Reaction Flow Artificial Chemistries

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Abstract

Artificial chemistries have been analysed mostly under the precondition of a well-stirred reaction vessel. In other words, the localisation of molecules is ignored for simplicity. Here we drop this assumption and replace it with a spatial distribution of molecules given by a flow, i.e. molecules move according to a given vector field. This can be seen as a particular type of dynamics. It also gives additional parameters to the control over the development of the chemistry over time. In particular, the modelling of membranes and transport processes which occur in cells, for example, can be described using continuous vector fields instead of giving a discrete formulation. We give some examples and ideas for analysing such chemistries via a stochastic simulation, a PDE and chemical organisations.[1]

Introduction

So far many *artificial chemistries* assume a well-stirred reaction vessel (Speroni di Fenizio, 2002). This is a special type of dynamics for the application of rules of the chemistry. In particular, it means that any molecule in the reaction soup can potentially react with any other molecule in the soup at any time. Or in other words, there is no *localisation of molecules* taken into account. On the one hand, this is easier to handle from a technical point of view (Dittrich et al., 2001). In a well-stirred reactor the change of concentration of molecules in the vessel is often seen as a stochastic process and can be simulated using the Gillespie algorithm (Gillespie, 1977, 1976) or can be approximated using ordinary differential equations (ODE), e.g. with the assumption of mass action kinetics. On the other hand, thinking of molecules as not being localised is unrealistic in many situations, e.g. in living cells with their compartments, membranes and transport processes, or when modelling the origin of life (Fishkis, 2010).

There are several approaches to include the spatial organisation or localisation into artificial chemistries. Some of them employ means of *discrete spatial structures*, like P systems (Păun, 2000), vessels with dynamic compartments using Gillespie's algorithm (Versari and Busi, 2007) or MGS (Giavitto and Michel, 2001), some work with *continuous* additions to the dynamics, like reaction diffusion systems (Adamatzky, 2005). In the first case compartments and their creation and dissolution operations structure the reaction vessel. This gives a discrete description of geometrical information, where the definition of the chemistry is separate from the membrane structure, i.e. the membranes are not formed by molecules. Each of the compartments is subject to a well-stirred stochastic or deterministic dynamics. In the later case, molecules are localised in a Euclidean space. The assumption of a well-stirred domain is replaced by a diffusion process which results in a PDE model. This model describes the dynamics of the artificial chemistry accounting for the reactions and the movement by diffusion. This means that there is no further control over the behaviour possible except of the choice of diffusion constants.

The two examples show that including space into the dynamics brings more *complexity* with it. Still, there is extensive theory at hand for both of them. Going a step further in terms of complexity, we loose this advantage of rigid theoretical descriptions. For example, we have molecular dynamics simulations which can also be combined with rule-based spatial models (Grünert et al., 2010). They use the full generality of possible movement and reactions of molecules at the price of computational costs, predictability and controllability. Furthermore there are approaches, like the swarm chemistry (Sayama, 2009) using space for the representation of molecules.

Here we propose using *vector fields* for modelling spatial organisation and transport processes in artificial chemistries. By this we mean that molecules move along the flow lines of the vector field of a region in $\mathbb{R}^N$ (most of the time N will equal to 2 or 3). Reactions are only applicable if enough molecules of the left hand side can be found together close enough. In other words, we do not intend to stir the reactor with our molecules well, but just stir in a particular way defined by a vector field. We can still formulate this as a

[1]further information and videos available at `http://www.biosys.uni-jena.de/Research/Projects/Reaction+Flow+Artificial+Chemistries.html`

stochastic process and approximate it with a partial differential equation (PDE). Another advantage is the gain of control over the behaviour of the chemistry by using different types of vector fields in contrast to, for example, diffusion, where we only have the diffusion coefficients as parameters.

The description of *transport processes* and *membranes* with vector fields, i.e. continuous objects, rather than discrete structures, does not seem to be as convenient or powerful at a first glance. To our understanding membranes and transport are integral part of the dynamics and should therefore be handled with continuous objects fitting in with the usual modelling via ODEs, for example. Therefore we would like to give a proof of concept for non-discrete membranes, compartments and transport. Also we focus here on the spatial aspect rather than on the artificial chemistries and their reactions used.

The paper is organised as follows. First we give the definition of a general reaction flow artificial chemistry. Then a differential model, using a PDE and Mathematica for a numerical computation of solutions is presented. We also describe a stochastic simulator providing us with a tool to run example chemistries. Then we show how to analyse the behaviour of reaction flow artificial chemistries with the help of chemical organisations (Dittrich and Speroni di Fenizio, 2007; Speroni di Fenizio and Dittrich, 2007). Finally we give more examples.

Reaction Flow Artificial Chemistries

Let M be a set and R be a subset of $\mathcal{P}_{mult}(M) \times \mathcal{P}_{mult}(M)$ where $\mathcal{P}_{mult}(M)$ denotes the set of multisets over M. The pair (M, R) is called *reaction network* and we call M the set of *molecules* and R the set of *reactions*.

By *applying* a reaction $(l, r) \in R$ to a multiset over M we mean replacing the subset l by the subset r. To be able to do so, we assume that the multiset considered is large enough, i.e. that it consists of enough molecules as required on the left hand of the rule.

For $(l, r) \in R$ we also write $l \longrightarrow r$ or

$$\sum_{m \in M} l_m m \longrightarrow \sum_{m \in M} r_m m$$

where we denote by $l_m, r_m \in \mathbb{N}_0$ the multiplicity of m in l, r respectively. This resembles notation from chemistry. Furthermore the *support* and the *product* of (l, r) are

$$\text{supp}(l, r) := \{m \in M \mid l_m > 0\},$$

$$\text{prod}(l, r) := \{m \in M \mid r_m > 0\}.$$

Let A be a subset of M. We define R_A, the set of reaction applicable to A, by setting

$$R_A := \{(l, r) \in R \mid \text{supp}(l, r) \subseteq A\}.$$

Abusing notation we use a reaction $(l, r) \in R$ as an index as well and define the *stoichiometric matrix* $S_A \in \mathbb{R}^{|A| \times |R_A|}$ for A by

$$(S_A)_{a,(l,r)} = r_a - l_a, \quad a \in A, (l, r) \in R.$$

If we add to a reaction network (M, R) a domain for the molecules and an algorithm that determines how the rules are applied to the molecules within the domain, we get an *artificial chemistry* (Dittrich et al., 2001). For a *reaction flow artificial chemistry* we choose a region U in $\mathbb{R}^N$ as the domain. The elements of an initial multiset are placed in this region. Molecules can then only react if they are "suitably" close. What this means exactly is of course to be defined from case to case. Here, we will always choose a small number for the maximum distance in which molecules can still react. Additionally, molecules change their position according to the flow lines of a given *vector field* $V : U \to \mathbb{R}^N$. This means that in one iteration of the algorithm a molecule at position $\mathbf{x} \in \mathbb{R}^N$ changes to the position $\mathbf{x} + V(\mathbf{x})$. We assume that the new position is again in U. The described way of movement can be interpreted as mixing molecules according to a fixed scheme or algorithm. In contrast to a reaction diffusion system even after a long time period there is no guarantee that the multiset of molecules will be stirred well.

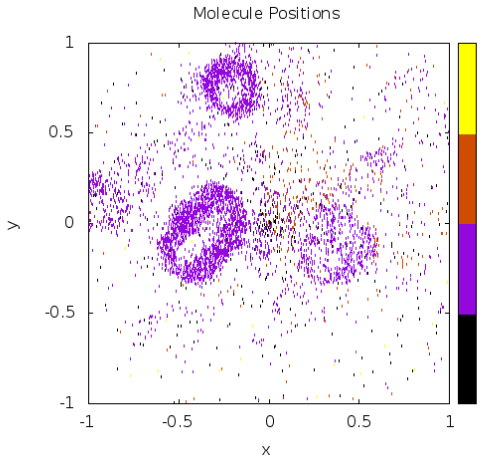

Figure 1: Stochastic simulation of the reaction flow artificial chemistry (M_1, R_1) in the region U_1 with vector field V_1 after 400 iterations, for details see Section II. Species are marked with colours from black for a to yellow for d.

Figure 1 shows the state of the following reaction flow artificial chemistry after 400 iterations. The reaction network we chose is $M_1 = \{a, b, c, d\}$ with

$$R_1 = \{a + b \to a + 2b, a + d \to a + 2d, b + c \to 2c, c \to b, b + d \to c, b \to \emptyset, c \to \emptyset, d \to \emptyset\}.$$

As a domain $U_1 = [-1,1] \times [-1,1]$ is used and a starting set of molecules of size 2500 is placed randomly around $(0,0)$. The vector field responsible for the movement is a swirl given by

$$V_1(x,y) = \frac{1}{\sqrt{2}} \left(\left(1 - \sqrt{2}\right) x - y, x + \left(1 - \sqrt{2}\right) y \right),$$

see Figure 2.

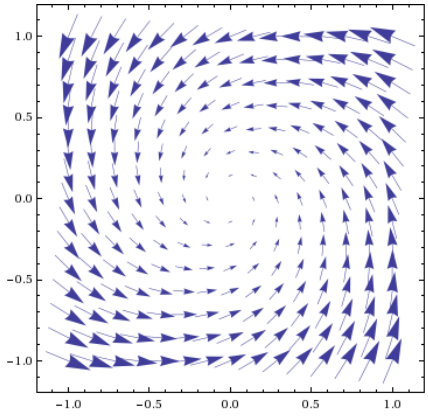

Figure 2: The vector field V_1 in the region $U_1 = [-1,1] \times [-1,1]$. The length of vectors is scaled by 0.3 for a better readability.

The parameters of the simulation (for the detailed description see Section IV) we set to $n = 1600$, $s = 400$, $rad = 1.0$, $u = 1.0$ and $r = 0.1$.

We see a development of patches of the species b over time. This is a rather different behaviour compared to the same reaction network, when investigated using a well-stirred system or diffusion. When we do a simulation using these dynamics in our particular case of the reaction network (M_1, R_1), the system is completely described by concentration alone without taking position of molecules into account.

We give some ideas for slight *generalisations* of this approach, though they are not used here. Separate flows for different molecular species can be used, i.e. there is a set of fields $V_{m_1}, \ldots, V_{m_{|M|}}$ such that each field is responsible for the movement of a single species. Maybe this makes sense if, for example, taking the different weight of molecular species or semi-permeable membranes into account. Also the vector field(s) could be time depended, i.e. there is a dynamical change of the transport of molecules over time. Another interesting way of extending the concepts is by letting the underlying reaction network influence the vector field, e.g. particular types of (bigger) molecules could block (smaller) other ones.

We investigate two models for this kind of artificial chemistry. The first one is a PDE describing the continuous change of concentration of the molecules. The second one is a stochastic simulation of the movement of molecules in the flow and the reactions they take part in.

Differential Model

We concentrate on the case $N = 2$ to keep it simple, but still easily generalisable. For the differential model we assume that every point $(x,y) \in \mathbb{R}^2$ bares concentrations of all the species $M = \{m_1, \ldots, m_{|M|}\}$. The concentration of a species m_i, $i \in \{1, \ldots, |M|\}$ in (x,y) at time $t \geq 0$ is $[m_i](x,y,t)$, so

$$[m_i] : \mathbb{R} \times \mathbb{R} \times \mathbb{R}^+ \to \mathbb{R}.$$

For readability we omit the coordinates and write simply $[m_i]$.

We describe the change of concentration over time with two summands. The change of molecule concentration given by the vector field V is the *directional derivative* of $[m_i] \cdot ||V||$ in the direction of V. This is exactly the formalisation of the statement that molecules follow the flow lines of the vector field. The change caused by the reactions is summarised in the *reaction terms* $R_{\mathbf{k},i}$. They depend on the concentrations of all molecules $[m_1], \ldots, [m_{|M|}]$ and the constant reaction rates $\mathbf{k} \in \mathbb{R}^{|R|}$.

When assuming the mass action kinetics for the dynamics of the reaction network (M,R), we can write down the reaction terms as follows. Let us denote the *flux vector function* by

$$v_{M,\mathbf{k}} : \mathbb{R}_{\geq 0}^{|M|} \to \mathbb{R}_{\geq 0}^{|R|}.$$

Still abusing notation we use a reaction $(l,r) \in R$ as an index as well and define

$$\left(v_{M,\mathbf{k}}([m_1], \ldots, [m_{|M|}])\right)_{(l,r)} = \mathbf{k}_{(l,r)} \prod_{i=1}^{|M|} [m_i]^{l_{m_i}}.$$

The ith reaction term is the ith component of the vector yielded by the product of the stoichiometric matrix with the flux vector function,

$$R_{\mathbf{k},i}([m_1], \ldots, [m_{|M|}]) = \left(S_M \cdot v_{M,\mathbf{k}}([m_1], \ldots, [m_{|M|}])\right)_i.$$

The equation defining the behaviour of the reaction flow artificial chemistry is

$$\frac{\partial [m_i]}{\partial t} = -\frac{1}{||V||} \left\langle \nabla \left([m_i] ||V|| \right), V \right\rangle + R_{\mathbf{k},i}([m_1], \ldots, [m_{|M|}])$$

where the gradient $\nabla = \nabla_{(x,y)}$ is taken for (x,y), $||V|| = ||V(x,y)||_2$ is the Euclidean norm of the field and $\langle \cdot, \cdot \rangle$ denotes the Euclidean scalar product.

In the case of an integrable field, i.e. there is $f : \mathbb{R}^2 \to \mathbb{R}$ with $\nabla f = V$, the molecules follow a gradient flow to the sinks of the function.

As a simple example we numerically solve the equation for the reaction flow artificial chemistry given by the reaction network (M_1, R_1) as defined before with the radially symmetric field

$$V_2(x,y) = \frac{\cos 10r}{10r}(x,y),$$

i.e. the above case with $f(x,y) = -0.01 \sin 10r$, where we abbreviate $r = ||(x,y)||_2 = \sqrt{x^2+y^2}$. We assume mass action kinetics with all reaction constants equal to 1.

Since the directional derivative is independent of the chosen coordinate system and since our field is radially symmetric, it suffices to solve the equation for one spatial dimension. Therefore we solve the equation dependent on r. The solution on $\mathbb{R}^2$ is then the solution we get in the one dimensional case extended to $\mathbb{R}^2$, i.e. we apply it to the distance $\sqrt{x^2+y^2}$. We arrive at the equations

$$\begin{aligned}
\frac{\partial[a]}{\partial t} &= -0.1\frac{\partial[a]\cos 10r}{\partial r} \\
\frac{\partial[b]}{\partial t} &= -0.1\frac{\partial[b]\cos 10r}{\partial r} + [a][b] - [b][c] + [c] - [b][d] - [b] \\
\frac{\partial[c]}{\partial t} &= -0.1\frac{\partial[c]\cos 10r}{\partial r} + [b][c] - [c] + [b][d] - [c] \\
\frac{\partial[d]}{\partial t} &= -0.1\frac{\partial[d]\cos 10r}{\partial r} + [a][d] - [b][d] - [d].
\end{aligned}$$

This can be numerically solved. We assume an initial constant concentration of 1 for all species and use Mathematica's NDSolve to get Figure 3 compared to the stochastic simulation Figure 4.

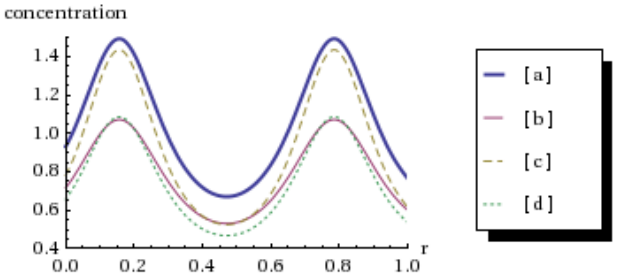

Figure 3: Numerical solution to the equation system at time 0.4 in one dimension.

Stochastic Model

Additionally to the rather theoretical approach via a PDE we also implemented a stochastic simulator for the reaction flow artificial chemistries. This allows us to run some concrete examples.

We assume a reaction network (M, R) is given. As the domain or region the set $[-1,1] \times [-1,1] \subset \mathbb{R}^2$ is used for all our examples even though the size of the square is variable.

Different ways of initially placing molecules can be used. In the examples shown here, we initially place n molecules randomly around the origin in a circle of radius rad. More precisely, in Figure 4 we choose random coordinates x and y such that $\sqrt{x^2+y^2} < rad$ to achieve a uniform distribution of molecules. In the other examples we choose a random

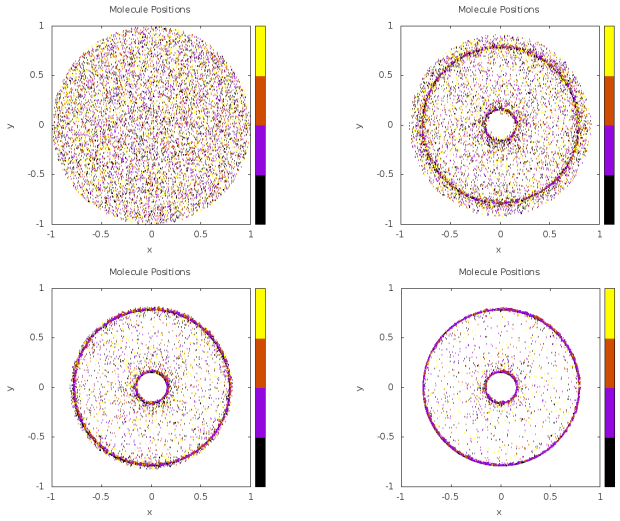

Figure 4: Stochastic simulation of the reaction flow artificial chemistry (M_1, R_1) in the region U_1 with vector field V_2 after $0, 1, 2$ and 3 iterations. Parameters are $n = 10000$, $rad = 1.0$, $u = 1.0$ and $r = 0.01$.

angle between 0 and 2π and a random length between 0 and rad to position them. Each starting molecule is assigned a random type of species.

For s simulation steps we apply the vector field V and the rules of R in the following manner. A molecule at position (x,y) is moved to position $(x,y) + V(x,y)$. As mentioned before, we assume that the new molecule position is again in our region $[-1,1] \times [-1,1]$. If this is not the case, we can use cyclic or solid boundary conditions or increase the size of the region. Typically several vector fields are added up or are applied at suitable parts of the domain region to account for different effects in time and space to generate the required behaviour.

Then the reaction rules are applied to a randomly chosen u percent of the molecules present in the domain. For each chosen molecule m with, we assume, position (x,y) we look at neighbouring molecules, i.e. molecules with no more than distance r to m. Let $A_r(m)$ be this multiset of molecules found in

$$U_r(m) = \{(x',y') \mid \text{dist}\,((x',y'),(x,y)) < r\} \subset \mathbb{R}^2.$$

There are several different ways of applying rules to $A_r(m)$ possible. For the examples given here only the following is used. A number of $|R|$ reaction rules are randomly chosen from R. It is checked whether they are applicable and if so applied to the multiset $A_r(m)$. By this we mean that if molecules have to be removed, they vanish from the domain and if they are added they are positioned randomly in $U_r(m)$.

Analysis through Chemical Organisations

A subset A of M is *closed* if for all reactions $(l, r) \in R_A$ we have $\text{prod}(l, r) \subseteq A$, i.e. if (A, R_A) is a reaction network. A being closed means that by applying reactions from R_A to multisets over A we do not get molecules outside A.

A subset A of M is *self-maintaining* if there is a vector $v \in \mathbb{R}^{|R_A|}$ with strictly positive entries such that $S_A v \in \mathbb{R}^{|A|}$ has only non-negative entries. A being self-maintaining means that applying reactions from R_A at certain rates to a multiset over M does not reduce the number of molecules of any species of A.

A subset of M is a *chemical organisation* (Dittrich and Speroni di Fenizio, 2007) if it is closed and self-maintaining. The set of organisations is called $\mathcal{O}$.

As proposed in (Speroni di Fenizio and Dittrich, 2007) we can look at the chemical organisations at different spatial scales at different times. The idea is to identify functional units when looking at the development of a chemistry in the domain over time. Only the organisations, as the closed and self-maintaining sets, are able to stay in the domain for a longer time period. Therefore persistent structures should be an organisation. This can also be interpreted as identifying higher level units.

In the described stochastic model we looked for organisations in the following way. The domain is divided into squares of size $orgRad$. The species present in each square are collected and then the biggest organisation contained in this set is computed. In the examples presented here $orgRad$ is 0.1.

As an example for this analysis via organisations we demonstrate the formation of a membrane, see Figure 5. The used reaction flow artificial chemistry is defined by $M_2 = \{m, p1, p2, p3\}$,

$$R_2 = \{\alpha p1 + \beta p2 + \gamma p3 \to m, p1 + p2 + p3 \to 4p1 + p2,$$
$$p1 + p2 + p3 \to 2p1 + p3, p1 + p2 + p3 \to 4p2 + p1,$$
$$p1 + p2 + p3 \to 2p2 + p3, p1 + p2 + p3 \to 4p3 + p1,$$
$$p1 + p2 + p3 \to 2p3 + p2, \mid \alpha, \beta, \gamma \in \{0, 1\}\}.$$

This reaction network is constructed such that arbitrary combinations of the producer molecules p_1, p_2, p_3 build the membrane molecule m. The other reactions account for the rebuilding of the producers over time if enough of all three different species p_1, p_2, p_3 are present. The desired behaviour corresponds to the organisations $\mathcal{O} = \{\emptyset, \{m\}, \{m, p1, p2, p3\}\}$ the reaction network (M_2, R_2) exhibits. In this example we can think of $\{m\}$ as the representation of the membrane and of $\{m, p1, p2, p3\}$ as the membrane producing core. The vector field is defined by

$$V_2(x, y) = \begin{cases} 0.0005\frac{e^{5r}}{r}(x, y) & 0.2 < r < 0.8 \\ V_1(x, y) & \text{else} \end{cases}$$

where $r = \sqrt{x^2 + y^2}$ and V_1 is the earlier defined field. The field accounts for a mixing close to the origin, a transport away from it and a movement of the membrane. All molecular species are transported by the field, but the rules are constructed such that most of the producer molecules $p1, p2, p3$ are destroyed on their way to the membrane. Of course, we cannot guarantee that none of them appears in the membrane built by molecules of type m. The analysis via chemical organisations suggests that even if they make it to the membrane, they will not be able to stay for long, see Figure 6. When using separate flows for different molecular species, the formation of a membrane is even easier realised.

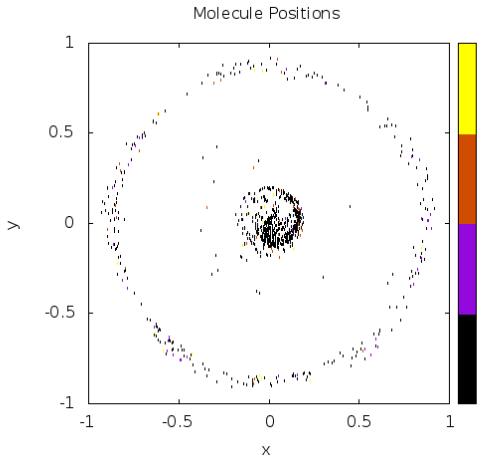

Figure 5: A core emitting molecules which form a membrane around the core. State after 100 iterations. Parameters are $n = 2500$, $rad = 0.2$, $u = 1.0$ and $r = 0.15$.

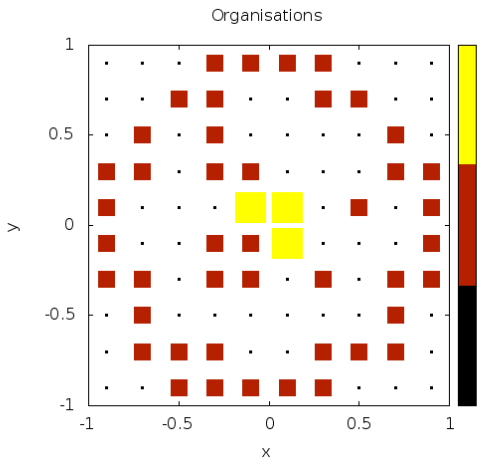

Figure 6: Analysis via chemical organisations. The biggest organisation $\{m, p1, p2, p3\}$ (yellow) shows primarily in the core, the smaller one $\{m\}$ (red) as the membrane. State after 100 iterations.

Further Experiments and Examples

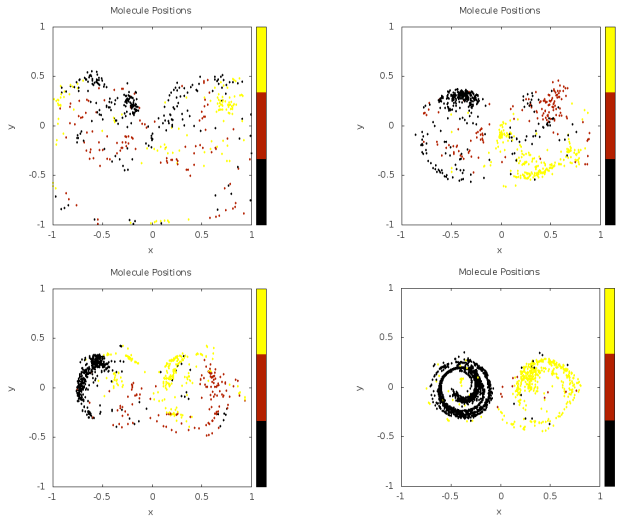

Figure 7: Formation of two compartments. State after $5, 15, 30$ and 150 iterations. Parameters are $n = 2500$, $rad = 0.8$, $u = 1.0$ and $r = 0.1$.

Formation of Compartments. This example shows the slow formation of two compartments in a domain for a reaction network of three competing species. Initially the molecules are distributed over the region. Due to a vector field pushing them to the left and right hand side respectively they gather in two different areas where they are stirred by another two fields, see Figure 7. The parameters for the simulation are as follows. The network is taken from (Neumann and Schuster, 2007) as a model for the rock-scissor-paper game. There are three different competing species present $M_3 = \{s_1, s_2, s_3\}$ with the reactions

$$R_3 = \{s_i \to 2s_i, 2s_i \to s_i, \\ s_i + s_j \to s_i, s_i + s_j \to s_j \mid i \neq j\}.$$

The vector field, see Figure 8, is given by

$$V_3(x, y) = \begin{cases} -0.01e^{5x}(x, 0) + V_1(x + 0.4, y) & x < 0 \\ 0.01e^{-5x}(x, 0) + V_1(x - 0.4, y) & x > 0 \end{cases}$$

Similar to V_2 in the last section the first part of V_3 accounts for the pushing of molecules away from the centre. The second part is a shifted swirl, as described in Section II.

Emergent Behaviour. In this example we use the same vector field V_3 as before, but with a different reaction network (M_4, R_4) and parameters. The network is the central sugar metabolism of *Escherichia coli* as described in (Puchalka and Kierzek, 2004) with the adaptations made in (Centler et al., 2007). We do not give the full definition here due to the size of the chemistry, $|M_4| = 92$ and $|R_4| = 198$.

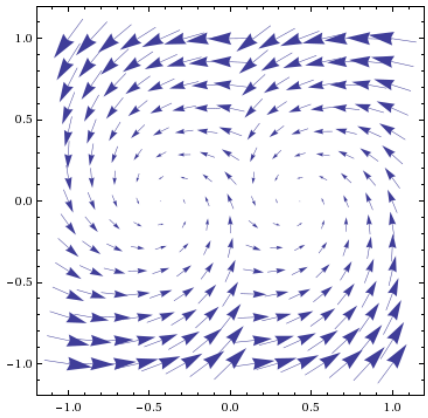

Figure 8: The vector field V_3 in the region $[-1, 1] \times [-1, 1]$. The length of vectors is scaled by 0.3 for a better readability.

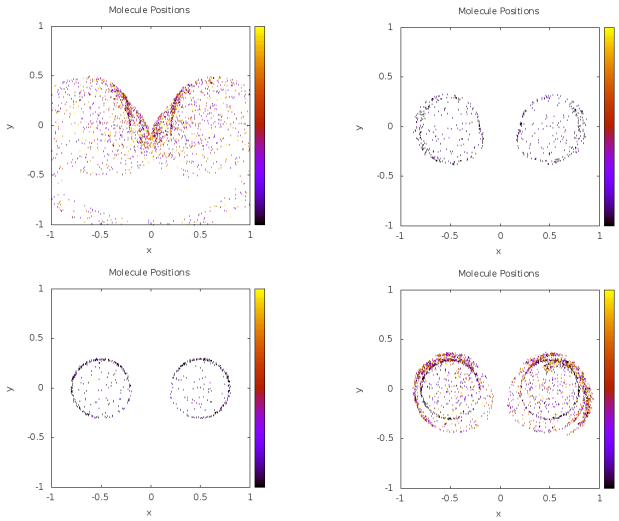

Figure 9: Emergent behaviour. State after $5, 15, 65$ and 70 iterations. Parameters are $n = 2500$, $rad = 1.0$, $u = 1.0$ and $r = 0.15$.

Here due to the movement of molecules an unexpected effect happens, in particular unexpected from the chemical organisation point of view. From Figure 9 we see that after 15 iterations (second picture) the chemistry seems to stabilise since till iteration 65 (third picture) no qualitative change happens. There are formed two rings of many molecules of one species. Then, due to the transport, there are reactions possible again, so that a qualitative change seems to happen (fourth picture). Molecules of other species are build again swirl around the ring and vanish after some more time.

Conclusion and Outlook

We suggested a new approach for introducing a structured space into the dynamics of an artificial chemistry. This is done by using a vector field to generate a flow of molecules

located in a Euclidean space. The introduction of vector fields as defining part for the movement of molecules in space gives additional parameters for the control of the dynamics. We have shown that by this means we can describe membranes, membrane channels and transport processes.

Our system can now be applied to study the influence of different flow structures on the *evolvability* of a chemical system. It is known that compartmentalisation is in a certain sense beneficial for pre-biotic (chemical) evolution (Fernando and Rowe, 2007). Since in a pre-biotic scenario various flow structures were likely present (Martin et al., 2008), it would be interesting to study whether and how particular flow structures can lead to "improved" chemical evolution. Note that space has already a positive effect when just assuming diffusion by counteracting on parasitism (Boerlijst and Hogeweg, 1991; Fishkis, 2010). But could a flow structure add further evolutionary benefits?

Another direction of research could investigate the role of different flow structures for *bio-chemical information processing*. Does a particular flow contribute additional information processing capability to those of reaction-diffusion systems (Adamatzky, 2005)? For a given (artificial) chemistry, we could evolve the flow instead of the chemistry itself. By doing so, we could study the role of flow for certain functions, separated from the reactions going on. This could have practical implications in the development of novel biochemical information technologies, since, it should be easier to change the flow, e.g. within a microfluidic system, than the chemistry.

Finally we can use the scenario presented here to extend the notion of a *spatial chemical organization* (Speroni di Fenizio and Dittrich, 2007) including flow and diffusion.

Acknowledgement

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