Supplementary Information for

## Atomic-level investigations on the amyloid- $\beta$ dimerization process and its driving forces in water

Song-Ho Chong and Sihyun Ham<sup>\*</sup>

Department of Chemistry, Sookmyung Women's University Hyochangwon-gil 52, Yongsan-gu, Seoul 140-742, Korea

## MD Simulation Method and Calculation of Collision Cross-Section

The A $\beta$ 42 dimerization simulations were performed for 100 ns at 300 K and 1 bar under neutral pH with SANDER module of AMBER9 program package<sup>1</sup> using the ff99 force filed.<sup>2</sup> Each A $\beta$ 42 monomer has a sequence of <sup>(1)</sup>DAEFR HDSGY EVHHQ KLVFF AEDVG SNKGA IIGLM VGGVV IA<sup>(42)</sup>, and is in the -3 charged state at neutral pH.

Two monomers, each having the unfolded structure in water studied in Ref. 3 (see Fig. 1), were initially placed at 45 Å apart from each other with a random orientation, and no artificial attraction force was employed between them. Two monomers were explicitly solvated with 24,708 TIP3P water molecules<sup>4</sup> in the rectangular box with 20 Å buffer, and periodic boundary condition was applied. Six Na+ counter ions were added to neutralize the system. The particle mesh Ewald method<sup>5</sup> was applied for treating long-range electrostatic interactions, while a 10 Å cutoff was used for the short-range non-bonded interactions. The hydrogen atoms were constrained to the equilibrium bond length using the SHAKE algorithm.<sup>6</sup> In order to

remove unfavorable van der Waals contacts, the system was subjected to 500 steps of steepest decent minimization followed by 500 steps of conjugate gradient minimization while each monomer was constrained by 500 kcal/(mol Å<sup>2</sup>) harmonic potential. Then, the whole system was minimized using 1,000 steps of steepest decent minimization followed by 1,500 steps of conjugate gradient minimization without harmonic restraints. The system was subsequently subjected to 20 ps equilibration process in which the temperature was gradually raised from 0 to 300 K. After the equilibration step, the production run was carried out for 100 ns with 2 fs time step and with *NPT* ensemble, i.e., a constant number of particles (*N*), pressure (*P*), and temperature (*T*). Temperature and pressure were controlled by Berendsen's thermostat and barostat with coupling constants of 1.0 and 2.0 ps, respectively.<sup>7</sup> Three independent dimerization simulations were performed with different random initial relative orientations and velocities.

The A $\beta$ 42 dimerization process was monitored via the center-of-mass distance between the monomers as well as the number of inter-monomer heavy atom contacts. The heavy atom contact is counted when the distance between two heavy atoms belonging to different monomers is less than 5.4 Å.

The collision cross-sections to be compared with the ion-mobility mass spectrometry measurements were calculated following the procedure described in Refs. 8 and 9. In order to better correlate with the solvent-free experiments on samples electrosprayed from solution phase, the protein structure from the simulation was instantaneously dehydrated through energy minimization (500,000 steps) in vacuum. The collision cross-section of the dehydrated structure was then calculated using the trajectory method implemented in the MOBCAL software.<sup>10</sup>

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## Solvation Free Energy Calculation Based on the Integral-Equation Theory

For each A $\beta$ 42 dimer conformation generated by the MD simulations, we calculated the solvation free energy in water by applying the 3D-RISM theory.<sup>11,12</sup> The 3D-RISM theory is an integral-equation theory based on statistical mechanics for obtaining the 3D distribution function  $g_{\gamma}(\mathbf{r})$  of the site  $\gamma$ , oxygen or hydrogen, of water at position  $\mathbf{r}$  around a molecular solute such as protein. The 3D-RISM equation is given by

$$h_{\gamma}(\boldsymbol{r}) = \sum_{\gamma'} c_{\gamma'}(\boldsymbol{r}) * \left[ W_{\gamma'\gamma}^{\nu\nu}(r) + \rho h_{\gamma'\gamma}^{\nu\nu}(r) \right].$$

Here  $h_{\gamma}(\mathbf{r})$  and  $c_{\gamma}(\mathbf{r})$  refer to the 3D total and direct correlation functions of the water site  $\gamma$ , respectively; the asterisk denotes a convolution integral;  $w_{\gamma'\gamma}^{\nu\nu}(r)$  and  $h_{\gamma'\gamma}^{\nu\nu}(r)$  are the site-site intramolecular and total correlation functions of the water, respectively; and  $\rho$  represents the average number density of water. The 3D-RISM equation is to be supplemented by an approximate closure relation, and in the present study we adopted the one suggested by Kovalenko and Hirata<sup>11</sup>

$$h_{\gamma}(\boldsymbol{r}) = \begin{cases} \exp[d_{\gamma}(\boldsymbol{r})] - 1 & \text{for } d_{\gamma}(\boldsymbol{r}) \leq 0, \\ d_{\gamma}(\boldsymbol{r}) & \text{for } d_{\gamma}(\boldsymbol{r}) > 0, \end{cases}$$

in which  $d_{\gamma}(\mathbf{r}) = -u_{\gamma}(\mathbf{r})/(k_B T) + h_{\gamma}(\mathbf{r}) - c_{\gamma}(\mathbf{r})$ . Here  $k_B$  denotes Boltzmann's constant, and  $u_{\gamma}(\mathbf{r})$  refers to the interaction potential acting on the solvent site  $\gamma$  which is generated by atoms in protein.

The 3D-RISM calculation for  $g_{\gamma}(\mathbf{r})$  was performed as follows. For each dimer conformation generated by the MD simulations, one can determine the interaction potential  $u_{\gamma}(\mathbf{r})$ . Based on the knowledge of  $u_{\gamma}(\mathbf{r})$ , the two unknown functions  $h_{\gamma}(\mathbf{r})$ and  $c_{\gamma}(\mathbf{r})$  can be determined by solving the 3D-RISM equation and the closure relation self-consistently, and the 3D water distribution function is obtained via  $g_{\gamma}(\mathbf{r}) = h_{\gamma}(\mathbf{r}) + 1$ . We used the dielectrically consistent RISM theory<sup>13</sup> for the site-site correlation functions of water determined at T = 300 K and  $\rho = 1$  g/cm<sup>3</sup> and with the dielectric constant of 78.4. After the convergence is achieved for the self-consistent calculation, one can obtain the solvation free energy  $\Delta \mu$  via the following analytical expression,<sup>11</sup>

$$\Delta \mu = \rho k_B T \sum_{\gamma} \int d\mathbf{r} \left[ \frac{1}{2} h_{\gamma}(\mathbf{r})^2 \Theta \left( -h_{\gamma}(\mathbf{r}) \right) - c_{\gamma}(\mathbf{r}) - \frac{1}{2} h_{\gamma}(\mathbf{r}) c_{\gamma}(\mathbf{r}) \right],$$

where  $\Theta(x)$  is the Heaviside step function. Technical details concerning the 3D-RISM calculation can be found in Ref. 11.

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