UMR 8640 PASTEUR, CNRS, Ecole Normale Supérieure, PSL University, Sorbonne University

PhD thesis proposal:
Theoretical characterization of single vesicular events in exocytosis in connection with oxidative stress and inflammation

Description. Vesicular exocytosis is a key biological mechanism through which cells communicate with each other or with their environment. For this purpose cells release messenger molecules stored in the vesicles into the extracellular space via the fusion pore formed when cellular and vesicular membranes begin to merge. Intimate involvement of exocytosis in many systems in our body (e.g. nervous, endocrine, digestive, etc.) make its understanding as well as its quantitative analysis a crucial problem for fundamental and biomedical research and healthcare, especially when considering that impaired exocytosis could be related to the onset of certain (e.g. neurodegenerative) diseases as well as being a target for drugs and for the development of new pharmaceuticals.

The aim of the project is to study theoretically vesicular exocytotic release of neurotransmitter by neurons and neuroendocrine cells on quantitative dynamic grounds. More precisely, the emphasis will be put on the very act of neurotransmitter release – the dimensions of fusion pore and its temporal dynamics with the intention to decipher by modelling a mode of release undertaken by a given vesicle. The time and space scales (milliseconds and nanometres, respectively) involved in exocytosis remain challenging for accurate experimental capturing of individual exocytotic events. The electrochemical activity of many neurotransmitters makes electrochemical methods adequate for exocytotic studies. Their oxidation fluxes permit quantification of the released amounts and offer invaluable and unrivalled kinetic information on exocytotic events at the single cell or synapse level especially when coupled with other techniques.

In particular, the effect of some naturally occurring molecules on neurotransmission in the neurons affected with Parkinson's disease will be investigated on the basis of the measurements performed with nanoelectrode inside a living synapse. The theoretical approach being developed will be based on previous elaborations made in the lab (e.g. references below) and strongly rely on experimental investigations performed within the framework of Laboratoire International Associé CNRS "NanoBioCatChem" and other internationally recognized collaborators.

The principal responsibilities of a successful candidate will thus be modelling of the neurotransmitter mass transport (within continuous level of description) inside the vesicles with the other relevant accompanying processes and further development of existing models;

experimental data treatment and analysis; solution of the inverse problem to reconstruct fusion pore size and its dynamics.

Requirements. We are looking for a highly motivated student with master 2 degree in a relevant discipline. The candidate should have theoretical background and interest in modelling of biological relevant phenomena within the framework of continuous level of description (see ref.3 below and references therein). Good knowledge of any programming language is an advantage. Strong motivation, good communication skills, bona fide, good ability to work with literature, good spoken and written English are assumed.

References

1. A. Larsson, S. Majdi, A. Oleinick, I. Svir, J. Dunevall, C. Amatore, A.G. Ewing. Intracellular Electrochemical Nanomeasurements Reveal that Exocytosis of Molecules at Living Neurons is Subquantal and Complex, *Angew. Chemie*, 59, **2020**, in press. DOI: 10.1002/anie.201914564.
2. L. Ren, A. Oleinick, I. Svir, C. Amatore, A. Ewing. Amperometric Measurements and Dynamic Models Reveal a Mechanism for How Zinc Alters Neurotransmitter Release, *Angew. Chemie*, 59, **2020**, in press. DOI: 10.1002/anie.201913184.
3. A. Oleinick, I. Svir, C. Amatore. "Full Fusion" is not Ineluctable during Vesicular Exocytosis of Neurotransmitters by Endocrine Cells. *Proc. Roy. Soc. A*, 473, **2017**, 20160684.
4. A. Oleinick, R. Hu, B. Ren, Z.Q. Tian, I. Svir, C. Amatore. New Theoretical Model of Neurotransmitter Release during in vivo Vesicular Exocytosis based on a Grainy Biphasic Nano-Structuration of Chromogranins within Dense Core Matrixes, *J. Electrochem. Soc.* 163, **2016**, H3014-H3024. DOI: 10.1149/2.0031604jes.
5. Y.-T. Li, S.-H. Zhang, X.-Y. Wang, X.-W. Zhang, A.I. Oleinick, I. Svir, C. Amatore, W.-H. Huang. Real-time monitoring of discrete synaptic release events and excitatory potentials within self-reconstructed neuro-muscular junctions. *Angew. Chemie* 54, **2015**, 9313-9318.

Info

Workplace location: Chemistry Department, Ecole Normale Superieure, 24 rue Lhomond, 75005 Paris.

Hosting team involves Alexander Oleinick (thesis supervisor), Irina Svir (CNRS Research Director) and Christian Amatore (Emeritus CNRS Research Director, member of Academy of Sciences).

Documents for selection process. (i) CV, max. 2 pages; (ii) motivation letter; (iii) diploma and transcript (score sheet); (iv) list of publications/conferences (if any); (v) letter(s) of recommendation or names and e-mails of one-two academic references.

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