Canadian Association of Physicists
Association canadienne des physiciens et physiciennes

Contribution ID: **2547** Type: **Oral (Non-Student) / Orale (non-étudiant(e))**

# Interplay between native state topology and sequence in two-state protein folding

*Tuesday, 4 June 2019 09:30 (15 minutes)*

One of the outstanding questions in protein folding is why the folding into some native state topologies, e.g. all-$\alpha$ folds, are more sensitive to sequence variations than other, more nonlocal protein folds, such as all-$\beta$ folds? To explore this question, we design and study three 35-54 amino acid sequences within a coarse-grained sequence-based model and show that they fold spontaneously into stable $3\alpha$, $4\beta+\alpha$ and $\beta$-barrel folds, respectively. Their thermodynamic behaviors, calculated using Monte Carlo techniques, exhibit features in line with experimental data including rank order of folding cooperativity and temperature-driven Hammond shifts of transition states. Using a novel generalized ensemble algorithm (A. Aina and S. Wallin, Journal of Chemical Physics 147, 095102, 2017) we then systematically study the effect of single- and double-point mutations on each of the three proteins. In total, $>$2,000 mutants are studied. We find that the proteins respond to sequence variations in a topology-dependent manner. In particular, the folding landscape of the $\beta$-barrel protein is the least perturbed of the three proteins, explaining previously observed mutational robustness of non-local folds. Moreover, we observe a link between the size of conformational fluctuations of these proteins and the divergence exhibited by their respective mutants. One consequence of such a link is that proteins with diverse folding pathways might be more sensitive to sequence variations than proteins with restricted folding pathways.

**Primary authors:** WALLIN, Stefan (Memorial University of Newfoundland); Mr TROTTER, Daniel (University of Ottwawa)

**Presenter:** WALLIN, Stefan (Memorial University of Newfoundland)

**Session Classification:** T1-8 Topics in medical physics and biophysics (DPMB) | Sujets en physique médicale et biophysique (DPMB)

**Track Classification:** Physics in Medicine and Biology / Physique en médecine et en biologie (DPMB-DPMB)