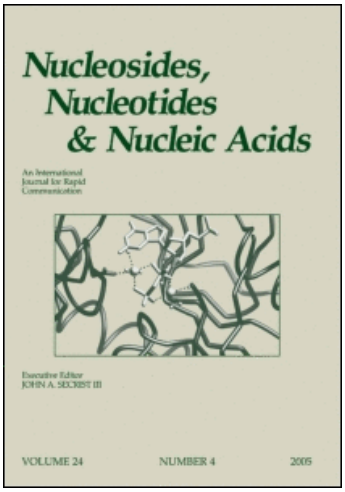

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Probability packaging of T4 coliphage DNA driven by oscillatory ATP consumption

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Probability packaging of T4 coliphage DNA driven by oscillatory ATP consumption

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An essay in honor of chemistry nobelist (1957) Lord Alexander R. Todd (1907-1997) who, together with J. Baddiley & A.M.Michelson, synthesized adenosine-5'triphosphate, identical with ATP from natural sources (J. Chem. Soc. London 1949, p. 582-586; see Nature **385**, 492, 1997).

Abstract

The strategies for packaging the T4 coliphage chromosome are presented. Our probability model based on fractality of DNA "globules" (fasces-like DNA globules) is consistent with transient condensation modelling to the final maximally condensed state.

Over the past decades new interpretations in natural sciences have brought forward *the physics of nonequilibrium processes* coupled with *self-organization concepts* and *dissipative structures*. Ilya Prigogine 1997 [1] describes these non-linear geometries as new in their applications, and includes self-similarities or joined ordered observations of biological structures. In addition, there is a useful knowledge of *fractal* geometries, and their mathematical scale-invariant characterization, in space and time [2-5]. This may be explored in molecular biology for giant macromolecules [6] as well as for molecular cell

structures [7]. One of the goals in fractality is to apprehend models, simulations, designs or derivatives that come out from intentional experimental data or observations in interdisciplinary studies. The data are obviously incomplete or snapshots within short-term or long-term processes showing growth, instabilities or chaos in networks [8], in nonstatic strings of higher complexity [9], in biorhythmics [10], or in synergetics [11]. *Fractal patterns* simplifying the conceptional visualization of dynamic processes are sought, and often found over several dimensions of scaling. An updated clarifying fractal recognition beyond experiments aids an apparently reductionistic interpretation. In this short paper we undertake looking for dynamic genomic viral DNA assemblies in structural simulations. Obligatory experiments we developed by transmission electron microscopy (electron spectroscopic imaging of phosphorus) belonging to these models, appear elsewhere. If DNA is subjected non-randomly to a self-assembly packaging, there must be also a general rule for internal DNA packaging as it already exists for virions, or the proteinaceous main part of virus particles, in icosahedral or other forms. The DNA self-assembly consumes ATP from the infected cells. The motor for intraviral DNA condensation waits for functional molecular description.

One of the most studied examples of molecular biology are the large tailed DNA bacteriophages T-even (T4) of *Escherichia coli* [12]. The phage T4 wildtype, lysing *E.coli* B cells rapidly (c. 25 min), represents a prototype for intracellular dynamic self-assembly of structural components (head, tail, collar, fibers etc.) as complexes of gene products encoded by T4 DNA. The phage chromosome is replicated in concatemeric branched homologous clusters. Morphogenesis operates similarly in many other DNA bacteriophages (T1, T3, T5, T7 and T-even; lambda, P22, phi29, and SPP1, in different host cells), and in some eukaryotic DNA viruses (e.g. herpesvirus, adenovirus). An early, plausible explanation was that the linear viral DNA was first intracellularly condensed, and then packaged in a protein shell [13,14,15]. It later transpired that the head (or the viral capsid) is preformed first to a processed prohead, and DNA is enzymatically inserted at the portal vertex during a third of the total lysis time of the infected host cell *E.coli* B. Finally a headful of DNA is cut by an active packaging mechanism at the open proximal T4 head [16,17]. Extracellular T-even coliphages also show a headful of coding DNA (166 kilobasepairs, two-ended duplex DNA) tightly packaged in the competent T4 head (occupying up to 55% of the inner space of the pronucleocapsid). The genes on the DNA genome are ordered circularly but are

permuted. A redundant DNA end piece is connected to the tail through which DNA ejection takes place [18]. We are interested in the process of intracellular DNA maturation, especially in the conformational self-assembly of one biomacromolecule of duplex DNA of coliphage T4 [19]. Its packaging into a prohead is the tight insertion of T4 DNA in limited nanospace (up to 100 nm maximal diameter) resulting in a nucleocapsid. The outcome is a densely packed DNA in a mature prolate delta-icosahedron (55-60% of inner volume). Then, the phage head is ready for infection. DNA injection occurs by release through a relaxed phage tail into an *E.coli* cell [20].

So far there exist three well-known molecular models of T4 DNA packaging (Fig.1a-c) in phage heads:

a) The concentric shell or toroidal model [21]: A shortcoming of this model is that it is necessary to rotate the T4 DNA in toto within the mature, quite rigid inner head space for quick injection into the *E.coli* cell.

b) The spiral-fold model [22]: During injection the unraveling of DNA is hindered by the inelastic icosahedron shell of the head.

c) The liquid crystal model [23]: No finite building blocks of liquid crystalline form [24] have so far been found in our examples.

For one physical reason or another, these three models (Fig.s 1a, 1b, 1c) have difficulties explaining the biological functions in relation to the allotted phage growth time; they neither satisfy the criteria of packaging nor those of release.

Most of the biochemical *in vivo* and *in vitro* processes involved in self-assembly are accompanied by the energy flow utilizing phosphorylation and dephosphorylation (for an early review see F. Lipmann [25]). Adenosine triphosphate is *the* soluble or membrane bound "master currency" (e.g. [26]) for a biological energy substrate in prokaryotes such as *E. coli*. ATP and ATP-dependent nucleoside tri- and diphosphates are used for a multitude of steps of anabolism and catabolism in prokaryotic and eukaryotic cells as well as for transport and mechanical work, membrane ion channels and muscle contraction (for example see [27,28]). More recently, rotary motion of proteins is described as a complex energy flow of ATP exemplified by continuous flagellar rotation, referred to in [29,30]. In these days, chemistry nobelists 1997 [31] are recognized for Fo/F1:ATP synthase (Fo:membrane factor, F1:ATPase) which shows an irreversible threefold or stepper rotation of F1 [32]. The multicomplex function is explained as a binding change mechanism [33]. Hence, there are many functional ATP

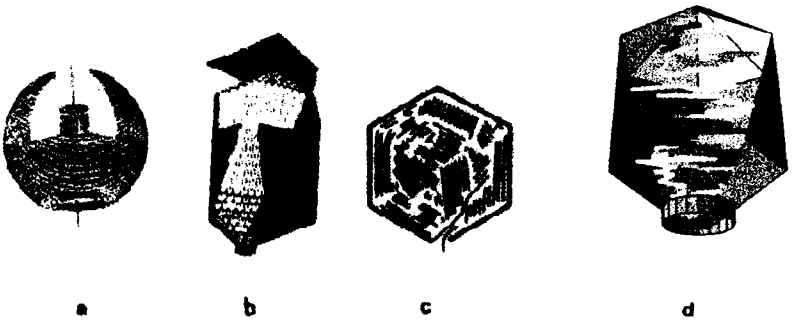

FIGURE 1

Models for T4-DNA packaging in a T4 coliphage head with dimensions from portal to distal vertex about 100nm. 1a. Toroidal model [21]. 1b. Spiral-fold model [22]. 1c. Liquid crystal model [23] 1d. Ratchet-like model [40], with ATP-consuming process at one move of high variability in DNA length. The head is shown with part of the collar (connector); the DNA is randomly oriented, in B-conformation.

consuming (ATP binding and ATPase acting) structures differing in many details. A more general theoretical discussion arises from "ratchet motion" and ATP consumption with directionality and deterministic oscillatory move [33a].

Packaging of the bacteriophage DNA genome [34] is the one ATP consuming process. After the DNA packaging period is ended, or is near its end, another ATP-consumptive process, apoptosis [35], is under way in E. coli cells. These are two interdependent processes [36], in changing DNA structures under packaging. We assume that in lytic infected *E.coli* B, the DNA of T-even coliphages fills the phage head under variably piecewise ATP consumption, far from equilibrium (Fig. 1d) and thus of the energy flow [37] at the orifice of the prohead (procapsid with proximal opening along the main axis). During the period of phage self-assembly in the prokaryotic cell, the DNA is finally packaged in the processed prohead of T4 bacteriophage, a headful in an icosahedron, by the terminase complex (gene products gp16, gp17 [19,38]). The intake of relaxed, multiply nicked DNA is a multistep-ordered, phage-specific, allosteric enzyme activity [17,19] upon variable DNA segments. The steps unidirectionally condense the phage genome under ATP uptake by a multiprotein gp16 system [39]. A

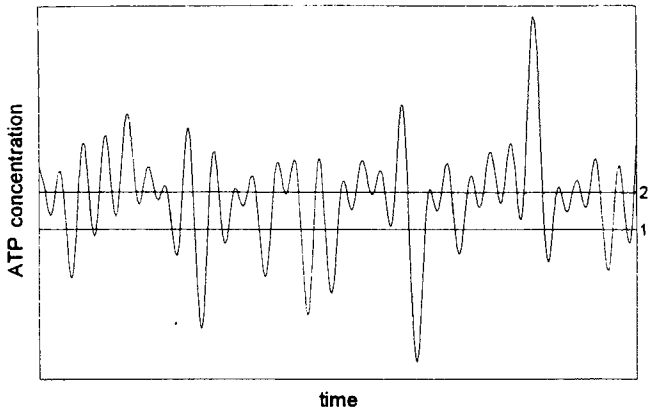

FIGURE 2

Schematic oscillations of ATP concentration at the T4 head. The pulsating changes in the concentration have two origins. First, the decrease in ATP is a result of the packaging of DNA. Second, the increase in ATP results from a continuous transport of ATP towards the portal complex where the "packasome" gp16 gp17 controls the input of DNA into the head. The packaging of DNA starts above a critical concentration (indicated by 2) and stops below a second threshold (labeled by 1). These two thresholds define the Lévy distributed periods of active packaging [40]. During these periods DNA is pulled into the head in nm-lengths (in the average <50 nm) and folded inside in metastable forms of globules.

first prominent characteristic is the stepwise move of the viral genome under final tension into an icosahedric container [40]. At the end, the T4-DNA is cut by a terminase component gp17 at the orifice. The gp16, gp17 motor might be called a transient "packasome" [17]). The T4 gene products gp16, gp17, located at the portal opening (3-4 nm diameter wide) of the proximal prohead, and additionally gp23 at the inner knobbed phage delta-icosahedron, produce a package of T4-DNA [16] in highest known DNA concentration (Fig. 1d).

The mechanism of the T4-DNA maturation within pre-nucleocapsids of an infected bacterial cell is assumed to be a metastable, non-symmetric DNA packing under sufficient free energy (tension), available for DNA ejection but being able to rearrange DNA segments to variations in local packaging pattern. An equivalent DNA

condensation may be widely distributed in similar fashion to bacteriophages and other viral genomes in isometric virion forms [41]. DNA may be filled in by energetic biochemical oscillations [10,42] and thus converts stepwise to a DNA package in the icosahedral head container. In T4-DNA, it carries intrinsic capacity of quick injection through the relaxed phage tail into a virginal new bacterial cell. Cellular ATP is a ubiquitous free energy source which gives rise to non-linear consumption. The small orifice three times the diameter of DNA at the proximal end of the prophage limits free diffusion of ATP complexes into the phage prohead. Our new model of pulsatile (or burst) DNA input in the T4 phage head should follow DNA packaging in an oscillatory, pulsatile, or quantal burst mode (Fig.2). The condensation is incrementally polarized through processes at gp23, a single-strand endonuclease at the knobbed internal head surface. The condensation processes are based on fractal measures, far from a simple idealized or random packaging mechanism.

From the electron microscopic demonstration of elongated "globules" in nm-range (we call fasces-like [40]), also found in T7 DNA packaging [43] we simulate a self-similar oscillatory filling mechanism. For each DNA move toward the container in the average two ATP molecules are needed. The quasi "necklace" structure of high DNA concentration in the head makes plausible a release of the single thread of T4-DNA in a period ten times shorter than the packaging that needs about one third of total lysis time of competent *E.coli* cells under normalized T4 coliphage growth.

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