Proteins are fundamental biological molecules involved in virtually all essential processes in living organisms—from catalyzing chemical reactions to enabling immune responses. Understanding how proteins fold into their functional structures, move, and interact is crucial for elucidating cellular mechanisms and developing therapies to cure diseases such as cancer, neurodegenerative disorders, and viral infections. One of the most important factors influencing protein behavior is temperature. Even slight temperature changes significantly affect protein stability, folding pathways, and intermolecular interactions, especially in the crowded environment of the cell. Due to this temperature dependence, virtually all living organisms can function only in narrow ranges of temperatures.

To study the complex and biologically relevant phenomena that involve proteins, researchers increasingly rely on computer simulations. However, atomistic simulations of proteins, in which the temperature is manifested explicitly as the motions of the atoms, are computationally demanding and often impractical for large molecular systems or long timescales. *Coarse-grained* (CG) models offer an efficient alternative by simplifying the system, replacing groups of atoms with single interaction centers, allowing for much faster simulations while preserving essential physical properties. However, the motions of the atoms are replaced with the motions of larger parts of the system, thus omitting part of the temperature influence on the system. This missing part has to be considered in the model by making the force field (which governs the motions as gravity governs the motion of a falling stone) dependent on temperature. One of the coarse-grained models is UNRES (UNited RESidues), which has been widely used to simulate protein folding, aggregation, and structural transitions. Although UNRES is known for its high efficiency and accuracy and some of its terms depend on temperature, the potentials of side-chain interactions, which are critical for structure formation, are not dependent on temperature. Because these potentials reflect the solvent-mediated, in particular hydrophobic interactions, which implicitly embed the highly mobile water molecules, they should depend on temperature. Consequently, the temperature-dependent phenomena such as cold denaturation or liquid–liquid phase separation (LLPS) are modeled correctly with UNRES only around room temperature. As a result, the model is currently unable to precisely capture the experimentally observed behavior of temperature-sensitive proteins.

The goal of this project is to improve the predictive capabilities of the UNRES model by introducing the temperature dependence of the side-chain interaction potentials through scaling these potentials by a quadratic function of the temperature. This approach will enable us to model the dependence of protein behavior on temperature without having to embark in computationally expensive and long simulations with explicit water treatment. Consequently, this enhancement will enable the UNRES model to reflect actual biological conditions better and to simulate protein folding, aggregation, and responses to temperature fluctuations more accurately. Moreover, the improved UNRES model will retain its computational efficiency, making it suitable for studying large systems such as virus-like particles or membraneless organelles, which are key objects of interests of modern biomedicine, biotechnology, and synthetic biology.