From champagne bubbles, dance parties and disease to new nanomaterials

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Whether it is clouds or champagne bubbles forming, or the early onset of Alzheimer's disease or Type 2 diabetes, a common mechanism is at work: nucleation processes.

Nucleation processes are a first step in the structural rearrangement involved in the phase transition of matter: a liquid morphing into a gas, a gas becoming a liquid and so on. Clouds, boiling water, bubbles, and some disease stages are all characterized by the formation of a new thermodynamic phase which requires some of the smallest units of the new structure to form before this new phase can grow. Understanding this process is critical for preventing, halting or treating cases of nucleation processes gone wrong—such as in human disease. Now, a team of researchers from University College London and the University of Cambridge in Great Britain in collaboration with Harvard University have made headway toward understanding this problem from a molecular point of view in a new study. Their finding is significant across an array of phenomena, from human disease to nanotechnology.

"Perhaps an intuitive example of nucleation would be the way in which a quiet dinner party suddenly transforms into a dancing one; such a transition usually requires several people to start dancing at once, acting as a 'nucleus' around which the dancing party assembles," explained Anđela Šarić, lead coauthor at the University College London and the University of Cambridge. The results of this study will appear this week in The *Journal of Chemical Physics*.

"As commonly observed, if this group of dancers is too small, it tends to be ignored; however, above a certain size, this dancing nucleus attracts more and more people, eventually dominating the room," adds Thomas Michaels, the other lead coauthor. This minimum number of dancing people required to transform the party is what in thermodynamic terms is commonly known as the "critical nucleus."

In their research, the team considers a particularly intriguing example of a nucleated process: the formation of protein filaments. Many filamentous structures of proteins such as actin and tubulin are key for the growth, structural formation, movement and division of cells. They are an essential characteristic of living systems. However, protein filaments can also be disease-causing: Over 50 common disorders, including Alzheimer's disease, Parkinson's disease, and Type 2 diabetes, are associated with the formation and deposition in the brain or other organs of protein filaments commonly known as amyloids.

Using a combination of theory and computer simulations the authors explored the nucleation of protein filaments. Their goal was to establish the fundamental physical principles behind it. Their results showed that a seemingly complicated process of fibril nucleation is actually governed by a relatively simple physical mechanism: Unorganized clusters of proteins—so-called oligomers—are formed initially.

These structures do not resemble protein filaments yet, but have to undergo a structural conversion before they can grow into mature filaments, Šarić explained. They found that among many different steps in fibril nucleation, the shape change inside oligomers is the rate-determining step. Therefore, conformational changes in the protein inside oligomers (leading to the formation of β-sheet configurations) are crucial to understand fibril nucleation. Previously, the size of critical nucleus was considered the rate-determining factor.

The study represents an important step forward in the mechanistic understanding of the way in which protein filaments form. Such an understanding is key for studying the early stages in the onset of diseases associated with protein aggregation, as oligomers are increasingly believed to be the prime cause for cellular toxicity.

"Understanding which microscopic-level steps are determining for the formation of protein fibrils can provide invaluable information for designing rational therapies aimed at suppressing pathogenic oligomer generation," Šarić explained

Moreover, due to their unique physicochemical properties, protein filaments are finding extensive applications in materials science as biomaterials for nanotechnology," Michaels said. "Better control of filamentous growth would benefit the production of novel functional materials that have extensive applications in materials science as biomaterials for nanotechnology."

More information: "Kinetics of spontaneous filament nucleation via oligomers: Insights from theory and simulation," *Journal of Chemical Physics*, DOI: 10.1063/1.4965040

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