

# Coping with Dynamical Structures for Interdisciplinary Applications of Membrane Computing

Thomas Hinze<sup>1,2</sup>(✉)

<sup>1</sup> Department of Bioinformatics, Friedrich Schiller University Jena,  
Ernst-Abbe-Platz 2, 07743 Jena, Germany  
`thomas.hinze@uni-jena.de`

<sup>2</sup> Institute of Computer Science, Brandenburg University of Technology,  
Postfach 10 13 44, 03013 Cottbus, Germany

**Abstract.** Biological information processing and maintenance of life mainly utilise *dynamical structures* at different levels from a nanoscopic up to a macroscopic scale. Providing a high degree of reliability, reproducibility, unambiguousness, and addressability, underlying compositional processes appear as ideal candidates to perform computational tasks in a discretised manner. In this essay, we consider four levels in which dynamical structures enable an efficient handling with information: (1) the molecular level, (2) the level of reaction network modules, (3) the level of membranes, and (4) the level of higher-order organisms and populations. All of them have in common the capability of controlled memory-based state transitions and hence dedicated systems's configurations encoding behavioural patterns. Due to its discrete algebraic nature, *membrane systems* represent advantageous frameworks in order to formalise corresponding activities. This in turn paves the way towards efficient tools inspired by nature with manifold smart applications in engineering, computer science, and systems biology. We illustrate membrane system's abilities, benefits, and progress for coping with dynamical structures from an integrative perspective.

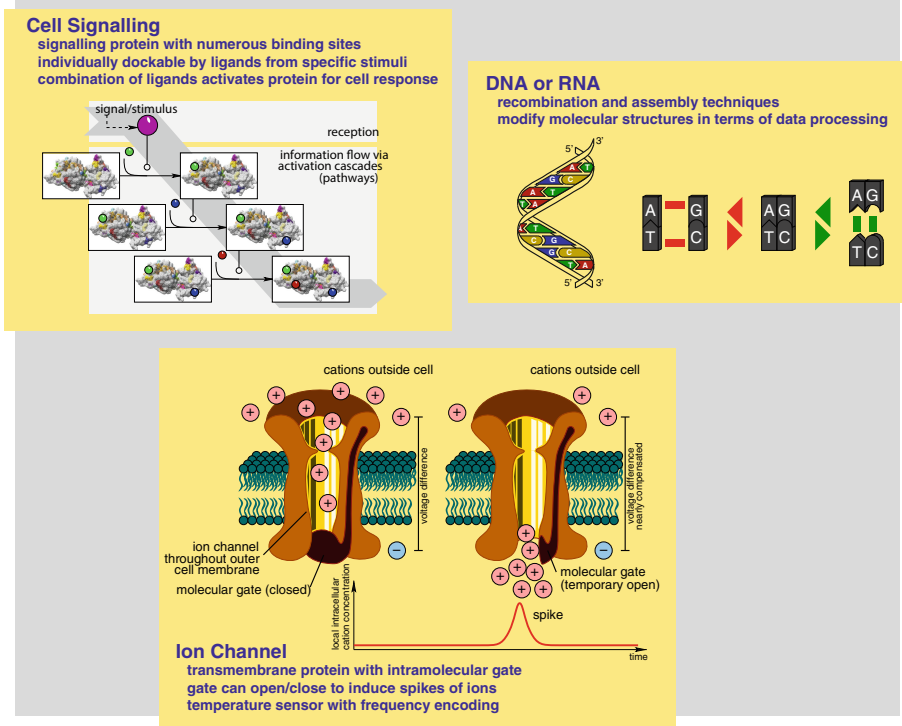
## 1 Introduction

Living organisms comprise astonishing capabilities of information processing resulting in complex behavioural patterns and in the presence of fascinating properties like intelligence, creativity, self-organisation, strategy, cognition, awareness, and many others. There is a widespread intuitive imagination about these phenomena but most of them still lack a comprehensive understanding based on formal methods. Over the last decades, we observe a deeper and deeper *formalisation* of natural sciences. Starting from big theories in physics and inorganic chemistry, nowadays the fine-grained nature of biochemical reactions along with detailed shaping of macromolecules becomes more and more unravelled. Underlying principles and laws have been formulated in a conclusive and consistent way. Highly productive experimental equipment, precise measurement,

visualisation, and particle tracing at nanometre scales provide a huge amount of interwoven data. By means of statistical analysis in conjunction with data mining techniques, a growing essence of new knowledge emerges which is characterised by a strictly mathematical denotation using formal expressions and formal methods. In addition, even previously informal pure evidence-based or empirical knowledge became specified by deduced formalisms which in turn enable computer-based simulation and integration towards more holistic systems hierarchically composed of functional units. Formalisation can be seen as crucial clue for understanding and for obtaining substantiated conclusions. After physics and chemistry, formalisation is going to pervade biology and life sciences. This comes along with tremendous re-organisation and extension of the particular scientific subject. Medical, social and economic sciences represent further candidates still awaiting a rigorous formalisation of its facets as a whole. From a visionary point of view, it seems possible that complex issues – like cognition abilities or existence of a circadian clock [1] an organism is equipped with – can be defined exclusively by usage of formal methods and afterwards automatically checked using reasoning techniques. Currently, this objective is still far away to be reached soon, but it gives a strong motivation.

When considering technical principles of information processing invented in engineering, it turns out that data storage as well as data manipulation is typically organised in a strictly *discrete manner* which means that the underlying system carries out well-defined *state transitions* controlled by a program or by external signal courses. Toggling between (pre)defined states ensures a high degree of safety and diminishes the danger to loose correct data or to initiate undesired effects of processing steps on the underlying data. Discretisation of information processing comes with a certain redundancy which implies that the physical implementation of a state might slightly vary without any consequences on the encoded information. Interestingly, dynamical structures evolved in living organisms perfectly permit a discrete manner of information processing.

A *structure* in this context is a spatial or topological arrangement of physical constituents. Composition of constituents together with the shape of the resulting formation defines evaluable individuals for clear identification of *data values*. In concert with the basic concept of the *von-Neumann* computer architecture, data values can represent instructions or operators as part of a program on the one hand but also input data, operands, or final results of computations on the other. In order to distinguish whether a data element is treated as operator or as an operand, an *addressable memory* is needed which also facilitates pointing to the next instruction to execute. Within the sphere of living organisms, the positional location or inner placement of an information-encoding *structure* inside the organism's body reflects the notion of addressability. In geometrical relation to its environment, presence or absence of a certain structure might cause specific effects forming a chain or sequence of activities at different places of the organism. Thus, addressability within a biological memory can be seen as more or less associative form of storage technique due to its dependence on local characteristics of the involved structures. Completing the image of a biological



**Fig. 1.** Three typical examples of dynamical structures at **molecular level**: composition of molecules from monomeric constituents like strands of DNA or RNA (**upper right part**), three-dimensional shape and orientation of complex macromolecules shown by an ion channel (**lower part**), and combination of composition and shape found for instance in cell signalling by successive activation of transcription factors for stimulus-induced gene expression (**upper left part**).

computation, structures are able to modify over time. The underlying *dynamics* of the structure makes accessible dedicated changes of the represented data values. To this end, the structure undergoes controllable interactions with other structures or with the environment resulting in behavioural patterns.

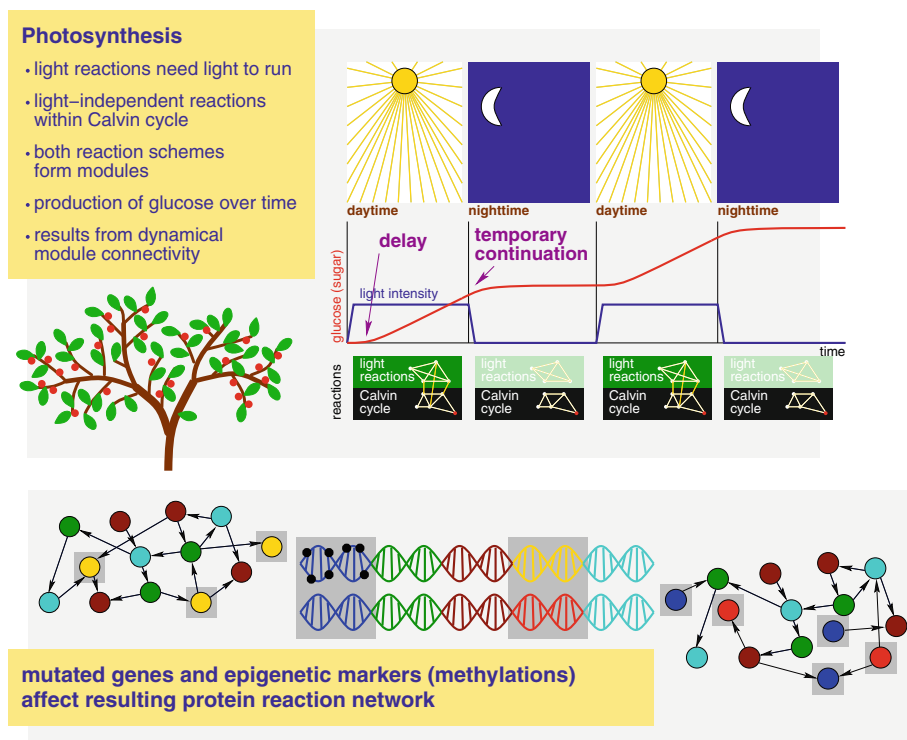
The general term of a dynamical structure in living organisms subsumes many forms of occurrences and facets which makes corresponding systems complex but also extremely powerful and flexible. Having in mind that a typical biological cell is composed of  $10^8$  up to  $10^9$  interacting molecules while an adult human being consists of approximately  $10^{14}$  cells, it becomes obvious that detection and understanding of biological information processing requires appropriate *levels of abstraction* complemented by purposive formalisation. Since membrane systems allow hierarchical composition and decomposition of algebraic elements and structures in a rule-based or functionally controlled manner, they are ideal candidates to model systems with dynamical structures even at different scales.

In the next section, we identify four corresponding levels. Section 3 assigns a membrane system for each level taken from our previous research. It stands out that the variety of membrane systems throughout all levels complements to each other in a way that structures obtained as outputs of lower-level systems can act as elementary constituents of higher-level systems finally producing a hierarchically organised meta-system. This consistently perceived modular approach encourages a subsequent setup of tools and instruments for further analysis and interdisciplinary applications like identification and classification of capabilities or detection of algorithmic strategies found in organisms. Section 4 is dedicated to this visionary topic discussing in brief some first ideas prone to attract membrane computing beyond computer science.

## 2 Biological Information Processing Primarily Utilises Dynamical Structures at Different Levels

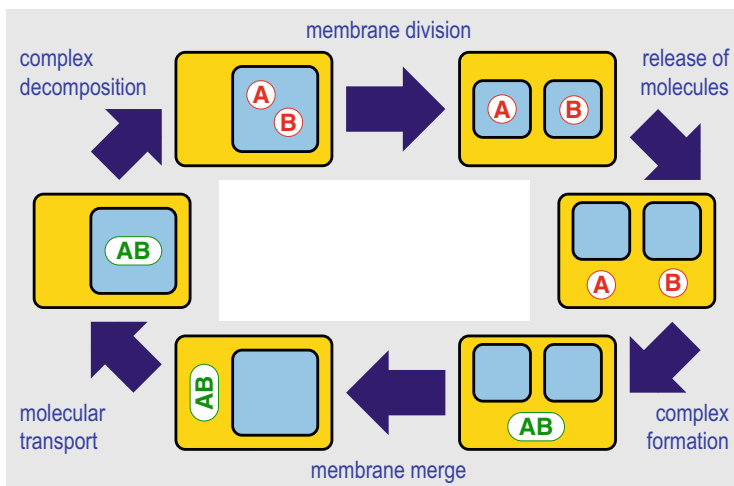
Coping with *dynamical structures* turns out to be both, a challenging task but also a crucial clue in understanding, fine-grained modelling, and utilisation of biological and biologically inspired information processing [10]. Principles of molecular computing are mainly based on modifiable spatial and topological arrangements in different forms, contexts, and scales ranging from nanoscopic surface shapes up to complex macroscopic behavioural patterns. From a composition-oriented point of view, we identify at least *four levels* in which dynamical structures essentially occur:

1. The **molecular level** comprises spatial grouping of atoms by chemical bonds forming macromolecules. Figure 1 illustrates typical examples by schematic representations. Most notably, intramolecular structures of DNA, RNA, and proteins constitute their functionality as data carrier and storage medium along with a co-ordinated set of biochemical reaction schemes. *Cell signalling* gives an illustrative example. Here, external stimuli like hormones or environmental factors reach receptors at the outer face of a cell membrane. At its inner part, signalling proteins and second messengers (ligands) are released. By passing a signalling cascade, signalling proteins become activated by a specific combination of ligands residing at protein binding sites. This results in composition of a dedicated molecular structure acting as transcription factor which in turn can enter the cell nucleus and afterwards initiate a specific gene expression producing a cell response. Even without modification of chemical bonds, we can observe dynamical molecular structures in a functional context. Let us consider an *ion channel*: It mainly consists of a transmembrane protein incorporating a controllable gate. Cations accumulate close to the channel entry outside the cell. As far as enough cations are present, the gate temporarily opens for a short moment, and an amount of cations can pass the channel into the cell inducing a spiking signal. The function of the underlying gate is based on a dynamically movable side chain inside the transmembrane protein. Ion channels can for instance act as temperature sensors producing a frequency-encoded oscillatory spiking signal [8].



**Fig. 2.** Two representative examples of dynamical structures at the **level of reaction networks**: topological changes can be caused by external stimuli. Here, the processing scheme of photosynthesis varies by the intensity of brightness: light-dependent reactions dynamically join or leave in accordance with presence or absence of environmental sunlight during daytime and nighttime (**upper part**). Alternatively, changes of a reaction network structure can also result from intrinsic reasons like mutations of genomic DNA or influences of epigenetic factors (**lower part**).

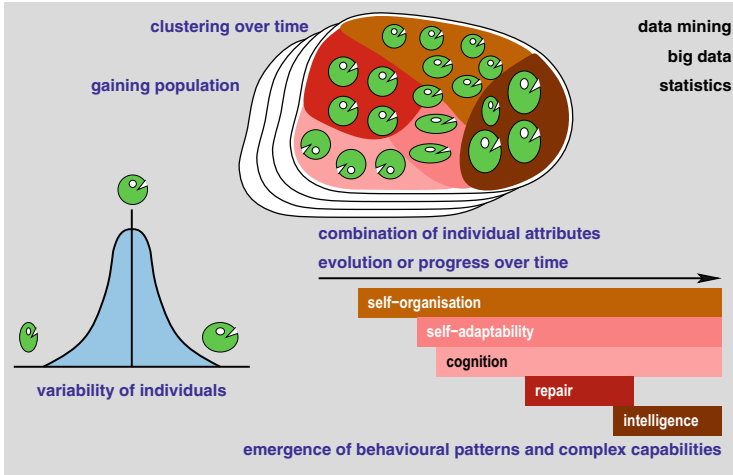
2. The **level of reaction network modules** opens the next stage of dynamical structures, see Fig. 2 for an overview of case scenarios. Chemical reaction schemes, particularly those found in living organisms, appear to represent *invisible* networks. Nevertheless, they provide the driving force in information processing by conducting state transitions from one molecular configuration to another one. The topology of a chemical reaction network is commonly treated as a static structure due to its highly conserved genetic blueprint. A corresponding network of densely interwoven reactions forms a *module*, an elementary unit also called *motif*. Structural dynamics becomes visible when studying the interplay of reaction network modules over time. It turns out that several modules merge or couple to each other temporarily while modular compounds can also dissolve, re-arrange, or re-assembly. Initiated by trigger signals, by perturbances, or simply by random, network re-compositions arise.



**Fig. 3.** Information processing at the **level of dynamical membrane structures** might also incorporate oscillatory behaviour resulting in a cycle of system's configurations. A toy example addresses a cycle composed of six stages. Let A and B symbolise molecular constituents able to form a complex which is promoted by the outer membrane. In contrast, the inner membrane(s) enhance complex decomposition. Membrane division and membrane merge complement the processing loop.

*Photosynthesis* is representative for that: Depending on presence or absence of light, different reaction schemes are active. Light intensity toggles between several underlying reaction network topologies composed of a set of modules. Another obvious example is given by *mutation* or *recombination* of genetic DNA which results in modified reaction network structures. Also *infection* of a cell by a virus or *bacterial gene transfer* can have similar effects. When aiming at understanding of maintenance of life, dynamics of reaction network structures is essential.

- Increasing within the hierarchy, the **level of membranes** characterises a new quality of dynamical structures. Membranes enable a *compartmentalisation* of spatial structures in which chemical reactions and transportation processes appear. Having in mind that membranes form a physical *boundary* and they offer a selective or general *permeability* for molecules at the same time, it becomes obvious that dynamics at this level can imply powerful features [13]. *Cell division* is probably the most popular example of a dynamical membrane structure. Following this line, the formation of *tissues*, *organs*, and finally multi-cellular *organisms* exhibits an amazing capability of self-organisation [3] and self-coordination [2]. For instance, the spatial derivation of cytokines manages the progress in *cellular differentiation*. *Exocytosis* as well as *endocytosis* in conjunction with membrane creation and dissolution provides molecular containers for directed transportation. Often, membrane structures need to be assembled in an optimal way in order to achieve a certain



**Fig. 4.** Individuals within a population come with specific combinations of properties and attributes. An extensive variability among the occurrences in conjunction with a combinatorial multiplicity of potential individuals leads to an assessable population whose members can be clustered using *categorised counting* [7] for instance. Each cluster stands for a certain common capability of its members. A cluster in this context forms a structure whose emergence over time implies dynamics at the **level of organisms and populations**.

functionality at its best. *Optimal placement* of branches and junctions within capillar blood vessels for adequate supply of neighboured cells keeping low the overall need of molecular resources is a typical outcome. Even oscillatory behaviour might include circular modifications of membrane structures, see Fig. 3. More notably, using *neural plasticity* the process of (re)mapping the brain structure emerges.

4. The **higher-order organism or population level** marks the topmost instance of dynamical structures found in complex biological systems. Unequivocally, underlying rules, principles, or laws responsible for control and development of the corresponding structures are often hard to identify and sometimes prone to errors, misinterpretations, or incompleteness. State-of-the-art approaches attempt to identify the rules by comprehensive statistical analyses of huge amounts of experimentally observed data resulting from macroscopic behavioural patterns [12]. A simple example is a *predator-prey system* for instance consisting of a population of rabbits and a population of foxes sharing the same living area. Dependent on relevant parameter values like rabbit's birth rate, fox's death rate and feeding activity, the system exhibits various behavioural patterns like stable oscillation with variable periodicity, extinction of foxes, or exponential growth of involved populations. An opposite example is *symbiosis* of organisms or populations. Moreover, *swarms*, *colonies*, and *societies* create highly complex behavioural patterns

incorporating fascinating properties like cooperation, altruism, cognition, consciousness, or *intelligence*. Many of these properties still lack a formal definition based on substantiated understanding. Figure 4 sketches the general idea and principle which is based on categorised counting among individuals with a combination of attributes.

### 3 Membrane Systems for Explicit Formalisation of Structural Dynamics at Different Levels

Due to its discrete nature composed of algebraic elements, membrane systems appear to be an ideal candidate able to describe dynamical structures on adequate levels of abstraction [14]. Within research projects during the last years, we developed several P systems frameworks coping within dynamical structures at molecular level, at the level of reaction network modules, and at the level of membranes. Most of these descriptive frameworks come with simulation software tools employed for tackling a number of application case studies.

P systems for cell signalling modules ( $\Pi_{\text{CSM}}$ ) act at the *molecular level* [6]. Here, each molecule is represented by a regular expression denoted as a string. The characters within the string reflect the underlying signalling protein name together with an arbitrary number of ligands which in turn can be individually present or absent in the protein structure. Unknown or irrelevant binding situations are allowed to be written by a placeholder symbol ( $\star$ ). A multiset of strings constructed in this way defines the initial pool of molecules. The set of reaction rules is also allowed to utilise placeholder symbols when describing substrates or products. Hence, the number of reaction rules can be kept low. Execution of a reaction rule includes a matching process which identifies the affected substrate molecules. We equipped the system's specification with a discretised form of reaction kinetics estimating the selection of substrate molecules taken into account per time step for each available reaction. Based on the  $\Pi_{\text{CSM}}$  framework, the simulation software SRSim emerged in which SR stands for "structural rules" but also for "spatial rules" [4]. In addition to the string describing a molecule, three-dimensional cartesian coordinates together with bond length and angles can be assigned to each molecular component. In this way, a reactive calotte-like model of each molecule is obtained.

Within the *level of reaction network modules*, we introduced the P meta framework for polymorphic processes [5, 9]. Here, the main focus of attention is laid to dynamical composition and decomposition of modules towards formalisation of more complex system's behaviour. We permit modifications of the module connectivity at arbitrary points in time but also subject to conditional trigger signals. This feature offers a high flexibility in formalisation of measurable system's properties which can be helpful to bring in silico-simulations closer to experimental observations. Furthermore, a compact but expressive formalism is provided to manage dynamical topologies of reaction network structures. The underlying concept resembles an *event-based programming language*: A program



is built of a final set of *instructions*. Each instruction contains a specific *condition* (a boolean term based on evaluation of elapsed model time and conditional trigger signals) followed by a corresponding *action*. An action could be the connection of two dedicated modules including coupling of shared species and supply of affected signal values. Other actions incorporate disconnection of modules, coupling/decoupling of additional species, module exchange, or module reset. The sequence of instructions defines individual priorities in order to prevent ambiguities.

Aimed at exploring abilities of self-organisation by dynamical structures within the *level of membranes*, we currently elaborate the idea of grid-exploring P systems assuming an initial grid of membranes. Each membrane on its own acts in terms of a module. It can be entered, passed, and left by molecules. In some dedicated modules called processing units, molecules can be processed by reactions of different types like composition ( $a + b \rightarrow c$ ), incorporation ( $a + b \rightarrow a$ ), and unification ( $a + a \rightarrow b$ ). Molecules initially placed at different positions of the grid's boundary individually run through the grid visiting a sequence of designated membranes in which they become successively processed. Using artificial evolution, the arrangement of membranes within the grid becomes optimised for shortening the total time duration necessary for complete passage and processing of all molecules. We employ grid-exploring P systems for topological grid optimisation using artificial evolution which in turn cares for variation of grid elements following the metaphor of *walking membranes*.

Advantageously, the aforementioned membrane systems flanking different levels of dynamical structures can be coupled in order to interact by bridging these levels. Let us consider this feature by a case study addressing the existence of a circadian clock which generates an endogenous oscillation whose periodicity resembles the duration of one earth rotation (24 h). Furthermore, a circadian clock is able to get entrained by adaptation to external stimuli like alteration between sunlight and darkness. Organisms equipped with a circadian clock typically possess an advantage over those who do not since they can for instance better exploit the sunlight by initiation of biochemical processes accurately timed before sunrise. The  $\Pi_{\text{CSM}}$  framework provides appropriate instruments to model an underlying reaction scheme taking into account submolecular structures like successive protein phosphorylations and dephosphorylations or formation of protein complexes within the reaction cycle. Corresponding courses of molecular amounts express the (core) oscillatory behaviour which becomes complemented by additional influencing factors. Most of them control the oscillation and its periodicity by inhibition or by activation (amplification) of selected reactions. Since this effect strongly depends on the brightness of environmental light (for instance measured by light-sensitive substances like chlorophyll), we achieve a dynamical overall reaction scheme over time. Some reactions have been iteratively switched on or switched off, or their velocity is diminished or accelerated. Here, the P meta framework for polymorphic processes represents a sufficient tool in order to capture the entire system's description in an appropriately formalised way. Organisms in general and especially those comprising a

circadian clock undergo a life cycle consisting of different phases like nutrition, growth, and reproduction. Since organisms coexist in a population embedded into a more or less heterogeneous environment, the life span of an individual can be seen as a walking tour through various places, each of them dedicated to a specific task or function. Organisms unable to reach a desired place to perform the next task in time run into serious danger to die. Grid-exploring P systems offer a descriptive formal framework for the behaviour of a resulting population. From a technical point of view, the orchestrated interplay of membrane systems at different levels of abstraction and among different levels of dynamical structures opens a strategy to cope with the complexity of biological systems.

## 4 Usefulness of Membrane Systems Managing Dynamical Structures

Convincing simulations and visualisations of biological and biologically inspired processes utilising dynamical structures can be seen as a first and essential step towards a beneficial toolbox of complementary membrane system instances. Beyond pure system's definition along with estimation of its computational capacity, our research is focused on identification and exploration of useful practical applications and application scenarios for membrane systems managing dynamical structures. Projects and case studies are motivated by finding hypotheses to *explain* phenomena and afterwards being able to *predict* a system's behaviour. Having this knowledge at hand, it is worth to become *adopted* and *adapted* for suitable engineering tasks in terms of bionics like construction of a girder inspired by a bone structure. Another application objective is dedicated to *optimise* a system's behaviour like the best possible topological arrangement of processing units on a grid. We believe that bringing together the descriptive advantages of membrane systems with the existence of biological phenomena under study and capabilities of data mining could be a fruitful strategy. To this end, we closely collaborate with experts of life sciences, engineering, or natural sciences in an interdisciplinary manner.

Focussing on interdisciplinarity turns out to be a fascinating driving force towards beneficial utilisation of membrane systems. It becomes still more attractive if a huge amount of raw data – for instance from experimental studies, from monitoring, from archival storage, or from direct observations – is available waiting for computational analysis and employment of deductive algorithms directed to get new insights. By following this line of research, evidence-based knowledge can be made available along with a consistent formalisation. In systems biology, it is helpful to elucidate complex behavioural capabilities obtained from specific combinations of attributes. So, the existence of a circadian clock together with its suitability for fast entrainment or for precise synchronisation could be derived automatically from the underlying parameterised low-level reaction scheme. Moreover, its evolutionary potential might be disclosed as well resulting from subsequent studies of artificial evolution. This in turn lays the foundation to indicate effective starting points for development of drugs able to

restore the functionality of an impaired circadian clock system and related diseases. Using membrane systems, a comprehensive pervasion of life sciences and medicine inspired by methods from engineering and supported by approaches of high-performance computing is ahead with no doubt.

## References

1. Aschoff, J.: Circadian rhythms in man. a self-sustained oscillator with an inherent frequency underlies human 24-hour periodicity. *Science* **148**, 1427–1432 (1965)
2. Bernardini, F., Gheorghe, M., Krasnogor, N., Giavitto, J.-L.: On self-assembly in population P systems. In: Calude, C.S., Dinneen, M.J., Păun, G., Pérez-Jiménez, M.J., Rozenberg, G. (eds.) *UC 2005. LNCS*, vol. 3699, pp. 46–57. Springer, Heidelberg (2005). doi:[10.1007/11560319\\_6](https://doi.org/10.1007/11560319_6)
3. Camazine, S., Deneubourg, J.L., Franks, N.R., Sneyd, J., Theraulaz, G., Bonabeau, E.: *Self-Organization in Biological Systems*. Princeton University Press, Princeton (2003)
4. Grünert, G., Ibrahim, B., Lenser, T., Lohel, M., Hinze, T., Dittrich, P.: Rule-based spatial modeling with diffusing, geometrically constrained molecules. *BMC Bioinform.* **11**, 307 (2010)
5. Hinze, T., Schell, B., Schumann, M., Bodenstein, C.: Maintenance of chronobiological information by P system mediated assembly of control units for oscillatory waveforms and frequency. In: Csuhaj-Varjú, E., Gheorghe, M., Rozenberg, G., Salomaa, A., Vaszil, G. (eds.) *CMC 2012. LNCS*, vol. 7762, pp. 208–227. Springer, Heidelberg (2013). doi:[10.1007/978-3-642-36751-9\\_15](https://doi.org/10.1007/978-3-642-36751-9_15)
6. Hinze, T., Behre, J., Bodenstein, C., Escuela, G., Grünert, G., Hofstedt, P., Sauer, P., Hayat, S., Dittrich, P.: Membrane systems and tools combining dynamical structures with reaction kinetics for applications in chronobiology. In: Frisco, P., Gheorghe, M., Pérez-Jiménez, M.J. (eds.) *Applications of Membrane Computing in Systems and Synthetic Biology. ECC*, vol. 7, pp. 133–173. Springer, Cham (2014). doi:[10.1007/978-3-319-03191-0\\_5](https://doi.org/10.1007/978-3-319-03191-0_5)
7. Hinze, T., Grützmann, K., Höckner, B., Sauer, P., Hayat, S.: Categorised counting mediated by blotting membrane systems for particle-based data mining and numerical algorithms. In: Gheorghe, M., Rozenberg, G., Salomaa, A., Sosik, P., Zandron, C. (eds.) *CMC 2014. LNCS*, vol. 8961, pp. 241–257. Springer, Cham (2014). doi:[10.1007/978-3-319-14370-5\\_15](https://doi.org/10.1007/978-3-319-14370-5_15)
8. Hinze, T., Kirkici, K., Sauer, P., Sauer, P., Behre, J.: Membrane computing meets temperature: a thermoreceptor model as molecular slide rule with evolutionary potential. In: Rozenberg, G., Salomaa, A., Sempere, J.M., Zandron, C. (eds.) *CMC 2015. LNCS*, vol. 9504, pp. 215–235. Springer, Cham (2015). doi:[10.1007/978-3-319-28475-0\\_15](https://doi.org/10.1007/978-3-319-28475-0_15)
9. Hinze, T., Behre, J., Kirkici, K., Sauer, P., Sauer, P., Hayat, S.: Passion to P for polymorphic processes in practice. In: Gheorghe, M., Petre, I., Perez-Jimenez, M.J., Rozenberg, G., Salomaa, A. (eds.) *Multidisciplinary Creativity. Spandugino* (2016)
10. Kitano, H.: Computational systems biology. *Nature* **420**, 206–210 (2002)
11. Martin-Vide, C., Paun, G., Pazos, J., Rodriguez-Paton, A.: Tissue P systems. *Theor. Comput. Sci.* **296**(2), 295–326 (2003)

12. Matsumaru, N., Lenser, T., Hinze, T., Dittrich, P.: Toward organization-oriented chemical programming: a case study with the maximal independent set problem. In: Dressler, F., Carreras, I. (eds.) *Advances in Biologically Inspired Information Systems: Models, Methods, and Tools. SSCI*, pp. 147–163. Springer, Heidelberg (2007)
13. Porreca, A.E., Leporati, A., Mauri, G., Zandron, C.: P systems with active membranes working in polynomial space. *Int. J. Found. Comput. Sci.* **22**(1), 65–73 (2011)
14. Păun, G.: *Membrane Computing: An Introduction*. Springer, Heidelberg (2002)

Membrane Computing

17th International Conference, CMC 2016, Milan, Italy,

July 25-29, 2016, Revised Selected Papers

Leporati, A.; Rozenberg, G.; Salomaa, A.; Zandron, C.

(Eds.)

2017, X, 363 p. 52 illus., Softcover

ISBN: 978-3-319-54071-9