Real-time Protein Aggregation Monitoring with a Bloch Surface Wave-based Approach

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The misfolding and aggregation of amyloid proteins has been associated with incurable diseases such as Alzheimer’s or Parkinson’s disease. In the specific case of Alzheimer’s disease, recent studies have shown that cell toxicity is caused by soluble oligomeric forms of aggregates appearing in the early stages of aggregation, rather than by insoluble fibrils (see Fig. 1) [1]. Research on new strategies of diagnosis is imperative to detect the disease prior to the onset of clinical symptoms [2].

In this work, we exploit the unique properties of an optical label-free refractometric sensing platform to propose a novel approach for investigating the initial lag-phase of Aβ(1-42) aggregation. Our sensing approach allows the real-time optical detection of local refraction index changes occurring as aggregation takes place. The method is based on the optical interrogation of a dielectric multilayer (one-dimensional photonic crystal) sustaining an electromagnetic surface wave. The sensing technique is reminiscent of surface plasmon resonance (SPR). Instead of having a surface plasmon propagating on a thin metallic film, an evanescent wave called “Bloch surface wave” (BSW) is coupled on a purely dielectric multilayer structure [3]. Depending on the materials used and the layout of the periodic dielectric multilayer, the BSW can be produced in a wide spectral range, from the visible to the near-infrared. This spectral tunability represents one of the main advantages of BSW-based optical transduction systems, as compared to SPR. In addition, BSWs present very narrow resonances that can increase the resolution and improve the limit of detection in label-free detection schemes. BSWs generated on dielectric multilayers are sensitive to external perturbations of the refractive index close to the surface of the photonic multilayer [4]. In the following, we report on a proof of principle of the BSW-based detection technique for sensing protein aggregation by monitoring in real-time the refractive index variation of an aqueous solution containing the Aβ(1-42) peptide during early aggregation and fibril formation. The multilayer surface is directly contacted with the probed aqueous medium and the sensing chamber is positioned vertically. Hence, we exploit BSWs to locally probe the refractive index variations of a solution wherein the Aβ(1-42) peptide is initially injected in a monomeric form and is progressively aggregating to form fibrils. During this process, the Aβ(1-42) peptide tends to precipitate away from the multilayered surface, therefore, the measurements using BSWs monitor a local variation of the refractive index of the solution, which is directly related to the depletion of the concentration of the Aβ(1-42) monomeric form during aggregation (see Fig. 2).

We demonstrate the efficacy of the BSW approach by monitoring in real-time the first crucial steps of Aβ42 oligomerization (see Fig. 3) [5]. Furthermore, we provide new insights into the complex mechanism of aggregation of this protein system in the presence of small molecular probes able to interfere with the dynamics of amyloid formation. As a control method, Transmission Electron Microscopy has been used to morphologically characterize the sample during aggregation.

References

Figure 1. Simplified sketch of the amyloid aggregation pathway, from the soluble monomers, through the soluble toxic oligomers, to the mature insoluble fibrils.

Figure 2. It is possible to correlate the optical properties of the sample to its concentration, and this means, indirectly, to correlate it to the aggregation state of the abeta peptide: if the concentration decreases, the insoluble aggregate has formed [5].

Figure 3. Real-time refractive index variation, in angular shift, of an Aβ(1-42) monomer peptide solution incubated at 37°C at the initial concentration of 17.3 µM in 10 mM Tris HCl, pH 7.4 [5].