A Membrane Computing View on Tumours

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Abstract. In this paper we discuss about the potential usefulness of P systems as natural tools for modelling tumours. This is done both from a macroscopic point of view, by considering the tumour as a growing mass of cells, as well as from a microscopic point of view, by studying molecular signalling pathways. In each of these approaches we work with appropriate variants of P 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 [16], where the basic computing devices are the so-called *membrane systems* or *P systems*.

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 in a synchronous non-deterministic maximally parallel manner[1]. P systems offer two levels of parallelism: on the one hand, the rules within a membrane are applied simultaneously; on the other hand, these operations are performed in parallel in all the membranes of the system.

To sum up, P systems have the following properties:

- P systems can be considered as structures of nested processors placed in a tree-structure, i.e., we can consider computations on many scales.
- If we consider P systems where membranes can be dissolved, divided or created, we usually obtain a geometrical shape too irregular to be described in traditional geometrical language, both locally and globally.
- Computations in P systems are obtained by the application of a finite set of rules. The application of these rules allows to obtain a configuration C_{n+1} from another configuration C_n.
- The computation of a P system is discrete, i.e., it is a process performed *step* by *step*.

In this paper we address the issue of using P systems in order to provide a better understanding of tumours. From an intra-cellular point of view, one can try to express the molecular interactions happening in the cytoplasm of a tumoral cell by means of P systems. We will recall some ideas from [20], where the EGFR signalling pathway is studied, but we are not going to focus on this approach. We will also consider a macroscopical point of view, looking at the whole tumour.

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, the growing tumour and not only the single cell must be investigated and treated as a self-organising complex dynamic system. This cannot be done with currently available in vitro/in vivo models or common mathematical approaches.

We follow here a number of recent studies (see [1, 3, 5, 10, 11, 14, 21, 22]) postulating that tumours have a *fractal* shape. The massive parallelism, the synchronous application of the rules, and the discrete

[1] A layman-oriented introduction can be found in [18], a formal description in [17], and further bibliography at [24].

nature of their computation, among other features, lead us to consider P systems as natural tools for dealing with fractals. Several examples of fractals represented by P systems are presented, and we propose to use P systems as a new tool for representing and simulating the fractal nature of tumours.

The paper is organised as follows. First we deal with tumours at macroscopic level. We recall de definition of P systems with membrane creation in Subsection 2.1, and we explain how the evolution of a P system can be linked to the construction of a classical fractal, the Koch curve. Subsection 2.3 concludes the macroscopic approach, and it addresses 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 continuous P systems and we briefly present the EGFR signalling pathway in Subsection 3.2.

2 Macroscopic View: Tumours and P Systems

An individual tumour cell has the potential, over successive divisions, to develop into a cluster of tumour 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.

In [8] we proposed a first approach to the simulation and the study of the growth of a tumour by using P systems. The model followed there was the *spheroid model*. The vast majority of classic models apply specifically to multicell spheroids which have 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 the surface of the tumour is far from being a smooth 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 [11], 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, and this is maybe one of the most promising applications of fractals. This study will need new tools for handling information and 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.*

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

2.1 P Systems with Membrane Creation

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

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

1. $m \geq 1$ is the initial degree of the system;
2. O is the alphabet of *objects*;
3. H is a finite set of *labels* for membranes;
4. μ is a *membrane structure* consisting of m membranes labeled (not necessarily in a one-to-one manner) with elements of H;
5. $w_1, \ldots, w_m$ are strings over O, describing the *multisets of objects* placed in the m regions of μ;
6. R is a finite set of *rules*[2], of the following forms:

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

(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.
(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, a new membrane is created. This new membrane is placed inside of the membrane of the object which triggers the rule and has associated an initial multiset v and a label, h_2.

Rules are applied according to usual principles in Membrane Computing (see [9] for details).

2.2 The Koch Curve

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[3].

The seminal work on fractals presented by Mandelbrot [15] in 1982 put the basis of the theory to deal with mathematical sets not sufficiently regular. 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 a definition of fractals which considers *every* case. Instead of a formal definition, a set F is considered a fractal (in informal sense) if it fulfils several properties (see [7] 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 a few rules.
- 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 organs of animals, this has led to fractal branching structures. For example, in a tree the branching structure 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 [19]). Although the self-similarity in these objects is not strict, we can identify the building blocks of the structure.

An in–detail introduction on fractals falls out of the scope of this paper. Let us just present here one of the classic fractals, the *Koch curve* [12, 13], 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 other ingredient: as in every computational process, we store the information in some kind of structure data 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. In a similar way as in the middle third Cantor set,

[3] For more applications of fractals, see, for example, [4, 6, 19, 23].

we split K_0 into three segments of length 1/3. Then 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 on length 1/3.

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 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

$$\begin{array}{ll}
\mathbf{R}_1 = [\,\alpha \rightarrow [\,abc\alpha\,]_4\,]_1, & \mathbf{R}_a^i = [\,a \rightarrow [abc\alpha]_1\,]_i, \quad i \in \{1,2,3,4\}, \\
\mathbf{R}_2 = [\,\beta \rightarrow [\,abc\beta\,]_4\,]_2, & \mathbf{R}_b^i = [\,b \rightarrow [abc\beta]_2\,]_i, \quad i \in \{1,2,3,4\}, \\
\mathbf{R}_3 = [\,\alpha \rightarrow [\,abc\alpha\,]_4\,]_3, & \mathbf{R}_c^i = [\,c \rightarrow [abc\alpha]_3\,]_i, \quad i \in \{1,2,3,4\}, \\
\mathbf{R}_4 = [\,\gamma \rightarrow [\,abc\gamma\,]_4\,]_4. &
\end{array}$$

In 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 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 the 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 the 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 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.

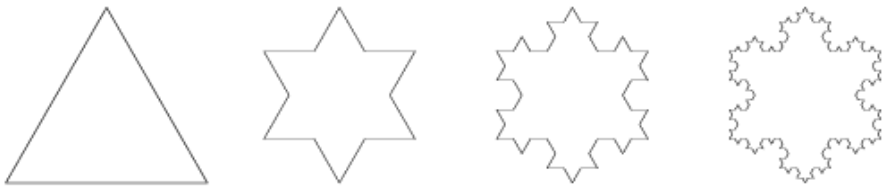

Fig. 1. First steps for the Koch Snowflake

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 found the symbol α. Finally, in the last membrane we found the symbol γ to mark 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 equal 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.

2.3 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.

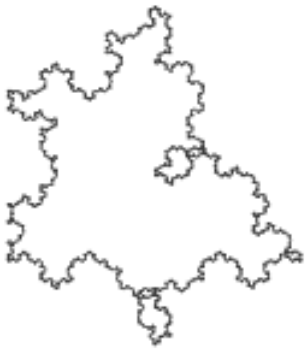

Fig. 2. Random Koch Snowflake

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 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 Section 2.2 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

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

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

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 that in this P system only configurations in an *even* step 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 a similar way as in the deterministic case.

3 Microscopic View: P Systems Modeling Molecular Interactions

Besides modularity and easy extensibility, in favor 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 modeling cancerous processes. Instead of considering the tumour as a whole, here we use P systems in order to simulate the molecular pathways inside the cell.

3.1 Continuous P Systems

Usual variants of P systems are discrete models of computation where in every step the rules are applied in a maximal way an integer number of times; we refer to [17] for details. Here we use a variant whose systems can evolve in every instant applying a maximal set of rules a positive *real number of times* determined by a certain function $\mathcal{K}$. This variant is inspired by the fact that in vivo chemical reactions evolve in a continuous way following a *rate* that depends on the concentration of the reactants.

Roughly speaking, a continuous P system consists of a membrane structure, a hierarchically arranged set of membranes, where one places multisets of objects that represent the concentration of chemical substances. Usual P systems deal with discrete multisets over an alphabet Σ but here we work with *continuous multisets* (mappings from Σ to $\mathbf{R}^+$, the set of non-negative real numbers). These multisets evolve according to a finite set of rules that represent chemical reactions.

A *continuous* P *system* of degree $n \geq 1$ is a construct, $\mathbf{\Pi} = (\Sigma, \mu, w_1, \ldots, w_n, \mathcal{R}, \mathcal{K})$, where:

1. $\Sigma = \{c_1, \ldots, c_m\}$ is the alphabet of *objects*.
2. μ is a *membrane structure* (a rooted tree) consisting of n membranes (nodes of the tree) labeled with $1, \ldots, n$.
3. $w_1, \ldots, w_n$ are continuous multisets associated with each membrane of μ.
4. $\mathcal{R}$ is a finite set of *rules* of the form:

$$u\,[\,v\,]_i \;\rightarrow\; u'[\,v'\,]_i,$$

   where $u, v \in \Sigma^*$ represent the reactants, $u', v' \in \Sigma^*$ represent the products, and $i \in \{1, \ldots, n\}$ is the label of the membrane where the reaction is carried out.
5. $\mathcal{K}$ is a map from $\mathcal{R} \times \mathcal{M}_{n\times m}(\mathbf{R}^+)$ to $\mathbf{R}^+$, called the *rate of application function*, where $\mathcal{M}_{n\times m}(\mathbf{R}^+)$ is the set of matrices of order $n \times m$ over $\mathbf{R}^+$.

A *configuration* of a continuous P system $\mathbf{\Pi}$ is an instantaneous description of it, that is, an assignment of continuous multisets to the membranes of the system that can be seen as an association of each region with the concentration of chemical substances present in it. Formally, a configuration of $\mathit{\Pi}$ is a matrix of $\mathcal{M}_{n\times m}(\mathbf{R}^+)$ where the element in row i and column j represents the multiplicity of the object c_j in the membrane i.

Then, the *rate of application function* $\mathcal{K}$ associates with each rule and each configuration, a non-negative real number considered as the rate of application of the rule.

An *evolution* E of a continuous P system associates with each instant $t \in \mathbf{R}^+$ a configuration $E(t)$ of the system. For each $t \in \mathbf{R}^+$ and i, $1 \leq i \leq n$, we denote by $v_i(t)$ the continuous multisets over $\Sigma = \{c_1, \ldots, c_m\}$ defined as follows: $(v_i(t))(c_j) = a_{ij}(t)$ for $1 \leq j \leq m$, where $a_{ij}(t)$ is the element in row i and column j from $E(t)$. So, we can describe the configuration $E(t)$ by a tuple $(v_1(t), \ldots, v_n(t))$.

The way a continuous P system, $\mathbf{\Pi} = (\Sigma, \mu, w_1, \ldots, w_n, \mathcal{R}, \mathcal{K})$, evolves is determined by the initial multisets $w_1, \ldots, w_n$ and the rate of application function $\mathcal{K}$. We define the *initial configuration* of $\mathbf{\Pi}$ as the tuple $(w_1, \ldots, w_n)$.

The rules are applied during the evolution of the system in a continuous way according to the *rate of application function* $\mathcal{K}$. At an instant $t \in \mathbf{R}^+$, a rule $r \in \mathcal{R}$ is applied exactly $\mathcal{K}(r, E(t))$ *times* (in this sense, we can say that the rules are applied in a $\mathcal{K}$-maximal way). Given an object $c_j \in \Sigma$ and a membrane i, we denote by $\mathit{production}_i(c_j)$ (resp. $\mathit{consumption}_i(c_j)$) the set of rules where c_j is a product (resp. a reactant) in membrane i. Therefore the real number $(v_i(t))(c_j)$ is determined by the next formula:

$$\begin{aligned}(v_i(t))(c_j) = (v_i(0))(c_j) + &\sum_{r \in \mathit{production}_i(c_j)} \int_0^t \mathcal{K}(r, E(s))\, ds - \\ - &\sum_{r \in \mathit{consumption}_i(c_j)} \int_0^t \mathcal{K}(r, E(s))\, ds,\end{aligned}$$

where $v_i(0)$ is the initial continuous multiset w_i.

In computers, real numbers are represented by a finite set of rational numbers. Therefore, like in most continuous models we need to develop approximations in order to simulate evolutions of continuous P systems in computers.

As shown above, in order to determine the effect of a rule on the evolution of a system during an interval of time $[t, T]$ we only need to compute an integral of the rate of application function $\mathcal{K}$. Hence, in order to approximate the evolution of a continuous P systems in a finite set of instants $t_0, \cdots, t_q$ we can use any suitable known numerical method to approximate integrals. Here for simplicity we use the rectangle rule; that is, we suppose $t_{l+1} - t_l = p$ is *small enough* to assume that $\mathcal{K}$ remains constant and equal to $\mathcal{K}(r, E(t_l))$ in the interval $[t_l, t_{l+1}]$ for $l = 0, \ldots, q-1$. With this assumption we can

approximate the effect of a rule during an interval of time of length p by $Ef(r, t_l, t_{l+1}) \approx p\mathcal{K}(r, E(t_l))$. Therefore, we have approximated the evolution of a continuous P system by the computation of an usual discrete P system working in a $p\mathcal{K}$ bounded parallel manner.

3.2 EGFR Signalling Cascade

In this subsection we briefly describe a EGFR signalling cascade[4]. During the signal transduction which takes place in this cascade, the information about the concentration of the EGF in the outside of the cell is translated into kinetic information inside the cell by EGFR phosphorylation.

The epidermal growth factor receptor (EGFR) belongs to the tyrosine kinase family of receptors. 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. EGFR has been identified as a key biological target for the development of novel anticancer therapies.

In our model we consider two marginal pathways and two principal pathways starting from the phosphorylated receptor.

In the first marginal pathway phospholipase C-γ (PLC_γ) binds to the phosphoryrated receptor, then it is phosphorylated (PLC^*_γ) and released into the cytoplasm where it can be translocated to the cell membrane or desphosphorylated. In the second marginal pathway the protein PI3K binds to the phosphoryrated receptor, then it is phosphorylated ($PI3K^*$) and released into the cytoplasm where it regulates several proteins that we do not include in our model.

Both principal pathways lead to activation of Ras-GTP. The first pathway does not depend on the concentration of the Src homology and collagen domain protein (Shc). This pathway consist of a cycle where the proteins growth factor receptor-binding protein 2 (Grb2) and Son of Sevenless homolog protein (SOS) bind to the phosphorylated receptor. Later the complex Grb2-SOS is released in the cytoplasm where it dissociates into Grb2 and SOS.

In the other main pathway Shc plays a key role, it binds to the receptor and it is phosphorylated. Then either Shc^* is released in the cytoplasm or the proteins Grb2 and SOS binds to the receptor yielding a four protein complex (EGFR-EGF2*-Shc*-Grb2-SOS). Subsequently this complex dissociates into the complexes Shc^*-Grb2-SOS, Shc^*-Grb2 and Grb2-SOS which in turn can also dissociate to produce the proteins Shc^*, Grb2 and SOS.

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 using a continuous P system $\mathbf{\Pi}_{EGF} = (\Sigma, \mu, w_e, w_s, w_c, \mathcal{R}, \mathcal{K})$. Our model consists in more that 60 proteins and complexes of proteins and 160 chemical reactions.

• **Alphabet:** In the alphabet Σ we collect all the proteins and complexes of proteins that take part in the signalling cascade.

• **Membrane Structure:** We consider three relevant regions, namely the *environment*, the *cell surface* and the *cytoplasm*. We represent them in a nested membrane structure as the membranes labeled with: e for the environment (external region), s for the cell surface and c for the cytoplasm.

• **Initial Multisets:** In the initial multisets we represent the initial concentrations of the chemical substances in the environment, the cell surface and the cytoplasm. These concentrations have been obtained from references in the literature.

• **Rules and Rate of application function:** In the rules we model the chemical reactions described which form the signalling cascade. To model the reactions we use the *Law of Mass Action* which states

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

that the rate of a reaction is proportional to the product of the concentrations of the reactants. That is, if we have a reaction of the form:

$$r_1 + \cdots + r_k \rightarrow p_1 + \cdots + p_{k'},$$

then the rate of this reaction is $k|r_1| \cdots |r_n|$, where k is called *kinetic constant*.

As an example of the procedure we have followed to develop our model, we next present the derivation of one of the 160 rules.

Let us consider the binding of EGF to EGFR:

$$\text{EGF EGFR} \rightarrow \text{EGF-EGFR}$$

We know from biological experiments that EGF, which is present in the environment, binds to EGFR, which is present in the cell surface at a rate of $0.003\, nM^{-1}s^{-1}$. According to this, the relevant membrane in this reaction is the cell-surface because it separates the two regions involved in this reaction. Besides following the Mass Action Law the reaction takes place at a velocity of $0.003|EGF||EGFR|$. Therefore, in our model we represent this chemical reaction by the following rule and rate of application:

$$\text{EGF } [\text{EGFR}]_s \rightarrow [\text{EGF-EGFR}]_s \quad \mathcal{K}(r, E(t)) = 0.003|EGF(t)|_e|EGFR(t)|_s$$

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 show that continuous membrane systems are a reliable framework for modelling networks of biochemical signalling cascades, because the results obtained using this model 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 tumour genesis.

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