PRAMANA
— journal of
physics



Vol. 58, No. 2
February 2002
pp. 439–442

# Mesoscopic biology

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**Abstract.** In this paper we present a qualitative outlook of mesoscopic biology where the typical length scale is of the order of nanometers and the energy scales comparable to thermal energy. Novel biomolecular machines, governed by coded information at the level of DNA and proteins, operate at these length scales in biological systems. In recent years advances in technology have led to the study of some of the design principles of these machines; in particular at the level of an individual molecule. For example, the forces that operate in molecular interactions, the stochasticity involved in these interactions and their spatio-temporal dynamics are beginning to be explored. Understanding such design principles is opening new possibilities in mesoscopic physics with potential applications.

**Keywords.** Gene expression; DNA; single molecule physics; genetic networks; optical tweezers; single molecule detection.

**PACS No. 87.10.+e**

## 1. Introduction

This paper outlines some of the current research work that is just beginning to be explored in the author's laboratory. Biomolecular machines at the nanometer length scales operate at low Reynolds number ($R < 1$), where viscous forces are dominant. For example the typical viscous drag force on a nanometer scale object is of the order of 10–15 N. In this Brownian environment these machines function far from equilibrium since they are driven by energy, generated by the hydrolysis of ATP and its analogs. A subtle interplay between force, energy, specific molecular recognition and self-assembly governs the spatio-temporal dynamics of these machines. These systems are stabilized by non-covalent weak forces thus allowing error correction and evolvability in the system. Examples of such a molecular machinery at work are seen in DNA-protein interactions that govern genetic processes, viral entry and its assembly, ligand-receptor interactions that lead to biosignal detection and transduction – to name a few. In cell signaling, for a given input, the output response is a result of complex biochemical circuits dictated by stochastic events at specific nodes. An understanding of such circuits (much in analogy with electronic circuits) require a quantitative analysis of the underlying biomolecular machines. Recent progress in mole-cular manipulation methods using optical, mechanical and microchip techniques combined with functional genomics has opened new possibilities in the study of mesoscopic biology. New optical probes such as quantum dots and single molecule fluorescence tracking and detection are allowing the study of biomolecular machines in complex biological environment.

Eventually this may also help in engineering nanoscale devices. In the following paragraphs we discuss the above themes in the context of DNA.

## 2. DNA – A charged polymer and an information template

The elucidation of the structure of DNA and the realization that DNA provides an information template for protein synthesis has been the corner stone of modern biological research [1]. DNA serves as an information template for gene expression, while being a flexible polymer chain. A specific DNA sequence, called the gene, is the element of information. The sequence of information and the mechanical properties of the DNA polymer affect molecular recognition during DNA-protein interactions that mediate gene expression. In such processes the polymer might undergo a conformational change through stretching and bending. The flexibility of DNA is thus an important parameter defining the molecular interactions. In higher biological systems DNA is in a highly condensed state (called the chromosome) due to its self-assembly around histone protein complexes. This enables the long DNA polymer to be organized into the cell nucleus. The chromosome is remodeled to access information during genetic processes. The physical mechanisms of DNA organization by proteins and its temporal expression are just beginning to be explored [2,3].

Charge plays an important role in the biology of DNA, its mechanical flexibility and its interactions with proteins and lipids. Recent progress in single molecule methods has brought to focus the study of intrinsic charge transport in DNA molecules. The typical values of measured electronic conductivity suggest that DNA may be a conducting polymer with interesting physical mechanisms of one-dimensional charge transport that remain to be understood [4].

A DNA polymer in a solution attains a random coil conformation to maximize entropy. The typical radius of gyration or the end-end distance of the coil is determined by its length and the bending rigidity. Thus the mechanical response of a DNA molecule, to an applied external force, has two regimes – entropic and enthalpic. The entropic regime is driven by the thermal energy and the enthalpic regime by the base pair stacking interactions. The entropic forces are typically of the order of 5 picoN ($K_{\mathrm{B}}T$/nm) and the enthalpic forces are of the order of 100 picoN (eV/nm, where eV is of the order of chemical bonds energy).

It is thus apparent that the manipulation of single molecules requires ultra sensitive methods of force detection [5,6]. In these experiments, a single DNA polymer is anchored at one end to a solid substrate and a dielectric particle at the other end, acting as a molecular handle. The particle is manipulated using physical methods such as an optical tweezer or an atomic force microscope. An optical tweezer is a device based on focusing an intense laser beam into a diffraction limited spot – thus creating an electric field gradient. A dielectric Brownian particle in a solution can then be trapped at the focal point of the laser beam where the scattering and gradient light forces on the particle are balanced thus creating a harmonic potential. A typical micron scale particle can be confined in a potential of $\sim 150K_{\mathrm{B}}T$ using a 100 mW infrared laser. These methods, with sub-picoN forces and nanometer scale displacement resolution, enable the study of the dynamics of biomolecular machines that act on the DNA [7].

## 3. Gene expression – The biomolecular machines at work

The transfer of information from DNA to protein (gene expression) involves remarkable biomolecular machines, such as the RNA polymerase to transcribe and the ribosome to translate genetic information. The various molecular processes involved in gene expression include – the assembly of transcription machinery on a DNA template, the act of transcription, the coupling of newly synthesized mRNA template to the translation machinery, the synthesis of nascent protein from the mRNA template and its folding to a functional molecule. The single molecule experiments may clarify the underlying physics of these processes.

Biomolecular machines such as the polymerase and the ribosome are about 5 nm to 20 nm in diameter. Central to gene expression is the binding of the polymerase to a specific promoter sequence on the DNA, followed by its stepwise translocation with respect to the DNA polymer during transcription and at the next level the binding and translocation of the ribosome on the messenger RNA polymer during translation. Energy is consumed in these processes by the hydrolysis of ATP. Typical velocities of these machines are of the order of 40 base pairs/s, which turns out to be around 13 nm/s. Given the helical nature of DNA, these protein machines have both linear as well as rotatory motion. On a more speculative note one can explore to realize directed nanoscale motion of these machines along specifically aligned DNA polymers on a microchip substrate and as such control their motion using the underlying sequence information. In analogy one can imagine DNA as a railway track and the molecular machines such as the RNA polymerase as the train. Motion from point A to B on the track requires a defined start sequence, called the promoter sequence at point A and a terminator sequence at point B. The polymerase motion from A to B on DNA also carries with it the encoded message. From this one can hope to realize nanomechanical devices that move on DNA based on the designed sequence and carry along with its motion an information template for further processing. Given that such nanoscale motion is unrealizable by semiconductor nanotechnology, biomolecular machines may offer novel possibilities in this direction.

## 4. Genetic circuits – Interacting biomolecular machines

Complex regulatory circuits control gene expression in response to external as well as internal stimuli [8,9]. This regulatory feedback process is often enhanced by thermal fluctuations at the level of DNA-protein interactions and the variability in the regulatory protein concentration. For example a repressor protein bound to a specific DNA sequence, that follows the promoter sequence, inhibits the movement of the RNA polymerase thus turning off the gene expression. Hence the repressor protein in the above case acts as a negative feedback regulatory element. The study of spatio-temporal fluctuations in protein concentrations using single molecule tracking techniques within a biological cell leads to the analysis of these genetic circuits. Single molecule tracking techniques are based on confining a laser beam to a diffraction limited confocal volume to excite the fluorescent reporter proteins in this volume. A typical protein tagged with a fluorescent reporter emits around $10^5$ photons within its lifetime. This allows the study of protein dynamics using single photon counting methods. Using the advances in solid state technologies such as

quantum dots, which have longer lifetimes, may improve the efficiency of single molecule tracking methods.

Bacterium is a simple model organism to study genetic regulatory circuit. It is about a micron in diameter, femto-litre in volume and has a genome comprising of about 4000 genes. At any given time only a small subset of these genes are expressed. Complex gene expression patterns and their interactions orchestrate the bacterial function. The genetic circuits can be described in analogy with electronic circuits, with the protein concentration being analogous to the electron concentration defining the signal amplitude. The noise is equivalent to discrete electronic events with a high signal/noise and high bandwidth. In correspondence, the noise in genetic circuits is due to discrete biochemical interactions with a low signal/noise and low bandwidth. The dynamics in gene expression patterns are beginning to be analyzed using microelectronic based DNA chips by detecting the global messenger RNA and protein expression levels. Such analysis will lead to the understanding of the biological feedback algorithms in living cells. This may also provide means to artificially realize robust designable feedback algorithms using the basic information elements, such as DNA and by invoking physical controls of gene expression [10].

## 5. Conclusions

At the nanometer length scales, biology offers interesting design principles that may open new avenues in mesoscopic physics [11]. Here we have considered the example of DNA as a self-assembling charged polymer and an information template for genetic processes. However, there are other elegant biomolecular machines in biological systems that participate in a variety of cellular functions; for example cell movement, signal detection and transduction, cell division and development. Clearly the study of these machines using mesoscopic methods may help in understanding the biological processes. In turn they may provide model systems in soft matter physics and nanotechnology.

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