DPD Model of Foraminiferal Chamber Formation: Simulation of Actin Meshwork – Plasma Membrane Interactions

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Abstract. Foraminifera are unicellular organisms which are widespread especially in marine environments. They produce protective shells (called tests) around their cell bodies, and these may be hardened by either secreted $CaCO_3$ or by the agglutination of sediment grains from the environment. Such mineralized shells readily fossilize, which makes them useful in paleo/environmental and related geological applications. The morphology of foraminiferal chambers emerges from a cascade of complex genetically-controlled processes ultimately controlled through the interactions among morphogenetic components. From studies on the morphogenesis and movements of foraminiferan pseudopodia, we presume that actin meshwork, microtubules, plasma membrane and their various associated proteins all contribute to chamber formation. Here, we apply dissipative particle dynamics (DPD) simulation techniques to model interactions between the plasma membrane and actin meshwork to test their role in the formation of cell body and test architecture. The present studies mark the first stage of "in silico" experiments aimed at developing an emergent model of foraminiferal chamber formation and shell morphogenesis.

Keywords: foraminifera, dissipative particle dynamics, cell physiology, complex fluids.

1 Introduction

Computer modeling can be a powerful approach to achieve a better understanding of complex dynamic systems. Building a computer model of any phenomenon requires in-depth analyses of all involved processes and serves as a virtual laboratory for experiments testing the effects of varying the magnitude of those

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processes on the emergent properties of the complex system. The strength of modeling is that it provides predicted observation of simulated processes that otherwise are out of spatial and/or temporal scales for any direct examination.

Following this approach, we have applied the dissipative particle dynamics (DPD) method ([1], [2], [3]) to simulate foraminiferal shell morphogenesis. Processes that "shape" foraminiferal shells are most likely similar in every cell in living organisms. The novelty of our approach is to gather selected components and phenomena into one computational framework. Our aim is to build a virtual tool that can give insight into processes that control the shapes of newly formed foraminiferal chambers.

Foraminifera are a familiar group of unicellular eukaryotic organisms (kingdom Protista) distributed worldwide mostly in marine and brackish habitats, although freshwater species are known to exist. These organisms produce protective shells (properly called "tests" because they are sometimes vested by protoplasm) to protect their relatively large and sensitive cell body and its nucleus. While much of the structural template for the test consists of organic material produced and fashioned by the cells, various taxonomic groups further fortify and harden the test with agglutinated mineral grains selected from the sediment, or by secreted $CaCO_3$. These mineralized shells are long lived and readily fossilize. As a result, foraminifera have left an impressive fossil record that shows very specific distributions of forms in both time and space that make them perfect targets for micropalaeontologic, biostratigraphic, paleoecologic, paleoceanographic, and paleoclimatologic studies (e.g. [4], [5]).

The shells of living and fossil foraminifera display a variety of test shapes and patterns (Fig. 1). They grow by iterative, successive formation of chambers attached to an embryonic shell, called the proloculus. The theoretical morphology of foraminiferal shells has been studied for more than 40 years ([6], [7], [8]), using models that construct the theoretical morphospace employing geometrical operations parameterized by ratios of translation and rotations. However, to date such models have not been able to simulate shells that reveal complex growth patterns, e.g., switching from one coiling mode to another during their virtual ontogenesis. Topa and Tyszka ([9], [10], [11]) demonstrated that the limited capacities of these models were a result of neglecting the role of the aperture in the process of chamber formation. The moving reference model [10] uses the aperture as a reference point with respect to which a new chamber is located (see Fig. 1). This assumption comes from the fact that the aperture (or multiple apertures) are shell openings responsible for communication between an internal cell body and external microhabitat explored by pseudopodial extensions called granuloreticulopodia ([5], [12], [13]). The same apertures define the initial position of successive chambers during shell growth.

Recent investigations aim at constructing a new emergent model of chamber formation (see [10]). Shapes of foraminiferal chambers emerge from the cascade of complex morphogenetic processes, basically controlled by genetic information. A new chamber follows a shape of the primary organic membrane ([14], [18]), and we presume that the primary organic membrane is shaped by cytoskeletal

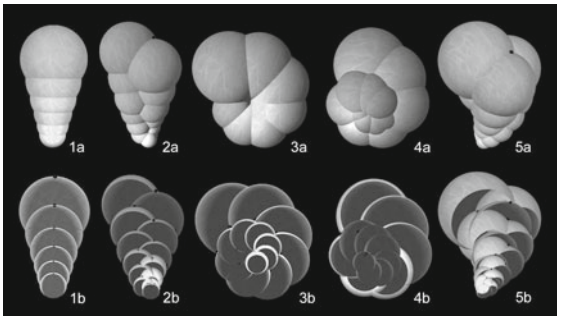

Fig. 1. Simulation of foraminiferal shells applying the moving reference model. Black dots represent foraminiferal apertures. Upper row presents external views of shells. Lower row shows cross-sections of these shells, showing their internal architecture. 1. uniserial chamber arrangement; 2: biserial; 3: planispiral; 4: low trochospiral (low helicoidal); 5: triserial high trochospiral. Such real shells range from 0.05 to 2 mm. Some complex foraminifera are much larger and reach up to several centimeters.

filaments and their associated motors and cross-linking proteins [15]. To gain insight into chamber morphogenesis, we need a technique that enables us to model the interactions between components responsible for cell architecture, such as a plasma membrane, sub-membrane actin filament meshwork, microtubules, and various associated proteins (e.g. [16], [17], [15]). The plasma membrane and its associated cytoplasm and extracellular domains can be classified as a complex fluid composed of liquid and suspended solid structures, making it amenable for study by Dissipative Particle Dynamics, one of the computer modeling methods frequently employed to study such fluids ([1], [2], [3]).

The DPD model consists of a set of particles that move off-lattice interacting with each other through the three type of forces: repulsive conservative force, dissipative force and stochastic force [1]. From a physical point of view, each particle can be regarded not as a single molecule but rather as a cluster of molecules. One of the most attractive features of the DPD technique is its enormous versatility in constructing simple models of complex fluids. For example, a simple Newtonian fluid can be made "complex" by adding additional interactions between fluid particles. Different particle-particle interactions can be introduced to model various other types of fluids. Polymers may be modeled as chains of molecules linked by springs.

The DPD method was applied to model selected phenomena associated with biological cells and tissues, as well as their components, such as plasma membranes, which can be approximated as complex fluids. For example, Basan et al. [19] proposed a DPD model for investigating the properties of tissue. Cells in this model were represented by DPD particles that adhere to each other, expand in volume, divide after reaching a specific size checkpoint, and undergo apoptosis at a constant rate, which ultimately leads to a steady-state homeostatic pressure in the tissue. Blood cells and the properties of blood flow have also been

investigated using the DPD approach. Fedosov [21] modeled the behavior of red blood cell membranes, and Filipovic at al. [22] investigated various blood flow properties. Similarly, Boryczko and Dzwinel [23] tested the application of DPD to model blood flow in capillaries. Other investigations have been devoted to modeling of the cell membrane - lipid bilayer. Lipowsky et al. intensively studied the properties of lipid bilayers with various particles based on computational methods, including DPD ([24], [25], [20]). In their models, the lipid bilayer was formed from short chains of DPD particles; each chain consisted of hydrophilic "head" particles and hydrophobic "tail" particles. These chains self-organized into well-ordered bilayer structures due to strong repulsion parameters between water and hydrophobic particles. This approach was used in other models that investigated various properties of lipid bilayers and its behavior under various conditions ([26], [27], [28]).

Here, we present a preliminary DPD model of interactions between the actin meshwork, plasma membrane, and a solid wall as a part of processes most likely happening during foraminiferal chamber formation. The ultimate goal is to obtain a realistic model of the primary organic membrane shaped by pseudopodial cytoskeleton structures, such as an actin meshwork and microtubules.

2 Model

The DPD method was introduced to simulate the hydrodynamic behavior of complex fluids [1]. The elementary units of the DPD model are soft particles with mass m_0 and radius of interaction r_0. Their evolution is governed by Newton's equations of motion:

$$\frac{d\mathbf{r}_i}{dt} = \mathbf{v}_i, m_i \frac{d\mathbf{v}_i}{dt} = \mathbf{f}_i. \tag{1}$$

The force $\mathbf{f}_i$ acting on a particle is given by the sum of a conservative force, a dissipative force and a random force [2]:

$$\mathbf{f}_i = \sum_{j \neq i} (\mathbf{F}_{ij}^C + \mathbf{F}_{ij}^D + \mathbf{F}_{ij}^R) \tag{2}$$

A particle i interacts only with other particles j located at a distance less than a certain cutoff radius r_c.

The conservative force $\mathbf{F}_{ij}^C$ acts as soft repulsion force along the line of centers and it is defined as [2]:

$$\mathbf{F}_{ij}^C = a_{ij}(1 - \frac{|\mathbf{r}_{ij}|}{r_0})\hat{\mathbf{r}}_{ij} \tag{3}$$

where:

- a_{ij} is the maximum repulsion force between particle i and particle j,
- r_0 is the diameter of DPD particles,
- $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$,
- $\hat{\mathbf{r}}_{ij} = \frac{\mathbf{r}_{ij}}{|\mathbf{r}_{ij}|}$.

The dissipative force $\mathbf{F}_{ij}^D$ [2] removes energy from the system by decreasing the velocity if the two particles in relation to each other. The force does not affect particles that either move parallel to each other or overlap. By slowing down fast moving particles, the dissipative force makes the system more controllable and predictable.

$$\mathbf{F}_{ij}^D = -\gamma_{ij}(1 - \frac{|\mathbf{r}_{ij}|}{r_0})^2(\hat{\mathbf{r}}_{ij}\mathbf{v}_{ij})\hat{\mathbf{r}}_{ij} \tag{4}$$

where:

– γ_{ij} — friction coefficient that scales dissipative force.

The random force compensates for the loss of kinetic energy due to the dissipative force. It provides for the random motion of particles [2]:

$$\mathbf{F}_{ij}^R = \sqrt{2\gamma_{ij}k_BT}(1 - \frac{|\mathbf{r}_{ij}|}{r_0})\xi_{ij}\hat{\mathbf{r}}_{ij} \tag{5}$$

where:

– ξ_{ij} — a random variable with zero mean and unit variance,
– k_B — Boltzmann's constant,
– T — desired equilibrium temperature on the system in Kelvin.

In the DPD method, the particle radius r_c defines the length scales for the simulation. We assume that a single particle represents a volume equal to 3 water molecules [26]. Thus, the r_c is approximately equal to $0.7nm$. All other dimensions in our model are related to r_0, and later in the text, these values are expressed in r_0 units. Density of these particles are set to 3 per unit volume ($\rho r_c^3 = 3$). The time scale is much more difficult to evaluate in DPD. Usually it is individually calculated from other parameters as a diffusion rate [26] or thermal velocity [29].

Our model focuses on the influence of an underlying actin meshwork on plasma membrane behavior. At this stage the model is significantly simplified. The system consists of a partly opened box made of wall particles that cannot move (see Figure 2) and acts as a kind of "virtual shell". The box and space above is filled with liquid particles and actin filament - polymer chains. One of the walls of the box is made of a flexible membrane, which models the plasma membrane of a newly formed chamber. The membrane is made of particles that initially are organized in a regular mesh (see Figure 3B). Each membrane particle is connected with its four neighbors via discrete spring potentials, with connections that remain unchanged during the simulation. Additionally the bond angle potential is defined for every three membrane particles that form a straight line. These connections also remain unchanged during the simulation. The membrane sheet is attached to the hard walls also by spring potentials but with different k_1 parameters. All other types of particles interact with walls by applying the conservative repulsion force.

In this model, several types of particles are introduced (see Fig. 2):

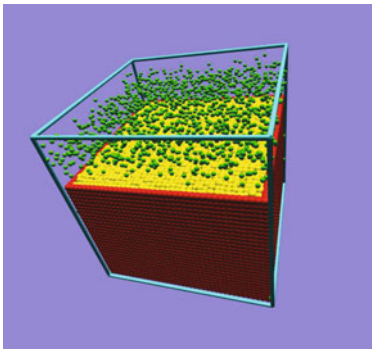

Fig. 2. System configuration tested during model development

- fluid (water) particles (F — vizualized with green color)
- actin particles (A — grey)
- membrane particles (M — yellow)
- wall particles (W — red)

The actin meshwork is composed of particle chains (see Figure 3A). Between neighboring particles in chains additional spring force is defined (see Figure 3C):

$$F_{ij}^{S} = -k_1(\mathbf{r}_{ij} - \mathbf{r}_0) \tag{6}$$

where:

- k_1 is the spring constant (as in Hook's law),
- $\mathbf{r}_0$ is the unstretched length between two neighbouring particles in chain.

In order to prevent chains from excessive bending we define an additional three-particle potential that straightens chains of particles, which follows the concept of bond angle potential introduced by Shilcock and Lipowsky [24] (see Figure 3 D).

$$U_B(i-1, i, i+1) = k_2(1 - cos(\phi - \phi_0)) \tag{7}$$

Various properties of particles in the model are defined through the conservative repulsion parameter a_{ij}. For water particles, we used a standard value of 25 (in units of $\frac{k_B T}{r_0}$) (following [3]). Actin particles repulse each other with a conservative force of the same value as the repulsive parameter $a_{ij}^{AA} = 25$. The spring constant k_1^A for chains of actin particles is set to 200, and the bending potential parameter k_2^A is set to 20. Membrane particles also interact each other with the repulsive parameter $a_{ij}^{MM} = 25$. Spring and bending parameters are: $k_1^M = 100$ and $k_2^M = 20$. Membrane particles that are initially located on the edge of the mesh are connected to the walls with spring constant $k_1^{MW} = 200$.

Spring and bending potentials are responsible for shapes and structures of actin chains and the membrane. Mutual interactions between fluid, actin meshwork, plasma membrane, and walls of the "virtual" chamber are controlled

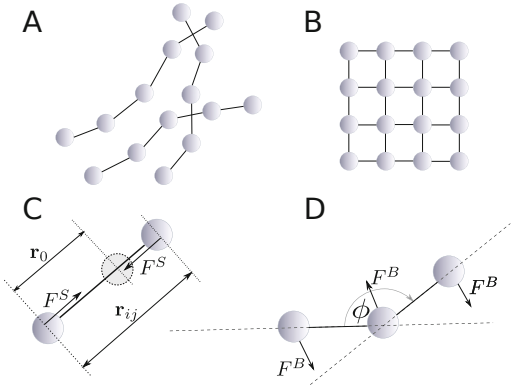

Fig. 3. Structures made of bounded particles and their potentialls: A) actin meshwork modeled as chains of particles, B) regular mesh of membrane particles, C) two-body spring potential, D) three-body angle potentiall

mainly by the repulsive conservative force parameter a. In our experiments we focus on analyzing the behavior of the virtual actin meshwork for different sets of repulsive force parameters:

- a^{AM} — interaction between actin particles and membrane particles,
- a^{AW} — interaction between actin particles and wall particles,
- a^{AF} — interaction between actin particles and fluid particles.

In all simulations, the step of integration is set to typical value $\delta t = 0.04$ that follows Groot and Warren [3] suggestions. The simulations involve about 40 000 particles. For integration of Newton's equation of motion we use Velocity Verlet scheme. The model was implemented in C++ language for Linux platform. Algorithms are parallelized with OpenMP API. Results are visualized with OpenGL library.

3 Results

Figure 4 presents sample results of our simulations. Fluid and wall particles are removed for clarity. Parameters of conservative force was set to the following values: Fig.4**A** $a^{AW} = 6, a^{AM} = 6, a^{AF} = 12$, Fig.4**B** — $a^{AW} = 12, a^{AM} = 6, a^{AF} = 12$. Actin filaments fill all available space and act on the membrane so as to deform it. In both cases, it can be observed that single actin filaments have penetrated through the membrane, due to fact that actin and membrane particles are "soft" particles that can interpenetrate. This effect can be controlled by modifying the conservative force parameter.

Figure 5 presents results of "in silico" experiments conducted on a model actin meshwork. Simulations were performed for different sets of the repulsive force parameter: Fig. 5A: $a^{AW} = 50, a^{AM} = 2, a^{AF} = 25$ and Fig. 5B:

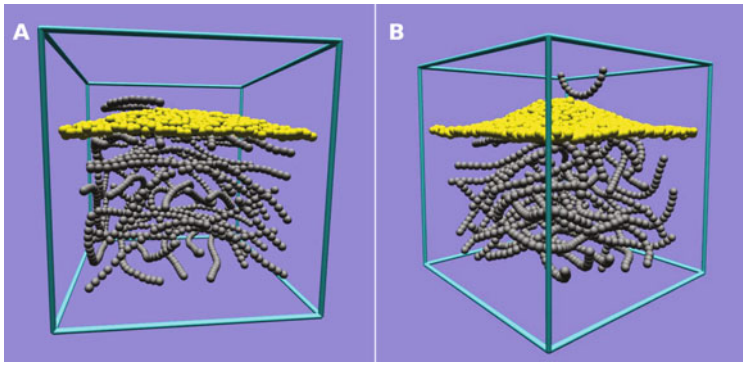

Fig. 4. Sample results of simulation with actin meshwork (grey) influencing membrane shape (yellow), see text for details

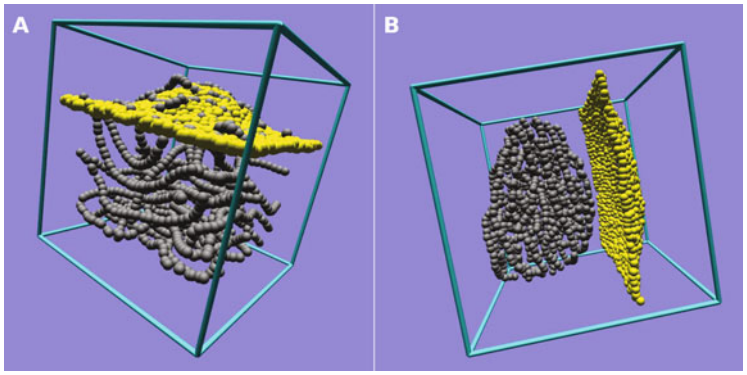

Fig. 5. Sample results of "in silico" experiments (see text for details)

$a^{AW} = 25, a^{AM} = 2, a^{AF} = 50$. We observed different behaviors of the actin meshwork and plasma membrane. Fig. 5A shows attachment of actin filaments to the membrane. The meshwork is also strongly repulsed from the walls. The simulation in Fig 5B shows a strong repulsion between actin and fluid particles compressing the meshwork into a globular tangle of filaments.

4 Conclusions

We present a preliminary version of our DPD model of foraminiferal chamber morphogenesis. Our model, at this stage of its development, focuses on simulating the actin filament meshwork. We represented it by a set of particle chains connected with two kind of potentials: spring and bending. Actin filaments

interact with the membrane which is made of particles also connected with spring and bending potentials. We are searching for proper behavior of the modeled system by modifying parameters of the conservative force. Our future works will focus on:

- improving the membrane model by incorporating the lipid bilayer model defined by Lipovsky et al. [24];
- introducing microtubules as a main morphogenetic component;
- modeling mechanical properties of membrane in contact with microtubules.

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