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BDI-Modelling of Intracellular Dynamics

Catholijn M. Jonker[1], Jacky L. Snoep[2,3], Jan Treur[1,4],
Hans V. Westerhoff[3,5], and Wouter C.A. Wijngaards[1]

[1]Vrije Universiteit Amsterdam
Department of Artificial Intelligence
De Boelelaan 1081a
1081HV Amsterdam
The Netherlands
jonker@cs.vu.nl
http://www.cs.vu.nl/ai/

[2]University of Stellenbosch
Department of Biochemistry
Private Bag X1
Matieland 7602
Stellenbosch
South Africa
jls@maties.sun.ac.za

[3]Vrije Universiteit Amsterdam
Department of Molecular Cell Physiology
De Boelelaan 1087
1081HV Amsterdam
The Netherlands
hw@bio.vu.nl

[4]Utrecht University
Department of Philosophy
Heidelberglaan 8
3584CS Utrecht
The Netherlands
treur@cs.vu.nl

[5]University of Amsterdam
Swammerdam Institute for Life Sciences
Plantage Muidergracht 12
1018TV Amsterdam
The Netherlands

ABSTRACT

Existing chemical models of bacteria are complicated, due to the thousands of interacting chemical reactions within the cell. To gain a higher level of understanding, more transparent and abstract models are needed. In this paper an intentional dynamic modelling approach is introduced and used to simulate the behaviour of *Escherichia coli*. A model of the entire cell is presented that covers *E. coli*'s behaviour, including its intracellular processes and their control. The intentional state properties used in the model are in a one-to-one correspondence to chemical state properties: concentrations of specific substances within the cell. Via these correspondences the dynamic relationships between intentional state properties are justified by chemical laws. A software environment has been developed for simulation and automated analysis of such a model.

Categories and Subject Descriptors

I.2.11 [**Computing Methodologies**]: Artificial Intelligence – Distributed AI – *Intelligent Agents*

Keywords

Agent, dynamics, cell, intentional, *E. coli*

1. INTRODUCTION

Even the simplest life forms require the interaction of more than 400 chemical processes that are encoded by genes (Hutchison *et al.*, 1999). The sequencing of many *complete* genomes should bring cell biochemistry to full fruition, at last: efforts can now be directed at clarifying the dynamic functioning of genes within the ensemble of cellular processes. But how should one manage and understand hundreds of biochemical processes simultaneously? After ages of qualitative or quasi-quantitative modeling, a mathematical biochemistry approach is coming within reach (Westerhoff, 2001). The biochemical processes are described by the appropriate differential or algebraic equations, the parameter values are taken from experimental studies, and are integrated numerically (Mendes, 1997). For some unicellular organisms such as the bacterium *E. coli* (Rohwer *et al.*, 2000, Wang *et al.*, 2001, Ben-Jacob *et al*., 1997), the yeast *S. cerevisiae* (Teusink *et al*., 2000; Rizzi *et al.*, 1997), *D. discoideum* (Wright and Albe, 1994) and *T. brucei* (Bakker *et al*., 1997), and for the red blood cell (Mulquiney and Küchel, 1999) some of the chemical pathways are understood in sufficient kinetic detail to obtain a description of their import and primary processing of food.

As close to the aims of our scientific endeavor as this approach may seem to be, it does have major limitations: (1) Even for relatively short biochemical pathways, a hundred or more reaction parameters are needed, which have rarely been determined under the appropriate experimental conditions (Teusink *et al*., 2000). (2) Due to non-linearities in the dynamics, results can depend strongly on parameter values, such that simple estimates may not suffice. (3) Biochemical pathways are integrated with other pathways, including ones of signal transduction and gene expression, for which reliable parameter estimates are even rarer (Kholodenko *et al*., 1999). (4) It is still unclear whether parameter values determined *in vitro* are relevant *in vivo* (Visser *et al*., 2000; Rohwer *et al*. 1998). (5) Actual behavior of intracellular pathways may be much less complex than possible in principle on the basis of their complexity (e.g. Van Rotterdam *et al*., 2002). (6) At best this approach delivers a computer replica of (part of) the living cell, which is almost as remote from human understanding, as the cell itself; this modeling approach gives too detailed and complex an account, where the human mind tends after understanding merely the essence.

Indeed, in order to grasp the workings of the cell, approaches abstracting from biochemical detail might be helpful. One type of such approaches focuses on a particular facet of cell function, such as its energetics, control, performance, optimisation, type of dynamics, or flux distributions (Westerhoff and Van Dam, 1987; Heinrich and Schuster, 1996; Moller *et al.*, 2002) thereby allowing substantial approximations to rate equations. A second type recognizes that some conglomerates of biochemical processes act as functional units such as "metabolic pathway", "catabolism", "transcriptome" and "regulon". Some of these concepts have been or are being defined formally (Kahn & Westerhoff, 1991; Rohwer *et al.*, 1996b; Schilling *et al.*, 200), but optimal implementation is still in its infancy. A third type of approach recognizes a less than full complexity in cell functioning, for instance in the limited dimensionality of the transcriptome, or the metabolome. Indeed,

viewed from the functional side, the cell effectively makes decisions regarding its internal and externally observable behavior, given its environmental circumstances, and implements these decisions into appropriate actions. The exact time it takes to make these decisions, and hence the precise integration of the differential equations, may be much less important than the fact that the decision is taken within some reasonable time interval. This suggests that considering a cell from the perspective of an *agent* sensing the environment, integrating that information with its internal state, and then choosing between possible behavioural patterns of action, may provide the basis of an alternative modelling approach. The fact that the agent will consist of a number of biochemical elements marries this to the second type of approaches (chemical processes as functional units), the emphasis on regulation to the first type (focusing on a particular facet).

Within the field of Artificial Intelligence, the area of Agent Systems addresses the modelling of artificial and natural decision makers. One sort of these agent models are the BDI-models describing agents in terms of internal state properties such as Beliefs, Desires and Intentions (*e.g.* Rao and Georgeff, 1991). In (Jonker, Snoep, Treur, Westerhoff, and Wijngaards, 2002) the BDI-modelling strategy identifies and analyses steady states within the cell in relation to environmental circumstances. The BDI-models available in the literature do not adequately address the dynamics of the internal state properties over time, however, nor do they specify in which order and at what time the appropriate beliefs, desires and intentions are generated in relation to environmental conditions. Since Jonker *et al*. (2002) dealt with steady states only, this limitation of the BDI-model was harmless, and relating the steady states to different environmental circumstances fitted well to the logic of a BDI-modelling strategy which abstracts from internal dynamics.

A main problem to be addressed in non-steady dynamics, is to characterise for changing environmental conditions, for example, what internal dynamics realise the transitions over time from one steady state to another. The dynamics become even less trivial when the environment is changing continuously so that the cell never reaches any steady state. An underlying fundamental problem is how to relate *discrete*, binary decision processes to *continuous* dynamics over time as occurring in the biochemical reaction network.

In agent simulation models, time is often chosen to be discrete and dynamics is based on step by step state transitions from one discrete point in time to the next (e.g., Sloman and Poli, 1995; the Executable Temporal Logic of Barringer *et al.* 1996 and Fisher, 1994, the step-logic of Elgot-Drapkin and Perlis, 1990). These discrete modelling approaches do not fully capture the continuous dynamics of processes in the real world, which is the basis of, for example, the internal dynamics of cellular processes.

For the analysis of concurrent real-time processes, also some temporal requirement specification languages have been introduced; e.g., (Dardenne *et al.*, 1993; Darimont and Lamsweerde, 1996; Dubois *et al.*, 1995). In (Chaochen, Hoare, and Ravn, 1991) a calculus is presented to model requirements and designs for real-time systems. Another logic based approach using time durations is presented in (Sandewall, 1997). These approaches can be used for analysis of non-discrete dynamics but are not aimed at simulation.

The current paper addresses the problem of continuous versus discrete time in yet another way. It is shown how the BDI-model that abstracts from internal dynamics can be extended or *temporalised* by adding a (continuous, real time) temporal dimension for the internal dynamics of the beliefs, desires and intentions over time (cf. Finger and Gabbay, 1992). It is shown that this temporalised Continuous Time BDI-model covers the (non-steady state) dynamics of a cell's biochemical pathways. By using this model to describe the cell's internal processes in terms of state properties such as beliefs, desires and intentions, the amount of biochemical detail can be reduced by abstracting from them. This abstraction is systematic/scientific, yet much in parallel with intuition. Since most researchers intuitively (but informally) use intentional state properties to describe the apparently intelligent behaviour of the cell, this model is easier to understand than the more usual differential equation type of model.

The formal treatment using the temporalised BDI-model has the additional advantage of making it suitable for simulation in a software environment that is based on an extension of the paradigm of executable temporal logic (Barringer, Fisher, Gabbay, Owens, and Reynolds, 1996). Because no numerical integration has to be done, these algorithms are efficient to use.

The paper is structured as follows. In Section 2 the living cell is described from two viewpoints; connections are indicated:

- the biochemical viewpoint, based on relationships between genes, mRNAs, enzymes and metabolism, and cofactors involved in these relationships
- the intentional viewpoint, based on relationships between beliefs, desires, intentions and actions, and additional factors involved in these relationships

Section 3 introduces a continuous-time interval-based temporal modelling approach in which (discrete) state properties of some duration lead to the occurrence of another state property for a certain time duration, after some time delay. This approach combines discrete state aspects with continuous real-time aspects. Subsequently, in Section 4, the behaviour of the common bacterium *E. coli* is modelled using temporal relationships between BDI notions. Some simulation results are also shown. Section 5 concludes the paper.

2. RELATING CHEMICAL AND INTENTIONAL STATE PROPERTIES IN E. COLI

Bacteria are small autonomous living systems that interact with their environment; the understanding of the regulation of the behaviour is complicated by the enormous complexity of the chemistry in the living cell. Using intentional state properties to model the regulation of a bacterium, this regulation may be more easily understood. First, the regulation in bacteria is briefly explained in biochemical terms. Second, the behaviour of an agent is explained using intentional state properties. Third, the relationships between the intentional state properties and the chemicals in the bacterial regulation are presented.

2.1 Bacterial Regulation

In bacteria, as in every living cell, the regulation of its internal processes consists of several steps (Neidhardt, Curtiss III, Ingraham, Lin, Brooks Low, Magasanik, Reznikoff, Riley, Schaechter & Umbarger, 1996). In this paper, the regulation of the lactose import is taken as an illustration; other regulation paths follow similar steps as depicted on the left side of Figure 1. Regulation is based on substances that indicate the outside conditions.

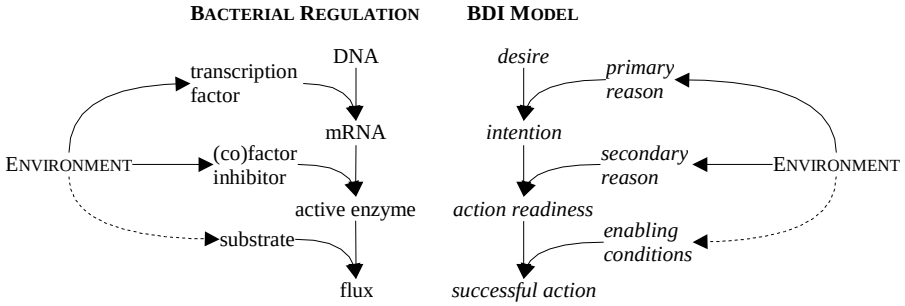

Figure 1. The correspondence between the bacterial regulation and the temporal dependencies in the BDI model

Transcription is a process that, given parts of the DNA (operons) that code for proteins, conditionally specific types of mRNA are created. Transcriptional regulation means that activation proteins must be present and certain repressors must be absent for a particular operon to be transcribed. *Translation* is a process that, given a specific mRNA creates specific proteins: enzymes. Translational regulation enables or disables the translation of mRNA by (co)factors. Enzymes catalyze chemical reactions, causing flux leading, for example, to growth. The product of one reaction is often used as the source for the next producing a *pathway*. Some enzymes can be deactivated by inhibitors, this process is called *metabolic control*, deactivating the entire pathway.

So, the regulation of the processes within a bacterium consists of several steps. First, circumstances in the external environment lead to certain concentrations of specific internal substances. Then, depending on circumstances, the transcriptional regulation is done, possibly resulting in mRNA. Subsequently, also depending on circumstances, the translational regulation is done, possibly resulting in proteins. The metabolism, comprised of energy production, transport and growth pathways, further regulates the activation and inhibition (inactivation) of certain enzymes. When all this is done, enzymes may be ready to catalyse chemical reactions. When enzymes catalyse reactions, they cause an increased flux, leading to growth of the bacterium.

2.2 Intentional State Properties

The intentional properties used to describe behaviour are taken from socalled BDI (Beliefs, Desires and Intentions) models; e.g., (Dretske, 1991; Rao and Georgeff, 1991). The *beliefs* represent what the agent deems to be true in its environment. A belief is present due to sensing (in the present or in the past). *Desires* are interpreted as what the agent wants to accomplish or fulfil. Agents can have desires contradictory in their fulfilment, for example desiring lots of ice creams and slim waist. A desire, together with a sufficient additional reason, leads to an intention to fulfil the desire. An *additional reason* is a belief that has to hold, in order for the intention to be generated. *Intentions* are interpreted as that the agent will make something happen (action), as soon as a belief in an opportunity (for the action) occurs. *Opportunities* are states of the environment that give the possibility to perform an action. *Actions* performed by the agent affect its internal or external physical environment. The relations between the intentional state properties are depicted on the right side of Figure 1.

2.3 Intentionalisation

The intentional state properties used to describe the behaviour can be related to the substances used in the bacterial regulation. The internal substances relating to the situation in the environment are chosen to correspond with the beliefs. DNA parts are chosen to correspond to desires. Within the BDI model a desire together with an additional reason results in an intention. The conditions for transcriptional regulation are the substances relating to circumstances in the external environment. These substances must bind to the DNA in order to get mRNA. Therefore, the presence of the necessary amounts of these substances is chosen to correspond with the set of beliefs that make up the additional reason. In other words, the conditions needed for the transcriptional regulation correspond with the primary additional reasons of the intentional model. As can be seen from the left side of Figure 1, DNA is used to create mRNA. Therefore, with DNA as desire, mRNA is chosen to correspond with an intention to perform an action. The enzymes created by the translation are used to increase the flux of chemical reactions (which correspond to actions in the intentional model). Thus, active enzymes are chosen to correspond with action initiations. The (co)factors necessary for the translation of mRNA into enzymes correspond with the secondary additional reasons for the creation of action initiations. Moreover the absence of inhibitors of the enzymes is a condition for the action to be initiated, given the intention. When enzymes cause flux, (i.e., successfully catalyse reactions), this corresponds to succesful action performance in the world (enabling conditions are fulfilled).

In Figure 1 the correspondence between the intentional state properties and the chemical regulation of the bacterium is displayed. In summary, the following correspondences are made:

DNA	-	desire
mRNA	-	intention
active enzyme	-	initiated action (or action readiness)
flux	-	succesful action

3. TEMPORAL MODELLING APPROACH

The bacterial behaviour results from a multitude of biochemical processes. These operate on each other over time, producing the behavioural regulation. The overall regulation process is not easy to understand; for example, a number of feedback loops between different stages of the regulation process and a high number of chemical reactions are involved.

A more abstract model for the dynamics of biochemical processes can be obtained by introducing categories of concentrations of substances, and relating different categories of the same and of different substances over time. In this section temporal relationships are used to express the timing dynamics. The resulting abstract model captures the timing dynamics of the biochemical reactions in logical temporal relationships using continuous time.

3.1 Temporal Modelling of Chemical Processes

A generally accepted way to describe biochemical reactions is in the form: A + B ↔ C + D. This expresses that substances A and B can be transformed into substances C and D, and that the reverse process is also possible. In the cell the pathways consist of several reactions chained together. For example (1) sketches the pathway for the transcription of the lac operon. The transcription of the lac operon (Neidhardt et al., 1996) will be the leading example.

transcription lactose: (1)
nucleotides + DNA_lactose ↔ … ↔ mRNA_lactose + DNA_lactose

Formulae like (1) do not express inhibitors, activators, speed and equilibrium conditions. For example lactose and CRPcAMP are the activation proteins regulating the transcription of the lac operon. Within the well-known Michaelis-Menten equations the rate of a reaction can be derived on the basis of concentrations of substances, binding constants, stoichiometry values and equilibrium constants. Michaelis-Menten provides formulae for the reactions in continuous time. Equations such as Michaelis-Menten equations can be extended with inhibitors and activators. Using these formulae, a complete description of the processes in the cell could be given if all the reactions and their parameters were known, which is not the case. Example parameter values are given for the transcription of the lac operon reaction, see (2).

Regulators: lactose 0.01, CRP_cAMP 0.01, kcat=0.01, keq=100. (2)

Viewed from a more abstract perspective, what does this reaction do over time? When enough of lactose, CRPcAMP and nucleotides are present, the mRNA_lactose will start to be produced, and after a certain delay a significant amount of mRNA_lactose will be present. The concentrations of lactose and CRPcAMP need to be sufficiently high for a certain period of time in order for the reaction to proceed, a concentration of at least 0.1 mmolair (the threshold) of both is sufficient in the example. The amount of nucleotides needed for the reaction to proceed is at least about 0.1 mmolair again. A ready supply of nucleotides is always synthesised by the cell. In order for the reaction to happen, the amount of mRNA must not be so high as to impede the reaction, a concentration lower than about 10 mmolair in this example. When the reaction proceeds, the amount of nucleotides will slowly decrease. The amount of mRNA will slowly accumulate by this reaction. Other parts of the system will supply new nucleotides and the mRNA will degrade after some time.

The large amount of unknown variables, and computational complexity of integrating the resulting differential equations make a model using only chemical differential equations unwieldy. Therefore a more abstract description is introduced. The process is modelled in our temporal environment as follows. Temporal relationships are defined between a number of sources and an effect. Parameters are used to specify the minimal duration of the sources, the delay before the effect becomes apparent, and the duration of the effect; for the delay a minimum and maximum value can be set. As an illustration, the temporal relationship between the substances in the transcription of the lactose operon is determined. Since nucleotides are always present, these do not need to be mentioned in the temporal relationship, as it does not influence behaviour. The temporal relationship to determine when the mRNA_lactose is produced is denoted as:

$$\text{DNA\_lactose} + \text{lactose} + \text{CRP\_cAMP} \bullet\!\!\rightarrow\!\!\!\!\rightarrow_{e,f,g,h} \text{mRNA\_lactose} \quad (3)$$

On the left-hand side the conditions that have to be met are listed. The DNA_lactose, meaning the presence of the lactose operon in the DNA. Also lactose, meaning the presence of lactose and CRP_cAMP, meaning the presence of CRP_cAMP to bind to the activation sites of the operon are listed on the left side. It is necessary to know at which concentration of the substance the 'presence' state property holds; a threshold value is used to determine this. On the right hand side, the change that will happen later is listed, mRNA_lactose meaning the presence of lactose mRNA that is produced. The parameters e, f, g and h are positive real numbers that set the minimum and maximum delay (e and f), the condition duration (g) and the result duration (h). Realistic parameters for the values of e, f, g and h for the example are e = 60, f = 60, g = 1 and h = 40, as the process to create the mRNA takes about 60 seconds, and the mRNA will stay in existence for about 40 seconds on average. When the condition holds for 1 second or more, the transcription process starts.

In the next section the temporal relationship used here is explained in more mathematical detail.

3.2 The Temporal Modelling Framework

In the previous section a temporal model has been presented of chemical processes using categories of substances and temporal relationships between these. This section defines more precisely the temporal relation $\bullet\!\!\rightarrow\!\!\!\!\rightarrow$ that is called the "leads to" relation. The relation is defined in terms of its semantics. In order to understand the definition, a few semantic notions must be understood.

Definition (State and Trace)
The state of a system at a certain time point is described by a mapping that assigns a truth-value (true, or false) to all state atoms, i.e., all atomic statements relevant for a state of that system. A trace or trajectory of a system is a specific sequence of states of the system over a continuous time frame T (chosen to be the real numbers). The set $\mathcal{W}$ is the set of all possible traces. Let $\mathcal{T}$ be a trace, and t a time point, then state($\mathcal{T}$, t) denotes the state of the system in trace $\mathcal{T}$ at time point t. Let α be a state statement (i.e., a proposition in atomic state statements), then state($\mathcal{T}$, t) $\models \alpha$ is used to denote that in a given trace $\mathcal{T}$ at time t the statement α holds.

The formal definition of the temporal operator $\bullet\!\!\rightarrow\!\!\!\!\rightarrow$ is expressed in two parts, the forward in time part and the backward in time part. Time intervals are denoted by [x, y) (from and including x, to but not including y) and [x, y] (the same, but includes the y value).

Definition (The $\bullet\!\!\rightarrow\!\!\!\!\rightarrow$ relationship)
Let α and β be state statements. Then α *leads to* β, denoted by $\alpha \rightarrow\!\!\!\!\rightarrow_{e,\ f,\ g,\ h} \beta$, with time delay interval [e, f] and duration parameters g and h if

$\forall \mathcal{T} \in \mathcal{W}$ $\forall$t1:

[$\forall$t $\in$ [t1 - g, t1) : state($\mathcal{T}$, t) $\models \alpha \Rightarrow$

$\exists$d $\in$ [e, f] $\forall$t $\in$ [t1 + d, t1 + d + h) : state($\mathcal{T}$, t) $\models \beta$]

Conversely, the state property β *originates from* state property α, denoted by $\alpha \bullet\!\!-_{e,\,f,\,g,\,h} \beta$, with time delay in [e, f] and duration parameters g and h if

$\forall \mathcal{T} \in \mathcal{W}$ $\forall$ t2:

[$\forall$t $\in$ [t2, t2 + h) : state($\mathcal{T}$, t) $\models \beta \Rightarrow$

$\exists$d $\in$ [e, f] $\forall$t $\in$ [t2 - d - g, t2 - d) state($\mathcal{T}$, t) $\models \alpha$]

If both $\alpha \twoheadrightarrow_{e,f,g,h} \beta$, and $\alpha \bullet\!\!-_{e,f,g,h} \beta$ hold, this is denoted by: $\alpha \bullet\!\!\twoheadrightarrow_{e,f,g,h} \beta$.

The definition of the relationships as given above, can be applied to situations where the sources hold for longer than the minimum g. The result for a longer duration of α for $\alpha \bullet\!\!\twoheadrightarrow \beta$ is depicted in Figure 2. The additional duration that the source holds, is also added to the duration that the result will hold, provided that the condition e + h ≥ f holds. This is because the definition can be applied at each subinterval of α, resulting in many overlapping intervals of β. The end result is that the additional duration also extends the duration that the resulting state property β holds.

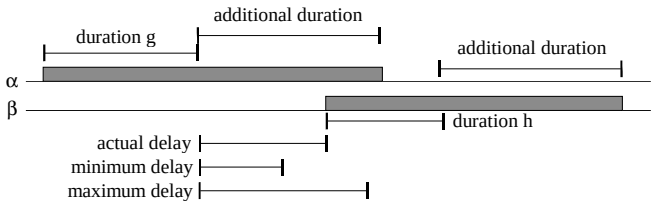

Figure 2. Temporal relationships for longer durations

Using these temporal relationships, the bacterial regulation can be modelled from the chemical perspective. The temporal relationships capture the timing of the underlying chemical reactions. The durations and delay minimum and maximum can be specified to fit the timing of the chemistry. The formal definition of the temporal relation operator aids the construction of simulation and derivation software to support the inspection of modelling results.

4. INTENTIONAL DYNAMIC MODELLING OF *E. COLI* BEHAVIOUR

Models for intentional state properties like those of (Dretske, 1991; Rao and Georgeff, 1991) usually do not take into account their dynamics well. To be able to closely relate an intentional model to the bacterial realisation in chemical processes, such dynamics are crucial. Therefore the temporal modelling approach based on the temporal 'leads to' relation introduced in Section 3 is applied to the dynamics of intentional state properties. The resulting model is a transparent high level description of the cellular processes and their control, understandable for the reader not versed in the technicalities of the detailed chemical pathways in the cell.

The model covers the whole behaviour of *E. coli*, from food import to internal metabolism to growth. First an example of the use of temporal relationships between intentional state properties to model their dynamic interactions is discussed. Next, an overview of part of the model is presented.

4.1 Dynamic Interactions between Intentional State Properties

As a simplified example, the temporal relationships modelling the interaction between a desire, some beliefs and an intention is discussed. The following notations are used for the intentional state properties:

- δ denotes a *desire*
- β denotes a *belief*
- ρ_1 denotes a *reason* for an intention, given a desire for an intention (this is a specific conjunction of beliefs)
- ι denotes an *intention*
- ρ_2 denotes a *reason* for action initiation, given an intention (this is a specific conjunction of beliefs; i.e., beliefs in an *opportunity*)
- α is used to denote *action initiation* or *readiness*
- θ denotes an action's successfulness condition on the actual world state (*enabling condition*)

The example concerns the desire δ(lactose_import), the intention ι(lactose_import), and beliefs β(lactose_externally_present) and β(not glucose_externally_present). The general idea is that the desire and the beliefs together lead to the intention, i.e., in a trace where the desire and the beliefs hold for some time interval, always the intention will hold for some later time interval. The desire and the beliefs (the reason for the creation of the intention) must hold for at least some time duration g. After a delay larger than some minimum delay e and shorter than some maximum delay f, the intention starts to hold for some time duration h. This temporal relationship is denoted in relation (4). In Figure 3 the timing relationships between the arguments are visualised.

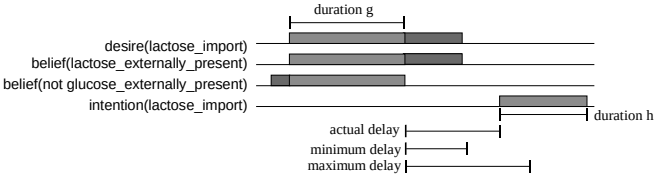

Figure 3. Explanation of timings for temporal relationships

For each intentional state property, its status over time is depicted. Time increases towards the right. The shaded boxes indicate when the state properties hold.

δ(lactose_import)
$\wedge$ β(lactose_externally_present)
$\wedge$ β(not glucose_externally_present)
$\bullet\!\!\twoheadrightarrow_{e,f,g,h}$ ι(lactose_import). (4)

The intentional state properties are related to the substances, as discussed in the Section 2.3. In relation to (4), the presence of lactose and the presence of CRPcAMP substances are interpreted as the beliefs in the second and third line, respectively. The presence of a specific DNA part relates to the desire and the presence of a specific mRNA to the intention. The nucleotides and other, intermediate, substances are not labelled with intentional state properties; these substances are only part of the detailed machinery of bacterial processes, and play no decisive role in the lactose uptake behaviour. Leaving out these, the intentional model provides a more abstract picture of the processes; if new insights were to prove that some substances play

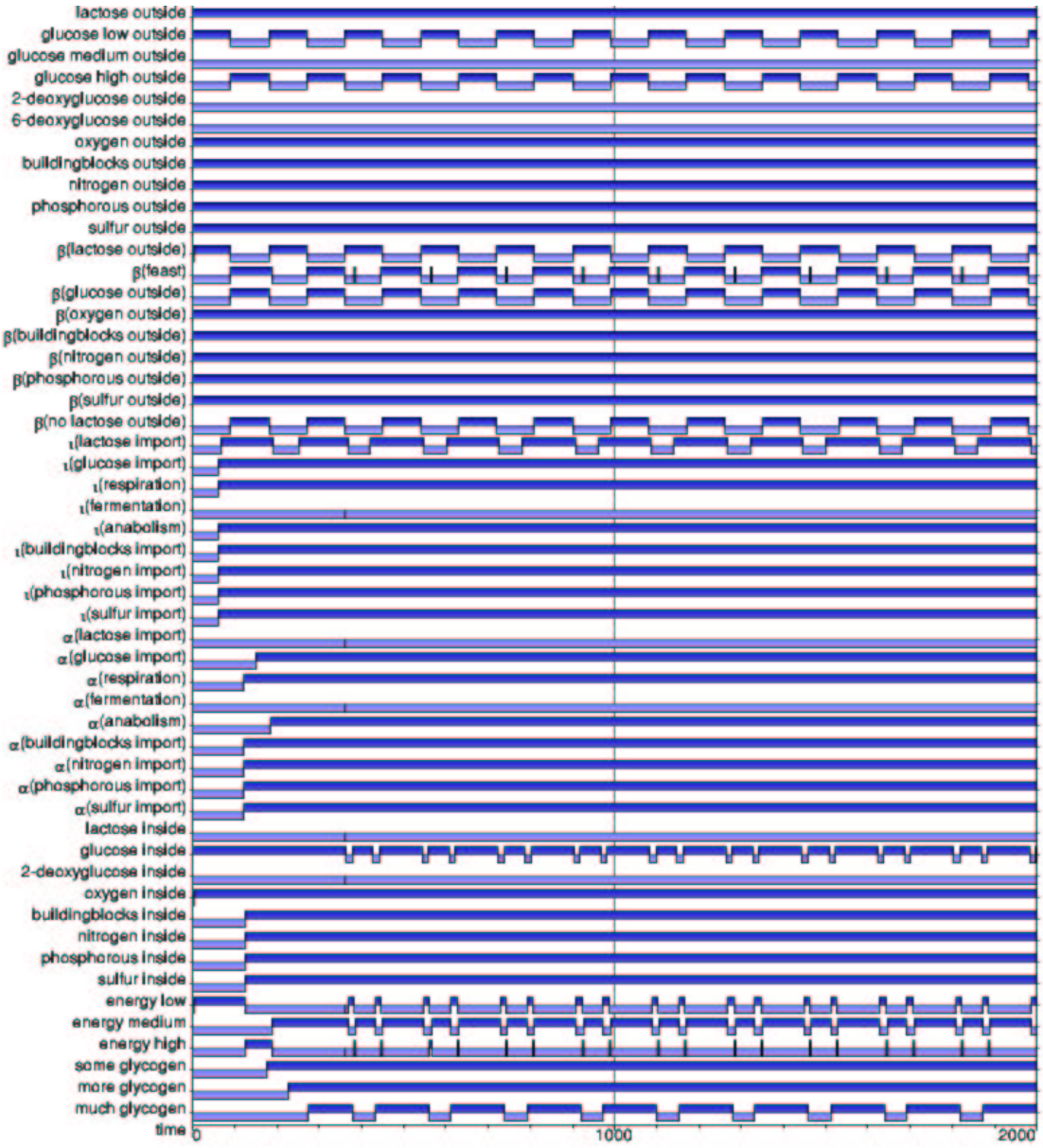

Figure 4. Abbreviated simulation results when glucose is 90 seconds present, then absent, fluctuating. The negative beliefs (reverse of the postive beliefs) and the desires (all hold) have been left out to reduce the size

a significant role in the decision process, these can easily be added. The timing parameters e, f, g, and h are the same as those found in the abstract chemical model, see Section 3.1, thus relation (5) holds.

$$\begin{aligned} &\delta(\text{lactose\_import}) \\ &\quad \wedge\ \beta(\text{lactose\_externally\_present}) \\ &\quad \wedge\ \beta(\text{not glucose\_externally\_present}) \\ &\qquad \bullet\!\!\rightarrow\!\!\!\!\rightarrow_{60,60,1,40}\ \iota(\text{lactose\_import}). \end{aligned} \tag{5}$$

4.2 Overview of Part of the *E. coli* Model

A model has been made describing in an abstract manner the processes of the entire cell, including the intracellular processes and their control and metabolism. Due to lack of space, only part of the model is discussed. The e, f, g and h values for the temporal relationships are given in seconds.

Belief generation

The presence of certain substances in the environment leads to the generation of beliefs. The observation of glucose is shown, it is complicated by inhibitors and the energy level.

(glucose_high_outside or 2-deoxyglucose_outside) &
no 6-deoxyglucose_outside & (energy_high or energy_medium)
$\bullet\!\!\rightarrow\!\!\!\!\rightarrow_{0,0,0.230,0.230}$ β(glucose_outside) &
not β(no glucose_outside).
(glucose_medium_outside or glucose_high_outside or
2-deoxyglucose_outside) &
no 6-deoxyglucose_outside & energy_low
$\bullet\!\!\rightarrow\!\!\!\!\rightarrow_{0,0,0.230,0.230}$ β(glucose_outside) and
not β(no glucose_outside).

Desires
The cell has a large number of innate desires: it always desires to grow, it desires to import nitrogen, to import lactose, and so on.

δ(grow).
δ(nitrogen_import).

Intentions
The cell will intend to perform an action if a desire and sufficient additional reasons are present. The desire to import lactose, combined with the additional reason ρ_1(lactose_import) to import lactose results in the intention to import lactose. The additional reasons to import lactose are the belief that lactose is present outside and the belief that glucose is not present outside.

δ(lactose_import) & ρ_1(lactose_import)
$\bullet\!\!\rightarrow\!\!\!\!\rightarrow_{60,60,1,40}$ ι(lactose_import).
δ(phosphorous_import) & ρ_1(phosphorous_import)
$\bullet\!\!\rightarrow\!\!\!\!\rightarrow_{60,60,1,40}$ ι(phosphorous_import).

ρ_1(lactose_import) $=_{def}$ β(lactose_outside)
& β(famine).
ρ_1(phosphorous_import) $=_{def}$ β(phosphorous_outside).

Initiating actions
When the cell has the intention to perform an action, and an additional reason or opportunity ρ_2(lactose_import) presents itself, it generates the action to be performed. For example, when there is an intention to perform lactose import, and beliefs are present that no glucose is presenrt outside and lactose is present outside, the lactose import action is initiated.

ι(lactose_import) & ρ_2(lactose_import)
$\bullet\!\!\rightarrow\!\!\!\!\rightarrow_{0,0,60,600}$ α(lactose_import).

ρ_2(lactose_import) $=_{def}$ β(lactose_outside)
& β(no glucose_outside).

Succesful action performance
Actions will succesfully produce effects, depending on the state of the environment (enabling conditions). The sulphur import action will result in sulphur inside, if it is present in the environment. The effects of inhibitors is also included, for example, as glucose is imported, and no 6-deoxyglucose is blocking the import, also the useless 2-deoxyglucose will be imported if present.

α(sulfur_import) & θ(sulfur_import)
$\bullet\!\!\rightarrow\!\!\!\!\rightarrow_{0,0,4,1}$ sulfur_inside.
α(glucose_import) & θ(2-deoxyglucose_import)
$\bullet\!\!\rightarrow_{0,0,4,1}$ 2-deoxyglucose_inside.

θ(sulfur_import) $=_{def}$ sulfur_outside.
θ(2-deoxyglucose_import) $=_{def}$ no 6-deoxy_glucose_outside & 2-deoxyglucose_outside & (energy_medium or energy_high).

5. SOFTWARE ENVIRONMENT

Automated support for the continuous time modelling approach has been developed for both simulation and analysis, written in about 18000 lines of C++.

5.1 Simulation Software

As a continuous time extension of the paradigm of executable temporal logic, cf. (Barringer et al., 1996), a simulation program has been written to automatically generate a simulated trace on the basis of a set of temporal 'leads to' relationships. The program is a special purpose tool to derive the results reasoning forwards in time, similar to what happens in executable temporal logic.

In order to derive the consequences of the temporal relationships within a specific interval of time, a cycle is performed, starting at time 0. For each rule, for which the consequent does not already hold, the earliest starting time that the antecedent is satisfied, is computed. The rule with the earliest start time of the antecedent is chosen. If several rules have a satisfied antecedent at exactly the same time, the rule appearing the first in the specification is taken. This rule is then processed at that time, adding the consequent to the trace. This process is repeated until the end point of the simulation time interval is reached or until no rules can be found anymore that can be processed.

Figure 4 gives some sample simulation results. The figure was automatically generated, but because of space only a selection of intentional state properties is shown. The timelines are in seconds, time flows to the right. Dark boxes above the line mean the state property holds, light boxes below the line mean that the state property does not hold. In Figure 4 glucose fluctuates rapidly in the environment; due to the speed of the fluctuations, the cell is able to maintain a stable internal (steady) state.

5.2 Analysis Software

The analysis program that has been constructed takes a set of 'leads to' relationships and an existing trace of behaviour as input and creates an interpretation of what happens in this trace and a check whether all temporal relationships hold. The program marks any deficiencies in the trace compared with what should be there due to the temporal relationships. Both the $\rightarrow\!\!\!\!\rightarrow$ and $\bullet\!\!-$ parts of the temporal relationships are checked.

If a relationship does not hold completely, this is marked in the picture by the program and saved to a log. The program produces yellow marks for unexpected events. At these moments, the event is not produced by any temporal relationship; the event cannot be explained. This indicates whether the model, consisting of the temporal relationships provided to the checking program, is complete with regards to the trace given; the yellow marks show the facts that the given model cannot predict. The red marks indicate that an event has not happened, that should have happened. This indicates faults in the model provided, the red marks signify rules that predict wrongly. In addition to checking whether the rules hold, the checker produces an informal reading of the trace. The reading is automatically generated, using a simple substitution, from the information in the intentional trace.

6. DISCUSSION

The relationship between the chemical regulation substances and the intentional state properties for the behaviour description shows that the intentional model presented in Section 4, encompassing the whole cell, is justified. The simulation of the intentional model proves that the intentional model corresponds to the chemical bacterial regulation. In other words, the BDI model apparently matches well with the regulation that happens in living cells.

In general, the work presented here shows how to intentionalise continuous (real) time processes. The presented method of intentionalisation bridges the gap between processes occurring as a continuous flow and discrete binary decision processes.

For the intentional model, the approach implies that a BDI-model is needed in which temporal relationships are defined between the different intentional state properties, and in relation to events in the external world. In the processing of the temporalised BDI-model introduced, a temporal simulation process replaces the inference process as usually applied to process BDI-models.

The intentional model describes *E. coli* as having a body, the biochemical processes in the real world. Apart from the significance of having a body, it is coupled with its environment; e.g., (Clark, 1997). For work on embodiment see (Dautenhahn, Ogden & Quick, 2002). For an approach to simulating biochemical processes, without using state or time, see (Regev, Silverman & Shapiro, 2001). In (Romero & Karp, 2001), the EcoCyc pathway/genome database is used to predict what substances *E. coli* will produce in a particular growth medium. Also the database is checked for completeness. In (Ideker, Thorsson & Karp, 2000) an acyclic boolean network computes the steady state. It cannot handle varying time delays as the approach in this paper does, yet they plan to in further work. The boolean approach describes each gene with a single logical value. The authors note it can be extended to allow abstracted properties (several genes at once), as well as that the approach could be extended to include different levels of cell regulation, as the approach in this paper does. In contrast to the approaches mentioned, our approach covers continuous time dynamics, also for non-steady state situations.

The value of this work for Biology lies in managing the complexity of living systems. For example, the internal processes within organisms often are so complex that explanations of their behaviour in terms of a large variety of physical and chemical processes are inaccessible. This paper shows how, at least for moderately complex organisms, abstraction and intentionalisation of such continuous processes can be done in a justifiable manner.

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