## Behaviors of Colloidal Particles in Macromolecular Solutions; Mesoscopic Phase in Space and in Time

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This is a personal historical review of our study in the field of colloid physics.

Fifty years ago, we presented a theory on interaction between two colloidal particles in macromoleular solutions. In general a long range attractive force appears between particles. The key idea was that the small space between particles into which macromolecules are difficult to enter is regarded as a phase separated from the solution outside where macromolecules are free to move. Then, the osmotic pressure difference between two phases produces an attractive force between particles. Calculations were performed in combinations of various shapes of colloidal particles and macromolecules. Our theory was first proposed to understand, based on a common mechanism, aggregations of red blood cells, soil particles, bacterial cells, etc., by macromolecules. After about thirty years, people in colloid science and also in many different fields began to pay much attention to this attractive force.

The force makes important contributions to form higher order structures of various colloidal particles and macromlecules including assemblies of protein molecules often observed in living cells. We performed the in vitro experiment on the formation of anisotropic phase of oriented actin polymers in the presence of actin monomers and polymers of various concentrations, regulating concentrations of total actin molecules and monovalent salts.

A similar idea, the two phase approximation, was very powerful in polyelectrolytes. In rodlike polyions, a thin cylindrical volume surrounding the polyion was regarded as a phase separated from the outside solution. Then, the equilibrium distribution of counter ions between two phases readily leads to "the counter ion condensation". Further in the presence of added salt ions, "the additivity law" is derived.

Condensed counter ions are mobile along polyions. Their thermal movements produce fluctuating electric dipoles and electric fields parallel and perpendicular to the polyion. If macromolecules, which can assume two states having different polarizabilities, are put in such a fluctuating field around the polyion, their free energies in two states fluctuate. Then, the rate constants of the transition between two states are expressed as functions of time having the fluctuating field in the exponential term. The fluctuation has non-linear effects. Indirect cooperative transition may occur in two macromolecules via fluctuating field. Similar situation can be supposed on charged planar polyions or membranes. In the above idea, at every moment of fluctuation the free energy and the transition rate of the state are assumed to be defined as functions of time. The space and time correlations of field fluctuation must not be too short.

Living cells have higher order structures composed of various protein filaments, so that the electric potential and field inside are not always uniform but often have large fluctuation. We have been interested in spontaneous activities of the cells, the origin of which is in the field fluctuation intracellular or across the membrane. Then, the area or volume and the time of correlated field fluctuation are important factors for those cells to control spontaneous behaviors.