**CA17139 “EUTOPIA”**

**Activity report of WG3: Tangled and Self-Entangled Proteins**

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WG3 currently comprises 31 members including PhD students. The vast majority of its members are theoreticians, and most of them are male scientists. Likewise, it would be desirable to attract more female scientists into WG3 as well as more experimentalists to level the imbalance between theory and experimental know-how. This is particularly important since two (of the 4) objectives of the MoU imply a close collaboration between theory and experiment, namely:

1 - “*Push the integration of simulation and experiments to guarantee the exchange of ideas between the two approaches*”

2- “*Establish a joint and coordinated effort to employ knotted protein design for pharmaceutical applications. Develop computational strategies to design proteins with target topologies and structures, and to validate the most successful candidates in vitro through the partnership with experimental groups*”

**Summary of activities**

The WG3 organized a Mini-workshop in the first EUTOPIA Meeting held in Trento (Italy) from 5-8 February 2019 entitled “Tangled and Self Entangled Proteins: Open problems and questions”. The submitted abstracts were selected by the WG leader and co-leader based on two guidelines: 1) they should address problems that fit as much as possible within one or more of the 4 objectives of WG3, and 2) young scientists should have an opportunity to present their work. The mini-workshop was organized in two sessions. The first session comprised three talks of 15 minutes: *Dimos Goundaroulis (Switzerland):* **Knotoids and Protein Structure: A primer on the mathematical theory and the available computational tools**; *Marek Cieplak (Poland):* **Knots in intrinsically disordered proteins**, *Ivan Colluzza (Spain):* **Transferable coarse-grained potential for *de novo* protein folding and design***)* followed by discussion and round table. The second part of the mini-workshop included two 15 minuntes contributions by junior researchers: *Pawel-Dabrowski-Tumanski (Poland)*: **Deterministic knots in protein** and *Bartosz Greń (Poland)*: **Non-trivial lassos in proteins and polymers**.

**Novel collaborations prompted by participation in EUTOPIA**

1. Joanna Sulkowska (Poland), Szymon Niewieczerzal (Poland) and Patrícia Faísca (Portugal) are planning to explore the mechanism of chaperonin-assisted knotting beyond steric-confinement by extending recent results that reported the role of hydrophobicity on the folding and knotting transitions of proteins with shallow knots (Especial et al., *Phys. Chem. Chem. Phys.*, 2019, 21, 11764-11775) to deeply knotted proteins and proteins with splinkots.
2. Rafaello Potestio (Italy), Ivan Coluzza (Spain), Patrícia Faísca (Portugal) and João Especial (PhD student, Portugal) are planning to start a novel collaboration that will address the problem of understanding the knotting mechanism in an evolutionary context. In particular, they plan to explore how the size of the amino acid alphabet affects the mechanism of knotting in the context of coarse-grained models.
3. Joanna Sulkowksa, Pawel Dabrowski (Poland), Adnrzej Stasiak (Switzerland) and Dimos Goundaroulis (Switzerland) are planning to start a novel collaboration that will focus on theory and protein realization of selected topological structures (this fits the goals of both WG1 and WG3). An application for a 14 days STSM (of PD to Switzerland) to take place by the end of September 2019 will be submitted.

**Publications in which EUTOPIA has been acknowledged**

Hydrophobic confinement modulates thermal stability and assists knotting in the folding of tangled proteins, João Especial, Ana Nunes, Antonio Rey & Patrícia F.N. Faísca, *Phys. Chem. Chem. Phys.* (2019) **21**, 21, 11764-11775

https://dx.doi.org/ 10.1039/C9CP01701A

Knotted proteins: Tie Etiquette in Structural Biology, Ana Nunes & Patrícia F.N. Faísca, *Contemporary Mathematics*, AMS (in press)

Computational methods in the study of self-entangled proteins: a critical appraisal, Claudio Perego and Raffaello Potestio, Journal of Physics: Condensed Matter (accepted)
https://iopscience.iop.org/article/10.1088/1361-648X/ab2f19

**Conferences in which EUTOPIA has been acknowledged**

Marek Cieplak,*Disordered peptide chains in an a-C-based coarse-grained model*

(Contributed talk), **American Physical Society March Meeting**, Boston, USA, March 4-8, 2019

Marek Cieplak*, Emergence of knots in intrinsically disordered proteins (Keynote lecture)*, **Workshop on Integrative Approaches to Protein Folding & Aggregation**, Lisbon, Portugal, 11-12 June 2019

Raffaello Potestio*, Searching the optimal folding routes of a complex lasso protein (Invited talk),* **Workshop on Integrative Approaches to Protein Folding & Aggregation**, Lisbon, Portugal, 11-12 June 2019

João Especial, *Hydrophobic confinement modulates thermal stability and assists knotting in the folding of tangled proteins* (Contributed talk and poster)

**Workshop on Integrative Approaches to Protein Folding & Aggregation**,

Lisbon, Portugal, 11-12 June 2019