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Autonomous oscillation in supramolecular assemblies: Role of free energy landscape and fluctuations

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HIGHLIGHTS

- Autonomous oscillations in an equilibrium supramolecular assembly explained.
- Oscillations can result from the interplay of energy landscape and fluctuations.
- Demonstration system is $T = 1$ icosahedral virus capsid consisting of 12 pentamers.
- Langevin model accounting for interactions among neighboring pentamers is used.
- Limit cycle dynamics emerges after driving the system slightly out of equilibrium.

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ABSTRACT

Molecular dynamics studies demonstrated that a supramolecular assembly can express autonomous structural oscillations about equilibrium. It is demonstrated here that for nanosystems such oscillations can result from the interplay of free energy landscape and structural fluctuations. Furthermore, these oscillations have intermittent character, reflecting the conflict between a tendency to oscillate due to features in the free energy landscape, and the Second Law's repression of perpetual oscillation in an isothermal, equilibrium system. The demonstration system is a $T = 1$ icosahedral structure constituted of 12 protein pentamers in contact with a bath at fixed temperature. The oscillations are explained in terms of a Langevin model accounting for interactions among neighboring pentamers. The model is based on a postulated free energy landscape in the 24-dimensional space of variables describing the centrifugal and rotational motion of each pentamer. The model includes features such as basins of attraction and low free energy corridors. When the system is driven slightly out of equilibrium, the oscillations are transformed into a limit cycle, as expressed in terms of power spectrum narrowing.

1. Introduction

A corollary of the Second Law is that a macroscopic system in contact with a single bath of constant temperature cannot exhibit perpetual cyclic motion. Microscopic systems subject to isothermal conditions do exhibit normal mode fluctuations with amplitude that typically increases as $T^{1/2}$. Mesoscopic systems can exhibit apparent Second Law violation [1], although no oscillatory phenomenon was reported until recently [2]. The fluctuation theorem does allow for time intervals during which entropy decreases, but with probability that exponentially decays with the duration of such intervals [1]. This theorem was validated via MD simulation [1b], and experimentally for 6.3 μm diameter latex particles in an optical trap [3].

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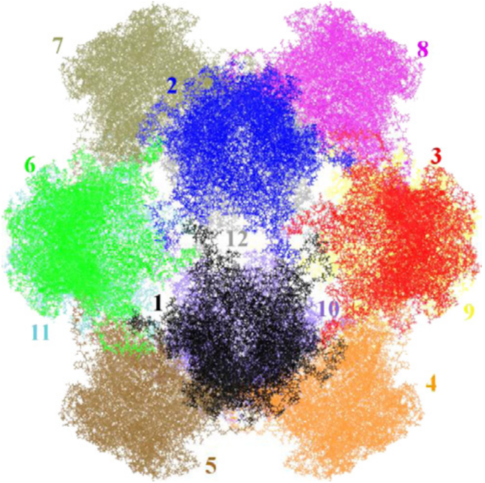

Fig. 1. Twelve pentamers of the $T = 1$ HPV16 VLP, PDB ID: 1DZL.

Recently, autonomous structural oscillations in the human papillomavirus type 16 (HPV16) virus-like particle (VLP) were discovered via isothermal MD [2]. These VLP structural oscillations are surprising for several reasons [2]:

- the system is friction-dominated (i.e., noninertial) and in contact with a single bath at fixed temperature;
- phenomenological studies of VLPs based on stress–strain laws can explain their structure and stability [4], suggesting that VLPs are large enough to display some macroscopic character;
- oscillation amplitude decreases when departing from room temperature, and oscillation is not expressed at low temperatures;
- the quasi-periodicity of these oscillations is expressed in the power spectrum, and notably the width and height of the peaks.

These notions suggest that autonomous oscillations in VLP structure are not straightforward to rationalize from existing perspectives.

It was hypothesized that VLP oscillations emerge via the interplay of features in the free energy (FE) landscape with omnipresent thermal fluctuations [2]. The objective of the present study is to assess this hypothesis and identify a more detailed mechanism of these autonomous oscillations. The approach used is based on Langevin equations [5] for VLP structural variables and a simple FE landscape.

The role of fluctuations in promoting non-linear phenomena was well studied in non-equilibrium systems [6]. Since the VLP oscillations occurred in equilibrium, they are distinct from the nonequilibrium oscillations studied earlier.

The autonomous nanostructure oscillations could be of interest in virology and vaccine design since it was demonstrated that immunogenicity of nanoparticles derived from virus building blocks increases as the amplitude of structural fluctuation (notably in selected regions, i.e., epitopes of the proteins) decreases [7]. Furthermore, preliminary studies on selected VLPs show that a hepatitis E protein $T = 1$ structure also shows oscillation, while a poliovirus type 1 $T = 3$ structure does not [unpublished]. There is an order of magnitude difference in the frequencies between HPV16 and hepatitis E protein assemblies. Since these VLP oscillations have frequencies in the 1–10 GHz range, they could likely be observed via existing spectroscopic techniques [8]. These results suggest that spectroscopic methods could be used to detect and identify viruses.

The oscillations in the $T = 1$ icosahedral structure of the HPV16 particle [9] (Fig. 1) involve radial motion of the twelve L1 protein pentamers relative to the center of the VLP [2]. The interplay of pentamer or hexamer translation and rotation was shown to be critical for understanding other nonlinear dynamical phenomena in VLPs, notably the swelling transition in CCMV [10]. Here, the oscillations are understood in terms of the dynamics of the translation and rotation of each of the 12 pentamers constituting the $T = 1$ icosahedral structure of the HPV16 nanoparticle [11]. From experience with the multiscale analysis of nanosystem dynamics [5b–d,12], it is expected that these 24 coarse-grained (CG) variables satisfy Langevin equations. Langevin models are standard in the study of fluctuations [13]. The coherent driving force in these equations is the gradient of the FE with respect to the CG variables. Frictional effects and their relation to random forces are accounted for by stochastic aspect of the Langevin equations and their relation to drag coefficients via correlation functions [5b,5d,14]. Coupling between neighboring pentamers is accounted for via the FE landscape and friction between neighboring pentamers.

Here, the notion is explored that the key feature in a FE landscape that promotes VLP oscillation is the existence of low-FE tunnels ("wormholes" henceforth) in the space of the CG variables. It is hypothesized that when these wormholes have closed loops, temporal oscillation can emerge as the system gets trapped in them. Repeated cycles of system deformation are fostered by confinement of motion to these loops and omnipresent fluctuations which drive the system over FE barriers within a loop. It is assessed whether quasi-periodicity follows if the coherent evolution back to the barrier is slow as the