Autonomous Oscillation in Supramolecular Assemblies: Role of Free Energy Landscape and Fluctuations

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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.

Keywords: supramolecular assembly, virus-like particle, autonomous oscillation, the Second Law, Langevin dynamics, free energy landscape, limit cycle.

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 μ m diameter latex particles in an optical trap.³

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 equations⁵ 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 to 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 particle⁹ (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 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.

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

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 system progresses around the loop, i.e., return to the barrier takes much longer than surmounting it. However, in a complex FE landscape the system can occasionally transition from one closed loop to another; in this way, the oscillation can be intermittent as the system switches between loops separated by barriers.

In this study, a minimal model of 24 CG variables, with one translational and one rotational degree of freedom for each of the 12 pentamers, is explored via Langevin equation techniques. A Langevin model of structural oscillations is introduced in Sect. 2 and simulation results are presented in Sect. 3. Discussion and summary of the observed dynamical behaviors, and conclusions are given in Sect. 4.

2. Materials and Methods

A framework for casting a model of autonomous structural oscillation is provided by multiscale perturbation theory applied to a nanosystem that is a composite of subsystems.^{5b, 12a} The result is Langevin equations for a set of CG variables describing the state of the subsystems (i.e., protein pentamers for the T=1 icosahedron of Fig. 1). In the following, the theory is developed in a series of steps to capture more and more of the complexity of the full system of Fig. 1.

2.1 One-Dimensional Langevin Model of Autonomous Oscillation of a Single Pentamer

The objective of the following formulation is to demonstrate that there can be features in the FE landscape which foster oscillation in the friction-dominated regime for an isothermal system. Consider a FE barrier with steeper ascent and smoother descent parts (Fig. 2) and such that the system has periodic boundary conditions (i.e., represents a loop the distance around which is denoted Φ). After overcoming the barrier, the system slowly returns to its foothill, completing one circulation around the loop in the CG configuration space. The presence of the barrier enables the system to have an equilibrium state. The barrier would have repressed oscillation if there were no thermal fluctuations. As is seen in the following, thermal fluctuations enable occasional surmounting of the barrier and consequent oscillatory dynamics as the system progresses around the loop. The smoothness of the descending part of the FE landscape is shown in Sect. 3 to make oscillations more periodic by forcing the system to spend more time while returning to the barrier foothill, rather than time needed for the noise-driven surmounting of the barrier.

Fig. 2. FE barrier along the loop for representative values of the 1D model parameters (20), distance along the loop is Φ (denoted ϕ after making model dimensionless).

In the following, a mathematical model is presented for a single moving pentamer with fixed neighbors and which is subjected to a fluctuating thermal force. Consider a single CG variable Φ

characterizing the state of **a system**, and notably measuring distance along a loop in CG variable space. As suggested by multiscale analysis,^{5b, 5d, 12a, 15} Φ is taken to satisfy **a** Langevin equation,

$$\frac{d\Phi}{dt} = Df + \xi \quad (1)$$

for diffusion factor $D(\Phi)$, thermal force $f(\Phi)$, and random force $\xi(t, \Phi)$. The dependence of D and ξ on Φ reflect possible differences in the noise before and after the barrier. The correlation properties of ξ are constrained by D (i.e., through the classic fluctuation-dissipation relation^{5b}). Such equations arise in the theory of **noninertial**, friction-dominated systems.^{5d, 16}

Consider a simple piecewise-linear periodic model for the FE with one barrier of height b at $\Phi = \Phi_{\max}$ and loop circumference Φ_0 ,

$$F = \begin{cases} b\Phi / \Phi_{\max}, & 0 < \Phi \leq \Phi_{\max}; \\ b(1 - (\Phi - \Phi_{\max}) / (\Phi_0 - \Phi_{\max})), & \Phi_{\max} < \Phi \leq \Phi_0. \end{cases} \quad (2)$$

With this, $F(\Phi)$ linearly increases from 0 to its maximum value b as Φ changes from an integer multiple of Φ_0 to $(\Phi \bmod \Phi_0) = \Phi_{\max}$, and linearly decreases to zero as Φ reaches the next integer multiple of Φ_0 . This model introduces a FE barrier (at $\Phi_{\max}$) and a slow FE descent back around the loop to the barrier (Fig. 2). The diffusivity is taken to have different constant values before ($D = D_1$) and after ($D = D_2$) the barrier, **to reflect the many smaller-scale barriers underlying the roughness of the potential energy landscape** after the barrier in this illustrative model. The CG variable Φ is driven by the FE gradient,

$$f = -\partial F / \partial \Phi. \quad (3)$$

The system has a FE barrier that can be crossed due to the fluctuating force ξ . When the barrier location $\Phi_{\max}$ is small compared to Φ_0 , the F profile is a steep rise followed by a smooth downward slope (Fig. 2). This one-dimensional (loop) model was simulated numerically using standard stochastic differential equation methods.¹⁷

The objective is to find a domain of model parameters within which oscillation is supported. The model (1), (2) contains six parameters: timestep dt , barrier location $\Phi_{\max}$, FE scale b , loop length Φ_0 ,

diffusivities before and after the barrier top, D_1 and D_2 . Two of the parameters can be eliminated by making the model dimensionless. It is convenient to eliminate dt and Φ_0 by the following scaling:

$$t = \tau \Delta t, \Phi = \phi \Phi_0, D_2 = \sigma D_1, D_1 = \delta \frac{\Phi_0^2}{\Delta t}. \quad (4)$$

To preserve accuracy, Δt is taken to be a small fraction of the characteristic time of system evolution. After scaling (4), Langevin Eq. (1) with FE (2) becomes a model with four dimensionless parameters:

$\nu = \frac{\Phi_{\max}}{\Phi_0}$ - relative position of the FE maximum, $\sigma = \frac{D_2}{D_1}$ - ratio of diffusivities after and before the

barrier, b measuring the energy and force, and δ measuring the diffusivities, where $0 < \nu < 1$, $0 < \sigma \leq 1$, $b > 0$, and $\delta > 0$:

$$0 < \phi \leq \nu \text{ (before the barrier), } F = \frac{\phi}{\nu} b, f = -\frac{b}{\nu \Phi_0}, \frac{d\phi}{d\tau} = -\frac{\delta}{\nu} b + \sqrt{\delta} \xi_1(\tau), \quad (5)$$

$$\nu < \phi \leq 1 \text{ (after the barrier), } F = \left(\frac{1-\phi}{1-\nu} \right) b, f = \frac{b}{\Phi_0(1-\nu)}, \frac{d\phi}{d\tau} = \frac{\sigma \delta}{1-\nu} b + \sqrt{\sigma \delta} \xi_2(\tau). \quad (6)$$

The subscripts in the noise terms in Eqs. (5), (6) reflect the differences in the before- and after-barrier

diffusivities used in the noise scaling.^{5b} $\xi_1(\tau) = \sqrt{\frac{\Delta t}{D_1}} \xi(t)$, $\xi_2(\tau) = \sqrt{\frac{\Delta t}{D_2}} \xi(t)$. In this model, the time

step Δt for numerical integration and loop length Φ_0 are equal to one after scaling.

While the deterministic term Df in the Langevin Eq. (1) can be handled using standard numerical techniques, the Maple package ‘stochastic’¹⁷⁻¹⁸ was chosen as the integrator for the random force ξ with a first-order Euler integration scheme. First, the noise with diffusion-limited time correlation was related to the stochastic Wiener process used in this package and representing white noise.¹⁷⁻¹⁸ The initial condition was $\phi(\tau=0)=0$. The diffusivity after the barrier is taken to be lower than that before ($\sigma < 1$) so as to probe the conjecture that this promotes oscillatory behavior.

2.2 Displacement-Rotation Langevin Dynamics of a Single Pentamer

Earlier studies on structural transitions in capsids show that changes in capsomer orientation can play a key role.¹⁹ This suggests the need for an extension of the simple model of Sect. 2.1 to include a pair of

variables, one for pentamer position and the other for orientation. Consider a 2D model built on a pair of variables describing pentamer translational (X) and rotational (Y) motion. The FE landscape is taken to have a valley that **turns** back on itself, constituting a loop within which the FE is low (Fig. 3).

Let X be the distance of the pentamer CM from the center of the capsid (Fig. 1) and Y be an angle of the pentamer relative to a ray from the center of the capsid to the CM of the pentamer. Introduce two auxiliary variables r, ϕ such that

$$X = X_0 + X_1 r \cos(2\pi\phi), Y = Y_0 r \sin(2\pi\phi), \quad (7)$$

where X_0 , X_1 , and Y_0 are constants. X_0 is the average distance of a pentamer's CM from the capsid center, X_1 is roughly the amplitude of the pentamer in- and outward motions, and $r \cos(2\pi\phi)$ is the dimensionless deviation of the pentamer's CM from X_0 as scaled by X_1 . Y_0 is roughly the maximum amplitude of pentamer rotational angle. The range of r is determined by the topography of the FE landscape manifested in the $\frac{k}{2}(r-r_0)^2$ term added to the 1D FE expression (5)-(6) (see Fig. 3). With this, the dimensionless FE is taken to be

$$F(r, \phi) = \frac{k}{2}(r-r_0)^2 + \begin{cases} \frac{b}{\nu}\phi^*, & \text{if } 0 < \phi^* \leq \nu \\ \left(\frac{1-\phi^*}{1-\nu}\right)b, & \text{if } \nu < \phi^* \leq 1 \end{cases}, \quad \phi^* = \phi \bmod 1, \quad (8)$$

where the k -term drives the system to the valley bottom ($r \approx r_0$). The constants ν and b have the same meaning as in the 1D model of Sect. 2.1. Driving forces f_r and f_ϕ are given by

$$f_r = k(r_0 - r), f_\phi = \begin{cases} -\frac{b}{\nu}, & \text{if } 0 < \phi^* \leq \nu \\ \frac{b}{1-\nu}, & \text{if } \nu < \phi^* \leq 1 \end{cases}. \quad (9)$$

Fig. 3. An illustrative FE landscape for a single pentamer described by the radial and angular displacements X and Y (7). Parameter values in the FE expression (8) are as in Eq. (22), except $r_0 = 1$ was taken for visual enhancement. *Blue* color signifies lower FE, *white* – higher FE. Interval between contours is $0.1b$.

The Langevin equations are

$$\frac{dr}{d\tau} = D_r f_r + \sqrt{D_r} \xi_r(\tau), \quad \frac{d\phi}{d\tau} = D_\phi f_\phi + \sqrt{D_\phi} \xi_\phi(\tau). \quad (10)$$

Here, ξ_r and ξ_ϕ are two independent noise terms for the variables indicated. Stochastic terms in Eqs. (10) constitute stationary random processes with associated implications for their autocorrelation functions, as for the 1D model. Constants D_r and D_ϕ are radial and angular diffusivities, respectively. It is assumed that the diffusion matrix is diagonal **in pentamer index**. In analogy to the 1D model, the diffusion factors are allowed to have different values before and after the barrier:

$$D_r = \begin{cases} \delta_r, & \text{if } 0 < \phi^* \leq \nu \\ \sigma_r \delta_r, & \text{if } \nu < \phi^* \leq 1 \end{cases}, \quad D_\phi = \begin{cases} \delta_\phi, & \text{if } 0 < \phi^* \leq \nu \\ \sigma_\phi \delta_\phi, & \text{if } \nu < \phi^* \leq 1 \end{cases}. \quad (11)$$

In this simple model the only $r - \phi$ coupling is via $D_r(\phi)$ (11).

2.3 Twenty Four-Dimensional Dynamics of a T=1 VLP

Consider T=1 VLP with its 12 pentamers (Fig. 1), the n -th of which is described by the radial displacement X_n and tilt angle Y_n ($n=1, \dots, 12$). In analogy to the one pentamer problem of Sect. 2.2, the dimensionless variables used are r_n and ϕ_n :

$$X_n = X_0 + X_1 r_n \cos(2\pi\phi_n), Y_n = Y_0 r_n \sin(2\pi\phi_n). \quad (12)$$

Interpentamer coupling is explored here via the following dependence of the barrier heights b_n on the state of the five neighboring pentamers $\{n\}$ and the n -th pentamer itself:

$$b_n(\phi_n, \phi_{\{n\}}) = b_{\max} e^{-\beta(\cos(2\pi\phi_n) - \langle \cos(2\pi\phi) \rangle_{\{n\}})^2}, \quad (13)$$

where $\langle \cos \phi \rangle_{\{n\}}$ is the average of $\cos(\phi)$ over the neighbors of pentamer n . As temperature increases, one expects that the FE landscape flattens, which could be crudely modeled by $b_{\max} \rightarrow 0$.

Considering the structural equivalence of pentamers, the location of the barrier along the ϕ_n axis is taken to be independent of n and equal ν . The total distance in ϕ_n to go around a loop is, by construction, one (see Eq. (12)). The radial and angular diffusivities D_ϕ and D_r are assumed to be constant, and similarly for the ratios of diffusivities before to after the barrier, σ_ϕ and σ_r (Sect. 2.2).

The FE F is written as a sum of contributions from each pentamer,

$$F(r_1, \dots, r_{12}, \phi_1, \dots, \phi_{12}) = \sum_{n=1}^{12} \left[\frac{k}{2} (r_n - r_0)^2 + \begin{cases} \frac{\phi_n^*}{\nu} b_n, & \text{if } 0 < \phi_n^* \leq \nu \\ \left(\frac{1 - \phi_n^*}{1 - \nu} \right) b_n, & \text{if } \nu < \phi_n^* \leq 1 \end{cases} \right], \quad \phi_n^* = \phi_n \bmod 1. \quad (14)$$

The contribution to F from n -th pentamer is the sum of the quadratic term in r_n and the interaction term which is similar in form to that used for the single pentamer case (Eq. (2)), except now b_n (13) depends on the state of pentamer n and its five neighbors $\{n\}$. The driving forces $f_{r,n} = -\frac{\partial F}{\partial r_n}$ and

$f_{\phi,n} = -\frac{\partial F}{\partial \phi_n}$ for auxiliary variables r_n and ϕ_n are

$$f_{r,n} = k(r_0 - r_n), f_{\phi,n} = \begin{cases} -\frac{b_n}{\nu}, & \text{if } 0 < \phi_n^* \leq \nu \\ \frac{b_n}{1-\nu}, & \text{if } \nu < \phi_n^* \leq 1 \end{cases} - \sum_{m=1}^{12} \begin{cases} \frac{\phi_m^*}{\nu} \frac{\partial b_m}{\partial \phi_n}, & \text{if } 0 < \phi_m^* \leq \nu \\ \left(\frac{1-\phi_m^*}{1-\nu} \right) \frac{\partial b_m}{\partial \phi_n}, & \text{if } \nu < \phi_m^* \leq 1 \end{cases} \quad (15)$$

(where only those pentamers m contribute for which $m=n$ or which are adjacent to n , i.e., $m \in \{n\}$).

The radial and angular diffusivities, D_r and D_ϕ , are given by Eq. (11) with r replaced by r_n , and ϕ replaced by ϕ_n . The Langevin equations for r_n and ϕ_n are

$$\frac{d r_n}{d \tau} = D_r f_{r,n} + \sqrt{D_r} \xi_{r,n}(\tau), \frac{d \phi_n}{d \tau} = D_\phi f_{\phi,n} + \sqrt{D_\phi} \xi_{\phi,n}(\tau). \quad (16)$$

These equations are similar to Eq. (10) for a single pentamer (Sect. 2.2). From the above, there are two contributions to the rate of change for ϕ_n (16) for FE driving force $f_{\phi,n}$ (15). There is a direct effect (i.e., as if the barrier height is nearest-neighbor independent and constant), and an indirect one from the derivatives $\partial b_{n'}/\partial \phi_n$ where n' is a nearest neighbor of n , and $\partial b_n/\partial \phi_n$, reflecting the influence of nearest pentamers' and the given pentamer's states on the barrier.

As in the single-pentamer models of Sects. 2.1 and 2.2, the autocorrelations of the random forces $\xi_{r,n}$ and $\xi_{\phi,n}$ are constrained by the values of the diffusivities^{12b} $\mathcal{D}$ or $\sigma\mathcal{D}$.

The lists of neighboring pentamers $\{n\}$ for each of the 12 pentamers of T=1 virus capsid structure in the expression for barrier height b_n (13) are generated using icosahedral symmetry (Fig. 1).

The derivatives in the angular forces $f_{\phi,n}$ (15) are

$$\frac{\partial b_m}{\partial \phi_n} = 2\beta b_m \left(\cos(2\pi\phi_m) - \langle \cos(2\pi\phi) \rangle_{\{m\}} \right) \left(2\pi\delta_{m,n} \sin(2\pi\phi_n) + \frac{\partial \left(\langle \cos(2\pi\phi) \rangle_{\{m\}} \right)}{\partial \phi_n} \right) \quad (17)$$

where $\frac{\partial}{\partial \phi_n} \langle \cos(2\pi\phi) \rangle_{\{m\}} = -\frac{2\pi}{5} \sin(2\pi\phi_n)$ if $n \in \{m\}$, and 0 otherwise. Thus, if $m \neq n$ and $n \notin \{m\}$,

then $\frac{\partial b_m}{\partial \phi_n} = 0$. If $m \neq n$ and $n \in \{m\}$, then $\frac{\partial b_m}{\partial \phi_n} = -0.2c_m \sin(2\pi\phi_n)$, where

$$c_n = 4\pi\beta b_n \left(\cos(2\pi\phi_n) - \langle \cos(2\pi\phi) \rangle_{\{n\}} \right). \quad (18)$$

Lastly, if $m = n$, then $\frac{\partial b_n}{\partial \phi_n} = c_n \sin(2\pi\phi_n)$. With the above and Eq. (15), one obtains

$$f_{\phi,n} = \begin{cases} -\frac{b_n}{\nu} - \frac{\phi_n^*}{\nu} c_n \sin(2\pi\phi_n), & \text{if } 0 < \phi_n^* \leq \nu \\ \frac{b_n}{1-\nu} - \left(\frac{1-\phi_n^*}{1-\nu} \right) c_n \sin(2\pi\phi_n), & \text{if } \nu < \phi_n^* \leq 1 \end{cases} + \\ + 0.2 \sin(2\pi\phi_n) \sum_{\substack{m \neq n, \\ n \in \{m\}}}^{12} \begin{cases} \frac{\phi_m^*}{\nu} c_m, & \text{if } 0 < \phi_m^* \leq \nu \\ \left(\frac{1-\phi_m^*}{1-\nu} \right) c_m, & \text{if } \nu < \phi_m^* \leq 1 \end{cases}. \quad (19)$$

2.4 Nonequilibrium Phenomena in a VLP

It might be expected that the above 24D VLP system can support nonlinear phenomena such as a limit cycle²⁰ when the system is driven out of equilibrium. Limit cycle is a coherent state of oscillation with stable amplitude. In the present picture, the oscillation would correspond to repeated traversal around a wormhole loop. As with other limit cycle-supporting systems, the system approaches the wormhole loop in the 24D space if displaced from it, i.e., indicating a degree of stability for the evolution of X_n, Y_n after some initial period. These effects were studied by adding a constant external force f_e acting before the **barrier** ($0 < \phi_n^* \leq \nu$) to the RHS of Eq. (19). This driving force is introduced to model non-equilibrium condition. It facilitates overcoming the FE barrier, reducing the time for random fluctuations to drive the system over it. This then transforms the ϕ_n trajectories to more monotonic increase with time, thus enhancing the periodicity of the X_n, Y_n dynamics.

3. Results and Discussion

3.1 One pentamer, 1D model

Three types of evolution for the position ϕ along the wormhole loop in the 1D model (5)-(6) of Sect. 2.1 were observed: (1) thermal noise in a high barrier system (Fig. S1a), (2) autonomous oscillation in a

system surmounting a steep FE barrier (Fig. 2) and smoothly returning to its foothill (Figs. 4a and S1b), and (3) forward-reverse fluctuation (Figs. S1c and S1d), including without overall preferential directionality (Fig. S1e), and purely reverse motion via a gentle upward slope through the top of the barrier (Fig. S1f).

The autonomous oscillations emerge in a narrow domain of parameters, and are intermittent in time (Fig. 4b). For instance, at $\nu = 0.1$, $\sigma = 0.5$ this domain is within the following range of the barrier heights and diffusivities: $\{b \in [0, 4], \delta \in [0.02, 0.33]\}$. Beyond this range, nothing interesting appears to happen (Fig. S1). Autonomous oscillation of a pentamer as a result of repeated surmounting of the barrier and regular cycling around the loop back to the barrier is achieved for a limited simulation time, e.g., at the following values of the 1D model parameters (Fig. 4a):

$$\nu = 0.1, b = 0.3, \delta = 0.12, \sigma = 0.5. \quad (20)$$

Sensitivity of the autonomous oscillation of Fig. 4a to values of individual parameters was studied to understand their influence on the existence and stability of the oscillatory phase. Analysis of the effects of each model parameter is given in Supplementary Materials. In brief, **the autonomous oscillations occur in a domain in** the space of four model parameters surrounding case (20) and stems from the balance between forward and backward forces mediated by fluctuations. E.g., at high barrier or low diffusivity after the barrier the backward force in the pre-barrier zone dominates and prohibits crossing the barrier, while at low barrier both regular forces vanish and the dynamics is a random walk.

Fig. 4. Evolution of a pentamer's CG variable $\phi(\tau)$ measuring distance along the wormhole loop in the 1D Langevin model. Initial data is $\phi(0) = 0$. a) Quasi-periodic forward jumps at lower barrier and larger diffusivity in the pre- and after-barrier regions. Parameters of the dimensionless model (5)-(6) are given in Eq. (20). b) Intermittent character of the autonomous oscillation, as seen from the switching of the sign of the $\phi(\tau)$ overall rate around $\tau = 35,000$ and $\tau = 75,000$. Model parameters are same as above. c) Power spectrum obtained using the Fourier transform of $\cos \phi(\tau)$. The most intensive harmonic has period of 435 timesteps.

3.2 One pentamer, 2D model

The following set of 2D model parameters (Sect. 2.2) was considered:

$$k = 10^5, r_0 = 0.1, b = 0.0029, \nu = 0.44, D_r = 10^{-6}, \sigma_r = 0.5, D_\phi = 0.023, \sigma_\phi = 0.25, \\ X_0 = 220, X_1 = 22, Y_0 = 50. \quad (21)$$

This set of parameters was chosen to optimize the regularity of the oscillation (e.g., there are no appreciable jumps in ϕ due to low angular diffusivity D_ϕ) and ensure accuracy of the numerical solution of Eq. (10). **Scaling parameter X_0 is related to realistic VLP size.** For this set of parameters, the pentamer overall has advanced in the forward direction for long periods of time, with the maximum contiguous excursion in ϕ corresponding to 35 periods of X oscillation, and maximum 13 consecutive periods during the first 10^6 evolution timesteps (Fig. 5a).

The FE increases rapidly as r deviates from r_0 for large k values (unlike in the illustrative FE landscape on Fig. 3, while for parameters (21) used here the FE valley is narrow) and the radial

diffusivity D_r is low, thereby confining the trajectory to a narrow ring $r(\tau) \approx r_0$ formed by the FE valley (Fig. 5b). The barrier creates the global FE minimum, i.e., equilibrium. For large k , the model is essentially equivalent to the 1D model studied above.

Overall, the nearly coherent oscillations of Fig. 5c and the power spectrum of pentamer outward motion $X(7)$ in Fig. 5d (*black curve*) confirm agreement with MD simulations that inspired this study and where autonomous oscillations of T=1 HPV VLP pentamers were discovered.² The intermittent nature of the oscillation is seen on a long-time trajectory (Fig. 5a).

Fig. 5. a) Intermittent forward-backward evolution of $\phi(\tau)$. b) Stochastic trajectory of the pentamer in the XY -plane demonstrating a quasi-periodic circulation around the FE valley (as in Fig. 3). First 10^4 time steps are shown. 2D model parameters given in Eq. (21) were used; no large jumps in ϕ result (i.e., the trajectory stays well within the loop). The initial conditions $r(0) = r_0$, $\phi(0) = 0$ were used; they do not

affect the long-time behavior due to ergodicity of the Langevin model. c) Autonomous oscillation of the pentamer displacement $X(\tau)$ (7). d) Power spectra at different time intervals during which ϕ increases or decreases essentially monotonically: *black* – increasing at $t = 399573 - 443525$, *blue* – decreasing at $t = 443525 - 562347$. Much broader peaks are seen for the reverse motion of ϕ .

3.3 Twelve pentamer, 24D model

Evolution of radial and angular variables (16) of the 12 pentamers was simulated using the following model parameters:

$$k = 3, r_0 = 1, b = 0.3, \nu = 0.1, D_r = 0.2, \sigma_r = 0.3, D_\phi = 0.12, \sigma_\phi = 0.5, \quad (22)$$

$$X_0 = 220, X_1 = 22, Y_0 = 50;$$

these were chosen based on results for the 1D model (20). Two types of initial data were considered. In the first type of run, identical initial values

$$r(0) = 1.1r_0, \phi(0) = 0 \quad (23)$$

were taken for each pentamer. In the second, individual initial values were selected as follows: $r_1(0)$ through $r_{12}(0)$ were

$$1, 0.99, 0.97, 1.01, 1.2, 1.01, 0.9, 0.98, 0.99, 1.1, 1.2, 0.89 \text{ in units of } r_0, \quad (24)$$

and $\phi_1(0)$ through $\phi_{12}(0)$ were taken to be

$$0, 0.1, 0.15, 0.21, 0.3, 0.32, 0.39, 0.45, 0.57, 0.65, 0.72, 0.81. \quad (25)$$

After an initial transient period, all subsequent results are expected to be identical due to the ergodicity of a Langevin model, and are as follows.

Effects of interpentamer coupling via the dependence of barrier height b_n of pentamer n on the phases $\phi_{\{n\}}$ of the five neighboring pentamers (13) are illustrated in Figs. 6, S3, and 8. Increase of the coupling parameter β from 0 leads to decrease in the barrier heights b_n , thus making the pre- and after-barrier FE gradients gentler. Monotonic decrease of the ϕ_n rates as β increases from 0 to 0.4 (Fig. 6)

implies lower rate of barrier crossing (and longer time to circulate around the 12 wormhole loops, one loop directly related to each of the 12 pentamers, as in Fig. 5b), and indicates that the effect of decreasing the after-barrier slope dominates over the speed-up due to decreasing barrier height. As β increases further, the barrier effectively disappears and the stochastic component of the dynamics dominates deterministic forces. As a result, directionality of the evolution is lost (the phases ϕ_n express random walk), as seen in Fig. 6 at $\beta = 0.4$. That the overall ϕ_n slopes are small and negative at $\beta = 0.6$ can be explained by the absence of the barrier and regular forces. When the coupling constant β is negative and its magnitude grows, b_n tend to be larger and the FE gradients before and after the barrier increase. As for positive β , the effect of the change in FE gradient after the barrier dominates, as evidenced by the increase of overall ϕ_n rates (Fig. 6, *brown curve*). After achieving maximum rate at $\beta \approx -0.2$, the ϕ_n rates start decreasing (see *green curve* in Fig. 6). Further decreasing β leads to increased tendency to reverse circulation around the wormhole loop (and intermittency, see *violet curve* in Fig. 6). For overall ϕ_n evolution, the effect of increasing barrier height makes the pre-barrier reverse force dominate over the forward force in the post-barrier region. At $\beta = -0.5$, the barrier becomes so high as to block progress of ϕ_n (cyan curve in Fig. 6). Eventually, the ϕ_n slope becomes negative and monotonically growing in magnitude due to increasing domination of the backward pre-barrier force.

Fig. 6. Influence of coupling parameter β on the evolution of angular coordinate for pentamer one. As β is increased from 0 (see legend), the pentamer oscillation period grows (the overall slope of $\phi_1(\tau)$ is positive and decreases). At $\beta \approx 0.3$, the overall rate of ϕ_1 becomes close to zero (i.e., random walk, see

orange curve). At $\beta \approx 0.6$, the slope becomes negative and remains small at higher β . As β is decreased from 0, the rate of $\phi_1(\tau)$ first increases and, starting at $\beta \approx -0.2$ (*brown curve*), tends to decrease (*green curve*), becomes intermittent at $\beta \approx -0.45$ (*violet curve*), then becomes close to zero at $\beta \approx -0.5$ (*cyan curve*), and eventually acquires increasingly negative slope (*dark green curve*). Similar behavior is observed for each of the 12 pentamers.

Effects of interpentamer coupling on the power spectrum of the outward pentamer displacement $X_n(\tau)$ are discussed below. As β is increased from 0 (Fig. 7a) to 0.2, more peaks emerge and the period of the dominant one increases (Fig. S4a-b). This tendency corresponds to the decrease in the overall rate of ϕ_n change and appearance of some backward evolution tendency (Fig. S3a-c). At $\beta = 0.4$, only two major peaks survive, and are well isolated (Fig. 7b), showing the existence of two well-defined oscillatory modes and implying their enhanced periodicity. Yet another indicator of improvement in the periodicity is an increase of the peak heights (as obtained after averaging over normalized spectra for 12 pentamers). For β decreasing below 0, the period of the dominant peaks first decreases (Fig. S4c-d) and then increases (Fig. S4e-f), while much of the power is for small periods (Fig. S4c-f).

Fig. 7. Power spectrum of X averaged over the 12 pentamers for different coupling parameter values.

Negative values of β induce clustering of the pentamers based on their $\phi(\tau)$ rate of change. For $\beta = -0.4$, pentamers 4, 7, 10, and 11 form a cluster with higher slope of $\phi(\tau)$, and the remaining eight form a second cluster with lower (and less different from each other) slopes (Fig. 8) after about 700,000

timesteps. However, this clustering only emerges when interpentamer coupling is sufficiently strong. Similar clustering was achieved using random initial data (24)-(25) (Fig. S5), confirming the ergodic character of the Langevin system. Clustering only emerges after an induction period during which the pentamers become correlated.

Fig. 8. Two groups of pentamers with different overall rate of change of $\phi(\tau)$ induced by the interpentamer coupling via the FE barrier (13) for the coupling factor $\beta = -0.4$ and the remaining parameters as in Eqs. (22)-(23).

3.4 Emergence of a limit cycle under nonequilibrium conditions

The effect of non-equilibrium conditions was considered in light of the possibility that multiple steady states^{20a} and limit-cycle oscillations²¹ could be expressed in nanoscale systems for the model of Sect. 2C. Non-equilibrium conditions were introduced by inducing the system to surmount the barrier, presumably such that there was enhanced light absorption for the configuration at the foothill of the barrier, **for a time-independent** illumination. This is achieved by introduction of **a** constant external force in the pre-barrier zone. For the parameters considered, the **system expressed** a noisy oscillatory behavior in the absence of illumination (such as in Fig. 9a); as the driving force is increased, more regular oscillations emerge (Fig. 10).

Fig. 9. Effect of the constant force f_e on the accumulated phase for each of the 12 pentamers. Values of f_e are indicated, units are in f_c (26). As f_e increases, the individual and average slopes of $\phi_n(\tau)$ increase and the periods of pentamer motion decrease.

In absence of interpentamer coupling ($\beta = 0$) and under increasing constant force f_e imposed in the pre-barrier zone, the following occurs. The $\phi_n(\tau)$ slopes monotonically increase, i.e., periods of oscillation shorten due to increasing f_e pushing the system over the barrier (compare Figs. 9a-c). Simultaneously, the smoothness of the $\phi_n(\tau)$ curves increases and deviations between their overall rates decrease. However, a mismatch between rates of change of ϕ_n between pentamers first grows with increasing f_e in the early stage of evolution and then, around $f_e = 0.9f_c$, it starts decreasing and, upon

reaching f_c , becomes smaller than at $f_e = 0$ (see Fig. 9c). This can be explained by changing the balance between stochastic and regular forces. As the external force increases (and therefore so does the coherent force), it effectively decreases the barrier that stochastic fluctuations must overcome. As a result, some of the pentamers slightly increase their rate of ϕ change. As f_e is further increased, more and more pentamers increase their oscillation frequency, and the mismatch between frequencies becomes larger (as in Fig. 9b at $t \approx 100,000$) for this early stage. However, at sufficiently high f_e and after some evolution time, the pentamers regain their similarity in the overall rate of ϕ , i.e., after the initial transient (see Fig. 9b after $t \approx 200,000$). Eventually, greater external forces f_e dominate the stochastic effects and all pentamers evolve with essentially the same frequency (see Figs. 9c and 10b).

Next consider the effect of the external force f_e on the power spectra of the radial pentamer displacements X_n . The power spectra were constructed using IFFT,²² and normalized such that the maximum power for each pentamer was one. To obtain an overall view, these normalized individual power spectra were averaged over the 12 pentamers. In absence of external force ($f_e = 0$), the average power was mostly distributed among four periods at 1306, 1032, 95, and 502 timesteps (in order of decreasing heights, Fig. 7a). The period of $X(\tau)$ is seen from the $\phi(\tau)$ profile when the latter is approximately linear, as is the case of Fig. 9. E.g., for the case of Fig. 9a, this implies that the periods of pentamer motion are in the range [510, 675] timesteps, which corresponds to the fifth major peak observed in Fig. 7a. That the dominating period is shorter (Fig. 7a) can be explained by the fact that part of the time pentamers move in reverse direction (Fig. 9a), that makes visually determined period seem longer, while the Fourier transform does not reflect the directionality of the motion and accounts for both forward and reverse jumps in ϕ_n . Note that increasing the external force to $f_e = 0.5f_c$, where

$$f_c = \frac{b}{\nu} D_\phi, \quad (26)$$

simplifies the spectrum (i.e., only two major peaks remain, compare Figs. 7a and 10a), and the narrowing of the peaks reflects enhancement of periodicity induced by f_e . At higher external force $f_e = f_c$, more peaks arise for the shorter periods (Fig. 10b). This is because the barrier gets effectively masked and evolution becomes stochastic; therefore, the periodicity of X_n is expected to become poor (Fig. 10b).

Fig. 10. Power spectrum averaged over 12 pentamers in absence of interpentamer coupling ($\beta = 0$) and for increasing external force f_e . The number of major peaks decreases and the period of the dominant one shortens as f_e increases.

3.5 Combined effect of interpentamer coupling and external force

Further improvement in the periodicity of pentamer oscillations was achieved when the effects of interpentamer coupling and external force were combined. The effect of interpentamer coupling at non-zero fixed external force f_e is similar to the case of $f_e = 0$ studied in Sect. 3.3. As β increases from 0, the dominant period increases (Figs. 11a-b, S6a), in the same way as for $f_e = 0$ (compare to Fig. 6). The rate of change in $\phi_n(\tau)$ becomes lower and thus the period of $X_n(\tau)$ becomes longer due to inclusion of positive coupling, signifying domination of decreasing the downward FE slope after barrier over smoothening the ascending part of the FE before barrier for the given values of β . As β decreases below 0, the dominant period first decreases, while it starts increasing when β decreases further (Fig. S6b-c), similarly to the case $\beta = 0$ (compare to Fig. 6). The latter trend is especially pronounced for $\beta < -0.2$ due to the exponential dependence of the barrier height b on β (13) (compare difference between Figs. S6b,c to that of Figs. 11a,b).

Fig. 11. Angles $\phi_n(\tau)$ of 12 pentamers in the presence of interpentamer coupling β and the external force f_e , whose values are given in the legend, with f_e in the units of f_c (26).

Fig. 12 shows the power spectrum averaged over 12 pentamers for different values of β and f_e . The power spectrum narrows, the number of prominent harmonics decreases, and dominant periods increase as β increases from 0 (Figs. 12a-b). This narrowing implies enhanced periodicity of the pentamer motions and is especially pronounced at high $\beta = \pm 0.4$ and high $f_e = 0.5f_c$ (Figs. 12c-d). In the latter cases, there is only one major peak whose height greatly exceeds that of others, indicating further improvement in periodicity due to the combined effect of interpentamer coupling and external force (compare to the same values of β for $f_e = 0$ in Figs. 7b and S4e). Coupling parameter β has stronger effect on the power spectrum than does the external force f_e / f_c ; however, it is noteworthy that $f_e = 0.5f_c$, which is less than characteristic value f_c , maintains a high degree of periodicity (Fig. 12c,d). The pentamer phases ϕ_n are plotted in Figs. S6d,e for the above cases of enhanced periodicity.

Fig. 12. Power spectrum averaged over 12 pentamers in the presence of interpentamer coupling and external force. β and f_e values are given in the legend, f_e is in units of f_c (26). Narrowing of the power spectrum due to (inserts a-b) interpentamer coupling at fixed external force, and (inserts c-d) combined effect of the interpentamer coupling β and external force f_e .

The effect of external force at fixed interpentamer coupling is as follows. Increase in f_e leads to shortening of the dominating period (Fig. 13, similarly to the case $\beta = 0$ in Fig. 10) and increase of its domination, as reflected in the increase of its power relative to that of other peaks (compare Figs. S7c-d). This effect is more pronounced for negative β (due to the related increase in barrier height).

Fig. 13. Phases ϕ_n for different values of external force and fixed interpentamer coupling.

Enhancement of periodic character of the X_n oscillations occurs via increasing both interpentamer coupling and external force (with strongest effect for positive β , Fig. 12c-d).

4. Conclusions

The autonomous oscillations studied here were first discovered using all-atom MD simulation of a T=1 icosahedral structure constituted of 60 HPV16 L1 proteins (Fig. 1).² The present study shows that such oscillations can emerge through the interplay of the FE landscape and thermal fluctuations. The FE model considered is based on the conjectured existence of low-FE corridors (wormholes) in the space of CG variables describing the structure of a supramolecular assembly. The FE landscape considered here was a function of positions and orientations of the 12 L1 protein pentamers of the T=1 icosahedral VLP structure. Thermal effects are embedded in the FE landscape which loses relief as temperature increases; as a consequence, the oscillations disappear with increasing temperature, as observed in MD simulations.²

Nanosystems have mixed microscopic-macroscopic character, the latter suggesting some restrictions on oscillation due to the Second Law. This would mediate against the possibility of sustained oscillation in an equilibrated isothermal nanosystem. However, the present Langevin simulations suggest that intermittent oscillation can be expressed at equilibrium when the FE landscape contains corridors which form loops. In this way, the system appears to be in a conflict in which oscillatory dynamics is expressed, only to be destroyed with Second Law-dominated epochs of essentially random fluctuation.

Others have shown that systems with multiple equilibria could express limit cycle oscillation very near equilibrium. These oscillations have period that diverges as equilibrium is approached.²³ Current study shows that autonomous oscillation can occur in a system with only one equilibrium state. In addition, there is a richness of oscillatory and non-oscillatory behaviors that can be fostered by varying the parameters of the Langevin model. Physical effects modifying these Langevin parameters include mutation/deletion/insertion of building blocks constituting the supramolecular assembly, or changes in temperature, pH or other conditions in the host medium. It is suggested here that the induction of nonlinear phenomena²⁴ such as limit cycles,²⁵ toroidal dynamics,²⁶ and strange attractors²⁷ can occur when nanosystems such as studied here are driven out of equilibrium.

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Supporting Information Available: Additional figures are provided that help trace influence of the Langevin model parameters on the evolution and power spectrum of the oscillating pentamers. This material is available free of charge via the Internet at <http://www.elsevier.com>.

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