物理所胡進錕教授團隊找出影響蛋白質群集現象的關鍵因素

為防治神經退化性疾病開了希望之門

本所「統計與計算物理實驗室」研究員胡進錕博士與合作者研究蛋白質群集現象最近有突破性的進展。他們發現影響蛋白質群集現象的關鍵因素，研究論文已經刊於”物理評論通訊(Physical Review Letters， 簡稱PRL)”與”日本物理學會期刊（Journal of the Physical Society of Japan， 簡稱JPSJ）”。這些發現可望有助於揭開蛋白質群集現象的神秘面紗，為預防或治療神經退化性疾病開了一扇希望之門。

神經退化性疾病是指神經結構和功能逐步喪失而造成的疾病，包括阿茲海默症（Alzheimer's disease, 簡稱AD），巴金森症（Parkinson's disease，簡稱PD，也稱為震顫麻痺綜合症），杭丁頓舞蹈症(Huntington's disease，簡稱HD)，小腦脊髓萎縮症（Spinocerebellar Atrophy），額顳葉退化症（Frontotemporal lobar degeneration，簡稱FTLD-U）等。這些疾病源於蛋白質在腦部發生群集現象而造成腦神經退化或死亡。例如：AD乃源自蛋白質Aβ40（含40個胺基酸）和Aβ42（含42個胺基酸）群集現象。而HD和小腦脊髓萎縮症乃源自 PolyQ蛋白質(包含許多穀氨醯胺的蛋白質)的群集現象。瞭解造成蛋白質群集現象的關鍵因素是學術上和神經醫學上極重要的問題。

在一篇與波蘭、美國和越南研究人員合作而於 2010 年 11 月 19 日，發表於 PRL 論文中，胡進錕博士和合作者用晶格模型研究影響群集速率的關鍵因素。他們發現可以由計算單獨一條蛋白質出現在群集形態的機率，決定該蛋白質最容易產生群集現象的溫度。他們也發現群集時間與蛋白質上正負電荷作用強度的相關性，此一發現與實驗數據相符。

在另四篇與國立政治大學應用物理研究所助理教授馬文忠博士合作而於 2010 年二月、五月和十月發表於 JPSJ 的論文中，胡博士和馬博士用分子動力學模擬蛋白質的簡化模型在各種情況下的鬆弛和群集現象。他們發現影響群集現象的關鍵因素是和彎曲角(bending angle) 和雙面角(torsion angle)有關的作用力。當二者都是 0 或是很小時，蛋白質就容易形成群集現象。此一結果可以解釋何以 Aβ40 和 Aβ42 會產生群集現象。

胡研究員表示,下一步他與合作者將透過電腦模擬和解析分析建立蛋白質群集現象的一般性理論，以便於預測藥物，變異及蛋白質所處的環境，如何影響蛋白質群集的速率或抑制群集的發生。

參考網站：統計與計算物理實驗室網站
http://proj1.sinica.edu.tw/~statphys/.
PRL 論文: http://prl.aps.org/abstract/PRL/v105/i21/e218101
JPSJ: http://jpsj.ipap.jp/

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Dr. Chin-Kun Hu and Collaborators Discovered Key Factors for Protein Aggregation with Potential Applications in Attacking Neurodegenerative Diseases

Dr. Chin-Kun Hu of the Laboratory of Statistical and Computational Physics and his collaborators have made a breakthrough discovery about key factors for protein aggregation. The research results have been published in a series of papers at Physical Review Letters (PRL) and Journal of the Physical Society of Japan (JPSJ). Such results are useful for uncovering the mystery of protein aggregation and opening an avenue to guard against or cure neurodegenerative diseases.

Neurodegenerative diseases include Alzheimer's disease (AD)，Parkinson's disease (PD)， Huntington's disease (HD)，Spinocerebellar Atrophy，Frontotemporal lobar degeneration (FTLD-U), etc. Such diseases are due to progressive loss of structure or function of neurons, including death of neurons caused by protein aggregation. For example, AD is considered to be related to aggregation of Aβ40 (protein with 40 amino acids) and Aβ42 (protein with 42 amino acids) and HD and Spinocerebellar Atrophy are related to aggregation of PolyQ (protein with a long sequence of glutamine). Understanding the conditions and mechanism of protein aggregation is a very important academic and biomedical research problem.

In a paper published at PRL on 19 November 2010, Dr. Hu and collaborators at Poland, Vietnam and USA used a lattice model to study the aggregation rates of proteins. They found that the probability for a protein sequence to appear in the conformation of the aggregated state can be used to determine the temperature at which proteins can aggregate most easily. They also found a correlation between aggregation time and the strength of interactions between charged amino acids, which is consistent with experimental observation.

In a series of four papers published in JPSJ in February, May and October 2010, Dr. Wen-Jong Ma (now at Graduate Institute of Applied Physics, National Chengchi University, Taipei) and Dr. Hu used molecular dynamics to study relaxation and aggregation of protein chains under various conditions. They found that when the bending-angle dependent and torsion-angle dependent interactions are zero or very small, then protein chains tend to aggregate at lower temperatures. Such result is

useful for understanding aggregation of A β 40 and A β 42.

Dr. Hu said that in the next step he and collaborators would like to combine results from computer simulations, analytic calculations, and experimental data to formulate a general theory of protein aggregation so that one can predict the influence of environments, mutations, and drugs on protein aggregation rates or conditions for prohibiting the protein aggregation.

Related website:
Laboratory of Statistical and Computational Physics:
http://proj1.sinica.edu.tw/~statphys
PRL paper: http://prl.aps.org/abstract/PRL/v105/i21/e218101
JPSJ: http://jpsj.ipap.jp/.

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