Bridging Qualitative and Quantitative Modeling of Complex Systems with FuzzX

Simone Spolaor[0000−0002−3383−367X]

Department of Informatics, Systems and Communication
University of Milano-Bicocca, Milan, Italy
simone.spolaor@disco.unimib.it

Abstract. The modeling of complex systems often has to deal with the presence of features emerging at multiple scales of complexity, and the availability of data in both qualitative and quantitative form. Correspondingly, many mathematical formalisms were developed to define either quantitative or qualitative models of such systems. Bridging the gap between these two worlds would allow to exploit the advantages provided by both approaches: however, to date the attempts in this direction were limited. A novel, general-purpose computational framework, named FuzzX, is here presented to address this limitation. FuzzX enables the analysis of hybrid models consisting in a quantitative (or mechanistic) and a qualitative module, reciprocally controlling each other's behavior. FuzzX leverages quantitative information about the system by means of a mechanistic module. At the same time, it describes the behavior of not fully characterized system components by exploiting fuzzy logic to define a qualitative module. FuzzX is here applied for the analysis of a hybrid model of a complex biochemical system, characterized by the presence of several feedback regulations. The results show that FuzzX can reproduce known emergent system behaviors, in normal and perturbed conditions.

Keywords: Complex systems · Fuzzy logic · Hybrid modeling.

1 Introduction

Complex systems show emergent dynamic behaviors that arise from the functional interactions among their components. In order to grasp the inner workings of such systems, researchers relied on mathematical modeling, bringing to significant breakthroughs in many fields of science [1]. In the last decades, a plethora of frameworks and mathematical formalisms have been developed to represent several characteristics of these systems. The resulting modeling approaches can be roughly partitioned into two categories: *quantitative* (or mechanistic) modeling and *qualitative* modeling [15]. Mechanistic models are regarded as the closest to the physical reality of the system under investigation, as they describe its inherent processes in detail. They exploit numerical data, and they feature the presence of parameters that control the system's dynamic behavior. Conversely, qualitative models are closer to human perception and natural language: their definition is based on qualitative data, and they describe the underlying physical phenomena in approximate terms. These two approaches have been separately used to address different problems [6, 15], while efforts in trying to bridge them have been limited to domain-specific applications [2]. However, complex systems often show features that could benefit from a description that simultaneously exploits both approaches. Thus, integrating uncertain and qualitative information with precise and quantitative data could result in the definition of more complete models, possibly uncovering unexpected or unknown emergent behaviors.

A novel framework named FuzzX (Fuzzy-mechanistic modeling of compleX systems) was presented in [13]. Designed for the definition and simulation of hybrid models, FuzzX integrates mechanistic and qualitative modules into a unified approach. In FuzzX, the mechanistic module can be defined by means of any fully parameterized modeling formalism, such as algebraic equations, ordinary differential equations (ODEs), Markov jump processes, etc. Any variable belonging to the mechanistic module can serve as input for the qualitative module, formalized as a fuzzy inference network [5], controlling either some variables or parameters of the mechanistic module. Exploiting a fuzzy module allows to define models with a higher degree of interpretability, thanks to the use of linguistic terms, and to exploit the flexibility of fuzzy sets to handle heterogeneous data. Moreover, FuzzX could be beneficial to analyze systems characterized by partial uncertainty about the underlying mechanisms, or to reduce the computational effort posed by detailed mechanistic models by mitigating their complexity. Examples of such applications include economics and finance models [8], cyber-physical systems [12], and biochemical reaction networks [9].

To show its advantages, FuzzX is here employed to redefine, as a hybrid model, a mechanistic model of a biochemical pathway characterized by non-linear behaviors arising from the presence of several feedback regulations among its components [4]. Although a part of the mechanistic interactions is substituted by a set of expert-defined fuzzy rules, the hybrid model can reproduce the emergent behaviors that were observed in the original model, such as the presence of a transient phase and the establishment of stable oscillations.

2 Methods

Let a hybrid model of a complex system Ω be formalized by specifying two elements: a *mechanistic module* $\mathcal{M}$ and a *fuzzy module* $\mathcal{F}$. The module $\mathcal{M} = \langle \mathcal{V}^{\mathtt{M}}, \theta^{\mathtt{M}}, \mathcal{P} \rangle$ consists in three disjoint sets corresponding to, respectively, the set of variables, the set of parameters and the set of mechanistic processes that govern the functioning of Ω. The module $\mathcal{F} = \langle \mathcal{V}^{\mathtt{F}}, \mathcal{R} \rangle$ consists in two disjoint sets corresponding to, respectively, the set of linguistic variables and the set of fuzzy rules. Notably, in FuzzX the *interface* of Ω is defined as the set $\mathcal{I} = (\mathcal{V}^{\mathtt{M}} \cap \mathcal{V}^{\mathtt{F}}) \cup (\theta^{\mathtt{M}} \cap \mathcal{V}^{\mathtt{F}})$. This interface allows the communication between the mechanistic and the fuzzy module, effectively resulting in the two modules af-

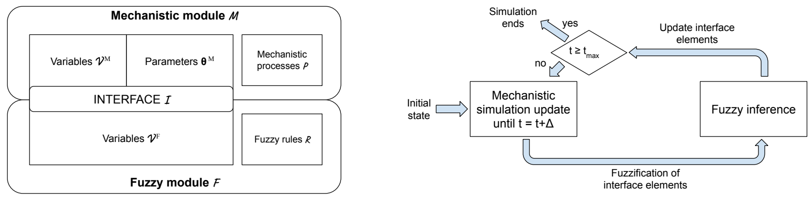

Fig. 1: Scheme of FuzzX framework (left) and its simulation procedure (right).

fecting each other's behavior. It should be noted that the module $\mathcal{M}$ treats the elements belonging to the interface as variables, if they belong to $\mathcal{V}^{\mathtt{M}} \cap \mathcal{V}^{\mathtt{F}}$, or as parameters, if they belong to $\theta^{\mathtt{M}} \cap \mathcal{V}^{\mathtt{F}}$. Conversely, the module $\mathcal{F}$ treats all elements of the interface as fuzzy variables. This allows the fuzzy module to effectively control its mechanistic counterpart, driving the overall dynamic behavior of the hybrid model and making FuzzX able to deal with complex systems that require the handling of both precise and uncertain data. Fig. 1, left side, shows a graphical schematization of the modules and the interface.

Let now $\mathcal{V}^{\mathtt{M}} = \{x_1^{\mathtt{M}}, \ldots, x_m^{\mathtt{M}}\}$ and $\mathcal{V}^{\mathtt{F}} = \{x_1^{\mathtt{F}}, \ldots, x_f^{\mathtt{F}}\}$ denote the elements in the sets of mechanistic and fuzzy variables, respectively. The variables in $\mathcal{V}^{\mathtt{M}}$ assume values in some given set $\mathcal{X}_M$, according to the mathematical formalism adopted to define the module $\mathcal{M}$, while the variables in $\mathcal{V}^{\mathtt{F}}$ assume values in $\mathbb{R}$. Additionally, let $\mathbf{X}^{\mathtt{M}}(t) = (x_1^{\mathtt{M}}(t), \ldots, x_m^{\mathtt{M}}(t))$ denote the state of the mechanistic module at time t, and $\mathbf{X}^{\mathtt{F}}(t) = (x_1^{\mathtt{F}}(t), \ldots, x_f^{\mathtt{F}}(t))$ denote the state of the fuzzy module at time t. These two vectors represent overall the state of the hybrid model describing Ω. The update of $\mathbf{X}^{\mathtt{M}}(t)$ and $\mathbf{X}^{\mathtt{F}}(t)$ is carried out by means of two functions, $U^{\mathtt{M}}$ and $U^{\mathtt{F}}$. $U^{\mathtt{M}} : \mathcal{X}_M^m \to \mathcal{X}_M^m$ maps the current state $\mathbf{X}^{\mathtt{M}}(t)$ of $\mathcal{M}$ into the state $\mathbf{X}^{\mathtt{M}}(t')$ at the next time step, taking into account the parameters in $\theta^{\mathtt{M}}$ and the mechanistic processes in $\mathcal{P}$. This function describes the temporal evolution of the processes present in $\mathcal{M}$, and can be evaluated by means of any computational method suitable for the formalism employed in the definition of $\mathcal{M}$ (*e.g.*, if $\mathcal{M}$ is formalized as a system of ODEs, $U^{\mathtt{M}}$ can be a numerical integration algorithm; if $\mathcal{M}$ is formalized as a reaction-based model, $U^{\mathtt{M}}$ can be a stochastic simulation algorithm). $U^{\mathtt{F}} : \mathbb{R}^f \to \mathbb{R}^f$ maps the current state $\mathbf{X}^{\mathtt{F}}(t)$ of $\mathcal{F}$ into the state $\mathbf{X}^{\mathtt{F}}(t')$ at the next time step, taking into account the fuzzy rules specified in $\mathcal{R}$. Thus, in FuzzX a simulation step of a hybrid model consists in the application of $U^{\mathtt{M}}$ to compute the dynamics of the mechanistic module, followed by the application of $U^{\mathtt{F}}$ to perform a fuzzy inference with the fuzzy network defined in the fuzzy module (see Fig. 1, right side). In particular, the dynamics of $\mathcal{M}$ is simulated by applying $U^{\mathtt{M}}$ for a user-defined time interval of length Δ, for some $\Delta \in \mathbb{R}^+$. The choice of Δ determines how often the two modules interact.

The application of both $U^{\mathtt{M}}$ and $U^{\mathtt{F}}$ on the elements belonging to the interface allows the two modules to communicate and exert their mutual regulation. Specifically, the value of an interface element $I \in \mathcal{V}^{\mathtt{M}} \subseteq \mathcal{I}$ is first updated by $U^{\mathtt{M}}$, and then fuzzified during the fuzzy inference operated by $U^{\mathtt{F}}$, affecting the dynamics of the fuzzy module; at the same time, an element $I \in \mathcal{I}$ can be updated by $U^{\mathtt{F}}$, thus modifying the values of variables and/or parameters of $\mathcal{M}$, and eventually affecting its dynamics during the next simulation step. A simulation ends when a user-defined time limit $t_{max} \in \mathbb{R}^+$ is reached, therefore lasting exactly $k = \lceil \frac{t_{max}}{\Delta} \rceil$ steps.

3 Results

To show its potentiality, FuzzX was tested on a hybrid model of a complex network of biochemical reactions. This network describes the Ras/cAMP/PKA pathway in the yeast *S. cerevisiae*, a cellular process involved in the regulation of metabolism and cell cycle [11]. This system is characterized by the presence of positive and negative feedback controls that ensure, under certain conditions, the establishment of stable oscillations in the dynamics of some essential proteins, such as Ras2-GTP. A thorough description of the pathway can be found in [4].

The hybrid model appearing in this work is a modified version of the original mechanistic model [4], which was formalized as a reaction-based model (RBM) [3] consisting of 39 reactions and 33 molecular species, and simulated by means of the Stochastic Simulation Algorithm (SSA) [7]. The mechanistic module of the hybrid model consists in the first 10 reactions of the original model, and its dynamics (*i.e.*, the implementation of $U^{\mathtt{M}}$) is obtained by means of SSA. The fuzzy module describes the feedback controls, it consists in a set $\mathcal{V}^{\mathtt{F}}$ of 8 linguistic variables and a set $\mathcal{R}$ of 16 fuzzy rules, adopting a 0-order Sugeno inference system [14]. The species Ras2-GTP belongs to $\mathcal{V}^{\mathtt{M}} \cap \mathcal{V}^{\mathtt{F}}$, and the 3 kinetic parameters controlling the strength of the feedback regulations belong to the set $\theta^{\mathtt{M}} \cap \mathcal{V}^{\mathtt{F}}$: together, these four elements constitute the interface $\mathcal{I}$ of the hybrid model. A complete description of the hybrid model can be found in [13].

Fig. 2 shows the effects of different values of Δ on the overall dynamics of the hybrid model, as shown in [13]. For small values of Δ (*e.g.*, smaller than 10, as in Fig. 2, left side) with respect to the scale of the phenomena modeled by the fuzzy rules, the dynamics present damped oscillations, slowly converging to a steady state. On the contrary, for larger values of Δ (*e.g.*, $\Delta \geq 10$, Fig. 2, right side), the hybrid model produces the stable oscillations characterizing the behavior of the system. Increasing values of Δ correspond to increased values of the frequency, phase and amplitude of the oscillations (see [13] for a complete analysis). As a matter of fact, since the firing of fuzzy rules is instantaneous, Δ must be chosen according to the temporal scale of the modeled phenomena. Small values of Δ could result in small modifications of the interface elements by $\mathcal{M}$, leading to the firing of the same subset of fuzzy rules at each iteration; large values of Δ imply longer intervals between the fuzzy inferences, decreasing the impact of the fuzzy regime on the dynamics. Therefore, Δ should be carefully chosen by the modeler, by comparing the resulting dynamics with respect to known behaviors of the system. In the case of the Ras/cAMP/PKA model, Δ was set to 10.

Following this analysis, several simulation of the hybrid model were carried out by perturbing elements of $\mathcal{M}$ or $\mathcal{F}$. The hybrid model was able to qualitatively reproduce most of the known behaviors of the system reported in [4], as shown

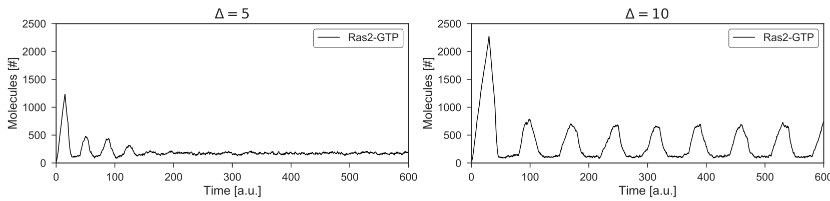

Fig. 2: Dynamics of Ras2-GTP with $\Delta = 5$ (left) or 10 (right).

in [13]. Worthy of note, the computational demand of the hybrid model is reduced: a single simulation with FuzzX is approximately $25\times$ faster than a single stochastic simulation of the original model. Altogether, these results highlight the advantages provided by FuzzX: the simplification of model complexity by means of fuzzy rules close to natural language, notably requiring a reduced number of free parameters; the possibility to run simulations of hybrid models, conveying both quantitative and qualitative information, exploiting a unified approach; the capability of hybrid models to reproduce known behaviours of the system and, once the model has been validated, to possibly predict unknown ones.

4 Conclusion

FuzzX is a novel framework for the modeling and simulation of complex systems that, for the first time, combines a module based on detailed processes and numerical data with one based on fuzzy logic. To test its effectiveness, FuzzX was employed for the definition and analysis of a hybrid model of the Ras/cAMP/PKA pathway in yeast. Provided that a suitable Δ is chosen, FuzzX was able to qualitatively reproduce known behaviors of the system, proving that an interface between mechanistic approaches and fuzzy logic can be a suitable and useful structure to model heterogeneous complex systems.

Notably, the definition of a fuzzy module requires less precise information with respect to a fully mechanistic model: this provides a cost-effective solution (in terms of number and accuracy of parameters) to the modeling of complex systems, allowing to reproduce and predict emergent behaviors even when mechanistic information is not fully available. Moreover, a hybrid approach can reduce the computational demand with respect to a fully mechanistic model. The flexibility of fuzzy sets and their ability to connect qualitative and quantitative data allow to define models that take into account heterogeneous components (*e.g.*, non-real-valued, spanning different orders of magnitude, having different units of measure). Thus, taking into account all these key points, FuzzX could be leveraged to facilitate the modeling of systems characterized by multiple scales of time, spatial and functional organization, as well as to revise and extend validated mechanistic models by describing mechanisms that are not fully characterized, possibly gaining new insights on the systems under investigation. In the future, I plan to apply FuzzX to analyze the repair of DNA double strand breaks in yeast [10], a phenomenon that is only partially characterized in mechanistic detail.

References

1. Bar-Yam, Y.: Dynamics of Complex Systems, vol. 213. Addison-Wesley Reading, MA (1997)
2. Berleant, D., Kuipers, B.J.: Qualitative and quantitative simulation: bridging the gap. Artificial Intelligence **95**(2), 215–255 (1997)
3. Besozzi, D.: Reaction-based models of biochemical networks. In: Beckmann, A., Bienvenu, L., Jonoska, N. (eds.) Pursuit of the Universal. 12th Conference on Computability in Europe, CiE 2016, Proceedings. LNCS, vol. 9709, pp. 24–34. Springer International Publishing, Switzerland (2016)
4. Besozzi, D., Cazzaniga, P., Pescini, D., Mauri, G., Colombo, S., Martegani, E.: The role of feedback control mechanisms on the establishment of oscillatory regimes in the Ras/cAMP/PKA pathway in *S. cerevisiae*. EURASIP Journal on Bioinformatics and Systems Biology **2012**(1), 10 (2012)
5. Cherkassky, V.: Fuzzy inference systems: a critical review. In: Computational Intelligence: Soft Computing and Fuzzy-Neuro Integration with Applications, pp. 177–197. Springer (1998)
6. Coyle, G.: Qualitative and quantitative modelling in system dynamics: some research questions. System Dynamics Review: The Journal of the System Dynamics Society **16**(3), 225–244 (2000)
7. Gillespie, D.T.: Exact stochastic simulation of coupled chemical reactions. The Journal of Physical Chemistry **81**(25), 2340–2361 (1977)
8. Hommes, C.H.: Heterogeneous agent models in economics and finance. Handbook of Computational Economics **2**, 1109–1186 (2006)
9. Karr, J.R., Sanghvi, J.C., Macklin, D.N., Gutschow, M.V., Jacobs, J.M., Bolival Jr, B., Assad-Garcia, N., Glass, J.I., Covert, M.W.: A whole-cell computational model predicts phenotype from genotype. Cell **150**(2), 389–401 (2012)
10. Khanna, K.K., Jackson, S.P.: DNA double-strand breaks: signaling, repair and the cancer connection. Nature Genetics **27**(3), 247 (2001)
11. Santangelo, G.: Glucose signaling in *Saccharomyces cerevisiae*. Microbiology and Molecular Biology Reviews **70**, 253–282 (2006)
12. Serpanos, D.: The cyber-physical systems revolution. Computer **51**(3), 70–73 (2018)
13. Spolaor, S., Nobile, M.S., Mauri, G., Cazzaniga, P., Besozzi, D.: Coupling mechanistic approaches and fuzzy logic to model and simulate complex systems. IEEE Transactions on Fuzzy Systems (2019)
14. Takagi, T., Sugeno, M.: Fuzzy identification of systems and its applications to modeling and control. IEEE Transactions on Systems, Man, and Cybernetics (1), 116–132 (1985)
15. Zadeh, L.A.: Outline of a new approach to the analysis of complex systems and decision processes. IEEE Transactions on Systems, Man, and Cybernetics (1), 28–44 (1973)