Simulating signalling pathways through BioWays

Davide Chiarugi [1] Moreno Falaschi[2] Diana Hermith[3]

Dip. Scienze Matematiche e Informatiche
Università degli Studi di Siena. Italy.

Michell Guzman[4]

Escuela de Ingeniería de Sistemas y Computación.
Universidad del Valle Cali. Colombia.

Carlos Olarte[5]

Departamento de Electrónica y Ciencias de la Computación.
Universidad Javeriana Cali. Colombia.

Abstract

We report on a technique for modelling biological systems based on the `ntcc` calculus, a model of concurrency where systems are specified by means of constraints (i.e., formulae in logic). We show that the ability of `ntcc` to express partial information, concurrency, non-determinism and timed behaviour allows us to neatly model and simulate biochemical reactions networks. Based on this technique, we introduce BioWays, a software tool for the quantitative modelling and analysis of biological systems. We show the applicability of the tool in the context of two well studied biological systems: the glycogen breakdown pathway and the HIV life cycle.

Keywords: Signaling pathways, Concurrent Constraint Programming, biological systems.

[1] Email: chiarugi3@unisi.it
[2] Email: moreno.falaschi@unisi.it
[3] Email: diana.hermith@unisi.it
[4] Email: michell.guzman@correounivalle.edu.co
[5] Email: carlosolarte@javerianacali.edu.co

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1 Introduction

Computational biology aims at using the typical methods of computer science for integrating the existing knowledge concerning individual genes, proteins and molecules and to investigate the behaviour and relationships among the various elements composing a biological system. A technique widely used in computational biology consists in the construction of executable models (EMs) [16] describing the studied systems as computer programs. EMs are typically specified through formal languages based either on process algebras (e.g. [10,12,11,14,3]) or other formalisms such as logic [9] or rewriting logic [15], constraint programming [21,13] or Petri nets [7]. These models can be used for analysing either static, qualitative properties of biological systems [8] or their quantitative, dynamical behaviour. In the latter case, for taking into account dynamical aspects, the evolution of the model is driven by algorithms that, given the state of the system at one initial time t_0, allow to compute the state of the system at a subsequent time t. Depending on the chosen algorithm the model results to be stochastic or deterministic.

Recently there has been a significant interest in (executable) discrete stochastic (DS) models of biological systems, mainly because experimental data are providing evidences that stochasticity arising at the molecular level plays an important role in determining the overall behaviour of living organisms [29]. In DS models the evolution of the system is driven by a stochastic algorithm which computes the probability of state transitions according to given probability density functions (PDFs). Biochemical reactions are often modelled through DS approaches, typically following the proposal of some authors (e.g. Bartholomay[4]) that consists in describing the reaction system in hand as a discrete-state continuous-time Markov process (DCMP). Gillespie's Stochastic Simulation Algorithm (SSA) [18], based on previous proposals (e.g. [4]), is the most widespread algorithm used for implementing DS simulations of biological systems. Gillespie's SSA requires that some hypotheses are satisfied, namely solutions are well stirred and in thermal equilibrium and, more importantly, it holds only for elementary chemical reactions i.e. those reactions occurring in one reactive event. Even though it has ben shown that the SSA can work besides the prescribed scope of applicability as proved by the success of various stochastic models against experimental data, it is difficult to describe biochemical systems in terms of elementary reactions: often there is an incomplete knowledge of the full set of elementary reactions and mesoscopic or macroscopic transformations are the only observable ones. Most commonly this problem is circumvented abstracting away the not observable elementary steps, lumping them in a single reaction event modelled as a single "Markov jump" with the waiting time τ sampled from a negative exponential distribution depending on an overall rate constant. However abstractions usu-

ally introduce approximations in the behaviour of the models whose impact is not easy to evaluate or estimate, as noticed by Gillespie in [30] for enzymatically catalysed reactions. One crucial point in this abstraction approach concerns the modelling of the time needed for a reaction to occur: even though the elementary reactions underlying a given biochemical process can be modelled as a DCMP (and, thus, with waiting times distributed according to a negative exponential PDF) on a mesoscopic or macroscopic scale the process may exhibit different dynamics such as non-Markovian behaviours, as pointed out also in [24] and [10] and shown by various experimental evidences, e.g. [33]. These arguments suggest the need of proposing modelling approaches embedding a more general notion of transition times allowing to describe the observed time courses of biological phenomena without subsuming a memoryless process. Various approaches have been proposed for addressing this issue. The work in [7] proposes an extension for Petri Nets and in [24] for the Beta Workbench in which transition times can be sampled from non-exponential PDFs. BioPEPAd [10] allows to add deterministic delays to the duration of a reaction.

In this paper we propose an approach based on the `ntcc` calculus [26], a temporal extension of CCP [31], designed for specifying and verifying timed and reactive systems. In particular we report on BioWays, a PHP based application designed for specifying and executing `ntcc` models of biological systems. As we shall show, `ntcc` offers several advantages in the modelling of biochemical reaction systems. (1) the timed nature of the calculus allows us to faithfully model *temporal information about interactions* (e.g., whether an unexpected interaction actually happens), *information about the temporal occurrence of an event* (e.g., when a binding occurs), and *information about the relative velocities of reactions* (e.g., the duration of an interaction) thus allowing to take into account non-markovian dynamics. (2) Constraints in `ntcc` provide a compact representation of the *state of the system*, (e.g., the concentration of the components along the time). (3) `ntcc` models can be seen as executable: `ntcc` processes can be straightforwardly executed and the evolution of the system can be observed. Finally, (4) the `ntcc` calculus is equipped with an underlying temporal logic that allows to formally specify and verify properties of the model. Through two working examples we will show how our framework can be used for modelling biological systems. The use of `ntcc` for modelling biological systems was proposed also by other authors (see e.g., [2,20,1]). The contribution of this paper is twofold: on the one hand we present a systematic discussion of the main features that makes `ntcc` suitable for modelling biological systems; on the other hand we present a working software designed for simulating biological phenomena enjoying the features of the `ntcc` based approach.

The rest of the paper is structured as follows: In Section 2 we present

the timed constraint language that we use for modelling. In Section 3 we present our software tool (BioWays) on two examples (the glycogen breakdown pathway and the HIV life cycle). Section 4 draws some conclusions.

2 Timed Concurrent Constraint Programming

Process calculi such as CCS and the π-calculus among several others have arisen as mathematical formalisms to model and reason about concurrent systems. They treat concurrent processes much like the λ-calculus treats computable functions. They then provide a language in which the structure of terms represents the structure of processes together with an operational semantics to represent computational steps.

In this paper we shall use as modelling language Concurrent Constraint Programming (CCP) [31], a model for concurrency that combines the traditional operational view of process calculi with a declarative view based on logic. This allows CCP to benefit from the large set of reasoning techniques of both process calculi and logic [31,26].

Agents in CCP *interact* with each other by *telling* and *asking* information represented as *constraints* to a global store. Constraints (e.g., $x > 42$) can be thought of as formulae in a first-order language and they represent (partial) information about the variables of the system. Partial must be understood here as the fact that constraints do not necessarily determine completely the values of the variables.

The basic constructs in CCP are the tell agent $\mathbf{tell}(c)$ that adds the constraint c (via logical conjunction) to the store, thus making it available to the other processes; and the *ask* process $\mathbf{when}\ c\ \mathbf{do}\ P$ that queries if the current store d can entail (deduce) the guard c, written $d \models c$; if so, it behaves like P. Otherwise it remains blocked until more information is added. This way, ask processes define a synchronisation mechanism based on entailment of constraints.

CCP features also constructs for declaring local variables as in $(\mathbf{local}\, x)\, P$ and for executing processes in parallel as in $P \parallel Q$.

The `ntcc` calculus [26] extends CCP with the notion of discrete time-units to model timed and reactive systems. Roughly speaking, a CCP-like process is executed in a time-unit. When the resting point is reached, i.e., no further evolution is possible, the store is output and a new time-unit is created to later execute the continuation of the process. In order to specify when a process must be executed, the CCP language of processes is extended with operators such as $\mathbf{next}\, P$ that delays the execution of P one time-unit; $!\, P$ that executes P in all the time-units; and $\mathbf{unless}\ c\ \mathbf{next}\, P$ that executes P in the next time-unit if c cannot be deduced from the store. Furthermore, `ntcc`

introduces non-deterministic choices of the form $\sum_{i \in I} \mathbf{when}\ c_i\ \mathbf{do}\ P_i$ where one P_i is chosen for execution if the guard c_i can be entailed from the store. When this happens, the other alternatives are precluded from execution.

The notion of constraint and the language of processes in `ntcc` are expressive enough to specify the biological behaviour we are interested in modelling:

- Quantitative information can be naturally expressed by means of constraints. For instance $x > y$ states that the concentration of x is greater than that of y.
- Constraints provide also an elegant mechanism to represent partial information. For instance, $x > 42$ gives some information regarding the concentration of x but it does not give a specific value for it. This can be helpful when some components of the system are not well known or we do not have enough quantitative information about them.
- Synchronisation of ask processes via constraint entailment allows us to trigger actions when some information can be derived from the system. For instance, it is natural to express in the language that a given reaction occurs only when certain component is present in the system.
- The ability of CCP to compose models (i.e., components) by parallel composition leads to a robust modelling strategy: we can study separately components of a system and then, observe the behaviour of the whole system.
- Timed operators as $\mathbf{next}\, P$ allows us to describe actions (more precisely reaction in the biological context) that can take several time-units to be completed.
- Furthermore, since `ntcc` is a model of concurrency, we can use several reasoning techniques to reason about the models we build. For instance, operational and denotational semantics, model checking techniques and logical interpretation of processes [26].

2.1 BioWays: a `ntcc` model of biochemical reactions

The tool that we propose here models biological systems by means of a set of stoichiometric equations of the form

$$a_1X_1 + ...a_nX_n \dashrightarrow b_1Y_1... + b_mY_m \tag{1}$$

The constants $a_1, ..., a_n$ and $b_1, ..., b_m$ are the stoichiometric coefficients. Therefore, $a_1X_1, a_2X_2, ..., a_nX_n$ are reactants that interact (and are consumed) yielding to the products $b_1Y_1, b_2Y_2, ..., b_mY_m$.

In order to represent the reaction above, we model in `ntcc` each type of

molecule as a variable (e.g., X_i) and Equation (1) as the process

$$\begin{aligned}\texttt{eq-proc} = \textbf{when } X_1 \geq a_1 \wedge ... \wedge X_n \geq a_n \textbf{ do} \\ \textbf{next}\,{}^{(t)}\textbf{tell}(Y_1 = Y_1' + b_1 \wedge ... \wedge Y_m = Y_m' + b_m) \parallel \\ \textbf{next}\,\textbf{tell}(X_1 = X_1' - a_1 \wedge ... \wedge X_n = X_n' - a_n)\end{aligned}$$

Intuitively, when the reactants are available, they are consumed and the right hand components are produced t time units later. Hence, the kinetic parameter t allows us to represent the speed of reactions.

Assume now a set of n stoichiometric equations. We need a process that chooses one of the reaction to occur at a given time-unit. This can be done by composing each process $\texttt{eq-proc}_i$ in a non-deterministic choice of the form:

$$\sum_{i \in 1..n} \texttt{eq-proc}_i$$

If the propensity of each reaction to occur is available, we replace the non-deterministic choice with a probabilistic one. Then, reactions are chosen by following the assigned probabilities.

Summing up, in BioWays it is possible to express two important features of biochemical reactions: the propensity (i.e. the probability of occurring) and the duration, i.e. the time steps needed for the products to appear in the system.

The model as a runnable specification

Processes in `ntcc` can be seen as runnable specifications of a system: the model can be directly simulated by using the operational semantics (SOS) of the calculus. The SOS dictates how processes evolve along time units. For instance, a process $\textbf{tell}(c)$ evolves into **skip** (the inactive process) by adding c to the current store d:

$$\text{R}_{\text{TELL}}\ \frac{}{\langle \textbf{tell}(c), d\rangle \longrightarrow \langle \textbf{skip}, d \wedge c\rangle}$$

Similarly, for the rest of the processes. The reader may refer [26] for a complete description of SOS rules of `ntcc`.

Following the operational rules of the calculus, we built an interpreter of `ntcc` on top of the Mozart programming language (http://www.mozart-oz.org/). Central to this implementation is the Mozart abstraction *computation spaces* (CS). A CS is a constraint store where multiple threads can access (concurrently) the shared variables and impose constraints on them. In Mozart, different constraint systems are available. Here we used the Finite Domain Constraint System (FD). In FD variables are assumed to range over finite

domains and, in addition to equality, we may have predicates that restrict the possible values of a variable to some finite set as in $x > y$. We thus model `ntcc` processes as threads that post and query constraint in the CS until a resting point is reached. When this happens, we output the final store that contains the information about the variables of the model. This gives a simple way to "execute" the `ntcc` model and observe the behaviour of the modelled system in each time-unit.

In order to make available the tool on internet, we embedded the `ntcc` interpreter into Bioways, a PHP based application freely available at `http://escher.puj.edu.co/~michellrad/bioways_web/`. Users can build models of biological systems in Bioways through a wizard that comprises the following steps:

(i) System's variables: Define the reacting species and their initial amount.

(ii) System's reactions: Define the type of reaction that describes how molecules interact.

(iii) Propensity of reactions: Define the probability of each reaction to occur.

(iv) Duration of reactions: Define the duration of each type of interaction.

(v) Number of time-units: Define the total time of the simulation (time steps) for generating and simulating the system.

The following section presents two examples of the use of Bioways in the modelling of biological systems.

3 Modeling

In this section we outline the use of our toolkit through the specification and simulation of two well studied biological scenarios: (*i*) the signaling pathway leading to the *glycogen* breakdown into *glucose 1-phosphate*, and (*ii*) the life cycle of HIV (Human immunodeficiency virus).

3.1 The glycogen breakdown pathway: A model of intracellular processes

In higher organisms such as mammals glycogen is stored in the liver as a reservoir of glucose. When the concentration of glucose in the blood is low the α cells of the pancreas secrete glucagon, a polypeptidic hormone which triggers the process of glycogen breakdown (Glycogenolysis). This process is started by the interaction of glucagon with its receptor expressed by liver cells [6]. Once the glucagon receptor embedded in the cell membrane binds its ligand, it activates a signal transduction pathway inside the cell leading to a glycogenolysis. More precisely, the signal transduction system for the glycogen degradation pathway is modular and is made of three type of proteins: *(i)* a receptor, *(ii)* a transducer, and *(iii)* an effector. Glucagon recog-

nises and binds to its receptor causing an allosteric change [17]. Responding to this structural modification, the transducer (a G-Protein – *Guanine nucleotide-binding protein*– located in the inner side of the cell membrane) interacts with the hormone-receptor complex stimulating a reaction in which a GDP (*Guanosine diphosphate*) molecule bound to the G-Protein is replaced by GTP (*Guanosine-5'-triphosphate*). This reaction activates the G-Protein, which then interacts with the effector, the enzyme adenylyl cyclase. This protein catalyses the conversion of ATP (*Adenosine-5'-triphosphate*) to $cAMP$ (*Cyclic adenosine monophosphate*), an intracellular second messenger. Thus, the binding of glucagon at the cell-surface stimulates the synthesis of a second messenger inside the cell, which in turn stimulates a metabolic response (see Figure 1). The first interaction triggers a cascade of biochemical reactions in a signal transduction pathway through the activation of G-Proteins [6].

We apply a compositional approach to model the signalling pathway above by adding iteratively biochemical interactions. This is particularly straightforward in our framework: new information can be added to the system by posting constraints and the subsystems can be easily composed by sharing variables. Compositionality allows to build complex biological models combining partial information coming from different sources. This result is certainly more difficult to achieve, for example, in models based on ordinary differential equations (ODE) because the large number of parameters needed and, in general, ODE are not compositional. On the contrary, the idea of partial information represented as constraints makes CCP appropriate for this aim.

Note that our technique allows the description of a biological scenario at different levels of abstraction. For example, in a previous work [21] based on our method we considered the interactions between the transmembrane receptor and G-Proteins in three different environments (extracellular, transmembrane, and intracellular). Now, we expand this perspective by zooming into the intracellular domain with the aim to analyse the system's behaviour at this level. This should allow us to gain a better understanding of the system dynamics in response to the presence or absence of the ligand molecule.

We described the glycogen breakdown pathway through a set of algebraic equations resembling [13,21]. In this way we obtained a simple description of the system by means of a stoichiometric-like formulation of the reactions. We considered the actions of binding, dissociation, complex formation, and transfer of molecule groups.

When taking into account a biochemical system we emphasise on the interactions between different species during time. The occurrence of reactions during a time unit, expressed by their reaction rates, sets the behaviour of the system. Our representation allows to compute the current concentration of the components according to the concentration of them in the previous time unit. Additionally, we can set a parameter t that stands the duration for the

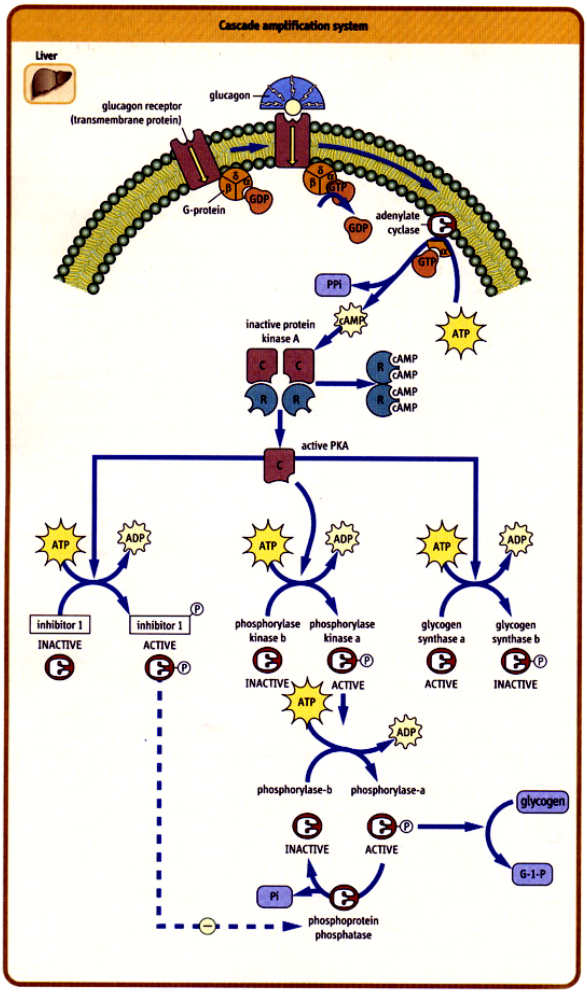


Fig. 1. A reaction pathway for the glycogen breakdown. Taken from [5,23].

reaction to occur. Furthermore, we can assign a probabilistic execution for the reactions (in the examples presented here we assume the same probability for each reaction).

We then have a simple and scalable representation of the system based on a set of biochemical reactions involving a single transition between reactants and products, with rate constants for each reaction and initial concentrations of each species. Given the fact that we are setting a system of coupled reactions into a concurrent constraint approach, as a first approximation we were able to explore the system under different initial conditions comparable with the literature. Information about rate constants and the amount of system molecules were obtained from literature (see for instance [25,34]). The complete set of this parameters is reported in Appendix B as well as the full specification of the model.

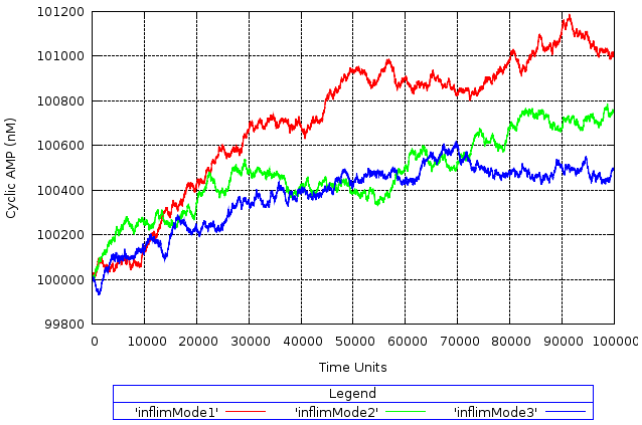
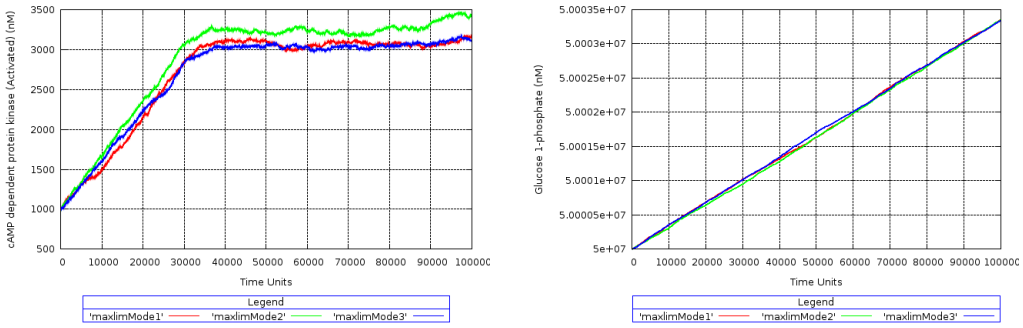


Fig. 2. Temporal trace of $cAMP$ involved in the glycogen breakdown cascade. Can be observed an increased formation of $cAMP$ in presence of lower values of concentrations and rate constants, particularly in terms of the extracellular *ligand*. (For further details about the different 'modes' or configurations used for simulations, please see B in Appendix)

Our simulations show that the behaviour of our model is consistent with that of the real counterpart. In particular, in liver cells, in response to the hormone *glucagon*, the transmembrane protein *adenylyl cyclase* is stimulated and catalyses the conversion of ATP into $cAMP$, an intracellular second messenger (For further details, see Figure B.1 in Appendix). This step of the signal transduction pathway is called an amplification process of the signal given that a small amount of glucagon is capable to produce an increased amount of $cAMP$ (see Figure 2).

Throughout the signal cascade, $cAMP$ is capable to activate the enzyme *protein kinase A* (*cAMP dependent protein kinase (cAPK)*). Thus, it is observed high levels of $cAPK$ in the system (see Figure 3a). This environment is a requirement for the activation of others intracellular signalling molecules (see EQ8-EQ12.1 in Figure B.1) and to promote the degradation of *glycogen* into molecules of *glucose 1-phosphate* (see Figure 3b). Therefore, the processing of information from the external environment to the intracellular medium, starts at the level of the cell membrane through the binding of the hormone glucagon to its respective receptor in a 'physical interaction' followed by a set of biochemical reactions (transduction pathway) in which the initial stimulus is greatly amplified.

Our representation of the interactions is in agreement with [32]: the following enzymes must be both present and available for activation: *glycogen phosphorylase kinase* and *glycogen phosphorylase*, as well as *protein kinase A* must be available for activation by $cAMP$. The enzyme *adenylyl cyclase* must be present according with [27]. In line with [32,27] in almost all species the activity of *glycogen synthase* increases rapidly while *glycogen phosphorylase* remains low, and the ratio of the active forms of *glycogen phosphorylase* and *glycogen synthase* might be of major importance in the regulation of metabolism. Our



(a) (b)

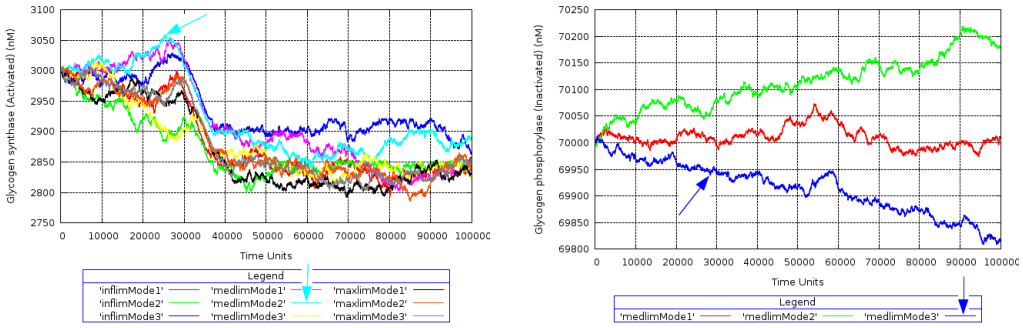
Fig. 3. 3a Temporal trace for enzyme *protein kinase A* (*cAMP dependent protein kinase (cAPK)*) and 3b *glucose 1-phosphate*.

simulations (see Figure 4) reproduce this behaviour: enzyme *glycogen synthase* (activated) increases in an overshoot and after decreases and remains in a constant level (see Figure 4a) especially when is taken the configuration 'medlimMode2' to perform the simulations (see Figure B.4, B.5 in Appendix) where the mid values of concentrations and rate constants of the molecules and reactions in the network are taken. While *glycogen phosphorylase* (inactivated) decreases to lower levels of concentration (see Figure 4b) when is taken the configuration 'medlimMode3' to perform the simulations (see Figure B.5, B.6 in Appendix). Moreover we can notice that the ratio and behaviour of the inactive/active forms of *glycogen phosphorylase* and *glycogen synthase* affects not only the degradation of *glycogen* to *glucose 1-phosphate* (the active form of the *glycogen phosphorylase* degrades *glycogen*, see EQ11-11.1 in B.6) but also the *glycogen* synthesis (the active form of *glycogen synthase* catalyzes the formation of *glycogen* polymers, see EQ12-12.1 in B.6).

These results allow to gain some insight in the regulation of glycogenolysis by using a toolkit that permits the observation of the system when parameters are adjusted, built on a powerful model for concurrency that allows the specification of reactive systems where: *i)* the environment reacts continuously with the system; *ii)* the system evolves in discrete time units; *iii)* some components may not be fully specified (partial information); and *iv)* the components can react accordingly to stochastic laws.

3.2 The HIV life cycle: A representation based on biochemical interactions

Since the discovery of the human immunodeficiency virus (HIV), the etiologic agent of the acquired immune deficiency syndrome (AIDS), scientists have focused in understanding the dynamics and details of the HIV life cycle in order to develop efficient antiviral therapies. In the context of computational biology the dynamics of cell-virus interactions have traditionally been investigated through both ODEs and EMs. In the latter case the proposed modelling



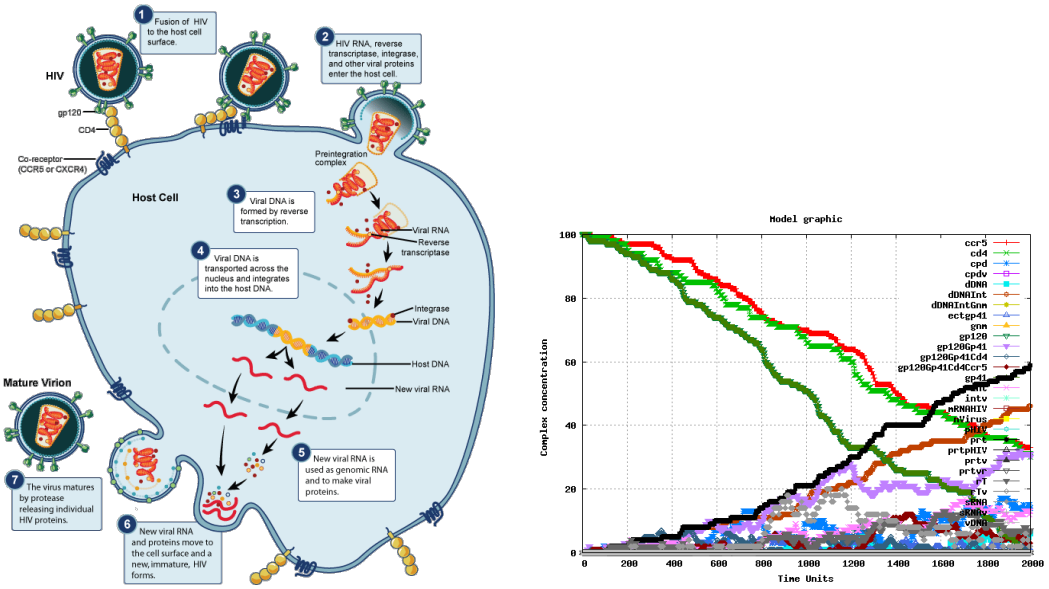
(a) (b)

Fig. 4. 4a Temporal trace for proteins *glycogen synthase* (active form) and 4b *glycogen phosphorylase* (inactive form).

approaches mainly focus on membrane interactions as e.g. in [11]. We will instead use BioWays for building a model of the HIV infection cycle shifting the focus on quantitative issues. Our aim is to track the time course of a set of molecules during the various steps of the infection cycle. Our investigation is driven by well known experimental observations describing the progression throughout the infection cycle as conditioned by the presence of certain molecules in each phase. In other words, each stage of the infection cycle is characterised by a precise set of molecules which are necessary for bootstrapping the following step. Our interest in modelling the timing of this process reflects one research strategy in drug discovery, aiming at blocking the infection cycle by interfering with the bootstrapping molecules. Our framework results particularly suited for our purpose. Indeed, we enjoyed the parallel composition of `ntcc` to progressively build our model integrating information coming from different sources, as well as the possibility of specifying explicitly the duration of each reaction. The various steps of the HIV infection process can be described as follows (see [19] for a detailed description and Figure 5a):

- Binding and Fusion: HIV binds to a specific receptor (CD4) and one of two co-receptors on the surface of a CD4+ T-lymphocyte and fuses with the host cell releasing its RNA genome.
- Reverse Transcription: reverse transcriptase converts the single-stranded HIV RNA to double-stranded HIV DNA.
- Integration: the HIV DNA enters the host cell's nucleus where it may remain inactive producing few or no new copies of HIV.
- Assembly: new virus particles are assembled in the host cell.
- Budding: the newly assembled virus pushes out ("buds") from the host cell.

Using BioWays we described the interactions amongst the molecules of both the virus and the host cell involved in the infection cycle, specifying for each reaction its duration and the initial amount of reactants. The equation com-



(a) (b)

Fig. 5. 5a Steps of the replication [28] and 5b the time course of molecules concentration involved in the HIV life cycle.

posing the model and the chosen parameters are reported in the Appendix A. Simulating the model we obtained the time course of the modelled molecules during the life cycle. A sketch of the obtained results is reported in Figure 5b.

Analysing the outputs of our simulations, we correctly identified a set of molecules whose presence is a necessary condition for proceeding throughout each step of the infection cycle. Consistently with experimental data, for instance, we found that in our model the presence of the complex $[gp120]gp41$ is necessary for both the Binding and Fusion and the Budding phases. Interestingly, drugs called Fusion Inhibitors, such as Maraviroc, block the fusion phase interfering with the binding of the host-cell co-receptor $ccr5$ and the complex $[[gp120]gp41]cd4$ thus avoiding the HIV life cycle to continue.

4 Conclusions and future work

We have defined a technique based on a Temporal extension of Concurrent Constraint Programming (CCP) for modelling biological systems that allows to represent straightforwardly transition times and incomplete information. In this paper we have presented also a software tool (BioWays) for modelling and analysis of biochemical interaction networks. Through two working examples we have shown how our method can be used for gaining insights on the dynamics of biological phenomena.

We are currently developing an extension of our toolkit allowing to manage also stochastic waiting times distributed according with non-exponential

probability distribution functions. This should allow to describe a larger set of biological scenarios.

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A HIV infection cycle

The HIV infection cycle comprises the follows phases:

The process of fusion.	$1gp120 + 1gp41 \rightarrow 1[gp120]gp41$ $1[gp120]gp41 + 1cd4 \rightarrow 1[[gp120]gp41]cd4$ $1[[gp120]gp41]cd4 + 1ccr5 \rightarrow 1[[[gp120]gp41]cd4]ccr5$ $1[[[gp120]gp41]cd4]ccr5 \rightarrow 1ectgp41$
The process of reverse transcription and integration.	$1ectgp41 \rightarrow 2cpd$ $1cpd \rightarrow 1rT + 1int + 1prt$ $1cpd \rightarrow 2sRNA$ $2sRNA + 1rT \rightarrow 1dDNA$ $1dADN + 1int \rightarrow 1[dADN]int$
The process of transcription.	$1[dDNA]int + 1gnm \rightarrow 1[[dDNA]int]gnm$ $1[[dDNA]int]gnm \rightarrow 1vDNA$ $1vDNA \rightarrow 1mRNAHIV$
The process of transduction, division, assembly and releasing.	$1mRNAHIV \rightarrow 1pVIH$ $1prt + 1pVIH \rightarrow 1[prt]pVIH$ $1[prt]pVIH \rightarrow 4prtv$ $1prtv \rightarrow 1rTv$ $1prtv \rightarrow 1prtvr$ $1prtv \rightarrow 1intv$ $1prtv \rightarrow 2sARNv$ $1rTv + 1prtvr + 1intv \rightarrow 1cpdv$ $2sARNv \rightarrow 1cpdv$ $2cpdv \rightarrow 1nVirus$

In the simulation, the rates were all set to one, all reactions have the same probability to occur, the initial concentration are 100 copies for $ccr5$, $cd4$, $gp120$, $gp41$, and 0 for complexes.

B Glycogen breakdown pathway: the model in detail

Here we present a more detailed description of the simulation parameters and the input data such as the kinetic constants for the reactions, the molar concentration of the species and the encoding in the BioWays software tool. For each mode of simulation, is used the lower, medium and upper limit of the molar concentration of each variable as well as for the kinetic constant of the reactions according with the available scientific literature.

Variables			Variables definition	Variables encoding	Biochemical equations
$R_{glcgn}[G_\alpha GDP]$			GPCR-transmembrane glucagon receptor-G_α subunit	rgp:recept_gprotein	**EQ1:** $R_{glcgn}[G_\alpha GDP]+L_{glcgn} \rightleftharpoons R_{glcgn}[G_\alpha GTP]L_{glcgn}$
[200]nM	[350]nM	[500]nM			
L_{glcgn}			Ligand (glucagon)	l:ligand	**EQ2:** $R_{glcgn}[G_\alpha GTP]L_{glcgn} \rightleftharpoons G_\alpha GTP + R_{glcgn}L_{glcgn}$
[1]nM	[500]nM	[1000]nM			
$R_{glcgn}[G_\alpha GTP]L_{glcgn}$			GPCR-G protein-Ligand Complex	rgtpl:recpt_gtp_ligand	**EQ3:** $G_\alpha GTP + GAP \rightleftharpoons [G_\alpha GTP]GAP \xrightarrow{k_{hydr}} G_\alpha GDP + GAP + P_i$
[200]nM	[350]nM	[500]nM			
$G_\alpha GTP$			G protein	gtp:gAlpha_GTP	**EQ4:** $G_\alpha GDP + R_{glcgn} \rightleftharpoons R_{glcgn}[G_\alpha GDP]$
[200]nM	[1400]nM	[3000]nM			
$R_{glcgn}L_{glcgn}$			Ligand Receptor complex	o:receptor_ligand	**EQ5:** $R_{glcgn}L_{glcgn} \rightleftharpoons R_{glcgn} + L_{glcgn}$
[1]nM	[250]nM	[500]nM			
GAP			GTP hydrolysis enzyme	g:gap	**EQ6:** $G_\alpha GTP + AC \rightleftharpoons AC[G_\alpha GTP]$
[10]nM	[145]nM	[300]nM			
$[G_\alpha GTP]GAP$			Complex of GTP hydrolysis	h:gtp_hydrolysis	$AC[G_\alpha GTP]+ATP \rightleftharpoons$ **EQ7:** $[AC[G_\alpha GTP]]ATP \longrightarrow cAMP + 2P_i + AC[G_\alpha GTP]$
[200]nM	[250]nM	[300]nM			
$G_\alpha GDP$			G protein	gdp:gAlpha_GDP	**EQ8:** $4cAMP + 2cAPK_{inact} \rightleftharpoons 2cAPK_{act}$
[200]nM	[1400]nM	[3000]nM			
R_{glcgn}			GPCR-transmembrane glucagon receptor	ir:receptor_inact	**EQ9:** $cAPK_{act} + GPK_{inact} \rightleftharpoons [cAPK_{act}GPK_{inact}]$
[1]nM	[250]nM	[500]nM			
AC			Adenylate cyclase enzyme	ac:aden_cycl	**EQ9.1:** $[cAPK_{act}GPK_{inact}]+ATP \xrightarrow{k_3} (GPK-P)_{act} + ADP + cAPK_{act}$
[1]nM	[250]nM	[500]nM			
$AC[G_\alpha GTP]$			Complex of AC enzyme and G protein	acgp:aden_cycl_gtp	**EQ10:** $(GPK-P)_{act} + GP_{inact} \rightleftharpoons [(GPK-P)_{act}GP_{inact}]$
[200]nM	[350]nM	[500]nM			
ATP			Adenosine triphosphate	atp:atp	**EQ10.1:** $[(GPK-P)_{act}GP_{inact}]+ATP \xrightarrow{k_4} (GP-P)_{act} + ADP + (GPK-P)_{act}$
[4000]nM	[4000]nM	[4000]nM			
$[AC[G_\alpha GTP]]ATP$			Complex of AC enzyme, G protein and ATP	acgpatp: aden_cycl_gtp_atp	**EQ11:** $(GP-P)_{act} + Glycogen \rightleftharpoons (GP-P)_{act}Glycogen$
[200]nM	[350]nM	[500]nM			
$cAMP$			Cyclic AMP	camp:cyclic_amp	**EQ11.1:** $(GP-P)_{act}Glycogen + P_i \longrightarrow Glucose1-P + (GP-P)_{act}$
[100.000]nM	[450.000]nM	[1'000.000]nM			
P_i			Inorganic phosphorus	p:inor_phosp	**EQ12:** $(GPK-P)_{act} + cAPK_{act} + GS_{act} \rightleftharpoons [cAPK_{act}GS_{act}(GPK-P)_{act}]$
[4000]nM	[4000]nM	[4000]nM			
$cAPK_{inact}$			cAMP dependent protein kinase (Inactivated)	capki:cAPK_inact	**EQ12.1:** $[cAPK_{act}GS_{act}(GPK-P)_{act}]+ATP \xrightarrow{k_5} (GS-P)_{inact} + ADP + cAPK_{act} + (GPK-P)_{act}$
[1000]nM	[1000]nM	[1000]nM			

Fig. B.1. A model of the control system of the intracellular processes in the signaling pathway of the glycogen breakdown (Part1)

$cAPK_{act}$			cAMP dependent protein kinase (Activated)	capka:cAPK_act
[1000]nM	[1000]nM	[1000]nM		
GPK_{inact}			Glycogen phosphorylase kinase (Inactivated)	gpki:gpk_inact
[3000]nM	[3000]nM	[3000]nM		
$[cAPK_{act}GPK_{inact}]$			Complex $cAPK_{act}GPK_{inact}$	agpk:cAPKa_GPKi
[2000]nM	[2000]nM	2000]nM		
$(GPK-P)_{act}$			Phosphorylate glycogen phosphorylase kinase	gpkp:gpk_P_act
[3000]nM	[3000]nM	[3000]nM		
ADP			Adenosine diphosphate	adp:adp
[4000]nM	[4000]nM	[4000]nM		
GP_{inact}			Glycogen phosphorylase (Inactivated)	gpi:glyc_phosp_inact
[70.000]nM	[70.000]nM	[70.000]nM		
$[(GPK-P)_{act}GP_{inact}]$			Complex glycogen phosphorylase kinase- glycogen phosphorylase	gpkpi:gpkp_gp
[3000]nM	[3000]nM	[3000]nM		
$(GP-P)_{act}$			Glycogen phosphorylase (Activated)	gpa: glyc_phosp_act
[70.000]nM	[70.000]nM	[70.000]nM		
$Glycogen$			Glycogen	glyc:glyc
[50.000.000]nM	[50.000.000]nM	[50.000.000]nM		
$(GP-P)_{act}Glycogen$			Complex Glycogen phosphorylase - glycogen	gpaglyc: glyc_phosp_act_glyc
[70.000]nM	[70.000]nM	[70.000]nM		
$Glu\cos e1-P$			Glucose 1-phosphate	gluc:gluc_1_phosp
[50.000.000]nM	[50.000.000]nM	[50.000.000]nM		

GS_{act}			Glycogen synthase (Activated)	gsa:glyc_synt_act
[3000]nM	[3000]nM	[3000]nM		
$[cAPK_{act}GS_{act}(GPK-P)_{act}]$			Complex protein kinase glycogen synthase	pkgs:prot_kin_glyc_synt
[1000]nM	[1000]nM	[1000]nM		
$(GS-P)_{inact}$			Glycogen synthase (Inactivated)	gsi:glyc_synt_inact
[3000]nM	[3000]nM	[3000]nM		

Fig. B.2. A model of the control system of the intracellular processes in the signaling pathway of the glycogen breakdown (Part2)

Concentration of variables (nM) : GPCRs (Receptor and AC): [1-500:[ ]$_{InfLim}$=1; [ ]$_{MedLim}$=250; [ ]$_{MaxLim}$=500],
$R[G_\alpha GDP]$ & $AC[G_\alpha GTP]$: [200-500: [ ]$_{InfLim}$=200; [ ]$_{MedLim}$=350; [ ]$_{MaxLim}$=500], P_i **&ATP&ADP:** [4000],
G-proteins: [200-3000:[ ]$_{InfLim}$=200; [ ]$_{MedLim}$=1400; [ ]$_{MaxLim}$=3000], $[AC[G_\alpha GTP]]ATP$ **:** [200-500: [ ]$_{InfLim}$=200; [ ]$_{MedLim}$=350; [ ]$_{MaxLim}$=500],
$R[G_\alpha GTP]L$ **:** [200-500: [ ]$_{InfLim}$=200; [ ]$_{MedLim}$=350; [ ]$_{MaxLim}$=500], **GAP:** [10-300: [ ]$_{InfLim}$=10; [ ]$_{MedLim}$=145, [ ]$_{MaxLim}$=300],
$[G_\alpha GTP]GAP$:[200-300: [ ]$_{InfLim}$ =200; [ ]$_{MedLim}$ =250; [ ]$_{MaxLim}$=300],
cAMP*[15]:** [100000-1000000: [ ]$_{InfLim}$=100000; [ ]$_{MedLim}$=450000; [ ]$_{MaxLim}$=1000000], ***cAPK*$_{inact,act}$[16]:** [1000], ***GPK*$_{inact}^*$:** [3000], **[*cAPK*$_{act}$*GPK*$_{inact}$]:** [2000], (GPK-P***)$_{act}^*$**:** [3000], (***GP***)$_{inact}^*$**:** [70000], [(***GPK-P***)$_{act}$(***GP***)$_{inact}$]: [3000], (***GP-P***)$_{act}^*$**:** [70000], ***Glycogen**:** [50000000], (***GP-P***)$_{act}$ ***Glycogen*:** [70000], ***Glucose1-P**:** [50000000], ***GS*$_{act}^*$:** [3000], $[cAPK_{act}GS_{act}(GPK-P)_{act}]$ **:** [1000], (***GS-P***)$_{inact}^*$**:** [3000], L [17]**:** [1-1000:[ ]$_{InfLim}$=1; [ ]$_{MedLim}$=500; [ ]$_{MaxLim}$=1000],
Receptor-Ligand: [1-500:[ ]$_{InfLim}$=1; [ ]$_{MedLim}$=250; [ ]$_{MaxLim}$=500]
Time Simulation: 1'000.000 (time-units)

MODE 1		
Duration of the reaction (time-units) Rate constants (sec^{-1})	**Biochemical equations**	**Equations encoding**
Activation of the receptor and G-protein unkown rates = 1	**EQ1:** $R_{glcgn}[G_\alpha GDP]+L_{glcgn} \rightleftharpoons R_{glcgn}[G_\alpha GTP]L_{glcgn}$	eq1:1 = rgp:~1 l:~1 rgtpl:1; eq2:1 = rgtpl:~1 l:1 rgp:1;
Dissociation of G-protein from the ligand unkown rates = 1	**EQ2:** $R_{glcgn}[G_\alpha GTP]L_{glcgn} \rightleftharpoons G_\alpha GTP + R_{glcgn}L_{glcgn}$	eq3:1 = rgtpl:~1 gtp:1 o:1; eq4:1 = gtp:~1 o:~1 rgtpl:1;

GAP-driven GTPase
unkown rates = 1
 	
$k_{hydr} = 1$
	EQ3:
	$G_\alpha GTP + GAP \rightleftharpoons [G_\alpha GTP]GAP \xrightarrow{k_{hydr}} G_\alpha GDP + GAP + P_i$
		eq5:1 = gtp:~1 g:~1 h:1;
		eq6:1 = h:~1 g:1 gtp:1;
		eq7:1 = h:~1 gdp:1 g:1 p:1;

G-protein inactive bound to the receptor unkown rates = 1	**EQ4:** $G_\alpha GDP + R_{glcgn} \rightleftharpoons R_{glcgn}[G_\alpha GDP]$	eq8:1 = gdp:~1 ir:~1 rgp:1; eq9:1 = rgp:~1 ir:1 gdp:1;
Dissociation of the ligand from the receptor unkown rates = 1	**EQ5:** $R_{glcgn}L_{glcgn} \rightleftharpoons R_{glcgn} + L_{glcgn}$	eq10:1 = o:~1 ir:1 l:1; eq11:1 = l:~1 ir:~1 o:1;
Association of G-protein activated to the enzyme adenylate cyclase (AC) unkown rates = 1	**EQ6:** $G_\alpha GTP + AC \rightleftharpoons AC[G_\alpha GTP]$	eq12:1 = gtp:~1 ac:~1 acgp:1; eq13:1 = acgp:~1 ac:1 gtp:1;

Production of *cyclic AMP* (*cAMP*)
 	
unkown rates = 1
	EQ7:
	$AC[G_\alpha GTP] + ATP \rightleftharpoons$
	$[AC[G_\alpha GTP]]ATP \longrightarrow$
	$cAMP + 2P_i + AC[G_\alpha GTP]$
		eq14:1 = acgp:~1 atp:~1 acgpatp:1;
		eq15:1 = acgpatp:~1 atp:1 acgp:1;
		eq16:1 = acgpatp:~1 camp:1 p:2 acgp:1;

Activation of *cAMP dependent protein kinase* (*cAPK*) unkown rates = 1	**EQ8:** $4cAMP + 2cAPK_{inact} \rightleftharpoons 2cAPK_{act}$	eq17:1 = camp:~4 capki:~2 capka:2; eq18:1 = capka:~2 capki:2 camp:4;
Phosphorylation of glycogen phosphorylase kinase (GPK) unkown rates = 1, $k_3 = 2^*$	**EQ9:** $cAPK_{act} + GPK_{inact} \rightleftharpoons [cAPK_{act}GPK_{inact}]$	eq19:1 = capka:~1 gpki:~1 agpk:1; eq20:1 = agpk:~1 gpki:1 capka:1;
	EQ9.1: $[cAPK_{act}GPK_{inact}] + ATP \xrightarrow{k_3} (GPK-P)_{act} + ADP + cAPK_{act}$	eq21:2 = agpk:~1 atp:~1 gpkp:1 adp:1 capka:1;

Fig. B.3. A model of the control system of the intracellular processes in the signaling pathway of the glycogen breakdown (Part3) . Some of the parameters taken from $(15,+)$[22], $(16,*)$[25], (17)[34]

Phosphorylation of glycogen phosphorylase (GP) unkown rates = 1, $k_5 = 2^*$	**EQ10:** $(GPK-P)_{act} + GP_{inact} \rightleftharpoons [(GPK-P)_{act} GP_{inact}]$	eq22:1 = gpkp:~1 gpi:~1 gpkpi:1; eq23:1 = gpkpi:~1 gpi:1 gpkp:1;
	EQ10.1: $[(GPK-P)_{act} GP_{inact}] + ATP \xrightarrow{k_5} (GP-P)_{act} + ADP + (GPK-P)_{act}$	eq24:2 = gpkpi:~1 atp:~1 gpa:1 adp:1 gpkp:1;
Degradation of glycogen to glucose 1-phosphate unkown rates = 1	**EQ11:** $(GP-P)_{act} + Glycogen \rightleftharpoons (GP-P)_{act} Glycogen$	eq25:1 = gpa:~1 glyc:~1 gpaglyc:1; eq26:1 = gpaglyc:~1 glyc:1 gpa:1;
	EQ11.1: $(GP-P)_{act} Glycogen + P_i \longrightarrow Glu\cos e1-P + (GP-P)_{act}$	eq27:1 = gpaglyc:~1 p:~1 gluc:1 gpa:1;
Phosphorylation of *glycogen synthase* (*GS*) unkown rates = 1, $k_7 = 2^*$	**EQ12:** $(GPK-P)_{act} + cAPK_{act} + GS_{act} \rightleftharpoons [cAPK_{act} GS_{act} (GPK-P)_{act}]$	eq28:1 = gpkp:~1 capka:~1 gsa:~1 pkgs:1; eq29:1 = pkgs:~1 gsa:1 capka:1 gpkp:1;
	EQ12.1: $[cAPK_{act} GS_{act} (GPK-P)_{act}] + ATP \xrightarrow{k_7} (GS-P)_{inact} + ADP + cAPK_{act} + (GPK-P)_{act}$	eq30:2 = pkgs:~1 atp:~1 gsi:1 adp:1 capka:1 gpkp:1;

MODE 2		
Duration of the reaction (time-units) Rate constants (sec^{-1})	**Biochemical equations**	**Equations encoding**
Activation of the receptor and G-protein unkown rates = 1	**EQ1:** $R_{glcgn}[G_\alpha GDP] + L_{glcgn} \rightleftharpoons R_{glcgn}[G_\alpha GTP] L_{glcgn}$	eq1:1 = rgp:~1 l:~1 rgtpl:1; eq2:1 = rgtpl:~1 l:1 rgp:1;
Dissociation of G-protein from the ligand unkown rates = 1	**EQ2:** $R_{glcgn}[G_\alpha GTP] L_{glcgn} \rightleftharpoons G_\alpha GTP + R_{glcgn} L_{glcgn}$	eq3:1 = rgtpl:~1 gtp:1 o:1; eq4:1 = gtp:~1 o:~1 rgtpl:1;

GAP-driven GTPase
unkown rates = 1
 	
$k_{hydr} = 1$
	EQ3:
	$G_\alpha GTP + GAP \rightleftharpoons [G_\alpha GTP] GAP \xrightarrow{k_{hydr}} G_\alpha GDP + GAP + P_i$
		eq5:1 = gtp:~1 g:~1 h:1;
		eq6:1 = h:~1 g:1 gtp:1;
		eq7:1 = h:~1 gdp:1 g:1 p:1;

G-protein inactive bound to the receptor unkown rates = 1	**EQ4:** $G_\alpha GDP + R_{glcgn} \rightleftharpoons R_{glcgn}[G_\alpha GDP]$	eq8:1 = gdp:~1 ir:~1 rgp:1; eq9:1 = rgp:~1 ir:1 gdp:1;
Dissociation of the ligand from the receptor unkown rates = 1	**EQ5:** $R_{glcgn} L_{glcgn} \rightleftharpoons R_{glcgn} + L_{glcgn}$	eq10:1 = o:~1 ir:1 l:1; eq11:1 = l:~1 ir:~1 o:1;
Association of G-protein activated to the enzyme adenylate cyclase (AC) unkown rates = 1	**EQ6:** $G_\alpha GTP + AC \rightleftharpoons AC[G_\alpha GTP]$	eq12:1 = gtp:~1 ac:~1 acgp:1; eq13:1 = acgp:~1 ac:1 gtp:1;

Production of *cyclic AMP* (*cAMP*)
 	
unkown rates = 1
	EQ7:
	$AC[G_\alpha GTP] + ATP \rightleftharpoons$
	$[AC[G_\alpha GTP]] ATP \longrightarrow$
	$cAMP + 2P_i + AC[G_\alpha GTP]$
		eq14:1 = acgp:~1 atp:~1 acgpatp:1;
		eq15:1 = acgpatp:~1 atp:1 acgp:1;
		eq16:1 = acgpatp:~1 camp:1 p:2 acgp:1;

Fig. B.4. A model of the control system of the intracellular processes in the signaling pathway of the glycogen breakdown (Part4)

Activation of *cAMP dependent protein kinase* (*cAPK*) unkown rates = 1	**EQ8:** $4cAMP + 2cAPK_{inact} \rightleftharpoons 2cAPK_{act}$	eq17:1 = camp:~4 capki:~2 capka:2; eq18:1 = capka:~2 capki:2 camp:4;
Phosphorylation of glycogen phosphorylase kinase (GPK) unkown rates = 1, $k_3 = 20^*$	**EQ9:** $cAPK_{act} + GPK_{inact} \rightleftharpoons [cAPK_{act} GPK_{inact}]$	eq19:1 = capka:~1 gpki:~1 agpk:1; eq20:1 = agpk:~1 gpki:1 capka:1;
	EQ9.1: $[cAPK_{act} GPK_{inact}] + ATP \xrightarrow{k_3} (GPK-P)_{act} + ADP + cAPK_{act}$	eq21:20 = agpk:~1 atp:~1 gpkp:1 adp:1 capka:1;
Phosphorylation of glycogen phosphorylase (GP) unkown rates = 1, $k_5 = 20^*$	**EQ10:** $(GPK-P)_{act} + GP_{inact} \rightleftharpoons [(GPK-P)_{act} GP_{inact}]$	eq22:1 = gpkp:~1 gpi:~1 gpkpi:1; eq23:1 = gpkpi:~1 gpi:1 gpkp:1;
	EQ10.1: $[(GPK-P)_{act} GP_{inact}] + ATP \xrightarrow{k_5} (GP-P)_{act} + ADP + (GPK-P)_{act}$	eq24:20 = gpkpi:~1 atp:~1 gpa:1 adp:1 gpkp:1;
Degradation of glycogen to glucose 1-phosphate unkown rates = 1	**EQ11:** $(GP-P)_{act} + Glycogen \rightleftharpoons (GP-P)_{act} Glycogen$	eq25:1 = gpa:~1 glyc:~1 gpaglyc:1; eq26:1 = gpaglyc:~1 glyc:1 gpa:1;
	EQ11.1: $(GP-P)_{act} Glycogen + P_i \longrightarrow Glu\cos e1-P + (GP-P)_{act}$	eq27:1 = gpaglyc:~1 p:~1 gluc:1 gpa:1;
Phosphorylation of *glycogen synthase* (*GS*) unkown rates = 1, $k_7 = 20^*$	**EQ12:** $(GPK-P)_{act} + cAPK_{act} + GS_{act} \rightleftharpoons [cAPK_{act} GS_{act} (GPK-P)_{act}]$	eq28:1 = gpkp:~1 capka:~1 gsa:~1 pkgs:1; eq29:1 = pkgs:~1 gsa:1 capka:1 gpkp:1;
	EQ12.1: $[cAPK_{act} GS_{act} (GPK-P)_{act}] + ATP \xrightarrow{k_7} (GS-P)_{inact} + ADP + cAPK_{act} + (GPK-P)_{act}$	eq30:20 = pkgs:~1 atp:~1 gsi:1 adp:1 capka:1 gpkp:1;

MODE 3		
Duration of the reaction (time-units) Rate constants (sec^{-1})	**Biochemical equations**	**Equations encoding**
Activation of the receptor and G-protein unkown rates = 1	**EQ1:** $R_{glcgn}[G_\alpha GDP] + L_{glcgn} \rightleftharpoons R_{glcgn}[G_\alpha GTP] L_{glcgn}$	eq1:1 = rgp:~1 l:~1 rgtpl:1; eq2:1 = rgtpl:~1 l:1 rgp:1;
Dissociation of G-protein from the ligand unkown rates = 1	**EQ2:** $R_{glcgn}[G_\alpha GTP] L_{glcgn} \rightleftharpoons G_\alpha GTP + R_{glcgn} L_{glcgn}$	eq3:1 = rgtpl:~1 gtp:1 o:1; eq4:1 = gtp:~1 o:~1 rgtpl:1;

GAP-driven GTPase
unkown rates = 1
 	
$k_{hydr} = 1$
	EQ3:
	$G_\alpha GTP + GAP \rightleftharpoons [G_\alpha GTP] GAP \xrightarrow{k_{hydr}} G_\alpha GDP + GAP + P_i$
		eq5:1 = gtp:~1 g:~1 h:1;
		eq6:1 = h:~1 g:1 gtp:1;
		eq7:1 = h:~1 gdp:1 g:1 p:1;

G-protein inactive bound to the receptor unkown rates = 1	**EQ4:** $G_\alpha GDP + R_{glcgn} \rightleftharpoons R_{glcgn}[G_\alpha GDP]$	eq8:1 = gdp:~1 ir:~1 rgp:1; eq9:1 = rgp:~1 ir:1 gdp:1;
Dissociation of the ligand from the receptor unkown rates = 1	**EQ5:** $R_{glcgn} L_{glcgn} \rightleftharpoons R_{glcgn} + L_{glcgn}$	eq10:1 = o:~1 ir:1 l:1; eq11:1 = l:~1 ir:~1 o:1;
Association of G-protein activated to the enzyme adenylate cyclase (AC) unkown rates = 1	**EQ6:** $G_\alpha GTP + AC \rightleftharpoons AC[G_\alpha GTP]$	eq12:1 = gtp:~1 ac:~1 acgp:1; eq13:1 = acgp:~1 ac:1 gtp:1;

Production of *cyclic AMP* (*cAMP*)
 	
unkown rates = 1
	EQ7:
	$AC[G_\alpha GTP] + ATP \rightleftharpoons$
	$[AC[G_\alpha GTP]] ATP \longrightarrow$
	$cAMP + 2P_i + AC[G_\alpha GTP]$
		eq14:1 = acgp:~1 atp:~1 acgpatp:1;
		eq15:1 = acgpatp:~1 atp:1 acgp:1;
		eq16:1 = acgpatp:~1 camp:1 p:2 acgp:1;

Fig. B.5. A model of the control system of the intracellular processes in the signaling pathway of the glycogen breakdown (Part5)

Activation of *cAMP dependent protein kinase* (*cAPK*) unkown rates = 1	**EQ8:** $4cAMP + 2cAPK_{inact} \rightleftharpoons 2cAPK_{act}$	eq17:1 = camp:~4 capki:~2 capka:2; eq18:1 = capka:~2 capki:2 camp:4;
Phosphorylation of glycogen phosphorylase kinase (GPK) unkown rates = 1, $k_3 = 200^*$	**EQ9:** $cAPK_{act} + GPK_{inact} \rightleftharpoons [cAPK_{act}GPK_{inact}]$	eq19:1 = capka:~1 gpki:~1 agpk:1; eq20:1 = agpk:~1 gpki:1 capka:1;
	EQ9.1: $[cAPK_{act}GPK_{inact}] + ATP \xrightarrow{k_3} (GPK-P)_{act} + ADP + cAPK_{act}$	eq21:200 = agpk:~1 atp:~1 gpkp:1 adp:1 capka:1;
Phosphorylation of glycogen phosphorylase (GP) unkown rates = 1, $k_5 = 200^*$	**EQ10:** $(GPK-P)_{act} + GP_{inact} \rightleftharpoons [(GPK-P)_{act}GP_{inact}]$	eq22:1 = gpkp:~1 gpi:~1 gpkpi:1; eq23:1 = gpkpi:~1 gpi:1 gpkp:1;
	EQ10.1: $[(GPK-P)_{act}GP_{inact}] + ATP \xrightarrow{k_5} (GP-P)_{act} + ADP + (GPK-P)_{act}$	eq24:200 = gpkpi:~1 atp:~1 gpa:1 adp:1 gpkp:1;
Degradation of glycogen to glucose 1-phosphate unkown rates = 1	**EQ11:** $(GP-P)_{act} + Glycogen \rightleftharpoons (GP-P)_{act}Glycogen$	eq25:1 = gpa:~1 glyc:~1 gpaglyc:1; eq26:1 = gpaglyc:~1 glyc:1 gpa:1;
	EQ11.1: $(GP-P)_{act}Glycogen + P_i \longrightarrow Glucose1-P + (GP-P)_{act}$	eq27:1 = gpaglyc:~1 p:~1 gluc:1 gpa:1;
Phosphorylation of *glycogen synthase* (*GS*) unkown rates = 1, $k_7 = 200^*$	**EQ12:** $(GPK-P)_{act} + cAPK_{act} + GS_{act} \rightleftharpoons [cAPK_{act}GS_{act}(GPK-P)_{act}]$	eq28:1 = gpkp:~1 capka:~1 gsa:~1 pkgs:1; eq29:1 = pkgs:~1 gsa:1 capka:1 gpkp:1;
	EQ12.1: $[cAPK_{act}GS_{act}(GPK-P)_{act}] + ATP \xrightarrow{k_7} (GS-P)_{inact} + ADP + cAPK_{act} + (GPK-P)_{act}$	eq30:200 = pkgs:~1 atp:~1 gsi:1 adp:1 capka:1 gpkp:1;

Fig. B.6. A model of the control system of the intracellular processes in the signaling pathway of the glycogen breakdown (Part6)