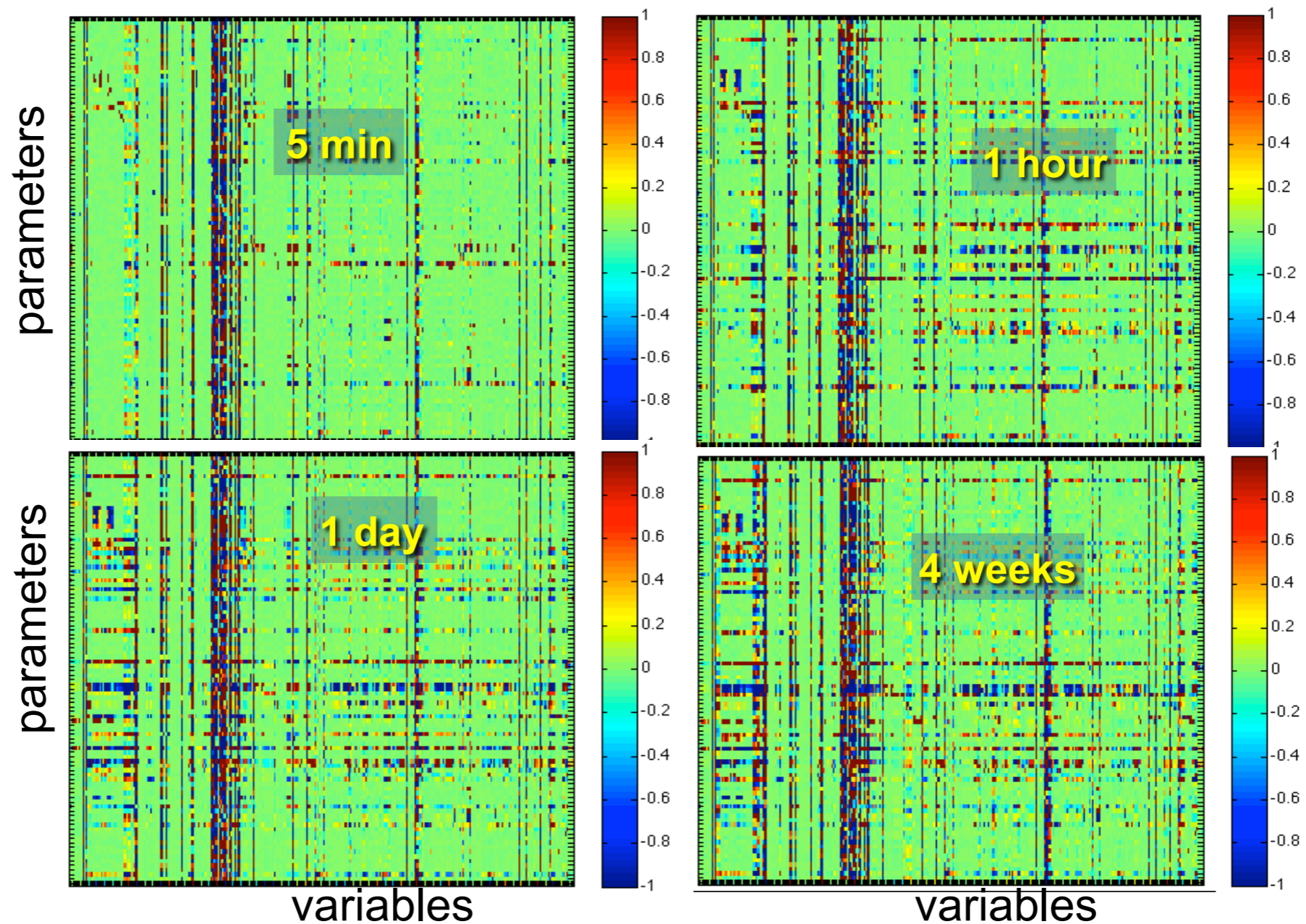
from Guyton, A. C. (1980). Circulatory Physiology III. Arterial Pressure and Hypertension. Philadelphia, W.B. Saunders.

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:
 - the mean \pm SD of the effect of each parameter on each variable,
 - estimates of the interactions among the parameter effects (covariance analysis provides details), and
 - a virtual population of env. 500 000 randomized individuals, and

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 $\pm 1\%$.

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

In addition to the sensitivity analysis, *per se*: A Large Population of "Virtual (Guyton) Individuals"

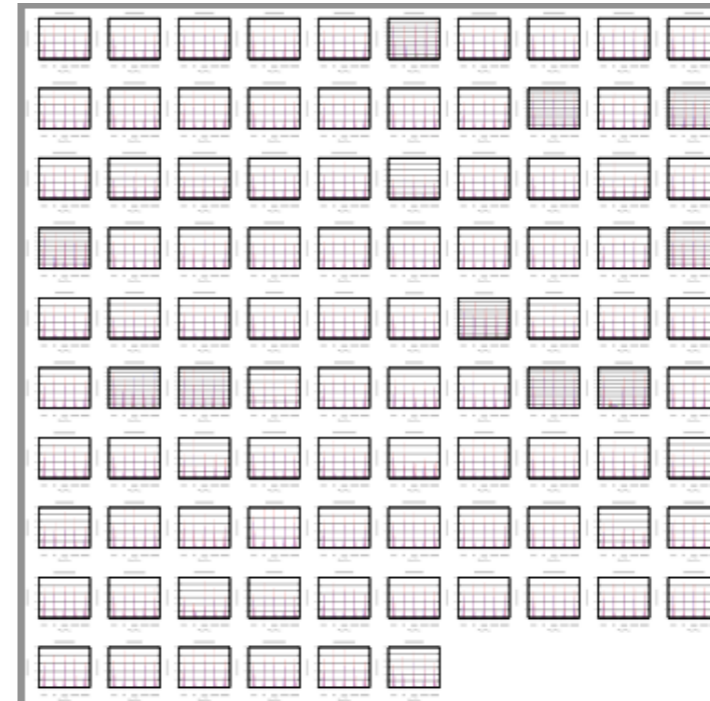
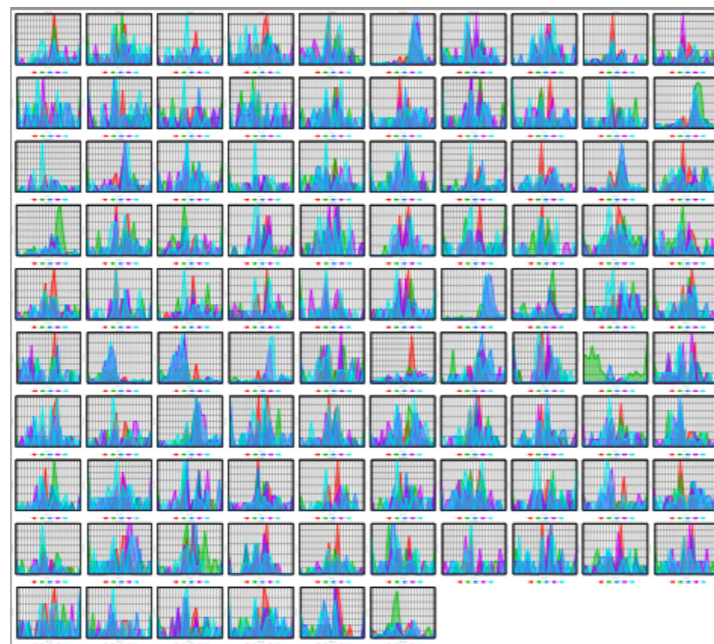
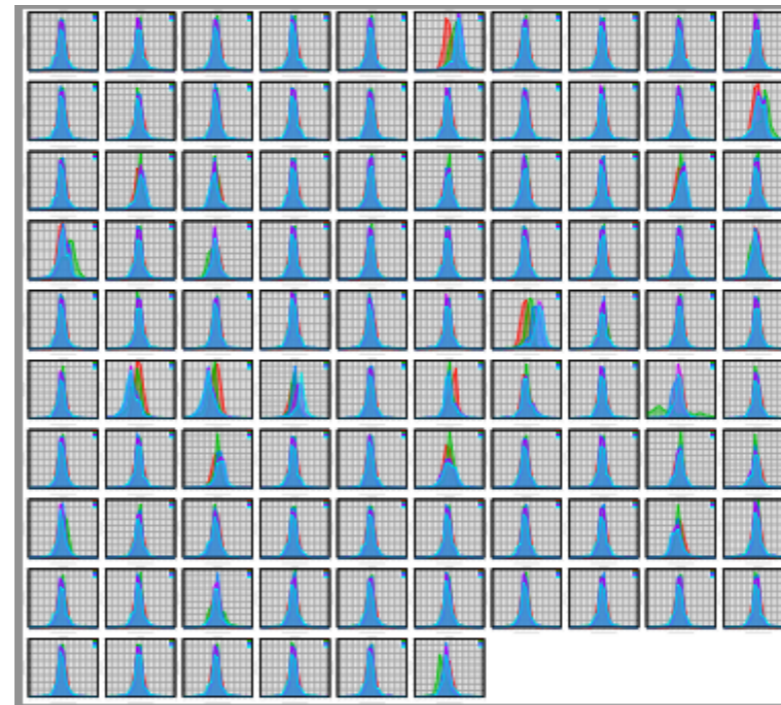
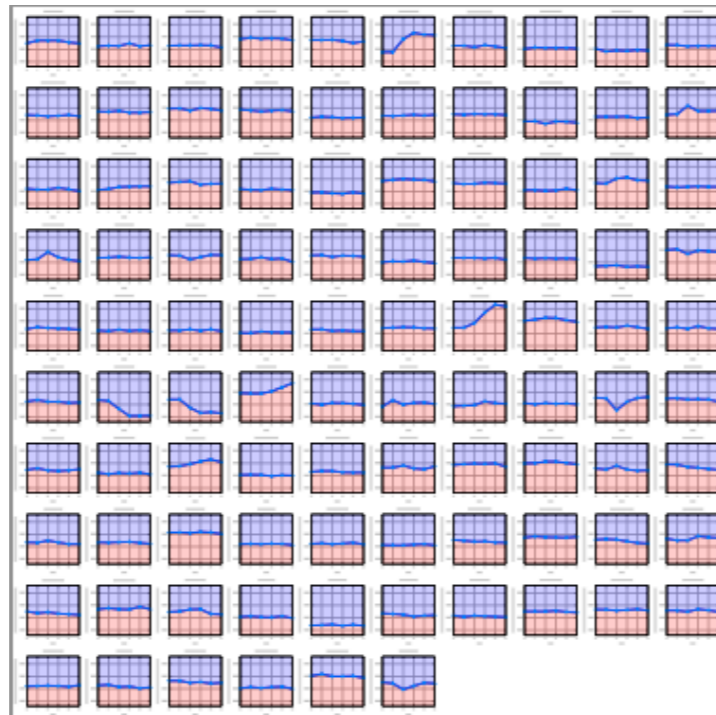
Randomized parameters --> analogous to "genotype"

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...**

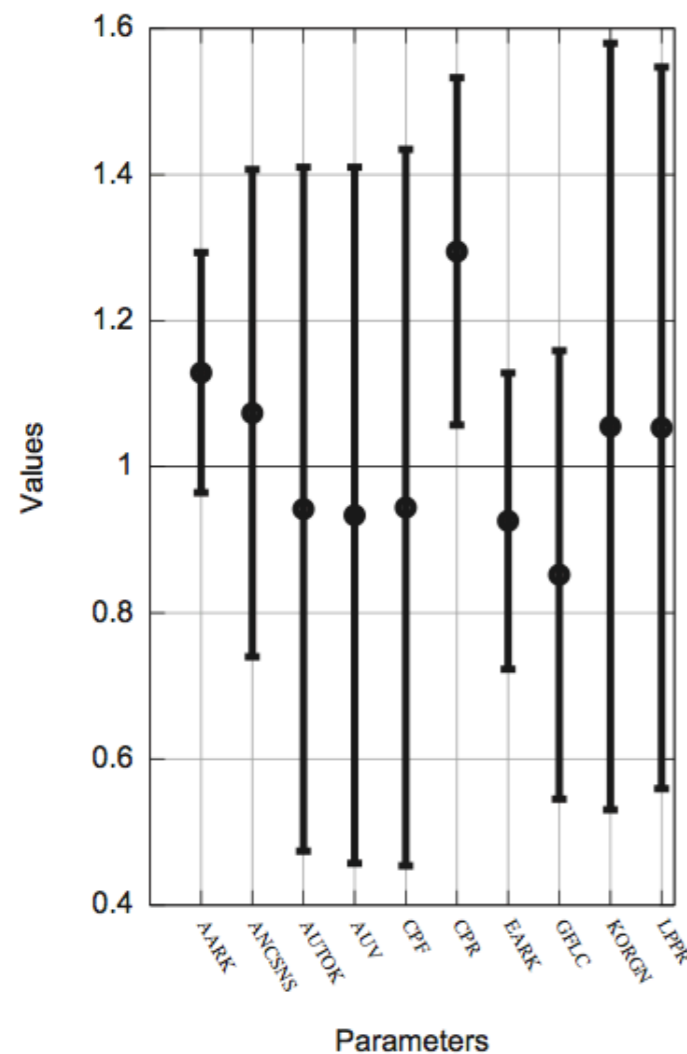
Multi-plots to visualize sensitivity results



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 the hypertensive subpopulation compared to normotensive subpopulation



Increased by >5% in hypertensives:

AARK basic afferent arteriolar resistance

ANCSNS 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

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

How to model the gene-to-organism relationship?

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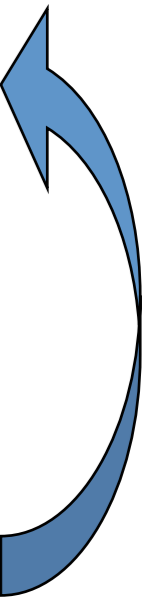
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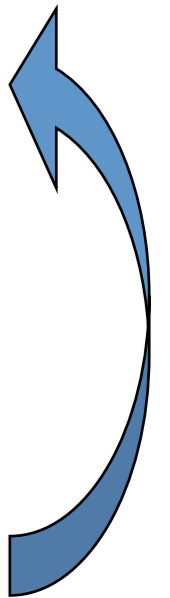


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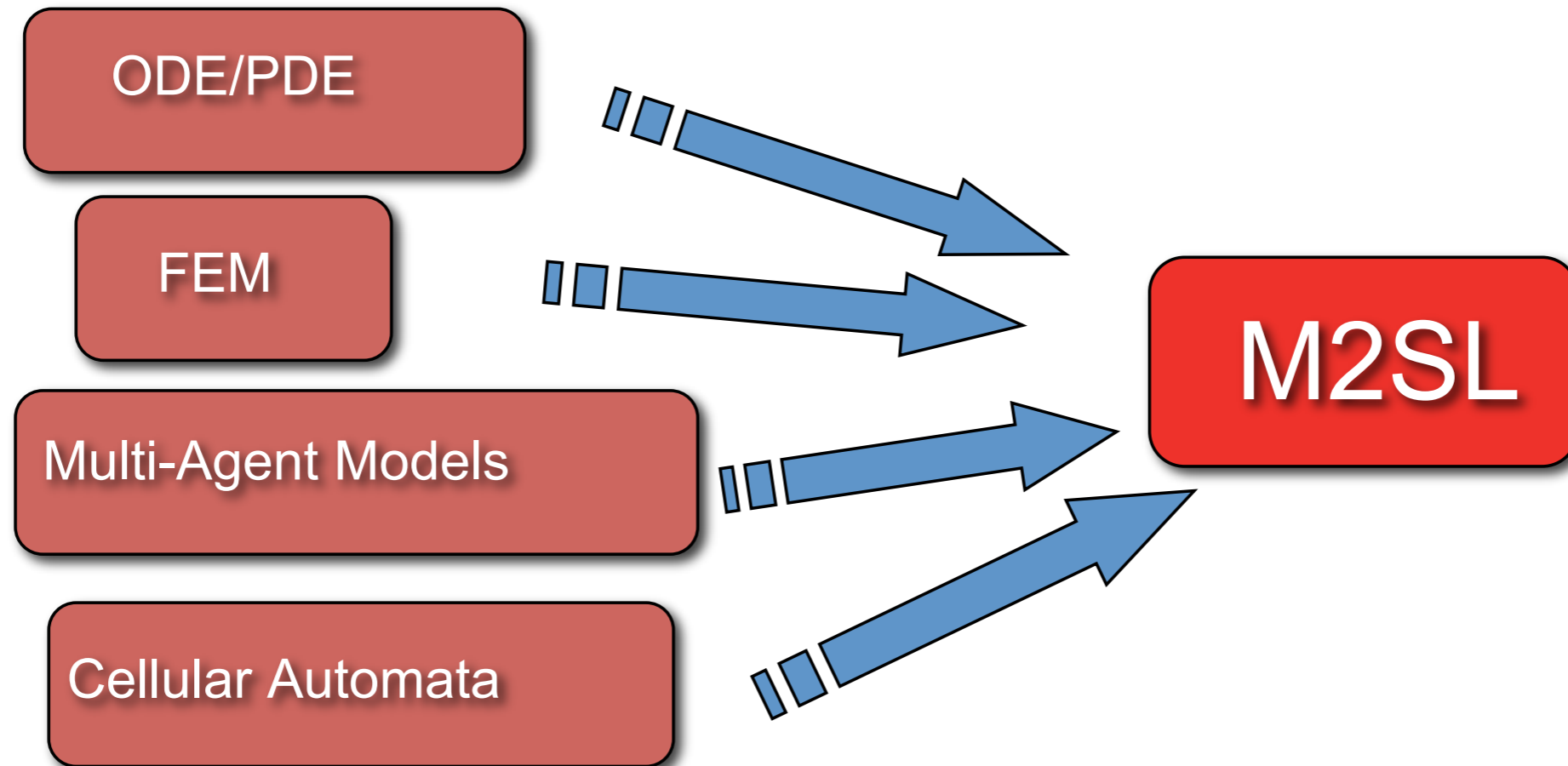
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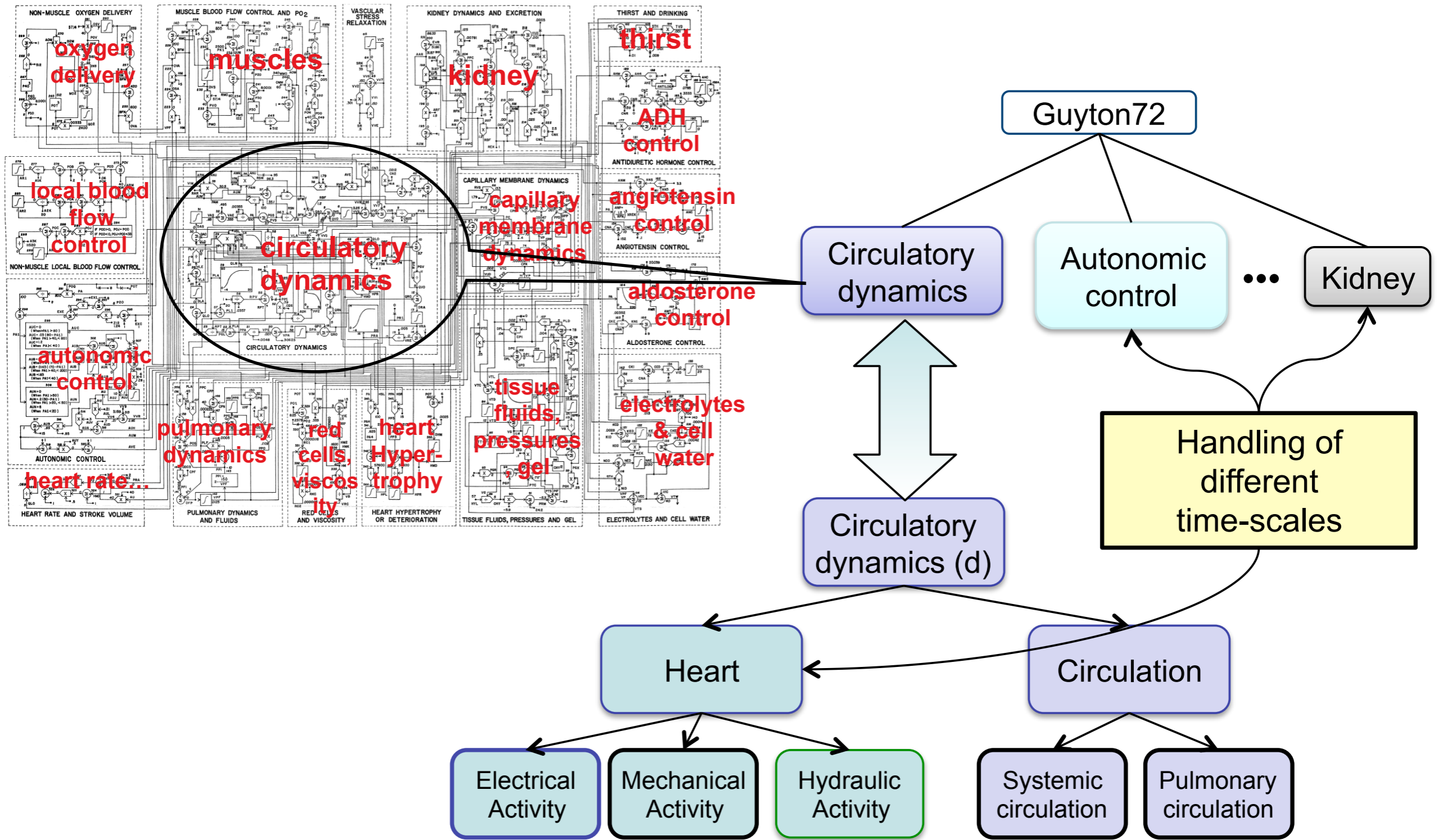
BUT keep execution time manageable!

M2SL: *Multiformalism Multilevels Simulation Library*®

A. Hernandez(Rennes)

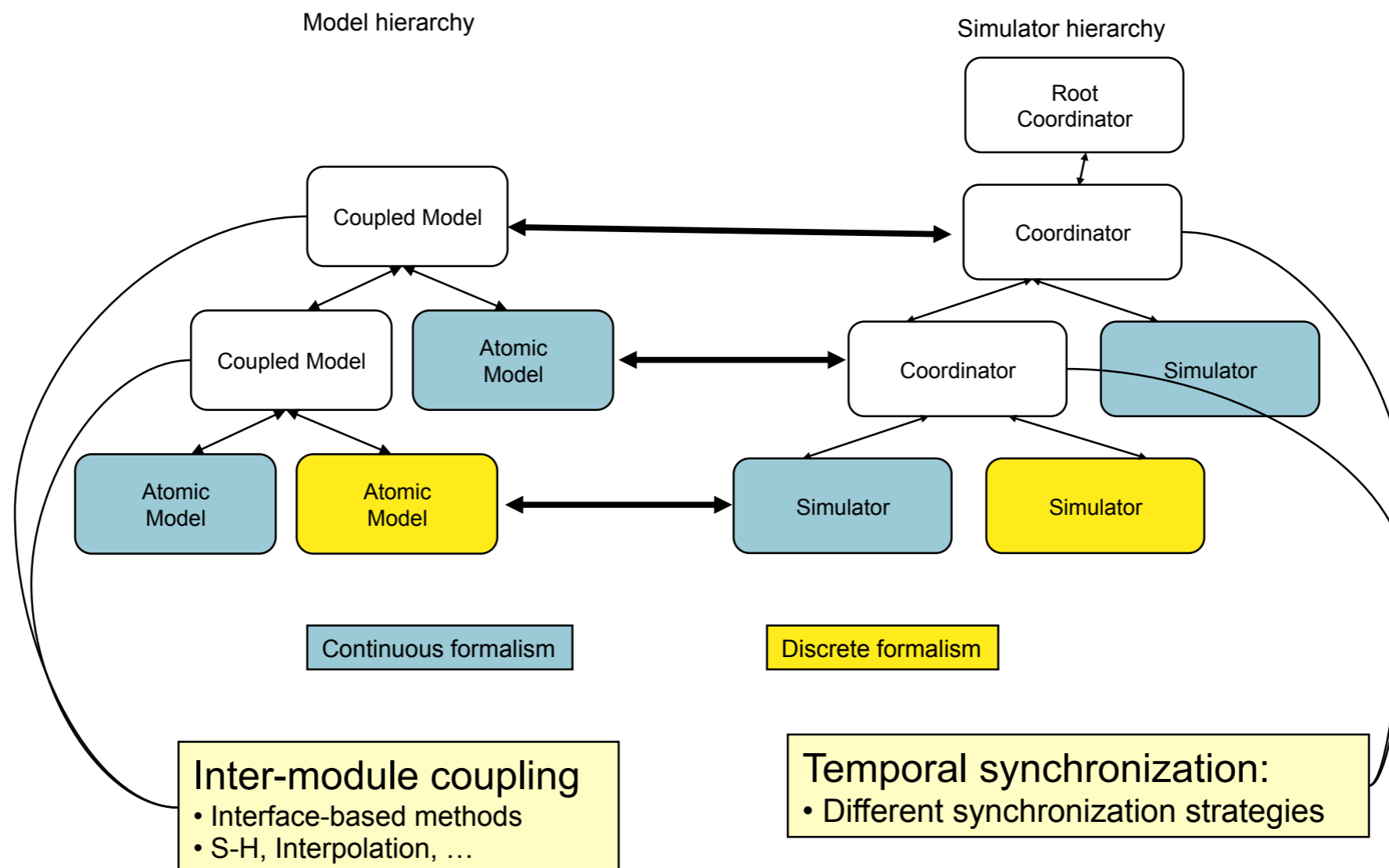


Core-model environment: Guyton CVS models



Modeling & simulation method/tool: M2SL

- M2SL: Multi-formalism modeling library, based on a co-simulation approach
- Object-oriented (C++)
- Hierarchical structures for Models and simulators



A. Defontaine, A. I. Hernández, *Acta Biotheoretica*, vol. 52, pp. 273-90, 2004

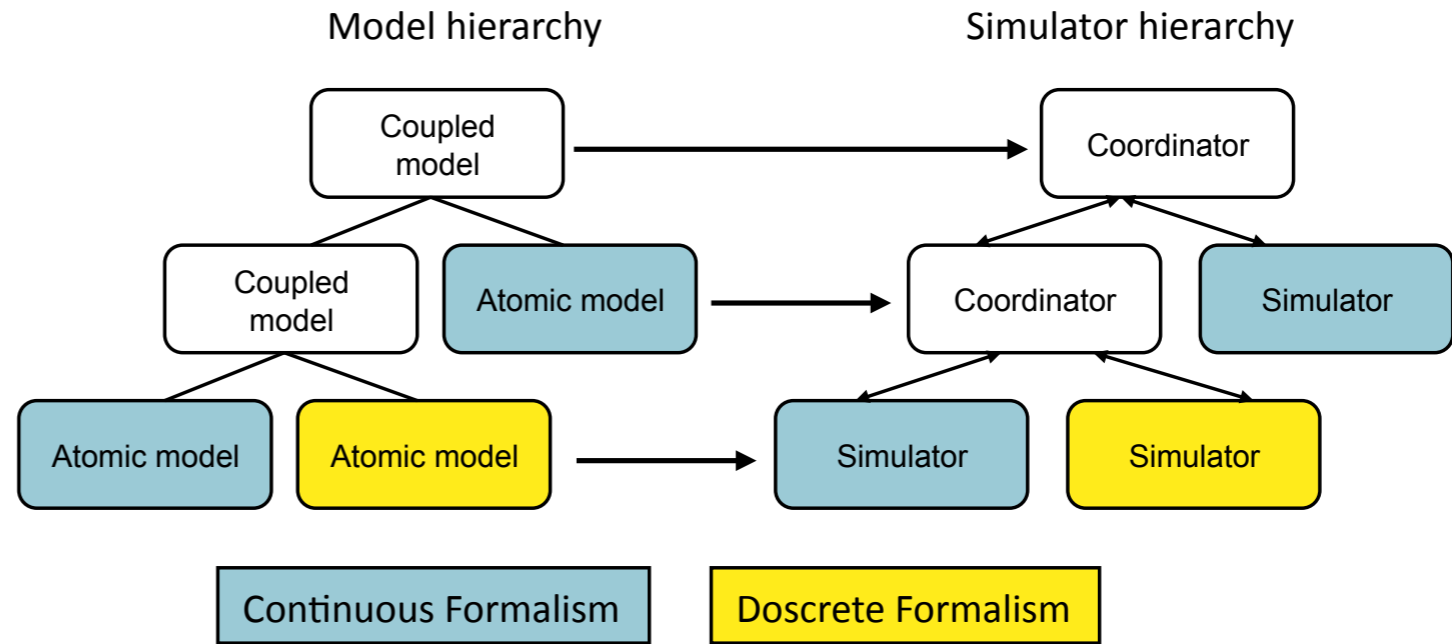
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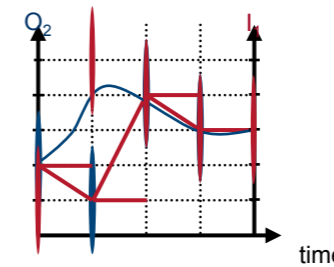
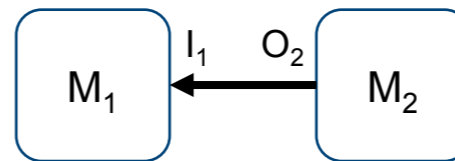
A. Hernandez(Rennes)

Multi-formalism modeling by co-simulation

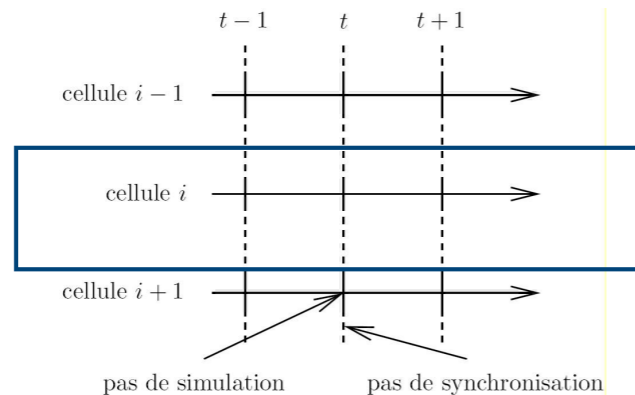
- Hierarchical structure
- Object-oriented
- Distributed approach



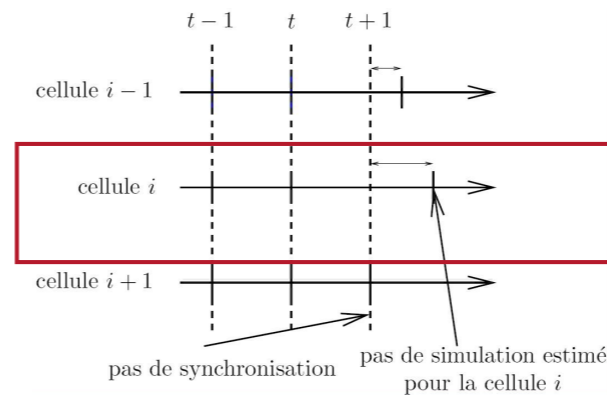
Input/output coupling



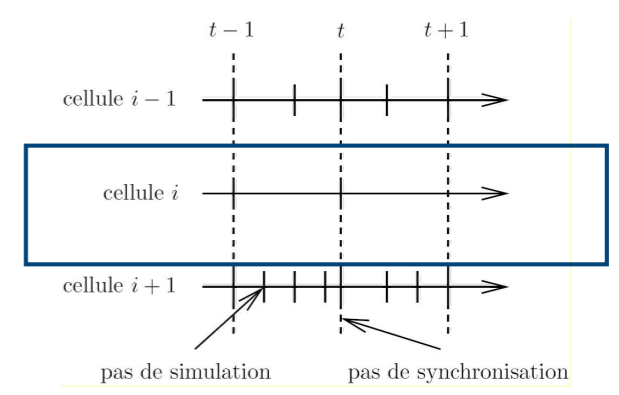
Temporal Synchronization



Synchronisation & simulation at fixed timestep



Synchronisation & simulation both adaptive



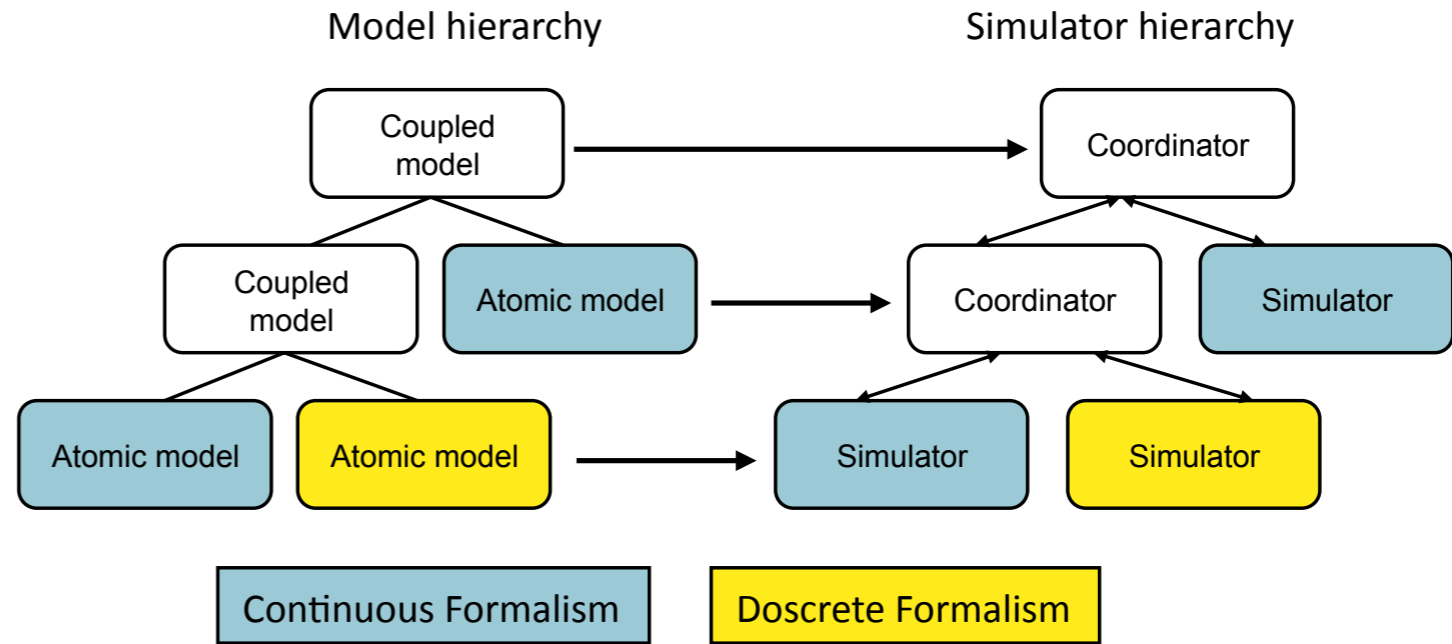
Synchronisation at fixed timestep & adaptive simulation

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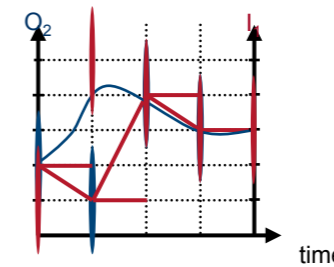
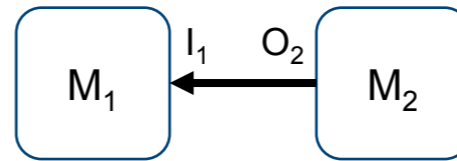
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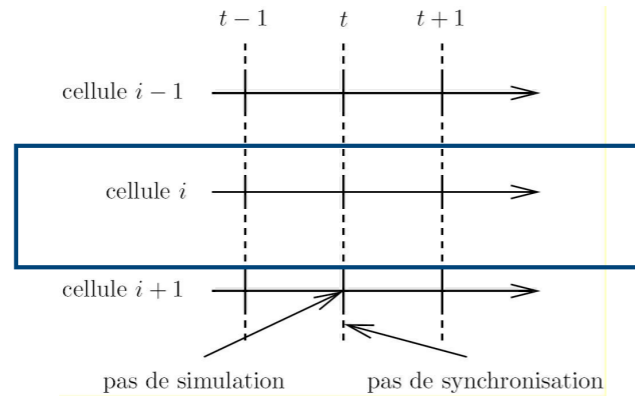
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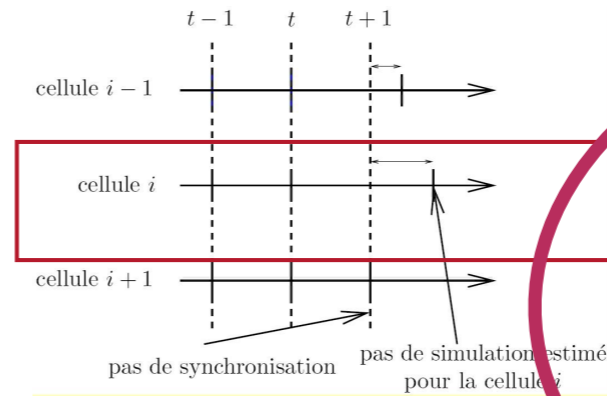
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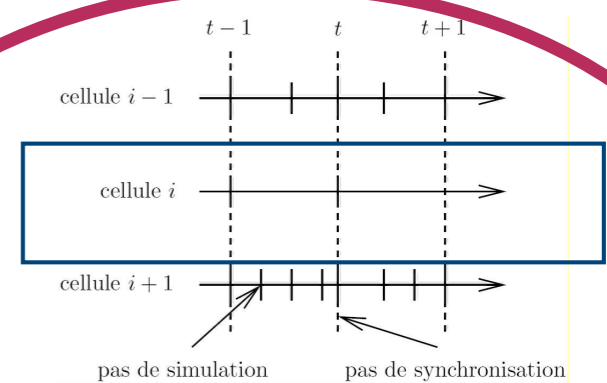
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Synchronisation at fixed timestep & adaptive simulation

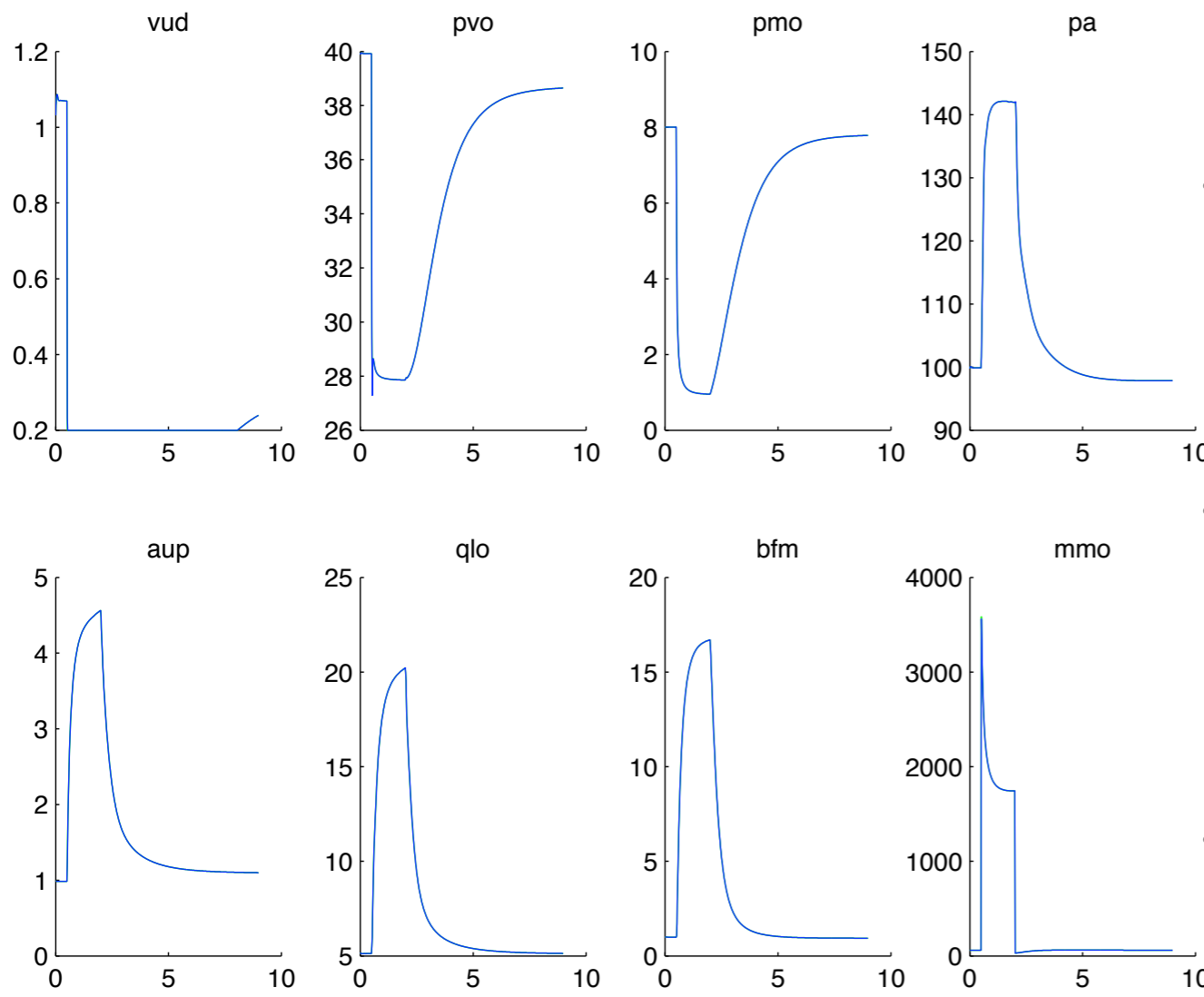
Simulation example of the G72 model with M2SL

Simulation of 2 min. of intense exercise

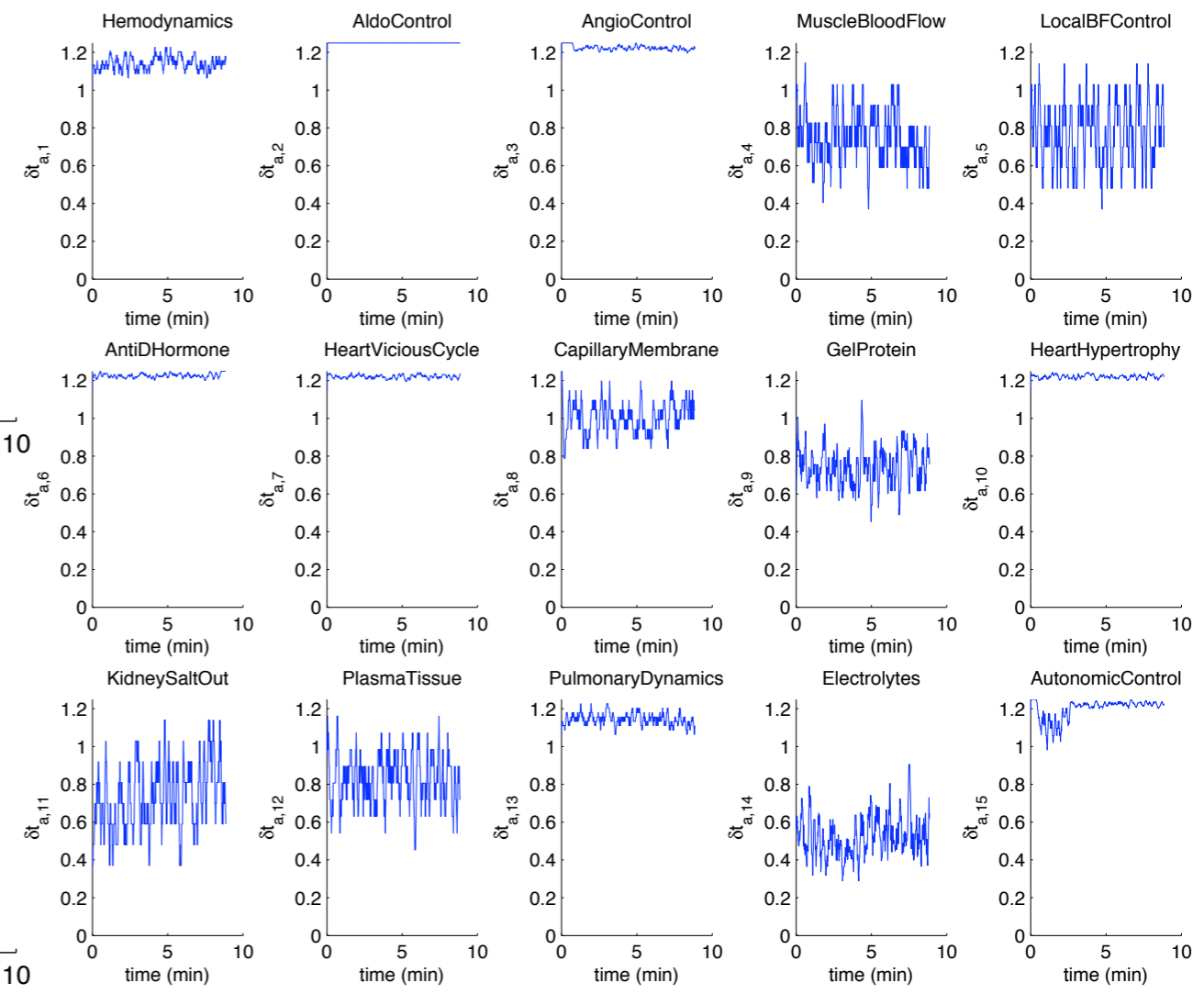
Benchmark – Adaptive with fixed coupling

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

Model Outputs match reference benchmark



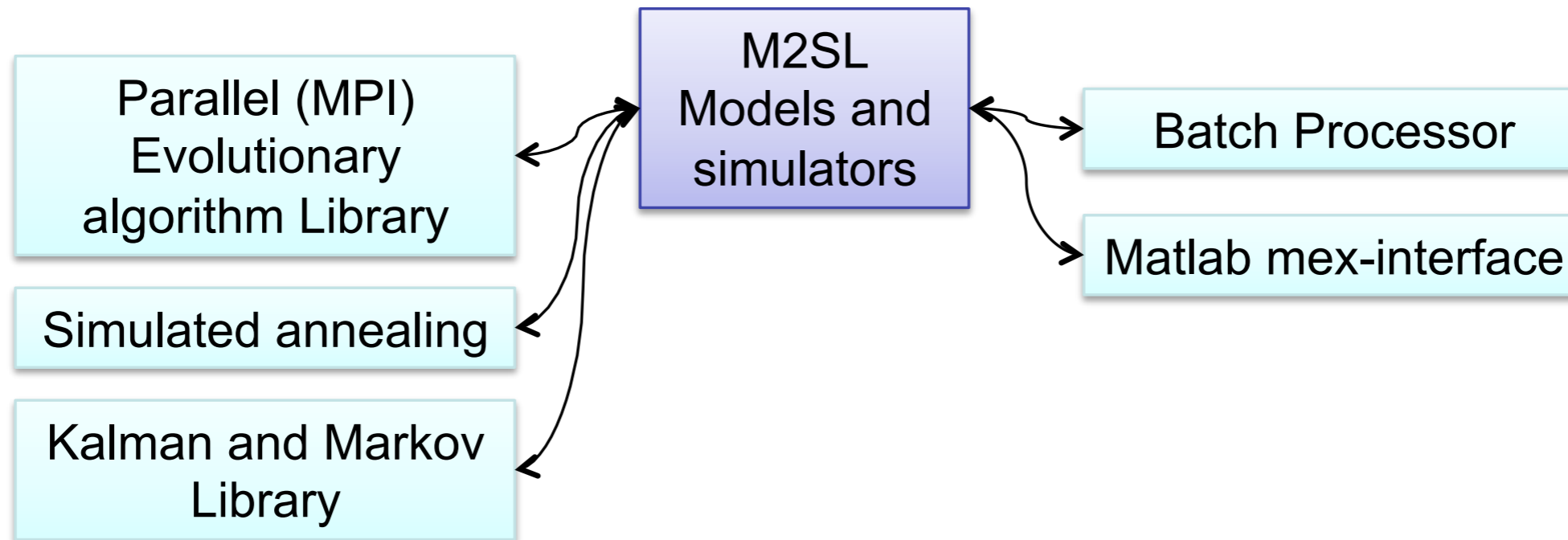
ΔT of each sub-model



A. Hernández, et al. PTRS-A v.367, pp 4923-4940, 2009.

Parameter identification

Sensitivity analysis



Analysis of intracerebral EEGs:

Wendling F., Hernández A. Journal of Clinical Neurophysiology, 2005

Analysis of the ANS:

Le Rolle V., Hernández A. Modelling and Simulation in Engineering 2008

Analysis of cardiac strain signals:

Le Rolle V., Hernández A. Art. Int. Medicine. 2008

Integration of renal function into a CVS model

R. Thomas, et al. PTRS-A, vol. 366, pp. 3175–3197 2008.

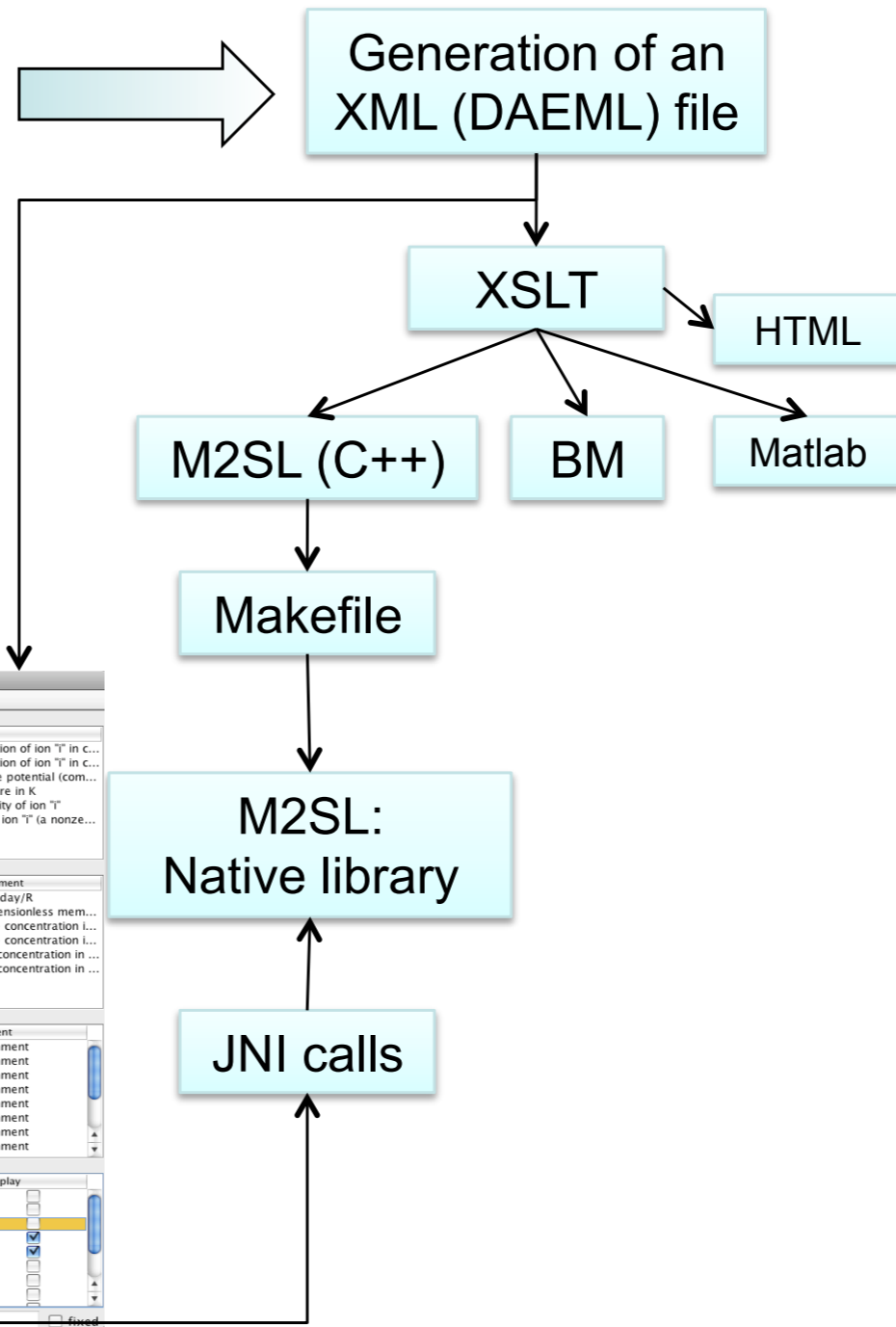
Multiresolution integration of pulsatile heart into a CVS model

A. Hernández, et al. PTRS-A, vol. 367, pp. 4923-4940, 2009

Analysis of long-term pacemaker data

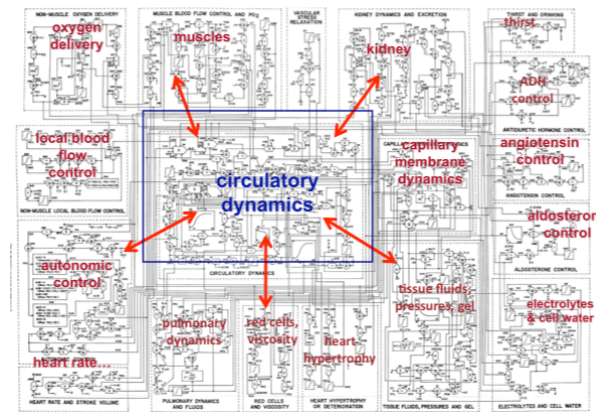
V. Le Rolle. IEEE TBME, vol. 58, pp. 2982-2986, 2011.

The screenshot displays the M2SL software interface. The top window is the 'Model Editor' with a menu bar (New, Edit) and a 'Save' button. It features a 'Model nam' field (Guyton92), 'Model typ' options, and a 'Component' list on the left. The central workspace shows a diagram, and the right pane contains code for 'int ModelInitSim()'. Below this are sections for 'Inputs', 'Parameter', and 'Outputs'. The bottom window is the 'GUI Test' window, which includes a 'Results' plot showing 'VARIABLES' vs 'TIME' and three tables: 'Inputs', 'Parameters', and 'Outputs'.

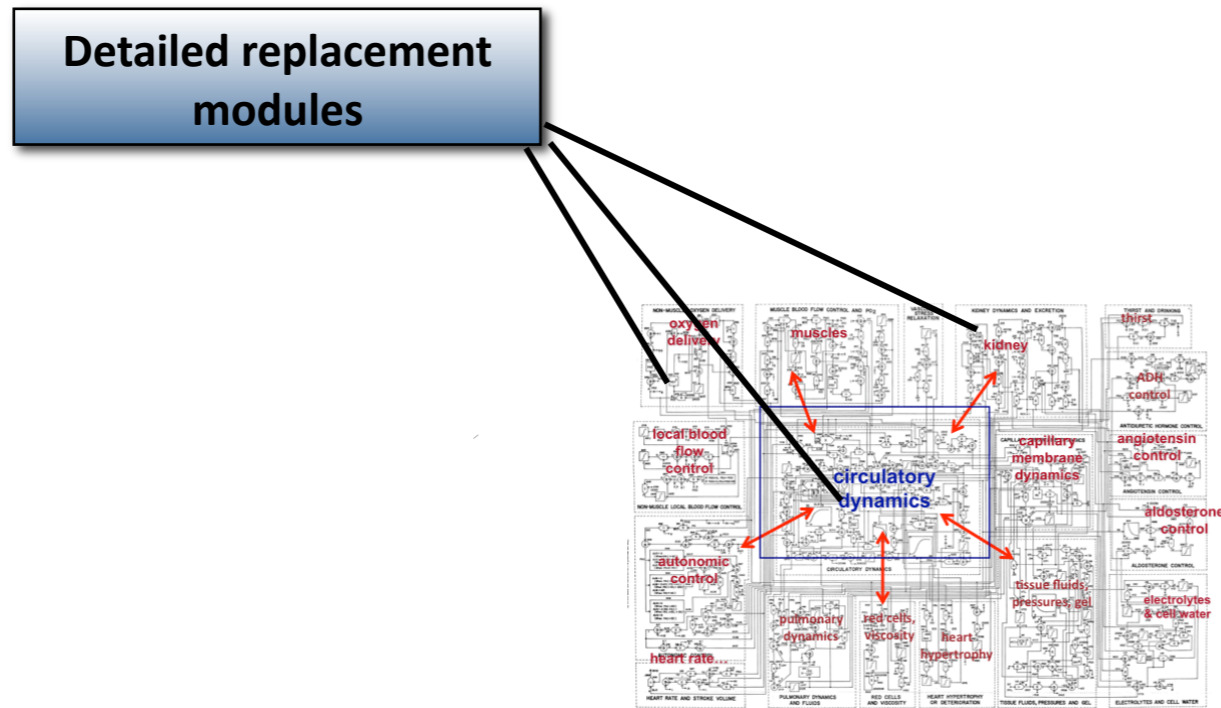


Thank you

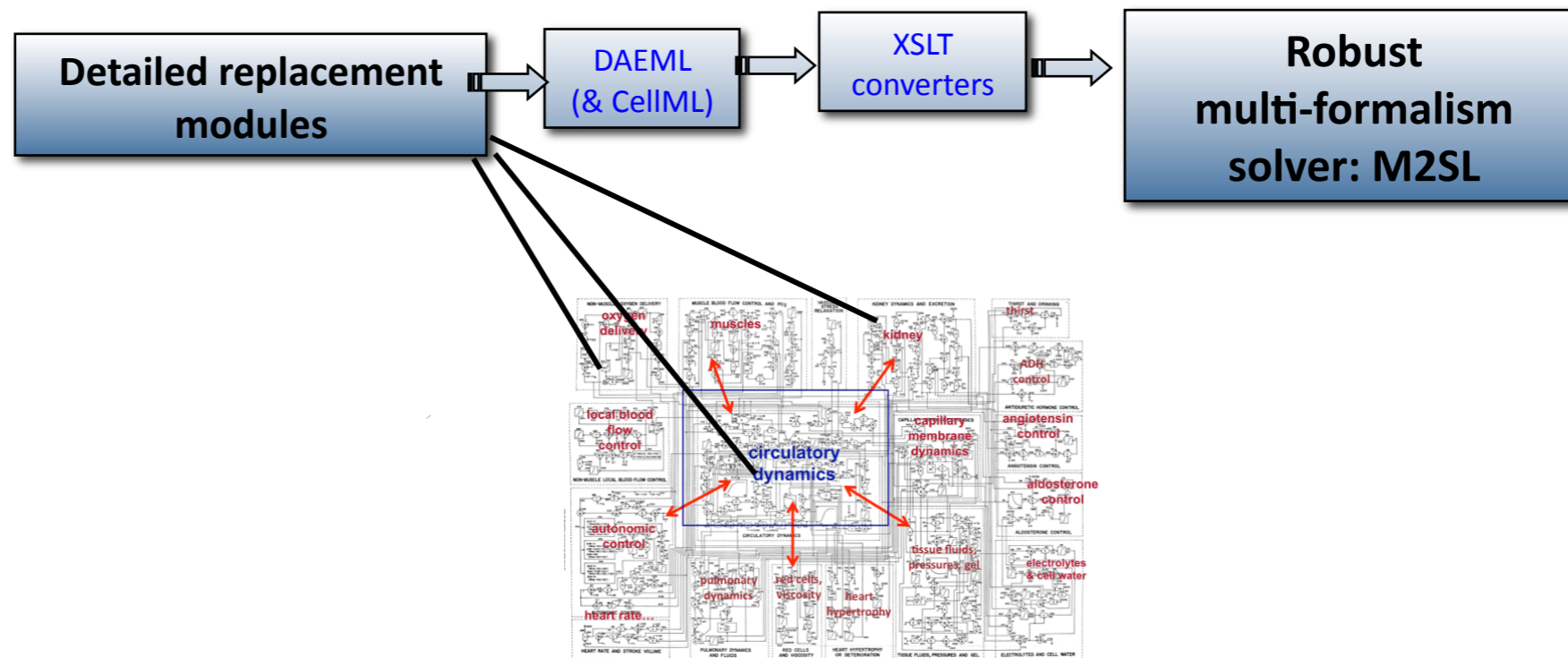
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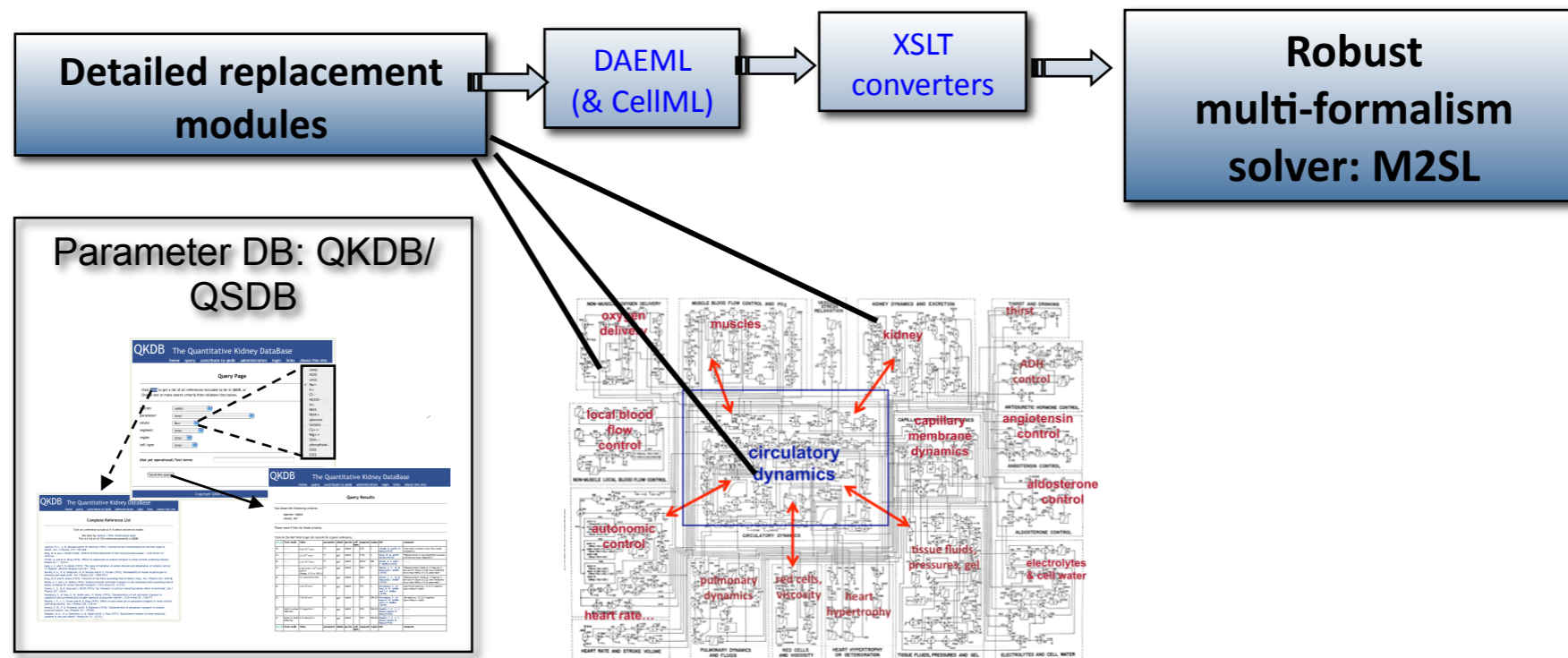
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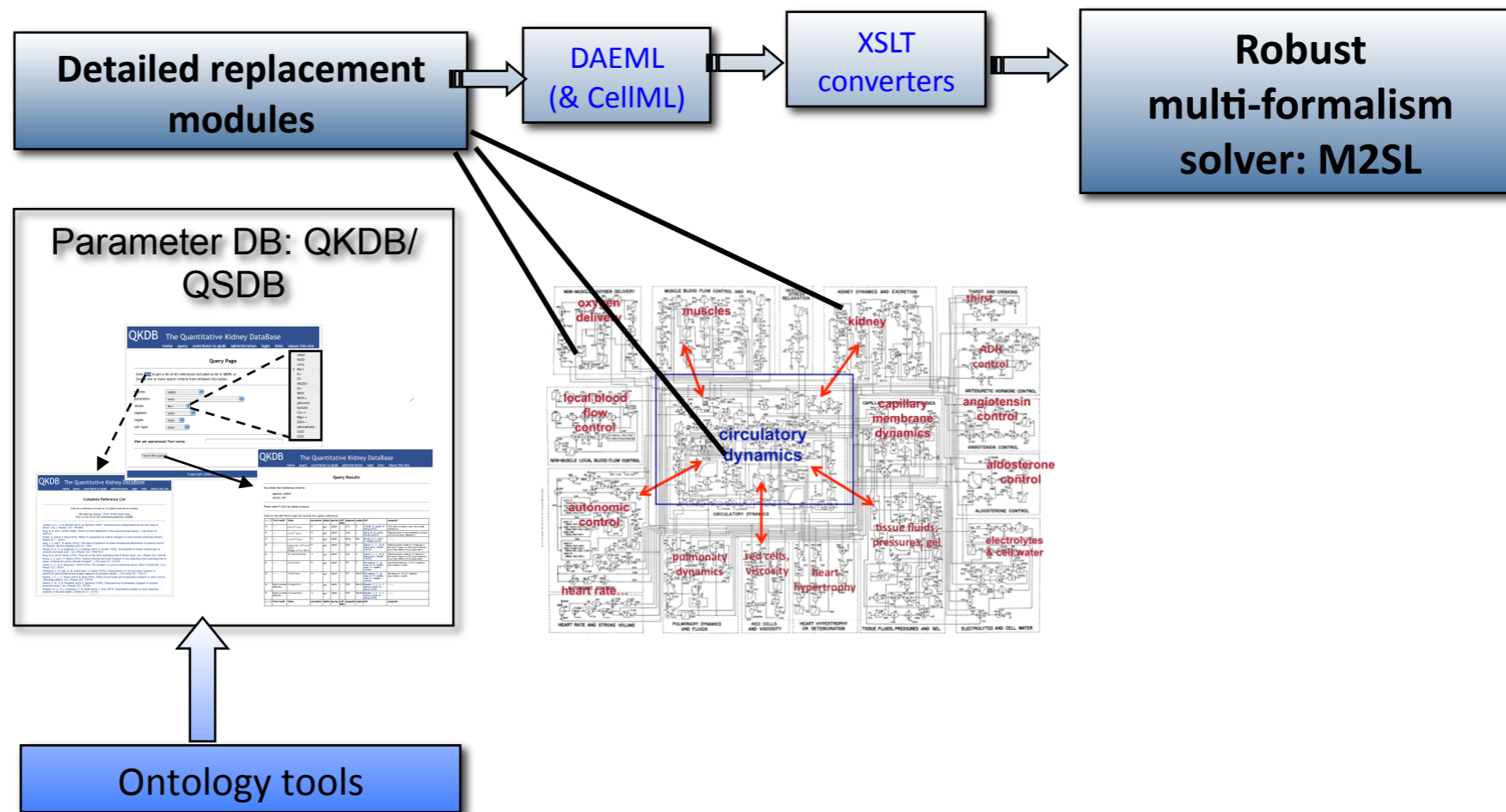
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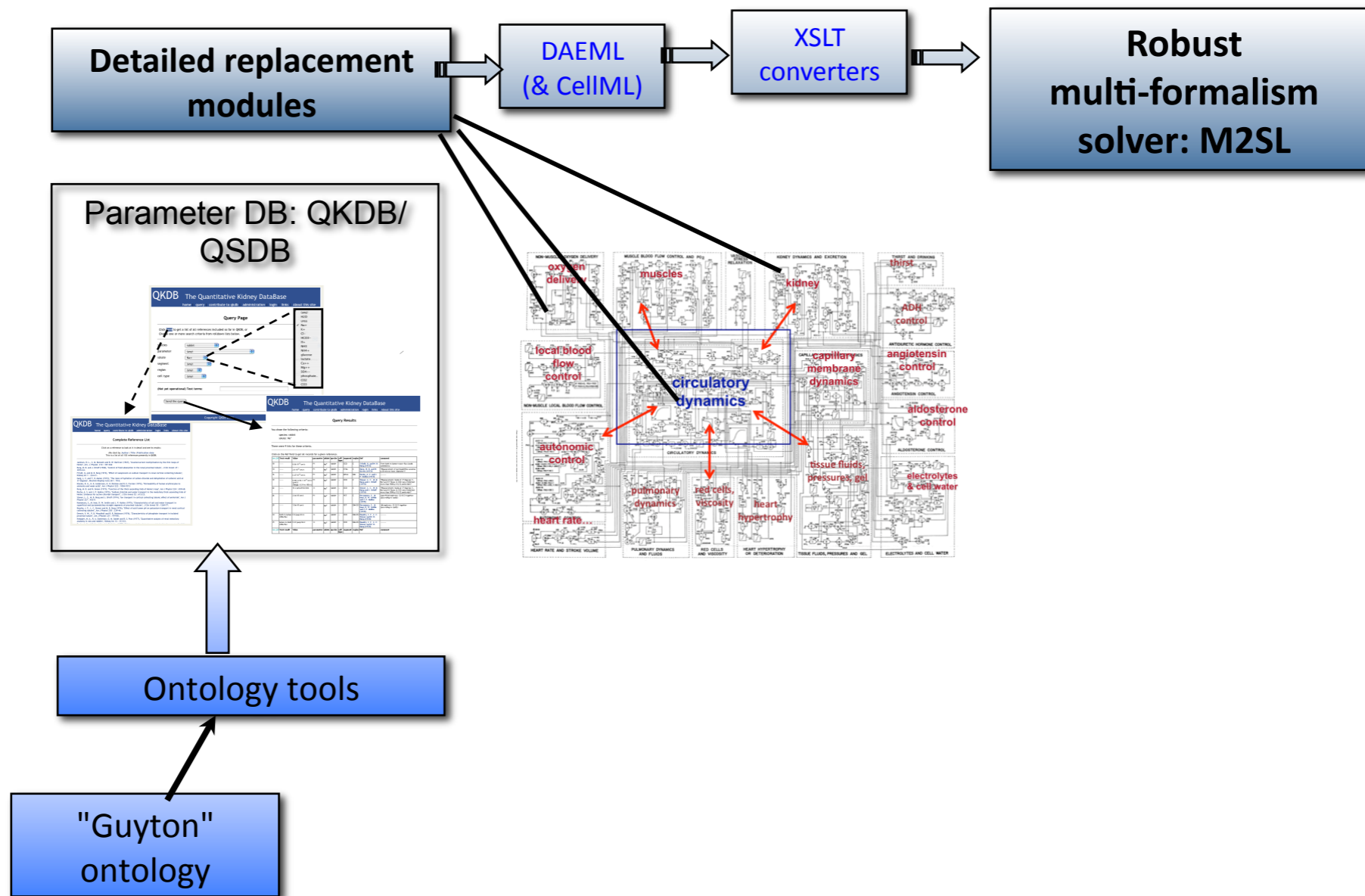
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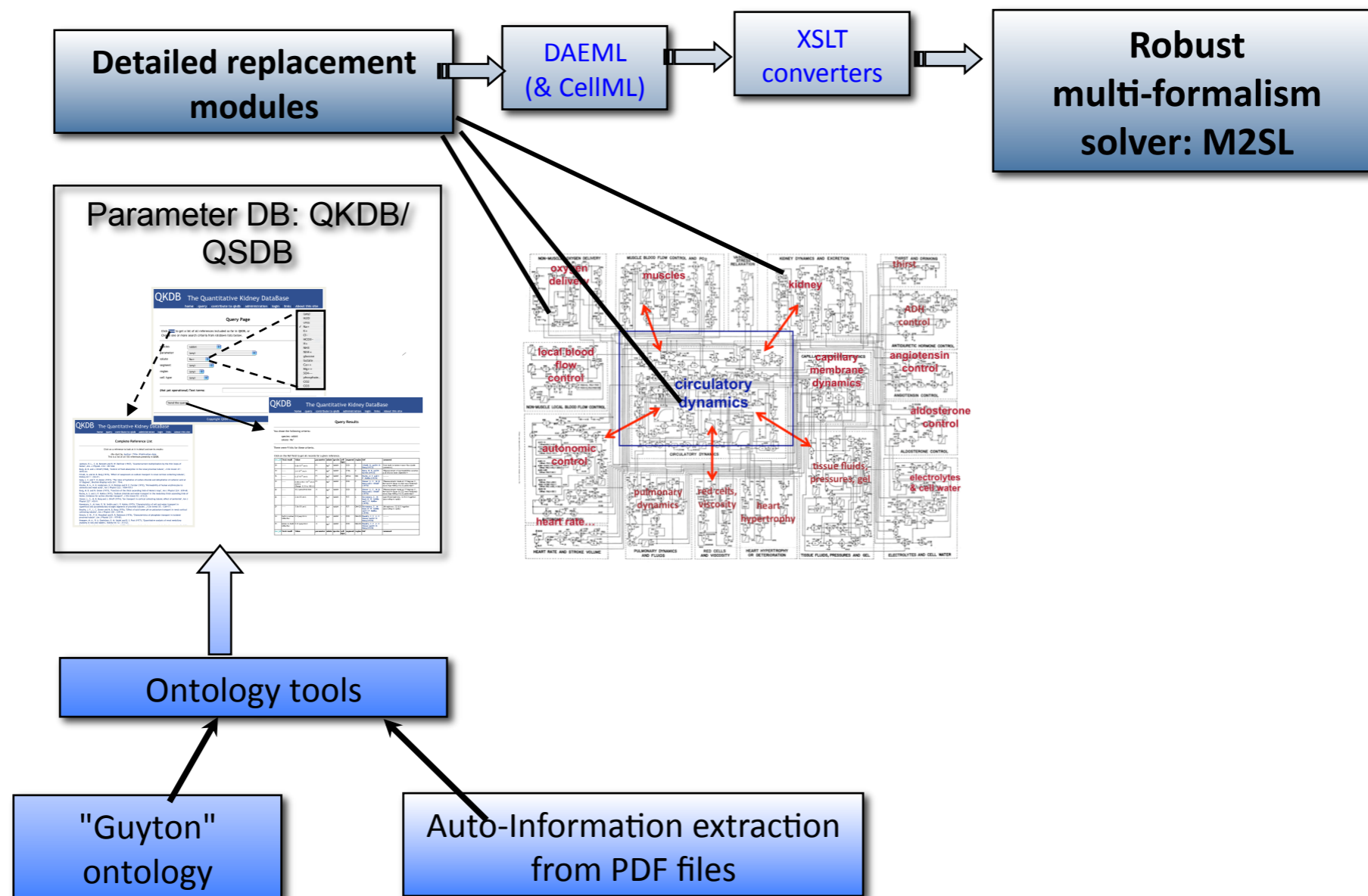
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