MLCSB 2018
Santiago do Chile
December 17-18

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and
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Acknowledgements

This event is financed by the ERDF – European Regional Development Fund through the Operational Programme for Competitiveness and Internationalisation - COMPETE 2020 Programme and by National Funds through the Portuguese funding agency, FCT - Fundação para a Ciência e a Tecnologia, within project (02/SAICT/2017) and project UID/MAT/04106/2013 (at CIDMA).

Overview

Synthetic biology aims at the design of biological systems in a systematic way, a process whose hallmark characteristics closely resemble the composition of software: off-the-shelf parts and devices with standard connections, the usual ingredients for assembling components into increasingly complex systems. Of course, a number of key enabling technologies are specifically biological, for example, DNA sequencing and fabrication. But, on the other hand, there is also a need for new models to cope with the complex and heterogeneous nature of biological systems. In this context, the Symposium starting point is to regard a network of interacting genes and proteins as a dynamic system evolving in time according to fundamental laws of reaction, diffusion and transport. These laws govern how a regulatory network, confronted by any set of stimuli, determines the appropriate response of a cell. The emerging behavioural patterns can be described in precise mathematical terms, combining discrete, continuous and stochastic features, and resorting both to specific or general-purpose analysis and verification techniques. Molecular logic, focussed on computing logical operations on molecules, a fruitful conceptual crossover between chemistry and computation with unsuspected applications, is a possible path in this research map. Actually, this Symposium emerged from a series of informal workshops on Molecular Logic which, for the last four years, have brought together researchers from different latitudes and backgrounds.

The new International Symposium aims at harnessing logical and algebraic methods for modelling and verifying systems on the interaction of Nature and Computation, around two main themes: development of biological computation models and devices application of new computing paradigms to the design of biological systems.

Original submissions were required in any topic from the following, non exclusive list:

Molecular logic
Chemistry, biology and computation
Quantum computing applications to biology
Computational synthetic biology
Control theory and/or algorithms for biological systems
Reconfigurability and adaptation
Probabilistic biological models
Hybrid systems for biology

A very good list of talks will be presented at the symposium!

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Program

17th December

Time	Activity	Speaker	Title
09:15-09:45	Reception		
09:45-10:45	Invited Talk	Alexandre Madeira	Verification for everyone? An overview in Dynamic Logics
10:45-11:15	Coffee Break		
11:15-11:45	Talk	Claudio Fuentes	Molecular Logic: Brief Introduction and Some Philosophical Considerations
11:45-12:15	Talk	Amy Felty	A Logical Framework for Modelling Breast Cancer Progression
12:15-12:45	Talk	Eugénio Rocha	Oscillatory behaviour on a non-autonomous hybrid SIR-model
12:45-14:30	Lunch		
14:30-15:30	Invited Talk	Marta Kwiatkowska	Computing Reliably with Molecular Walkers
15:30-16:00	Talk	Eugénio Rocha	Efficient Choice of Parameters on Delta-Reachability Bounded Hybrid Systems
16:00-16:30	Coffee Break		
16:30-17:00	Talk	Daniel Figueiredo	An essay on weighted state transition models with reactivity
17:00-17:30	Talk	Hillel Kugler	Temporal Logic Based Synthesis of Experimentally Constrained Interaction Networks
17:30-18:00	Talk	Claudio Fuentes	Molecular Logic and the Problem of Computational Implementation

18th December

Time	Activity	Speaker	Title
08:45-09:00	Reception		
09:00-10:00	Invited Talk	Hidde de Jong	Boolean regulatory networks
10:00-10:30	Talk	Tomas Gedeon	Combinatorial dynamics for regulatory networks
10:30-10:50	Coffee Break		
10:50-11:20	Talk	Daniel Figueiredo	Reactive models for biological regulatory networks
11:20-11:50	Talk	Tomas Veloz	On the existence of synergies and the separability of closed reaction networks
11:50-12:20	Talk	Daniela Flores	Reaction network modeling of endosymbiotic interactions
12:20-13:40	Lunch		
13:40-14:10	Talk	Alejandro Sanchez	Proteins as dynamic architectural patterns
14:10-14:40	Talk	Leandro Gomes	Synchronous searching for DNA patterns
14:40-15:10	Talk	Carlos Tavares	Quantum simulation of quantum chemistry: a case study using IBM Q
15:10-15:30			
15:30-16:00	Talk	Julio Fenner	Random chromatin neighborhoods in 2n=40 Mus m. domesticus meiotic cells: P-percolation and image segmentation
16:00-16:30	Talk	Delfim Torres	A Susceptible-Infected-Removed Model on Time Scales
16:30-17:00	Talk	Cristiana J. Silva	Optimal control of a delayed HIV/AIDS-PrEP model

Contents

Invited contributions

Natural and synthetic control of resource allocation in bacteria

Hidde de Jong[1]

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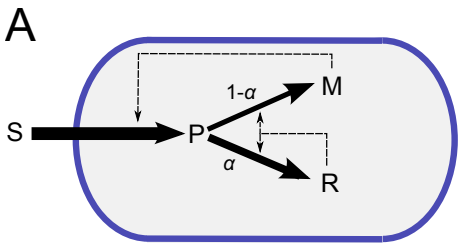
The fitness of microorganisms is defined by their capacity to propagate in environments hosting a variety of competitors for available resources. The situation faced by these single-cell organisms can be seen as an optimization problem: the allocation of resources to different cellular functions so as to maximize fitness. In many situations, microbial fitness amounts to maximizing the growth rate of the population, allowing the cells to outgrow competitors. However, depending on the structure of the environment and the properties of metabolic pathways, other fitness criteria may apply as well [13, 14]. While experimental conditions can be kept constant in the laboratory, in most natural environments microorganisms are exposed to changing conditions [11, 19]. This requires microbial cells to continually adapt their functioning and the allocation of resources to maximize fitness can be viewed as a dynamic optimization problem.

Self-replicator models [6] have been shown to provide a fruitful description of microbial growth. Despite their simplicity, self-replicator models are remarkably expressive and are capable of accounting for observed correlations between variables in microbial physiology [10, 15, 16, 18, 21]. In recent years, they have been used to formulate resource allocation in microorganisms as an optimal control problem (Figure 1; [4]). For the purpose of optimal control, self-replicator models are interesting, since they reduce the mathematical and computational complexity of the problem. The optimal solutions thus obtained may give new insights into the functioning of microorganisms, by comparing them with control strategies that microorganisms have evolved to distribute available resources over cellular functions, involving complex networks of regulatory interactions on the molecular level [2, 12].

In addition to gaining a better understanding of naturally-evolved resource allocation, optimal control theory is also beneficial in biotechnology, where the objective is not to optimize microbial growth, but to exploit the synthetic capacities of microorganisms for maximizing the production of a compound of interest [17]. Optimal control theory has contributed a rich variety of mathematical and computational tools for achieving this, notably through on-line estimation and adaptive control of process conditions [1, 20]. The emergence of systems biology and synthetic biology has provided new tools for the implementation of control strategies, by increasing our understanding of the functioning of regulatory networks on the molecular level and facilitating their (re)engineering [2, 8]. Self-replicator models provide a useful conceptual framework for expressing the dynamic reallocation of resources in microorganisms as an optimal control problem [3, 4]. In particular, the model of Figure 1 has been extended to account for the reorientation of metabolic fluxes from growth to the production of a compound of interest *via* external control of RNA polymerase, a central component of the gene expression machinery [7, 22]. An optimal control analysis of this model may provide useful guidelines for maximizing the production of the compound in a biotechnological context.

The above discussion exemplifies the contributions that optimal and feedback



B

$$\frac{dp}{dt} = v_m(s,m) - v_r(p,r) - \mu\, p$$
$$\frac{dr}{dt} = \alpha\, v_r(p,r) - \mu\, r$$
$$1/\beta = m + r$$
$$\mu = \beta\, v_r(p,r)$$

Figure 1: **Self-replicator models of resource reallocation in microbial cells [4]. A.** Solid arrows represent material flows and dashed arrows regulatory interactions. Incoming nutrients S are transformed into precursor metabolites P, which are then consumed by several cellular functions, here limited to gene expression and metabolism. More precisely, the precursor metabolites are utilized for ribosomes and other components of the gene expression machinery (R) as well as the enzymes making up the metabolic machinery (M). M enables the conversion of external substrates into precursors, while R is responsible for the production of M and R itself. The (auto-)catalytic activity of M and R thus allows the cell to replicate its protein contents, the major constituent of biomass. **B.** ODE model describing the self-replicator in panel A. The variables s, p, r, m represent the concentrations of substrate, precursor, gene expression machinery, and metabolic machinery in a growing population, respectively. v_m and v_r are the rates of the macroreactions converting S into P, and P into M and R, respectively. The rates are nonlinear saturating functions of s and m in the case of v_m, and of p and r in the case of v_r [4]. The growth rate μ is proportional to the protein synthesis rate v_r, with a proportionality constant β representing the cytoplasmic density. α is a possibly time-varying control input ($0 \leq \alpha \leq 1$), defining the fraction of the protein synthesis rate dedicated to making new gene expression machinery (and thus the growth rate).

control theory can make to biology and biotechnology, that is, to better understanding natural strategies and designing synthetic strategies of resource allocatio. While these applications are highly promising, as argued in a number of reviews [5, 9], their potential is far from being exploited. In addition to the difficulty of defining the (optimal) control of regulatory networks in microbial cells in a biologically meaningful way, many mathematical challenges remain. In particular, the nonlinearity of biological systems, parameter uncertainty, the co-existence of different time-scales, a continually changing environment, and the existence of various physical and chemical constraints make finding admissible optimal solutions and designing quasi-optimal feedback laws very difficult. Moreover, the experimental quantification of resource allocation strategies and their redesign for biotechnological purposes require state-of-the-art techniques in genome modification and biophysics.

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Computing Reliably with Molecular Walkers

Marta Kwiatkowska [1]

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DNA computing is emerging as a versatile technology that promises a vast range of applications, including biosensing, drug delivery and synthetic biology. DNA logic circuits can be achieved in solution using strand displacement reactions, or by decision-making molecular robots-so called 'walkers'-that traverse tracks placed on DNA 'origami' tiles. Similarly to conventional silicon technologies, ensuring fault-free DNA circuit designs is challenging, with the difficulty compounded by the inherent unreliability of the DNA technology and lack of scientific understanding. This lecture will give an overview of computational models that capture DNA walker computation and demonstrate the role of quantitative verification and synthesis in ensuring the reliability of such systems. Future research challenges will also be discussed.

Verification for everyone? An overview in Dynamic Logics

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Propositional Dynamic Logic [2] was introduced in the 70's by Pratt in [6] as a suitable logic to reason about, and verify, classic imperative programs. Since then, the original intuitions evolved to an entire family of logics, which became increasingly popular for assertional reasoning about a wide range of systems.

This talk intends to make an overview on this path. Starting in the seminal motivations of Pratt, we present a method to the parametric generation of Graded Dynamic Logic. The dynamisation method [3, 4] contributed on this direction with a systematic parametric way to construct Multi-valued Dynamic Logics able to handle systems where the uncertainty is a prime concern. We conclude the talk recalling other less conventional Dynamic Logics on the literature, including the Differential Dynamic Logic [5] and Quantum Dynamic Logic [1], opening the discussion about what and how these features can be useful on the goals of the current symposium.

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Hopes, Ideas and Principles of Molecular Logic-based Computation – A Chemist's View

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Abstract. A personal historical view is offered on some of the issues that arise in a growing field attracting diverse adherents. An example issue of general interest – whether humans compute – is discussed in terms of the human visual response and its emulation by computers and by molecules.

One of the pleasures of working in the field of molecular logic-based computation 1, 2 is to experience the wide variety of backgrounds which its practitioners come from. As a consequence, a similarly wide variety of opinions about meanings of words can be seen, because of the different mother languages (both personal and professional). It is up to all of us to learn at least a little of each other's languages from positions of mutual respect. Then the accompanying issue of the triviality or not of certain ideas will subside since one person's meat is another's poison.

Our field nearly died at birth 3 because of differences of opinion due to cultural origins. Giants of the semiconductor-based electronic computing industry challenged the nascent field via the editors of Nature 25 years ago. Their argument was basically that the achievement of a sodium, proton-driven AND gate molecule showing a fluorescence output was trivial because such gates don't have the input-output homogeneity of semiconductor devices and therefore would be impossible to concatenate. Then no computing of significance would arise.

Our field has survived that challenge to reach the present moment, with around 750 laboratories having contributed (sometimes inadvertently). However, that discourse strengthened our field by educating us about the strengths and weaknesses (yes, there are weaknesses) of semiconductor computers, as well as of our own little molecular information processors. That discourse was also a reminder that long-term success and dominance breeds an arrogance about other lines of thought, e.g. significant information processing can only happen along the semiconductor electronic path. Interestingly, the fact that human- and other biological- information processing are silicon-free did not seem relevant to those computing industry giants, nor did the fact that input-output homogeneity is poor in the molecular devices inside us. Good thing too, because exact quantitative input-output homogeneity would have short-circuited all our insides and there would be no one to engage in any discourse.

To take an example of another discourse, consider the question 'Do humans compute?' I think so. I am no professional philosopher, but I do love ideas and principles in a wide sense. Some of the recent work from Belfast will be described where molecules emulate some aspects of human function which are also emulated by semiconductor electronic computers. The ideas and principles of molecular logic are clearly applicable to matters of deep human interest. At least within the scope of this work, the difference between the behaviour of humans, conventional computers and little molecules appears more quantitative than qualitative.

How do we visually detect approaching objects so that we are not threatened by them? (4) This is done by a process of edge detection in our eyes followed by a check against line profiles held in easily-accessible memory in our brains 5. Stored-program computers achieve edge detection during machine vision and during image processing 6. Common software such as the Canny algorithm locates the edge by finding where the non-zero gradient of light intensity is. The pixels of the image can be raster-scanned. A particular pixel is chosen and the intensity of the pixel in front minus the intensity of the pixel at the back in the horizontal line is taken. The intensity at each pixel is averaged according to a Gaussian distribution with intensities in pixels along the vertical line. The edge pixels are those which have non-zero values, after suitable thresholding. A contiguity check is also applied to these edge pixels.

Given the human experience, it should be no surprise that living things like genetically-engineered bacteria 7 and biomolecular systems like reactive DNA networks 8 also perform edge detection. However, it might be more of a surprise that small synthetic molecules can do the same. The key molecule is a fluorescent pH sensor which switches 'on' in acid solution 9. This is actually a YES logic gate with proton input and light output. The other necessary molecule is a photoacid generator 10. When these two are paired up on moist paper, the system is complete 11. Further analysis showed a light dose-driven 'off-on-off' fluorescence function 12, 13, 14 in the centre of the image (away from the edges), with binary XOR and ternary logic behaviour. Slow diffusion of protons, and the photo-production of a bimolecular quencher besides protons are key principles to understanding the molecular processes involved. In the end, the non-zero gradient of light intensity is translated into a gradient of protons which then flow due to the gradient.

What about human high-cultural pursuits like outline drawing? Now it appears that we perform this artistic function by faithfully reproducing the detected edges of an object. So it is no wonder that our molecular edge detection system is also capable of performing outline drawing 15. Detailed curves and angles of the object are reproduced in good-fidelity by the drawing program embedded within the molecular system 2.

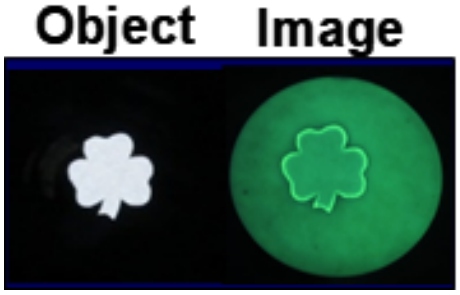

Figure 2: Outline drawing accomplished by a synthetic molecular logic system.

We can conclude that molecules can emulate, if not match, some rather sophisticated human functions just like semiconductor computers do. It might therefore be hard to distinguish between the three in certain chosen actions.

What about hopes for the future of our field? The above examples suggest that

more aspects of human behaviour can be emulated by small synthetic molecules. When coupled with the growing interest in performing molecular logic-based computations within living cells, it seems clear that small molecular logic will contribute more and more to biology and ourselves.

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Short Contributions

An essay on weighted state transition models with reactivity

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Abstract. The term reactivity is used by Gabbay to refer state transition systems whose accessibility relation is not fixed but can vary according to the edges crossed.
On this work, the possibility of assign weights to edges is considered. In particular, we are interested into apply these ideas to biological modeling and we discuss about the theoretical tools we would need. Furthermore, the possibility of using the software PRISM to study such models is discussed and we consider already some initial results obtained for simple toy models.

Preliminaries.

Gabbay and his collaborators have been introducing the concept of reactive model as a model composed by a digraph whose the set of edges can be altered depending on the edges which are crossed. This idea was completely new because other authors such as van Benthem and Areces have already proposed some logics with relation-changing operators (1,2,3). In particular, Gabbay and his collaborators proposed switch graphs (see 5) as a graphical representation to these systems.

Switch graphs are defined as a pair (W, S) where W is a set of vertices and S a set of generalized edges. Contrarily to usual graph where the edges only connect two vertices, the edges of switch graphs can connect two edges. In this context, we say that edges connecting vertices are basic and the ones connecting two other edges are higher-level edges. These higher-level edges are used to describe reactive dynamics (which, in some sense, can be seen as a system allowing reconfiguration). In order to accomplish this, we consider that each higher-level edge can either activate or inhibit the edge it points. Formally, switch graphs are defined recursively as:

- $S_0 \in W \times W$
- $S_n \in S_0 \times S_{n-1} \times \{\circ, \bullet\}$, for $n \geq 1$
- $S = \bigcup_{i \geq 0} S_i$

Above if $s = (a, b, *) \in S_n$ with $n \geq 0$, then $* = \circ$ means that the edge b should be inhibit (*i.e.*, temporarily removed from the model) whenever a is crossed. On its turn, if $* = \bullet$, then it means that the edge b should be activated (*i.e.*, reintroduced in the model) whenever a is crossed. If the edge is already inhibit or active (correspondingly) when a is crossed, then nothing happens to the model. We note that higher-level edges only determine the activation and inhibition of other edge and cannot be crossed.

In the examples, we distinguish between an higher-level edge which is an activator and one which is an inhibitor by using a black head for activators and a white head for inhibitor. Also, we represent an inhibited edge by a dashed line. Finally, in this abstract, we only consider finite models, which means that both W and S are finite.

Example 0.0.1 *Let us consider an example of a switch graphs like the one presented in the left box of Figure 0.0.1. We can see that* $W = \{w\}$ *and* $S = \{(w, w), e_1, e_2\}$. *Furthermore* e_2 *is initially inhibited. Starting at* w*, we can only cross the edge* (w, w)*. Thus,* e_2 *will be activated by* e_1 *because* e_1 *is an activator higher-level edge and is pointing it. Again, we can only cross* (w, w) *and, when we do it,* e_2 *which is now active, will inhibit* (w, w) *itself because* e_2 *is a inhibitor higher-level edge. After this, we can no more move from* w*.*

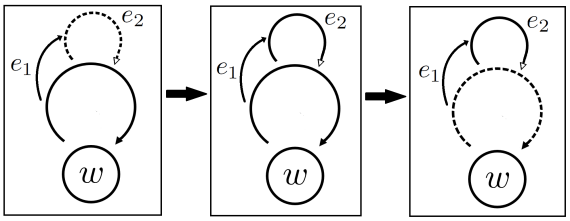

Figure 3: Evolution of a switch graph.

Introducing weights

The natural idea to generalize switch graphs to comprise weights must be something mixing the activation/inhibitor of edges, coming from switch graphs, and an assignment of weights to edges connecting vertices.

At this point, it is important to define some main guidelines. First of all, we must decide how to interpret reactivity in a weighted context. We can think about two functions to the higher-level edges:

- Each edge, with its fixed weight, can be activated and inhibited by higher-level edges;
- Each edge remains always active but its weight can be altered by higher-level edges.

Although each one of these options is interesting by itself, for now, we will consider a syntactical structure based on the second idea. The other one is left for future work.

A *one-level weighted switch graph* is a pair (W, S) with $W \neq \{\}$ and $S = S_0 \cup S_1$ such that:

- $S_0 \subseteq W \times W$
- $S_1 \subseteq S_0 \times S_0$

along with an initial *instantiation* $I_0 : S \to \mathcal{W}$, where $\mathcal{W}$ is the set of weights.

The evolution of such systems is given by the notion of *instantiation* which is a function $S \to \mathcal{W}$. Given a one-level switch graph (W, S) and an instantiation I, we say that an arc $s \in S$ has weight $I(s)$.

Given a one-level weighted switch graph and an initial instantiation I_0, we can consider the evolution of the one-level weighted switch graph as updates to the instantiation. Consider a one-level weighted switch graph (W, S) and an instantiation I, when some edge $s \in W \times W$ is crossed we update the actual instantiation I to I^+ in the following way:

- $I^+(t) = \begin{cases} I(t), & \text{if } (s,t) \notin S \\ I(s,t), & \text{otherwise.} \end{cases}$

This means an edge $(s, t) \in S_1$ assign its weight to t whenever s is crossed. To exemplify the application of these models, we consider the following biological example.

Example 0.0.2 (circadian rhythm) *Let us consider circadian rhythm in a cyanobacteria as referred in 4. There, a model considering two proteins – KaiA and KaiC – is proposed. Moreover, three phosphorylated of KaiC are also integrated in the same model. In this example, only the KaiC protein along with its phosphorylated forms are consider. To do this, we consider the variables u ("unphpsphorylated"), t, s and ts (the three phosphorylated forms). Using a one-level weighted switch graph, we model the KaiC cycle in the way shown in Fig. 0.0.2.*

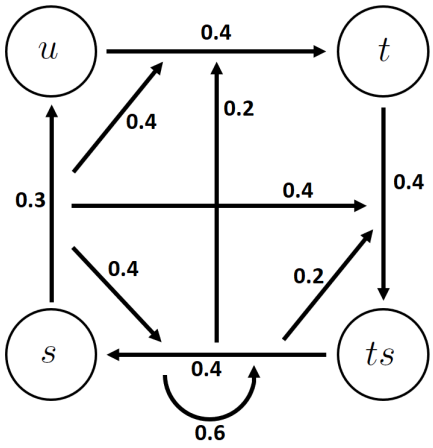

Figure 4: Model representing the KaiC cycle in a circadian rhythm.

In the figure, the numbers assigned to each edge represent the initial instantiantion and, in particular, the weights of each basic edges represent rates associated to the phosphorylation (or unphosphorylation) of each form of KaiC. We see that this rate can change according to the chemical reactions occurring. The value of the rates were chosen taking in a meaningful way but they were not, in fact, estimated. This reactivity is introduced to reflect the interference that KaiA would produce in the system, if considered.

Moreover, we were able to test our model and perform simulations on it using the software PRISM. In Figure 5, we can find a graph with the evolution of the amount of each substance during he simulation.

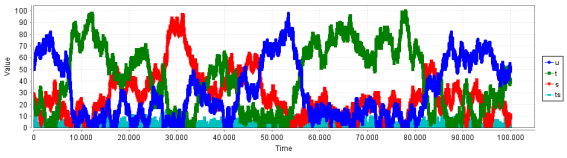

Figure 5: Simulation of a one-level weighted switch graph representing KaiC cycle.

We note that we still obtain a periodic behavior has would be expected for this systems.

Conclusion and further work

In this work we introduced the concept of one-level weighted switch graphs and discuss how can it be applied to model biochemical phenomena. In particular, we used PRISM to simulate one of such models.

Although in this work we did not define it nor used it, we note that in the theoretical part we can chose to consider a more general framework in order to allow more than one level of higher-level weighted edges or even to allow edges to be inhibited (temporarily removed) from the system. This can, in future, lead to other applications.

Finally, as future work, we plan to apply it to other contexts such as probabilistic Boolean networks. Also, despite we already used PRISM in our applications, we intend to develop a algorithmic procedure to the application of PRISM to weighted reactive models.

Acknowledgments.

This work is financed by the ERDF – European Regional Development Fund through the Operational Programme for Competitiveness and Internationalisation - COMPETE 2020 and by National Funds through the Portuguese funding agency, FCT - Fundação para a Ciência e a Tecnologia within the project with reference POCI-01-0145-FEDER-016692, the project with reference POCI-01-0145-FEDER-030947 and the project with reference UID/MAT/04106/2013 at CIDMA. D. Figueiredo also acknowledges the support given by FCT via the PhD scholarship PD/BD/114186/2016.

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Reaction network modeling of endosymbiotic interactions

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The theory of endosymbiosis developed by Lynn Margulis, describes the origin of plastids and mitochondria from prokaryotes that were acquired and conserved within host cells giving rise to eukaryotic cells. Although structural, biochemical and morphological evidence has focused on mitochondria and chloroplasts to demonstrate their prokaryotic ancestry, it has been postulated that several organelles and more structurally complex organisms have been originated by endosymbiosis, giving rise to new species and lineages (Margulis & Sagan., 2000). An endosymbiosis study model corresponds to the interrelation between corals (Cnidaria, Anthozoa) and photosynthetic algae of the genus Symbiodinium (also known as Zooxanthellae), which correspond to the most common endosymbionts among coral reefs (Trench., 1997; Rowan ., 1998). In this coupling between host and endosymbiont, the alga acquires nutrients through the host and produces organic compounds to satisfy not only the requirement of the endosymbionts, but also the energy demanded by the host, which provides an advantage to both organisms in warm, shallow waters and with low nutrient availability, which has allowed the success and survival of coral reef communities despite recent climate changes (Yellowlees et al., 2008, Baker et al., 2004). In general, the establishment of this type of interaction gives rise to new properties, structures, morphologies and competencies for the organisms that underlie the relationship. The latter hinders the experimental study of this phenomenon because the members cannot be studied separately. For this reason, a framework to this phenomenon from a mathematical and computational perspective would be crucial importance, but unfortunately no framework of this kind has been yet developed. In the present study we propose such framework to model endosymbiotic relationship. In particular, we provide a simple model of the interaction between anthozoan corals and symbiont algae of the genus Symbiodinium by means of a framework based on reaction networks (Chemical Organization Theory) that has recently proposed to represent ecological interactions at the mechanistic level, and we discuss the capabilities of this framework to model endosymbiotic interactions in general.

Molecular Logic and the Problem of Computational Implementation

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De Silva defines the Molecular Logic-based Computation, as "(...) an approach that deals with molecules and chemical systems that have an innate ability to compute, at least in a rudimentary way, as machines based on transistors, semiconductors or people "[2013: 12]."

The criticism that can be raised is that conceptualization is trying to elucidate the notion of logic in terms of the notion of computing. The elucidation of this question then shifts to what we are going to understand by computation. The issue is important, especially in light of the abundant specialized literature on the concept of computing, and the meaning of expressions of the type "the S system performs a computational process C".

Depending on the way in which the notion of computing is understood, the thesis that living systems have a "logic", in the sense that they perform certain computational processes, can be a trivial and philosophically uninteresting thesis (see, for example: Piccini, G. (2015)

The mechanistic conceptualization (Piccinini 2007, 2015, Kaplan 2011, Milkowski 2013) explains the concrete calculation in terms of the mechanical properties of a system. According to the mechanistic account, concrete computer systems are functional mechanisms of a special type, that is, mechanisms that perform specific calculations.

A given calculation can be implemented in multiple physical media (eg, cells), provided that the media possess a sufficient number of dimensions of variation (or degrees of freedom) that can be appropriately accessible and manipulated and that the components of the mechanism are functionally organized in the proper way.

The objects studied in the mathematical theory of computation - Turing machines, algorithms, etc. - are usually implemented by specific physical systems. This poses a problem: how can a particular physical system perform a calculation when the calculation is defined by an abstract mathematical formalism? This can be called the problem of computational implementation.

Synchronous searching for DNA patterns

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The uniqueness of each living organism is reflected in its DNA pattern. In that sense, it is of core importance for biologists to study the genome of living beings, in order to understand their growth, functioning and reproduction. We have seen, in particular, that the process of searching for a specific sequence of nucleotides in a DNA molecule become indispensable in biological research [1]. Its range of applications varies from diverse fields such as medical diagnosis, forensics and synthetic biology [9]. For the last one, the methods used in DNA sequencing are relevant in distinct directions: they provide information of natural organisms, which can be used to construct synthetic parts and devices; it is used to verify fabricated systems; facilitates detection and identification of synthetic organisms [11].

String matching techniques, which are basis of DNA sequencing, can be found in the literature divided in two distinct approaches: exact matching [2] and approximate matching [12]. Approximate DNA matching techniques [3] are becoming more relevant than the ones based on exact matching, as they can address very common situations like acquisition errors, small differences in the sequences due to mutations or evolutionary modifications, or even present themselves useful to reconstruct phylogenetic trees [7]. The long tradition of finite state automata in many text search methods make them suitable computational models to address problems related with DNA matching, either exact [5] or approximate [10].

Parallel computation is nowadays a pervasive paradigm to several application domains. Consequently, formalisms to model these kinds of computations begun to emerge, namely, Concurrent Kleene algebra (CKA) [4] and Synchronous Kleene algebra (SKA) [8], The notion of synchronism was added to Kleene algebras in [8], combining the expressiveness of Kleene algebras for axiomatising regular expressions and finite automata, with an operator to model parallelism. In SKA, the notion of parallelism is based in the process algebra CCS calculus [6], where two independent actions are processed at the same time. In [8], the author directed the work on SKA in two phases: first, its semantics was given by sets of synchronous strings; then, he presented a new construction for nondeterministic finite automata, based on the semantics of the synchronous operator of SKA.

We propose to adapt this formalism in order to construct a semantics for handling fuzzy synchronous computations. First, we start by presenting a new model for *SKA*, based on the one of [8], but now considering a set of fuzzy synchronous sets and operators over them instead of taking the set of synchronous sets. So, summing up, given the set of strings Σ^* built over an alphabet Σ, we denote the set of all fuzzy sets over Σ^* by $\mathbf{A}^{\Sigma^*}$. For any $S \subseteq \mathbf{A}^{\Sigma^*}$, we construct a model, that we call the algebra of *fuzzy synchronous languages (FSL)*

$$FSL(\mathbf{A}) = (S, \cup, \cdot, ^*, \times, \varnothing, \chi)$$

where $\cup$, $\cdot$, *, $\times$, $\varnothing$ and χ are operators defined, for given fuzzy synchronous sets $\mathcal{L}$, $\mathcal{L}_1$, $\mathcal{L}_2 \in S$ and for all $w \in \Sigma^*$, as:

$\varnothing(w) = 0$, for all $w \in \Sigma^*$

$$\chi(w) = \begin{cases} 1 & \text{if } w = \epsilon \\ 0 & \text{otherwise} \end{cases}$$

$(\mathcal{L}_1 \cup \mathcal{L}_2)(w) = \mathcal{L}_1(w) + \mathcal{L}_2(w)$

$(\mathcal{L}_1 \cdot \mathcal{L}_2)(w) = \bigvee_{u,v} \mathcal{L}_1(u); \mathcal{L}_2(v)$, with $w = uv$ being the concatenation of strings u and v

$\mathcal{L}^*(w) = \bigvee_{i \geq 0} \mathcal{L}_1^i(w)$, with $\mathcal{L}^0 = \mathbf{1}(w)$, $\mathcal{L}^{(i+1)}(w) = (\mathcal{L}.\mathcal{L}^i)(w)$

$(\mathcal{L}_1 \times \mathcal{L}_2)(w) = \bigvee_{u,v} \mathcal{L}_1(u); \mathcal{L}_2(v)$, with $w = u \times v$ defined as:
$u \times \epsilon = u = \epsilon \times u$
$u \times v = (x \cup y)(u' \times v')$ where $u = xu'$ and $v = yv'$, with $x, y \in \Sigma$

A basic fuzzy synchronous set is defined only for basic actions $a \in \mathcal{A}_B$ and is given by

$$\mathcal{L}_B(w) = \begin{cases} \alpha \in \mathrm{A} & \text{if } w = a, \text{ with } a \in \mathcal{A}_B \\ 0, & \text{otherwise} \end{cases} \tag{1}$$

The definition of the model lies on the classical results of fuzzy sets and fuzzy languages [13]. In such definitions, a generic residuated lattice is taken, to act as a model for handling "weighted" computations and propositions evaluated in a (possible) many valued truth space. We construct our model on top of an arbitrary action lattice $\mathbf{A}$, which can vary depending on the computational setting we want to describe. Let us denote by $\mathcal{FASS}$ the smallest algebra of $\mathbf{A}^{\Sigma^*}$ which contains $\varnothing$, χ and all $\mathcal{L}_B$, for all $a \in \mathcal{A}_B$.

The syntactic terms T_{SKA} of our algebra are the ones generate by the grammar

$$\alpha ::= a \mid \mathbf{0} \mid \mathbf{1} \mid \alpha + \alpha \mid \alpha \cdot \alpha \mid \alpha \times \alpha \mid \alpha^*$$

where a is a basic action. We interpret these expressions as fuzzy synchronous sets through a homomorphism $\hat{FI}_{SKA} : T_{SKA} \to \mathcal{FASS}$ and prove that for each term α we can construct a fuzzy automaton $M = (\Sigma, X, i, f, \delta)$ which accepts precisely $\hat{FI}_{SKA}(\alpha)$, and where:

- Σ is the input alphabet;

- X is a set of states;

- $i : X \to \mathbf{2}$ and $f : X \to \mathbf{2}$ defined as

- $i(s) = \begin{cases} 1 & \text{if } s = s_0 \\ 0 & otherwise \end{cases}$

- $f(s) = \begin{cases} 1 & \text{if } s \in F \\ 0 & otherwise \end{cases}$
  are the *function of initial states* and *function of final states*, respectively;

- $\delta : X \times \Sigma \times X \to \mathbf{A}$ is the fuzzy transition function

Finally, we use the expressiveness of this new model to incorporate parallelism into approximate DNA matching. Based on the examples given in [5], we present an illustration which handles string matching of two DNA sequences simultaneously, by performing the synchronous product of the automata which accept those sequences [10].

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Efficient Choice of Parameters on Delta-Reachability Bounded Hybrid Systems

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In this work, we combine two techniques, i.e. bounded δ-reachability for hybrid systems (*from logic/computation*) with frontier analysis (*from optimization/linear programming*). The aim is to extend the dReach tool[1] by determining the set of most efficient choices of parameters for a given finite set of combinations values and a set of input/output generating functions. In fact, in real applications the so-called inverse problem is common, which stands to find the best[2] parameters for the model need to be found. Although, in practice, the set of parameter values tends to be finite, the concept of best choice is understood as efficiency, so optimality on a continuous parameter space is not adequate. For efficiency the notions of inputs (or resources) and outputs (or outcomes) are key requirements. Here, we propose a functional and parallelized scheme to produce the inputs and outputs, from the trajectories of the solutions of the hybrid systems, obtained by dReach, and then apply the Multidirectional Efficiency Analysis algorithm to rank the simulations.

For a hybrid system $H =< X, Q, flow, jump, inv, init >$, where $flow$, $jump$, inv, $init$ are SMT formulas encoded as first-order logic formulas over the real numbers, any formula ϕ can have its δ-perturbation counterpart ϕ_δ, by specifying a numerical error bound δ. Such perturbed formulas are handled by implementing the framework of δ-complete decision procedures. Then, a δ-perturbation of H is defined as $H_\delta =< X, Q, flow_\delta, jump_\delta, inv_\delta, init_\delta >$ by relaxing the logic formulas in H. Thus, choosing $n \in \mathbb{N}$ to be a bound on the number of discrete mode changes, $T \in \mathbb{R}_+$ an upper bound on the time duration, and unsafe to encode a subset of $X \times Q$, the bounded δ-reachability problem asks for one of the following situations: (a) "*safe*", if H cannot reach unsafe in n steps within time T; (b) "*δ-unsafe*", if H_δ can reach δ-unsafe in n steps within time T. The literature on this subject is growing, with variations and extensions of the initial algorithm [4] been proposed, e.g. a version for stochastic hybrid systems (see [5]).

The most common technique in Frontier Analysis for measuring efficiency is the so-called Data Envelopment Analysis (DEA), introduced by Charnes et al. [1]. Here, we consider an improved non-parametric deterministic method for measuring efficiency, namely based on the Multidirectional Efficiency Analysis (MEA), proposed by Bogetoft and Hougaard [2]. In contrast to DEA, the input reduction and output expansion benchmarks in the MEA approach are selected proportional to the potential improvements in efficiency identified, while is considered the improvement potential separately in each input and output variable. Thus, in addition to efficiency levels, MEA allows investigating changes in efficiency patterns. Let us set that $[m]$ denotes the set $\{1, ..., m\}$; for notation convenience. From what was

[1] which deals with the bounded δ-reachability problem and it was developed by Sicun Gao and co-authors, e.g. see [4]

[2] in some precise sense

discussed above, to any given simulation it is possible to associate $J \in \mathbb{N}$ outputs $y_j(\rho)$, $j \in [J]$ and $I \in \mathbb{N}$ inputs $x_i(\rho)$, $i \in [I]$. Some of the input variables may be discretionary (i.e. their values can be changed) but others may be non-discretionary (i.e. they are fixed). From now on, the discretionary variables are represented by the first indices from 1 to $d \in [1, I]$. So, $x(\rho)$ is the vector of all the inputs and $y(\rho)$ is the vector of all the outputs. Furthermore, the DEA/MEA model change with respect to a chosen set of complementary variables. We use the so-called variable returns to scale (VRS) model [3], by defining the set

$$\Lambda^N = \left\{ \lambda \in \mathbb{R}^{\mathbb{N}} : \sum_{n=1}^{N} \lambda_n = 1 \wedge \lambda_n \geq 0 \right\}, \tag{2}$$

where N is the number of sequences under study. Alternative definitions of Λ^N allow other models, not relevant in this work. Then, the MEA score is found by solving the following linear optimization problems

$$\begin{array}{ll}
\underline{\text{Problem } P_m^{\alpha}(\bar{\rho}):} & \underline{\text{Problem } P_j^{\beta}(\bar{\rho}):} \\
\min \alpha_m(\bar{\rho}) \ s.t. & \max \beta_j(\bar{\rho}) \ s.t. \\
\sum_{\rho} \lambda_\rho x_m(\rho) \leq \alpha_m(\bar{\rho}), & \sum_{\rho} \lambda_\rho x_i(\rho) \leq x_i(\bar{\rho}),\ i \in [I], \\
\sum_{\rho} \lambda_\rho x_i(\rho) \leq x_i(\bar{\rho}),\ i \in [I],\ i \neq m, & \sum_{\rho} \lambda_\rho y_s(\rho) \leq \beta_j(\bar{\rho}),\ S \in [J], \\
\sum_{\rho} \lambda_\rho y_l(\rho) \leq y_l(\bar{\rho}),\ l \in [J]. & \sum_{\rho} \lambda_\rho y_l(\rho) \leq y_l(\bar{\rho}), l \in [J],\ l \neq j.
\end{array}$$

$$\begin{array}{l}
\underline{\text{Problem } P^{\gamma}(\alpha, \beta, \bar{\rho}):} \\
\max \gamma(\bar{\rho}) \ s.t. \\
\sum_{\rho} \lambda_\rho x_i(\rho) \leq x_i(\bar{\rho}) - \gamma(\bar{\rho})(x_i(\bar{\rho}) - \alpha_i^*(\bar{\rho})), i \in [I], \\
\sum_{\rho} \lambda_n x_i(\rho) \leq x_i(\bar{\rho}), i \in [I] \setminus \{m\}, \\
\sum_{\rho} \lambda_\rho y_l(\rho) \geq y_l(\bar{\rho}) + \gamma(\bar{\rho})(\beta_l^*(\bar{\rho}) - y_l(\bar{\rho})), l \in [J].
\end{array}$$

where $\lambda \in \Lambda^n$, $\alpha_m^*(\bar{\rho})$ and $\beta_j^*(\bar{\rho})$ are the optimal solutions to the problems $P_m^{\alpha}(\bar{\rho})$ and $P_j^{\beta}(\bar{\rho})$ respectively. On the other hand, $P^{\gamma}(\alpha, \beta, \bar{\rho})$ represents the global solutions for the efficiency analysis. The MEA score is obtained by the directional contribution of each input and each output variable, formulate as

$$MEA(\rho) = \frac{\frac{1}{\gamma^*(\rho)} - \frac{1}{D} \sum_{i=1}^{D} \frac{x_i(n) - \alpha_i^*(\rho)}{x_i(\rho)}}{\frac{1}{\gamma^*(\rho)} + \frac{1}{J} \sum_{j=1}^{J} \frac{\beta_j^*(\rho) - y_j(\rho)}{y_j(\rho)}} \in [0, 1]. \tag{3}$$

In practice, a simple but raw rule to decide which are the inputs versus outputs may be to consider as inputs, the variables to decrease, and as outputs, the variables to

increase. Then, the best choices of parameters are the ones with higher MEA score, since MEA gives a relative ranking between the simulations with such parameters.

A computational package in C++, for the sDL computational platform (see http://sdl.mathdir.org), implementing the concepts described in this work is under development and testing.

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Proteins as dynamic architectural patterns

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Predicting and designing the dynamics of proteins is a challenging task that can help in the identification of the causes of diseases and in the design of specific drugs for therapies. The problem shares a number of similarities with the architectural design of distributed, heterogeneous and dynamically reconfigurable software systems. We propose exploiting such similarities by addressing the task using the architectural description language ARCHERY[4, 5], which supports the modelling, animation, analysis and verification of this kind of systems.

Proteins have a hierarchical structure. They are synthesized as a sequence of amino acid residues that evolves following a folding process until they reach a stable spatial arrangement called native conformation. This native conformation is regarded as hierarchically built by four levels of structures respectively called primary, secondary, tertiary and quaternary.

The conformation of proteins is dynamic in a twofold manner. The first refers to the changes in a conformation that define the specific functional interactions it can engage. These interactions take place in active sites, which are locations exposed by the conformation. The second relates to the reconfigurations that expose different active sites and thus lead to conformations enabling other functional interactions. These reconfigurations can be triggered by the interaction with activation or inhibition molecules, or by changes in temperature, pressure of pH. The structures reached in the latter case are called soft modes and provide flexibility to the protein. In both cases changes are structurally encoded and range from local – affecting primary and secondary structures, to global – involving tertiary and quaternary structures. Thus, predicting and designing the flexibility of proteins is far from trivial due to the size and complexity of the problem, and requires suitable abstractions [2, 1].

We adopt ARCHERY for such purpose. The language is organized as a core and a number of modules. The basic specification concept of the core is that of an architectural pattern, which comprises a set of architectural elements (connectors and components) specified in terms of their interfaces (set of ports) and behaviours. An architecture describes a particular configuration of instances of pattern elements through a set of attachments linking their ports, and a set of renamings changing the externally visible names of ports. An architecture can itself be regarded as an instance of the corresponding pattern, exhibiting an emergent behaviour. Both patterns and elements act as types of configurations, which are kept and referenced through typed variables. The hierarchical composition of instances is allowed.

The language modules are for specifying reconfiguration scripts and constraints. A reconfiguration script consists of operations intended to cope with the creation and removal of instances, attachments, renamings and variables, as well as with moving instances. A constraint restricts either structure, behaviour or possible reconfigurations of a system. Reconfiguration scripts are executed by a configuration manager when conditions, specified as constraints, hold. The language semantics

is given by a translation into a process algebra [4], for the behavioural part, and by an encoding into bigraphical reactive systems [5], for the structural part. Constraints are translated into a modal logic and are verified against models derived from architectural specifications [6, 7, 3, 8].

A protein is modelled as a pattern instance built of types of quaternary structures. These types differ in the ports they have which represent the active sites of the protein. If necessary, quaternary structures can be defined as the hierarchical composition of tertiary structures, and this scheme repeated until amino acid residues are used as basic building blocks. The environment in which a protein lives, for instance, a cell, is modelled by a pattern instance with element types for modelling temperature, pH, proteins, and activation and inhibition molecules. The different soft modes a protein is known to reach are modelled using constraints triggering reconfiguration scripts. The former are used to indicate under which conditions a soft mode must be selected, and the later perform the actual change, for instance, in the quaternary structures of the protein to model the active sites that correspond to the selected soft mode. Constraints are also used to specify properties that must be preserved as soft modes are selected.

Acknowledgments

This work was supported by ERDF - The European Regional Development Fund through the Operational Programme for Competitiveness and Internationalisation - COMPETE 2020 Programme and by National Funds through the Portuguese funding agency, FCT - Fundação para a Ciência e a Tecnologia, within project POCI-01-0145-FEDER-030947 (KLEE).

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Optimal control of a delayed HIV/AIDS-PrEP model

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Pre-exposure prophylaxis (PrEP) consists in the use of an antiretroviral medication to prevent the acquisition of HIV infection by uninfected individuals and has recently demonstrated to be highly efficacious for HIV prevention. In this work, we propose a HIV/AIDS-PrEP model, given by a system of delayed differential equations (DDE), based on the model proposed in [3].

The HIV/AIDS-PrEP model subdivides human population into five mutually-exclusive compartments: susceptible individuals (S); HIV-infected individuals with no clinical symptoms of AIDS (the virus is living or developing in the individuals but without producing symptoms or only mild ones) but able to transmit HIV to other individuals (I); HIV-infected individuals under ART treatment (the so called chronic stage) with a viral load remaining low (C); HIV-infected individuals with AIDS clinical symptoms (A); and individuals that are under PrEP (E). The total population at time t, denoted by $N(t)$, is given by $N(t) = S(t)+I(t)+C(t)+A(t)+E(t)$. Effective contact with people infected with HIV is at a rate λ, given by

$$\lambda = \frac{\beta}{N}\left(I + \eta_C\, C + \eta_A A\right), \tag{4}$$

where β_0 is the effective contact rate for HIV transmission. The modification parameter $\eta_A \geq 1$ accounts for the relative infectiousness of individuals with AIDS symptoms, in comparison to those infected with HIV with no AIDS symptoms. Individuals with AIDS symptoms are more infectious than HIV-infected individuals (pre-AIDS) because they have a higher viral load and there is a positive correlation between viral load and infectiousness [4]. On the other hand, $\eta_C \leq 1$ translates the partial restoration of immune function of individuals with HIV infection that use ART correctly [2]. All individuals suffer from natural death, at a constant rate μ. We assume that HIV-infected individuals with and without AIDS symptoms have access to ART treatment. HIV-infected individuals with no AIDS symptoms I progress to the class of individuals with HIV infection under ART treatment C at a rate ϕ, and HIV-infected individuals with AIDS symptoms are treated for HIV at rate α. Individuals in the class C leave to the class I at a rate ω. We also assume that an HIV-infected individual with AIDS symptoms A that starts treatment moves to the class of HIV-infected individuals I, moving to the chronic class C only if the treatment is maintained. HIV-infected individuals with no AIDS symptoms I that do not take ART treatment progress to the AIDS class A at rate ρ. Note that only HIV-infected individuals with AIDS symptoms A suffer from an AIDS induced death, at a rate d. The proportion of susceptible individuals that takes PrEP is denoted by ψ. We assume that PrEP is effective so that all susceptible individuals under PrEP treatment are transferred to class E. The individuals that stop PrEP become susceptible individuals again, at a rate θ. Individuals under PrEP may suffer of natural death at a rate μ.

In this work, we consider the case where the implementation of PrEP suffers a discrete time-delay, τ, with $\tau \geq 0$, and analyze the impact of this delay on the number of new HIV infections, see equation (9). The time delay, τ, is related to barriers that block an effective implementation of PrEP, such as, stigma, cost and adherence. The access and delivery of PrEP to population in high risk faces serious limitations, and many times the population that should benefit from PrEP are those who have more difficulties to come routinely to a health service [**??**]. Adherence problems and high costs of the medicines may also be responsible for a delayed implementation of PrEP at the target population.

The model is given by the system of delayed differential (DDE) (5)–(9):

$$\dot{S}(t) = \Lambda - \frac{\beta\left(I(t) + \eta_C\, C(t) + \eta_A A(t)\right)}{N(t)} S(t) - \mu S(t) - \psi S(t) + \theta E(t), \tag{5}$$

$$\dot{I}(t) = \frac{\beta\left(I(t) + \eta_C\, C(t) + \eta_A A(t)\right)}{N(t)} S(t) - (\rho + \phi + \mu) I(t) + \alpha A(t) + \omega C(t), \tag{6}$$

$$\dot{C}(t) = \phi I(t) - (\omega + \mu) C(t), \tag{7}$$

$$\dot{A}(t) = \rho\, I(t) - (\alpha + \mu + d) A(t), \tag{8}$$

$$\dot{E}(t) = \psi S(t - \tau) - (\mu + \theta) E(t). \tag{9}$$

We consider the biologically feasible region

$$\Omega_P = \left\{ (S, I, C, A, E) \in R^5_{+0} \,:\, S \leq \frac{(\theta + \mu)\,\Lambda}{\mu\,(\theta + \psi + \mu)}, E \leq \frac{\psi\,\Lambda}{\mu\,(\theta + \psi + \mu)},\, N \leq \frac{\Lambda}{\mu} \right\}. \tag{10}$$

The model (5)–(9) has two equilibrium points: a disease free and an endemic equilibrium points.

The stability of the two equilibrium points depends on the delay τ. The local asymptotic stability of the equilibrium points will be proved, for any positive discrete time delay.

We introduce a control function $u(t)$ on the system of DDE (5)–(9), which represents the fractions of susceptible individuals that start the treatment with PrEP at each instant of time t, with $t \in [0, t_f]$. In other words, the constant parameter ψ is replaced by the control function $u(t)$:

$$\dot{E}(t) = u(t) S(t - \tau) - (\mu + \theta) E(t). \tag{11}$$

We consider the model (5)-(6)-(7)-(8)-(11) and formulate an optimal control problem with the aim to determine the PrEP strategy u over a fixed interval of time $[0, t_f]$ that minimizes the number of individuals with pre-AIDS HIV-infection I as well as the costs associated with PrEP, that is, that minimizes the cost functional

$$J(u) = \int_0^{t_f} \left[w_1 I(t) + w_2 u(t) \right] dt, \tag{12}$$

where the constants w_1 and w_2 represent the weights associated with the number of HIV infected individuals I and on the cost associated with the PrEP prevention

treatment, respectively. It is assumed that the control function u takes values between 0 and 1. When $u(t) = 0$, no susceptible individual takes PrEP at time t; if $u(t) = 1$, then all susceptible individuals are taking PrEP at time t. The objective is to minimize the number of newly infected individuals with HIV, I, while keeping the cost of implementation of PrEP as low as possible.

Let

$$x(t) = (x_1(t), \ldots, x_5(t)) = (S(t), I(t), C(t), A(t), E(t)) \in R^5. \tag{13}$$

The optimal control problem consists to find the optimal trajectory $\tilde{x}$, associated with the control $\tilde{u}$, satisfying the control system (5)-(6)-(7)-(8)-(11) , the initial conditions,

$$x(0) = (x_{10}, x_{20}, x_{30}, x_{40}, x_{50}) \tag{14}$$

with

$$x_{10} \geq 0,\ x_{20} \geq 0,\ x_{30} \geq 0,\ x_{40} \geq 0,\ x_{50} \geq 0,$$

and where the control $\tilde{u} \in \Omega$ minimizes the objective functional (12) with

$$\Omega = \left\{ u(\cdot) \in L^\infty(0, t_f) \,|\, 0 \leq u(t) \leq 1 \right\}. \tag{15}$$

In this work, the proposed delayed optimal control problem will be solved theoretical and numerically. The optimal solutions will be compared with the non-delayed case. The mathematical results will be discussed from an epidemiological point of view.

Acknowledgements: Supported by the Portuguese Foundation for Science and Technology (FCT) within projects UID/MAT/04106/2013 (CIDMA), PTDC/EEI-AUT/2933/2014 (TOCCATA) and to the FCT post-doc fellowship SFRH/BPD/72061/2010.

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Quantum simulation of quantum chemistry: A case study using IBM Q

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As quantum computing finally comes of age, with its first commercial implementations, quantum simulation emerges as a ground-breaking technology for several domains, including biology and chemistry, where it finds, already, a large amount of possible applications.

The construction of quantum simulations for quantum chemistry, however, raises a number of conceptual and practical challenges at different layers, from the Hamiltonian modelling of the molecular system and its corresponding circuit, to the actual execution of the circuit in a quantum device, which, nowadays, is technically challenging.

In this work we aim at going through all such steps, thus contributing to a better understanding of the issues and techniques involved. We do so, by exploring a case study of the conception and execution of a quantum simulation, for the calculation of the ground state and the dissociation energy of the *hydrogen* (H_2) and *Lithium-hydride* (LiH) molecules, in an actual commercially available quantum computer, the IBM Q, accessed through the QuantaLab UMinho Academic Q Hub, from which values close to the theoretical expectations were obtained.

Hamiltonian modelling of quantum chemistry. The objects of study in quantum chemistry are chemical phenomena, from a point of view of sub-atomic particles, such as atoms, electrons and molecules, governed by quantum mechanical laws.

Depending on the system under study, one may be interested in the calculation of different properties, from the states of minimal energy (ground states), dissociation energies, to thermal rates and many others. The behaviour of a physical system governed by quantum mechanical laws, can be modelled by a Hamiltonian operator, which yields the energy of the system, provided by individual particles and their interactions, and is divided in *potential* and *kinetic* components.

For a wide class of quantum chemistry systems, a Hamiltonian only involving *fermions* (electrons, atoms, etc.) and their electrical interactions suffices, and hence, in this work, we use the so-called the Born-Oppenheimer approximation Hamiltonian [13]. This approximation only considers the potential energy coming from the electron-nuclei and electron-electron electrical interactions, as well as the kinetic energy of electrons, and it consitutes a good approach to the physical system under consideration in this work. The correspondent Hamiltonian reads as follows [3]:

[3] The Hamiltonian is written in atomic units ($e = \hbar = \mu_0 = 1$), the first term corresponds to the kinetic energy of electrons, the second to their attraction to nuclei, and the third to the repulsive forces between electrons. Z_A is the charge of nucleus A, r_{xy} are the distances between elements x and y, which can be nucleus (in upper case) or electrons (in lower case). ∇_i^2 corresponds to the *Laplacian* operator, which provides velocity of a particle.

$$H_{elec} = -\sum_{i=1}^{N} \frac{1}{2}\nabla_i^2 - \sum_{i=1}^{N} \frac{Z_A}{r_{iA}} + \sum_{i=1}^{N}\sum_{j>i}^{N} \frac{1}{r_{ij}} \tag{16}$$

In Fig. 6 are depicted the structure of hydrogen atom and molecule, which illustrates the use of a fermionic Hamiltonian in actual chemical elements.

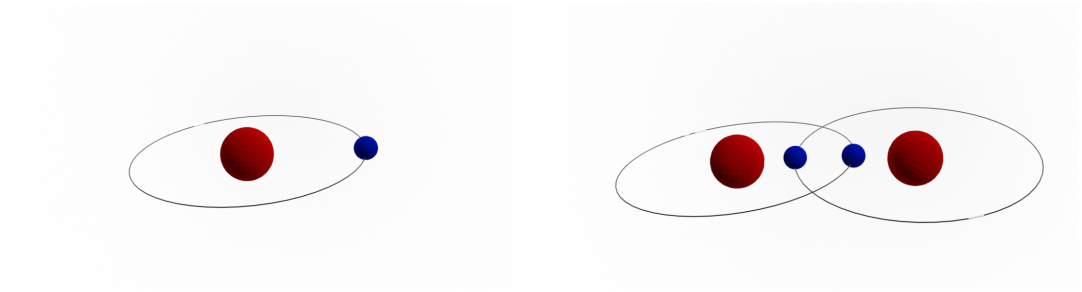

Figure 6: The atom of hydrogen has a single electron, moving around the nucleus carrying kinetic energy, and angular momentum. Also, while in such motion, the electron maintains a distance to it, originated by the electrical *repulsive* interaction that occurs between the two elements. In hydrogen molecule, H_2, there will be two nuclei and two electrons moving around the nuclei, and similar interactions apply.

For systems with many particles, the computational complexity of the Hamiltonian can be greatly reduced by expressing it in terms of the second quantization formalism, which introduces invariance to permutations between particles, making system order independent. The formalism also introduces the notion of creation and annihilation operators, which among other advantages, allows the handling of physical systems with variable dimension. Using this formalism, the Hamiltonian of equation (16) can be rewritten as follows:

$$H = H_1 + H_2 = \sum_{\alpha,\beta=0}^{M-1} \tau_{\alpha\beta} a_\alpha^\dagger a_\beta + \frac{1}{2} \sum_{\alpha,\beta,\gamma,\delta=0}^{M-1} \mu_{\alpha\beta\gamma\delta} a_\alpha^\dagger a_\gamma^\dagger a_\delta a_\beta \tag{17}$$

where $\tau_{\alpha\beta}$ is the matrix element (scalar) representing the kinetic energy of the electrons and the potential energy they experience by interacting with the nucleus (*one-dimensional operator*):

$$\tau_{\alpha\beta} = \int dx_1 \psi_\alpha^*(x_1) \left(\frac{-\nabla^2}{2} + \sum_i \frac{Z_i}{|r_{i1}|} \right) \psi_\beta(x_1) \tag{18}$$

while the term $\mu_{\alpha\beta\gamma\delta}$ (also a scalar) represents the interactions caused by Coulomb forces (*two-dimensional operator*):

$$\mu_{\alpha\beta\gamma\delta} = \int dx_1 dx_2 \psi_\alpha^*(x_1)\psi_\beta(x_1) \left(\frac{1}{|r_{12}|} \right) \psi_\gamma^*(x_2)\psi_\delta(x_2) \tag{19}$$

In equations (18) and (19), the wave functions ψ^- are the ones of equation (20), evaluated on the points x and they correspond to the *eigenfunctions* of the Hamiltonian operator, which are not known beforehand. Therefore, to make the numerical

evaluation of those integrals possible, approximations must be used, for which, the *STO-3G* ones, linear combinations of Gaussian functions, were the preferred:

$$\Psi_{STO-3G}(s) = c_1 \left(\frac{2\alpha_1}{\pi}\right)^{\frac{3}{4}} e^{-\alpha_1 r^2} + c_2 \left(\frac{2\alpha_2}{\pi}\right)^{\frac{3}{4}} e^{-\alpha_2 r^2} + c_3 \left(\frac{2\alpha_3}{\pi}\right)^{\frac{3}{4}} e^{-\alpha_3 r^2} \quad (20)$$

The actual numerical calculation of such integrals, was calculated in PyQuante [10] and PyScf [12], both open-source Python libraries targeted to do quantum chemistry calculations.

Circuit Generation. Once the second quantization Hamiltonian is defined and calculated, the next step is to build a quantum circuit, operating over qubits, that approximates it. The theoretical ground for these transformations is given by the Jordan-Wigner transformation [14], which is based on the isomorphism between creation and annihilation operators and the algebra of half-spin systems (a possible model of qubits) and establishes how a second quantization Hamiltonian can translated into a combination of *qubit* raising and lowering operators, a *qubit Hamiltonian*. A practical enumeration of these translations can be found in table A2 of [14] and its actual calculation can be performed by Quipper [4], a quantum programming language based on Haskell, where a built-in library is available for such purpose.

The Variational-Quantum-Eigensolver. The actual calculation of the properties of interest, such as the ground state and the dissociation energy, require the calculation of the ground state of the qubit Hamiltonian of previous section. Such optimization problems are know to be very hard (NP-HARD) and there are several quantum computational techniques available to solve them.

The method used in this work was the Variational-Quantum-Eigensolver (VQE), depicted in Fig. 7, which may be considered as an adaptation of the classical variational method to a quantum setting [9]. The main idea is to start by a possible solution for the problem (a possible parameterizable function approximating the eigenfunctions of the Hamiltonian, denominated *ansatz*), and refine it (by changing the parameters of the function) until the optimal solution of the problem is found, which corresponds to the ground state of the physical system under consideration.

The method involves classical and quantum parts: the control routines and the evaluation of the Hamiltonian action. All control routines, from the preparation of the *ansatz* state to the actual calculation of energy and optimization of the parameters λ, are classical, while the actual calculation of the Hamiltonian action is quantum. In this method, the function to be optimized is the energy of the system where the Hamiltonian H acts, which is calculated as follows:

$$\epsilon[\Psi(\lambda)] = \frac{\langle \Psi(\lambda) | H \Psi(\lambda) \rangle}{\langle \Psi(\lambda) | \Psi(\lambda) \rangle} \quad (21)$$

In equation (21), $\Psi(\lambda)$ denotes the *ansatz*, corresponding in this case to a subspace of the vector space spanned by all *eigenvectors* Ψ, dependent on a set of arbitrary parameters λ, and ϵ the function to be minimized. The correctness of the method is ensured by the variational principle:

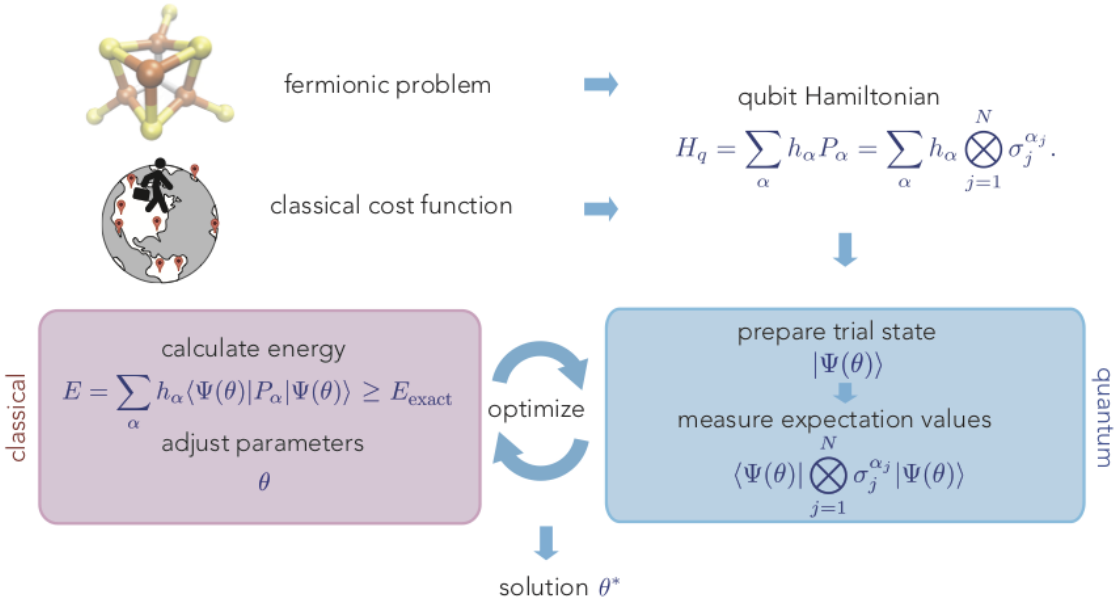

Figure 7: Application of the variational method to fermionic problems, adapted from [9]

- $\epsilon \geq E_0$, where E_0 is the state of lowest energy (ground state) of the Hamiltonian
- $\epsilon = E_0$, iff $\epsilon[\Psi]$ is the ground state.

This principle entails that any valid $\Psi(\lambda)$ function, will always provide an upper bound for the ground state of the Hamiltonian.

Simulations. We conducted simulations for both the H_2 and LiH molecules, in the commercially available quantum computer, IBM Q, accessed through the QuantaLab UMinho Academic Q Hub, resorting to the Qiskit platform and the AQUA framework, to do the necessary programming. In both molecule simulations, two ground-state calculation methods were employed: the *ExactEigensolver* (classical method) and the VQE (Variational Quantum Eigensolver). In both cases the former was used as baseline, and all the simulations were performed using the *local_statevector_simulator* backend, a quantum device simulator supplied within the IBM Q environment. All the relevant files to the replication of these experiments (pyquant, pyscf, quipper and HDF5 files, as well as Qiskit code) are available in the following url: `http://arca.di.uminho.pt/experiments_quantum_chemistry/`.

For the specific case of the H_2 molecule, as presented in table 1, a convergence to the theoretical value calculated with the *ExactEigensolver* method was verified, which seems to suggest that the simulation was successful.

We also conducted studies on the calculation of the dissociation energy, the energy necessary to break the bond between the two H atoms, as depicted in Fig. 8. In theory, the highest dissociation energy corresponds to the equilibrium distance between the atoms, which also corresponds to the ground state energy.

Table 1: The energy unit used is the *Hartree*[13], an atomic unit of energy. The variation is the absolute error between the values obtained through Exacteigensolver and VQE method. Experiences made with several configurations of the parameters *max_trials*, *depth* and *shots*. Full table available in the following url: `http://arca.di.uminho.pt/experiments_quantum_chemistry/Ground_State_Energy_Tables.zip`.

Ground State Energies				
			ExactEigensolver	
			-1,137306035753	
			VQE method	
max_trials	depth	shots	Value	Variation
1	1	1	-0,712503938173	4,2E-01
		2048	-0,102521694036	1,2E+00
	7	1	-0,313978701260	8,2E-01
		2048	-0,593980785118	5,4E-01
5000	1	1	-1,137262155450	4,4E-05
		2048	-1,137304046500	2,0E-06
	7	1	-1,137304559058	2,3E-06
		2048	-1,137304311791	1,7E-06

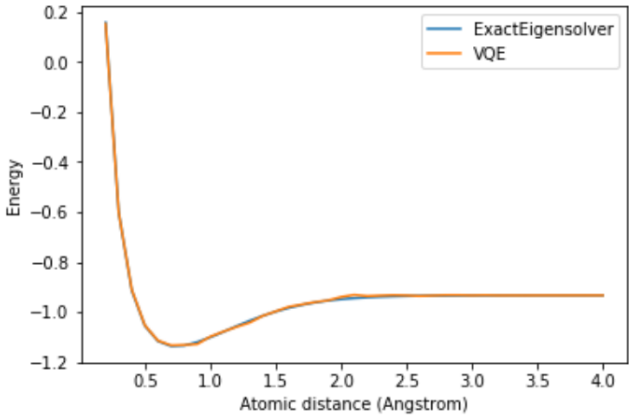

Figure 8: Variation of the H_2 dissociation energy as the distance between atoms increases. Parameters used in the VQE method: *max_trials=350*, *depth=3* and *shots=2048*

Once more, it can be verified the similarity between the theoretical results obtained *classically* and the results obtained in the quantum device simulator.

In the case of LiH, the experiences made led to a slower converge to the theoretical value, perhaps due to the greater complexity of the molecule. However, the error obtained is in order of 10^{-3} and some degree of convergence is verified.

Table 2: Same as Table 1.

Ground State Energies				
			ExactEigensolver	
			-7,88240193229	
			VQE method	
max_trials	depth	shots	Value	Variation
1	1	1	-7,021299390490	8,6E-01
		2048	-7,191895551060	6,9E-01
	7	1	-7,052667867887	8,3E-01
		2048	-6,973986243448	9,1E-01
5000	1	1	-7,862023833205	2,0E-02
		2048	-7,857451742601	2,5E-02
	7	1	-7,880613192926	1,8E-03
		2048	-7,879721385780	2,7E-03

Conclusions. The results obtained are different for the molecules involved: in the case of the H_2 molecule, the values obtained are quite close, and converged rapidly, to the theoretical calculations, while in the case of the LiH molecule, the smallest error obtained in experiments is on the order of 10^{-3}, but convergence was verified. This implies that more refinement iterations and more processing time is required be required. However, both cases seem to provide evidence for the feasibility of the use of this quantum computer for small molecules, with an appropriate number of iterations.

The current quantum computation and simulation technology has not attained the maturity required to simulate systems of relevant size, in order to answer relevant questions in biology and chemistry, and doubts remain about if this is going to happen soon. However, the good results obtained with small systems, for which this work is yet another piece of evidence, undoubtedly constitute important milestones in that direction.

Acknowledgments. The authors wish to thank to Luís Barbosa and Mikhail Vasilevskiy, for the helpful discussions and suggestions during the course of this work, and to the students of physics engineering of University of Minho, for the helpful contributions for the preliminary part of this work: Carolina Alves, Daniel Carvalho, Michael de Oliveira and Paulo Ribeiro.

The first author was funded by an individual grant of the first author, of reference SFRH/BD/116367/2016, supported the FCT - Fundação para a Ciência e Tecnologia under the POCH programme and MCTES national funds. This work is also a result of the project "SmartEGOV: Harnessing EGOV for Smart Governance (Foundations, Methods, Tools) / NORTE-01-0145-FEDER-000037", supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (EFDR)

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Dynamic equations on time scales; deterministic epidemic model; closed-form solution

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We investigate an epidemic model based on Bailey's continuous differential system. In the continuous time domain, we extend the classical model to time-dependent coefficients and present an alternative solution method to Gleissner's approach. If the coefficients are constant, both solution methods yield the same result. After a brief introduction to time scales, we formulate the SIR (susceptible-infected-removed) model in the general time domain (including the continuous, the discrete, and hybrid cases) and derive its solution. In the discrete case, this provides the solution to a new discrete epidemic system, which exhibits the same behavior as the continuous model. The last part is dedicated to the analysis of the limiting behavior of susceptible, infected, and removed, which contains biological relevance.

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