# Cellular Dynamics in a 3D Molecular Dynamics System with Chemistry

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**Abstract**

We present a three-dimensional model of the formation of simple protocellular structures. The model is based on an earlier lattice artificial chemistry due to Ono and Ikegami which consisted of a primitive metabolic system built on an artificial chemistry. This model computed the interactions of simple amphiphilic molecules which organized into membrane-like structures. The current model, however, treats space as continuous rather than a lattice. Moreover, although forces between atoms are computed in a more realistic manner, an adaptive method of computing intermolecular forces allows for efficient computation.

## Introduction

A number of simple reaction-diffusion systems have been shown to exhibit self-organizing and self-reproducing patterns, without requiring any detailed structures to support these processes(Turing, 1953; Pearson, 1993). However, these patterns do not permit any significant individuality and such systems seem too simple to be useful models of early pre-cellular structures. In an attempt to distinguish biological cells from simple, driven, dissipative devices, Varela and Maturana (Varela et al., 1974) highlighted one essential feature of living systems - "autopoiesis", the ability for a cell to produce and maintain its own boundary. In the spirit of their work, there have been more recent studies into the organization and maintenance of protocellular structures in computational models (McMullin and Varela, 1997; Breyer et al., 1998). In (Edwards et al., 1998) a simple model of the self-assembly of two-component lipids (similar to those considered here) is described. In contrast to these more abstract models, several realistic models of the molecular dynamics of amphiphilic lipid self-assembly have been studied, corresponding well to experiment (Marrink et al., 2000). Mayer and Rasmussen have studied the dynamics of micellar self-reproduction using a modified lattice gas technique (Mayer and Rasmussen, 2000). We note that the present work is inspired by some previous studies by Ono (see e.g. the third chapter of (Ono, 2001)). A primary distinction between these and the present work is that we place abstract models of protocellular chemistry in an accurate molecular dynamics framework, comparable to the popular AMBER (Pearlman, 1995) and NAMD (Skeel, 1999) packages. In a previous attempt to bridge the realism gap between highly abstract and highly accurate models, we presented a three-dimensional version (Madina et al., 2003) of "Lattice Artificial Chemistry" (LAC) (Ono and Ikegami, 1999; Ono and Ikegami, 2001). LAC simulates both simple repulsive forces and chemical reactions between abstract molecules using a simple lattice method. In the 2D version of LAC, spontaneous emergence of cellular structures, maintenance and self-reproduction of cellular structures, and evolution of metabolic systems through cellular selection were observed. In the 3D version of LAC, a much richer variety of cellular morphologies was observed, while preserving many of the qualtitative features of the 2D version. As a small step towards to studying the way in which cell membranes are not merely passive vehicles which delimit chemical networks, but instead more actively affect the chemical reactions which occur within them, we attempt to study more realistic membranes while maintaining an abstract, efficiently computable representation of cell metabolics. Our present model, therefore, allows for selected molecular dynamics (such as the inter-lipid interactions of a protocellular membrane) to be computed with near-arbitrary accuracy, while at the same time allowing metabolic or other intracellular reaction pathways to be implemented more abstractly.

## The Model: A 3D Molecular Dynamics System with Chemistry

The present model is essentially a molecular dynamics system: various substances are represented as atoms, point particles with particular properties such as charge and mass, and which are bonded in particular ways. Atoms have continuously variable locations and velocities, and interact through various standard forces such as Coulomb ($r^2$) repulsion and Lennard-Jones ($r^6$ / $r^{12}$) attraction. The force field is given as:

$$F = \sum k_q \frac{q_i q_j}{r_{ij}} - \sum \left( k_{lj} \frac{A}{r^6} - \frac{B}{r^{12}} \right) + \sum k_{bond} (r_i - r_{rest})^2 + \sum k_{angle} (\theta_i - \theta_{rest})^2$$

Standard bond forces are also employed: bonds between

pairs of atoms are parameterised by a rest length and a force constant, while bonds between atom triplets employ a similar spring force which attempts to preserve bond angles. However, a key deviation of our model from standard molecular dynamics methods is that we also permit coarser, molecule/atom and molecule/molecule interactions in addition to ordinary atom/atom interactions, though these are defined in terms of the basic forces above. In particular, we additionally define a "hydrophobic" force which is a strong, Coulomb-like repulsive force between certain atoms tagged as hydrophobic (these comprise the hydrophobic half of our simplified lipids) and water molecules. We summarise the key differences between the present model and our previous work in the table below. In particular, a primary difference is that we no longer rely solely on repulsive diffusion forces. In addition, we no longer define an anisotropic potential function for pointlike membrane particles as in our previous work. In particular, we do not assign individual membrane particles an orientation. Instead, the present membrane *molecules* are free to move and change their orientation continuously. In other words, treat lipid particles and the remainder of the system equally. This allows the formation of more complex, self-organizing membrane bilayers. This is a key difference between the present work and the relatively unstructured membranes we have studied previously.

Our model contains a simple metabolic system as illustrated in Fig.1, below. We implement this as chemical reactions which spontaneously alter atoms and molecules. The following transitions may occur: Resource particles **X** are generally free to move through the system. If a pair of resource particles are seperated by a distance **r** which is similar to the natural (rest) bond length of lipid, they may "react" to form either an autocatalytic molecule (a bonded pair of autocatalytic particles **A** or a lipid molecule (a bonded pair of lipid particles **H** and **T**). The rate at at which these reactions may occur is proportional to both the distance **r** between resource particles and the local density of autocatalyst molecules. In this way, autocatalyst molecules catalyze both their own reproduction and the production of lipid (membrane) molecules. The rate of production of these molecules is bounded as this process consumes resource particles **X** which are in limited supply. Both autocatalytic and lipid molecules continually decay into nonbonded pairs of waste particles **Y**. Finally, the main driving force in the model is an externally imposed "recycling" which continuously transforms waste particles back into resource particles at a fixed rate.

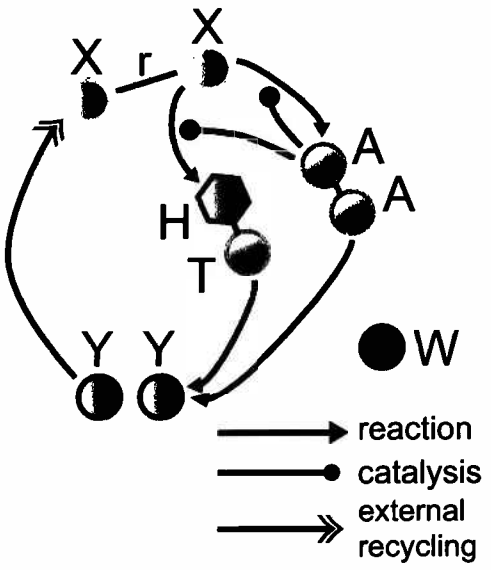


Figure 1: The simple metabolic system of the present model.

## Implementation

We use a somewhat unconventional implementation of molecular dynamics which we describe here. The dynamics of the system is evaluated over time which increases in relatively large, discrete intervals which are not generally of the same size. This serves two main purposes. Firstly, it allows periods of relatively uninteresting dynamics to be processed more quickly. Periodically, the system is evaluated with both high and low and precision integrators. If the difference in the dynamics (specifically, total system energy) is greater than a certain threshold (typically around 0.1%), the results of the low precision integrations are discarded. Secondly, stepping through time in this manner allows the system to adaptively cope with the occasionally significant perturbations caused by the chemistry in our model, i.e. the instantaneous transformation of atom types and formation and removal of bonds between atoms. Note that while the reaction pathways presented here conserve the total number of atoms in the system, this need not be the case, and it is possible to explicity include flows of matter into or out of the system. We also use a multi-level integration scheme: strong bonding forces which operate on short timescales and are susceptible to ringing are integrated on timescales approximately one order of magnitude smaller than weaker, inter-molecular forces which contribute periodic "impulses" to the integration of forces in the system. Further, a "rip-up and try again" scheme is implemented such that localised increases in system energy above a certain threshold are assumed to be integration errors. When such errors are detected, the system state is rolled back and integration is reattempted using a shorter timestep. We note that this addition is primarily of use when our "chemistry", the instantaneous modification of atoms and/or bonds between them occurs. This leads to localised perturbations which would otherwise lead to fatal instabilities in the molecular dynamics. Finally, we employ a novel multigrid summation scheme where multi-molecule structures (primarily pairs and triplets of water molecules)

| Feature | 2D LAC | 3D LAC | Present Model |
|---|---|---|---|
| Basic Element | Particle | Particle | Atom |
| Space | Hexagonal Lattice | Face-Centered Cubic Lattice | Continuous 3D |
| Time | Discrete, Constant | Discrete, Constant | Discrete, Variable |
| Forces | Repulsive | Repulsive | Attractive and Repulsive |
| Metabolism | Complex, Multiple Catalysts | Single-Catalyst | Single-Catalyst |
| Membrane Particles | Single | Single | Pair |
| Membrane Structure | Monolayer | Monolayer | Monolayer and Bilayer |

Table 1: A summary of the key differences between the present work and its predecessors.

have their dynamics approximated by simpler proxy pseudo-molecules. These proxies may be described statically or determined dynamically; details of the algorithm by which the latter occurs will be described elsewhere (Madina, 2004). This effects of this summation scheme are generally restricted to regions of bulk water, waste and resource particles, away from membrane and catalytic activity. If used appropriately, the effect on the total system dynamics is negligble. Nevertheless, there is a price to be paid for the approximations made in our model; over very long timescales, results from our model can deviate substantially from physically correct values since small errors which would ordinarily lead to obvious errors in traditional molecular dynamics schemes may be suppressed by the approximation schemes we adopt. Having said that, since we are studying a driven system which artificially couples dynamics with very different timescales, such drift is fairly insignificant.

Figure 3: Lipid molecules may spontaneously aggregate to form micelles and vesicles.

## Results

Our model reproduces a number of well known phenomena of lipid aggregation, as well as the essential features of our metabolic system and its artificial chemistry. In addition to the spontaneous formation of spherical micells and vesicles, other structures such as bilayer sheets and tubes may form. Despite the constant transformation of certain lipid particles into waste particles which behave very differently, the structures which form can remain stable for long periods of time, provided that there are sufficient resource and catalytic particles present in the region. Moreover, the model exhibits a sensitive dependence on initial conditions. For the results presented here, 10000 molecules were placed randomly in a cubic volume with periodic boundary. Approximately 80% of the molecules are water, resource, catalysts and waste a further 5%, and the remainder are lipid molecules. Simulations were performed on Intel Pentium 4 systems which computed approximately one iteration per minute; basic protocell formation could be observed after a few hours of computation. One such randomly generated initial condition led to the formation of a tube structure as shown in Fig.2. We believe that this is simply due to the initial conditions having a distribution of lipids molecules that is denser is a roughly tube-like region, which seeds the formation of the tube later on. This tube becomes axis-aligned as a result of its seeing its mirror image in the periodic boundary.

Another randomly generated starting point, with the same parameters, instead led to the formation of the robust lipid protocell illustrated in Fig.3. A small number of lipids which gathered into a micelle are also visible in the upper right, though this relatively unviable structure ultimately decays.

By manually generating an initial condition consisting of a lipid bilayer in a water bath that is rich in resources and catalysts, a sheet of lipid molecules can be sustained for a long period of time, as shown in Fig.4.

The structures observed in this model exhibit a high degree of resistance to externally applied perturbations. For example, defects introduced into a spherical protocell (such as spontaneously removing a section of its membrane particles) are quickly repaired, providing that the defect is not so large that the contents of the protocell diffuse into the environment before it has a chance to recover. This resilience is due to the fact that our model is a driven system: whereas a defect introduced into a standard molecular dynamics simulation of a lipid membrane may quite easily destroy the structure, our model involves a constant external supply of

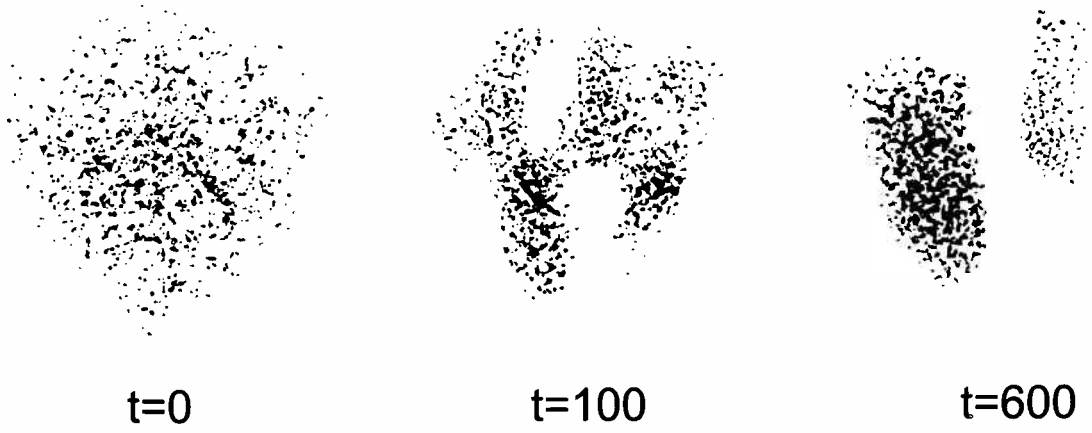


Figure 2: Random initial conditions may lead to stable structures such as tubes. Lipid molecules are nearby pairs of spots, while resources, catalysts are and water appear more faintly. Waste particles are not shown.

Figure 4: Bilayer sheets of lipid molecules are stable, provided there are sufficient resources in the surrounding water.

energy which is channeled by the metabolic system into the production of replacement membrane molecules and the repair of the membrane. There is an important relationship here: the metabolic system is only effective if the concentration of autocatalysts is sufficiently high, but the concentration of autocatalysts can only become sufficiently high if it is enclosed (at least partially) by membrane molecules.

## Discussion

We have presented a model which combines molecular dynamics and a simple "chemistry" to support the construction of simple metabolic systems which are contained by simple lipid membranes. From random initial configurations, we observed the emergence of different, protocell-like structures. These structures can exhibit a significant degree of homeostasis despite residing in a continually driven, non-equilibrium system. Varela and others have stressed the importance of "autopoiesis" as an essential feature of living organisms: structures such as a protocells should have the ability to create and maintain their own boundary. It is difficult to envisage a straightfoward molecular dynamics simulation of an autopoietic structure: while Varela's model was defined on a two dimensional lattice, in the real world, autopoietic structures are highly complex. While molecular dynamics can yield realistic and often quite accurate biophysical phenomena such as lipid aggregation and protein folding, these are almost trivial compared to autopoiesis. Both computational and conceptual difficulties alike would plague any attempt to construct an autopoietic structure in a molecular dynamics system. While we trust that these difficulties will eventually be overcome, we suggest the approach we have taken here - to equip standard molecular dynamics with an abstract, oracle-like chemistry, may be a possible way to shortcut these difficulties. Computation is made much simpler as the long timescales associated with real biological reaction pathways may be avoided, while the problem of engineering (let alone understanding) a biologically realistic autopoetic structure is reduced to the vastly smaller problem of designing a simple set of reaction pathways that can support autopoiesis more trivially. We note that while our model is rather simplistic, it does not necessarily have to be so. For example, the model may be made more simple by replacing the accurate TIP5 water model (Mahoney and Jorgensen, 2000) with a simpler 3-point or single-point model as in previous work. Or it may be made more complex by replacing the simple two-atom lipid molecules with more realistic phospholipids. The primary barrier to applying the present methods to highly realistic protocellular modelling

is implementing more detailed chemical pathways so that complex structures do not magically appear and disturb the system dynamics too greatly. Also, the increased computational cost of highly realistic models is also an important factor. Nevertheless, we feel that these difficulties are not insurmountable and that in the near future, it may be possible to synthesise a realistic protocell by adopting a hybrid molecular dynamics/chemistry model as presented here. Another advantage of the present model is that it permits cells to be somewhat more mobile than those in our previous work, where cells were fixed by rather strong potential forces, and each other. This is not to say that the cells we observe *do* move in any interesting sense - they simply repel each other and tend to relax into simple spatial configurations. Still, we wonder if it may be possible to add some source of cell motion to our model. Further, while only the simplest reaction pathways exist in the present model, we believe that it should be possible to implement more interesting chemistries which permits differentiation between cells, so that they may become a target of some simple evolution. This is one area of current work. Finally, we wonder if the range of membrane forms which may persist in the present model in spite of membrane decay may indicate that perhaps the shapes of the earliest proto-life forms may be significantly different from those of the living structures we observe today.

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