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Roles of hydrodynamic interactions in structure formation of soft matter: protein folding as an example

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Abstract

Soft matter usually contains a fluid as its component, but it is often treated as a minor component. This is primarily due to the fact that a fluid component does not play major roles in determining the static equilibrium properties in many cases. However, a fluid component can play a crucial role in the dynamic process of structure formation via long-range hydrodynamic interactions. Here we demonstrate a few examples of structure formation of soft matter, where hydrodynamic interactions drastically change the kinetic pathway. Using these examples as a guide, we consider how hydrodynamic interactions affect the kinetic process of protein folding. We speculate that hydrodynamic interactions play a key role in not only the selection of the kinetic pathway in the complex energy landscape, but also the selection of the final folded state itself.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

A fluid component such as water is one of the most important ingredients forming various kinds of soft matter and soft matter complexes. This component sometimes plays important roles in the selection of an equilibrium structure of soft matter through energetic interactions such as hydrophobic interactions. A fluid also plays a crucial role as the source of the thermal noises that induce Brownian motion of mesoscopic objects. However, the most prominent and unique character of a fluid component is its ability to flow, which for example induces long-range hydrodynamic interactions even between distant particles. Here we focus our attention on how hydrodynamic interactions via a fluid component in soft matter do affect the structure formation in the framework of the classical hydrodynamic theory at a low Reynolds number¹.

¹ The behaviour of fluid in soft matter can be well described by the coarse-grained hydrodynamic theory, namely, the Navier–Stokes equation, which is known to be quite robust and to be valid at least qualitatively even in the nanoscale. In reality, this continuum hydrodynamic description may not work in the late stage of protein folding, since the relevant length eventually approaches the molecular size of water. For example, the non-slip boundary condition is known to be rather easily violated in the nanoscale. However, we do not dwell on such crossover from the continuum to the molecular description of hydrodynamics in this paper. Instead, we consider the roles of hydrodynamics on protein folding on a qualitative level.

In particular, we consider the problem of protein folding [1, 2], which always occurs in a fluid (liquid water), as an important example.

2. Hydrodynamic interactions in macro- and microphase separation

The importance of hydrodynamic interactions on the phase-separation kinetics of binary fluid mixtures is widely known [4]. For example, the ordering of the composition field is significantly accelerated by the convective transport mechanism. Under the influence of wetting, hydrodynamic interactions crucially affect the kinetic pathway of phase separation [5]. In an extreme case, hydrodynamic effects even lead to the violation of the self-similar growth [6]. For phase separation of anisotropic liquid-crystal and isotropic molecules, the flow-alignment coupling unique to anisotropic molecules leads to the unconventional breaking of morphological symmetry of purely kinetic origin [7].

A more interesting example is the ordering of block copolymer melt. The following Hamiltonian, which is generic to a wide class of material, suffers from the frustration effects that originate from the competition between short-range attraction and long-range repulsion [8–10].

$$\beta H(\phi) = \int dr \left[\frac{1}{2} \phi(\mathbf{r}) [\tau + k_0^{-2} (\nabla^2 + k_0^2)] \phi(\mathbf{r}) + \frac{u}{4!} \phi(\mathbf{r})^4 \right]. \quad (1)$$

Here the energy scale β^{-1} characterizes typical thermal fluctuations. τ is a dimensionless temperature measuring the distance from an underlying critical temperature for $k_0 = 0$. The wavevector k_0 ($\neq 0$) characterizes the long-range order of a low-temperature microphase separated state. The nature of this type of Hamiltonian, namely, whether this Hamiltonian together with the standard Langevin dynamics leads to the glassy dynamics or not, is also a matter of active debate in the field of liquid–glass transitions [11–15].

In numerical simulations of microphase separation, it is widely recognized that the ordering process of block copolymer is very easily pinned to a metastable structure even though a well-defined thermodynamic state exists; numerical simulations often fail to reach the equilibrium state, into which the system should fall. There have been some efforts to overcome this difficulty in numerical simulations: for example, Teramoto *et al* [16] artificially introduced the inertial term in the time-dependent Ginzburg–Landau equation to find out the equilibrium pattern efficiently. Nonomura *et al* [17], on the other hand, employed a mode expansion method to avoid such trapping into metastable states by giving a constraint to the kinetic pathway in the k space. Although these methods are efficient, the numerically obtained kinetic pathway might not correspond to the real physical pathway. Thus, a more natural way to solve this problem is the introduction of hydrodynamic interactions. Groot *et al* [18] recently showed by comparing the results of dissipative particle dynamics (DPD) simulations with those of Brownian dynamics (BD) ones that the hydrodynamic flows can indeed help the system to overcome the barriers between basins and provide a new and smooth kinetic pathway to an equilibrium ordered structure.

3. Roles of hydrodynamic interactions in structure formation of colloidal suspensions

Before considering the problem of protein folding, we mention a few examples seen in colloidal suspensions, where hydrodynamic effects strongly affect the kinetics of structure organization. The following examples of colloidal suspensions are obtained by simulations using a fluid–particle dynamics (FPD) method, which was recently developed by us to simulate the phase-separation dynamics of colloidal suspensions by including full hydrodynamic interactions [19].

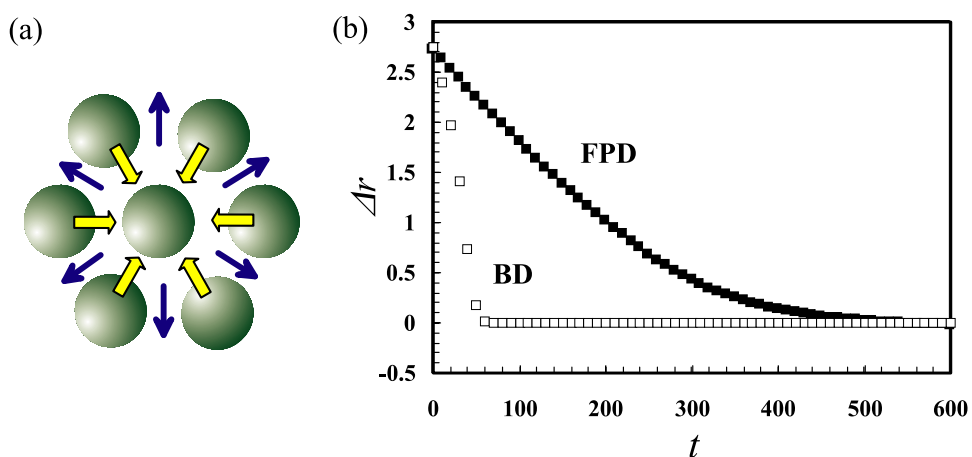


Figure 1. (a) The initial particle configuration used for the simulations. (b) Temporal change of Δr for FPD (filled squares) and BD (open squares).

3.1. Many-body hydrodynamic interactions

To investigate many-body hydrodynamic interactions in the aggregation process of particles interacting with a Lennard-Jones potential, we compare the result of an FPD simulation with that of a BD simulation, whose initial particle configuration is shown in figure 1(a) (see [19] for the details). The initial interparticle distance r is set to be $3a$ (a : particle radius). The parameters of the BD simulation were set to reproduce the same result as the FPD simulation for single-particle dynamics [19]. Figure 1(b) shows the temporal change in the interparticle distance Δr for the FPD and BD simulations. It clearly shows that for FPD it takes more than ten times longer for particles to contact than for BD, reflecting excess hydrodynamic friction for fluid drainage due to narrow channels between particles. We call this effect the ‘squeezing flow effect’.

3.2. Percolation in colloidal aggregation

Next we show hydrodynamic effects on the process of colloidal aggregation [19]. The left figure of figure 2 shows the initial stage of a phase-separation process of colloidal suspensions, which is simulated by including interparticle hydrodynamic interactions. Homogeneously distributed colloidal particles gradually form an open network structure after the initiation of phase separation. The effects of hydrodynamic interactions can be recognized evidently by comparing this with the results of the BD simulation, which are shown in the right figure of figure 2. Both simulations have the same initial particle configuration and there are no force noises. Thus all the differences should stem solely from hydrodynamic interactions. Without them, particles have a tendency to aggregate into a compact structure, as often reported in BD simulations. Thus we can conclude that the formation of the ‘open’ network structure at this volume fraction is due to interparticle hydrodynamic interactions. This is a clear example indicating that hydrodynamic interactions completely change the kinetic pathway of structural ordering. This means that conventional arguments on the percolation threshold, which are based on the diffusion and stick mechanism of aggregation, must be reconsidered. The formation of a transient network entirely changes the kinetic pathway of phase separation and leads to unusual phase separation called ‘viscoelastic phase separation’ [20].

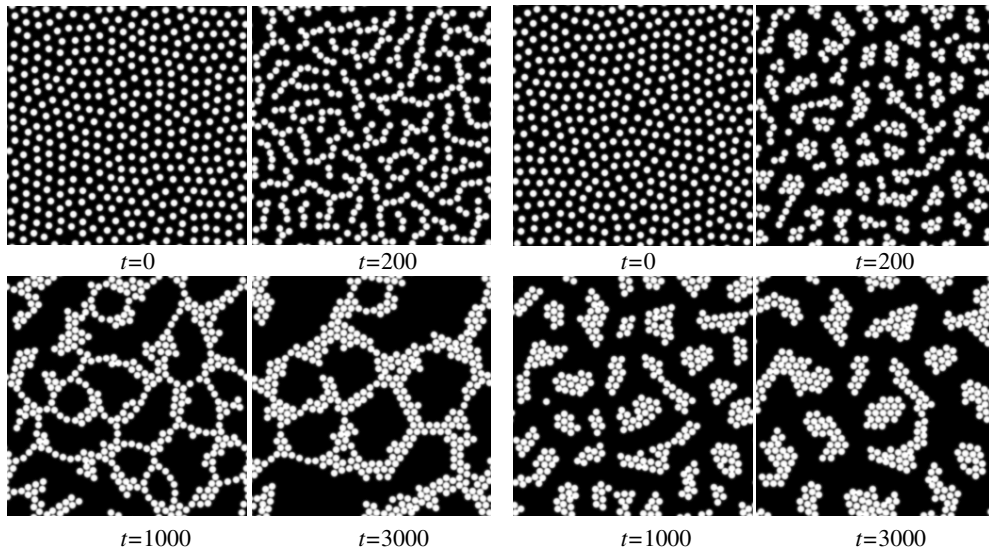


Figure 2. Phase-separation processes of a colloidal suspension simulated by the FPD (left) and the BD method (right). The initial configuration of particles is exactly the same between the two. Collidal particles are interacting with the Lennard-Jones potential: $V(r) = 4\epsilon[(\frac{\sigma}{r})^{12} - (\frac{\sigma}{r})^6]$, where r is the interparticle distance. In these simulations, $\phi = 0.279$, the number of particles was 400, the system size was 256×256 , and the viscosity ratio between colloid particles η_c and the surrounding fluid η_s was $R = 50$ ($\eta_c = 25.0$ and $\eta_s = 0.50$). The particle radius $a = 3.6$ and the interface thickness $\xi = 1$. The time step was $\Delta t = 0.01$. The parameters of the Lennard-Jones potential were $\epsilon = 0.25$ and $\sigma = 2a = 7.2$. See [19] for the meanings of the above parameters.

4. Hydrodynamic interactions in protein folding

In the above two sections, we learn that hydrodynamic interactions can significantly alter the kinetic pathway of macro- and microphase separation and colloidal aggregation. On the basis of these examples, we suggest that convective transport, or momentum flow, should be important for structure formation in any system with competing interactions, including proteins, to overcome the barriers in the complex energy landscape and prevent a system from being arrested in a metastable state.

In the above examples, however, the final equilibrium structure itself is not affected by hydrodynamic interactions. In the problem of protein folding, we speculate that hydrodynamic interactions may even affect the selection of the final nonergodic structure itself. Thus we expect that hydrodynamic interactions play even more important and essential roles in protein folding than in the above two examples.

Before starting the discussion, it may be worth mentioning the difference in the length scale of hydrodynamic units between colloids and proteins. The size of colloids is usually much larger than the size of hydrodynamic units of proteins. We note that our simulation methods do not involve any length scale characterizing hydrodynamics as long as the continuum hydrodynamic description works well. Note that the Reynolds number is so small for these systems in most cases that the Stokes approximation should be valid. Thus, the only problem is a possible breakdown of the continuum description of hydrodynamics. In this context, we must pay special attention to the final stage of protein folding, where we may have to deal with short-range hydrodynamics on a scale comparable to water molecules (see also

footnote 1). In such a case, we expect the breakdown of continuum hydrodynamics. We also have to seriously consider structuring of water molecules such as hydration and its coupling to flow. Since these problems are too complicated and beyond the scope of this paper, here we limit our interest to the regime where the continuum hydrodynamic description is valid.

4.1. *What do we care about protein folding?*

Protein folding is a complex process by which a stable and unique 3D structure is formed from a very large ensemble of less structured conformations [1, 2]. To understand this complex kinetic process, the concept of the energy landscape has often been used [1, 2, 21–24]. The energy landscape of a protein is believed to have a special characteristic different from that of random heteropolymers in the sense that the former has a single dominant basin and an overall funnel topology but the latter does not. This special topology of the energy landscape has often been ascribed to the evolutionary selection for realizing robust folding at ambient temperature from a random state to a stable 3D structure that is biologically meaningful. Thus a protein can be said to be a heteropolymer that can find a particular stable structure within a short time without falling into other biologically irrelevant nonergodic structures. Frustration is intrinsic to protein folding since protein is made of many different elements that energetically interact with each other via various types of potentials having different strengths and ranges under the constraint of 1D connectivity.

From this aspect, it has been suggested that protein folding has some similarity to that of crystallization under frustration effects (see, e.g., [21]). A stable state of protein can be regarded as a unique ordered state like a crystalline state. The difference between the two types of ordered states arises from the following fact. The former has a non-periodic, non-symmetrical structure due to (i) the existence of many different components (amino acids) and (ii) the finite size of a system, while the latter has a periodic, symmetric structure, reflecting a small number of components and its (in principle) infinite size. For both cases, however, the ordered states are in a unique thermodynamically stable and lowest energy state that is clearly distinguished from the other metastable states in the energy landscape. Thus, we should regard protein folding as the ordering phenomenon. Differently from usual ordering phenomena, it is difficult to find out and define the relevant order parameter. Thus, the physical description of this type of complex ordering into a non-periodic structure is a quite challenging problem of physics [1].

Crystallization may be frustrated, which leads to the kinetic arrest: glass transition. Thus we can view the glass-transition phenomena as a result of frustration effects on crystallization [3]. A glassy state is a nonergodic state. Thus once a system falls into a glassy amorphous state, a crystalline state cannot be attained in a usual experimental timescale. A similar situation can also happen in protein folding. At a low temperature below the glass-transition temperature of protein, T_g , protein should easily fall into a glassy state, which is distinct from a stable state. This means that the folding transition temperature T_f of a biologically active protein must be located above its T_g .

A fundamental question on protein folding in this physical picture is, thus, how protein can find out a unique stable structure from many possible configurations quickly without being trapped in a metastable state in the complex energy landscape [1]. In other words, what is the physical principle for setting T_f above T_g of a protein? This problem has so far been considered on the basis of complex local and nonlocal energetic interactions among amino acids. Here we consider this fundamental problem, putting a special focus on the roles of hydrodynamic interactions.

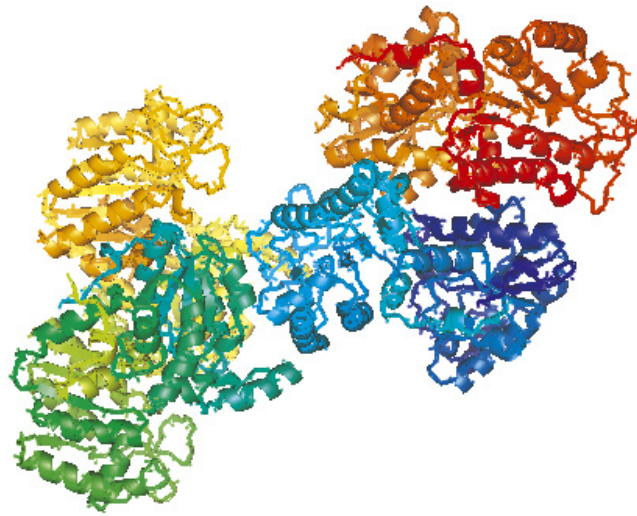


Figure 3. Coarse-graining picture of protein kinase. We can see helical and sheet structures as medium-range order.

4.2. Prototype of protein folding: coil–globule transition in a single polymer chain

The effects of hydrodynamic interactions on a coil–globule transition have recently been studied numerically [25, 26]. Chang and Yethiraj [25] found that a compact globule structure can be smoothly attained with hydrodynamic interactions, but it cannot be attained without them and instead a system is trapped in a nonergodic metastable state. Kikuchi *et al* [26], on the other hand, observed similar acceleration of the transition by hydrodynamic interactions, but did not observe such qualitative difference between cases with and without hydrodynamic interactions. Although there remains some controversy, both studies indicate that hydrodynamic interactions help and accelerate the transition.

The coil–globule transition is similar to protein folding, but a crucial difference arises from the fact that the globule state of a polymer is an amorphous state (just one of many nonergodic states that are degenerated), while the folded state of a protein is a unique ordered state (a stable equilibrium state).

4.3. Hierarchical ordering

The structure of a protein is stabilized by various interactions, including Coulomb, hydrogen bonding, dipole–dipole, dipole–monopole (hydration), hydrophobic, and van der Waals interactions. Under these complex interactions on a 1D spatial sequence of amino acids (the so-called first-order structure), the local short-range ordering is induced mainly by hydrophobic interactions, and the medium-range order (the so-called secondary structure) such as α -helix and β -sheet structures is also formed with the help of hydrogen bonding (see figure 3). The former process is known as hydrophobic collapsing [27], which may be the process of reducing the number of accessible conformations of proteins. Since the characteristic timescale of structural ordering τ_ξ increases with the characteristic length of the order ξ , it is natural to expect that the ordering takes place sequentially in the order of the short-range order, the medium-range order, and the long-range order (namely, the stable folded structure), although there may not exist a distinct time separation and ordering may even gradually proceed [27].

This hierarchical ordering with couplings between different levels is enough to make protein folding an unconventional problem of physics.

4.4. Possible hydrodynamic effects on the folding process

It is known (see, e.g., [27]) that the process of protein folding can at least be divided into three stages: initial rapid collapsing stage, intermediate stage, and final folding stage. The medium-range ordering including hydrophobic collapsing and formation of helices and sheets via hydrogen bonding proceeds in the rather local region of a chain, typically via hydrogen bonding. If we put a sequential number i to each amino acid along a chain contour, the medium-range ordering occurs for components having similar i . Thus, hydrodynamic interactions are expected to accelerate and help the formation of medium-range order since they help the 1D motion along the chain [25, 26]. Note that the directional motion of a particle creates the directional hydrodynamic flow that slowly decays both spatially and temporally. This is one kind of role of hydrodynamic interactions in a 1D chain.

In the intermediate stage of protein folding, on the other hand, we may view a protein in a coarse-grained scale, focusing on the medium-range order (see figure 3). The intermediate and final stage of folding includes the ordering among the components whose i s may be very different. The ordering mechanism in these stages is named the ‘collapse and search mechanism’ [27]. We propose that in these stages the squeezing flow effect discussed in the preceding section may play crucial roles in searching the lowest-energy state, together with long-range Coulomb interactions. Note that there should exist stronger hydrodynamic interactions among bigger and stiffer structures such as sheets and helices. The squeezing flow effect should lead to the retardation of the aggregation process. In the continuum limit of hydrodynamics, this effect even leads to the singular behaviour; it takes an infinite time for a direct hard-core contact between a pair of particles to take place². It is easy to imagine that without this retardation effect the system can be trapped in a local energy minimum state very easily. If this local minimum is deep enough compared to the thermal energy, the configuration is frozen in the metastable nonergodic state. With the retardation effects, a system is able to explore a lower-energy configuration before direct contacts of components and to have the correct tertiary contacts; for example, the orientational adjustment of the mesoscopic structures can be made before a direct contact.

Another effect of hydrodynamic interactions is the coupling of the shape of the medium-range order with the hydrodynamic motion. For example, sheet and helical structures tend to rotate upon their hydrodynamic motion or to translate upon their rotational motion. This is due to the translation–rotation coupling specific to asymmetric particles (see, e.g., [7, 28]). An anisotropic structure has a specific way of motion determined by its shape, which is selected to minimize the viscous dissipation upon the drag in a fluid. Furthermore, hydrodynamic interactions among anisotropic particles should help in adjusting specific orientational relationship among them.

In this way, the kinetics of hierarchical ordering and its cooperation with hydrodynamic effects should play crucial roles in the selection of the kinetic pathway in the complex energy landscape of protein folding towards forming the correct set of tertiary contacts. Although it is too early to make any strong statement on the roles of hydrodynamic interactions in protein folding, all the examples shown in this paper suggest that the kinetic pathway of protein folding should seriously be affected by momentum flow. The combined effects of hydrodynamic interactions and 1D connectivity should lead to a specific way of motion of a 1D chain and

² In such a process, we need to seriously consider the switching of the continuum description to the molecular one of hydrodynamics.

may give an important constraint to the kinetic pathway in the energy landscape. If this is the case, a simple funnel topology may not be a necessary condition for protein folding.

5. Summary

We demonstrate a few pieces of evidence that hydrodynamic effects seriously affect the kinetic pathway of structure formation of soft matter. Although in these cases hydrodynamic interactions do not affect the final equilibrium state, we speculate that for protein folding hydrodynamic interactions may even affect the selection of the final state itself. We propose that for protein folding hydrodynamic interactions can lead to acceleration of the 1D motion along the chain and deceleration for 3D gathering motion under the action of attractive interactions and also help orientational ordering of the secondary structures such as sheets and helices. These unique features should crucially affect the kinetic pathway of protein folding in the complex energy landscape. Such a hydrodynamic selection of the kinetic pathway of protein folding seems not to have been seriously considered so far. Although our discussion is speculative, we believe that we need to take these kinetic effects into account for the future research of protein folding since protein folding always takes place in a hydrodynamic medium. Upon the evolutionary selection of protein structures, in addition to the energetic and other kinetic factors, hydrodynamics may play a role.

We also speculate that hydrodynamic interactions allow protein folding even below T_g , which is theoretically or numerically determined on the basis of energetic interactions without invoking hydrodynamic interactions. This situation is somewhat similar to that of the ergodic–nonergodic transition in a liquid; the nonergodic state below the mode-coupling T_c , which is predicted by the schematic mode-coupling theory, can become an ergodic state if we consider momentum flow, or the hopping process of particles.

Finally, we mention the future direction of simulation studies. Although molecular dynamics simulations include hydrodynamic effects, we point out that we need a large simulation box to reproduce correct hydrodynamic effects. Thus, coarse-grained simulations of protein folding with full hydrodynamic interactions are highly desirable for checking the physical relevance of our conjecture.

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References

- [1] Pandle V S, Grosberg A Y and Tanaka T 2000 *Rev. Mod. Phys.* **72** 259
- [2] Broglia R A, Tiana G and Provasi D 2004 *J. Phys.: Condens. Matter* **16** R111
- [3] Tanaka H 1998 *J. Phys.: Condens. Matter* **10** L207
Tanaka H 1999 *J. Chem. Phys.* **111** 3163
- [4] Onuki A 2002 *Phase Transition Dynamics* (Cambridge: Cambridge University Press)
- [5] Tanaka H 2001 *J. Phys.: Condens. Matter* **13** 4637
- [6] Tanaka H and Araki T 1998 *Phys. Rev. Lett.* **80** 5750
- [7] Araki T and Tanaka H 2004 *Phys. Rev. Lett.* **93** 015702
- [8] Brazovskii S A 1975 *Sov. Phys.—JETP* **41** 85
- [9] Ohta T and Kawasaki K 1986 *Macromolecules* **19** 2621
- [10] Hohenberg P C and Swift J B 1995 *Phys. Rev. E* **52** 1828

-
- [11] Grousson M, Tarjus G and Viot P 2001 *Phys. Rev. Lett.* **86** 3455
 - [12] Schmalian J and Wolynes P G 2001 *Phys. Rev. Lett.* **85** 836
Schmalian J and Wolynes P G 2001 *Phys. Rev. Lett.* **86** 3456
 - [13] Geissler P L and Reichmann D R 2004 *Phys. Rev. E* **69** 021501
 - [14] Schmalian J, Wolynes P G and Wu S 2003 *Preprint* cond-mat/0305420
 - [15] Geissler P L and Reichmann D R 2003 *Preprint* cond-mat/0307176
 - [16] Teramoto T, Saeki A and Yonezawa F 2000 *J. Phys. Soc. Japan* **69** 679
 - [17] Nonomura M, Yamada K and Ohta T 2003 *J. Phys.: Condens. Matter* **15** L423
 - [18] Groot R D, Madden T J and Tildesley D J 1999 *J. Chem. Phys.* **110** 9739
 - [19] Tanaka H and Araki T 2000 *Phys. Rev. Lett.* **85** 1338
Tanaka H and Araki T 2005 *Chem. Eng. Sci.* at press
 - [20] Tanaka H 2000 *J. Phys.: Condens. Matter* **12** R207
 - [21] Angell C A 1995 *Science* **267** 1924
 - [22] Succi N D, Onuchic J N and Wolynes P G 1998 *Proteins* **32** 136
 - [23] Veitshans T, Klimov D and Thirumalai D 1997 *Folding Des.* **2** 1
 - [24] Plotkin S S and Wolynes P G 2003 *Proc. Natl Acad. Sci. USA* **100** 4417
 - [25] Chang R and Yethiraj A 2001 *J. Chem. Phys.* **114** 7688
 - [26] Kikuchi N, Gent A and Yeomans J M 2002 *Euro. Phys. J. E* **9** 63
 - [27] Uzawa T *et al* 2004 *Proc. Natl Acad. Sci. USA* **101** 1171
 - [28] Makino M and Doi M 2004 *J. Phys. Soc. Japan* **73** 2739