

TRANSPORT OF FATTY ACIDS THROUGH MEMBRANES. Chenyu Wei¹ and Andrew Pohorille²,
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Introduction: Fatty acids not only are necessary nutrients to cells, serving as energy sources by generating ATP through metabolism and playing important roles in cellular functions, but also may play a role in the emergence of Darwinian evolution at the origin cellular level [1-5]. Various experimental evidences indicate that ancestors of cells were built of membranes simpler than phospholipid bilayers, most likely containing a considerable fraction of fatty acids [6-8]. Processes inducing competitive growth and subsequent division have been identified in such vesicles, such as by stressing vesicles osmotically with encapsulated replicator of nucleic acids [2], adsorption of small peptides generated inside vesicles [5], photochemically driven redox chemistry [4], or incorporation of a small amount of phospholipids into the vesicle membrane [3]. All vesicle-growth processes would involve adsorption of fatty acids from the environment and their subsequent translocation from the outer leaflet to the inner one. The translocation process is the main focus of this presentation.

Results and Discussion: Extensive molecular dynamics (MD) simulations up to the time scale of several microseconds are used to understand the transverse of a fatty acid molecule through a membrane [9]. The flip-flop rate is predicted at $0.2 - 0.3 \mu\text{s}^{-1}$ with a barrier of $\sim 4.2 \text{ kcal/mol}$ at the center of the membrane bilayer. A two-dimensional diffusion model shows that along the minimum energy path the fatty acid molecule undergoes gradual and correlated translational and rotational motion, when translocating through the membrane (as shown in Fig. 1). The fast rate lends support to a direct diffusive pathway proposed for uncharged forms of fatty acid molecules through membranes [10]. Such a route can be crucial in early cellular systems where no protein transporters were yet available. It also provides a path to fatty acid-mediated proton transfer through membranes, whereby the hydroxyl proton from a protonated fatty acid molecule in the outer leaflet is released to the cell interior following flip-flop to the inner leaflet. It has been shown that vesicle growth leads to spontaneous generation of transmembrane proton gradients most likely by proton transport through flip-flop of protonated fatty acids [11].

An important implication of the fast rate of flip-flop is that the rate-limiting step in the diffusive transport of fatty acids across membranes is most likely its desorp-

tion from the membrane into the interior of the cell, as suggested by Hamilton et al. [12] and later by Szostak et al. [3, 5] in their experiments on growth and division of model protocellular systems. MD simulations have also shown a similar fast flip-flop in fatty acid vesicles, which is further enhanced by adsorptions of small peptide, a favorable factor for vesicle growth in the presence of such molecules [13]. Delivery of fatty acid molecules in the form of micelles and adsorption onto cell or vesicle membrane will also be discussed.

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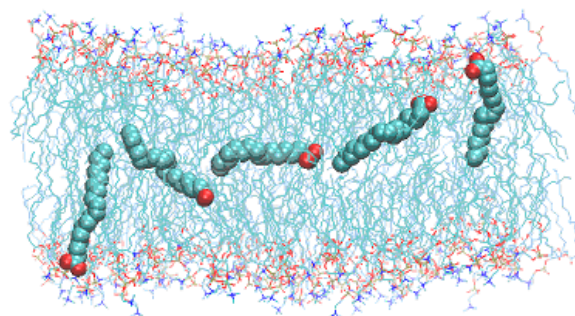


Fig. 1: An oleic acid molecule translocating through a POPC membrane with correlated translation along membrane normal direction and rotation motion.