BioSystems 121 (2014) 43–53

Contents lists available at ScienceDirect

BioSystems

journal homepage: www.elsevier.com/locate/biosystems

Modeling acclimatization by hybrid systems: Condition changes alter biological system behavior models

Rodrigo Assar[d,b,*], Martín A. Montecino[b,c], Alejandro Maass[e,c], David J. Sherman[a]

[a] INRIA Bordeaux Sud-Ouest, Project-team (EPC) MAGNOME common to INRIA, CNRS, and U. Bordeaux 1, Talence, France
[b] Centro de Investigaciones Biomédicas, Facultad de Ciencias Biológicas and Facultad de Medicina, Universidad Andrés Bello, Santiago, Chile
[c] FONDAP 15090007 Center for Genome Regulation, Santiago, Chile
[d] ICBM Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile, Santiago, Chile
[e] Departamento de Ingeniería Matemática y Centro de Modelamiento Matemático, Facultad de Ciencias Físicas y Matemáticas, Universidad de Chile, Santiago, Chile

ARTICLE INFO

Article history:
Received 26 July 2013
Received in revised form 6 March 2014
Accepted 28 May 2014
Available online 2 June 2014

Keywords:
Acclimatization
Hybrid systems

ABSTRACT

In order to describe the dynamic behavior of a complex biological system, it is useful to combine models integrating processes at different levels and with temporal dependencies. Such combinations are necessary for modeling acclimatization, a phenomenon where changes in environmental conditions can induce drastic changes in the behavior of a biological system. In this article we formalize the use of hybrid systems as a tool to model this kind of biological behavior. A modeling scheme called *strong switches* is proposed. It allows one to take into account both minor adjustments to the coefficients of a continuous model, and, more interestingly, large-scale changes to the structure of the model. We illustrate the proposed methodology with two applications: acclimatization in wine fermentation kinetics, and acclimatization of osteo-adipo differentiation system linking stimulus signals to bone mass.

1. Introduction

Biological systems are known for their high degree of complexity. System behavior depends on many factors that are often not controlled, and biological phenomena arise from different interacting processes. Different processes may be best described by different models: continuous models to describe gradual changes over time, discrete models for instantaneous changes, deterministic models to represent predictable behaviors, non-deterministic models to describe various possible responses, and stochastic models to introduce randomness (Wilkinson, 2006). Such is the case in the modeling of a population of cells, in which one has to define births, growths, divisions and deaths of cells; at each cell one describes the transport relations between compartments such as cytoplasm, mitochondrion and nucleus; and finally to model biochemical reactions responsible for metabolism (Maus et al., 2008). In addition to this complexity, at each level the system behavior can considerably change according to environmental conditions, a phenomenon defined as *acclimatization* (Varela et al., 1974; Watts et al., 1975; Coles and Brown, 2003). Acclimatization behaviors can affect system dynamic laws as well as the model itself. In some cases, the effect of such changes can be captured by model coefficients. However, in some situations strong effects can be induced in the system behavior, rendering coefficient changes insufficient. In fact, when different conditions are described by different types of models, the decision to unify models structurally different is expensive in terms of time and rewriting.

According to Minsky (1968), a model responds to questions about a system in a specific condition. To build a model that is valid in general conditions and that takes acclimatization into account, it is necessary to *reuse* and *combine* models at different regimes. Unfortunately, unifying all the existing models is expensive in terms of time and rewriting, and sometimes is not even meaningful. Furthermore, while efforts for finding a way to describe biological models that may be reused by third parties has finally established a common format in *SBML* (Hucka et al., 2010), the needs for combining models and simulation have not yet been sufficiently covered. Recently, research on combination of models has been intense (see the book sections Uhrmacher et al. (2005) and Maus et al. (2008)). Reusability and unambiguity have been identified as important

* Corresponding author at: ICBM Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile, Santiago, Chile. Tel.: +56 229786463; fax: +56 27373158

E-mail addresses: rodrigo.assar@gmail.com (R. Assar), mmontecino@unab.cl (M.A. Montecino), amaass@dim.uchile.cl (A. Maass), david.sherman@inria.fr (D.J. Sherman).

http://dx.doi.org/10.1016/j.biosystems.2014.05.007

challenges, but, to the best of our knowledge, there is no formalization of the combination process. Here we approach these challenges. In this study, we propose a *hybrid system*-based protocol to model complex biological systems, emphasizing acclimatization. In this context, system dynamics is represented by the variation of continuous variables described by a model, whose laws can change their form over time depending on discrete mode changes. These last changes can be stochastic, non deterministic or deterministic. Although it is well known that hybrid models are useful in biology and medicine[1] (Aihara and Suzuki, 2010), their relation to acclimatization has not been explored in depth and modeling protocols are limited. In best of our knowledge, most of publications focus on particular applications, or in theoretical aspects of the formalization and model checking using examples as illustration.

Although hybrid automata appears as the accepted formal description of hybrid systems, different implementations have been used depending on the particular application. Thus, some authors utilize the COPASI package (Hoops et al., 2006) to simulate SBML models of biochemical networks, but other researchers consider Matlab codes or they define new frameworks (see for example *Bio-PEPA* Ciocchetta and Hillston (2009) or *CellExcite* Bartocci et al. (2008)). They neither allow reusing *a priori* defined SBML models without rewriting them nor allow the possibility of different levels of behavior changes.

In order to consider systems with acclimatization, we adapt the classical idea of hybrid systems by allowing different levels of mode changes. We consider mode changes associated with environmental condition variations that modify the system behavior and which change the form of the continuous models. We propose two modeling schemes to describe the extended hybrid systems, named *coefficient switches* and *strong switches*.

In a more theoretical perspective, our protocols also allow us to consider the general problem of *reconciliation of models* for a given process, where one needs to combine models and choose them dynamically according to some external input. We show through an example how reconciliation allows us to build models valid for more general conditions than those described by the original models separately.

These two schemes correspond to concrete cases encountered in model reuse. Acclimatization is often accompanied by physiologically expensive and perhaps irreversible morphological changes to the individual, and a strong switch corresponds to this commitment. Furthermore, in model reuse, it is important to recall that the existing models have been experimentally validated at considerable expense. Modifying the existing models to combine them results in a new model that must be revalidated. Using a coefficient or a strong switch, however, preserves the existing validated models, and the combined model intelligently chooses between them.

We illustrate our approach with two applications where acclimatization plays a key role. In the reconciliation of wine fermentation kinetics, fermenting yeast cells acclimatize its behavior to the amount of sugar and nitrogen. In the modeling of the osteo-adipo differentiation system, osteo-adipo precursor cells acclimatize to signals favoring specific cell lineages. Both applications show acclimatization changes with direct relevance in Biotechnology (winemaking industry) and in Biomedicine (study of bone mass disorders). From a modeling point of view, these applications involve combining complementary models that have previously been validated for specific environmental conditions, through strong switches (reconciliation of wine fermentation kinetics) and coefficient switches (osteo-adipo differentiation). The platform we use for simulating these applications is *BioRica*[2], which is specially adapted to simulate hybrid models, reuse and combine models.

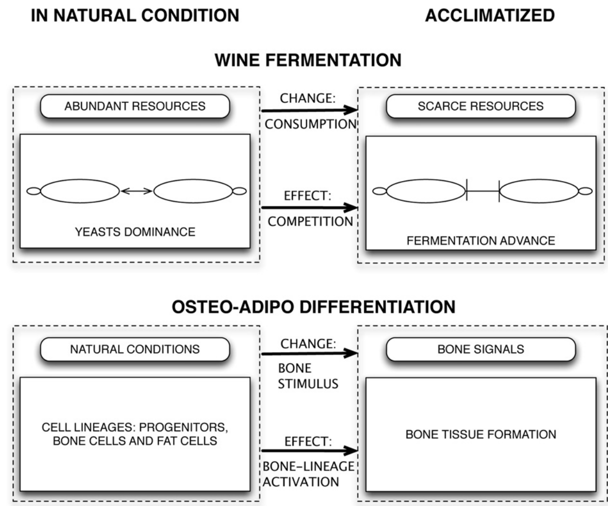

Fig. 1. Two study cases: Biological systems for wine fermentation kinetics and osteo-adipo differentiation. Systems acclimatize according to environmental conditions. When the resources are scarce yeasts compete and osteo-adipo precursor cells respond increasing osteoblasts for specific cell signals.

2. Basic notions of acclimatization and hybrid systems

2.1. Acclimatization

Acclimatization is the process in which morphological, behavioral, physical or biochemical traits are adjusted in response to environmental changes (Varela et al., 1974; Watts et al., 1975; Coles and Brown, 2003). Acclimatization occurs within the organism's lifetime, in contrast to *adaptation* (Williams, 1974), which is an evolutionary process. Acclimatization capacity is related top henotypic plasticity, that is the degree to which the organisms are able to acclimatize (Pigliucci et al., 2006).

To illustrate this phenomenon, environmental changes and acclimatization responses for two case studies treated in this article are shown in Fig. 1. In both of them, nutrient levels play an important role: organisms need to modify their function in order to survive with less nutrients (e.g. allostasis: Sterling et al., 1988; McEwen and Wingfield, 2003). As a result, competitive behavior between organisms or species is common when nutrients are scarce (case of fermenting yeast). From a cellular perspective, changes in environmental conditions can cause cellular stress and induce cell death. According to the organism's phenotypic plasticity, cells exhibit stress responses ranging from activating signaling pathways that promote survival to those that result in apoptosis that eliminates damaged cells (Fulda et al., 2010). Cells transmit and receive signals to stimulate differentiation into one lineage or another (case of osteo-adipo differentiation). Ideally, these signals respond to the organism's need of forming a specific tissue type. However, pathological states like cancer can also result when signals are anomalously propagated (Oberley et al., 1980; Vermeulen et al., 2008; van der Deen et al., 2011).

[1] HSCB 2009: http://www.eziobartocci.com/hscb/, HSB 2012: http://hsb2012.units.it/.

[2] http://biorica.gforge.inria.fr.