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Putting Intentions into Cell Biochemistry: An Artificial Intelligence Perspective

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The living cell exists by virtue of thousands of nonlinearly interacting processes. This complexity greatly impedes its understanding. The standard approach to the calculation of the behaviour of the living cell, or part thereof, integrates all the rate equations of the individual processes. If successful extremely intensive calculations often lead the calculation of coherent, apparently simple, cellular "decisions" taken in response to a signal: the complexity of the behavior of the cell is often smaller than it might have been. The "decisions" correspond to the activation of entire functional units of molecular processes, rather than individual ones. The limited complexity of signal and response suggests that there might be a simpler way to model at least some important aspects of cell function. In the field of Artificial Intelligence, such simpler modelling methods for complex systems have been developed. In this paper, it is shown how the Artificial Intelligence description method for deliberative agents functioning on the basis of beliefs, desires and intentions as known in Artificial Intelligence, can be used successfully to describe essential aspects of cellular regulation. This is demonstrated for catabolite repression and substrate induction phenomena in the bacterium *Escherichia coli*. The method becomes highly efficient when the computation is automated in a Prolog implementation. By defining in a qualitative way the food supply of the bacterium, the make-up of its catabolic pathways is readily calculated for cases that are sufficiently complex to make the traditional human reasoning tedious and error prone.

1. Introduction

Thanks to the sequencing of complete genomes, the complexity of the simplest forms of life is becoming delimited. The simplest life forms require some 300 processes (encoded by genes). Simple organisms such as *Escherichia coli* and yeast use a few thousand processes to "live". Due to nonlinear interactions the *true* complexity is of course substantially higher, but limited (Westerhoff *et al.*, 2000). The most straightforward way of understanding cell function on the basis of molecular processes is to write the rate equation for each process explicitly and then integrate all equations numerically. Only recently,

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biochemical information has become sufficiently complete for some parts of the functioning of some cells to make this possible (Bakker *et al.*, 1997; Demin *et al.*, 1999; Teusink *et al.*, 2000). Although this becomes possible for individual pathways, the calculation of larger chunks of the living cell is still much too complex.

It is being realized that simplifications may be possible. Biochemistry has developed simplifying abstractions, such as "metabolic pathway", "operon", "regulon", monofunctional unit (Rohwer *et al.*, 1996), transcriptome and metabolome (Oliver, 1998). In the case of a monofunctional unit the concept is well defined. The other concepts are still somewhat vague and *ad hoc* and not yet ready for immediate translation into mathematical equations that can be implemented in simplified cell modelling.

Accordingly, it may be appropriate to see if other scientific disciplines that may have come across similar problems may have developed systematical ways of dealing with them. Recognizing that cell biochemistry takes decisions effectively when responding to signals, this suggests that the field of Artificial Intelligence might have something to offer in these respects.

One Artificial Intelligence method that appears to correspond approximately to the essence of cell biochemistry is the so-called "BDI model" (Beliefs Desires Intentions model) of a system; for a formal treatment see Rao & Georgeff (1991), for executable models see Georgeff & Lansky (1987) and Brazier *et al.* (1999). Indeed, in informal biochemical discussions "intentions" are sometimes used to describe the apparent sense of purpose of a living cell; however, since this biochemical usage is not defined in a precise (mathematical) manner, it obtains no formal standing, even though it appears to be useful at least heuristically. In this paper, the BDI intentional notions are introduced formally. Moreover, the intentional notions are formally related to specific chemical properties of the cell. This then allows efficient modelling of cell behaviour.

Of course, the more traditional way of modelling bacterial behaviour, using differential equations (e.g. Bakker *et al.*, 1997) leads to a much more detailed description. On the other hand, the logical description to be developed in the present paper may prevent one from not seeing the forest for the trees.

This paper shows how important aspects of the regulation of cell physiology can be gauged in terms of the BDI model (Section 3). First, both the BDI model (Section 2) and the existing understanding of the regulation of cell function (Section 3) will be summarized. Then correspondences between molecular processes in the living cell and BDI concepts will be proposed (Section 4). In Section 5, description in terms of formal logic is developed. An implementation of this description is discussed in Section 6, and an overview is given of results obtained when the bacterium is challenged with various external conditions. In Section 7, it is shown how the implementation of the logical description can be used to derive properties of steady states for an extended model. In Section 8, we shall discuss the results of this paper.

2. The Notations of Belief, Desire and Intention

This section serves as an introduction of the Artificial Intelligence BDI models. In particular,

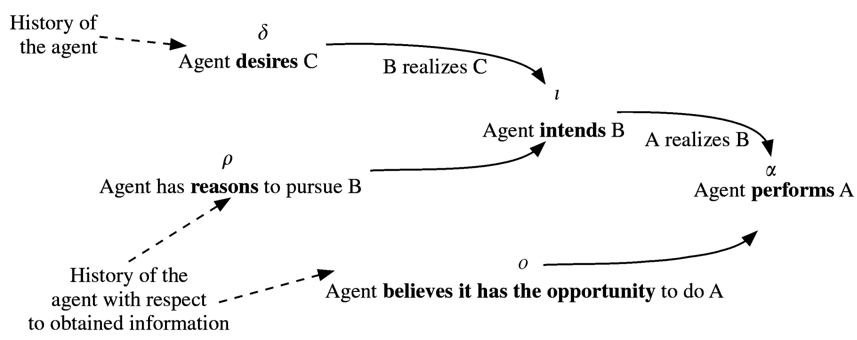

FIG. 1. Relationships for the BDI notions.

the intentional notions and their interdependencies (see Fig. 1) are delineated. The notions of *Belief*, *Desire* and *Intention* are often used to model *agents* in the field of Artificial Intelligence, see Cohen & Levesque (1990) and Rao & Georgeff (1991). Agents are autonomous entities that sense and act on the world (Wooldridge & Jennings, 1995). The interdependencies between the notions (Fig. 1), are based upon a number of simplifying assumptions on *beliefs*, *desires*, and *intentions*.

The history of the agent leads to a set of *desires* by the agent. It is taken that the agent *desires* C, and this *desire* is labelled δ. Also, the history of the agent is relevant for the information obtained previously, and this information is stored as a set of *beliefs*. Some of the *beliefs* are *reasons* for the agent to pursue some B. The *reason* is labelled ρ. As B realizes C, thus making B happen accomplishes C as well, the agent derives that it *intends* B. The *intention* is labelled ι. Based on the observations in the past, the agent might come to *believe* that it has the *opportunity* to do *action* A. The *opportunity* is labelled the Greek letter o. As A realizes B, thus by doing A the agents gets the result B as well, the agent derives that it *performs* A. The *performing* of an *action* is labelled α.

Assumptions on beliefs. In the simplest approach, beliefs are just based on information the agent has received by observation. *Beliefs* are persistent by default: the agent keeps beliefs until the *belief* is overridden by more recent information. This entails the first assumption relevant for modelling the biological cell: if the agent has observed a world fact, then the agent creates a *belief* on the world fact. The second assumption is the converse: for every *belief* on a world fact, the agent observed this world fact.

Assumptions on intentions and desires. In the first place, when an *action* is performed, the agent is assumed to have had an *intention* to do that. Moreover, the second assumption is that an agent who has an *intention* to perform an *action* will execute the *action* if an *opportunity* in the external world (or in the cell's own physical internal state) occurs. Thirdly, it is assumed that every *intention* is based on a *desire*. An agent can have a *desire* for some state of the world as well as a *desire* for some *action* to be performed. When the agent has a set of *desires*, it can choose to pursue some of them. A chosen *desire* can only lead to an *intention* to engage in an *action* if an additional *reason* (Dretske, 1991) is present: the third assumption is that for each *intended action* there is a *reason* and a *desire* as well. The fourth assumption is that if both the *desire* is present and the agent *believes* the *reason* to pursue the *desire* is present, then the *intention* to perform the *action* will be generated.

3. Hierarchical Levels in *E. coli*

A simple biological organism, the bacterium *Escherichia coli*, was chosen as the biological model system. *E. coli* is the best studied bacterium (Neidhardt *et al*., 1996). It is often challenged by changes in the environment and versatile in its responses to these changes. The complete cycle of import, metabolic processing and growth is covered in this paper. For reasons of presentation, the principles are explained using a restricted part of the example (food import), see Section 5. Later, the more complex model is presented in Section 7. With respect to the selection of food, the known preference of glucose over lactose (catabolite or glucose repression) will be considered.

The nutrition import processes are regulated metabolically but also at the levels of transcription and translation. In Fig. 2, four levels of regulation are depicted. The DNA may change through evolution but remains the same within one individual. The DNA is read at the transcription level, assembling ribonucleotides into mRNA when metabolic substances from the metabolism level bind indirectly to specific parts of the DNA. The mRNA molecules are unstable and are read by the translation process (at the translation level). The translation process creates

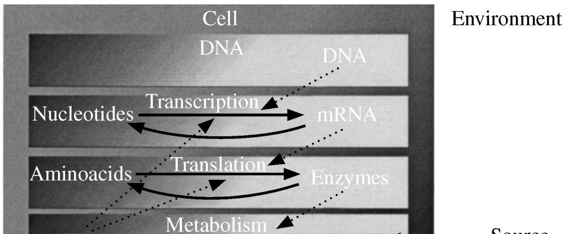

FIG. 2. The levels of regulation in the cell.

enzymes from amino acids. Most enzymes decay rather slowly. At the lowest, metabolic level in the diagram, the processes perform the major cell functions. The catabolic processes release Gibbs energy from food, synthesizing ATP molecules from ADP and inorganic phosphate. The anabolic processes build complex molecules. The transport processes effect the import of sources and an export of waste across the cell membrane.

Although the living cell depend on thousands of processes, it is less than maximally complex, because it is organized in a number of ways. One such organizational principle was made explicit in hierarchical control analysis (Kahn & Westerhoff, 1991; Hofmeyr & Westerhoff, 2001) and is reflected in Fig. 2. Chemistry in the living cell occurs at different levels, at the transcription level, the translation level and the metabolism level. Essentially, there is no chemistry between these levels (this chemistry is neglected) in the sense that substances at the one level are converted to substances at another level. There is, however, influence of chemical substances of one level on processes at other levels. This influence is indicated by dashed lines. Within each level biochemical conversions occur, indicated by full-line arrows. At the mRNA levels this is mRNA synthesis, mRNA processing and mRNA degradation. The levels are not identical in function. The metabolic level is where the primary functions of the cell are effected. The other two levels serve to regulate that metabolic level.

Thus, there are different regulation levels in the bacterium. The metabolism level, the translation level, and the transcription level together control the cell's processes. Substances and process from these regulation levels need to be interpreted in conceptual terms in order to capture the regulation in the cell in a logical perspective.

4. Interpretation of Regulation in BDI Concepts

The notions of belief, desire and intention are used to create a logical perspective of the bacterium. The chemical perspective is the model of a bacterium in terms of substances and chemical reactions (cf. Fig. 3). Two relations are introduced, which are each other's inverse: a *representation* relation, connecting the notions from the logical perspective to the notions from the chemical perspective and an *interpretation* relation, connecting the notions from the chemical perspective to the notions from the logical perspective. The logical *belief* concepts are also the interpretation of chemical notions. They are the result of the observation of the external world (i.e. the growth medium) by the cell. This observed state of the external world is represented inside the cell by a specific configuration of the internal chemistry, for example the cAMP (cyclical AMP) concentration (change) effected by the presence or the absence of glucose in the external world. In this manner, the observation of (external) physical circumstances leads to *beliefs* in the cell.

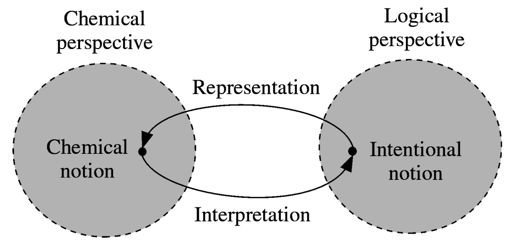

FIG. 3. Relationships between the chemical perspective and the logical perspective.

The easiest case for a cell should be the observation of a substance that passes freely through the cell membrane, the internal concentration of the substance being a clear indication of the external concentration of the substance. In most cells, most external substances may require more subtle means of detection, such as through active transport. In *E. coli*, for many substances the external concentration affects the importing process, by changing the concentration of an inducer substance inside the cell. This inducer then binds to a repressor protein, which then loses its affinity for DNA. The absence of the repressor activates an operon in the DNA, enabling the operon for transcription. The transcription produces mRNA, which will be translated to enzymes, which will change the functioning of the cell. Having acquired these internal configurations representing the external world, the cell can modify its behaviour to act accordingly.

Sometimes more than one option exists for the representation of a belief. The question then is which substance is the most appropriate representation of the *belief*. In the literature (Godfrey-Smith, 1996; Ballim & Wilks, 1991), an external condition is related to an internal substance that represents the *belief* that the external condition is present. The mechanism that produces the *belief* is not considered. Instead, the *belief* is analysed in relation to the chosen internal substance, even though an organism as small as a single cell has elaborate mechanisms for performing observation and establishing *beliefs*. All the other internal substances involved in the observation mechanism may have some bearing on the external substance that is observed as well, and thus also give some indication of the external world state. For example, the external glucose concentration becomes known during its uptake via the phosphotransferase system. One of the components of this uptake system, GlcIIA is predominantly present in its dephosphorylated state when glucose is taken up, while in the absence of glucose it is phosphorylated to GlcIIA-P. The phosphorylated form of GlcIIA activates the adenylyl cyclase enzyme leading to an increase of CRPcAMP levels in the cell necessary for expression of the lac operon. Here, low concentrations of both GlcIIA-P and CRP-cAMP indicate that glucose is outside, but in our model a choice has been made as to which substance represents the *belief*. In our model, the last substance from the mechanism, i.e. the signal that regulates the decisive processes is taken as the *belief*. The reason for this is that affecting these substances directly affects the decision processes. In the example of glucose import, changing the CRPcAMP concentration will cause the cell to make a different decision, but changing the IIAglcP concentration will only cause different behaviour indirectly through a change of CRPcAMP.

4.1. REGULATION IN BACTERIA

The enzyme complement that is present in a living cell can be altered by changes in gene expression, or by changes in protein degradation rates. Adaptation to altered environmental conditions often involves the former. The best-documented cases of regulated gene expression consist of alterations of the frequency of transcription of sets of genes (operons) into mRNA. This is called *transcriptional regulation* (Fig. 4). In the figure only information flow is given, the material flow is not depicted. Thus, the material effects of the chemical reactions are not shown, but the regulatory information effects are. Repressors and activation proteins can bind to the DNA. Chemical substances that are substrates, intermediaries or products of metabolic pathways can bind to such repressors and affect the affinities of the latter for the corresponding DNA. Thus, although all DNA is always present, not all possible mRNAs are synthesized at any moment, but a selection is made. This selection is made during transcription. The mRNA is translated to a polypeptide chain during translation, but again this can be affected by (co)factors. Once mRNA is

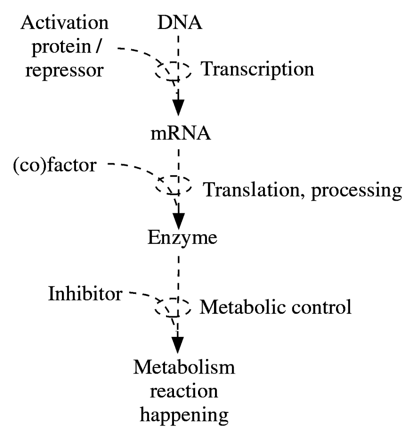

FIG. 4. Transcriptional regulation. Only information flow is shown. The activation protein, e.g. cAMP receptor protein.

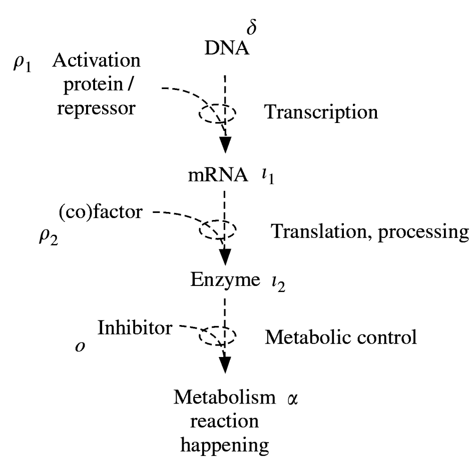

FIG. 5. The transcriptional regulation and corresponding intentional concepts. Only information flow is shown. Legend: δ desire; ρ reason; ι intention; o belief in opportunity; α action.

translated to polypeptide chains, the latter are assembled into enzymes during further processing. The enzymes catalyse metabolic conversions. Inhibitors can modify the enzyme effect, called metabolic control.

4.2. BDI MODEL FOR BACTERIAL REGULATION

In this paper, the BDI model is used to interpret the regulation in bacteria. In order to fit the BDI model to the bacterial regulation model two levels of *intentions* are identified. Thus, a *desire* with an appropriate *reason* gives rise to an *intention*, which in turn when combined with another appropriate *reason* gives rise to another *intention*, and only the latter *intention* when combined with a *belief* in an *opportunity* is capable of causing an *action* to be concluded. This double layer of *intentions* is a small extension of the BDI model.

Figure 5 depicts the transcriptional regulation process (taken from Fig. 4) annotated with an intentional interpretation. The intentional concepts are taken from Fig. 1 in Section 2. Each type of depicted material or process is associated with an intentional notion.

The DNA encodes for masses of unrealized potential substances, and thus chemical reactions and thus things the bacterium can do. Since some of those things may be in conflict with each other, the DNA is interpreted as a *desire* (δ). The inducers and active proteins that bind to the DNA to enable or hamper the transcription of mRNA are decisive factors, and are interpreted as the *beliefs* (β) constituting the *reason* (ρ_1) to pursue the *desire* encoded by the operon being transcribed.

The obtained mRNA is interpreted as an *intention* ι_1) to prepare to execute an *action*. Depending on cofactors that can influence the translation of the mRNA to enzymes, the *action* actually is prepared. These cofactors are interpreted as *beliefs* (β) constituting the *reason* (ρ_2) to prepare for the *action*. The produced enzymes are interpreted as *intentions* (ι_2) to perform the *actions*. When the cell believes that the *opportunity* arises ($\mathbf{o}$),

EXAMPLE. *Transcriptional control of the lac-operon*

Biological facts	*Intentional interpretation*
The *lac*-operon coding for the transport and the first steps in the catabolism of lactose is under both negative and positive control.	The *lac*-operon is part of the DNA, and thus it is a *desire* (δ) for the transport and start of catabolism of lactose. There is a *reason* (ρ_1) affecting the creation of an *intention* (ι_1) from it.
Negative control is mediated by the lac gene product. This lac repressor is constitutively expressed and its binding to the operator site of the operon prevents binding of RNA polymerase to the promoter site. Lactose binds to the repressor thereby decreasing its affinity for the operator site.	The *belief* (β) represented by the lacI gene product being not present is a part of the *reason* (ρ_1) The lacI gene product being present denotes that the bacterium *believes* there is no lactose outside. When lacI is bound to lactose, the bacterium *believes* there is lactose outside.
For efficient transcription of the operon also the cAMP-receptor protein (CRP) needs to be bound near the lac promoter. CRP mediates the positive control, it is activated by binding of cAMP. When *E. coli* is growing on lactose the intracellular concentration of cAMP is high enough to form the CRP. In addition, lactose binds to the lac repressor. In the presence of CRP and inducer bound to the repressor the lac operon is transcribed. When glucose is added to such a cell culture growing on lactose the constitutive expression of the PTS enzymes ensure its uptake. Furthermore, glucose uptake leads to a decreased activity of adenylate cyclase causing the cAMP levels to drop. Thus, the CRP concentrations decrease and the lac operon is no longer transcribed although lactose is still present.	Another part of the *reason* (ρ_1) needed for making the *intention* (ι_1) to import lactose is the *belief* represented by CRP. The cAMP level is high when no glucose is used, thus CRP represents the *belief* that no glucose is present outside. When glucose is present the cAMP level drops, and the *belief* that there is no glucose disappears. And so the *reason* for having the *intention* to import lactose disappears, and the *intention* will be removed.
This preference for the cell to use glucose above other free energy sources is termed catabolite repression.	The term catabolite repression used in biology is modelled by the knowledge that the *intention* (ι_1) to import lactose is only created when there is a *belief* (β) that no glucose is present, which is represented by the presence of CRPcAMP. Similar reasons for other energy sources exist.

meaning (represented by) no inhibitors are present, the metabolic reactions can take place. The metabolic reactions happening together constitute the *action* (α).

In the next example, an intentional interpretation of the transcriptional control of the *lac*-operon is given. Since it is about the control of transcription of a piece of DNA to mRNA, *reason* ρ_2, *intention* ι_2, *opportunity* o and *action* α will not be needed in the interpretation. The use of *belief* β, *desire* δ, *reason* ρ_1 and *intention* ι_1 suffices.

5. A Logical Description for Steady States

In order to reason with the BDI model for bacterial regulation, described in Section 4, and to enable further formal analysis of steady-state behaviour of *E. coli*, a *logical description* has been developed for it. This logical description is not expressed in terms of chemicals or the chemical reactions between chemical substances. The logical description consists of logical formalizations of the intentional notions and logical relationships between these logical notions. These notions and relationships are then used to describe control in bacteria.

Note that propositional predicate logic is used here, with β, δ, ι and α as predicates. The logical symbols used are: $\neg$ which means *not*, $\wedge$ meaning *and*, $\vee$ denoting *or*, $\rightarrow$ meaning *implies* and $\leftrightarrow$ which is the *bi-implication* (if and only if).

Bacteria have many complex chemical reactions inside them, but for constant environmental circumstances (a world state, growth medium) these reactions reach the so-called *steady states* where the fluxes through the reactions remain constant. For each growth medium the steady state can be determined in terms of intermediary concentrations and reaction fluxes. A growth medium can be the basis on which a logical reasoning process can derive the interpretations in terms of BDI notions. This logical reasoning process can be automated and analysed using some rigorous formalization.

For reasons of presentation, a simple model is discussed in this section. In Sections 5.1 and 5.2, the concepts used to describe the material and intentional views on the bacterium are defined, first the growth medium description (Section 5.1) then the intentional notions (Section 5.2). The chemical criteria and logical notations for concepts used are summarized in Tables 1 and 2.

TABLE 1
Logical notions and their chemical criteria

Logical notion	*Chemical criterion*	*Informal reading*
`glucose_externally_present`	Glucose concentration outside the cell at least 0.1 mmol l^{-1}	In the external world glucose is present.
`lactose_externally_present`	Lactose concentration outside the cell at least 0.1 mmol l^{-1}	In the external world lactose is present.
`glucose_internally_present`	Glucose-6-phosphate concentration inside the cell at least 0.1 mmol l^{-1}	Inside the cell glucose is present.
`lactose_internally_present`	Lactose concentration inside the cell at least 0.1 mmol l^{-1}	Inside the cell lactose is present.
`deoxyglucose_internally_present`	Deoxyglucose-6-phosphate concentration inside the cell at least 0.1 mmol l^{-1}	Inside the cell deoxyglucose is present.
`deoxyglucose_externally_present`	Deoxyglucose concentration outside the cell at least 0.1 mmol l^{-1}	In the external world deoxyglucose is present.
`some_nutrition_outside`	Glucose or lactose concentration outside at least 0.1 mmol l^{-1}	At least one source of nutrition is present outside the cell.
`some_nutrition_inside`	Glucose-6-phosphate or lactose concentration inside at least 0.1 mmol l^{-1}	At least one source of nutrition is present inside the cell.

TABLE 2
A concise listing of the concepts and their chemical criteria and logical notations

Belief	*Chemical criterion*	*Logical notation*
Glucose externally present *belief*	CRPcAMP not internally present, concentration at most 0.01 $mmol\,l^{-1}$	β(glucose_externally_present, pos)
Lactose externally present *belief*	Lactose internally present, concentration above 0.1 $mmol\,l^{-1}$	β(lactose_externally_present, pos)
Glucose not externally present *belief*	CRPcAMP internally present, concentration above 0.01 $mmol\,l^{-1}$	β(glucose_externally_present, neg)
Lactose not externally present *belief*	Lactose internally absent, concentration at most 0.1 $mmol\,l^{-1}$	β(lactose_externally_present, neg)
Desire		
Growth *desire*	DNA is present	δ(grow)
Nutrition import *desire*	Lactose and glucose import operons present in DNA	δ(food_import)
Glucose import *desire*	Glucose import operon internally present in DNA	δ(glucose_import)
Lactose import *desire*	Lactose import operon internally present in DNA	δ(lactose_import)
Reason for creation of		
Prepare glucose import *intention*	None	true
Prepare lactose import *intention*	Belief that no glucose is present outside, belief that lactose is present outside	β(glucose_externally_present, neg) $\wedge$ β(lactose_externally_present, pos)
Perform glucose import *intention*	Belief that glucose is present outside	β(glucose_externally_present, pos)
Perform lactose import *intention*	Belief that lactose is present outside	β(lactose_externally_present, pos)
Intention		
Prepare glucose import *intention*	Glucose import mRNA internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(prepare_glucose_import)
Prepare lactose import *intention*	Lactose import mRNA internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(prepare_lactose_import)
Perform glucose import *intention*	Glucose import enzymes internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(perform_glucose_import)
Perform lactose import *intention*	Lactose import enzymes internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(perform_lactose_import)
Opportunity for activity		
Glucose import *action*	None	true
Lactose import *action*	Belief that no glucose is externally present	β(glucose_externally_present, neg)
Action		
Glucose import *action*	Glucose import enzymes are catalysing reactions, flux above 0.1 $mmol\,s^{-1}$.	α(glucose_import)

TABLE 2

(*Continued*)

Belief	*Chemical criterion*	*Logical notation*
Lactose import *action*	Lactose import enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	α(lactose_import)
At least one nutrition import *action*	Lactose or glucose import enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	some_nutrition_import

These concepts used with propositional predicate logic form a logical language with which the logical description can be formally described. In Section 5.3, the logical relationships between these concepts are then given, enabling derivation.

5.1. GROWTH MEDIUM DESCRIPTION

The statements glucose_externally_present and lactose_externally_present denote *external world state statements* expressing that in the external world glucose is present, resp. lactose is present (see Table 1). The statement deoxyglucose_externally_present denotes that deoxyglucose, a glucose look-alike, is present outside, also an external world state statement. The statement some_nutrition_outside denotes that at least one nutrition source is present outside the cell, and the statement some_nutrition_inside denotes that at least one nutrition source is present inside the cell.

The reaction of the cell to the substance deoxyglucose (2-deoxyglucose) has been modelled in this paper. The reaction of the cell to deoxyglucose is similar to the reaction to glucose. The effect of deoxyglucose on the phosphotransferase system that imports glucose seems to be by way of the mannose (a sugar) import system and the HPR substance shared by the glucose and the mannose import system. The reaction of the cell to the sugar alpha-methyl-glucoside is similar to that of deoxyglucose, see Stock *et al.* (1982). The alpha-methyl glucoside is imported directly using the glucose import system, which is a slightly more direct mimicking of glucose. In this paper, the model is restricted to the reaction of the cell to deoxyglucose.

The statement lactose_internally_present denotes that lactose is present inside the bacterium and the statement glucose_internally_present denotes that glucose is present inside the bacterium. Since the glucose import pathway, the phosphotransferase system, deposits the glucose inside the cell as glucose -6-phosphate, the concentration of glucose-6-phosphate is taken as indicating that glucose is present inside the cell. Also, deoxyglucose is phosphorylated on import, resulting in deoxyglucose-6-phosphate inside the cell, denoted as deoxyglucose_internally-present. These statements denote *internal world state statements*. Together with the external world state statements, these denote the *world state statements*.

The necessary situations have already been informally explained, but more rigorous criteria can be applied, making the notions well-defined, see Table 1. The logical notions are taken to hold when the internal chemical state has crossed a particular threshold value, so that glucose_externally_present holds when glucose outside the cell has a concentration of 0.1 mmol l^{-1} or above. Similar chemical criteria are given for the other notions.

In Table 1, the logical notions are listed together with the chemical criterion, stated using chemical notions. This defines the representation and interpretation relations between the logical and chemical notions, see Fig. 3. When the chemical criterion holds, the logical notion is true, and conversely. To explain the notions an informal reading is added as well.

5.2. INTENTIONAL NOTIONS AND CHEMICAL REPRESENTATIONS

The following intentional notions are used.

5.2.1. *Belief Statements*

The logical statement β(glucose_externally_present, pos) denotes that the bacterium has the (positive) *belief* that in the external world glucose is present, i.e. the *belief* that the world fact glucose_externally_present holds, see Table 2. Moreover, β(glucose_externally_present, neg) denotes the *belief* that in the external world glucose is *not* present, i.e. the *belief* that the world fact glucose_externally_present is not true in the world. Similarly, β(lactose_externally_present, pos) and β(lactose_externally_present, neg) denote the *beliefs* about the presence of lactose.

The positive *belief* in glucose β(glucose_externally_present, pos) is the interpretation of CRPcAMP having a very low concentration, below a threshold of 0.01 mmol l^{-1}, see Table 2. The positive *belief* in lactose β(lactose_externally_present, pos) is the interpretation of the lactose concentration being elevated, above a threshold of 0.1 mmol l^{-1}. The *beliefs* in the negation of the world facts are interpretations of the reverse of these situations.

The cell does not have any indication of the presence of only glucose outside, without confusing glucose and deoxyglucose. The cell cannot distinguish glucose from deoxyglucose, and the *belief* that the glucose is present holds for the presence of either glucose or deoxyglucose. Rationally, the import of glucose would only be expected when glucose is present, but because the cell cannot distinguish glucose from deoxyglucose, it will import when either is present. When neither the *belief* that a world fact holds nor the *belief* that it does not hold is true, this means the bacterium has no knowledge about the world fact. Notice that the *belief* that a fact both holds and not holds is expressible, i.e. a *belief* may contradict other *beliefs*. This is not problematic, for the formalization at least, since a *belief* does not always describe the way the world actually is. The bacterium may encounter severe difficulties though if it were to hold such contradictory *beliefs*, as it may readily take the wrong actions.

5.2.2. *Desire Statements*

The logical statement δ(grow) denotes that the bacterium has the *desire* to grow. The more specific statement δ(food_import) states that the bacterium would like to import nutritious substances. The statement δ(glucose_import) denotes the more specific *desire* for the bacterium to import glucose. Similarly, δ(lactose_import) denotes the *desire* to import lactose.

The *desire* δ(grow) is linked to the chemical criterion that the DNA is present in the cell. The *desire* for food import is the interpretation of the part of the DNA that concerns nutrition importing, and the glucose and lactose import *desires* are the interpretation of the glucose and lactose operons.

5.2.3. *Intention Statements*

The statement ι(prepare_glucose_import) denotes that the bacterium has the *intention* to prepare the import of glucose. Similarly, ι(prepare_lactose_import), ι(perform_glucose_import) and ι(perform_lactose_import) denote their corresponding *intentions*.

The material counterpart of ι(prepare_glucose_import) is the existence of mRNA transcribed from the glucose operon. The statement ι(prepare_lactose_import) is the interpretation of the mRNA encoding for lactose import enzymes. The ι(perform_glucose_import) is the interpretation of the glucose import enzymes and ι(perform_lactose_import) is the interpretation of the lactose import enzymes.

5.2.4. *Reason Statements*

Statements for *reasons* to choose an *intention* are specific *belief* statements. A *reason* can be represented by a complex statement using several *beliefs*, connected with $\neg$, $\wedge$ and $\vee$. No *reason* for *intending* to prepare the import of glucose is needed; it is denoted as true. The *reason* for *intending* to prepare to import lactose is that the cell *believes* that both lactose is present outside and no glucose is present outside the cell, denoted as β(lactose_externally_present, pos) $\wedge$ β(glucose_externally_present, neg). The *reason* for *intending* to perform lactose import is the *belief* in the presence of lactose, β(lactose_externally_present, pos) and the *reason* for *intending* to perform glucose import is the *belief* in the presence of glucose outside, denoted as β(glucose_externally_present, pos).

5.2.5. *Opportunity Statements*

Opportunities for the execution of an *action* are world states that will enable the *action* to succeed. The cell needs to *believe* in the *opportunity* being present to conclude to actually perform the *action*. This *belief* can be a complex *belief*. Performing an *action* when there is no *opportunity* for it will not engender the effect aimed for, perhaps no effect at all. The *opportunity* for the import of glucose activity is true, as no *opportunity* is needed. The *opportunity* for the import of lactose is that no glucose is available, thus the *belief* β(glucose_externally_present, neg) is needed to conclude and to actually perform the lactose import *action*.

5.2.6. *Action Statements*

The statement α(glucose_import) denotes that the bacterium is *performing the action* of importing glucose. Similarly, α(lactose_import) denotes that the bacterium is performing the *action* of importing lactose. And some_nutrition_import denotes that the bacterium is performing at least one nutrition import action. They are the interpretations of the glucose, resp. lactose, import reactions. Thus, the intentional notions of *action* have not the interpretation of a material substance, but of a process. The *actions* refer to metabolic processes.

5.3. LOGICAL RELATIONS

The assumptions discussed in Section 2 lead to the following relations (equivalences) assumed between the representations discussed in the previous section.

glucose_externally_present
$\vee$ lactose_externally_present
  $\leftrightarrow$ some_nutrition_outside
glucose_internally_present
$\vee$ lactose_internally_present
  $\leftrightarrow$ some_nutrition_inside
glucose_externally_present $\vee$
  deoxyglucose_externally_present
  $\leftrightarrow$ β(glucose_externally_present, pos)
lactose_externally_present
  $\leftrightarrow$ β(lactose_externally_present, pos)
$\neg$glucose_externally_present $\wedge$
  $\neg$deoxyglucose_externally_present
  $\leftrightarrow$ β(glucose_externally_present, neg)
$\neg$lactose_externally_present
  $\leftrightarrow$ β(lactose_externally_present, neg)

In the above logical relationships, the observation by the bacterium is defined. Thus, the history of the agent is used to conclude *beliefs* (see Fig. 1 in Section 2), here the very recent history when perception has taken place. The *belief* that glucose is present outside is derived when glucose is present outside or deoxyglucose is present outside; if this does not hold, the *belief* does not hold either. The presence of lactose outside leads to the conclusion of the *belief* that lactose is present outside. When both glucose is absent and deoxyglucose is absent, the *belief* that glucose is not present can be derived. Also, from the *belief* that glucose is not present it can be derived that glucose is absent as well as that deoxyglucose is absent. When no lactose is present outside the *belief* that no lactose is present outside can be derived, and conversely. Also, when glucose or lactose is present outside, it can be derived that there is some nutrition outside.

δ(grow)
δ(grow) $\leftrightarrow$ δ(food_import)
δ(food_import) $\leftrightarrow$ δ(lactose_import) $\wedge$
  δ(glucose_import)
δ(lactose_import) $\wedge\, \rho_{1.1}$ $\leftrightarrow$
  ι(prepare_lactose_import)
δ(glucose_import) $\wedge\, \rho_{1.2}$ $\leftrightarrow$
  ι(prepare_glucose_import)

$\rho_{1.1} =_{\text{def}}$ β(lactose_externally_present, pos) $\wedge$
  β(lactose_externally_present, neg).
$\rho_{1.2} =_{\text{def}}$ true.

The statements ρ are *beliefs* for the *reasons*. The reasons are *beliefs* about the external world.

Here, the *desires* of the cell can be used for derivation. The *desire* to grow is always present, and can always be derived. The *desire* to grow implies the *desire* to import food and the *desire* to import food implies the *desire* to grow, since that is the part of the cell behaviour that has been modelled. The desire to import food implies the desire to import lactose and the desire to import glucose, and conversely. The desires in the first three lines are from the history of the agent (see Fig. 1 in Section 2). A desire to import lactose and sufficient reason gives rise to the intention to prepare the import of lactose. Conversely, the intention to prepare the import of lactose leads to the desire to import lactose and the reason to do so (it is assumed that this is the only way to derive the intention to prepare the import of lactose). The desire to import glucose with sufficient reason also gives rise to the intention to prepare to import it and vice versa. In the last two relationships a desire is combined with a reason to imply an intention (see Fig. 1 in Section 2 again), and conversely.

ι(prepare_lactose_import) $\wedge \rho_{2.1}$
  $\leftrightarrow \iota$(perform_lactose_import)
ι(prepare_glucose_import) $\wedge \rho_{2.2}$
  $\leftrightarrow \iota$(perform_glucose_import)
ι(perform_lactose_import) $\wedge o_1$
  $\leftrightarrow \alpha$(lactose_import)
ι(perform_glucose_import) $\wedge o_2$
  $\leftrightarrow \alpha$(glucose_import)

$\rho_{2.1} =_{\text{def}} \beta$(lactose_externally_present, pos).
$\rho_{2.2} =_{\text{def}} \beta$(glucose_externally_present, pos).
$o_1 =_{\text{def}} \beta$(glucose_externally_present, neg).
$o_2 =_{\text{def}}$ true.

The statements o are the *beliefs* in *opportunities*.

In the first two lines, the *intentions* to prepare the import of a substance combined with a *reason* to do so lead to *intentions* to perform the import of the substance, and conversely. The *intention* to perform the import combined with *beliefs* in the *opportunity* to do so gives rise to the actual *action* to import the substance (see Fig. 1 in Section 2). It is assumed that these relationships are the only options to conclude the *action* to import a substance.

α(lactose_import) $\rightarrow$
 (lactose_externally_present $\rightarrow$ lactose_internally_present)
α(glucose_import) $\rightarrow$ (
 (glucose_externally_present $\rightarrow$ glucose_internally_present)
 $\wedge$ (deoxyglucose_externally_present
  $\rightarrow$ deoxyglucose_internally_present))
α(glucose_import) $\vee$ α(lactose_import)
  $\rightarrow$ some_nutrition_import

The effects of *actions* can be derived using these lines. The lactose import *action* will cause the presence of lactose outside to imply the presence of lactose inside. The glucose import *action* means that glucose outside implies that glucose will be present inside the cell and that deoxyglucose outside implies that deoxyglucose will be present inside the cell. For our logical description, it can be assumed that these are the only possibilities to achieve these effects. If the glucose or the lactose import *action* is taken, it can be said that some nutrition import is happening.

In the logical description as given above, the cell can be fooled into falsely *believing* that glucose is present outside by presenting it with deoxyglucose. The cell will also import deoxyglucose with its glucose import mechanism. After prolonged exposure to deoxyglucose, the cell will eventually die. This effect has not been modelled above, as the cell ceases to function when it dies. The logical description represents the behaviour of the cell when it is alive.

This concludes the presentation of the logical description. The representations, from Tables 1 and 2, together with propositional predicate logic form the language to express these relations. The logical notions used in the relations have material representations, linking the logical description to the chemical description. The relations also allow for the derivation of consequences given a growth medium, making an implementation possible.

6. Implementation of the Logical Description

In Artificial Intelligence in the past decades, techniques and tools have been developed to automate reasoning processes. As an example, the logic programming language, *Prolog*, has been developed (Bratko, 2001; Clocksin & Mellish, 1987) that can be used for such automated derivation. A computer program has been implemented in this logic programming language Prolog for the logical formalization. This program is able, for example, to automatically derive the actions and steady state predicted by the logical description given any growth condition. The program has been used to reason from a growth medium towards subsequently determining the *beliefs*, *desires*, *intentions*, *actions* and their effects. In Section 6.1, the Prolog program is presented, followed by an example of automated derivation in Section 6.2. An overview of the derivation results, for the different specific growth conditions, is given in Section 6.3.

6.1. THE PROLOG PROGRAM

In the Prolog code the operator :- is used. It signifies an if–then, an implication, with the conclusion at the front and the conditions afterwards. Thus, the rule `conclusion:- condition1, condition2` will lead to the conclusion whenever both `condition1` and `condition2` have been derived. When no conditions are listed, the conclusion is always derived.

The rules implementing the logical formalization of Section 5.3 are shown in Table 3. The rules in the program are grouped by the type of intentional concept they are to conclude. A growth medium has to be given. Contrary to the notation used in Section 5.3, in the

TABLE 3

A set of Prolog rules to derive intentions, actions and effects for a growth medium

```
01 belief(glucose_externally_present, pos):- world_state(glucose_externally_present, pos).
02 belief(glucose_externally_present, pos):- world_state(deoxyglucose_externally_present, pos).
03 belief(lactose_externally_present, pos):- world_state(lactose_externally_present, pos).
04 belief(glucose_externally_present, neg):- world_state(glucose_externally_present, neg).
   world_state(deoxyglucose_externally_present, neg).
05 belief(lactose_externally_present, neg):- world_state(lactose_externally_present, neg).

06 desire(grow)
07 desire(food_import):- desire(grow).
08 desire(lactose_import):- desire(food_import).
08 desire(glucose_import):- desire(food_import).

10 intention(prepare_lactose_import):- desire(lactose_import),
   belief(lactose_externally_present, pos), belief(glucose_externally_present, neg).
11 intention(prepare_glucose_import):- desire(glucose_import).

12 intention(perform_lactose_import):- intention(prepare_lactose_import),
   belief(lactose_externally_present, pos).
13 intention(perform_glucose_import):- intention(prepare_glucose_import),
   belief(glucose_externally_present, pos).

14 performs(lactose_import):- intention(perform_lactose_import),
   belief(glucose_externally_present, neg).
15 performs(glucose_import):- intention(perform_glucose_import).

16 world_state(lactose_internally_present, pos):- performs(lactose_import),
   world_state(lactose_externally_present, pos).
17 world_state(glucose_internally_present, pos):- performs(glucose_import),
   world_state(glucose_externally_present, pos).
18 world_state(deoxyglucose_internally_present, pos):- performs(glucose_import),
   world_state(deoxyglucose_externally_present, pos).
```

implementation the predicate `world_state` is used to denote the growth conditions, for clarity. Furthermore, in the program β is denoted as `belief`, δ as `desire`, ι as `intention` and α as `performs`.

The first rules, line 1–5, take a world state and conclude the corresponding *belief.* Lines 1–5 show observation of the environment, which is not hindered in any way. If observations were to be hindered, then for each *belief* the rule can be given that concludes the *belief* only if it has been successfully observed. Glucose can be observed correctly, but also it can falsely be observed by concluding the *belief* that glucose is present, based on the fact that deoxyglucose is present. As can be seen in lines 1 and 2, the *belief* that glucose is present can be concluded when glucose is present outside (as in line 1) or when deoxyglucose is present outside (as in line 2). Line 4 concludes the *belief* that no glucose is present, because deoxyglucose and glucose are both absent outside. Lines 3 and 5 conclude the *beliefs* that lactose is present or absent, depending on the situation outside the cell.

The growth *desire* is stated as a fact that is always derived, since it is always true, in line 6. It implies a food importing *desire* in line 7, which in turn implies lactose and glucose uptake *desires* in lines 8 and 9, respectively.

No *reasons* are needed to derive the *intention* to prepare to import glucose from the *desire* in line 11. For deriving the *intention* to prepare to import lactose the *reasons* that lactose is *believed* present and glucose is *believed* absent are needed, see line 10. The *intentions* to perform the import of glucose and lactose are only derived when the preparation for importing is *intended* and the glucose or lactose is *believed* present in lines 12 and 13.

To derive the *action* of importing lactose, the *intention* to perform it must be there and an *opportunity* to do so, here the fact that no glucose is present outside, see line 14. The *action* of importing glucose is derived when the *intention* to perform it exists and no deoxyglucose is present outside, see line 15.

The effects to the world state are derived as well in lines 16, 17 and 18. Lactose becomes present inside when the import is performed and lactose is present outside. Glucose becomes present inside the cell when the import is performed of glucose together with the fact that glucose is present outside. Deoxyglucose becomes present inside the cell when the glucose import *action* is attempted and deoxyglucose is present outside. If both glucose and deoxyglucose are present, the glucose import *action* will import some of both.

6.2. EXAMPLE OF AN AUTOMATED DERIVATION USING THE PROLOG PROGRAM

Thus far, a formalization and implementation for steady states has been discussed. In this section, an example derivation using the Prolog rules given in Table 3, and an overview of the results is discussed after that in Section 6.3.

In this example the growth condition is the following.

Facts on the external world state:

```
glucose_externally_present,
¬lactose_externally_present,
¬deoxyglucose_externally_present.
```

This is denoted as input for the Prolog program as follows:

```
world_state(glucose_externally_present,
pos).
world_state(lactose_externally_present,
neg).
world_state(deoxyglucose_externally_
present, neg).
```

First, it will be shown how the *actions* to perform are derived, these are our goals for the reasoning. Along the way all interesting parts of the program will be visited in this manner.

As Prolog reasons in a goal-directed manner, the first question is whether the statement `performs(lactose_import)` can be derived, see Fig. 6. Note that the numbers given in the picture refer to the program lines in Table 3. A large X means that the goal is considered underivable, a $\surd$ means that a goal can be derived successfully. Line 14 in Table 3 is considered, and the conditions are examined. Whatever the result for `intention(perform_lactose_import)`, the condition `belief (glucose_externally_present, neg)` is not fulfilled, since that would have to be concluded

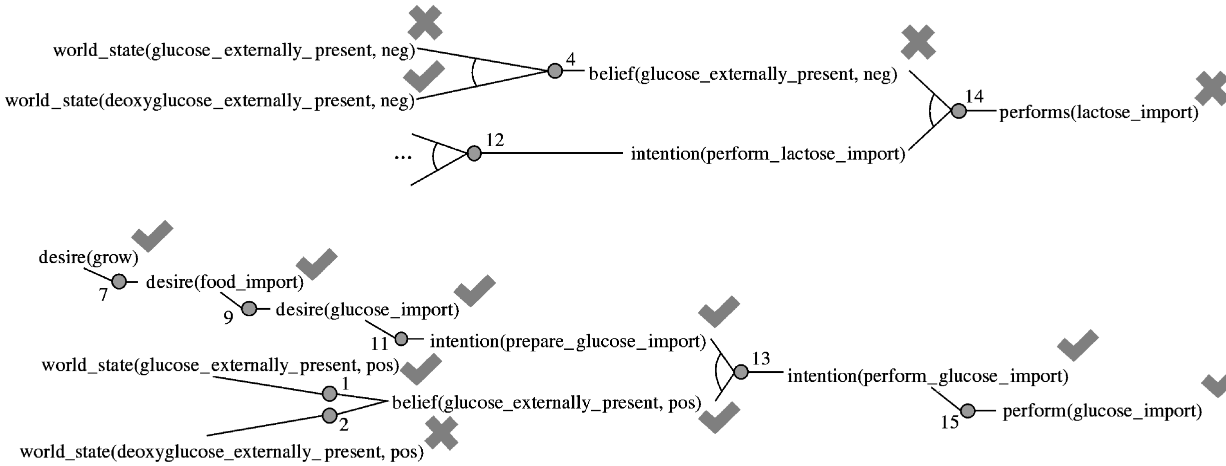

FIG. 6. The derivation depicted as an AND/OR graph with line numbers (an arc means *and*).

by line 4, requiring `world_state(glucose_externally_present, neg)`, and `world_state(deoxyglucose_externally_present, neg)`, of which only `world_state(deoxyglucose_externally_present, neg)` can be derived. Thus, the conclusion is not derived.

Next, a look is taken at the other goal, namely `performs(glucose_import)` see Fig. 6. This leads to examining line 15 of Table 3. The statement `intention(perform_glucose_import)` must be derived. For the *intention* a look is taken at line 13, and it will turn out that `intention(prepare_glucose_import)` can be derived as well as `belief(glucose_externally_present, pos)`. The *belief* can be derived using line 1. For the statement `intention(prepare_glucose_import)` take a look at line 11. To derive `intention(prepare_glucose_import)` the statement `desire(glucose_import)` should be derived.

The statement `desire(glucose_import)` can be derived using line 9. It needs that `desire(food_import)` is derived, which can be derived via line 7, needing `desire(grow)` in turn. The statement `desire(grow)` is stated as a fact, not needing any conditions to be derived, using line 6.

At this point, enough lines of code have been examined and the conclusion can be drawn that the cell performs glucose import. The Prolog interpreter performed these derivations automatically for each intentional notion, as well as the importing effects, to make Table 6 in the next section.

7. Extended Model and Results from the Implementation for Different Growth Conditions

In this section, a more complex example is built, as an extension of the smaller example. This increased complexity results in predictions made by experts for the effects of a certain growth medium being tedious and often wrong. First, the notions used in the more complex example are presented. Then, the intentional notions used in this extended example are discussed. Finally, the results obtained from a set of computer calculations are explained, showing that they are correct and proving that the model is of value for making predictions.

7.1. GROWTH MEDIUM DESCRIPTION

This example builds upon the smaller example, describing the cell regulation in more detail and complexity. The situations described and predicted by this model are hard to derive by means other than by a computer. Biologists are often wrong when trying to assess these situations, as the complexity is getting larger. First, the set of external world state statements are described, then the internal world state statements. Then the intentional notions are described, and the logical relationships are given. These logical relationships then enable the use of a computer as a calculator, in order to predict states.

The external world state statements describe the situation in the external world, the growth conditions. The presence or absence of nutrition sources, inhibitors and growth resources can be stated.

The statements `glucose_low_externally_present`, `glucose_medium_externally_present` and `glucose_high_externally_present` denote the amount of glucose present outside the cell. The three categories are used in order to distinguish the behaviour of the cell in the different cases. The statement `lactose_externally_present` denotes the presence of lactose.

The presence of the inhibitors 2-deoxyglucose and 6-deoxyglucose can be denoted using the statements `2-deoxyglucose_externally_present` and `6-deoxyglucose_externally_present`. The effect of these inhibitors is the same as in the smaller example.

The presence of oxygen outside the cell can be denoted using the statement `oxygen_externally_present`. The presence of the carbon providing buildingblocks, of the sources for nitrogen, phosphor and sulphur are denoted using the statements `buildingblocks_externally_present`, `nitrogen_externally_present`, `phosphor_externally_present` and `sulphur_externally_present`.

The internal state statements of the cell concern the physical situation inside the cell. The nutrition sources are denoted by the statements `glucose_internally_present` and `lactose_internally_present`. The discrimination between several levels of glucose presence is not needed when glucose has been imported for the description of the regulation behaviour.

The oxygen present inside is denoted by the statement `oxygen_internally_present`. The sources for carbons in the buildingblocks, the sources for nitrogen, phosphor and sulphur are denoted using the statements `buildingblocks_internally_present`, `nitrogen_internally_present`, `phosphor_internally_present` and `sulphur_internally_present`.

The energy in the cell is described using the statements `energy_low`, `energy_medium` and `energy_high`. These statements describe the ATP concentration in the cell.

In Table 4, the logical notions are listed together with the chemical criterion, stated using chemical notions for the world state statements. This defines the representation and interpretation relations for the world state statements and the chemical conditions inside and outside the cell. An informal reading is added in the table for explanation.

All the intentional notions used are presented here, sorted by intention.

7.1.1. *Belief Statements*

The logical statement β`(glucose_externally_present, pos)` holds when the bacterium *believes* that glucose is present outside, which is an interpretation of the concentration of the substance CRPcAMP. When the CRPcAMP concentration is at most 0.01 mmol l^{-1} the *belief* holds, as glucose is detected. When the CRPcAMP contraction is above 0.01 mmol l^{-1}, then the *belief* will not hold. The logical statement β`(glucose_externally_present, neg)` is another interpretation of the concentration of CRPcAMP, which holds when no glucose is detected. Similarly, there are *beliefs* for the lactose, oxygen, buildingblocks, nitrogen, phosphor and sulphur presence outside, see Table 5. These *beliefs* also are interpretations of substances in the cell, see Table 5.

7.1.2. *Desire Statements*

The logical statement δ`(grow)` denotes that the bacterium has the *desire* to grow. This is the interpretation of the fact that the cell has DNA. More specific parts of the DNA code for more specific desires. When the nutrition import operons are present in the DNA, δ`(food_import)` holds. When the glucose import operon is present in the DNA, δ`(glucose_import)` holds. When the lactose import operon is present in the DNA, δ`(lactose_import)` holds.

When the energy production operons, the catabolism operons, are present in the DNA, δ`(energy)` holds. When the respiration operon and fermentation operon are present, δ`(respiration)` and δ`(fermentation)` hold. When the anabolism operons are present in the

TABLE 4
Logical notions and their chemical criteria

Logical notion	*Chemical criterion*	*Informal reading*
glucose_low_externally_present	Glucose concentration outside the cell below 0.01 $mmol\,l^{-1}$	In the external world there is almost no glucose present.
glucose_medium_externally_present	Glucose concentration outside the cell at least 0.01 $mmol\,l^{-1}$ but below 0.1 $mmol\,l^{-1}$	In the external world some glucose is present.
glucose_high_externally_present	Glucose concentration outside the cell at least 0.1 $mmol\,l^{-1}$	In the external world a lot of glucose is present.
lactose_externally_present	Lactose concentration outside the cell at least 0.1 $mmol\,l^{-1}$	In the external world lactose is present.
2-deoxyglucose_externally_present	2-Deoxyglucose concentration outside the cell at least 0.1 $mmol\,l^{-1}$	In the external world 2-deoxyglucose is present.
6-deoxyglucose_externally_present	6-Deoxyglucose concentration outside the cell at least 0.1 $mmol\,l^{-1}$	In the external world 6-deoxyglucose is present.
oxygen_externally_present	Oxygen concentration outside the cell at least 0.1 $mmol\,l^{-1}$	In the external world oxygen is present.
buildingblocks_externally_present	The building blocks' concentration outside the cell is at least 0.1 $mmol\,l^{-1}$	Building blocks are present outside the cell.
nitrogen_externally_present	Nitrogen concentration outside the cell is at least 0.1 $mmol\,l^{-1}$	Nitrogen is present outside the cell.
phosphor_externally_present	Phosphor concentration outside the cell is at least 0.1 $mmol\,l^{-1}$	Phosphor is present outside the cell.
sulphur_externally_present	Sulphur concentration outside the cell is at least 0.1 $mmol\,l^{-1}$	Sulphur is present outside the cell.
glucose_internally_present	Glucose-6-phosphate concentration inside the cell at least 0.1 $mmol\,l^{-1}$	Inside the cell glucose is present.
lactose_internally_present	Lactose concentration inside the cell at least 0.1 $mmol\,l^{-1}$	Inside the cell lactose is present.
2-deoxyglucose_internally_present	2-Deoxyglucose-6-phosphate concentration inside the cell at least 0.1 $mmol\,l^{-1}$	Inside the cell 2-deoxyglucose is present.
oxygen_internally_present	Oxygen concentration inside the cell at least 0.1 $mmol\,l^{-1}$	Inside the cell oxygen is present.
buildingblocks_internally_present	The building blocks' concentration inside the cell is at least 0.1 $mmol\,l^{-1}$	Building blocks are present inside the cell.
nitrogen_internally_present	Nitrogen concentration inside the cell is at least 0.1 $mmol\,l^{-1}$	Nitrogen is present inside the cell.
phosphor_internally_present	Phosphor concentration inside the cell is at least 0.1 $mmol\,l^{-1}$	Phosphor is present inside the cell.
sulphur_internally_present	Sulphur concentration inside the cell is at least 0.1 $mmol\,l^{-1}$	Sulphur is present inside the cell.
energy_low	Inside the cell the ATP concentration is below 0.1 $mmol\,l^{-1}$	Little energy is available inside the cell.
energy_medium	Inside the cell the ATP concentration is at least 0.1 $mmol\,l^{-1}$ but below 0.15 $mmol\,l^{-1}$	Some energy is available inside the cell.
energy_high	Inside the cell the ATP concentration is at least 0.15 $mmol\,l^{-1}$	Much energy is available inside the cell.

TABLE 5

A concise listing of the concepts and their chemical criteria and logical notations

Belief	Chemical criterion	Logical notation
Glucose externally present *belief*	CRPcAMP not internally present, concentration at most 0.01 mmol l^{-1}	β(glucose_externally_present, pos)
Glucose not externally present *belief*	CRPcAMP internally present concentration above 0.01 mmol l^{-1}	β(glucose_externally_present, neg)
Lactose externally present *belief*	Lactose internally present concentration above 0.1 mmol l^{-1}	β(lactose_externally_present, pos)
Lactose not externally present *belief*	Lactose internally absent concentration at most 0.1 mmol l^{-1}	β(lactose_externally_present, neg)
Oxygen externally present *belief*	Oxygen internally present concentration above 0.1 mmol l^{-1}	β(oxygen_externally_present, pos)
Oxygen not externally present *belief*	Oxygen internally absent concentration at most 0.1 mmol l^{-1}	β(oxygen_externally_present, neg)
Buildingblocks externally present *belief*	Buildingblocks internally present concentration above 0.1 mmol l^{-1}	β(buildingblocks_externally_present, pos)
Buildingblocks not externally present *belief*	Buildingblocks internally absent concentration at most 0.1 mmol l^{-1}	β(buildingblocks_externally_present, neg)
Nitrogen externally present *belief*	Nitrogen internally present concentration above 0.1 mmol l^{-1}	β(nitrogen_externally_present, pos)
Nitrogen not externally present *belief*	Nitrogen internally absent concentration at most 0.1 mmol l^{-1}	β(nitrogen_externally_present, neg)
Phosphor externally present *belief*	Phosphor internally present concentration above 0.1 mmol l^{-1}	β(phosphor_externally_present, pos)
Phosphor not externally present *belief*	Phosphor internally absent concentration at most 0.1 mmol l^{-1}	β(phosphor_externally_present, neg)
Sulphur externally present *belief*	Sulphur internally present concentration above 0.1 mmol l^{-1}	β(sulphur_externally_present, pos)
Sulphur not externally present *belief*	Sulphur internally absent concentration at most 0.1 mmol l^{-1}	β(sulphur_externally_present, neg)
Desire		
Growth desire	DNA is present	δ(grow)
Nutrition import *desire*	Lactose and glucose import operons present in DNA	δ(food_import)
Glucose import *desire*	Glucose import operon internally present in DNA	δ(glucose_import)
Lactose import *desire*	Lactose import operon internally present in DNA	δ(lactose_import)
Energy *desire*	Respiration and fermentation operon internally present in DNA	δ(energy)
Respiration *desire*	Respiration operon internally present in DNA	δ(respiration)
Fermentation *desire*	Fermentation operon internally present in DNA	δ(fermentation)

Anabolism *desire*	Anabolism operons internally present in DNA	δ(anabolism)
Resources import *desire*	Resources import operon internally present in DNA	δ(resources)
Buildingblocks import *desire*	Buildingblocks import operon internally present in DNA	δ(buildingblocks_import)
Nitrogen import *desire*	Nitrogen import operon internally present in DNA	δ(nitrogen_import)
Phosphor import *desire*	Phosphor import operon internally present in DNA	δ(phosphor_import)
Sulphur import *desire*	Sulphur import operon internally present in DNA	δ(sulphur_import)
Reason for creation of		
Prepare glucose import *intention*	None	true
Prepare lactose import *intention*	*Belief* that no glucose is present outside, *belief* that lactose is present outside	β(glucose_externally_present, neg) ∧ β(lactose_externally_present, pos)
Prepare anabolism *intention*	*Belief* that buildingblocks are present outside, *belief* that nitrogen is present outside, *belief* that phosphor is present outside, *belief* that sulphur is present outside	β(buildingblocks_externally_present, pos) ∧ β(nitrogen_externally_present, pos) ∧ β(phosphor_externally_present, pos) ∧ β(sulphur_externally_present, pos)
Prepare respiration *intention*	*Belief* that oxygen is present outside	β(oxygen_externally_present, pos)
Prepare fermentation *intention*	*Belief* that no oxygen is present outside	β(oxygen_externally_present, neg)
Prepare buildingblocks import *intention*	*Belief* that buildingblocks are present outside	β(buildingblocks_externally_present, pos)
Prepare nitrogen import *intention*	*Belief* that nitrogen is present outside,	β(nitrogen_externally_present, pos)
Prepare phosphor import *intention*	*Belief* that phosphor is present outside,	β(phosphor_externally_present, pos)
Prepare sulphur import *intention*	*Belief* that sulphur is present outside	β(sulphur_externally_present, pos)
Perform glucose import *intention*	*Belief* that glucose is present outside	β(glucose_externally_present, pos)
Perform lactose import *intention*	*Belief* that lactose is present outside	β(lactose_externally_present, pos)
Perform anabolism *intention*	*None*	true
Perform respiration *intention*	*None*	true
Perform fermentation *intention*	*None*	true
Perform buildingblocks import *intention*	*None*	true
Perform nitrogen import *intention*	*None*	true
Perform phosphor import *intention*	*None*	true
Perform sulphur import *intention*	*None*	true
Intention		
Prepare glucose import *intention*	Glucose import mRNA internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(prepare_glucose_import)

TABLE 5

(*Continued*)

Belief	Chemical criterion	Logical notation
Prepare lactose import *intention*	Lactose import mRNA internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(prepare_lactose_import)
Prepare anabolism *intention*	Anabolism mRNA internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(prepare_anabolism)
Prepare respiration *intention*	Respiration mRNA internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(prepare_respiration)
Prepare fermentation *intention*	Fermentation mRNA internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(prepare_fermentation)
Prepare buildingblocks import *intention*	Buildingblocks import mRNA internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(prepare_buildingblocks_import)
Prepare nitrogen import *intention*	Nitrogen import mRNA internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(prepare_nitrogen_import)
Prepare phosphor import *intention*	Phosphor import mRNA internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(prepare_phosphor_import)
Prepare sulphur import *intention*	Sulphur import mRNA internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(prepare_sulphur_import)
Perform glucose import *intention*	Glucose import enzymes internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(perform_glucose_import)
Perform lactose import *intention*	Lactose import enzymes internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(perform_lactose_import)
Perform anabolism *intention*	Anabolism enzymes internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(perform_anabolism)
Perform respiration *intention*	Respiration enzymes internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(perform_respiration)
Perform fermentation *intention*	Fermentation enzymes internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(perform_fermentation)
Perform buildingblocks import *intention*	Buildingblocks import enzymes internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(perform_buildingblocks_import)
Perform nitrogen import *intention*	Nitrogen import enzymes internally present, concentration above 0.1 $mmol\,l^{-1}$	ι(perform_nitrogen_import)

Perform phosphor import *intention*	Phosphor import enzymes internally present, concentration above 0.1 mmol l^{-1}	ι(perform_phosphor_import)
Perform sulphur import *intention*	Sulphur import enzymes internally present, concentration above 0.1 mmol l^{-1}	ι(perform_sulphur_import)
Opportunity for activity		
Glucose import *action*	None	true
Lactose import *action*	*Belief* that no glucose is externally present	β(glucose_externally_present, neg)
Anabolism *action*	None	true
Respiration *action*	*Belief* that oxygen is externally present	β(oxygen_externally_present, pos)
Fermentation *action*	*Belief* that no oxygen is externally present	β(oxygen_externally_present, neg)
Buildingblocks import *action*	None	true
Nitrogen import *action*	None	true
Phosphor import *action*	None	true
Sulphur import *action*	None	true
Action		
Glucose import *action*	Glucose import enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	α(glucose_import)
Lactose import *action*	Lactose import enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	α(lactose_import)
At least one nutrition import *action*	Lactose or glucose import enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	some_nutrition_import
Anabolism *action*	Anabolism enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	α(anabolism)
Respiration *action*	Respiration enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	α(respiration)
Fermentation *action*	Fermentation enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	α(fermentation)
Buildingblocks import *action*	Buildingblocks import enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	α(buildingblocks_import)
Nitrogen import *action*	Nitrogen import enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	α(nitrogen_import)
Phosphor import *action*	Phosphor import enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	α(phosphor_import)
Sulphur import *action*	Sulphur import enzymes are catalysing reactions, flux above 0.1 mmol s^{-1}.	α(sulphur_import)

DNA, δ(anabolism) holds. When the resource import operons are present, δ(resources) holds, and each of the resource import operons is interpreted as a *desire* too; buildingblocks import operon by δ(buildingblocks_import), nitrogen import operon by δ(nitrogen_import) phosphor import operon by δ(phosphor_import) and the sulphur import operon by δ(sulphur_import).

7.1.3. *Intention Statements*

The statement ι(prepare_glucose_import) denotes that the bacterium has the *intention* to prepare the import of glucose. This is the interpretation of the existence of mRNA of the glucose enzymes in the cell. The statements ι(prepare_lactose_import), ι(prepare_anabolism), ι(prepare_respiration), ι(prepare_fermentation), ι(prepare_buildingblocks_import), ι(prepare_nitrogen_import), ι(prepare_phosphor_import) and ι(prepare_sulphur_import) denote similar *intentions.*

The statement ι(perform_glucose_import) denotes that the bacterium *intends* to perform the import of glucose when the *opportunity* presents itself. This is an interpretation of the concentration of the glucose import enzymes, which is elevated. The statements ι(perform_lactose_import), ι(perform_anabolism), ι(perform_respiration), ι(perform_fermentation), ι(perform_buildingblocks_import), ι(perform_nitrogen_import), ι(perform_phosphor_import) and ι(perform_sulphur_import) denote similar *intentions.*

7.1.4. *Reason Statements*

The *reasons* for the creation of the *intentions* are interpretations of the regulation factors that, perhaps indirectly, cause the transcription or translation of the representation of those intentions in the cell. In the table, the chemical criterion for these *reasons* refers to the chemical criteria for zero or more *beliefs*, which should be taken together. For constitutionally produced substances, no *reason* is needed as they are always created.

7.1.5. *Opportunity Statements*

When the cell has an *intention* to perform an *action* and *believes* it has an *opportunity*, it will perform that *action.* The *opportunities* for *actions* are listed in the table, with the chemical criterion referring to the criteria of *beliefs.*

When the respiration enzymes are present, oxygen is needed in order to perform the respiration *action.* If no oxygen is present, the respiration enzymes will not function.

Also, the fermentation requires the absence of oxygen. This is not immediately obvious, but is nevertheless the case. The enzyme pyruvateformeatliase, in the front of the fermentation pathway, is sensitive to oxygen. Thus, the absence of oxygen is the *opportunity* that is needed to perform fermentation. As more understanding about the *opportunities* for specific metabolic *actions* is gained, these can easily be incorporated in the model, as the addition of the fermentation *opportunity* shows.

7.1.6. *Action Statements*

The statement α(glucose_import) denotes that the bacterium *is performing the action* of importing glucose. The statements α(lactose_import), α(anabolism), α(respiration), α(fermentation), α(buildingblocks_import), α(nitrogen_import), α(phosphor_import), α(sulphur_import), denote similarly that the cell is performing those *actions.*

The import of oxygen is not actively performed by the cell. This happens by the diffusion of oxygen through the membrane. It is modelled accordingly, as a relationship between physical states of the outside world and inside of the cell.

7.2. RELATIONSHIPS FOR THE EXTENDED EXAMPLE

The logical relationships in the complex example are presented here. Later, these relationships will be coded into a Prolog program, to be executed by a computer.

buildingblocks_externally_present $\leftrightarrow$
  β(buildingblocks_externally_present, pos)

$\neg$ buildingblocks_externally_present $\leftrightarrow$
  β(buildingblocks_externally_present, neg)

nitrogen_externally_present ↔ β(nitrogen_externally_present, pos)
¬ nitrogen_externally_present ↔ β(nitrogen_externally_present, neg)
phosphor_externally_present ↔ β(phosphor_externally_present, pos)
¬ phosphor_externally_present ↔ β(phosphor_externally_present, neg)
sulphur_externally_present ↔ β(sulphur_externally_present, pos)
¬ sulphur_externally_present ↔ β(sulphur_externally_present, neg)
oxygen_externally_present ↔ β(oxygen_externally_present, pos)
¬ oxygen_externally_present ↔ β(oxygen_externally_present, neg)
lactose_externally_present ↔ β(lactose_externally_present, pos)
¬ lactose_externally_present ↔ β(lactose_externally_present, neg)
(glucose_high_externally_present ∨ 2-deoxyglucose_externally_present) ∧ ¬6-deoxyglucose_externally_present ∧ (energy_high ∨ energy_medium) ↔ β(glucose_externally_present, pos)
(¬(glucose_high_externally_present ∨ 2-deoxyglucose_externally_present) ∨ 6-deoxyglucose_externally_present) ∧ (energy_high ∨ energy_medium) ↔ β(glucose_externally_present, neg)
(glucose_high_externally_present ∨ glucose_medium_externally_present ∨ 2-deoxyglucose_externally_present) ∧ ¬6-deoxyglucose_externally_present ∧ energy_low ↔ β(glucose_externally_present, pos)
(¬(glucose_high_externally_present ∨ glucose_medium_externally_present ∨ 2-deoxyglucose_externally_present) ∨ 6-deoxyglucose_externally_present) ∧ energy_low ↔ β(glucose_externally_present, neg)

The cell senses its environment. To this effect, the outside values determine the *beliefs* that the cell has. Conversely, the *beliefs* of the cell indicate the outside values. Most of these sensing rules are straightforward, but the glucose sensing needs further explication. First of all, 2-deoxyglucose looks just like glucose, and will cause the cell to *believe* that glucose is present outside. Second, the inhibitor 6-deoxyglucose inhibits the uptake, and sensing of the presence of glucose, blinding the cell to the presence of glucose. Moreover, the glucose sensing is further complicated by the fact that the sensitivity depends on the amount of energy available to the cell. At high and medium energy levels, the cell will only sense glucose that is abundantly present outside, glucose_high_externally_present. But at low-energy levels, the cell is more sensitive. At low energy the cell will sense glucose when glucose_high_externally_present as well as when glucose_medium_externally_present.

δ(grow).
δ(grow) ↔ δ(food_import) ∧ δ(energy) ∧ δ(anabolism) ∧ δ(resources)
δ(food_import) ↔ δ(lactose_import) ∧ δ(glucose_import)
δ(energy) ↔ δ(respiration) ∧ δ(fermentation)
δ(resources) ↔ δ(buildingblocks_import) ∧ δ(nitrogen_import) ∧ δ(phosphor_import) ∧ δ(sulphur_import).

The *desire* to grow is always present. The *desire* to grow means a *desire* to import nutrition, to have energy (catabolism), to make cellparts (anabolism) and to gather resources. The *desire* to import food means a *desire* to import lactose and a *desire* to import glucose. The *desire* to have sufficient energy means a *desire* to respire and the *desire* to fermentate. The *desire* to have sufficient resources means a *desire* to import building blocks, to import nitrogen, to import phosphor and to import sulphur.

δ(lactose_import) ∧ $\rho_{1.1}$ ↔ ι(prepare_lactose_import)
δ(glucose_import) ∧ $\rho_{1.2}$ ↔ ι(prepare_glucose_import)
δ(anabolism) ∧ $\rho_{1.3}$ ↔ ι(prepare_anabolism)
δ(respiration) ∧ $\rho_{1.4}$ ↔ ι(prepare_respiration)
δ(fermentation) ∧ $\rho_{1.5}$ ↔ ι(prepare_fermentation)
δ(buildingblocks_import) ∧ $\rho_{1.6}$ ↔ ι(prepare_buildingblocks_import)

δ(nitrogen_import) $\wedge$ $\rho_{1.7}$
$\leftrightarrow$ ι(prepare_nitrogen_import)
δ(phosphor_import) $\wedge$ $\rho_{1.8}$ $\leftrightarrow$
ι(prepare_phosphor_import)
δ(sulphur_import) $\wedge$ $\rho_{1.9}$
$\leftrightarrow$ ι(prepare_sulphur_import)

$\rho_{1.1} =_{def}$ β(lactose_externally_present, pos) $\wedge$ β(glucose_externally_present, neg).
$\rho_{1.2} =_{def}$ true.
$\rho_{1.3} =_{def}$ β(buildingblocks_externally_present, pos) $\wedge$
β(nitrogen_externally_present, pos) $\wedge$
β(phosphor_externally_present, pos) $\wedge$
β(sulphur_externally_present, pos).
$\rho_{1.4} =_{def}$ β(oxygen_externally_present, pos).
$\rho_{1.5} =_{def}$ β(lactose_externally_present, neg).
$\rho_{1.6} =_{def}$ β(buildingblocks_externally_present, pos).
$\rho_{1.7} =_{def}$ β(nitrogen_externally_present, pos).
$\rho_{1.8} =_{def}$ β(phosphor_externally_present, pos).
$\rho_{1.9} =_{def}$ β(sulphur_externally_present, pos).

The *desires* combined with *reasons* will give *intentions* to prepare the execution of *actions*. Conversely, the *intention* to prepare for an *action* ads to the *desire* for that *action* and a *reason* being present. The *reason* for lactose import is the *belief* in the absence of glucose and the *believed* presence of lactose. Glucose import is always done, so the *reason* is denoted as true. The *reason* to *intend* to prepare for anabolism is the *belief* in the presence of all resources. The *reason* to *intend* to prepare for respiration is the *belief* in the presence of oxygen, for fermentation this is the *belief* in the absence of oxygen. The *reason* to *intend* to prepare the import of a resource, such as the buildingblocks, nitrogen, phosphor or sulphur, is the *belief* that the resource is present outside the cell.

ι(prepare_lactose_import) $\wedge$ $\rho_{2.1}$ $\leftrightarrow$
ι(perform_lactose_import)
ι(prepare_glucose_import) $\wedge$ $\rho_{2.2}$ $\leftrightarrow$
ι(perform_glucose_import)
ι(prepare_anabolism) $\wedge$ $\rho_{2.3}$ $\leftrightarrow$
ι(perform_anabolism)
ι(prepare_respiration) $\wedge$ $\rho_{2.4}$ $\leftrightarrow$
ι(perform_respiration)
ι(prepare_fermentation) $\wedge$ $\rho_{2.5}$ $\leftrightarrow$
ι(perform_fermentation)
ι(prepare_buildingblocks_import) $\wedge$ $\rho_{2.6}$ $\leftrightarrow$
ι(perform_buildingblocks_import)
ι(prepare_nitrogen_import) $\wedge$ $\rho_{2.7}$ $\leftrightarrow$
ι(perform_nitrogen_import)
ι(prepare_phosphor_import) $\wedge$ $\rho_{2.8}$ $\leftrightarrow$
ι(perform_phosphor_import)
ι(prepare_sulphur_import) $\wedge$ $\rho_{2.9}$ $\leftrightarrow$
ι(perform_sulphur_import)
ι(perform_lactose_import) $\wedge$ o_1 $\leftrightarrow$
α(lactose_import)
ι(perform_glucose_import) $\wedge$ o_2 $\leftrightarrow$
α(glucose_import)
ι(perform_anabolism) $\wedge$ o_3 $\leftrightarrow$ α(anabolism)
ι(perform_respiration)
$\wedge$ o_4 $\leftrightarrow$ α(respiration)
ι(perform_fermentation) $\wedge$ o_5 $\leftrightarrow$
α(fermentation)
ι(perform_buildingblocks_import) $\wedge$ o_6 $\leftrightarrow$
α(buildingblocks_import)
ι(perform_nitrogen_import) $\wedge$ o_7 $\leftrightarrow$
α(nitrogen_import)
ι(perform_phosphor_import) $\wedge$ o_8 $\leftrightarrow$
α(phosphor_import)
ι(perform_sulphur_import) $\wedge$ o_9 $\leftrightarrow$
α(sulphur_import)
$\rho_{2.1} =_{def}$ β(lactose_externally_present, pos).
$\rho_{2.2} =_{def}$ β(glucose_externally_present, pos).
$\rho_{2.3} =_{def}$ true.
$\rho_{2.4} =_{def}$ true.
$\rho_{2.5} =_{def}$ true.
$\rho_{2.6} =_{def}$ true.
$\rho_{2.7} =_{def}$ true.
$\rho_{2.8} =_{def}$ true.
$\rho_{2.9} =_{def}$ true.
$o_1 =_{def}$ β(glucose_externally_present, neg).
$o_2 =_{def}$ true.
$o_3 =_{def}$ true.
$o_4 =_{def}$ β(oxygen_externally_present, pos).
$o_5 =_{def}$ β(oxygen_externally_present, neg).
$o_6 =_{def}$ true.
$o_7 =_{def}$ true.
$o_8 =_{def}$ true.
$o_9 =_{def}$ true.

The *intention* to prepare to execute an *action* together with a *reason*, gives the *intention* to perform the *action*. Conversely, the *intention* to perform the *action* leads to the *intention* to prepare for the *action* and the *reason* being present. Apart from glucose and lactose that require the presence of the nutrient as the *reason*, the *reasons* are all true.

Once the *intention* to perform an *action* holds, when the *opportunity* happens, the corresponding *action* will be performed. Conversely, when an *action* is performed, the *intention* to perform the *action* and an *opportunity* must hold. The import of lactose needs the *belief* that no glucose is present, and the respiration and fermentation need the presence and absence of oxygen as an *opportunity*. Other actions are concluded whenever the *intention* to perform them is present, the *opportunity* is denoted as true. Conversely, the performing of the other *actions* means the *intention* to perform the *action* is present.

```
α(lactose_import) → (lactose_externally_
   present → lactose_internally_present)
α(glucose_import) ∧¬6-deoxyglucose_
   externally_present → (
   (glucose_high_externally_present ∨
   glucose_medium_externally_present →
   glucose_internally_present) ∧
     (2-deoxyglucose_externally_present
    →2-deoxyglucose_internally_present))
oxygen_externally_present → oxygen_
 internally_present
α(respiration) ∧ ψ ∧ α(anabolism)∧
 ϕ → energy_medium
 α(respiration) ∧ ψ ∧
 (¬ α(anabolism)∨¬ϕ) → energy_high
α(fermentation) ∧¬ψ∧α(anabolism)∧ϕ
 → energy_low
α(fermentation)∧¬ ψ∧
 (¬α(anabolism)∨ϕ) →energy_medium
(¬α(respiration)∨¬ψ) ∧¬α(fermentation)
 → energy_low
 α(buildingblocks_import)
 → (buildingblocks_externally_present
 → buildingblocks_internally_present)
α(nitrogen_import) → (nitrogen_externally_
 present →nitrogen_internally_present)
α(phosphor_import) → (phosphor_externally_
 present → phosphor_internally_present)
α(sulphur_import) → (sulphur_externally_
 present → sulphur_internally_present)

ϕ =def nitrogen_internally_present
 ∧phosphor_internally_present
    ∧sulphur_internally_present
    ∧buildingblocks_internally_present.
ψ =def oxygen_internally_present.
```

The *actions* performed can lead to effects in the physical world. When the lactose import action is performed and lactose is present outside, lactose is present inside, and the converse. Glucose import and the absence of the inhibitor 6-deoxyglucose, which will prevent all glucose uptake, will result in the import of glucose and 2-deoxyglucose. If glucose is present at a high or medium level, then glucose becomes present inside by the glucose import action. The glucose import *action* will also import 2-deoxyglucose if this is present outside. Oxygen passes into the cell by diffusion, and is modelled without requiring an *action* from the cell. The *action* of anabolism, respiration and fermentation determine the amount of available energy to the cell. When the cell respires and does not have anabolism, much energy is available, energy_high. When the cell respires and does perform anabolism, less energy is available, energy_medium. Fermentation gives less energy than respiration does, leading to energy_medium when no anabolism is done, and energy_low when anabolism is done. If no respiration or fermentation is done, there will be very little energy, energy_low. Notice that these actions cause effects (on the energy level) together, and not separately. When a resource import *action* is done, the presence of the resource outside will cause the presence of the resource inside the cell, for the buildingblocks, nitrogen, phosphor and sulphur resources.

7.3. RESULTS

The complexity of this example makes listing all possible situations not feasible. There are 768 settings possible or the conditions in the outside environment in the example (3×2^8).

Does the computer program correctly predict the glucose uptake decision? In Table 6, the environment settings and the derived results for some relevant experimental runs are shown. The idea is to vary the substrate and oxygen, and see how this affects the glucose vs. lactose uptake decision. Many factors intertwine for this decision, especially when there is no excess glucose or no glucose at all, but in the grey area in between where there is a medium amount of glucose.

TABLE 6

Several experiments with different environment characteristics and the computed results. In all cases the environment, the growth medium, had no 2-deoxyglucose and no 6-deoxyglucose, present were lactose, (carbon) building blocks, nitrogen and sulphur.

	Environment			*Results*		
No.	*Glucose*	*O*	*P*	*Food used*	*Energy*	*Anabolism*
1	High	+	+	Glucose	Medium	Active
2	Medium	+	+	Lactose	Medium	Active
3	Low	+	+	Lactose	Medium	Active
4	High	−	+	Glucose	Low	Active
5	Medium	−	+	Glucose	Low	Active
6	Low	−	+	Lactose	Low	Active
7	High	+	−	Glucose	High	Inactive
8	Medium	+	−	Lactose	High	Inactive
9	Low	+	−	Lactose	High	Inactive
10	High	−	−	Glucose	Medium	Inactive
11	Medium	−	−	Lactose	Medium	Inactive
12	Low	−	−	Lactose	Medium	Inactive

In all the experiments some environmental conditions are kept constant, and some are varied. In all the experiments no 2-deoxyglucose and no 6-deoxyglucose are present, so as not to inhibit the glucose uptake. Also, in all the experiments lactose is present, as well as the (carbon) buildingblocks, nitrogen and sulphur sources. Glucose can be present in excess (high), or be totally absent (low), or somewhere in between (medium). Oxygen and phosphor can be present or absent.

The computed results, the behaviour that the simulated bacterium displays, are shown on the right. Of the behaviour of the bacterium, the interest for this experiment is in the food source used, the energy level and if it is growing. The food source is shown: lactose or glucose. The energy level in the cell is shown as low, medium or high. The activity of anabolism is also shown, as either active or inactive.

Each of the experiments is discussed briefly. First, a technical account of the derivation is given. Then an informal account is given.

In experiment 1 from Table 6, the environment is set to contain excess glucose, oxygen and phosphor.

In the steady state, the cell *believes* that glucose is present outside the cell, oxygen is present outside the cell and phosphor is present outside the cell. The cell *intends* to prepare to import glucose, to import phosphor, to respire and to perform anabolism. The cell does not *intend* to prepare to import lactose. The cell *intends* to perform the import of glucose, the import of phosphor, respiration and anabolism. The cell performs the import of glucose, the import of phosphor, respiration and anabolism. There is medium energy available in the cell. Glucose is present inside the cell.

In other, intentional words, the cell senses the environment around it. This information is used to make decisions. The cell decides to import glucose, to grow and to breathe. The cell is importing glucose, has an adequate amount of energy and is growing.

In experiment 2, the same situation as in experiment one is taken, but glucose is present outside the cell neither in excess, nor totally absent. The glucose presence is medium.

The cell *believes* the state of the outside world is as follows, it *believes* that oxygen is present, that phosphor is present, and that lactose is present. The cell does not *believe* that glucose is present. The cell *intends* to prepare to import glucose, import lactose, perform anabolism and import phosphor. The cell *intends* to perform the import of lactose, anabolism, and the import of phosphor. The cell does not *intend* to perform the import of glucose, because, as it does not *believe* glucose to be present outside, it has no *reason* to.

The cell performs the import of lactose, the import of phosphor and anabolism. The energy level is medium.

Informally, in comparison to experiment 1, here the cell does not observe the glucose outside and thus, it will not import glucose. Instead, it imports lactose, which it does notice.

In experiment 3, glucose is not at all present in the environment. In the steady state, the cell does not *believe* that glucose is present, as in experiment 2. The cell *believes*, *intends* and performs as in experiment 2.

Informally, glucose is totally absent now. The bacterium does not see any glucose, because there is none. The bacterium proceeds in the same way as in experiment 2, where it also did not sense any glucose.

In experiment 4, the same situation as experiment 1 is taken, but no oxygen is in the environment. So, glucose is present in excess, phosphor is present and no oxygen is present.

In the steady state, the cell *believes* that glucose is present, that oxygen is absent, and that phosphor is present. The cell *intends* to prepare to import glucose, import phosphor, and perform anabolism and perform fermentation. It does not *intend* to prepare to perform respiration. The cell *intends* to perform the import of glucose, import of phosphor, anabolism and fermentation. The cell performs the import of glucose, import of phosphor, anabolism and fermentation. The energy level is low.

Informally, the cell notices that there is no oxygen. It therefore does not respire, but fermentates instead. It also notices glucose and imports it. There is very little energy available in the cell. The cell grows.

In experiment 5, in comparison to experiment 4, the amount of glucose is differed. The glucose present is medium, instead of high. Glucose is not in excess nor totally absent.

In the steady state the energy level is low and therefore the cell is more sensitive to glucose. The cell believes that glucose is present, oxygen is absent and phosphor is present. It intends and performs as in experiment 4.

Informally, the cell has very little energy available. Even though glucose is not easily detected, the cell still senses the glucose. The cell imports glucose and grows.

In situation 6, glucose is removed, as compared to situation 4. Glucose is absent.

In the steady state, the cell does not *believe* that glucose is present, and does *believe* that lactose is present, oxygen is absent and phosphor is present. The cell *intends* to prepare to import glucose and lactose. The cell does not *intend* to perform the import of glucose, but does *intend* to perform the import of lactose. It performs the import of lactose. The other *intentions* and actions are the same as in experiment 4.

Informally, glucose is now totally absent, and the cell does not sense it any more. It imports lactose, fermentates and grows.

In experiment 7, the situation is changed in comparison to 1, by the removal of phosphor from the environment. So glucose is present in excess, oxygen is present and phosphor is absent.

In the steady state, the cell *believes* that glucose is present, oxygen is present and phosphor is absent. The cell *intends* to prepare to import glucose and respire, but not to import phosphor or perform anabolism. Since it *believes* that no phosphor is present, the cell has no *reason* to perform anabolism. The cell *intends* to perform the import of glucose and respiration. The cell performs the import of glucose and respiration. The cell does not perform anabolism. The energy level is high.

Informally, the cell sees that there is glucose and oxygen but no phosphor. It decides not to grow, and to import glucose. There is much energy available in the cell.

In experiment 8, the glucose is lessened but not entirely removed, compared to experiment 7.

In the steady state, the cell *believes* that lactose is present, oxygen is present and phosphor is absent. The cell does not *believe* that glucose is present. The cell *intends* to prepare to import glucose, lactose and to perform respiration, but not anabolism, nor the import of phosphor. The cell *intends* to perform the import of lactose and to respire. The cell performs the import of lactose and respiration. The cell does not perform anabolism. The energy level is high.

Informally, the cell does not see any glucose, and decides to import lactose. There is much energy available in the cell. The cell sees no phosphor available in the environment, and decides not to grow.

In experiment 9, glucose is totally removed from the environment, as compared to experiment 7.

In the steady state, the cell *believes* that no glucose is present. The rest is also the same as in experiment 8.

Informally, the cell sees no glucose in the environment, and does as in experiment 8.

In experiment 10, as compared to experiment 1, both oxygen and phosphor have been removed from the environment. Glucose is present in excess.

In the steady state, the cell *believes* that glucose is present, oxygen is absent, and phosphor is absent. The cell *intends* to prepare to import glucose, and perform fermentation. The cell does not *intend* to prepare to perform anabolism, nor the import of phosphor. Since the cell *believes* that phosphor is absent, there is no *reason* to *intend* to prepare to import phosphor or perform anabolism. The cell *intends* to perform the import of glucose and fermentation. The cell performs the import of glucose and fermentation. The cell does not perform anabolism. The energy level is medium.

Informally, the cell observes that there is glucose, but no air or phosphor. It decides not to grow and import glucose. An adequate amount of energy is available in the cell.

In experiment 11, some glucose is removed, but glucose is not totally absent, as compared to experiment 10.

In the steady state, the cell *believes* that lactose is present, as in experiment 10. Unlike experiment 10, the cell *believes* that glucose is not present. The cell *intends* to prepare to import glucose and lactose. The cell *intends* to perform the import of lactose, but not glucose. The cell imports lactose, but not glucose. The rest is the same as in experiment 10.

Informally, the cell sees no glucose, but still sees lactose in the environment. The cell decides to import lactose.

In experiment 12, glucose is removed completely from the environment as compared to experiment 10. In the steady state, the cell *believes*, *intends*, and performs as in experiment 11. Informally, the cell does not see any glucose in this experiment, just as in experiment 11. The cell decides to do the same things as in experiment 11.

As has been shown, the software can easily compute the decisions in complex situations. The computations took only a split second of time and match well with the view that biologists have of a bacterium. In this light, the bacterium can be seen as decision-making machine. The computation speed makes this a very useful technique.

8. Discussion

In this paper, we have shown that the behaviour of a biochemical network that determines much of the behaviour of a living cell, can be modelled highly efficiently by using methods stemming from Artificial Intelligence. Although less precise in the quantitative sense, the resulting method, especially after its implementation in Prolog, is much more efficient, and may well focus on the essence of decision making in biology rather than on the, in some cases less relevant, kinetic details.

Of course, there are trade-offs. One is that the implementation of the BDI method requires a higher level of abstraction: molecular processes need to be identified with the more abstract BDI notions. The abstraction is useful, however, in that it formalizes the tendency of biochemists to order their information in higher order concepts such as flux, regulon, operon pathway. For on the lowest level of abstraction of the biochemical reactions, control tends to be buried in the jumble of reactions. In the example used in this paper (i.e. description of the nutrition import regulation in *E coli*), this is clearly the case when confronted with the multitude of processes around catabolite repression. Judging from the success of the prolog simulations of *E coli* decision making, the BDI abstractions have not only structured biochemical knowledge, but they have also done so in a well-defined format and with more success, perhaps than the traditional biochemical higher order concepts. The description of the cell using these intentional notions leads to a small set of formal relationships (Section 5.3). With these relationships the cellular steady state could be characterized, even automatically.

Yet another positive trade-off of the BDI notions is that they are more anthropomorphic than the molecular notions. Consequently, they allow for more intuitively understandable theories of cell regulation, as illustrated with the adaptation to the nutrition sources by *E coli*. Indeed, an implementation capable of deriving the *actions* of the cell as a response to the nutritional status of its environment has been given. Other modes of analysis for which the formalization can be used should include those where the extracellular conditions are known and the state that the cell assumes as a response needs to be derived or, conversely when deriving the possible causes for the assumption of a certain state by the living cell.

In this paper, steady states have been described. It should also be possible to create a BDI description of the bacterium as it is changing over time, for example, the transition from one steady state to another due to changing environmental conditions. For such a description a static logic will no longer suffice; a dynamic logical formalization should be used.

In Thomas (1978, 1991) cell behaviour is also described in a formal manner, using asynchronous automata. Each state is a Boolean approximation of the cell state, as in the approach presented here. Their approach continues to examine in detail the feedback loops that are possible, and the interactions between feedback loops. The possible steady states and cycles resulting from a set of feedback loops can be derived automatically. In the approach presented here the logical derivation does not encounter feedback loops, as a statical logical description is made for a steady state. If a sequence of steady states were to be examined, thus using a dynamical logical description, and if the feedback loops of the system are the target of inquiry, then using the logical analysis of feedback loops could be worthwhile. The work on feedback loops is general, and can be applied to many domains, like the immune system, parts of neural networks or psychological problems. The BDI model is also generally applicable, and is used here to interpret the control mechanisms of the cell in intentional notions. The work by Thomas does not interpret any parts of the system it analyses, but extracts a set of simple feedback loops from the regulatory network.

Other extensions of the BDI model as developed in this paper are possible. Instead of creating a double intention layer, a double *desire* layering may be useful biochemically. Both in a double desire layering and in the double intention layering static *desires* of growing and importing, representations of which are part of each other within the DNA, play a role, all represented by the DNA. In the double *desire* case, a *desire* would lead to another *desire*, the latter of which leads to an *intention* which can cause an *action*. When applied to bacterial regulation this would mean that mRNA would be interpreted as a *desire*. This approach has not been taken, since the mRNA present in a bacterium at each steady state is a coherent set. Thus, mRNA existing together in a steady state will not contradict each other or cause chemical reactions which are at cross purposes. If such contradictions were to exist, mRNA would have to be interpreted as a *desire*, as *desires* can contradict one another in the BDI model, whereas *intentions* are assumed to be non-contradictory. However, mRNA does not contradict itself, and thus it can be and is interpreted as an *intention*.

In the case of iterated or meta-BDI notions, *beliefs*, *desires* and *intentions* are used to describe the underlying BDI model, so that an agent can *believe* that it has the *desire* for something, or an agent can have the *desire* to *believe* in something, and so on. In this manner, it can reason about itself. As yet there is no indication that such a self-referential model should be used for a bacterium, but it might be necessary for higher forms of life.

In the logical description given above, the sugar 2-deoxyglucose has been modelled. The 2-deoxyglucose can be imported just like glucose, but cannot be processed further. However, the sugar 6-deoxyglucose also exists. The 6-deoxyglucose cannot be phosphorylated, and will get stuck in the phosphotransferase system, blocking any more glucose import activity. In effect, the presence of 6-deoxyglucose blocks the observation and import of glucose altogether. Therefore, two mechanisms for the generation of *beliefs* can be distinguished, a situation also known in the literature on Artificial Intelligence (e.g. Brazier *et al*., 1999). The first mechanism is the regular observation, where a *belief* is formed based on the perceived state of the external world. The second mechanism is the assumption of a *belief* when confronted with a lack of perceptual information. It is an assumption made when a lack of information prevents proper determination of the world fact, for example, the *belief* is that when the extracellular concentration of glucose cannot be determined, it is deemed absent.

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