BIOCHEMISTRY SEMINAR

"The critical role of co-translational protein folding: a joint theoretical and experimental study"

Amir Bitran PHD

Postdoctoral Research Associate

UC Berkeley

Despite remarkable advances in our ability to predict protein structures with A.I. tools, we still do not fully understand *how* proteins fold in the complex cellular environment. The non-equilibrium dynamics associated with folding, which often begin on the ribosome, critically impact a protein's fate, including its ability to robustly form macromolecular complexes or conversely, its propensity to form disease-linked oligomers. Indeed, early co-translational folding events appear to be under widespread favorable selection, as evidenced by conserved, slowly-translating codons at specific sequence positions across protein orthologs. Yet the highly dynamic, multi-body process of folding on the ribosome cannot be probed by standard techniques and remains poorly understood. In this seminar, I will present a combination of theoretical/computational and experimental work on co-translational folding that addresses this gap. Using a powerful all-atom simulation platform we developed, we generate detailed predictions regarding how co-translational folding allows certain proteins to avoid misfolding traps, and how this process is modulated by local variations in translation rate. We then validate these predictions using FRET/PET assays (by collaborators) and a novel application of hydrogen-deuterium exchange mass spectrometry (HDX-MS) I am developing, which can uniquely probe folding at multiple sites across a nascent chain during active translation. Importantly, the real-time nature of this assay allows us to verify predictions regarding the coupling between translation and folding rates, which cannot be probed by most assays that investigate stalled nascent chains at equilibrium. These advances reveal key physical principles guiding the crucial process of co-translational folding and provide a starting point to probe related proteostasis mechanisms, including co-translational chaperones, and their links to age-related misfolding disease.

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PURDUE UNIVERSITY | James Tarpo Jr. and Margaret Tarpo Department of Chemistry