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SAPHIR - a multi-scale, multi-resolution modeling environment targeting blood pressure regulation and fluid homeostasis


Abstract—We present progress on a comprehensive, modular, interactive modeling environment centered on overall regulation of blood pressure and body fluid homeostasis. We call the project SAPHIR, for "a Systems Approach for PHysiological Integration of Renal, cardiac, and respiratory functions". The project uses state-of-the-art multi-scale simulation methods. The basic core model will give succinct input-output (reduced-dimension) descriptions of all relevant organ systems and regulatory processes, and it will be modular, multi-resolution, and extensible, in the sense that detailed sub-modules of any process(es) can be "plugged-in" to the basic model in order to explore, eg. system-level implications of local perturbations. The goal is to keep the basic core model compact enough to insure fast execution time (in view of eventual use in the clinic) and yet to allow elaborate detailed modules of target tissues or organs in order to focus on the problem area while maintaining the system-level regulatory compensations.

I. INTRODUCTION

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epite the development of ever more sophisticated models at many scales, from the level of gene regulation or intra-cellular signal transduction or cellular metabolism, through models of tissue function, epithelial transport, or even whole organ physiology, there is presently, no comprehensive, organism-level modeling environment (i.e., open for inspection, modification, & extension) that allows exploration of the whole chain of regulatory influences brought into play by a local perturbation such as a defect in a cell membrane ion transport protein.

In this paper, we present progress on a comprehensive, modular, interactive modeling environment centered on overall regulation of blood pressure and body fluid homeostasis. The project uses state-of-the-art multi-scale simulation methods to construct a basic, modular core model whose components can be replaced individually by higher resolution versions to address specific questions at the organ or tissue level without abandoning the systems-level feedback regulation. The basic core model gives succinct input-output (reduced-dimension) descriptions of all relevant organ systems and regulatory processes, and is modular, multi-resolution, and extensible, in the sense that detailed sub-modules of any process(es) can be "plugged-in" to the basic model in order to explore, e.g., system-level implications of local perturbations. The goal is to keep the basic core model compact enough to insure fast execution time (in view of eventual use in the clinic) and yet to allow elaborate detailed modules of target tissues or organs in order to focus on the problem area while maintaining the system-level regulatory compensations.

Development of the modeling environment is proceeding in several stages in order to provide practical tools even in the early phases of the project. The basic system variables of the core model, chosen to reflect the needs of the initial target problems, are blood pressure (both short- and long-term regulation), pH, concentrations of principal solutes, and the volumes of the various fluid compartments. The essential regulatory variables are autonomic tone and the levels of the hormones vasopressin, aldosterone, angiotensin. The core model includes basic descriptions of the heart, vasculature, intra- and extracellular spaces, lungs, kidneys, and muscles. Rather than starting from scratch, the core model is based on two legacy models that treated overall regulation of blood pressure (Guyton et al. 1972) and fluid regulation (Ikeda et al. 1979).

The resulting modeling resource will be provided as an Open Source project and will be made available to the general community as part of the IUPS Physieme effort.

In parallel to the model development, the project includes a datawarehouse for the vast collection of heterogeneous experimental data necessary not only for evaluation of the many parameter values but also for experimental and clinical validation of the simulation results. This will involve ontology development and implementation of grid computing systems-mediation software.

II. METHODS AND PRELIMINARY RESULTS

A. Core model development

The core systems model includes basic input-output, reduced-dimension formal representations of the essential components involved in whole body regulation of blood
modeling environment, the only restriction on each sub-
module is that it respect the imposed input/output
characteristics in order to correctly interface with the rest of
the systems model. Note that within a given submodule,
"local" variables may be defined, permitting to follow,
during actual in silico simulations, any additional
appropriate processes taking place within the considered
subsystem. For example, a hybrid (multi-formalism)
electrophysiological model of an ischemic cardiac tissue,
can be constructed as a set of coupled sub-models
representing healthy and ischemic cells [5, 6]. Healthy cells
can be represented by means of a simplified (discrete)
automaton model, while ischemic cells can be represented
with a detailed (continuous) model. We can choose to record
only the state variables of some ischemic cells (local
variables of the continuous submodels) and the global
activity at the tissue level (the EGM potential generated by
the set of cells), as the output of the global model.

Technically, this approach requires a robust and flexible
simulator architecture, in order to keep the many processes
in step with each other while minimizing computation time.
Numerical techniques must also be appropriate for the "stiff"
nature of the problem, since some processes are orders of
magnitude faster than others in this system (e.g., in the
above example, a fourth-order RK integration method with
adaptive step-size is used for detailed models, while a
discrete-time simulator is used for simplified models). The
LTSI/SEPIA team (Rennes) has developed such an
environment, called M2SL, based on the co-simulation
principle [7] and has demonstrated its use for several
problems in cardiovascular physiopathology and
epileptology [8-10].

These techniques scale up nicely to the systems model
level of the present project.

Database & ontology development, & grid architecture.
We are implementing a datawarehouse and a set of
ontologies in order to accommodate integration of renal,
cardiac and respiratory data. The data we are mostly
concerned with are physiological data needed for parameter
estimation and clinical data needed for model validation and
benchmarking. As development of detailed sub-modules
proceeds, this will extend to cellular and molecular level
information such as kinetic descriptions of membrane
channels and cotransport proteins.

This infrastructure is being built as an extension of QKDB
(http://physiome.ibisc.fr/qkdb/), the Quantitative Kidney
Database.

C. Development of detailed sub-modules
In parallel with development of the core model, we are
building a collection of detailed submodules for the major
organ systems involved in blood pressure regulation and
systems-level fluid and solute homeostasis. This involves
adaptation of legacy, published models of the heart, lung,
and kidney at many scales and at various levels of
resolution. The adaptation consists of implementation in the
'language' of the SAPHIR toolbox, with standardized
specification of input and output variables.
Figure 1. Diagram of the 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.

Renal module: The kidney is the main actor in long-term regulation of blood pressure and hydro-electrolytic equilibrium [11-14]. As such, it plays, for example, a pathogenic role in most forms of hypertension: hypertension accelerates diseased kidney function loss, whereas antihypertensive treatment slows renal diseases progression.

The primary role of the kidney module (KM) is to bestow the whole-body model with kidney-dependent functionality related to regulation of blood pressure, volemia, and sodium balance [15, 16]. At a minimum, the KM will implement glomerular filtration, tubule Na⁺ & water transport, tubulo-glomerular feedback, renin production, hormone actions, urine concentration in the renal medulla, and consequent natriuresis and diuresis. Additional factors might include endothelin, catecholamines, and dopamine.

Cardiovascular module: The analysis of autonomic nervous system (ANS) activity and, particularly, of the way it modulates the cardiovascular system (e.g. analysis of heart rate variability or ventricular contractility) has been shown to provide valuable information for risk-stratification and early detection of cardiovascular pathologies such as cardiac ischemia and heart failure [17, 18]. In clinical practice, the analysis of the ANS is commonly performed by applying a set of tests called autonomic manoeuvres (such as the Valsalva manoeuvre [19] or the Tilt test [20]). These manoeuvres are based on the controlled modification of a single cardiovascular variable in order to observe the regulatory response of the ANS. Various observations, such as the electrocardiogram (ECG), the noninvasive systemic arterial pressure (SAP) or respiration, are acquired concurrently, to better characterize this autonomic response. However, the interpretation of these data can be very difficult, due to the multidimensionality of the observed phenomena and the fact that the complex mechanisms involved in the autonomic regulation of the cardiovascular system are not fully understood. For example, the reduced blood flow and arterial pressure observed during heart failure lead to chronic sympathetic activation, decreased parasympathetic activity and impaired arterial baroreflex activity. These abnormalities in the autonomic control of the cardiovascular system are associated with pronounced heart failure, higher mortality rates, and cardiac arrhythmia. A model-based analysis of this pathology seems particularly appropriate, since it will help to take into account the variety of system-level functions.

To improve the core model, detailed sub-modules will eventually include more detailed models of: i) cardiac mechanical activity, ii) the arterial and venous vascular systems, iii) autonomic baroreflex loop including afferent and efferent pathways (short-term regulatory loop), and iv) the autonomic long-term regulatory loop.

A multi-resolution model of the electro-mechanical activity of the heart will enable simulation of the consequences of a local ventricular desynchronization on the function of the whole system.

Also underway is identification of model parameters from clinical observations: A database of cardio-respiratory
signals is in construction in collaboration with the University Hospital of Rennes, by applying Tilt tests and Valsalva maneuvers to a population of normal subjects and patients suffering from heart failure. Observations include: 12-leads ECG, continuous non-invasive blood pressure, impedance cardiography and a complete echocardiographic analysis. These data will also be recorded in GDF format and included in the database application mentioned above.

Previous models of cardiac electrical and mechanical activities [8,9,21,23] will be used as reference to create the new coupled multi-resolution model.

Lung module: Over the time scale of the respiratory rhythm, the effect of blood pressure changes on respiratory mechanics is rather well described. However, this is not the case at the cardiac frequency scale. Indeed, the effect of pleural pressure on the heart is quite well elucidated [22]. Nonetheless, to our knowledge, the reciprocal effect of heart on pleural pressure is not clear: the beating heart can be considered as a volume and/or pressure change generator inside the rib cage as evidenced by its effect on lung volume [23]. The Grenoble team is investigating this closed-loop mechanical interaction. Sensitivity analysis and parameter identification will be carried out using data obtained on healthy volunteers. Recorded physiological variables do not imply recourse to invasive techniques: airway flow, thoracic volume changes, and mouth pressure at occlusion give enough information for the parameter identification process.

Central cardio-respiratory interactions: Cardio-respiratory interactions are well documented on an experimental and pathological basis. A simple model of cardio-respiratory coupling [22,24] is being translated into the project formalism. At this stage, the simpler the better, since the first question is: what are the possible and effective mechanical and central cardio-respiratory interactions? An integrated model including both central and mechanical interactions should provide an answer to this typical integrative physiology question.

Users of the environment will be able to assemble a customized collection of core-modules and detailed sub-modules, depending on the question they wish to address.

I. CONCLUSION

This modular, comprehensive systems modeling resource will be an important step toward the general goal of the IUPS Physiome project to eventually attain an overall "gene-to-organism" modeling environment. One of the principal, immediate goals will be to contribute to improved management of hypertension, through more accurate prediction of antihypertensives such as certain diuretics, and to better understand the complex interplay of short- and long-term regulations.

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