Investigation of a Nucleated-Polymerization Model applied to Polyglutamine Aggregation

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Aggregation of polyglutamine (PolyQ)-containing proteins is responsible for several neurodegenerative disorders including Alzheimer's, Mad Cow and Huntington's diseases. PolyQ41 are peptides containing a repetition of 41 glutamine residues per monomer, which is a sufficient length to induce aggregation *in vitro* and in transfected cells. Due to its simplicity, PolyQ provides an excellent model to investigate nucleated polymerization. We can assume that neither fragmentation nor coalescence occur in a significant manner [1], which leads to a model that only includes nucleation (spontaneous reaction of i_0 monomers into a nucleus) and polymerization (addition of one monomer to a given polymer).

To describe such nucleation and polymerization processes, deterministic models consist of huge systems of ordinary differential equations. The coefficients defining these equations are unknown, and thus we have an inverse problem. In this talk, we will first present a numerical scheme for the forward problem, necessary to solve the inverse problem, approximating the system of ordinary differential equations for a given set of parameters. The difficulty lays in the size difference between a single monomer and an aggregate which might be several orders of magnitude. For large polymers, the system of ODEs can be well approximated by a PDE, however for small polymer sizes this is by no means accurate. We will therefore present a mixed model where we solve the ODE up to a certain polymer size and use the PDE with boundary conditions derived from the ODE solution thereafter.

In the second part of this talk, we will focus on the actual aim of this project, the inverse problem and parameter estimation, using experimental data obtained from our collaborators (H.Rezaei et al., INRA). We will discuss possible statistical models for the error in the data collection process on the basis of residual plots between a set of experimental curves and the corresponding simulated ones with best fit parameters. By choosing the statistical model correctly, we are able to determine, amongst others, confidence intervals and standard errors for the estimated parameter sets. This will give us an indication about the size of the model parameters and thus a mean to quantify the quality of the inverse problem solution.

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Références

[1] S. Prigent, A. Ballesta, F. Charles, N. Lenuzza, P. Gabriel, L.M. Tine, H. Rezaei, M. Doumic, *An Efficient Kinetic Model for Assemblies of Amyloid Fibrils and Its Application to Polyglutamine Aggregation*, PLoS ONE, 2012.

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