How to Express Tumours Using Membrane Systems

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Abstract

In this paper we discuss about the potential usefulness of membrane systems as natural tools for modelling tumours. This is done both from a macroscopic and a microscopic point of view. In the first case, one considers the tumour as a growing mass of cells, focusing on its external shape. In the second case, one descends to the microscopic level, studying molecular signalling pathways that are crucial to determine if a cell is cancerous or not. In each of these approaches we work with appropriate variants of membrane systems.

1 Introduction

Natural Computing is a field that tries to abstract ideas and new paradigms for introducing models of computation inspired by Nature. One of the branches within this field is Membrane Computing, presented by Gh. Păun in [15], where the basic computing devices are the so-called *membrane systems* or *P systems*[1].

Roughly speaking, a P system consists of a cell-like membrane structure in the compartments of which one places multisets of objects which evolve according to given rules (associated with membranes) in a synchronous non-deterministic maximally parallel manner.

From a classical computer science point of view, basic P systems can be considered as collections of parallel processors placed in a tree structure (each processor plays the role of a membrane). Actually, there exist two levels of parallelism in the model: on the one hand, the rules within a membrane are

[1] A layman-oriented introduction can be found in [17], a formal description in [16], and further up-to-date bibliography at [25].

applied simultaneously; on the other hand, these operations are performed in parallel in all the membranes of the system.

In this paper we address the issue of using P systems in order to provide a better understanding of tumours. First, we will consider a macroscopical point of view, looking at the whole tumour. In particular, we will follow a number of recent studies (see [1, 3, 5, 9, 10, 12, 20, 21]) postulating that tumours have a *fractal* shape, and we show how to use P systems as a new tool for representing and simulating such a fractal nature of tumours. The choice of P systems is based on their massive parallelism, the synchronous application of their rules, and the discrete nature of their computation, among other features.

From a mesoscopic point of view (i.e. at a cellular level), one can try to understand, by means of P systems, some biosignalling network functions that are very important for studying different diseases. In particular, one can study some proteinic interactions happening from the extracellular domain to the cytoplasm of tumoral cells. We will present some ideas from [19] concerning the epidermal growth factor receptor (EGFR) signalling pathway that permit to justify the robustness of the EGFR system (characterised by the simple behaviour that arises from complex processes).

The paper is organised as follows: First we deal with tumours at a macroscopic level. We recall some ideas about fractals and the definition of P systems with membrane creation in Subsection 2.2. Next, we explain how the evolution of a P system can be linked to the construction of a classical fractal, the Koch curve. Subsection 2.4 concludes the macroscopic approach, addressing random fractals, which are closer to the real shape of tumours. Section 3 is devoted to the intracellular scenario of tumoral cells. In this case we recall the definitions of P systems used to model signalling pathways and we briefly present the EGFR signalling pathway in Subsection 3.2. We conclude this paper by discussing some final remarks about the link that has been established between membrane computing and cancer research.

2 Macroscopic View: Tumours and P Systems

An individual tumoral cell has the potential, over successive divisions, to develop into a cluster of tumoral cells. Further grow and proliferation leads to the development of an avascular tumour consisting of approximately 10^6 cells which feed on oxygen and other nutrients present in the local environment.

The rapid growth and resilience of tumours make it difficult to believe that they behave as disorganised and diffuse cell mass and suggests instead that they are emerging, opportunistic systems. If this hypothesis holds true, then studying single cells is not enough, the growing tumour as a whole must be investigated and treated as a self-organising complex dynamic system.

A first approach to the simulation of a tumour growth by using P systems was proposed in [7]. The model followed there was the *spheroid model*, where the tumour is considered as a multicell spheroid with a characteristic structure of a proliferating rim and a necrotic core, separated by a band of quiescent cells.

The spheroid model has very nice mathematical properties, but recent studies in the growth of tumours show that it is too simple in order to explain the growth of the tumour in a realistic way. Indeed, the surface of the tumour is far from being a smooth surface, and actually it seems that this is one of the cases in which Nature produces a fractal-like surface. Even more, there seems to be a relation between the fractal dimension of the surface of the tumour and the stages of the disease. In [10], Kikuchi *et al.* point that *the surface of solid components in cystic epithelial ovarian cancers has a fractal structure and the mean fractal dimension may differ according to the stages of the disease and histologic types. Fractal geometry (...) can be used for describing the pathological architecture of ovarian tumours and for yielding insights into the mechanisms of tumour growth.*

These studies show the necessity of going deeper in the relation between fractals and tumours, which is currently maybe one of the most promising applications of fractals. This study will need new tools for handling information and for computing/simulating/predicting results. As pointed by Baish and Jain in [1]: *If carefully applied, fractal methods may someday have a significant impact in our understanding of challenges in treatment delivery and diagnosis of cancer.*

2.1 Fractals

One of the most important features of fractals is that they are far from being merely mathematical curiosities or computational art objects. Fractals are one of the most powerful tools for describing many natural objects both from alive and non-alive world[2].

The seminal work on fractals, presented by Mandelbrot [13] in 1982, put the basis of the theory dealing with mathematical sets that are not regular enough. In a first approach, we can consider that *fractal objects* exhibit complexity which holds constant under different scales. A *fractal* is a shape made of parts similar to the whole, in some way.

Nowadays there is no definition of fractals which considers *every* case. Instead of a formal definition, a set F is considered a fractal (in an informal sense) if it fulfils several properties (see [6] and [23]):

- F has a fine structure, i.e., detail on arbitrary many scales.
- F is too irregular to be described in traditional geometrical language, both locally and globally.
- Often F has some form of self-similarity.
- Usually, its *fractal dimension* (defined in some way) is greater than its topological dimension.
- Fractals are obtained by the application of recursive procedures, usually in a simple way. These procedures often consist of few rules.

[2]For more applications of fractals, see, for example, [4, 18, 23].

- The computational generation of a fractal is discrete. Fractals are usually defined as the limit of an iterative process performed *step* by *step*.

Self-similarity seems to be one of the fundamental geometrical construction principles in Nature. In many plants and also in animal organs, this has led to fractal branching structures. For example, the branching structure in a tree allows the capture of a maximum amount of sun light by the leaves; the blood vessel system in a lung is similarly branched so that the maximum amount of oxygen can be assimilated (see [18]). Although the self-similarity in these objects is not strict, we can identify the building blocks of the structure.

Next, we present a variant of P systems suitable to bridge Membrane Computing and Fractals, namely P systems with membrane creation.

2.2 P Systems with Membrane Creation

Membranes are created in living cells, for instance, in the process of vesicle mediated transport, and also in order to keep molecules close to each other facilitating their reactions. One can abstract the biological operation of creating new membranes under the influence of existing chemical substances to define P systems with membrane creation.

Recall that a *P system with membrane creation* of initial degree $m \geq 1$ is a tuple of the form $\Pi = (O, H, \mu, w_1, \ldots, w_m, R)$ where:

1. O is the alphabet of *objects*;
2. H is a finite set of *labels* for membranes;
3. μ is a *membrane structure* consisting of m membranes labelled (not necessarily in a one-to-one manner) by elements of H;
4. $w_1, \ldots, w_m$ are strings over O, describing the *multisets of objects* placed in the m regions of μ;
5. R is a finite set of *rules*, of the following forms[3]:
   (a) $[a \to v]_h$, where $h \in H$, $a \in O$, and v is a string over O describing a multiset of objects. These are *object evolution rules* associated with membranes and depending only on the label of the membrane.
   (b) $a[\,]_h \to [b]_h$, where $h \in H$, $a, b \in O$. These are *send-in communication rules*. An object is introduced in the membrane, possibly modified.
   (c) $[a]_h \to [\,]_h\, b$, where $h \in H$, $a, b \in O$. These are *send-out communication rules*. An object is sent out of the membrane, possibly modified.

[3] In this paper we will use a weak version of this model, since we do not use *dissolution* nor *communication* rules, nonetheless we present the model of *P systems with membrane creation* as found in the literature.

(d) $[a]_h \to b$, where $h \in H$, $a, b \in O$. These are *dissolution rules*. In reaction with an object, a membrane is dissolved, while the object specified in the rule can be modified.

(e) $[a \to [v]_{h_2}]_{h_1}$, where $h_1, h_2 \in H$, $a \in O$, and v is a string over O describing a multiset of objects. These are *creation rules*. In reaction with an object, a new membrane is created. This new membrane, labelled by h_2, is placed inside the membrane where the object which triggers the rule was located, and has associated with it an initial multiset v.

Rules are applied according to usual principles in Membrane Computing (see [8] for details).

2.3 A Membrane System Building the Koch Curve

Let us just present here one of the classic fractals, the *Koch curve* [11], and a P system which can be "interpreted" as this fractal, in a sense that will be discussed below. Following Barnsley [2], in order to describe the fractal we need to know the initial conditions (or *initial configuration* in terms of membrane computing) and the transformation rules, but we also need a further ingredient: as in every computational process, we store the information in some kind of data structure and in order to recognise the data as a *fractal* we need to give an *interpretation* to the data.

The geometric construction of the Koch curve can be easily described. Let us begin with a straight segment K_0 which we will consider of length one, then we split K_0 into three segments of length $1/3$ and we replace the middle third by an equilateral triangle and take away its base.

Therefore, the next stage on the construction of the Koch curve, K_1 consists of a continuous line composed by four straight segments of length $1/3$. The construction continues by iterating this procedure.

If we follow a similar construction starting from an equilateral triangle instead of starting from a segment, then we obtain the so-called Koch snowflake, depicted in Figure 1.

Next, we present a P system which can be interpreted as the Koch curve. In each step of computation we have a configuration corresponding to an intermediate step of the construction of the Koch curve. Let us consider the P

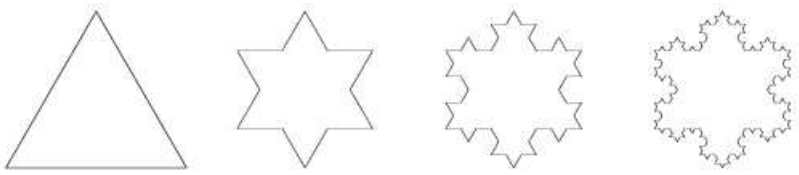

Figure 1: First steps for the Koch Snowflake

system $\Pi = (O, H, \mu, w_4, R)$ with $O = \{a, b, c, \alpha, \beta, \gamma\}$, $H = \{1, 2, 3, 4\}$, $\mu = [\,]_4$, $w_0 = \{abc\gamma\}$, and R the following set of 16 rules

$$\begin{array}{ll} \mathbf{R}_1 = [\,\alpha \to [\,abc\alpha\,]_4\,]_1, & \mathbf{R}_2 = [\,\beta \to [\,abc\beta\,]_4\,]_2, \\ \mathbf{R}_3 = [\,\alpha \to [\,abc\alpha\,]_4\,]_3, & \mathbf{R}_4 = [\,\gamma \to [\,abc\gamma\,]_4\,]_4, \end{array}$$

$$\begin{array}{ll} \mathbf{R}_a^i = [\,a \to [abc\alpha]_1\,]_i, & i \in \{1, 2, 3, 4\}, \\ \mathbf{R}_b^i = [\,b \to [abc\beta]_2\,]_i, & i \in \{1, 2, 3, 4\}, \\ \mathbf{R}_c^i = [\,c \to [abc\alpha]_3\,]_i, & i \in \{1, 2, 3, 4\}. \end{array}$$

In order to interpret each configuration, we collect for each elementary membrane the string composed by all the labels of the intermediate membranes between the considered elementary membrane and the skin, and we take into account the depth (in the membrane structure) of the elementary membranes, as well as the symbol occurring in the membrane denoted by a Greek letter (which can be either α, β, or γ).

- Each elementary membrane will represent a segment.
- The depth of the elementary membrane in the membrane structure will determine the length of the segment represented by the membrane. We will consider that the skin has depth 0 and that an elementary membrane at depth k represents a segment of length $1/3^k$.
- We will use the string of labels of the intermediate membranes from the elementary membrane to the skin to "order" the elementary membranes following the order $<_S$ defined as follows. Let us consider $w_1, w_2 \in H^*$ such that w_1 is not a suffix of w_2 and vice versa (consequently, $w_1 \neq w_2$), then we will say that $w_1 <_S w_2$ if and only if there exist $z_1, z_2, w \in H^*$ and $x_1, x_2 \in H$ with $w_1 = z_1 x_2 w$, $w_2 = z_2 x_2 w$ and $x_1 < x_2$ (where $<$ is an order over H). Note that $<_S$ is a sort of lexicographic order, but starting from right to left.
- Each stage of the construction of the Koch curve consists on a continuous line built with a certain amount of segments, all of them with the same length. If we know the number of such segments and their length, then in order to determine exactly an intermediate step of the construction of the Koch curve, the last data that we need is the angle between adjacent segments. This information is given by the symbol α, β, or γ placed inside each elementary membrane.
  - If a membrane representing a segment s contains the symbol α, then we will consider that the following segment has a deviation of $\pi/3$ radians with respect to the direction of s.
  - If a membrane representing a segment s contains the symbol β, then we will consider that the following segment has a deviation of $-2\pi/3$ radians with respect to the direction of s.

– Finally, if a membrane representing a segment s contains the symbol γ, we will consider that it is the last segment of the line and no other segment is after it.

The initial configuration has only one membrane, the skin, and the objects $abc\gamma$ inside. With the interpretation specified above, this initial configuration C_0 represents a unique segment of length $1/3^0 = 1$. The Greek symbol inside is γ and, coherently, it means that no other segment is after it.

By the application of rules $\mathbf{R}_a^4$, $\mathbf{R}_b^4$,$\mathbf{R}_c^4$, and $\mathbf{R}_4$, we obtain the configuration

$$C_1 = [\,[abc\alpha]_1\,[abc\beta]_2\,[abc\alpha]_3\,[abc\gamma]_4\,]_4.$$

This configuration has four elementary membranes at depth 1 that represent four segments of length $1/3^1$. The order among the strings of labels is $14 <_S 24 <_S 34 <_S 44$. The first segment (with string 14) contains the symbol α. This means that the second segment (with string 24) has a deviation of $\pi/3$ with respect the direction of the first one. The second segment contains the symbol β, so we will consider that the third segment has a deviation of $-2\pi/3$ with respect to the second one. Analogously, the fourth segment has a deviation of $\pi/3$ with respect to the the third one, since in the third membrane we find the symbol α. Finally, in the last membrane we find the symbol γ marking the end point.

With this interpretation, the configuration C_1 contains all the necessary information to construct the stage K_1 for building the Koch curve.

After j steps, we reach a configuration with 4^j elementary membranes at depth j with a sequence of angles that corresponds to the stage K_j of the Koch curve.

Thus, the above P system encodes all the information needed to build the Koch curve with any precision degree.

2.4 Random Fractals and P Systems

The Koch snowflake is not perceived as a close model for real world fractals (e.g. a coastline or a tumour). The reason lies in the lack of randomness. Randomising a deterministic classical fractal is the first approach generating a realistic natural shape.

For example, the method for including randomness in the Koch snowflake construction requires only a very small modification of the classical construction. A straight line segment will be replaced as before by a broken line of four segments, each one one-third as long as the original segment. However, there are two possible orientations in the replacement step: the small angle may go either to the left or to the right. If one of these orientations is chosen in each replacement step, we obtain a *random Koch curve*. Figure 2 shows a random Koch snowflake. Note that this fractal represents a *realistic* shape of a fractal from Nature.

In this process some mathematical characteristics of the Koch snowflake will be retained, for example the fractal dimension of the curve will be the same,

the area surrounded is finite but the length of the curve is infinite, etc., but the visual appearance is drastically different: it looks much more like the outline of the island or like a tumour than the original Koch curve.

In the previous subsection we presented a P system encoding the Koch curve with an appropriate interpretation of the objects. It was a deterministic system, and in its computation the configuration C_n was identified with the n-th stage in the construction of the fractal.

The construction of random fractals with P systems can be performed in a very natural way by using the non-determinism of P systems. For example, in the first step of the construction of the Koch curve we start with a straight line and there are two possible new reachable stages. Analogously, we can modify the P system presented in subsection 2.3 and obtain a non-deterministic P system such that two possible configurations are reachable from the initial configuration. Each of these configurations can be interpreted as one of the reachable stages in the construction of the Koch curve.

Let us consider the following P system with initial degree 1,

$$\Pi = (O, H, \mu, w_4, R),$$

with $O = \{s, a_r, b_r, c_r, a_l, b_l, c_l, \alpha_r, \beta_r, \alpha_l, \beta_l, \gamma\}$, $H = \{1, 2, 3, 4\}$, $\mu = [\ ]_4$, $w_4 = \{s\gamma\}$, and R the following sets of rules

$$\left.\begin{array}{l}[\, s \to a_r b_r c_r\,]_i \\ [\, s \to a_l b_l c_l\,]_i\end{array}\right\} i \in \{1,2,3,4\} \qquad \left.\begin{array}{l}[\, \alpha_j \to \alpha'_j\,]_1 \\ [\, \beta_j \to \beta'_j\,]_2 \\ [\, \alpha_j \to \alpha'_j\,]_3 \\ [\gamma \to \gamma']_4\end{array}\right\} j \in \{l, r\}$$

$$\left.\begin{array}{l}[\, a_j \to [\, s\alpha_j\,]_1]_i \\ [\, b_j \to [\, s\beta_j\,]_2]_i \\ [\, c_j \to [\, s\alpha_j\,]_3]_i \\ [\, \gamma' \to [\, s\gamma]_4\,]_4\end{array}\right\} \begin{array}{l} i \in \{1,2,3,4\} \\ j \in \{l, r\}\end{array} \qquad \left.\begin{array}{l}[\, \alpha'_j \to [\, s\alpha_j\,]_4\,]_1 \\ [\, \beta'_j \to [\, s\beta_j\,]_4\,]_2 \\ [\, \alpha'_j \to [\, s\alpha_j\,]_4\,]_3\end{array}\right\} j \in \{l, r\}$$

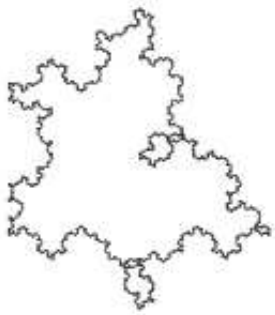

Figure 2: Random Koch Snowflake

In this case, the interpretation of the P system as a fractal is a little bit more complicated. In the same way as in the deterministic Koch curve, we will consider the elementary membranes, their depth, and for each elementary membrane, the string of labels of the membranes from the elementary membrane to the skin and the special symbol placed in the membrane, taken from the set $\{\alpha_r, \beta_r, \alpha_l, \beta_l, \gamma\}$.

The interpretation of these special symbols is quite natural. In the deterministic case, if a membrane representing a segment s contains the symbol α, we considered that the next segment had a deviation of $\pi/3$ radians with respect to the direction of s. In the random case, α_r represents a deviation of $\pi/3$ and α_l a deviation of $-\pi/3$. Analogously, β_r represents a deviation of $-2\pi/3$ and β_l a deviation of $2\pi/3$. Finally, if a membrane contains the symbol γ, we will consider that it represents the last segment of the line, and no other segment comes after it.

The main difference consists on the fact that in this P system only configurations in *even* steps will be interpreted as intermediate stages of the construction of the fractal. Odd steps are auxiliary steps without geometrical interpretation.

The remaining information is stored in the same way as in the deterministic case.

3 Microscopic View: P Systems Modelling Molecular Interactions

Besides modularity and easy extensibility, in favour of our approach we also mention the easy understandability and programmability, features not easily achieved in standard models used nowadays, mainly based on differential equations. In this section we propose P systems as a framework for modelling cancerous processes, from an intracellular point of view. Instead of considering the tumour as a whole, here we use P systems in order to simulate (some) signalling pathways occurring inside the cell.

3.1 P Systems to model signalling pathways

In this paper we consider the syntactic variant of P systems being tuples

$$\Pi = (O, L, \mu, M_1, M_2, \ldots, M_n, R_1, \ldots, R_n) \ ,$$

where:

- O is a finite alphabet of symbols representing objects (proteins and complexes of proteins);
- L is a finite alphabet of symbols representing labels for the compartments (membranes);
- μ is a membrane structure containing $n \geq 1$ membranes labelled with elements from L;

- $M_i = (w_i, l_i)$, $1 \leq i \leq n$, are pairs which represent the initial configuration of membrane i: $l_i \in L$ is its label, and $w_i \in O^*$ is the initial multiset.
- R_i, $1 \leq i \leq n$, are finite sets of rules associated with the membrane i which are of the form $u\,[\,v\,]_{l_i} \rightarrow u'\,[\,v'\,]_{l_i}$, where $u, v, u', v' \in O^*$ are finite multisets of objects and l_i is the label of membrane i.

The rules will model the following: (a) chemical reactions taking place inside a membrane (when $u = u' = \epsilon$); (b) reactions consisting in the binding of a ligand swimming in one compartment to a receptor placed on the membrane surface of another compartment (when $u' = \epsilon$), or debinding of substance from a receptor (when $u = \epsilon$); (c) the movement or diffusion of chemical substances from one compartment to another (when $u = v' = \epsilon$ or $v = u' = \epsilon$); and (d) the interaction between two chemicals in different compartments whereby one of them is recruited from its compartment by a chemical on the other compartment, and then the new complex remains in the latter compartment (when $v' = \epsilon$ or $v = \epsilon$).

The semantic of this variant is presented through a deterministic strategy based on the fact that in vivo chemical reactions take place in parallel in an asynchronous manner that we will refer to as *deterministic waiting times algorithm*. In that strategy, the time necessary for a reaction to take place, called waiting time, is calculated and the rule or rules with the minimal waiting time is applied, changing the number of molecules in the respective compartments. In each step when there is a change in the number of a molecules in a compartment, then the waiting time for the reactions using the changed molecule species has to be recalculated in that compartment.

Given a P system, in this strategy each rule r (representing a chemical reaction) in each membrane m has associated a *velocity*, v_r, by multiplying the mesoscopic rate constant (computed from the macroscopic constant used in differential equations) c_r by the multiplicities of the reactants according to the mass action law. Then we compute the waiting time for the first execution of the rule r as $\tau_r = \frac{1}{v_r}$.

This strategy have been implemented using Scilab, a scientific software package for numerical computations providing a powerful open computing environment for engineering and scientific applications [26].

3.2 EGFR Signalling Cascade

The epidermal growth factor receptor (EGFR) is one of the best understood receptor system. Computational models have been used to study EGFR dynamics, to interpret mutational studies and to understand processes including signal transduction, autocrine loops and developmental patterning [24]. The EGFR has been identified as a key biological target for the development of novel anticancer therapies.

In this subsection we briefly describe a EGFR signalling cascade[4], where the

[4] see `www.gcn.us.es/egfr.pdf` for details.

deterministic waiting times algorithm is suitable for describing its evolution.

The epidermal growth factor receptor (EGFR) was the first found to have tyrosine–kinase activity and has been used in pioneering studies of biological processes as receptor–mediated endocytosis, oncogenesis, mitogen–activated–protein–kinase (MAPK) signalling pathways, etc. [24].

During the signal transduction which takes place in this cascade, the information about the concentration of the EGF in the extracellular domain is translated into kinetic information inside the cell by EGFR phosphorylation.

The binding of the epidermal growth factor (EGF) to the extracellular domain of EGFR induces receptor dimerisation and autophosphorylation of intracellular domains. Then, on the one hand, a multitude of proteins are recruited starting a complex signalling cascade and, on the other hand, the receptor follows a process of internalisation, ubiquitination and degradation in endosomals.

In our model we consider two marginal pathways and two principal pathways starting from the phosphorylated receptor. Both principal pathways lead to activation of Ras-GTP. The first pathway does not depend on the concentration of Shc protein. In the other main pathway Shc plays a key role, it binds to the receptor and it is phosphorylated.

Finally, Ras-GTP is activated by these two pathways and in turn it stimulates the Mitogen Activated Protein (MAP) kinase cascade by phosphorylating the proteins Raf, MEK and ERK. Subsequently phosphorylated ERK regulates several cellular proteins and nuclear transcription factors that we do not include in our model.

There exist *cross-talks* between different parts and cycles of the signalling cascade which suggest a strong robustness of the system.

For a more detailed description of the cascade see the literature listed in the bibliography.

We have developed a model of the signalling cascade described above using the following P system:

$$\mathbf{\Pi}_{EGF} = (O, \{e, s, c\}, \mu, (w_1, e), (w_2, s), (w_3, c), \mathcal{R}_e, \mathcal{R}_s, \mathcal{R}_c)$$

Our model consists in more that 60 proteins and complexes of proteins and 160 chemical reactions. We will only give some details of the model. A complete description of $\mathbf{\Pi}_{EGF}$ with some supplementary information is available from the web page [25]. In what follows we give an outline of our model.

• **Alphabet:** In the alphabet O we collect all the proteins and complexes of proteins that take part in the signalling cascade. Some of the objects from the alphabet and the chemical compounds that they represent are listed below.

Object	Protein or Complex
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EGFR-EGF_2	Dimerisated Receptor
EGFR-EGF_2^*-Shc	EGFR-EGF_2^* and Shc complex
$\vdots$	$\vdots$
MEK	Mitogenic External Regulated Kinase
ERK	External Regulated Kinase

• **Membrane Structure:** We consider three relevant regions, namely the *environment*, the *cell surface* and the *cytoplasm*. We represent them in a the membrane structure as the membranes labelled with: e for the environment (external region), s for the cell surface and c for the cytoplasm. The skin of the structure is the environment, the cell surface is the son of the environment and the father of the cytoplasm.
• **Initial Multisets:** In the initial multisets we represent the initial number of molecules of the chemical substances in the environment, the cell surface and the cytoplasm. These estimations has been obtained from [14, 22].

$$\begin{aligned} w_1 &= \{EGF^{20000}\} \\ w_2 &= \{EGFR^{25000}, Ras\text{-}GDP^{20000}\} \\ w_3 &= \{Shc^{25000}, PLC_\gamma^{15000}, PI3K^{5000}, SOS^{4000}, Grb2^{8000}, TP_1^{10000}, TP_2^{45000}, \\ &\quad TP_3^{45000}, TP_4^{12500}, Raf^{8000}, MEK^{40000}, ERK^{40000}, P_1^{8000}, P_2^{8000}, P_3^{30000}\} \end{aligned}$$

• **Rules and Rate of application function:** In the rules we model the 160 chemical reactions which constitute the signalling cascade. For example, the set of rules associated with the environment, $\mathcal{R}_e$, consists only of one rule r which models the binding of the signal, EGF, to the receptor $EGFR$.

$$EGF\,[\,EGFR]_s \;\rightarrow\; [\,EGF\text{-}EGFR]_s\;, c_r$$

The meaning of the previous rule is the following: the object EGF in the membrane containing the membrane with label s (the environment), and the object $EGFR$ inside the membrane with label s (the cell surface) are replaced with the object $EGFR$-EGF in the membrane with label s; this object represents the complex receptor-signal on the cell surface. We associate the mesoscopic rate constant c_r, which measures the affinity between the signal and the receptor.

The deterministic waiting times algorithm is used in the evolution of the system and the waiting time associated to this rule will be computed using the next formula:

$$\tau_r = \frac{1}{c_r \cdot |EGF| \cdot |EGFR|}$$

In the simulation we stress the following results:

- The activation of the receptor is very fast reaching its maximum within the first 5 seconds and then it decays fast to very low levels.

- The number of doubly phosphorylated MEK is more sustained around 3 nM.
- The receptor autophosphorylation is clearly concentration dependent showing different peaks for different number of signals in the environment.
- the number of doubly phosphorylated MEK does not depend on the number of signals in the environment. That is, the system is not sensitive to increases in EGF level in the environment.

These results agree well with empirical observations, see [14, 22].

Supplementary information and details about the model are available on the web page `www.gcn.us.es/egfr.pdf`.

4 Final Remarks

In this paper two approaches bridging cancer research and membrane computing have been presented.

At the macroscopic level, fractals are nowadays one of the most powerful tools for describing the shape of tumours in a realistic manner. Nature is written in fractal language and we need tools for dealing easily with this language. In this paper we present a first work checking whether P systems provide an appropriate tool for handling fractals. On the one hand, the massive parallelism, the synchronous application of the rules, and the discrete nature of their computation, among other features, lead us to consider P systems as natural tools for dealing with fractals. On the other hand, the main drawback is that P systems work with data structures which do not have a *geometrical* intuition, in the sense that concepts as length or angle are not in membrane computing terminology. This leads us to the necessity of giving a geometrical interpretation to the data of the P systems in order to consider it as a fractal.

At the microscopic level, we present cell–like membrane systems as a reliable framework for modelling cellular signalling cascades, showing that P systems can be used as specification of some biological phenomena that can evolved through different strategies. In this paper we consider a deterministic waiting time strategy based on the fact that in vivo different chemical reactions proceed at distinct reaction rates and even more, a reaction may also have different rates at different times depending on the concentration of reactants. The results obtained using this P systems modelling are in well agreement with experimental data. We intend to expand our model to comprise other interactions between proteins which are known to play a key role in the regulation of cell cycle and tumourgenesis.

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