Thesis Summary

Robustness of the elastic network model against chemical or physical fitting of parameters
(パラメタの化学的・物理的最適化に対する弾性ネットワークモデルの頑健性)

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Elastic network model (ENM) is a simple representation of proteins where amino acids are considered as point-like particles and interactions as harmonic ones. Pairs of amino acids for which the distance is under a certain cut-off distance, are connected by linear springs with the same stiffness for all interactions. Within the assumption of small fluctuations, it has successfully been coupled with the normal mode analysis. Normal mode analysis (NMA) expresses the dynamics of the model through modes and decomposes the protein conformational motions into the fundamental motions vibrating along each mode. Although the ENM has been able to reproduce the motion of some proteins (e.g. HCV Helicase), it does not contain any chemical information about proteins. The springs are set in an empirical manner disregarding the chemical details of the protein. Many attempts have been made to include such properties in the modelling and especially, a recent study has proposed amino-acid dependent spring constants determined statistically using experimental data. For the latter models, improvements have been shown by measuring performance at the protein level. Here, we decided to investigate in depth these models by looking at the residue level in order to explain the origin of and how valuable is the improvement. For that, we have first looked, using the NMA, at the prediction of fluctuations of individual residues which reveal a poor sensitivity to the addition of the sequence specificity. The differences with classical models reside on unstructured parts, poorly connected, which bias the global improvement seen at the protein level. The study on collective behaviours (transitions, inter-residues fluctuations) has given the same conclusions. Without the assumption of small fluctuations (and hence of linearity), we have run molecular dynamics simulations using the ENM for relaxation trajectories. Again, no sensible improvement has been observed when considering the sequence of residues. Such conclusions have led us to consider the robustness of the elastic network model against the fitting of spring constants. Using the, same measuring

methods,we have studied some well-known heterogeneous ENM for which the spring constants are distance dependent. It appears that each of them gives similar results to a classical model with a certain cut-off distance. Finally, we have used an extreme method by totally randomising the spring constants in an incoherent way and look at the spring constant values of the most efficient random networks. The common point over several protein examples is the stiffening of the flexible regions. The rest of the structure has typically no incidence on the improvement at the protein level. In other words, the best random networks do not show any coherent heterogeneity in the spring constant values which could be related to the biological or chemical properties of the protein. Our conclusion is that the performance of the elastic network model is mainly determined by the structure itself and that the fitting of spring constants is not a valuable way of bringing chemical or physical details in the modelling.