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Modeling Stochastic Switched Systems with BioRica

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Abstract *Modeling physycal and biological dynamic systems needs to combine different types of models in a non-ambiguous way. We present an approach to integrate continuous, discrete, stochastic, deterministic and non-deterministic elements by using Transition Systems theory, reuse, composition of models, and the framework BioRica. The systems are described by interacting continuous and discrete models, and in addition continuous models are decomposed into two components: controlled and controller model. We define Stochastic Switched Systems whose continuous dynamics is modeled by differential equations and its discrete dynamics by transition systems, allowing stochastic and non-deterministic behaviours. We illustrated the use of our approach with examples of intrinsically and approximated hybrid systems. Our approach allows us to give a first step to integrate and to extend models of complex systems, such as cell differentiation.*

Keywords Hybrid Systems, Transition Systems, Switched Systems, Cell differentiation.

1 Introduction

[1] Physical phenomena often are described by combinations of different types of equations. These systems are called *Hybrid systems* ([1], [2]) due to the use of continuous and discrete features or *Switched systems* because they switch its equations over time ([3], [4], [5]). Switched systems are a way to introduce discrete behavior into continuous models. They are Hybrid systems with discipline.

In *dynamic models*, one considers two groups of variables: dependent and factors. Models give the dynamics of the dependent variables, considering factors affecting it. One talks of *continuous model* if the variables change continuously over time and it is relevant to know the behaviour at any time. Continuous models use functional relations between the variables, being a common type the differential equations. On the other hand, if the variables make discrete changes at instantaneous points in time, the model is *discrete*. *Hybrid models* join both types of models: some variables have continuous dynamics while other ones have discrete dynamics. These models allow the interaction of diverse components of a system to contribute to complete descriptions of the behaviour. Switched systems are one kind of Hybrid system that restricts way discreteness is added. Discrete variables modify the behaviour of the continuous model by controlling its coefficients.

Models try to accurately represent the reality, by using empirical observations and knowledge. With limited observations one wants to build models that are valid to explain the system in general conditions without testing it on all the conditions. As result, models are strongly dependent of the studied conditions. In order to get most valued out of existing models and to refine models to include more complex behaviours, it is necessary to define how to compose models. A system is built in a hierarchical way, composed of subsystems, where behaviours emerge from the association of components and its diversity ([6]). Complex biological processes can, in this way, be defined by interactions between basic functional entities called *modules* ([7]) and, to explain its behaviour, to each module is associated a model that represents it.

The existence of different types of models to explain connected processes makes it necessary to define theory and tools to integrate them. Such theory must be able to unify processes with different timescales and whose models have different stiffness levels. Sometimes, to see the changes in the behaviour it is necessary to compare nearby times, but other times the changes happen in distant times. Equations with high stiffness require

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a superior level of discretization to obtain good approximations. Both characteristics, different timescales and stiffness affect computation times and accuracy. To compose models one must consider these characteristics, and be capable of giving an unique and non-ambiguous semantics to the composition. Modeling biological dynamic systems by composition requires a framework in which existing models of different types can be combined without need of rewriting them.

Many dynamic biological systems, such as physiological processes ([8]), are represented by ordinary differential equations ([9]). Changes in the environmental conditions modify the development of the processes, switching coefficients in its continuous dynamics. In Gene Regulatory Networks, some biological facts such as a gene is activated by a transcription factor or regulator give power to the idea of using switched models.

We can group the different approaches of Hybrid Systems in two kinds: *function* and *implementation* oriented. Function oriented approaches favor human comprehension of models, while implementation orientation focuses in descriptions easy to interpret by machines. In the first orientation, the dynamics of systems are defined by functions. Continuous dynamics is commonly represented by differential equations, and the discrete dynamics affects it by switching its equations ([3], [4], [5]). Systems are called *Switched System*. The models are easy to understand, but too restrictive with respect to the dynamics. Implementations oriented approaches present more general descriptions of Hybrid systems, by using an abstract representation to implement the model ([1], [2]). Models describe the rules of the dynamics allowing many types of continuous dynamics.

Here, we relax the concept of Switched Systems to allow possible stochastic or non-deterministic changes in the continuous dynamics. Such systems, called *Stochastic Switched Systems*, are described from function and implementation orientations using Transition Systems ([10], [11]). We analize Gene Regulatory Networks ([12]), by approximating them by Switched Systems. Our representation of the recent osteo-chondro differentiation model ([13]), as Stochastic Switched System composed by two interacting components, allows us to improve the differentiation stimuli models separately and so improve the complete model. We suggest some experiments to model the effect of the Wnt pathway on the bone formation (osteogenic lineage) and include it as stimulus.

To simulate Hybrid models we use *BioRica*, available in BioRica. It is a high-level modeling framework that integrates discrete, continuous, stochastic, non-deterministic and timed behaviors in a non-ambiguous way allowing multi-scale dynamics, composition of models and hierarchical relations. The modeling language is an extension of the AltaRica Dataflow language ([14]), allowing hybrid systems and stochastic behaviors.

2 Approach

2.1 Modeling

The dependent variables are called *state variables* (in analogy with Transition Systems), while continuous and discrete factors are considered *controllers*. These systems are described using a mixture of continuous, discrete dynamics and logical relations to allow multiple interacting components.

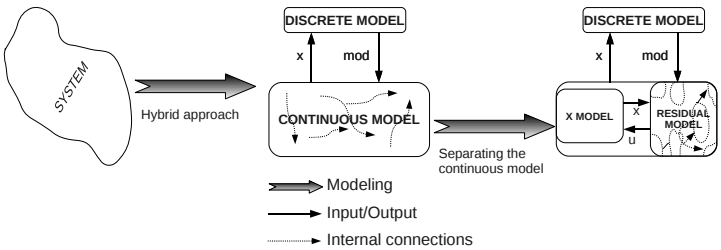

Figure 1. Modeling schema of Complex Biological Systems by Hybrid models. First it is identified the discrete and continuous interacting dynamics, then the continuous dynamics is separated into two interacting models: the *X MODEL* that describes the dynamics of X, and the residual model.

Let $x = (x_1, \ldots, x_n) \in \mathbb{R}^n$ be the *state variables* of the model. The variables $u = (u_1, \ldots, u_k) \in \mathbb{R}^k$ are the continuous control variables, and mod are the discrete controllers (Figure Fig. 1). We consider that the

dynamics of state variables is modeled by ordinary differential equations (explicit representation, equation 1) including continuous and discrete variables.

$$\dot{x}(t) = F(x(t), u(t), mod(t)) \tag{1}$$

The continuous dynamics is given by the changes in x over time, with F a function from $\mathbb{R}^n \times \mathbb{R}^k \times M$ to $\mathbb{R}^n$. The discrete dynamics is given by the evolution of the *mode* variable denoted $mod \in M$, where M is a finite or enumerable set and we denote $M = \{1, \ldots, M\}$ by identification of its elements.

The next step is to define how the discrete variables mod evolve over time. By considering hybrid systems as switches between continuous systems, represented by sets of differential equations, one talks of *Switched systems* and *Switched models* ([3], [4], [5]). Independent of x, the value of the right hand side function F changes as a function of the value of discrete variable mod (equation 1) that affects the form of the equations. We will say that changes in discrete variables values carry *switches* between model configurations.

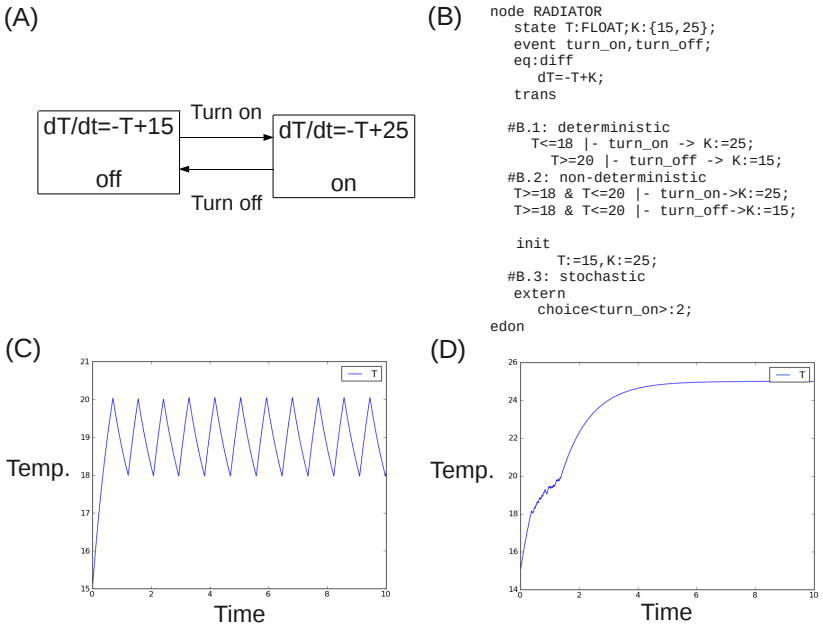

Figure 2. The radiator. (A)Schema of the Switched system. (B)Three models. (B.1) deterministic: it is turned on if $T \leq 18°C$ and turned off if $T \geq 20°C$, (B.2) non-deterministic: both events can happen if $18 \leq T \leq 20$, and (B.3) stochastic: turn on with probability $\frac{2}{3}$. (C)Temperature dynamics for (B.1), (D) For (B.3).

An example of Switched System is the behaviour of a radiator that controls the temperature (T) of a room (Fig. 2). A thermostat is activated when the temperature is detected to be low and it is regulated, if the temperature is high the system is turned off. This behaviour can be modeled in different ways: deterministic, non-deterministic or stochastic.

2.2 Composing Models

The act of building a model that is made of two or more modules is called *Composition*. The composition of two models is the model that explains the behaviour of both interacting modules. This allows us to the model to learn and to integrate knowledge of diverse types. The model can be extended and improved by introducing new modules that relate different functions. To be capable of describing the behaviour of a biological system over time, one needs to combine different types of models in a non-ambiguous way. A good implementation of this concept is essential to take advantage of the modularity of biological systems to build accurate and complete models. It must be sufficiently flexible to be capable of joining modules defined with different types of models, and reuse modules that have been *a priori* defined.

Our approach is based on the use of a global semantics to compose interacting modules. Flow conections and synchronizations allow to connect modules. Local clocks and solvers allow us to consider diverse types of dynamics.

The BioRica semantics is based on the automata semantics of AltaRica ([10], [14]), and Stochastic Transition Systems ([11]) that allow the inclusion of randomness and non-determinism. Given a BioRica node, one computes the probability of the state dynamics and considers non-deterministic decisions solved by random schedulers. The resulting semantics it is preserved with respect to flow relations and event syncronizations.

An important fact we approach here is that different processes have different timescales and stiffness levels. The use of modules solves in part this problem: each module has an specific timescale and discretization level. With this strategy, we improve the precision and the cumputation time. The processes with small timescales are observed at small time steps, while in case of long timescales we use longer time steps to reduce the number of simulations. So, if the equations solved by a module are stiff one uses small time intervals only at that module.

We implement models with these considerations in BioRica. A common specification of Systems Biology models is SBML ([15]), maybe the most popular abstraction for biochemical reactions models governed by temporal differential equations. Our framework includes a SBML parser that translates SBML models into BioRica models. So, it is possible to reuse and compose models previously specified in SBML to obtain more general models.

2.3 Stochastic Switched Systems

Our approach mixes both point of view of Hybrid Systems: function and implementation oriented. It is adapted to Hybrid models whose continuous dynamics is represented by differential equation systems, but we give more flexibility to the discrete dynamics allowing not only deterministic behaviours. We give function and implementation oriented descriptions of such systems.

The system dynamics is represented by transitions between different states. The interpretation of a model as dynamic entity, with possible changes on its form, turns it into a *Transition Systems* ([10]) with two types of transitions: state transitions and mode transitions. The state transitions are internal and controlled by the continuous dynamics of the model. The mode transitions are transitions in the sense of Transition Systems theory and they can be deterministic, non-deterministic or stochastic. The transitions can be modeled with stochastic components or including non-determinism to allow different behaviours (Fig. 2).

In the general theory of Stochastic Transition Systems ([11]) the transitions have possible stochastic behaviours. Given an action producing a transition, in this case a mode change, the next mode is randomly chosen according to transition probabilities if they exist. We will call *Stochastic Switched Systems* the extension of Switched systems that allows stochastic or non-deterministic transitions between modes. We consider two randomness sources: the moment (time) at which happens the action of changing mode, and the new mode that is chosen. The conditions that provoke the mode transitions are called *guards*. They are boolean formulas defined over state variables, external controllers and modes values. For each mode i, the mode transition arriving to i corresponds to an event (action in Transition Systems theory, [10] and [11]). In the radiator example (Fig. 2(B.1)), $T \leq 18$ is a guard condition provoking that event $turn\_on$ assigns the value 25 to the mode variable K.

We formally define a Stochastic Switched System as a hybrid system whose model is given by the equations 2-5. The first one defines the continuous dynamics and 3,4,5 the discrete dynamics at any time t. We denote $P(ev|(x(t), u(t), mod(t))$ the probability of choosing the event ev when the values of the state variables x are $x(t)$, the values of the continuous control variables u are $u(t)$ and the value of the mode variable mod is $mod(t)$, $time((x(t), u(t), mod(t)), ev)$ denotes the delay time of the event ev that is modeled to have distribution

$Dist_{ev}\{p_{event,1}, \ldots, p_{event,m}\}$.

$$\dot{x}(t) = F_{mod(t)}(x(t), u(t)), \tag{2}$$

$$P(ev|(x(t), u(t), mod(t)) = \frac{w_{ev}}{\sum_{e \in A(x(t),u(t),mod(t))} w_e}, \tag{3}$$

$$time((x(t), u(t), mod(t)), ev) \sim Dist_{ev}\{p_{event,1}, \ldots, p_{event,m}\}, \tag{4}$$

where w_e is the probability weight assigned to the event e, and $A(x(t), u(t), mod(t))$ is the set of available actions when x takes the value $x(t)$, u the values $u(t)$ and the mode variable m the value $mod(t))$ given by the equation 5.

$$A(x(t), u(t), mod(t)) = \{ev \in EVENTS : G_{ev}(x(t), u(t), mod(t)) = TRUE\}\ , \tag{5}$$

and $EVENTS$ is the set of events of the system (in Fig. 2 $EVENTS = \{turn\_on, turn\_off\}$).

Non-determinism appears with the presence of two or more available actions given a tuple $\langle (x(t), u(t), mod(t)) \rangle$. We simulate non-deterministic systems by using *random schedulers* with weights given by the external directives *choice*, so the event $turn\_on$ has probability $\frac{2}{3}$ for the non-deterministic radiator (Fig. 2(B.3)). The time delays can be stochastic, with $law < ev >: Dist\_ev\{pev\_1, \ldots, pev\_m\}$ denoting that the time delay of the event ev has distribution $Dist_{ev}\{pev_1, \ldots, pev_m\}$ with parameters $\{pev_1, \ldots, pev_m\}$. Between the possible distributions we include T (a deterministic time T), the Gaussian distribution $Normal\{\mu, \sigma\}$, the exponential distribution $Exponential\{r\}$ with r the rate and the uniform with parameters a, b $(a < b)$ $Uniform\{a, b\}$.

In the radiator example (Fig. 2), the simpler model is to consider a deterministic behaviour of the thermostat, where at any temperature at most one mode transition is observed: the radiator can be or active or not. For this model, it is obtained by considering the temperature of activation lower than the temperature where the radiator is turned off (18 and 20 respectively, Fig. 2(B.1)). With more ambiguous guard rules, given a temperature the radiator is accepted to be activated and turned off. This non-deterministic behaviour is obtained in case of activation if temperature is between 18 and 20 and deactivation if it is in the same interval (Fig. 2(B.2)).

2.4 BioRica Description of Stochastic Switched Systems

We represent and simulate Stochastic Switched Systems with BioRica. BioRica uses automata theory to represent *Stochastic Switched Systems* as a particular type of Hybrid Automaton ([1], [2]) where the continuous dynamics is given by differential equations. The continuous dynamics (equation 3) is described in *eqdiff* while the discrete one (equations 4 and 5) is described by transitions that change the form of the model.

In Fig. 2 is defined the BioRica node *RADIATOR*, with state variable T (temperature) and mode K. The possible events are defined with the keyword *event*, $turn\_on$ and $turn\_off$, and its effect is described in *trans*: $turn\_on$ provokes the assignment $K := 25$ when $T \leq 18$, $turn\_off$ assigns $K := 15$ if $T \geq 20$. With the keyword *eqdiff* one codes a set of differential equations, where $dxi = fi(x1, \ldots, xn, \_u1, ..., \_uk, mod)$ means that the rate of change of xi with respect to the time is equal to $fi(x1, \ldots, xn, \_u1, ..., \_uk, mod)$. In *init*, one defines the initial values of the variables. It is possible to define constant, $const$, and formula expressions, $formula$, to use in the equations.

In cases of non deterministic behaviours, BioRica decides what event select considering an aleatory decision between the possible events with weights given in the *choice* option of *extern*. In Fig. 2(B.3) the event *turn on* has weight 2, then at arriving to temperatures between 18 and 20 it selects the event *turn on* (activate the radiator) with probability $\frac{2}{3}$ and *turn off* with probability $\frac{1}{3}$. The keyword *extern* allows the inclusion of external directives about distributions of event delays and priority between events.

To decompose the dynamics we use the ideas of Fig. 1. With the keyword *flow*, one includes inputs (outputs) from (to) other BioRica nodes. Continuous and discrete dynamics can be modeled separately, the node *MAIN* represents the complete system and the keyword *sub* is used to define instances of other node (Fig. 3).

3 Application: Approximating Regulatory Systems by Stochastic Switched Systems

The dynamics of the radiator (Fig. 2) is hybrid in its nature because the switches are directly associated to the value of the mode. So, the mode K of the radiator is a piecewise-constant function. In less restrictive cases, where one identifies different underlying behaviours, we can use Switched Systems too. One can choose a set of factors to consider as *piecewise-order k* and approximate them to obtain a Switched model. A particular case is given by the regulation models with reduced Hill functions.

3.1 Reducing Hill Functions

Hill functions [16] are sigmoidal curves used to measure the continuous influence of an element on a target, depending on the concentration of the affecting element x, an exponent m to control the curve steepness, and on the mean point of influence θ. We denoted $h^+(x,\theta,m) = \frac{x^m}{x^m+\theta^m}$ the positive influence and $h^-(x,\theta,m) = 1 - h^+(x,\theta,m)$ the negative influence.

Dynamics systems with interacting elements often generate differential equation systems with Hill functions. The solution of such differential equation systems, equations 7-9 in case of the osteo-chondro cell differentiation model, can be complicate and use high computation times. More influence relations more difficult to solve the system. To simplify them, we reduce them into switched systems choosing some influence functions to be represented with piecewise-dependent behaviours. Thus, the system dynamics is obtained from the interaction of continuous and discrete dynamics.

Here, we show two reductions of the Hill functions: Piecewise-constant and Piecewise-linear approximation. The first idea is considering Hill function as step functions. It is to say, piecewise-constant functions to be 0 when x is lower or equal than the threshold θ and 1 after this threshold. With this simplification, the model moves between different modes in function of how high or low are the concentrations x with respect to the thresholds θ. The thresholds divide the state variables space into cuboids, each one with an associated system of equations. Despite one obtains information of the system behaviour by looking the form of the equations in each cuboid of the state spaces, the observations are only qualitative.

The second reduction of Hill functions is the Piecewise-linear approximation, in which the transition between 0 and 1 is smoothed by a linear function. It is to say, we use the approximation of equation 6 below:

$$h^+(x,\theta,m) \approx l^+(x,\theta_1,\theta_2) = \begin{cases} 0 \text{ if } x \leq \theta_1 \\ \frac{x-\theta_1}{\theta_2-\theta_1} \text{ if } \theta_1 < x < \theta_2 \\ 1 \text{ if } x \geq \theta_2 \end{cases} \tag{6}$$

With this second alternative, the switched system transits between a big set of modes according to how high are the mRNA concentrations compared with the thresholds θ_1 and θ_2 of each influence function.

3.2 An Osteo-chondro Differentiation Model

An application of Gene Regulatory Networks is cell differentiation modeling. Each possible differentiation of a cell is associated to the mRNA concentration of an specific gene. Here we use the model of Schittler *et al.* ([13]) to differentiate progenitor cells into osteoblasts (bone cells) or chondrocytes (cartilage cells). They are considered two mutually inhibiting genes, so called the *osteo-chondro switch*, one associated to the osteogenic differentiation (*Runx2*) and another (*Sox9*) to the chondrogenic option. A third gene (*Tweak*) is associated with the progenitor maintenance role that inhibits both genes of the osteo-chondro switch. The mRNA concentration associated to the progenitor state is denoted x_P, the mRNA concentration of the osteogenic state is denoted x_O and the associated to the chondrogenic differentiation is denoted x_C. To incorporate the external pro-differentiation, pro-osteogenic and pro-chondrogenic stimulus are included three inputs: z_D, z_O and z_C with positive value. The increase of any differentiation stimulus provokes an increase of the expression of the

```
const n=2;ap=0.2;bp=0.5;mp=10;cpp=0.1;kp=0.1;ao=0.1;ac=0.1;bo=1;
const n=2;ap=0.2;bp=0.5;mp=10;cpp=0.1;kp=0.1;ao=0.1;ac=0.1;bo=1;
const bc=1;mo=1;mc=1;coo=0.1;ccc=0.1;coc=0.1;cco=0.1;cop=0.5;
const ccp=0.5;ko=0.1;kc=0.1;

node DIFF
      state xp,xo,xc:FLOAT;
      flow zd,zo,zc:[0,1]:in;
      eqdiff
            dxp=(ap*xp^n+bp)/(mp+zd+cpp*xp^n)-kp*xp;
            dxo=(ao*xo^n+bo+zo)/(mo+coo*xo^n+coc*xc^n+cop*xp^n)
                  -ko*xo;
            dxc=(ac*xc^n+bc+zc)/(mc+ccc*xc^n+cco*xo^n+ccp*xp^n)
                  -kc*xc;
      init
            xp:=12,xo:=0,xc:=0;
edon

node STIMULUS
      state _zd,_zo,_zc:FLOAT;on_d,on_o,on_c:BOOL;
      flow zd,zo,zc:FLOAT:out;
      event to_diff,to_osteo,to_chondro;
      trans
            on_d=False |-to_diff -> _zd=1,on_d=True;
            on_o=False |-to_osteo -> _zo=0.8,on_o=True;
            on_c=False |-to_chondro -> _zc=0.8,on_c=True;
      init
       _zd:=0,_zo=0,_zc=0,on_d:=False,ond_o=False,on_c=False;
      extern
            law<to_diff>:Exponential{0.01};
            law<to_osteo>:Exponential{0.002};
            law<to_chondro>:Exponential{0.001};
      assert
            zd=_zd;
            zo=_zo;
            zc=_zc;
edon
node MAIN
      sub
            S:STIMULUS;
            D:DIFF;
      assert
            D.zd=S.zd;
            D.zo=S.zo;
            D.zc=S.zc;
edon
```

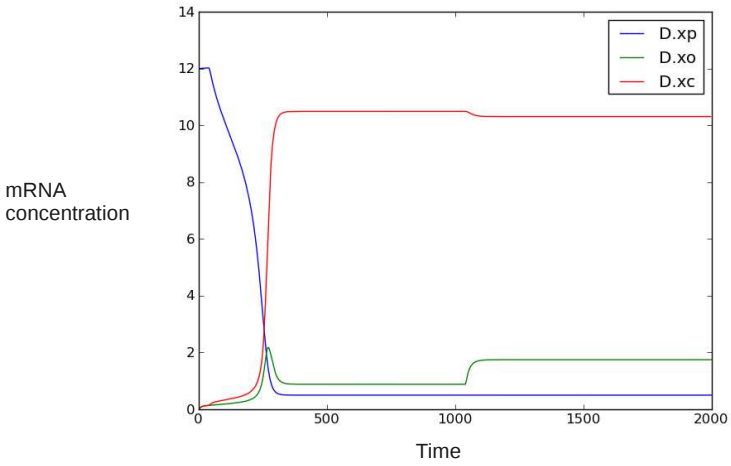

Figure 3. BioRica code and simulation of an osteo-chondro differentiation model ([13]). The pro-differentiation stimulus happens at time exponential with rate 0.01 (expected value $E(t) = 100$), the pro-osteogenic stimulus happens with rate 0.002 ($E(t) = 500$) and the pro-chondrogenic with $E(t) = 1000$.

associated gene. The model is given by the equations 7-9 above.

$$\dot{x}_P(t) = \frac{a_P \cdot x_P^n + b_P}{m_P + z_D + c_{PP} \cdot x_P^n} - k_P \cdot x_P, \tag{7}$$

$$\dot{x}_O(t) = \frac{a_O \cdot x_O^n + b_O + z_O}{m_O + c_{OO} \cdot x_O^n + c_{OC} \cdot x_C^n + c_{OP} \cdot x_P^n} - k_O \cdot x_O, \tag{8}$$

$$\dot{x}_C(t) = \frac{a_C \cdot x_C^n + b_C + z_C}{m_C + c_{CC} \cdot x_C^n + c_{CO} \cdot x_O^n + c_{CP} \cdot x_P^n} - k_C \cdot x_C, \tag{9}$$

with $n = 2$, $a_P = 0.2$, $b_P = 0.5$, $m_P = 10$, $c_{PP} = 0.1$, $k_P = 0.1$, $a_O = a_C = 0.1$, $b_O = b_C = 1$, $m_O = m_C = 1$, $c_{OO} = c_{CC} = c_{OC} = c_{CO} = 0.1$, $c_{OP} = c_{CP} = 0.5$, $k_O = k_C = 0.1$ known parameters.

We obtain the same results for the scenarios analyzed in [13], but the BioRica representation gives flexibility to the model. In Fig. 3 we considered another scenario, where pro-differentiation, pro-osteogenic and pro-chondrogenic stimulus happen with exponential probabilities over time (a Poisson process). The system corresponds to a strict Stochastic Switched System, in which delay times have random behaviours.

Since we separate between stimulus (node *STIMULUS*) and differentiation dynamics (*DIFF*), to specify each differentiation stimulus one needs only to modify such a node. The dynamics of *STIMULUS* controls the lineage decision by switching the values of the z coefficients, and depends on external factors. A factor that affects the lineage decision is the activation of the Wnt/$\beta-$catenin pathway. Since *Runx2* is a Wnt target gene, the accumulation of $\beta-$catenin in the nucleus stimulates the expression of *Runx2*, and consequently favors the bone formation ([17]). One can include this effect, on the synamics of z_0, by measuring the concentration of nuclear $\beta-$catenin over time and using *LiCl* to activate the pathway.

4 Conclusions and Discussion

We used the theory of Stochastic Transition Systems ([10] and [11]) to define an special type of Hybrid System: Stochastic Switched System (section 2.3). The model is formed by the continuous dynamics of the state variables, given by differential equations, and the discrete dynamics of the modes that change over time to transform the differential equations. We allow stochastic and non deterministic behaviours, and implemented such systems using BioRica.

We defined the osteo-chondro cell differentiation model in [13] as a Stochastic Switched System by composing *STIMULUS* and *DIFF* (differentiation) components giving more flexibility to extensions. As example, stimulis are considered with aleatory behaviour. By considering the activation of the Wnt/$\beta-$catenin pathway as factor of bone formation and measuring its effect, it is possible to improve the model.

We defined a non-ambiguous way to describe a complex system by decomposing it into different types of interacting models. Behaviour laws change over time, which is modeled by discrete changes of mode variables that transform the continuous dynamics, and complex processes are modeled by composing diverse models with flow connections and synchronization of events. Our approach allows us to reuse SBML specified models and exploits modular properties of systems, which can be separated into modules in function of the type of process and its timescale, and the complexity or type of model.

Acknowledgements

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