PhD Research Proposal Form
China Scholarship Council (CSC)
2026

FIELD

CHEMISTRY

Thesis subject title: DNA self-assembling structures as dynamic architectures for synthetic cells: from self-organizing protocells to DNA-encoded morphogenesis

Name of the French doctoral school/Ecole doctorale:
ED388 : Chimie Physique et Chimie Analytique de Paris Centre

Name of the Research team/Equipe de recherche: SOFT
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Lab Language/ Langue de travail: English

Research Proposal Abstract/Présentation du sujet:

Living cells are fascinating self-assembled structures with remarkable properties including morphogenesis, shape adaptability, division/replication, motility, and capability to manage complex metabolic pathways. Developing artificial systems (referred to as "synthetic cells"), which can reproduce, mimic or approach some of these characteristics is currently a highly desired scientific challenge, either to decipher the fundamental mechanisms underlying these functions or to develop smart materials combining life-like properties with user customizability. Moreover, identifying how cell-like organization could emerge from an inert mixture (referred to as "protocells") is also an active research goal, especially with the objective to elucidate possible scenarios for the origin of life. The first objective of this PhD project is to contribute to this double quest by developing and studying novel synthetic self-assembly processes that could lead to cell-like assemblies and behaviours.

Structural DNA nanotechnology relies on the precise assembly of synthetic DNA strands into virtually any desired morphology, with exquisite resolution, high-yield and site-specific functionality. It is currently exploited in many fields of research, ranging from materials science, chemistry and physics to diagnostics, immunology and biomedicine. One typical method, called DNA origami, consists in the user-programmed folding of a circular DNA scaffold into any desired 2D or 3D shape

with a size of around 100 nm, while scaffold-free structures, such as DNA nanotubes, can reach much larger dimensions (10 to 100 µm). Programmable DNA self-assembly thus looks as a promising synthetic self-assembly path to build sophisticated cell-mimicking components, and in particular cytoskeleton mimics. However, all the methods for DNA self-assembly have been relying on thermal annealing, where the system has to be heated to a high temperature (~80 °C) prior to a slow cooling down taking hours to days. Once formed, these structures can be incorporated into synthetic cells, and this has already been explored, but their self-assembly is incompatible with usual physiological conditions (a fixed and mild temperature). Moreover the structures produced by thermal annealing are usually rather static and thus far from the highly dynamic nature of most cellular components. Current methods for DNA self-assembly are thus inadequate for *in situ* implementation with synthetic cell or protocell research, either because they require improper temperature conditions or because they lead to static structures. Our team has recently established a revolutionary method to realize programmable DNA self-assembly in isothermal conditions.[1-3] Based on using a simple salt buffer ensuring electrostatic stability and reconfigurability, this method allows us to produce at room (25 °C) or physiological temperature (37 °C) any desired 2D or 3D structures, including DNA origami[1] and DNA nanotubes.[2] We have shown that the resulting structures are highly dynamic and reconfigurable, with notably the capability to change their shape,[1] grow to cell-size dimensions[2,3] or produce dynamic networks resembling cytoskeletons.[2] For this PhD project, we will implement this isothermal DNA self-assembly process in the context of synthetic cell and protocell research for the first time, with a particular focus on the realization of dynamic DNA architectures self-assembling together with self-assembling, or already self-assembled, membrane bricks (fatty acids, lipids) leading to cell models (protocells, synthetic cells).

In a first part of the PhD, various DNA programs coding from the formation of DNA origami of various shapes and nanotubes of various dimensions will be mixed with fatty acids. We will then study for the first time the interplay emerging between fatty acid self-assembly into vesicles and isothermal DNA self-assembly into complex architectures. These two assembly pathways will be studied in a sequential manner (DNA self-assembly followed by fatty acid assembly, or the opposite) or in a concomitant way (all DNA and fatty acid bricks mixed together at once). We will study the emergence of protocells in this system, in the form of membrane structures enclosing DNA architectures, and establish the structural and dynamic links that exist between protocell morphology, membrane assembly, DNA networks, and DNA self-assembly. The second part of the PhD will involve giant liposomes, that it, giant unilamellar vesicles made by lipids. Here, the synthetic cells will be pre-assembled and we will study how the implementation of dynamic DNA self-assembly can lead to interesting properties, such as membrane deformation or dynamic pore formation. In the third part of the PhD, we will establish design rules to create DNA nanostructures controlling the morphology of protocells or synthetic cells, which would constitute a first step toward DNA-encoded synthetic cell morphogenesis.

By combining the unique know-how of the team in isothermal self-assembly,[1-3] synthetic cell research[4] and DNA nanotechnology,[1-3] this PhD project aims at contributing to better understanding of self-organization, origin of life and cell morphogenesis while establishing novel methods for the design of smart synthetic materials with life-like properties.

References:

[1] C. Rossi-Gendron, F. El Fakih, L. Bourdon, K. Nakazawa, J. Finkel, N. Triomphe, L. Chocron, M. Endo, H. Sugiyama, G. Bellot, M. Morel, S. Rudiuk, D. Baigl. Isothermal self-assembly of multicomponent and evolutive DNA nanostructures. ***Nat. Nanotechnol.*** **2023**, 18, 1311–1318

[2] L. Bourdon, S. P. Afrose, S. Agarwal, D. Das, R. Singh, A. Di Cicco, D. Lévy, A. Yamada, D. Baigl, E. Franco. Nanotubes Growth by Self-Assembly of DNA Strands at Room Temperature. ***ACS Nano*** **2025**, 19, 18203

[3] L. Bourdon, X. Z. Xu, L. J. Michot, M. Morel, S. Rudiuk, A. Yamada, D. Baigl. DNA condensation-inspired assembly of DNA nanotubes into reversible superstructures: a base pairing-orthogonal way to create rings, bundles or vast networks. ***J. Am. Chem. Soc.*** **2025**, 147, 37317

[4] K. Nakazawa, A. Lévrier, S. Rudiuk, A. Yamada, M. Morel, D. Baigl. Controlled Lipid Domain Positioning and Polarization in Confined Minimal Cell Models. ***Angew. Chem. Int. Ed.*** **2025**, e202419529

Type of PhD:

1.Full PhD

- Joint PhD/cotutelle (leading to a double diploma) : NO
- Regular PhD (leading to a single French diploma) : YES

2. Visiting PhD (students enrolled at a Chinese institution who come to ENS for mobility period) : NO

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