SORBONNE UNIVERSITÉ

CHINA SCHOLARSHIP COUNCIL

Appel à projets
Campagne 2022
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Title of the research project :

Active membrane dynamics in the secretory pathway

Thesis supervisor (HDR) :

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Research Unit

Name : Physico-Chimie Curie
Code : UMR 168

Doctorate School

Thesis supervisor's doctorate school (candidate's futur doctoral school) : EDPIF - ED564

PhD student currently supervised by the thesis supervisor (number, year of the first inscription) :
One PhD, first year: 2019

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Description of the research project (*ENGLISH*)*:*

Summary of the Team's interests: Cell biology and soft matter physics both share similar orders of magnitude with two important differences: biological systems are clearly out of equilibrium and molecular specificity can be strongly relevant. We are using the tools of soft matter and statistical physics to provide a quantitative description of cellular systems, and with this analysis of biological systems, we are raising an interesting number of new and challenging physical questions. In collaboration with biologists, we mainly concentrate our efforts on understanding the physical features of intracellular organisation, and of the morphology, mechanics and of cells and tissues.

Summary of the proposed project: The secretory pathway is a foundational system used by all eukaryotic cells to distribute membrane and secretory proteins. Proteins synthesized in the endoplasmic reticulum (ER) are sorted and exported at ER exit sites (ERES) toward the Golgi apparatus, where additional sorting and protein processing occurs. This dynamics is orchestrated by coat protein complexes (COPII and COPI) able to polymerise into flexible protein scaffold to support membrane deformation and protein sorting. The classical view of ER to Golgi transport is that ER export membranes and proteins inside COPII coated spherical vesicles, while retrograde transport from Golgi to ER is occurs in COPI coated spherical vesicles. This view has recently been challenged by high resolution optical and electron microscopy studies [1,2] (see figure). These showed that ERES are highly intertwined and dynamical tubular networks continuous with the ER by a constricted neck where COPII proteins localize. Transport intermediates between the ERES and the Golgi are dynamical and pearled tubular membranes containing COPI. Proper ERES functioning requires the dynamical turnover of COPII component between the ER membrane and the cytosol, showing the importance of non-equilibrium processes.

- Building on these new observations, and on the recent interest of the cell biology and biophysics community on out-of-equilibrium phase separation with turnover [3], we will construct and analyze physical models of the ERES as resulting from active membrane flow driven by treadmilling of COPII proteins with the constricted connection between ER and ERES. This will involve a description of the out-of-equilibrium hydrodynamics of protein aggregation and a mechanical description of soft, deformable interfaces.

- In a second stage, we will study the dynamics of the tubular network emerging from the ERES, as resulting from the interplay between COPII driven influx of membrane and COPI driven budding off of ERES material [2]. During these two stages we will evaluate the ability of our model structures to perform protein sorting through the differential affinity of cargoes to either COPII or COPI components.

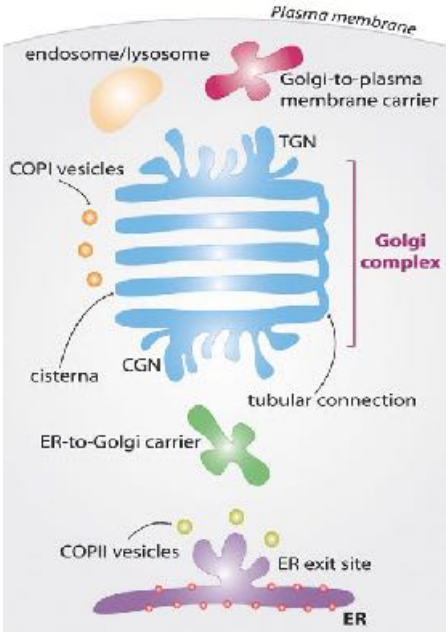
- In a third phase of the project, we will explore more general questions related to active tubular networks. Many cellular organelles, from the ER to mitochondria, form highly dynamical tubular networks maintained by active processes, which control the nucleation, elongation and branching of tubules [4]. We will aim at determining the global statistical properties of the tubular network, and in particular the possibility of coexistence between regions with high and low density of 3-way junctions in this network depend on cellular activity. In equilibrium systems, the usual way to approach such question is to derive a free energy and minimize it with respect to appropriate fields. This approach is inadequate for active systems, in which phase equilibrium can be derived by analyzing the entropy production in the system. We will follow this approach to obtain a phase diagram describing the range of parameters for which the clustering of 3-ways junction can be expected, and compare our results to experimental observations regarding the structural

[1] Uncoating of COPII from ER exit site membranes precedes cargo accumulation and membrane fission. O. Shomron *et al.* preprint. BioRxiv https://doi.org/10.1101/727107.

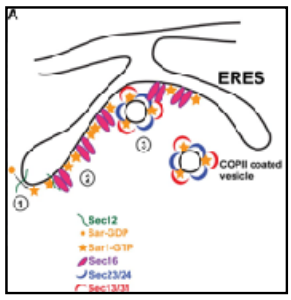
[2] ER-to-Golgi protein delivery through an interwoven tubular network extending from the ER. A.V. Weigel *et al.* Cell 184 (2021) 1

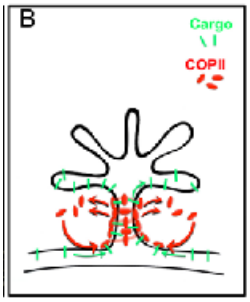
[3] Physics of active emulsions. C. A. Weber, D. Zwicker, F. Jülicher and C. F. Lee. Rep. Prog. Phys. 82 (2019) 064601

[4] Increased spatiotemporal resolution reveals highly dynamic dense tubular matrices in the peripheral ER. J. Nixon-Abell *et al.* Science 354 (2016) 433

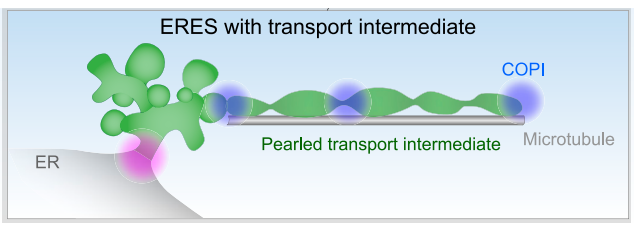


Secretory pathway - eukaryotic cells





ER exit sites: classical view **ER exit sites: alternative view** from [1]



Tubular transport intermediate from [2]

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Relevant publication from the team:

- Quentin Vagne, Jean-Patrick Vrel & P. Sens, eLife, 9 (2020) e47318: A Minimal Self-Organized model for the Golgi Apparatus
- Sami C. Al-Izzi, Pierre Sens & Matthew S. Turner, Phys. Rev. Lett. 125 (2020) 018101: Shear-driven instabilities of membrane tubes and Dynamin-induced scission
- Q. Vagne and P. Sens, Phys. Rev. Let. 120 (2018), 058102: Stochastic Model of Vesicular Sorting in Cellular Organelles
- S. Dmitrieff, M. Rao and P. Sens. PNAS. 110 (2013), 15692-15697: Quantitative analysis of intra-Golgi transport shows intercisternal exchange for all cargo

Keywords: out-of-equilibrium dynamics, phase separation, cellular organelles, biological membranes, tubular networks.

Profile of the candidate: The ideal candidate will be a physicists with proficiency in statistical physics and thermodynamics and with a strong motivation to work at the interface with biological science. Prior knowledge in soft condensed matter and complex systems will be an asset. Prior knowledge of cell biology is not required.