PHASE BEHAVIOR STUDY OF HUMAN ANTIBODY SOLUTION USING MULTI-SCALE MODELING

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Phase transformation in antibody solutions is of growing interest in both academia and the pharmaceutical industry. Recent experimental studies have shown that, as in near-spherical proteins, antibodies can undergo a liquid-liquid phase separation under conditions metastable with respect to crystallization. However the phase diagram of the Y-shaped antibodies exhibit unique features that differ substantially from those of spherical proteins. Specifically, antibody solutions have an exceptionally low critical volume fraction (CVF) and a broader and more asymmetric liquid-liquid coexistence curve than those of spherical proteins. Using molecular dynamics simulation on a series of trimetric Y-shaped coarse-grained models, we investigate the phase behavior of antibody solutions and compare the results with the experimental phase diagram of human IgG antibodies. With the fitted size of spheres, our simulation reproduces both the low CVF and the asymmetric shape of the experimental coexistence curve of IgG antibodies. The broadness of the coexistence curve can be attributed to the anisotropic nature of the inter-protein interaction. In addition, the repulsion between the inner parts of the spherical domains of IgG dramatically expands the coexistence region in the scaled phase diagram, while the hinge length has only a minor effect on the CVF and the overall shape of the coexistence curve. However the meta-stability gap between the solubility line and the coexistence curve sharply increases as the hinge length increases. We thus propose a seven-site model with empirical parameters that characterize the exclusion volume and the hinge length of the IgG molecules that provides a base for simulation studies of the phase behavior of IgG antibodies.