Scaling of the active transport systems in oocyte: 3D agent-based simulations

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Historically our understanding of the cellular active transportation mechanisms was and still is mainly descriptive. That is, microtubules (MT) form in a cell a bundle between cellular sites A and B, site A has an abundance of cargo C, while site B needs C. Then motor proteins specifically attach C, bind to the MTs and transport the cargo by walking unidirectionally along microtubule tracks (hydrolysing one molecule of ATP at each step). Particularly, such transport systems operate during oogenesis and zygote development (Fig.1), and a Drosophila oocyte is one of the main model objects for this study (Fig.1A). In case of developing objects, we know or expect that the transport systems must be very precise. The time, amount and site locations should be very precise to provide robust molecular basis for following early embryo development. However, all the components of the transport system can vary because of internal noise and external perturbations, including gene dosage and physical dimensions and form of oocyte. Hence, we should expect that the transport system is able to keep its functioning robustly and adjustably to ensure the robustness of the following early embryogenesis. However, the robustness and scalability of such transport systems are still poorly understood. In this report, we investigate the expected mechanisms of making the non-scalable active transportation system, like the one in Fig.1, scalable. We will do it by means of the 3D agent-based simulations.

Our approach: In this project, we use our extension of software Skeledyne worked out by Odell and Foe [2008] to develop 3D agent-based models of the cytoskeleton-based active transport systems for simulating the zygote behavior. Agent-based models are computational models simulating actions and interactions of autonomous agents (either individual molecules or collective molecular ensembles). The key notion on which the models are based is that

multiple agents interact according to simple rules.

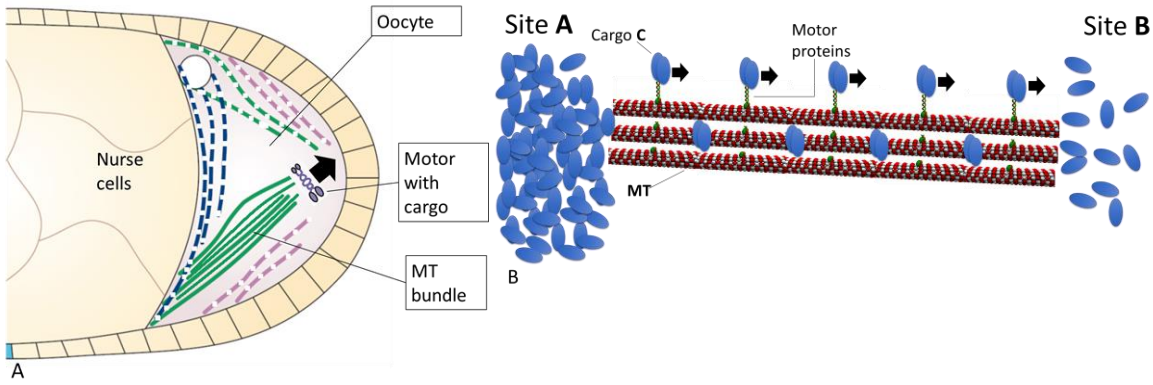

Figure 1. Arrangement of the cellular and molecular components for the active transport of some key mRNA by molecular motors via the oriented bundles of microtubules, MT (green, pink and blue). (A) Localization of some mRNAs along different populations of microtubules in the Drosophila melanogaster oocyte. Particularly, *oskar* mRNA might localize to the posterior by kinesin-dependent transport towards the plus ends of the microtubules nucleated from the anterior and lateral cortex [after St Johnston, 2005]. (B) Typical arrangement of the machinery for cellular active transport. MT form in a cell a bundle between cellular sites A and B. Site A has an abundance of cargo C, while site B needs C. Then, motor proteins specifically attach C, bind to the MTs and transport the cargo by walking unidirectionally along microtubule tracks.

Our extensions are mainly aimed at possibilities to develop models of Drosophila oocyte-early zygote. We study a rather simple active transport system (Fig.2) reminiscent of some crucial transportation systems in developing Drosophila oocyte (Fig.1). Namely, we implemented the following transportation system based on local bundles of oriented MTs and motor proteins with cargo molecules, as illustrated by Fig.2. The oriented bundles connect the cortex with the inside, core part of a cell. MTs organized in bundles are stable during the time-window of the computational experiments. The cargo-molecules (C) are initially scattered through the whole volume of the cell. The action of the transport system soon causes the local accumulation of the cargo (with the motors) in the core part of the cell. This site is steady and the system is able to keep it, at least, during the experiment duration. In the tests we were interested to detect what minimal preconditions and adjustments are necessary

to reproduce the behavior of the transportation system if we change the cell size.

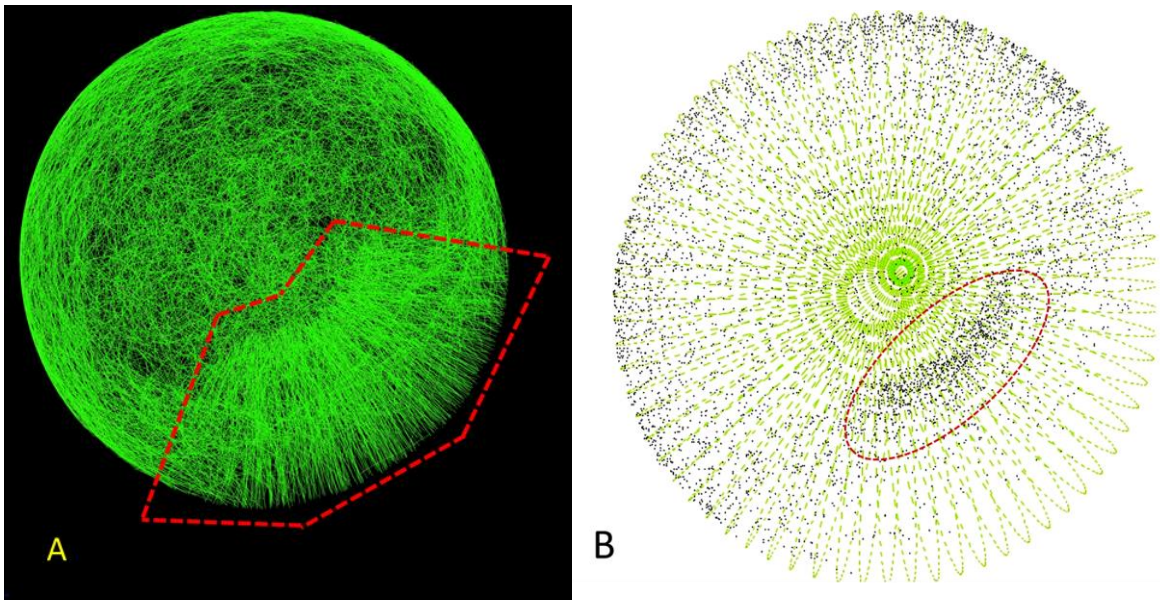

Figure 2. Our implementation of active cell transport system based on molecular motors and microtubules (MT). (A) The steady organization of the MT (green) in peripheral layers of cytoplasm: the oriented bundles of MT, connecting cortex to core plasm are outlined by red dotted line. In the rest of the peripheral cytoplasm MTs are not oriented. (B) With time, the oriented MT bundles by means of steady transport of the cargo molecules C accumulate C locally in the deeper part of the cell (the accumulation, C-cloud, is outlined by red dotted oval line). The accumulation is steady during the time-frame of the computational experiment. Cell contours are in light blue, soluble complexes of the kinesin molecules with cargo are black dots.

Results: Embryo size can vary in WT and from one Drosophila line to another. Early scaling of the mRNA patterning can be a result of a more effective mRNA transport for larger embryos (and vice versa: slower RNA transport for smaller embryos). The main problems we face if enlarge the cell in Fig.2, say, twice in radius are the following. We need the twice longer MTs in the oriented bundles. We need faster transportation of the cargo molecules if need to keep comparable time-scale for the both cases. Besides, we should distinguish the case when we have to keep the same concentration or the same amount of the cargo molecules in the C-cloud. Besides we should distinguish situations with the same and large amount of MTs and other components of the transport system.

Motor-based MT-transport is under control of negative and positive regulators. The

best-known negative regulators are kinases such as Par-1 and GSK-3. They can slow down transport by acting either on the motors (kinesins and dynein) or on the microtubule-associated proteins (destabilizing MTs or making them less smooth for motor movement). Some factors are supplied by nurse cells in proportion to oocyte volume (via feedback mechanisms), while other factors are accumulated by the oocyte in proportion to gene dosage (not oocyte volume). I.e., some factors are tuned by oocyte volume, others are not. Inhibitors (such as kinases) could be expected to be in the same absolute amounts in smaller and large embryos. But if so, concentrations in smaller and larger embryos would be different.

We tested the hypotheses by adjusting the speed and/or efficacy of our transport system when we change its scale (up to 2 times in linear dimension). It was found that we could achieve scalability via adjusting some parameters to the proportion of gene dosage, while the others in proportion to oocyte volume.

Conclusions: It was shown that the scaling property for bcd mRNA means the more effective mRNA transport for larger embryos (and slower transport for smaller embryos). Some factors (like bcd mRNA) are supplied by nurse cells in proportion to oocyte volume (via feedback mechanisms), while the other factors are accumulated by the oocyte in proportion to gene dosage (not oocyte volume). Particularly, the MT-transport inhibitors (like Par-1 & GSK-3 kinases) would be in the same absolute amounts in smaller and large embryos. But if so, concentrations in smaller and larger embryos will be different. This consideration could not only explain the gradient scaling in development but in evolution also.

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