

Spatial Simulation of Actin Filament Dynamics on Structured Surfaces

Arne T. Bittig
Adelinde M. Uhrmacher

Institute of Computer Science
University of Rostock
Albert-Einstein-Str. 22
Rostock, 18059, GERMANY

Claudia Matschegewski
J. Barbara Nebe

Dept. of Cell Biology
University Medical Center Rostock
Schillingallee 69
Rostock, 18057, GERMANY

ABSTRACT

We develop a simple model of actin filament growth in bone cells comprising integrin receptors, actin molecules able to form chains and cofilin molecules destroying chains. The model is expressed in the ML-Space modeling language and simulated using a particle-based approach. We find the model to be a promising starting point in reproducing *in silico* experimentally observed filament growth behavior of bone cells on different surface structures.

MOTIVATION, MODEL, AND DISCUSSION

Bone cells growing on titanium surfaces with regular geometry show significantly different emerging actin filament patterns (Matschegewski et al. 2012). However, the concentrations of key players in central signaling pathways like mitogen-activated protein (MAP)-kinase etc. do not differ much. By exploiting a modeling and simulation approach we investigate whether this can be explained based on biochemical reactions within the cell and between the cell and the extracellular matrix and the respective topology of the surface. The model being developed integrates information from existing cytoskeletal filament models, (e.g. Roland et al. 2008), comprising actin filament growth and a depolymerizing factor, with reactions at the membrane of the cell. Still it is a rather simplistic model. The modeling language used is ML-Space (Bittig et al. 2011), which supports an attributed, rule-based modeling approach and the combination of (mesoscopic) reaction-diffusion systems and (microscopic) particle based spatial simulation. Currently, our actin filament model is purely particle based.

An ML-Space model consists of constants/rate definitions, species definitions (containing common attributes like shape and movement properties of the different kinds of entities in the model) and initial state description, which we omit here, as well as reaction rules. An important distinction here is between collision- and time-triggered rules. In the former (recognizable here by two entities on the left hand side, or two entities inside a given other entity), the reaction rate is to be interpreted as probability of the reaction happening once the collision has already occurred. The latter type of rule refers to first-order reactions, where the rate shall be interpreted as with other (non-spatial) stochastic simulations.

One of the key players of modeling actin filament growth on different surfaces is the integrin receptor complex. In the model, it also takes the role of sensing the contact of the cell with a surface structure and serves as seed for the filaments. Then there are actin monomers which can bind to an integrin complex on a surface structure (first rule) or an already bound actin (anywhere; second rule) and become immobile in the process. Finally, cofilin is a depolymerizing agent, destroying actin filaments (third rule) when it is in active state (unusually, this is when the actual biological molecule is *not* phosphorylated) and being deactivated when "colliding" with an integrin complex (rule four). The reactivation of cofilin is the only example of a time-triggered rule here, as it does not depend on any other entity in the model. In addition, the surface structures (pillars in the micrometer dimension) itself are also model entities, into and out of

which the other kinds of entities can freely diffuse (rules not shown). Unlike the others, pillar are always immobile. In the initial simulation state, no molecule is bound to any other.

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1 Pillar() [Actin() <pointed:free> + Integrin() <bs:free>] ->
    Pillar() [Actin(diffusion:0) <pointed:bind> + Integrin(diffusion:0) <bs:bind>] @ pInit
2 Actin() <pointed:free> + Actin() <pointed:occupied,barbed:free> ->
    Actin(diffusion:0) <pointed:bind> + Actin() <barbed:bind> @ pFilBind
3 Cofilin(active:yes) + Actin() <pointed:occupied> ->
    Cofilin() + Actin(diffusion:actinDiff) <pointed:free> @ pActRelease
4 Pillar() [Integrin() + Cofilin(active:yes)] ->
    Pillar() [Integrin() + Cofilin(active:no)] @ pCofDeact
5 Cofilin(active:no) -> Cofilin(active:yes) @ rCofReact

```

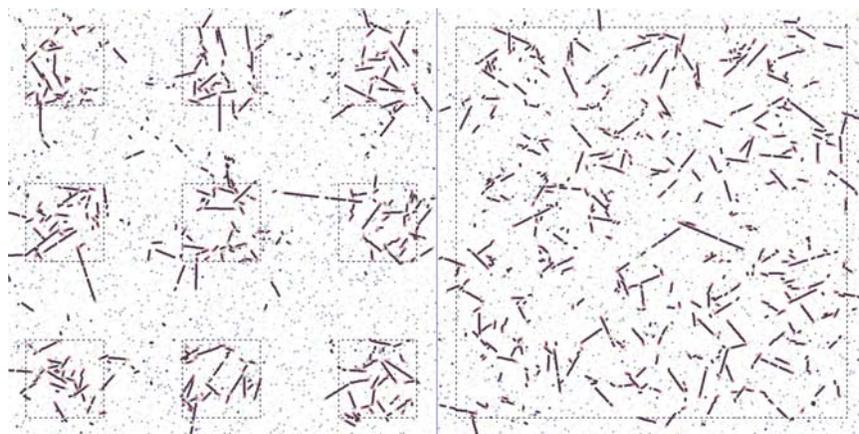


Figure 1: Results with pillared structure (left) and flat surface (modelled as one large pillar; right). Note the few filaments (actin chains; black except for the red initial integrin and the light brown barbed end actin) in non-pillar areas. Simulation was run until the amount of free actin (light blue) was roughly constant. Overall, filaments are still relatively short.

Our first simulation results clearly show the influence of the topology on the development of actin filaments, and seem to underline the importance of cofilin in this process. However, still the parameters need to be investigated more closely. This refers to the size, diffusion and reaction rates, and initial concentrations of the entities. Therefore, more simulation studies are required. In addition, as the current model is rather simplistic, considering further key players of the biochemical and filament growth processes is highly required. For more realistic results, we will add the branching of filaments by Arp2/3, investigate different forms of actin, the relevance of capping, and the need to include Src as intermediate step between integrin and cofilin deactivation. Last but not least the model shall be validated based on wet-lab data.

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