Towards Integrative CellML Modeling Technologies for Intracellular Research  

Cooling M. T. 1 (m.cooling@auckland.ac.nz), Matos E. E. 2, Zhou C. 1, Tao G. 1, Nielsen P. F. 1

1. Auckland Bioengineering Institute, The University of Auckland, New Zealand  
2. Organizational Knowledge Management Center, Federal University of Juiz de Fora, Juiz de Fora, Minas Gerais, Brazil

Modularity is crucial for the *in silico* design and testing of biological systems [1]. Recently, we developed an online library of modular mathematical model components for synthetic biology [2] using the modular model exchange format CellML [3]. In addition to synthetic biology, where new biological constructs are being created, this library is now being extended for general intracellular modeling in the biomedical context [4,5] as researchers seek to understand the wealth of systems already existing in the natural world.

To deliver the most benefit to researchers from the expanding repository contents, we seek to provide module classification, searching, composition, and visualization services to enable integrative modeling and analysis. These integrative technologies will be supported by annotation schemes adding biological and model structure semantics. Two prototype ontologies have already been developed, one supporting electrophysiological model composition [6], and the other supporting model visualization [7,8]. We are extending and integrating these ontologies with international standards [9,10,11] where appropriate, and have recently extended the visualization ontology to cater for synthetic biology modules from our new Repository (see Fig 1.).

Fig 1: a) A schematic of a GFP producing system, which is encompasses translation, transcript and RNA and product degradation. b) A computer-assisted visualization using standardized symbols of the same system, implemented as an annotated model composed from modular CellML components.

Once annotated, tools will be required to deliver core integrative functionality. Our provisional architecture for providing core services is shown in Fig 2.

Modular, annotated model components will be stored in the CellML Repository [12], accessible either via web interfaces [13] or through client-side applications. Search, composition, and visualization functionality will be implemented by extensions to the CellML API [14], supporting the augmented construction of intracellular models covering signal transduction, gene regulation, metabolism, and electrophysiological processes. Analysis services for these models will include simulation, sensitivity analysis, and parameter fitting. Due to the computation-intensive
nature of these functions, distributed parallel computing technology will be employed, with a prototype service currently under development with ‘BestGRID’ [15] in New Zealand and ‘Nimrod’ [16] in Australia.

Fig 2: The proposed architecture for integrative model services. The CellML API supports the development of services which can be executed on local machines, online via web services, and/or in GRID architectures.

The development of this technology will make the power of modular CellML available to all researchers, and simultaneously make it possible to compose models encompassing an increased proportion of cellular processes. This will lead to more realistic investigation of emergent functions and greatly facilitate the pursuit of solutions to scientific questions within the complex intracellular environment.

References