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Cellular Automata for Simulating Molecular Self-Assembly

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We present a lattice gas technique for simulating molecular self-assembly of amphiphilic polymers in aqueous environments. Water molecules, hydrocarbons tail-groups and amphiphilic head-groups are explicitly represented on a three dimensional discrete lattice. Molecules move on the lattice proportional to their continuous momentum. Collision rules preserve momentum and kinetic energy. Potential energy from molecular interactions are also included explicitly. Non-trivial thermodynamics of large scale and long time dynamics are studied. In this paper we specifically demonstrate how, from a random initial distribution, micelles are formed, and grow until they destabilize and divide. Eventually a steady state of growing and dividing micelles is formed.

Keywords: Cellular Automata, Lattice Gas, Molecular Self-Assembly, Statistical Mechanics, Thermodynamics

1 Introduction

Self-assembly is a process that generates higher order complexes from simpler molecular building blocks. Examples range from micelles and membrane formation to complex organelle structures in biological cells. Evolution and molecular self-assembly are the main sources for novelty in biological systems. This paper is a presentation of a computational framework that enables direct simulations of amphiphilic polymers self-assembling into micelles in aqueous environments where the water molecules are simulated explicitly. The simulation technique is a combination of a traditional molecular dynamics and a lattice gas cellular automaton. It fills the gap between molecular dynamics, which is highly detailed but too computationally expensive to simulate molecular self-assembly on longer time scales ($\sim ms$), and simple lattice models that are too oversimplified to capture many of the interesting physico-chemical and thermodynamic properties of self-assembly processes.

1.1 Thermodynamics of molecular self-assembly

The global equilibrium thermodynamics of molecular self-assembly processes can be described by minimizing Gibbs free energy. Gibbs free energy is defined as $G = H - TS$, where H denotes the enthalpy, T the temperature, and S the entropy. A minimum of Gibbs free energy can be viewed as a balance between the counteracting effects of energy minimization and thermal fluctuations, i.e., enthalpy and entropy. The importance of the entropy contribution increases with temperature, in accordance with our intuition of how disorder in created by thermal fluctuations.

The microscopic details of hydrophobic self-assembly in polar environments are rather complicated. Naively, one might assume that a phase separation occurs solely due to potential energy minimization, and that the entropic contribution to the free energy only counteracts the formation of coherent structures. Surely, visual inspection indicates that well mixed states display a lower degree of order than phase separated states. However, a closer examination reveals that this conclusion is premature. More intricate details need to be included.

In liquid water, extended hydrogen networks are formed based on the tetrahedrical structure of the water molecules, with two donor and two acceptor sites. The local interactions in these networks can roughly be classified as either satisfied ($H-O$) or frustrated ($H-H$ or $O-O$), making negative or positive contribution to the global potential energy. The number of micro-states corresponding to identical global potential energy effectively determines the entropy. The more available micro-states, the higher the entropy. When hydrophobic molecules are solvated in bulk water, possibilities for resolving some of the frustrations in the hydrogen networks appear. The water molecules around the solvated hydrophobic molecules have fewer neighboring water molecules available to form hydrogen bonds with, which results in in fewer available micro-states with the same potential energy, which corresponds to a decrease in entropy [PG88]. Therefore minimizing the interface area between the water molecules and the hydrophobic molecules maximizes the number of available micro-states with the same potential energy. This effect is significant (actually contributing more to the self-assembly process than potential energy minimization) when the potential energy contribution from the hydrogen network is approximately in balance with the kinetic energy, i.e., in a limited temperature range. This line of argument explains why the entropic contribution to the free energy, in certain temperature ranges, has the most significant influence on self-assembly processes.

Amphiphilic self-assembly processes also display a highly nontrivial phase diagram. Depending on the physico-chemical conditions of the system, a multitude of different geometrical configurations can appear as minimal free energy solutions. Possible geometries of the aggregates include: micelles, cubic or hexagonal symmetric sponge like super-aggregates, or extended flat lamellar structures. Close to critical states, slight changes in external parameters, such as temperature or concentration, may lead to extensive structural changes on several length scales. Elucidating the correlations between molecular structures and macroscopic properties poses a major scientific challenge.

1.2 Modeling molecular self-assembly

Traditionally, theoretical and computational studies of molecular self-assembly processes have mainly been performed by Monte Carlo methods, microscopic lattice models, Ginzburg-Landau theories, membrane theories, simple lattice gas models and lately also by molecular dynamics (MD) simulations. We briefly discuss some of these methods and argue how our technique complements existing approaches. For an overview on models of self-assembly see e.g., [GS94, GBSR94].

In Ginzburg-Landau (GL) models, e.g., [JLS00, SHE$^+$91], the free energy is described by a spatially localized scalar parameter (or possibly a set of such parameters). Global minimization of the free energy is then transformed into a local partial differential equation, which become the fundamental mathematical model for the system in equilibrium. This method has been very successful, especially it can reproduce qualitatively correct phase diagrams. However, the parameterization of the underlying micro-dynamics limits the connection to microscopic details in realistic systems.

In molecular dynamics (MD), e.g., [TvdSB00], the atoms are represented explicitly and the equation of motion as described by Newtonian dynamics is integrated explicitly. This gives a highly detailed representation, at the cost of limited system size and in particular simulation times. MD has, for example, been used to study spontaneous formation of micelles by hydrophobic molecules with amphiphilic head groups in bulk water, as well as stability of pre-configured micelles and membranes, see e.g., [MLC99].

Lattice gases are a particular kind of cellular automata that allow particles to propagate on the lattice in a natural manner. The original lattice gas automata (LGA) [FHP86, Wol86] are nice examples of how it is possible to simulate macroscopic effects (fluid flow) based on microscopic rules of interaction between the lattice particles. The computational simplicity of the lattice gas automata enables long time scale simulations on large systems.

The Lattice Boltzmann (LB) method is a more complex discrete computational technique based on the Boltzmann equation. The dynamics obeys local conservation of mass, momentum, and energy. A volume element of the fluid is assumed to be composed of a collection of particles, represented by a velocity distribution function for each fluid component at each lattice point. The dynamics of the model (translational movement and collision) is designed such that the time-average motion of the particles is consistent with the Navier-Stokes equation. The LB method has successfully been applied for modeling fluid flow in complex geometries, as well as multicomponent fluids [HSB89, MZ88, KZCH02].

Based on the LB concept, other research groups have further generalized the idea of lattice gases to include discrete methods for simulating molecular self-assembly systems. For example Bogosian et al. and [CMW^{+}98, BCL00] have developed models based on a microscopic discrete dynamical system, which produces the correct mesoscopic and macroscopic behavior of mixtures of oil, water and surfactant. Their model can accurately simulate many of the phases occurring in such systems, including droplets, bicontinua and lamellae phases. Similar to the LB method, the lattice gas technique is constructed from local conservation laws. However, the LG methods simulate the micro dynamics in higher resolution than the LB and each lattice site is only occupied by a small number of molecules (water, polymer or surfactant) at each time step.

In both the LB and the LG methods, each lattice point typically resides a collection of particles, rather than a single molecule. The LG method is more detailed than the LB, but even polymeric molecules are still represented as point particles (with possible internal structure). As indicated above in the discussion on microscopic contribution to the free energy, many aspects of the dynamics of amphiphilic self-assembly depend strongly on the details in the structure of the molecules and their interactions: water molecules form hydrogen networks, the length of the lipid polymer partly determines the stability of assembled structures, the strength and geometric properties of the interaction between amphiphiles and water can directly affect the size distribution of micelles, etc. Only MD include structural details of the interacting molecules; water, lipids and amphiphiles. However, the excessive computational resources required for MD simulations limits its applicability to relatively small systems and/or short time scales. The formation of an equilibrium micellar solution described in this paper can for example currently not be simulated by MD.

Our Molecular Dynamics (MD) lattice gas technique see e.g. [NRMW03] is designed to accurately (given the constraints from the lattice geometry) represent networks of hydrogen bond between water molecules, as well as the interaction between the water molecules and the hydrocarbon tail of amphiphilic polymers. Chemically, both these phenomena contributes significantly to the free energy of the system, and is the primary driving force behind lipid self-assembly processes in polar environments. We therefore argue that the MD lattice gas strikes an appropriate balance between computational efficiency and physico-chemical detail of molecular self-assembly processes.

Perhaps the most important systems to study using the MD lattice gas techniques are large molecular systems, over longer time periods, where the structural dynamics is mainly determined by non-covalent interactions, as e.g. the hydrophobic effect, which are the main driving force behind molecular self-assembly processes.

2 Molecular lattice gas dynamics

The MD lattice gas simulation described in this paper is a natural extension of the classical lattice gases. The basic idea is to allow more complicated update rules than those usually studied in cellular automata. In traditional lattice gases the micro-dynamics is determined by collision rules and movement of the molecules. In the MD lattice gas, we have generalized LGA concept along two lines:

- Detailed electromagnetic interactions between the particles or molecules are accounted for.
- Momentum of the particles is continuous and therefore allows non-trivial thermodynamic phenomena to be studied.

2.1 MD lattice gas simulation framework

Four main steps determine the dynamics in the MD lattice gas: (i) propagation of the field, (ii) rotation of the molecules to minimize the local energy (this also includes changing the local field configuration according to the new orientation of the molecule), and (iii) collisions, and (iv) movement of the molecules on the lattice. As a comparison the dynamics for the classical LGA only consists of two steps: (i) moment and (ii) and collisions (scattering). We use this formulation for the MD lattice gas because of its simplicity (modularity and parallizability) and because each part of the dynamics has a clear physical interpretation.

2.1.1 Molecular species

The molecular species included in the self-assembly simulations are water (H_2O) and amphiphilic polymers ($COOH[CH_2]_nCH_3$). The carboxyl acid ($COOH$) that forms the head-group of the polymer is hydrophilic (it can form hydrogen bonds with the water molecules). The hydrophobic tail consists of $(n+1)$ hydrocarbons ($[CH_2]_nCH_3$), which are usually referred to as monomers. The hydrophobic effect, describing phase separation of apolar compounds in a polar environment, is generated as a result of the relative balance between the water-water interactions, the water-monomer interactions, and the monomer-monomer interactions. If water likes water much more than water likes monomers and monomers like each other and water about equally well, there is a free energy gain from isolating the hydrophobic monomers from the water so that the water molecules can be in proximity to each other and participate in the hydrogen bond network.

2.1.2 Interactions

The molecules are located on a three dimensional lattice. The interaction between the molecules are propagated via fields. This allows for direct physical interpretation of the dynamics, as well as relatively easy modifications, e.g., inclusion of new molecular species. The fields are defined on a lattice dual to the molecular lattice, i.e. there is a field lattice point at the mid-point between each of the molecular lattice points. We use a scalar fields to account for interactions that on a fundamental level include relatively complicated quantum effects, all derivable as a perturbation expansion of the Schrödinger equation. The effective potential can be represented as

$$
\begin{aligned}
V_{total} &= \sum_{i=1}^{n}\sum_{j=1}^{q} V^{i,j}_{H-bond} + \sum_{i=1}^{n}\sum_{j=1}^{q} V^{i,j}_{dip.-ind.dip.} \\
&+ \sum_{i=1}^{n}\sum_{j=1}^{q} V^{i,j}_{ind.dip.-ind.dip.} + \sum_{i=1}^{n}\sum_{j=1}^{q} V^{i,j}_{coop.}
\end{aligned}
$$

These potential energy terms are implemented to account for specific physico-chemical properties of molecular species: hydrogen bonds, dipole - induced dipole, induced dipole - induced dipole, and cooperative effects, respectively. All of which are important for the generation of molecular self-assembly in a polar environment [MKR97]. This set of weak intermolecular interactions given in the above equation is commonly summarized as Van der Waals forces. In this presentation we only discuss the hydrogen bonds in some detail because they are energetically approximately one order of magnitude stronger than the other contributions to V_{total}. For a more extensive discussion all the interactions see [NRMW03].

To represent the key feature of a polar solvent like water, the capability of hydrogen bond formation has to be represented. Formally, the hydrogen bond has to be treated as a combination of a dipole-dipole interaction and a charge transfer reaction, and this type of non-covalent donor-hydrogen-acceptor bond is commonly represented via a Lennard Jones potential in force fields. An important aspect of hydrogen bonds is their strictly defined potential energy surface where the optimum geometry is given by a donor-hydrogen-acceptor-oxygen angle of 180 degrees and a donor-acceptor distance of around 3 Å (Ångströms). In this optimum configuration the hydrogen bond contributes with 1 - 2 $kcal/mol$ to the total potential energy. However, variation of this optimum geometry is immediately followed by an increase in potential energy. Hydrogen bonds are among the strongest intermolecular interactions, but their ideal geometry is highly constrained. To represent the geometrical structure as faithfully as possible, the water molecules have internal structure, and therefore their orientation determines the structure of the field (see Fig. 1).

2.1.3 Rotations

At each time step, the water molecules rotate in order to minimize the local potential energy. The individual molecules are updated in random order, similar to the procedure in a zero temperature simulated annealing. This process does not in general generate a state with globally minimized potential energy. Finding such a state is indeed a highly nontrivial task (similar to annealing of spin-glasses). We simply sweep all the molecules once, and assume that this gives an approximation of the realistic dynamics. Numerical investigations show that when the lattice is moderately occupied ($\sim 75\%$), this routine does in fact usually produce a state tolerably close to a global minima of potential energy.

2.1.4 Movements

A molecule is moved in a specific direction with a probability proportional to its velocity in that direction. The proportionality is adjusted so that only a small fraction ($\sim 10\%$) of the molecules are moved at each time step. If the lattice site into which a molecule is supposed to move is already occupied a collision occurs, and consequently the molecule does not move (but exchanges momentum with the molecule occupying the lattice site, see Section 2.1.5). Due to the possibility of collisions, movement of molecules does not always commute in time (compare with the rotation step, Section 2.1.3). To minimize undesired systematic effects of the unphysical temporal ordering of the update, we use a random update order.

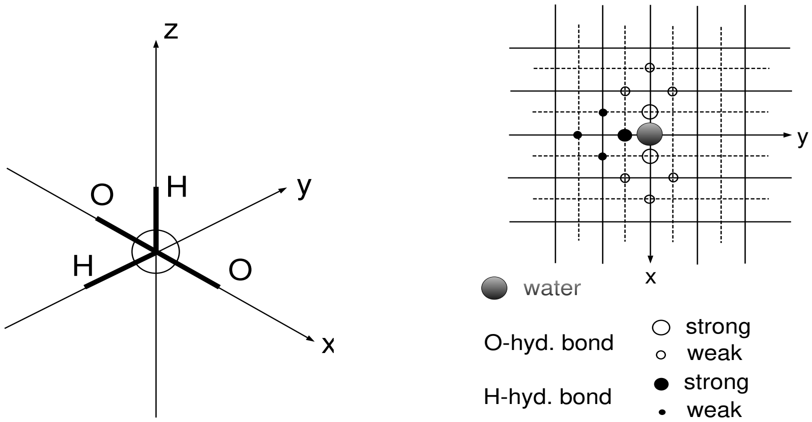

Fig. 1: The figure on the left shows the geometrical structure of the water molecules. The right figure shows a two dimensional slice of the local field configuration building up the hydrogen bonds.

In Section 2.1.2 the propagation of fields representing the local interactions of the molecules is described. When a molecule moves on the lattice, its momentum changes according to the laws of Newtonian mechanics defined by the local force fields. This asserts a relatively realistic exchange of potential and kinetic energy, which is important to obtain a realistic thermodynamics. The physical interpretation of the micro dynamics is that the system follows the micro-canonical ensemble, rather than the canonical ensemble which could be achieved by keeping the temperature (the kinetic energy) constant, e.g., by connecting the system to an external heat bath.

2.1.5 Collisions

During collisions the momentum is exchanged according to three dimensional hard sphere collisions, i.e., conserving the total momentum and energy. In three (or two) dimensions, the outcome of a collision is not well determined simply by demanding momentum and energy conservation. In general, the details of the collision needs to be taken into consideration, see Fig. 2.1.5. In the MD lattice gas simulation it is reasonable represent the geometrical uncertainty of a collision by a random point (or vector) in a circle with radius limited by the energy of the collision. For more details on the mechanics see e.g., [Tho72].

2.1.6 Other physical properties

Perhaps the most important parameter in the MD lattice gas simulation is the fraction of the lattice sites that are occupied. This parameter can be estimated through the following simple argument. Two closest neighbors on the lattice should be able to form natural hydrogen bonds. The distance between lattice sites should therefore correspond to the distance between the center of mass in two water molecules that have formed a hydrogen bond, i.e. approximately 2.8 nm. Using the lattice distance 2.8 nm, that H_2O has a molecular weight of about 18 g/mol, and a water density of about 1 kg/l, we can conclude that for consistency about 75% of the lattice points should be occupied by water molecules.

One advantage by using continuous momentum, probabilistic movement, and realistic three dimen-

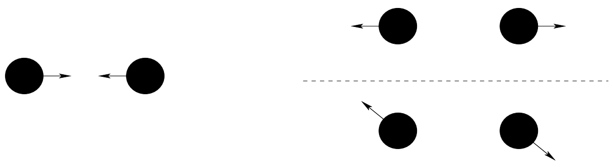

Fig. 2: The figure demonstrates how the outcome of a collision in two or more dimensions is not uniquely defined by conservation of energy and momentum. Both of the two final states on the right are consistent with the conservation laws.

sional collision rules, is that many affects imposed by the structure of the lattice are avoided. Self-diffusion, for example, follows the Einstein relation $\langle|\mathbf{r}(t)-\mathbf{r}(0)|^2\rangle = 6Dt$ for the mean square displacement. This is not the case in a traditional lattice gas on a cubical lattice, where momentum is only exchanged along the principal axis of the lattice. An alternative to the above mentioned approach which we have used to mitigate lattice imposed problems, is the standard "trick" which uses more complicated lattices, e.g., hexagonal lattice in two dimensional simulations. By introducing additional principal lattice directions, discrete probabilistic outcomes mimicking the situation in Fig. 2.1.5 can be introduced into the collision rules. In the MD lattice gas however, this is not an attractive alternative since the geometry of the lattice should prioritize a faithful representation of the interaction structure of the hydrogen networks.

Another advantage is that our system spontaneously relaxes into a state where the velocity distribution obeys both the equipartition theorem and the Maxwell-Boltzmann distribution, $f(v) \sim v^2 T^{\frac{3}{2}} \exp\{-\frac{\alpha v^2}{T}\}$.

3 Simulation results

We use the MD lattice gas to simulate a solution of amphiphilic polymers in water, at different concentrations. The amphiphilic polymers consist of a hydrophilic head group and a hydrophobic tail. The differentiated physico-chemical properties of the the head group and the tail produce more ordered structure compared to purely hydrophobic polymers. Fig. 3 shows snapshots from a simulation of amphiphilic polymers in an aqueous environment, resulting in the formation of bi-continuous (worm-like) structures. Water is not shown, hydrophilic head groups are green and the hydrophobic tail monomers are yellow. The structures are characterized by a hydrophobic core and a well solvated hydrophilic surface. The concentration of amphiphilic polymers is 25% (volume) compared to water.

When the relative concentration of amphiphilic polymers in decreased to 2.5%, the characteristic morphology of the self-assembled aggregates is changed from a bi-continuous phase to a phase where micelles are formed. The result is shown in Fig. 3. In this case the behavior of the system depends more sensitively on a balance between kinetic and potential energy. The initial configuration is a random state. The dynamics spontaneously relax the system into a state with lower potential energy. This process heats up the system, since potential energy is transferred into kinetic energy, because no external exchange of energy occurs (micro canonical ensemble). For appropriate initial temperatures, a steady state of growing and dividing micelles is eventually formed. The relaxation time of the system is long ($\sim 10^5$ time steps) an important observation since the simulation could be terminated too early for a steady state to be observed. This is also in agreement with observation in real systems, where the time scale for micellar formation is on the order of milli-seconds.

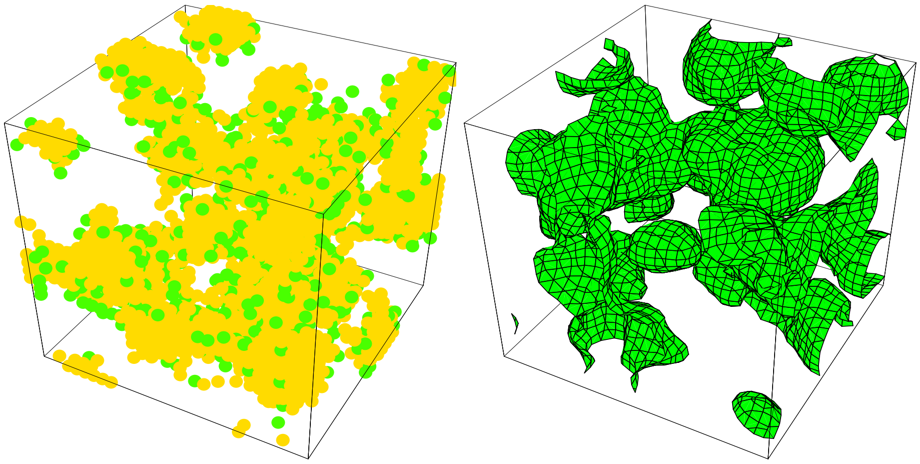

Fig. 3: Bi-continuous (worm-like) phase of amphiphilic pentamers. To the left we show the individual molecules explicitly (except for water which is not shown). Hydrophilic head groups are shown in green while the hydrophobic tail monomers are shown in yellow. The figure on the right shows iso-density contours of the amphiphilic polymers.

Another interesting aspect is the long time correlations. After the formation of a single large micelle (the energetically preferred state) at around $t \sim 5 \cdot 10^5$, a thermal fluctuation splits the micelle. The two resulting micelles do not re-unite for the full duration of the simulation ($> 10^6$ time steps). Simulations with other initial configurations also show that the state with one single micelle is indeed not always formed within the first 10^6 time steps.[†] This indicate that time correlations over 10^6 time steps are not negligible.

Fig. 3 also shows how the global potential energy fluctuates. We can conclude that the state with a single micelle is energetically preferable. However thermal fluctuations prevents the system from being stable in the lowest energy state. As can be seen from Gibbs free energy, the equilibrium of the system is characterized by a balance between highly ordered states with minimal internal energy, and thermal fluctuations which drive the system towards states with higher entropy.

4 Discussion

There is a vast array of interesting questions related to molecular self-assembly that can be addressed by a combined theoretical and computational approach. The molecular dynamics (MD) lattice gas simulation framework described in this paper has been developed to a point where thermodynamically realistic simulations of such systems are possible. In this paper, we have for example shown simulations of the transition from a random initial state to a quasi-equilibrium micellar solution. The computer simulation can be used for qualitative studies of at least parts of the phase behavior in ternary mixtures of oil, water, and amphiphiles. We hope to extend our framework to simulate transitions into the lyotropic phases (cylindrical micelles and lamellar structures). The computational requirement for this is relatively high,

[†] This is currently how long we have run the simulation. These simulations take approximately 6 weeks to perform on a 1 GHz machine.

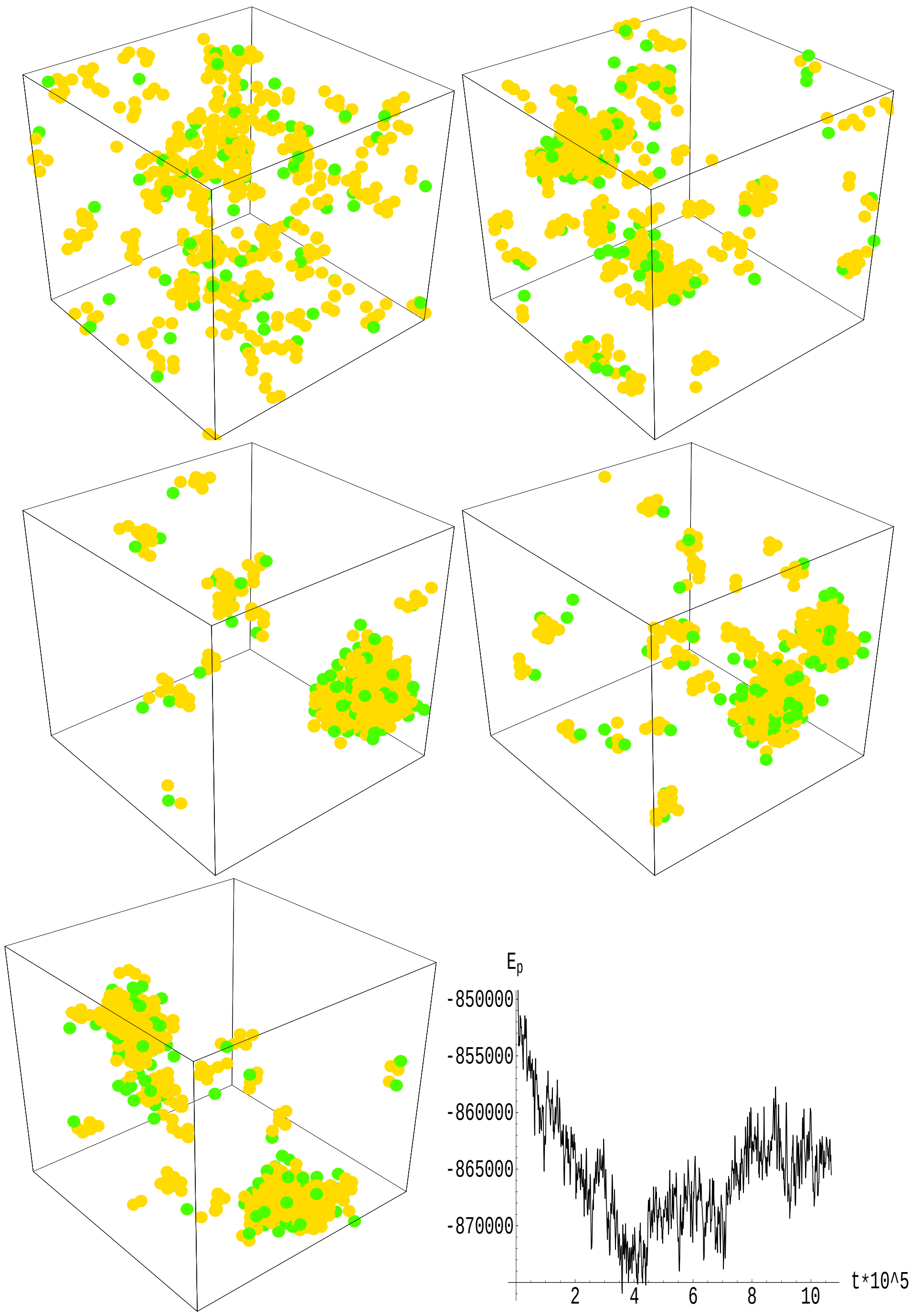

Fig. 4: Micellation process of amphiphilic polymers (hydrophilic head groups shown in green, and hydrophobic tail groups show in yellow) in water (not shown). The time (measured in simulation time steps) at the snapshots are, from upper left to lower right: $0, 120000, 428000, 474000, 675000$. The graph shows the fluctuations of total potential energy of the system as the micelle structures are formed. Note the long relaxation time before a single large micelle is formed, $t = 428000$, as well as the long time correlations (the system does not form a single micelle again after the thermal fluctuation that split the aggregate $t = 474000$). The last snapshot shows how the two micelles formed after the split move by diffusion over the lattice. The global potential energy shows that a single micelle is the energetically preferred state. The energetic advantage is balanced by counteracting thermal fluctuations, resulting in a an equilibrium of growing, dividing and merging micelles.

but the MD lattice gas is well suited for e.g., parallel implementation (development of a parallel version of the code is in progress). We also plan to use the simulation for studying membrane stability and the interaction between a membrane and other macromolecules, e.g., PNA molecules.

A weakness of the framework presented here is that, even though the translational movements (momentum) are relatively realistic, the implementation of the rotations is not. In principle, it is relatively straight forward to add angular momentum to the the state of each molecule. The collision rules can readily be generalized to exchange of angular momentum, and the rotations be driven by the torque rather than minimization of local potential energy. This scheme has indeed been implemented, but it has not been successful. When angular momentum is included, the total energy of the system tends to diverge. We believe that this is an effect of the lattice geometry. Due to limitations of the lattice, rotations must be discrete, quantified into $\frac{\pi}{2}$ steps. The dynamics of the MD lattice gas can be viewed as a discrete integration of the equations of motion. There is in general no guarantee that the discretization is stable, and instabilities such as divergence of energy is not unexpected (it could perhaps even be argued that the stability of the translational component of the kinetic energy is surprising). One possible way to circumvent this problem could be to force the temperature (kinetic energy) to stay constant by connecting the system to a heat bath. From a statistical mechanics perspective the system would then obey the canonical ensemble, instead of the micro canonical ensemble as is the case in the current version. Additional benefits of a connection to a heat bath is that many thermodynamic properties are easier to derive explicitly in this case, e.g., the entropy.

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