Studying and simulating the three-dimensional arrangement of droplets *

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Abstract. We present some work in progress on the development of a probabilistic chemical compiler, being able to make a plan of how to create a three-dimensional agglomeration of artificial hierarchical cellular constructs. These programmable discrete units offer a wide variety of technical innovations, like a portable biochemical laboratory being able to e.g. produce macromolecular medicine on demand, and of scientific investigations, like contributions to questions regarding the origin of life. This paper focuses on one specific issue of developing such a compiler, namely the problem of simulating the experimentally observed spatial transition from an originally one-dimensional lineup of droplets into a three-dimensional, almost spherical arrangement, in which the droplets form a network via bilayers connecting them and in which they are contained within some outer hull. The network created by the bilayers allows the droplets to "communicate" (like agents in a multi agent system) with each other and to exchange chemicals contained within them, thus enabling a complex successive biochemical reaction scheme.

Keywords: microfluidics · droplet agglomeration · Monte Carlo

1 Introduction

Over the last decades, huge progress has been made in biochemistry. A large amount of knowledge about the constituents and the processes within a cell has been gathered [1]. Even a new research field of synthetic biology has evolved [2], in which natural objects like the DNA in cells are purposedly altered or replaced in order to achieve some desired outcome, like producing a specific drug.

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Still, some questions remain unanswered so far, like one of the basic questions for the origin of life: Which constituent of a cell came first, the RNA or the cell membrane? Another problem turning up when considering the anthropic principle in cosmology is the discrepancy between the age of the earth and the time which would be needed by an ungoverned random evolutionary process to allow for the existence of higher-developed beings like humans.

In our approach, which we intend to follow within the European Horizon 2020 project *ACDC – Artificial Cells with Distributed Cores to Decipher Protein Function*, we do not consider fully equipped cells but the most simplified cell-like structures, being droplets comprised of some fluid, containing some chemicals, and surrounded by another fluid. As an additional feature, we also allow for droplets being contained within some outer hulls, playing the role membranes have for cells. These droplets arrange themselves in a three-dimensional way. Neighboring droplets, whose midpoints have a smaller distance to each other than the sum of their original radius values, can form bilayers between each other. Chemicals contained within the droplets can move to neighboring droplets through pores within these bilayers. Thus, a complex bilayer network is created, with the droplets being the nodes of this graph and the existing bilayers being represented by edges between the corresponding droplets. This bilayer network allows a controlled successive biochemical reaction scheme, leading to the intended macromolecules.

We aim at developing a probabilistic chemical compiler for a portable biochemical mini-laboratory, in which various desired macromolecules, like personalized antibiotics, can be produced on demand. Besides, we want to use this approach in order to determine up to which complexity higher-order macromolecules can be created by random agglomerations of droplets in order to make some contributions to Alexander Oparin's origin of life theory [3]. In small droplets, some metastable intermediate compounds can survive with larger probability than in the primordial soup, such that the generation of some macromolecules becomes more likely. Consequently, the time needed according to this theory for the development of life might be strongly reduced.

Summarizing, in the final stage of the project, our compiler for this biochemical device shall be able to solve the task to provide a recipe for producing the desired macromolecule, i.e., be able

- to determine the chemicals needed for the production of the macromolecule,
- to determine the gradual reaction steps leading finally to the desired macromolecule, with each reaction step being performed through a pore at the corresponding bilayer,
- to determine the bilayer network needed allowing for this reaction scheme, with the nodes of this network being the droplets filled with the chemicals determined in the first step and the edges being the bilayers, and finally
- to determine the experimental setup and parameters, leading to just this desired bilayer network.

Of course, in order to get there, our research has to start at the last item, in order to answer the question of how to design an experiment for generating and agglomerating droplets in a desired way.

2 Droplet generation

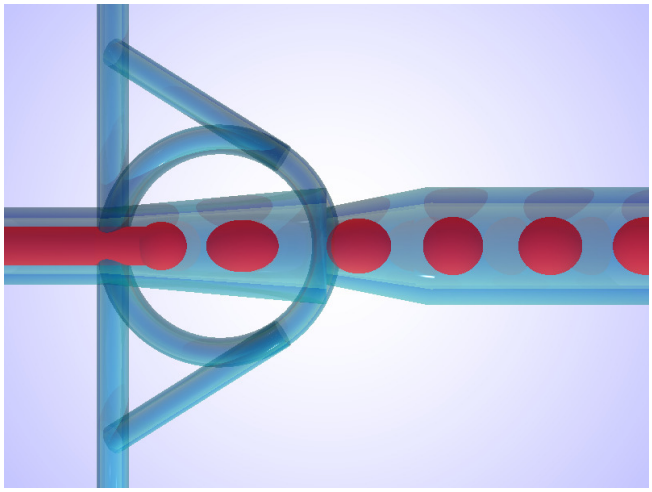

Fig. 1. Sketch of a so-called T-junction (schematically redrawn from [4]): the stream of the inner fluid is broken up under appropriate conditions. Spherical droplets are produced in the so-called dripping regime, in which the pressure within the fluid is neither too small nor too large.

Droplet generation, especially in the field of microfluidics, has been extensively studied over the past years [4–11]. A stream of fluid is broken up into droplets within a T-junction or some other antechamber, as shown in Fig. 1. The breaking-up of the stream is due to the fact that the shape of spherical droplets is energetically favorable when compared to a continuous stream of fluid under specific pressure conditions. The size of the droplets can be controlled by the respective flow rates. Due to the development of 3D printing technologies, producing such antechambers has become much easier and cheaper. Indeed, 3D printing has become a widely used technique in the field of microfluidics [12–19]. We thus consider the general problem of producing droplets to be solved, except that the compiler has to choose appropriate antechambers for the production process or even to create them using the 3D printing technology.

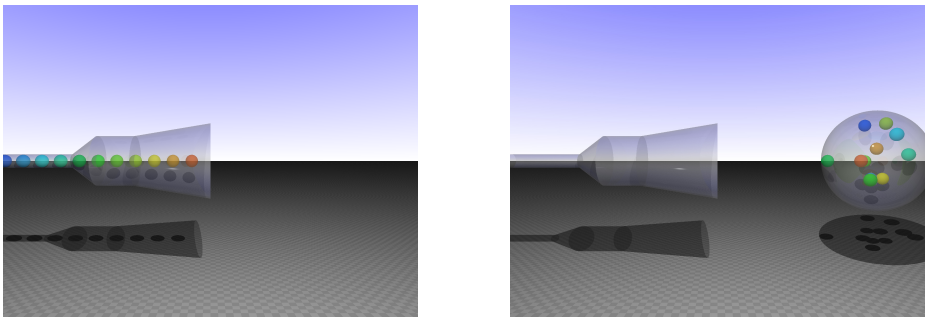

Fig. 2. Sketch of the initial and final states of the spatial rearrangement of droplets

3 3D rearrangement of droplets

In the experiments carried out by Jin Li, member of our collaborating group of David A. Barrow at Cardiff University, the droplets leave the antechamber and first enter a widening tube, in which they e.g. form a zig-zag line. Then they move on to an expansion chamber, in which they rearrange themselves in a three-dimensional way, where several of them are surrounded by some newly generated hull [4], as shown in Fig. 2. Our first main task in this problem will be to study and understand this rearrangement process at least so far that we can simulate it to obtain the same types of three-dimensional arrangements of droplets as found in experiments. We will of course never be able to reproduce the experiments exactly, first of all, because not all experimental parameters are known, secondly also because of lack of computing time.

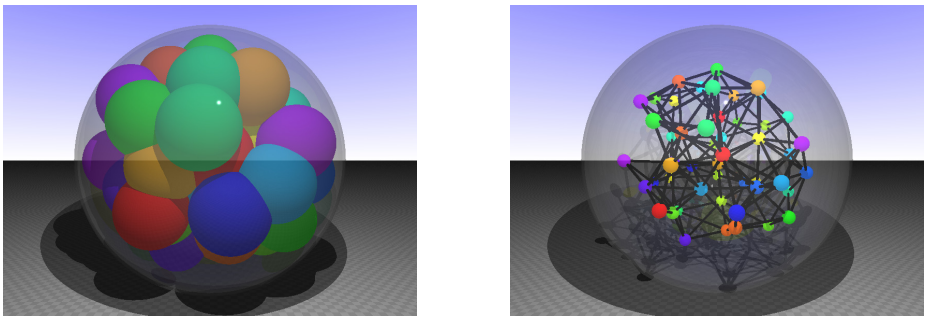

Fig. 3. Resulting 3D arrangement containing bilayers: These two graphics show the same configuration, but on the right, the size of the droplets is reduced in order to visualize the bilayer network.

In some experiments, the resulting three-dimensional arrangements indeed look like in Fig. 2: Jin Li managed to create configurations with up to roughly 100 small droplets swirling around within an outer hull with a diameter smaller

than 1cm [20]. We, on the other hand, are interested in those experiments in which the droplets are rather densely packed and in which they are enabled to create bilayers, such that resulting configurations look more similar to the one shown in Fig. 3. Here one finds that the droplets more or less lose their spherical shapes due to bilayer formation and that a complex graph is formed by these bilayers which shall be used later on for the successive chemical reaction scheme.

4 Limitations of the rearrangement process

This rearrangement process does not allow for the formation of any desired bilayer network, instead, it is restricted by mathematical and physical limitations. The surface tension of the droplets is rather high compared with the other forces (adhesion, inertial forces due to changes of the flow field) in the system, so the shape of the droplets remains more or less close to spherical. Volume changes can be neglected, as the velocity range is limited to incompressible flow, far below 1/10 of the sound velocity of the fluids involved. Therefore, as starting points of our discussion of examples for restrictions for the arrangement of the droplets, the exact solutions of packing problems for rigid spheres are suitable, and we will augment our discussions by taking into account deformations and bounding layers in the next step where necessary.

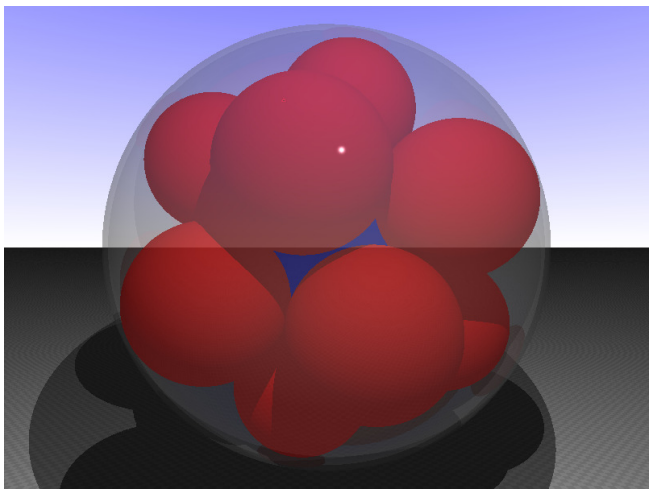

Fig. 4. Kissing number problem in three dimensions: The maximum number of spheres touching a sphere in their midst is 12. This configuration also resembles the optimum packing of 13 spheres in a sphere in three dimensions.

The most prominent of these examples limiting the types of achievable bilayer networks is related to the kissing number problem. The kissing number problem

is stated as follows: given equal spheres of the same size in D dimensions, what is the maximum number of spheres being able to touch a sphere in their midst? While this problem is trivial to solve in one and two dimensions, for which the kissing number is 2 and 6, rsp., it led to a famous dispute between David Gregory and Isaac Newton at the end of the 17th century, whose details however are still under debate [21]. According to the most widely accepted version of the anecdote, Newton proposed that the number was 12, while Gregory argued that the number had to be 13, as a further sphere could be placed close enough to also touch the sphere in the midst. It took till the 1950s to prove that Newton had been right [22], the space was just not sufficient to allow for a 13th sphere to touch the central sphere. Thus, if the droplets keep their spherical shapes, one droplet can only be touched by up to 12 other droplets of the same size. However, if the droplets lose their spherical shapes due to bilayer formation, 13 or even slightly larger numbers of touching droplets can be obtained.

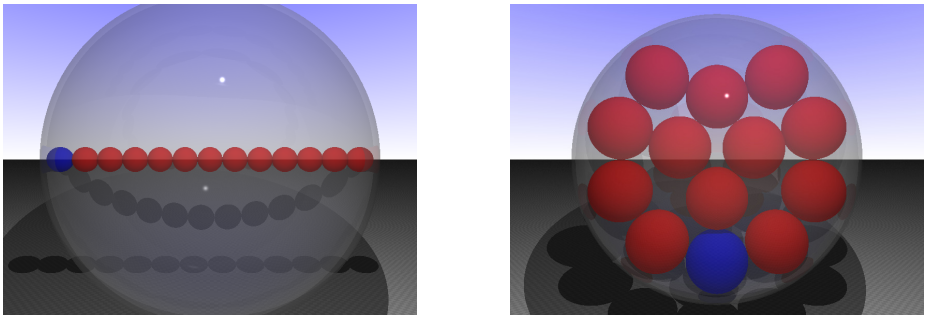

Fig. 5. One-dimensional sausage and two-dimensional pizza configuration for 13 spheres: The configuration on the right resembles the densest packing of 13 circles in a circle.

The next example to be considered here is related to the problem of gaining the densest configuration. If assuming that the volume enclosed in the convex outer hull is to be minimized, the question arises why the droplets rearrange themselves in a three-dimensional way at all. One wonders why they do not stay in a one-dimensional lineup, which is also called "sausage", or form a two-dimensional configuration, called "pizza" [23], as shown in Fig. 5. While it is trivial to determine the optimum one-dimensional lineup, the two-dimensional arrangement is derived from the optimum packing for N circles of equal radius r within a circumcircle of minimum radius R. The optimum value for the radius of the circumcircle of this two-dimensional arrangement was proven to be $R_{2D} = (2 + \sqrt{5})r$ [24] for $N = 13$. Then the convex outer hull does of course not need to be spherical, as depicted in Fig. 5, but it could enclose e.g. the one-dimensional lineup in a cylindric way with two half-spheres attached to the ends of the cylinder. For $N = 13$ spheres of radius r, the enclosed volume of this one-dimensional lineup would only have to be

$V_{1D} = \pi r^2 \times 2r(N-1) + 4\pi/3r^3 = 25\frac{1}{3}r^3\pi$, while for the corresponding three-dimensional configuration shown in Fig. 4, the enclosed volume would almost have to be $V_{3D} \lesssim 4\pi/3(3r)^3 = 36r^3\pi$. (Please note that the minimum value for the volume of the three-dimensional arrangement is slightly smaller than this value, as some small parts of the surrounding spherical hull can be cut off because surfaces over triangles of spheres can be made partially planar, while the hull still remains convex.) Only at larger numbers N of spheres, like $N = 56$ [25], a three-dimensional cluster is more densely packed than the one-dimensional sausage. This transition, which is also called sausage catastrophe, is still under research debate. According to the sausage assumption, intermediate dimensional structures like pizzas are never optimum. This can also be seen for our exemplary two-dimensional pizza configuration shown in the right half of Fig. 5: the four inner spheres can be neglected when calculating the volume V_{2D} of the convex surrounding hull of this configuration. V_{2D} consists of three parts: the inner part is given by the area A within the polygon, formed by the midpoints of the nine outer spheres, multiplied with the height $2r$. To each of the nine side planes, a half cylinder with radius r and a length corresponding to the length of the edge between the midpoints is attached. These lengths sum up to the length U of the closed polygon. At each node of the polygon, a spherical wedge is attached, connecting the two half cylinders ending at that node with each other. These spherical wedges add up to a sphere with radius r. Summarizing, we get $V_{2D} = A \times 2r + U \times r^2\pi/2 + 4\pi r^3/3 \sim 29.6 \times 2r^3 + 19.8 \times r^3\pi/2 + 4\pi r^3/3 \sim 94.5r^3$. Therefore, we have $V_{1D} < V_{2D} < V_{3D}$. Thus, the minimization of the volume within a hull has no dominating effect on the arrangement process, on the contrary, one even finds in configurations resulting in experiments that also the three-dimensional clusters are not most densely packed. They sometimes even contain holes in which a further droplet could be placed [4].
Another picture is obtained if we aim at minimizing the surface of the surrounding hull. If we again have a look at our example with 13 spheres, we find $S_{1D} = 12 \times 2r \times 2r\pi + 2 \times 2r^2\pi = 52\pi r^2 \sim 163r^2$ for the surface of the one-dimensional sausage, $S_{2D} = 2 \times A + \pi r \times U + 4\pi r^2 \sim 134r^2$ for the surface of the two-dimensional pizza, and $S_{3D} \lesssim 4\pi(3r)^2 = 36\pi r^2 \sim 113r^2$ in the case of three dimensions. Summarizing, we find that $S_{3D} < S_{2D} < S_{1D}$, i.e., the minimization of the surface of the hull or, physically speaking, the surface tension could have a large effect on the agglomeration process of the droplets. However, the minimization of the surface does not totally dominate this process, as the resulting shapes of the hulls as seen in the videos generated by Jin Li show perfectly spherical or elliptical shapes or sometimes oval shapes due to boundaries, but never shapes with triangular planes. But one must not forget that on the one hand not only droplets but also some fluid around them is contained within the outer hull and that on the other hand the surface tension tends to minimize local deviations from the average curvature radius.

Finally, we want to deal with the quest for the one and only central sphere. The so-called ideal picture which is often drawn on blackboards depicts a central sphere being surrounded by some number $N-1$ of other spheres touching it and

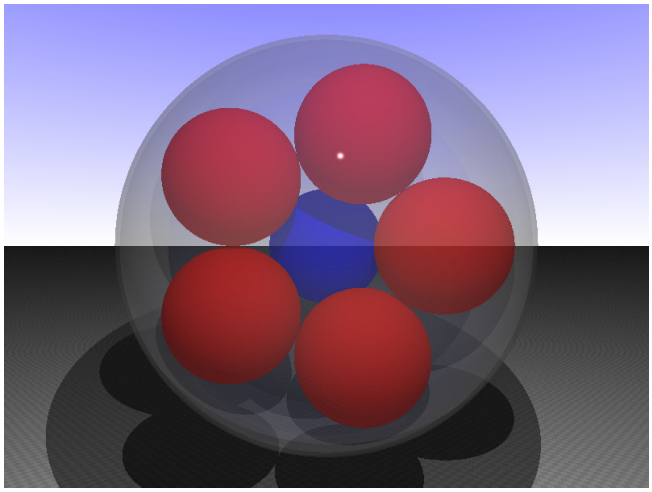

Fig. 6. Configuration consisting of five spheres with their centers being placed on the corners of a regular pentagon touching their neighbors and a sixth sphere touching all other spheres

touching their neighbors, as shown in Fig. 6. This picture is motivated by its two-dimensional analogon, in which six circles can be placed around a seventh circle. However, this picture with a central circle is only valid for $N \leq 9$ in two dimensions, as there are at least two inner circles in optimum packings of circles for $N \geq 10$. Transferring this picture to three dimensions by replacing the circles with spheres, the situation becomes unstable for $N \geq 7$ spheres, as the sphere in the center can move freely in the third dimension and would thus fall through the ring, due to the law of gravity. The densest packing of seven spheres within a spherical hull is obtained for $R \sim 2.59r$ but it does not contain a sphere which could be classified as center sphere [26]. Stable configurations with $N-1$ spheres being placed on a regular $N-1$-gon and touching their neighbors and an Nth sphere touching all the others can only be obtained for $N = 4, 5$, and 6, under the condition that the radius R of the outer hull has a specific value, such that the Nth sphere at the bottom of the configuration neither drops down nor presses the other spheres apart such that the connections between them are destroyed:

If placing three spheres on the edges of an equilateral triangle with side length $2r$ and a fourth sphere centered below them, touching the other three spheres, one gets the densest packing of four spheres in a sphere, which remains stable in a spherical hull with radius $R = (1 + \sqrt{6}/2)r \sim 2.22r$.

If placing four spheres on the edges of a square with side length $2r$ and a fifth sphere centered below them, touching the other four spheres, one gets the densest packing of five spheres in a sphere [26]. It remains stable within a spherical hull with radius $R = (1 + \sqrt{2})r \sim 2.41r$. One can even place a sixth sphere

symmetrically to the fifth sphere on the opposite side of the center square, thus achieving the densest packing of six spheres in a sphere.
If placing five spheres on the edges of a regular pentagon with side length $2r$ and then a sixth sphere below them, touching all of them, as shown in Fig. 6, one has to make a larger effort to determine a radius R of the spherical surrounding hull to get a stable configuration. The radius of the pentagon formed by the midpoints of the spheres can be easily determined as $r\sqrt{2/(1-\cos(2\pi/5))} \sim 1.7r$ geometrically or as $r\sqrt{50+10\sqrt{5}}/5$ making use of the golden ratio. If imagining the pentagon formed by the midpoints of the five spheres being placed in the xy-plane centered around the origin, one can place the sixth sphere, which is supposed to touch all the other spheres, on the z-axis at $z_6 = -r\sqrt{4-2/(1-\cos(2\pi/5))} \sim -1.05r$. In order to get a stable configuration in which this sixth sphere does not drop down, we need to blow up the radius of the surrounding hull to $R = r - 2r^2/z_6 - z_6 \sim 3.95r$, its midpoint lies at $z_M = -2r^2/z_6$.
Thus, mathematically speaking, for each of these scenarios, there is only one exact value R for the radius of the surrounding spherical hull, for which the inner configuration of hard spheres is stable. But, of course, if allowing some amount of deformation of the spheres and also of the hull, one gets a range of possible radius values instead of one exact sharp value only.

5 Simulating the rearrangement process

After these initial considerations, we now describe how we intend to simulate the rearrangement process. We will perform macroscale Monte Carlo movement simulations, imitating the movement behavior of the droplets being first lined up in an almost one-dimensional structure within the T-junction or some other antechamber and then entering the expansion chamber, in which they rearrange themselves in a three-dimensional way within some outer hull, as shown schematically in Fig. 2. During this rearrangement process, some droplets touching each other will form bilayers [27]. These bilayers can be reshaped, broken up, and newly formed, depending on the stability of the bilayers [28]. When bilayers are created, the droplets lose their spherical shape. We will test various ways to simulate the formation, change, and destruction of bilayers and the change of the shape of the cores in a computationally not too expensive way. A cheap way would be to place the particles on a regular or irregular lattice [29, 30] and even to make use of a cellular automata approach as in traffic dynamics [31, 32], but this approach is not feasible as it restricts the possibilities for resulting bilayer configurations too much. We intend to invent an entirely new method of Monte Carlo movement simulations of such droplets, as existing methods like in [33] put too much emphasis on the resulting network of droplets, introducing springs between these particles already from the very beginning, while these droplets move rather independently of each other at first in the experiments, as seen in movies generated by Jin Li [20]. Only at a later stage when they are already surrounded by some hull, the droplets gradually settle down, reducing their individual behaviors, and start to move coherently. While the specific spatial setup

of an experiment with preset values for widths and lengths of various parts of the junction can be easily employed also in the Monte Carlo simulation, it is a harder task to find appropriate values for the probabilities for braking and acceleration of droplets as well as for bilayer formation and destruction and also for some introduction of random movement. These values depend on various experimental parameters, like pressure and viscosity. We intend to adjust the parameters for the Monte Carlo simulation in a way that the resulting configurations reflect the three-dimensional arrangements of droplets as found in experiments.

In order to perform fast simulations with our limited computing time, we will at first consider spherical droplets only. If two droplets form a bilayer with each other, we will compensate the overlapping volumes by increasing the radii of the corresponding droplets. Furthermore, we will either select particles in random sequential order and ask the process which move to perform with them (but then some larger gaps in the configurations could occur and only be slowly resolved) or we start off with the outermost droplet at the right (if they are moving from left to right), then the second rightest droplet, and so on, until at last the outermost left droplet is chosen. Furthermore, we retain the information whether a droplet is connected to other droplets via bilayers, such that they can move with each other, or already part of a group of droplets, with which it moves more and more coherently within an outer hull. In this case, all droplets within such a group are simultaneously updated. The movement of the various droplets within a group is split in a movement process for the center of mass of that group and a movement process for the specific droplet relative to the center of mass.

Summarizing, we need to implement the following processes in the Monte Carlo movement simulation:

- acceleration process: With some probability, a droplet is accelerated until it reaches its desired velocity.
- braking process: If walls or other droplets provide obstacles for the movement of a droplet, it of course has to brake. Otherwise, there is also some probability for braking.
- random movement process: We will to some extent also allow random movement, i.e., the velocity vector can be slightly altered.
- bilayer formation process: With some probability, droplets touching (or in the simulation even overlapping) each other can form bilayers. The probability for bilayer formation increases with increasing overlap and increasing time for which the overlap already lasted.
- bilayer destruction process: With some probability, a bilayer formed can also be destroyed again. This probability could depend on the length of time for which the bilayer was in existence.

Related to these processes, we thus have the probabilities $p_{\mathrm{accelerate}}$, p_{brake}, $p_{\mathrm{randommovement}}$, $p_{\mathrm{bilayerformation}}$, and $p_{\mathrm{bilayerdestruction}}$. Thus, our simulations will not contain experimental parameters like viscosity in an explicit way, but we will find that implicitly e.g. the probabilities for braking and acceleration will depend on viscosity and other parameters, such that one task will be to find an

appropriate mapping between experimental input values and parameters in the computer simulations.

6 Summary

In this paper, we described the first step to be undertaken in the development of a chemical compiler for a biochemical micro-laboratory device, with which e.g. macromolecules shall be produced on demand. For this device, we want to make use of the ACDC technology, i.e., systems of droplets which agglomerate in a three-dimensional way, forming bilayers between them. This bilayer network will allow for a step-wise generation of some desired macromolecules, which are gradually constructed from smaller units, being contained in the various droplets, with the successive chemical reactions being enabled via the bilayers formed between neighboring droplets. Such a compiler has been exemplarily already developed for one specific molecule [34]. In this project, this compiler has to be generalized and also made probabilistic because of the variability in the rearrangement process. When performing simulations for the three-dimensional rearrangement of droplets as seen in experiments, our objective is not to find e.g. the densest configuration possible [35, 36], but to find configurations most similar to those resulting in experiments.

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