Critical Reviews in Biochemistry and Molecular Biology, 2011; 46(4): 310–326

ISSN 1040-9238 print/ISSN 1549-7798 online
DOI: 10.3109/10409238.2011.582081

informa
healthcare

REVIEW ARTICLE

Fundamental and functional aspects of mesoscopic architectures with examples in physics, cell biology, and chemistry

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Abstract

How small can a macroscopic object be made without losing its intended function? Obviously, the smallest possible size is determined by the size of an atom, but it is not so obvious how many atoms are required to assemble an object so small, and yet that performs the same function as its macroscopic counterpart. In this review, we are concerned with objects of intermediate nature, lying between the microscopic and the macroscopic world. In physics and chemistry literature, this regime *in-between* is often called *mesoscopic*, and is known to bear interesting and counterintuitive features. After a brief introduction to the concept of mesoscopic systems from the perspective of physics, we discuss the functional aspects of mesoscopic architectures in cell biology, and supramolecular chemistry through many examples from the literature. We argue that the biochemistry of the cell is largely regulated by mesoscopic functional architectures; however, the significance of mesoscopic phenomena seems to be quite underappreciated in biological sciences. With this motivation, one of our main purposes here is to emphasize the critical role that mesoscopic structures play in cell biology and biochemistry.

Keywords: Mesoscopic phenomena, mesoscale, non-equilibrium phenomena, functional architectures, cell biophysics, noise-induced phenomena, confinement effects, small biological systems

Introduction

Many centuries of scientific research has focused on exploring either microscopic systems containing a few entities, as in atomic and particle physics, or macroscopic systems that are composed of an overwhelmingly large number of entities, as in thermodynamics, ecology, and astrophysics. As a result, a substantial level of understanding of microscopic and macroscopic systems has been established. For the very small, there are experimental methods with impressive accuracy and well-developed theories at our disposal. A striking example is the knowledge of an intrinsic property of an electron, namely the anomalous magnetic dipole moment, for which the observed value and the value predicted by quantum electrodynamics agree up to eight decimal places (Gabrielse et al., 2006; Odom et al., 2006). In the opposite extreme, for the very large, our toolbox is not empty either. For instance, the behavior of many Avogadro's number of gas molecules can be well-characterized by thermodynamics. A simple and practical measure of how successful thermodynamics has been is the rapid development of engines starting with the industrial revolution (Kondepudi and Prigogine, 1998).

Between these two extremes lie *mesoscopic* systems (the prefix *meso* is Greek for "middle," which is used throughout the literature to emphasize the intermediate nature of many aspects of these systems). In contrast to the previous cases, our understanding and ability to control are both quite limited at this level. In this article, we focus on the current status in our understanding of mesoscopic systems with examples from physics, biology, and chemistry.

In many ways, the study of mesoscopic phenomena is the study of how small a macroscopic functional object

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(Received 01 March 2011; revised 14 April 2011; accepted 14 April 2011)

can get. In his recent book titled "Middle world," Mark Haw skillfully tells the story of how life is at the mesoscopic level by bringing many striking examples from the history of science to life (Haw, 2007). One of the questions that naturally comes up in Haw's book is: how small can an ordinary engine get? An ordinary engine, such as the thermal engine inside a truck, has macroscopic moving parts and runs by dissipating heat. This kind of engine works only in one direction, in accordance with the laws of thermodynamics, especially about the one which states that entropy will increase. Now let us think an extremely small version on this engine. It is well-known that in a small system, entropy can spontaneously decrease due to fluctuations (Sevick et al., 2008). The possibility of entropy decrease would have a profound effect, as it implies that a miniature engine may spontaneously work backward, consuming entropy. Nevertheless, it is still possible to have engines that work properly at this scale; however, with fundamentally different designs, as we will discuss later in this review in the context of molecular motors. We may argue that similar effects would also be observed while miniaturizing electronic devices. As we will discuss in the next section, even ordinary metals start to behave fundamentally differently as they become smaller and smaller (Imry, 2002; Akkermans and Montambaux, 2007). This does not mean that it is not possible to make small devices; however, the rules that govern how small, or mesoscopic, objects function are significantly different at this scale, requiring novel designs.

In our consideration, some of the distinctive properties of a mesoscopic system include: containing at least a few molecules, having a characteristic length between a few nanometers and a micron, and, in some cases, a characteristic energy comparable with the average energy of the random fluctuations in the surrounding medium.

It may look like the properties we have just listed were chosen quite arbitrarily. However, as we will argue in detail later on, these descriptive properties reflect the fact that in mesoscopic systems, many characteristic scales of the system match those in the surrounding medium or within itself. A typical example is a quantum dot, in which the wavelength of an electron is comparable with the size of the crystal that surrounds it (Reed et al., 1988). As a result, the quantum dot that is composed of many atoms behaves like a single atom as a whole.

Understanding how the machinery of cells works has proved to be a challenging task partly due to the large variability in experimental results, and the absence of a well-established theory that can guide us through the extremely rich collective behavior of these systems. This difficulty seems to stem from the mesoscopic nature of cellular processes. However, we think the notion of mesoscopic phenomena in biology is not well-established. With this motivation, one of our main goals is to emphasize the concept of mesoscopic phenomena in cell biology. Unlike the vast number of articles discussing the bulk biochemical reactions and cellular images, we would like to emphasize the importance of dynamics and flexibility in structure of biomolecular complexes containing several to several hundreds of molecules, rather than the ensemble average of the Avogadro numbers of molecules. In doing this, we discuss examples of mesoscopic functional architectures in cells, and their dynamics.

This review is mainly composed of three parts that discuss the behavior and function of mesoscopic architectures from the point of view of different disciplines. In the next section, we briefly review some of the well-known examples of mesoscopic phenomena in condensed matter and statistical physics. Afterward, we discuss the significance of mesoscopic effects in cell biology, and elaborate on examples of functional mesoscopic architectures in cells. In the third section, we consider examples of synthetic mesoscopic architectures in chemistry and material science, which is followed by our concluding remarks and future outlook.

Mesoscopic physics in brief

In physics literature, the term mesoscopic is often used to refer to systems of intermediate size, between an elementary particle and a macroscopic piece of material (Chow, 2000; Imry, 2002; Akkermans and Montambaux, 2007). At this scale, many novel phenomena have been observed, as we will discuss in the rest of this section. The majority of the body of work associated with mesoscopic physics is in the field of condensed matter and statistical physics, and is concerned with systems in which quantum mechanical effects are observable at a surprisingly large system size (Imry, 2002; Akkermans and Montambaux, 2007). In this sense, the objects of mesoscopic physics are those that behave like large quantum systems weakly coupled to their environment. Another context in which we encounter the word mesoscopic is non-equilibrium statistical mechanics of small systems (Ritort, 2008). With decreasing size, regardless of any quantum mechanical effects, the behavior of a system becomes increasingly sensitive to the fluctuations in the environment. This regime in which fluctuations are indispensable in describing the dynamics is the mesoscopic regime, and the systems of interest are mesoscopic systems. Having defined this paradigm, we cannot but remark that seeking a clear-cut definition of what is mesoscopic and what is not is probably an act in vain. However, we believe that these two classifications are useful in covering many instances of interesting phenomena.

Quantum physics and mesoscopic phenomena

One of the outstanding problems in physics is concerned with the transition from quantum to classical mechanics (Schlosshauer, 2007; Zurek, 2009). Although the details of this transition are poorly understood, many of the fundamental differences between quantum mechanical and classical phenomena have been revealed. One of the

key concepts in the study of these differences is phase coherence (Greenberger et al., 2009). For instance, what distinguishes a laser beam from light emitted from an incandescent light bulb is its well-defined phase, which makes it a coherent light source. If a laser beam passes through a cloud of atoms, it starts to lose its property of being phase coherent, and gradually turns into an ordinary light beam (Labeyrie et al., 2006). How long, or how far, does it take for a laser beam to lose its coherence? The answer depends on the detailed properties of the atoms that scatter the laser beam and defines the limits on the observability of quantum mechanical effects. Mesoscopic physics deals with systems whose length, time, and energy scales are comparable with those at which the system begins to lose its coherence (Imry, 2002; Akkermans and Montambaux, 2007). In the first part of this section, we will briefly review similar examples from physics and discuss the characteristics of mesoscopic phenomena.

Examples of mesoscopic phenomena in condensed matter and statistical physics

Many interesting phenomena can be observed in systems involving inhomogeneity. A typical example from condensed matter physics is an ordinary conductor that bears a certain amount of impurity (Altshuler et al., 1991). The presence of impurities gives rise to disorder in a conducting sample and affects its conductivity. In many experiments, it was found that the characteristics of conductivity can vary greatly between samples if the sample size is below a characteristic value (Imry, 2002). This characteristic value is intimately related to the length at which the electrons in the material lose their phase coherence (Webb and Washburn, 1988).

A striking example of how the qualitative behavior of a system can change dramatically as a function of its size is made by quantum dots. Quantum dots are semiconductor crystals whose dimensions range from a few to a few tens of nanometers (Reed et al., 1988; Reed 1993; Hanson et al., 2007). What is remarkable about them is that even though their size can be several orders of magnitude larger than an atom, they respond to light much like a single atom. When irradiated, a quantum dot can reach an excited state and subsequently return to its ground state, which is usually accompanied by emitting a photon. The frequency of the emitted photon depends on the size of the dot. In a quantum dot, the charge carriers are confined in all three dimensions, which results in quantized energy levels. The energy difference between the levels can be significant due to the similarity between the de Broglie wavelength of the charge carriers and the physical dimensions of the quantum dot. As a result, a quantum dot is a physical realization of a particle in a box, much like an artificial atom (Arndt, 2009).

Another interesting mesoscopic phenomenon is the wave-like behavior of large molecules. It is well-known that electrons and atoms behave like waves and produce an interference pattern in an experiment similar to Young's double slit experiment (Berman, 1997). For larger aggregates of matter, the wave-like properties become less and less important, and eventually the behavior of matter starts to obey classical mechanics. Surprisingly, experiments showed that large molecules such as fullerene can behave like a wave, and produce an interference pattern in an interferometer (Hackermüller et al., 2003; Arndt et al., 2005). Experiments of this kind show that the coherence length in a system composed of many molecules can be quite large, and give us a handle on to what physical extent mesoscopic phenomena can be observed.

A closer look at the conductivity of regular metals

As the mentioned in the previous section, mesoscopic samples from a conducting material that includes impurities can have very different conductivities. We would like to elaborate on this example to stress that each mesoscopic sample has its own signature, which is reproducible when two different experiments are conducted in identical conditions. For macroscopic samples whose sizes are much larger than the coherence length, the conductivity is characterized by ensemble averaged properties, and sample-to-sample variability becomes negligible.

The signature of a sample is determined by its detailed internal configuration, that is, the positions and states of each impurity it contains. Obviously, predicting this signature can be a daunting task, as it requires the knowledge of microscopic details about the sample which is often inaccessible. Since the early 1980s, many theoretical and experimental studies focused on mesoscopic conductors. For an extensive discussion on this subject and references, we refer the reader to the books by Imry (2002), and Akkermans and Montambaux (2007). Here, we would like to discuss one of the first observations that clearly showed the mesoscopic effects in a thin metal wire. Webb et al. demonstrated that the resistivity of thin metal rings, whose average diameters are below 1 μm, oscillates as a function of magnetic field (Webb et al., 1985). In their experiment, the authors measured the resistivity of a gold ring in the presence of a magnetic flux (see Figure 1A). As shown by Aharonov and Bohm (1959), the phase of an electron can be shifted due to magnetic flux in a predictable manner. Just like the bright and dark fringes that appear in an interference experiment, resistivity can take on cyclic high and low values due to interference between electrons in the conductor. In the presence of a magnetic flux, electrons in different arms of the gold ring acquire different amounts of phase shift. By varying the strength of the magnetic flux, the relative phase between the electrons in different arms can be tuned, which leads to constructive or destructive interference. This in turn modifies the properties of electron transport inside the conductor and gives rise to oscillations in resistivity. Remarkably, the oscillations in

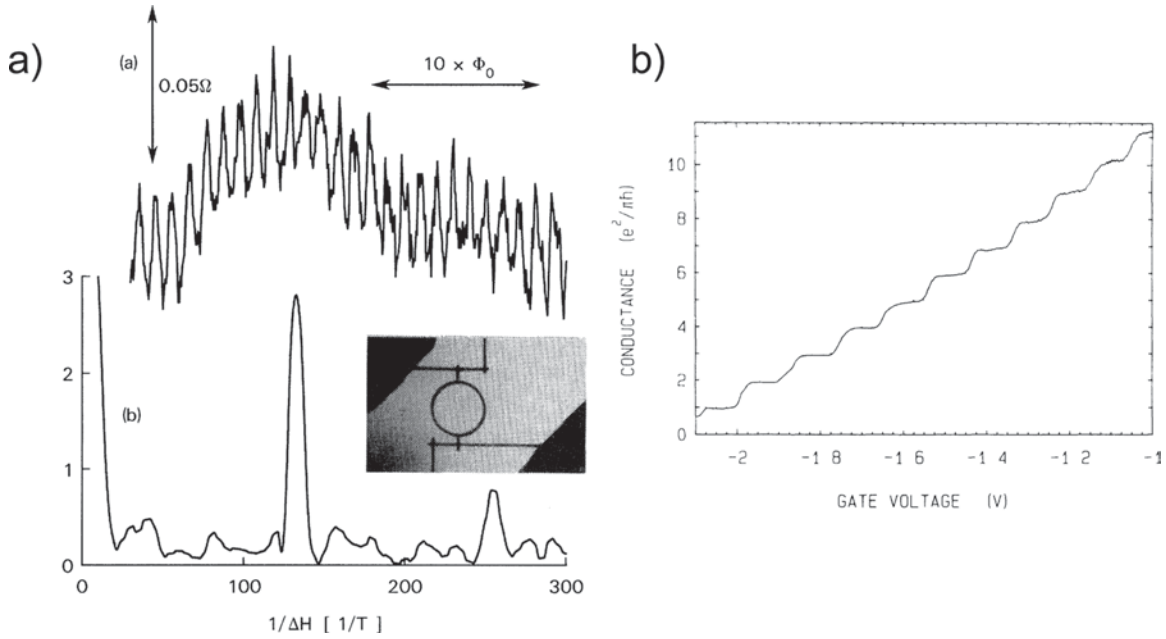

Figure 1. (A) Top: resistance of a gold ring as a function of the magnetic field. The gold ring used by Webb et al. in this study is shown in the inset. The diameter of the loop is 784 nm and the wires have a width of 41 nm. Bottom: frequency content of the resistance, clearly showing the Aharonov–Bohm oscillations. Adapted from Webb et al. (1985). Copyright (1985) by the American Physical Society. (B) Discreteness of the conductivity for a narrow conductor (measured conductance of point contacts). The plateaus in the conductivity are located at multiples of $e^2/\pi\hbar$, which is a combination of fundamental constants alone. The x-axis is proportional to the effective width of the conductor and varies between a few and 360 nm, with an estimated increment of 22 nm per step. Adapted from van Wees et al. (1988). Copyright (1988) by the American Physical Society.

resistivity are completely reproducible and are observable due to the smallness of the sample.

Not only sample-to-sample variability becomes significant near the coherence length, but also dramatic qualitative changes in the conductance occur. A typical length scale in a conductor is the Fermi wavelength of the electrons. When the sample size is comparable with the Fermi wavelength, the conductance may take only discrete values as opposed to a classical conductor whose resistance varies continuously, as first shown by van Wees et al. (1988) and Wharam et al. (1988). In Figure 1B, key result in their pioneering study is displayed.

Universality of mesoscopic conductance fluctuations

So far, we stressed the sample-to-sample variability in conductivity, which gives the impression that there is no room for generally applicable principles at the mesoscopic level. However, the truth is different. Even though this physical property differs greatly among different samples, its variance is shown to be the same, even among samples from materials of different kind, dimensionality, and impurity distribution (Altshuler, 1985; Lee and Stone, 1985; Béal-Monod, 1994). Under quite general conditions, the variance was shown to be of the order $(e^2/h)^2$, where e denotes the charge of the electron and h is Planck's constant. We refer the reader to the references cited for the details and applicability of this result. Both theoretical and experimental evidences exist for the remarkable universality of conductance fluctuations, which shows that mesoscopic materials can exhibit common behavior solely due to the fact that they are in the mesoscopic regime, which is determined by the coherence length in the system (Imry, 2002; Akkermans and Montambaux, 2007).

Mesoscopic phenomena in a noisy environment

So far, we discussed the mesoscopic systems as characterized by being intermediate between the quantum and classical worlds, and the example systems consisted of objects that are found in the shelter of a condensed matter physics laboratory. In general, small systems are surrounded by a restless world with which they constantly exchange energy. In the rest of this section, we will be concerned with a different face of mesoscopic phenomena, in which the word mesoscopic is used to indicate that the system is strongly coupled to a noisy environment. As the system gets smaller and smaller, fluctuations become more and more dominant in determining its behavior (Ritort, 2008). This is especially true for biological systems at the subcellular level, as we will discuss in more detail later (Bustamante et al., 2005). The strength of coupling between the system and the random environment depends on many variables. Size of the system is definitely an important variable; nevertheless, other factors such as characteristic energy and time scales also play equally important roles in determining how strongly

the system is coupled to the environment. Therefore, the mesoscale or the mesoscopic regime is determined by several factors that may change from one system to another, and are relevant for open systems (Weiss, 1993; Zwanzig, 2001).

Non-equilibrium dynamics of small systems

The environment in which a mesoscopic system finds itself usually has a great number of degrees of freedom, so that it is practically impossible to describe its state precisely, as noted in nearly every textbook on statistical physics. Due to the incomplete knowledge of the state of the environment, the behavior of a mesoscopic system is probabilistic, and the outcomes of measurements on a mesoscopic system are characterized by statistical distributions (van Kampen, 2007). A classic example is a Brownian particle: even though it cannot be determined precisely, the position of a Brownian particle at a certain time follows a well-known probability distribution (Einstein, 1905). Therefore, in order to quantitatively study a mesoscopic system, we need to characterize the fluctuations, and be able to relate the statistics of fluctuations to physical quantities. Starting in early 1990s, there has been significant development in our understanding of the non-equilibrium statistical mechanics of mesoscopic systems, under the name of fluctuation theorems (Sevick et al., 2008). Here, we would like to briefly review the fluctuation theorems and related experimental results.

In equilibrium, there is no net energy transfer between a system and its environment, such that the probability of absorbing a certain amount of energy from the environment is equal to the probability of releasing the same amount (Evans and Searles, 1994). Under non-equilibrium conditions, these probabilities would differ because energy is put into, or extracted from the system by an external influence. Fluctuation theorems provide a relation for the probability distribution of quantities such as entropy production, work done on the system, the amount of heat exchange, and so on, when the system evolves under non-equilibrium conditions (Ritort, 2007). The first fluctuation theorem was formulated by Evans and Searles (1994), and related the relative probability of entropy production and consumption as a function of the change in entropy. Their results are valid for a system initially in an equilibrium state that evolves toward a non-equilibrium steady state. Shortly after, Gallavotti and Cohen (1995) obtained results for systems that start and end in non-equilibrium steady states. A couple of years later, Jarzynski (1997) obtained a relation between the change in the free energy and work performed on a system, which became the celebrated Jarzynski equality. His result is applicable to systems that are taken from an equilibrium state to another by a non-equilibrium process. Afterward, the applicability of the Jarzynski equality has been extended to many situations of interest. An important generalization of the Jarzynski equality was given by Crooks (1999), who unified some of the previously obtained fluctuation theorems. With the works of Oono and Paniconi (1998) and Hatano and Sasa (2001), the Jarzynski equality was extended to systems that go through arbitrary transitions between non-equilibrium steady states. Similar fluctuation theorems for quantum systems have also been worked out. In this domain, Tasaki (1999) derived a Crooks-like relation for closed quantum systems and quite recently, Hanggi and collaborators generalized this relation to arbitrarily open quantum systems (Campisi et al., 2009).

Experimental tests of fluctuation theorems

The validity of fluctuation theorems has been tested in numerous experiments. Ciliberto and Laroche (1998) was the first to check the validity of Gallavotti–Cohen fluctuation theorem based on observations on turbulent Rayleigh–Benard convection. Another well-known test of the same fluctuation theorem was performed by Evans and collaborators, in which the system consisted of a colloidal particle pulled through water with the help of optical tweezers (Wang et al., 2002). By analyzing particle trajectories obtained in many different runs of the experiment, they demonstrated that the experimental value of the relative probability of entropy production and consumption agrees well with the theory.

In a pioneering experiment, Liphardt et al. (2002) verified Jarzynski's equality in a single molecule experiment by measuring the work done on a particle under both equilibrium and non-equilibrium conditions. In their experiment, a single RNA molecule is stretched with the help of optical tweezers, from the folded to the unfolded state of the molecule, and then allowed to relax to the folded state. The rate of stretching and relaxing was adjusted so that the process is sometimes reversible (slow) and sometimes irreversible (fast). In this optical tweezers experiment, the end-to-end extension of the RNA molecule is a controlled parameter, and the force on the molecule is a measurable. Therefore, it is possible to calculate the work done on the RNA molecule during each unfolding–folding cycle by integrating the force on the molecule over the change in the length of the molecule. The authors tested the validity of the Jarzynski's equality, which relates a particular average of the work done on the molecule (non-equilibrium quantity) to the change in the free energy (equilibrium quantity), both of which were experimentally determined. It was shown that the predicted value of the free energy difference obtained through non-equilibrium measurements, that is, by using the experimentally measured work and the Jarzynski's equality, agrees with the value obtained under equilibrium conditions to within less than a $k_B T$, where k_B is Boltzmann's constant and T is the absolute temperature. It is important to note that in this work, Liphardt et al. showed that it is possible to do single molecule manipulation experiments to infer an equilibrium quantity by performing measurements under non-equilibrium conditions.

In a recent experiment, Sano, Muneyuki, and collaborators tested a generalized fluctuation theorem in the presence of feedback control (Toyabe et al., 2010). Their experiment resembles to the realization of a Maxwell's demon that extracts useful work from thermal fluctuations, based on the idea proposed by Szilard, eponym of the Szilard engine (Szilard, 1929). By using a combination of time varying electric fields and polystyrene beads, the researchers realized a particle that moves in a staircase-like potential landscape, in which the energy of the particle increases or decreases by going up and down, respectively. The energy difference between the steps is comparable with $k_B T$, so that the particle can randomly climb a step, or descend, due to thermal fluctuations alone; however, the motion is biased downward as the potential energy decreases in this direction. The authors demonstrate that by developing a feedback control mechanism based on position measurements, it is possible to make the particle climb the stairs by extracting energy from thermal fluctuations. Toyabe et al. pointed out that this seemingly controversial situation that violates the second law of thermodynamics is resolved, by relating the information gathered in measuring the particles position to the energy extracted from thermal fluctuations. In this experiment, the authors also verified a previously derived generalization of the Jarzynski equality in the presence of feedback control. Very recently, Kim et al. (2011) presented a comprehensive theoretical study on the quantum mechanical version of the Szilard engine, whose realization in the laboratory is still a challenging task.

Finally, we would like to point out that experiments that demonstrate how information about the state of a system is used to drive it away from equilibrium can be performed at the molecular level as well. During the last decade, many different molecular machines that can convert energy input into directed molecular motion has been synthesized (Kelly et al., 1999; Koumura et al., 1999; Klok et al., 2008; Panman et al., 2010). In particular, Leigh and coworkers demonstrated that that it is possible to construct a *molecular information ratchet* by using a rotaxane, which is a dumbbell-shaped molecule that consists of a ring that moves along the long axis of the dumbbell (Serreli et al., 2007). The ring can switch positions between two different parts of the molecule, thus defining two different states. By using a clever combination of chemicals and light input, the researchers demonstrated that the position distribution of the ring can be driven away from its equilibrium value without affecting the binding affinity of the ring in different states of the molecule.

Fluctuations and function

As the last example shows, in the presence of appropriate machinery, fluctuations in the environment can drive a system away from equilibrium, performing useful work. This phenomenon has attracted a significant amount of interest in the last few decades, especially in the context of molecular motors (Reimann, 2002; Astumian and Hanggi, 2002). In the next section, we will elaborate on the concept of *rectifying* random motion in the context of biological systems.

As opposed to being a source of nuisance, the idea that fluctuations can alter the dynamics in a physical system, even in ways that increase its functionality, is not new (Horsthemke and Lefever, 1984; Wio and Lindenberg, 2003; Losick and Desplan, 2008). In nonlinear dynamics, it is well-known that the presence of fluctuations can alter the number and stability of steady states (Zaikin et al., 1999; Hutt, 2008), for instance in systems that can be used to model population genetics (Castro et al., 1995). Moreover, fluctuations can induce order in spatially extended systems (Garcia-Ojalvo and Sancho, 1999). The presence of fluctuations can induce phase transitions, and in some pattern forming systems, patterns can become sharper in the presence of noise (Swift and Hohenberg, 1977; Parrondo et al., 1996).

Mesoscopic dynamics in living systems

Components of a cell are essentially mesoscopic structures that need to function under the influence of thermal noise, and weak interactions due to the presence of other cellular components. In order to do so, it appears that living organisms have evolved mechanisms that allow them take advantage of their unpredictable environments. With the help of recently developed tools of observation, it has frequently been observed that not only do cells successfully operate under ever changing conditions, but also they do it much more efficiently than artificial nanomachines (Hugel and Lumme, 2010). In this section, we will go over several examples of cellular processes and emphasize how mesoscopic effects are ubiquitous in mechanisms that make the cell function.

Biochemical reactions with a small number of reactant molecules, and functional aspects of noise in gene networks

Biochemical reactions in a cell differ dramatically from those in a test tube due to the coexistence of a huge variety of weakly interacting molecules, the presence of mesoscopic structures that can enhance or decrease reaction rates, and the small number of molecules that take part in the reaction (Minton, 2006; Xie et al., 2006). Throughout this article, we elaborate on many of these points. Here, we would like to concentrate on the effects of small molecule numbers. For chemical reactions, small number of reactants means big fluctuations in the concentration of products (Delbruck, 1940).

It seems reasonable to argue that single molecule messages are usually not reliable due to high variability in the signal, and the difficulty in telling signal from noise. For instance, protein production that is vital for the cell depends on the translation of a single mRNA molecule.

However, mRNA produced in the nucleus can contain errors, which may lead to defective proteins. In order to avoid such events, mammalian cells have a well-developed screening process for mRNA leaving the nucleus (Lowe et al., 2010).

Interestingly, and quite contrarily, random fluctuations in a signal can sometimes be beneficial for a population of cells by increasing the diversity among cells with identical genes, which in turn may increase the chance of survival (Kussell and Leibler, 2005; Acar et al., 2008). Below, we provide several examples for how this could happen.

As a consequence of single molecule events, the fate of a cell can change dramatically (Eldar and Elowitz, 2010). It is well-known that in a population of genetically identical cells, different phenotypes can spontaneously arise (Arkin et al., 1998; Kaern et al., 2005). The bacterium *Escherichia coli* is one of the well-studied organisms in this respect, partly due to its pathogenic nature (Balaban et al., 2004; Xie et al., 2008). Here, we would like to discuss a case in which a single molecule event can trigger phenotype change in *E. coli*. In order to be able to make use of lactose, the *lac* gene in *E. coli* needs to be expressed (Choi et al., 2008). The expression of this gene is controlled by inducers such as the lactose analog thiogalactoside, in a concentration-dependent manner. When the inducer concentration is high, almost every cell in an *E. coli* colony expresses the *lac* gene; however, at low inducer concentrations, only a small fraction of them do. Xie and collaborators directly showed that at low inducer concentrations some cells in the population express the *lac* gene, whereas others do not, in a stochastic manner (Choi et al., 2008). The authors were able to relate this probabilistic difference between the cells to the expression mechanism of the gene by clearly demonstrating that the expression of lac is controlled by a single molecule event, namely the binding and unbinding kinetics of Lac1 repressor, whose dynamics is quite different depending on the concentration of the inducer. Another recent example of how cells genetically identical cells may behave differently under same conditions was given by Sharma et al., where the authors showed that a fraction of cancer cells in a colony can randomly become transiently drug-resistant (Sharma et al., 2010).

A critical phenomenon in developmental biology in which stochasticity seems to play an important role, and that has recently been extensively studied is the differentiation of stem cells (Suda et al., 1983; Morris et al., 2010). For medical purposes, it is highly desirable to induce differentiation of stem cells into a prescribed cell type with high efficiency. Nevertheless, it is usually found that only a fraction of cells can be successfully differentiated even with refined inducers (Shah et al., 1996; Kawasaki et al., 2002). Researchers have gained insight into this interesting phenomenon by monitoring the expression of genes among different cells in a stem cell colony. One gene that attracts particular attention is nanog, which is often used as a marker for pluripotency (Chan et al., 2011). It has been observed that the expression of nanog in stem cells varies over time, and that the cells respond differently depending on the concentration of nanog when a differentiation inducer is administered (Chambers et al., 2007; Kalmar et al., 2009). Many studies showed that the concentration of nanog in a randomly chosen cell in a colony could be either high or low compared with a baseline value, which can subsequently determine the fate of the cell in differentiation (Singh et al., 2007).

Lastly, we would like to point out to a different aspect of how fluctuations in signals can be functional for the cell in terms of management (Eldar and Elowitz, 2010). In any cell, the number of genes that need to be regulated is vast, and yet all the cellular processes run in harmony [for a discussion on the minimum possible genome size see, for instance, Forster and Church (2006)]. Recently, Cai et al. (2008) examined the mechanism with which yeast regulates a large number of genes in response to calcium. Their study found that the transcription factor Crz1 localizes to the nucleus in stochastic bursts, whose average frequency depends on the calcium concentration in the medium. Furthermore, the characteristics of each burst such as the duration and amplitude were found to be similar, so that the transcription factor affects every gene in more or less the same way during each burst. This shows that with *stochastic control*, in which the average frequencies of events are modulated, the expression of a large number of genes can be coordinated consistently.

The importance of dynamics in protein function: myoglobin and AMPA receptor

Two of the truly challenging problems in molecular biology are finding the relations between protein structure and function and understanding the dynamics of protein folding (Fields, 2001; Dobson, 2003). One of the most influential ideas in this field has been the assumption that proteins fold into a unique, kinetically stable state that subsequently determines their function, which is widely known as Anfinsen's dogma (Anfinsen, 1973). However, investigations on some biological processes showed that judgments based on the crystallographic structure of proteins and small architectures composed of a few proteins may not be enough to understand how they function. It is now becoming clearer that we need to combine the valuable information in the structure with that in dynamics, to fully understand how small architectures function. A classic example is the interaction between myoglobin and oxygen molecule, which clearly shows how the time-dependent behavior of mesoscopic architectures can be critical for function (Austin et al., 1975; Ansari et al., 1994; McMahon et al., 2000; Bourgeois et al., 2003). Myoglobin is a protein that is mostly found in the muscles of vertebrates, and plays an important role in metabolism, as it can bind oxygen due to the presence of an iron atom at its center. Intriguingly, the crystal structure of the protein did not show an opening in the protein that would allow the passage of an oxygen molecule (Kendrew et al., 1960).

It turned out that one picture is not enough. Starting with the pioneering work of Frauenfelder and his team, it was found that the myoglobin has many different conformations some of which allows the entrance of an oxygen molecule inside (Austin et al., 1975). At physiological temperatures, myoglobin can switch between different conformations due to the effect of thermal fluctuations, and when a particular conformation has a large enough gap, an oxygen molecule can move in.

Another recent example that highlights the significance of variability in protein structure and its effects on function is the agonist-mediated activation of the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor (Landes et al., 2011). The AMPA receptor is a glutamate receptor involved in neurotransmission, and plays an important role in memory and learning (Keinänen et al., 1990; Fleming and England, 2010). When glutamate binds to the agonist-binding domains of the GluA2 subunits of the AMPA receptor, a cation-permeable channel in the receptor is temporarily opened (Gouaux, 2004). The presence of glutamate then causes the channel to close; however, the nature of the closed state has not been clear. Using single molecule FRET (fluorescence resonance electron transfer) technique (Jares-Erijman and Jovin, 2003), Landes et al. showed that when glutamate is bound, the agonist-binding domain of the GluA2 subunit of the AMPA receptor explores a number of conformations as opposed to being locked in a rigid state (Landes et al., 2011). Therefore, single molecule observations indicated that in order to perform its function, subunits of the AMPA receptor goes through a number of different conformations rather than sitting at a free energy minimum with a unique structure. Experiments of this kind demonstrate the power of the single molecule FRET technique in probing the dynamics of mesoscopic architectures such as receptors and other functional molecular complexes.

Functional aspects of confinement in mesoscopic, subcellular domains

Since the time of first observations on cells, it has been known that the environment inside a cell is highly heterogeneous due to the presence of numerous organelles, and the cytoskeleton (Alberts et al., 2010). This spatial heterogeneity can be advantageous for the cell in increasing the diversity of possible cellular processes. In order for a cell to function, hundreds of different kinds of organic molecules need to react at the right place, and at the right time. One of the simplest examples of organization in the cell is probably the evolution of lysosomes and peroxisomes (Alberts et al., 2010). Lysosomes are vesicles inside the cells that contain enzymes that can break down proteins and enable the cell to digest. Although they are essential for the survival of the cell, as the cell itself if made up of proteins, these enzymes always need to be kept on leash, only to be used when needed. Similarly, peroxisomes are vesicles in which reactions producing hydrogen peroxide take place. Hydrogen peroxide is a highly reactive chemical that could lead to cell death if distributed freely in the cytoplasm. The presence of cellular architectures like these demonstrates that the inhomogeneous structure of a cell enables it to organize the wealth of chemical reactions, so that cellular functions can be performed with high efficiency and reliably.

In general, monitoring the kinetics of reactions inside a live cell is a challenging task. Therefore, experimental data comparing the kinetics of a biochemical reaction in a test tube to that within a cell is scarce. In their recent work, Schoen et al. demonstrated that kinetics of DNA hybridization can be surprisingly different in vitro and inside cells (Schoen et al., 2009). The authors measured the rate of the reversible bimolecular reaction for FRET-labeled double-stranded DNA probes in HeLa cells, and *in vitro*. It was found that the reaction rate depends on the length of the probe and the environment (see Figure 2A). The authors found that the reaction rate of short probes, consisting of 12 base pairs, is lower within the cell compared with the value *in vitro*. Surprisingly, for slightly longer probes made up of 16 base pairs, the result was opposite. Within one cell, the reaction rates were found to depend on the location, with faster kinetics in the nucleus compared with that in the cytoplasm for all probes. The investigation went further to reveal inhomogeneity in reaction rates at an even finer level by showing that kinetics in the nucleoli is slower compared with the rest of the nucleus. These findings clearly show that the components of a live cell are organized in a way that is far from random.

Confinement of molecules in mesoscopic domains have also been observed in the plasma membrane of many different mammalian cells, which is a highly heterogeneous medium that contains many different types of lipids, proteins, and complex structures made of proteins (Nabi, 2011). The question of how these molecules are organized in the membrane has been attracting a lot of attention. There are two prevailing ideas that aim to account for the general aspects of organization in the plasma membrane by referring to confinement effects. The first is that of *lipid rafts*, which are thought to be domains in the membrane where glycosphingolipids and cholesterol are abundant (Simons and Ikonen, 1997; Kusumi et al., 2004). The size of these domains are estimated to be between a few nanometers up to the diffraction limit (around 300 nm), which means that it is impossible to directly observe them by conventional light microscopy. Lipid rafts can be functional in processes that require prolonged interactions between membrane molecules. Recently Suzuki et al. (2007a,b) demonstrated that lipid rafts can enhance the interaction between receptor proteins and their downstream signaling molecules by increasing the stability of the complexes they form. The second idea is that the interaction between the actin cytoskeleton and the plasma membrane can lead to the temporary confinement of membrane molecules in mesoscopic domains of size

30–250 nm, with a typical duration of 1~100 ms, which is observed in many cell types in the pioneering works by Kusumi et al. (2005). Fujiwara et al. (2002) showed that even lipid molecules in the outer leaflet of the plasma membrane can be temporarily confined in domains induced by the cytoskeleton. Temporary confinement in cytoskeleton-induced domains can be functional in cellular processes such as chemotaxis, where the location of the signal needs to be well-defined (Kalay et al., 2011). Moreover, temporary confinement in these domains would modify the reaction kinetics in the membrane by altering the statistics of random collisions between molecules. This could have a significant impact on many processes in the membrane that involves molecular interaction. The details of how reaction kinetics would be modified in a surface partitioned into domains by permeable barriers, and its implications for cellular processes is currently being investigated by the present author and his collaborators. Unfortunately, experimental data showing the time-dependence of the interaction between membrane molecules is scarce. This is partly due to the modest signal to noise ratio in live cell observations at high frame rates, having a fraction of unlabeled, thus invisible, molecules, and the fact that powerful techniques such as single molecule FRET that can be used to reveal interactions between molecules is quite inefficient when the probes are on different molecules that are both mobile. Nevertheless, very recently, Kasai et al. successfully observed the dimerization kinetics of a G-protein-coupled receptor in live cells at single molecule level, and at millisecond time resolution, by carefully analyzing how often single molecule images overlap (Kasai et al., 2011).

Molecular motors and rectifying thermal fluctuations: kinesin-1

In order to perform its functions, the cell needs to actively reorganize molecular complexes, and to fight the ever increasing entropy, it needs to do a significant amount of housekeeping. The workhorses in these processes are molecular motors that convert chemical energy stored in phosphate bonds to useful work. Many different kinds of molecular motors have been discovered, including DNA and RNA polymerases that read and write genetic information, myosin that drives muscle contraction, kinesin that can deliver cellular cargoes, and many more (Vale and Milligan, 2000; Schliwa, 2004).

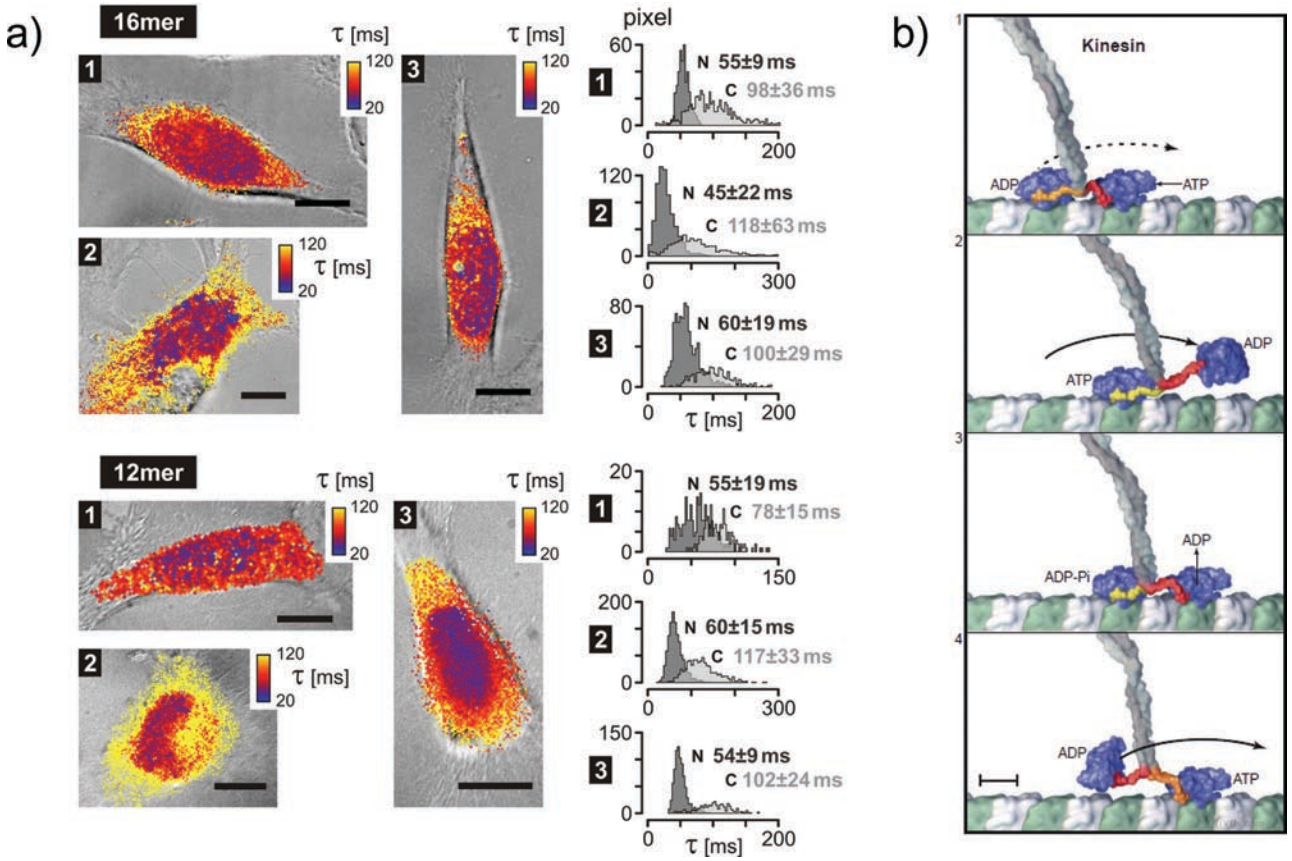

Figure 2. (A) A map of reaction time constants in single cells. The three figures on the top and the corresponding histograms pertain to the longer strand with 16 base pairs and the plots on the lower side are for the shorter molecules with 12 base pairs. The scale bars correspond to 10 μm. In the histograms N and C stand for nuclear and cytoplasmic regions, respectively. Adapted from Schoen et al. (2009). Reprinted with permission from Dieter Braun. Color version available online. (B) Illustration of the stepping mechanism of Kinesin, as described in the text. Scale bar, 4 nm. Adapted from: Vale and Milligan (2000). Copyright (2000) by the American Association for the Advancement of Science.

Although the mechanism by which motor proteins convert chemical energy to mechanical energy is still not completely elucidated, thermal fluctuations seem to play an important role in this process (Astumian and Bier, 1994; Taniguchi et al., 2005; Block, 2007). One of the well-studied molecular motors is kinesin-1 of the kinesin family, which moves unidirectionally on microtubules and can carry loads such as vesicles and organelles (Verhey et al., 2011). Kinesin-1 mainly consists of two parts one of which binds to a microtubule and the other to the load. The part that can bind to a microtubule consists of two heads that are separated by 8 nm. Kinesin-1 is involved in many cell functions and its malfunction can lead to neurodegenerative diseases (Schliwa and Woehlke, 2003). Although there are gaps in our understanding of how kinesin-1 walks along microtubules, many research groups agree on some of the steps involved during its motion. Here we briefly describe what is known about the process, as illustrated in Figure 2B, and as summarized in (Kawaguchi, 2008). In the absence of microtubules, ADP binds to both heads of the molecule. Once one of the heads binds to a microtubule, it releases the ADP and becomes strongly bound. The other head keeps the ADP and it either stays away from the microtubule or binds weakly until an ATP molecule binds to the microtubule bound head, which we will call the front head. After ATP binds to the front head, the rear head slightly moves forward by 1–2 nm, and performs a random search until it finds a binding site on the microtubule. The rear head could either bind to a site ahead of the front end, or behind it, which would displace the center of mass of the molecule forward or backward with respect to its previous position, respectively. Single molecule observations found that the rear end tends to take a step in the forward direction, making the center of mass move forward by 8 nm, although it sometimes binds to a site behind the front head, which can eventually lead to an overall backward motion. Therefore, the stepping mechanism of kinesin-1 seems to involve a biased random search, which is thought to be driven by the thermal fluctuations in the surroundings. By measuring the temperature dependence of the forward and backward stepping rates, Yanagida and coworkers proposed that taking a forward step toward the plus end of the microtubule is favorable over a backward step by ~6 $k_B T$ (Taniguchi et al., 2005; Yanagida et al., 2007). Finally, the system returns to its initial state after the ATP bound to the front head is hydrolyzed, so that the front head is left with an ADP and cannot bind to the microtubule strongly. During this process, the timing is critical such that the ATP should not be hydrolyzed before the rear head finds a binding site.

The question of how Brownian motion, or more general types of random walks, can be rectified attracted enormous interest in the context of both natural and engineered systems (Julicher et al., 1997; Astumian and Hanggi, 2002; Reimann, 2002; Hanggi and Marchesoni, 2009). In order for a small system like a molecular motor to extract energy from random fluctuations in the absence of any thermal gradients, there needs to be an asymmetry in the system, and an input of energy that drives it away from equilibrium. In an idealized picture consisting of a particle subject to random fluctuations, it is possible to give some of the conditions under which fluctuations can be rectified (Julicher et al., 1997). For instance, if a particle under the influence of fluctuations whose statistics is characterized by a normal distribution with zero mean and no correlations, that is, simple Brownian motion, is in a spatially periodic asymmetric potential energy landscape whose strength is a function of time, its overall motion can be biased in a certain direction. For a comprehensive analysis of how Brownian motion can be rectified, we refer the reader to Hanggi and Marchesoni (2009). One of the challenges in understanding how molecular motors operate is revealing the physical and chemical processes that could give rise to time-dependent asymmetries in the system. As we mentioned above, in the case of kinesin-1, binding of ADP to the heads of the molecule induces an asymmetry so that both heads of the molecule cannot be strongly bound to the microtubule at the same time, and the involvement of ATP in this process provides the input of energy that would to drive the system away from equilibrium (Block, 2007).

Mesoscopic machines that repair the DNA: RecA-mediated repair

Some tasks in the cell require searching for a specific target and manipulating it, especially concerning genetic material. The process of DNA repair is a good example for this (Forget and Kowalczykowski, 2010; Mimitou and Symington, 2011). Even though the mechanism that replicates DNA makes very few mistakes, around 1 per 10^9 nucleotides, DNA molecule suffers damage at a constant rate after its synthesis (Roca and Cox, 1997; Alberts et al., 2010). The most serious DNA damage is a double-strand break, which cannot be completely repaired unless the homologous pair of the DNA strand is nearby. If a double-strand break occurs, and the homologous pair of the DNA strand is nearby, the damage can be perfectly repaired through a mechanism called homologous recombination. Many different mechanisms of DNA repair has been evolved in eukaryotes and prokaryotes (O'Brien, 2006). One of the well-studied mechanisms of DNA repair is RecA-mediated pathway in bacteria (Roca and Cox, 1997). In RecA-mediated DNA repair, when a double-strand break occurs, presynaptic filaments made up of RecA molecules and a single-stranded DNA form at the broken site to find homologous sequences along the DNA (Levin-Zaidman et al., 2000). This is one of the first steps in the process of performing error-free DNA repair. At a first glance, this process seems to be plagued with complications because the sequence to be found is a difficult target, a rare sequence of nucleotides, and similar, thus competitive, sequences should exist in great abundance (von Hippel and Berg, 1989). Moreover, diffusion coefficients of the RecA–DNA presynaptic

filament and the chromosomal DNA sites were both found to be unusually low. However, they need to interact many times in order to determine whether they are a good match or not, which does not seem to be an easy task for slowly moving molecules. Despite all these difficulties, RecA-mediated DNA repair takes place quickly enough so that bacteria can survive even in harsh conditions. Evidence suggests that restricted diffusion plays a critical role in shortening the time necessary to perform the search for the homologous sequence (Minsky, 2003). Instead of performing a diffusional search in 3D with a relatively low diffusion coefficient, the presynaptic complex moves along the DNA. Therefore, the challenge of finding a specific location in 3D turns into finding a line segment in 1D, greatly reducing the complexity of the problem. Moreover, as the presynaptic complex moves along the DNA, the DNA template it carries is confined within the complex so that it can easily and consistently interact with the DNA to reliably detect sequence matches, as suggested in early theoretical works (Berg et al., 1981; von Hippel and Berg, 1989).

Coherent transport of charge during photosynthesis

We would like to finish this section with an example from biology that seems to display mesoscopic quantum effects, much like the objects of our discussion in the first section of this review. Some of the functional architectures in a living cell might be taking advantage of quantum mechanical effects. Evidence shows that electron transport across the photosynthetic machinery of cryptophyte, a eukaryotic marine algae, is coherent over several nanometers so that quantum mechanical effects can be clearly observed (Collini et al., 2010). During photosynthesis, antenna proteins capture and transfer electronic energy to a reaction center where the final products of photosynthesis are produced (Alberts et al., 2010). Therefore, the efficiency with which electrons are transferred between different parts of the photosynthetic structure is critical for the whole process. In the antenna proteins of cryptophytes, the distance between light-harvesting centers, the chromophores, is found to be almost double that of what it is in plants. One may expect that the extra distance that the electrons need to travel would reduce the efficiency of the process. Surprisingly, cryptophytes are so efficient that they can do photosynthesis even in low light conditions (Spear-Bernstein and Miller, 1989; van der Weij-De Wit et al., 2008). By using two-dimensional photon echo spectroscopy, Collini et al. demonstrated that electrons in the antenna proteins of two species of cryptophytes can be transported coherently over 2.5 nm and hundreds of femtoseconds, even at the ambient temperature of 294 K (Collini et al., 2010). This observation suggests that the efficiency of functional architectures in the cell could be strongly linked with their mesoscopic nature, even taking advantage of quantum coherence.

Some examples of synthetic mesoscopic functional architectures

In this section, we would like to point out to the effects of mesoscopic features in materials, by reviewing a few recent examples from chemistry and material science. Our discussion will focus on some of the properties of porous materials and elegantly synthesized mesoscopic constructs from DNA molecules.

Confinement of molecules in a volume comparable with their size can change their physical properties, and consequently the way they function (Anastasiadis et al., 2000; Rathore et al., 2006; Shen and Cheung, 2010). Porous solids are classified as micro-, meso-, and macroporous with characteristic pore sizes of: less than 2 nm, between 2 and 50 nm, and larger than 50 nm, respectively (Sing et al., 1985). Micro- and mesoporous solids have been extensively studied due to their surprising and often practically desirable properties (Horike et al., 2009). One of the most well-known families of microporous materials is zeolite, with pore sizes of <2 nm. Zeolites are employed widely in different applications, including petroleum processing, catalysis, water purification, and cleaning products because of their exceptional sorption properties (Corma, 1997). Another well-known family of microporous materials that appeared on stage more recently is metal organic frameworks, also known as porous coordination polymers [for references, see the recent review by Horike et al. (2009) and references therein]. These materials have been studied extensively mostly due to their ability to absorb gas molecules, which could be exploited in practical applications such as drug delivery (McKinlay et al., 2010), and CO_2 absorption for environmental purposes (Furukawa et al., 2010). Materials with larger pores, mesoporous solids, display even richer behavior that proved to be much difficult to understand compared with microporous solids. Some examples for mesoporous materials are: mesoporous silica and aluminosilicates, transition metal oxides, and hybrid nanocomposites containing both organic and inorganic molecules (Oye et al., 2001; He and Antonelli, 2002; Linssen et al., 2003). Mesoporous materials are also of great practical interest in applications ranging from drug delivery to optics (Parker et al., 2006; Vallet-regí et al., 2007; Sun and Bao, 2008).

Inside a mesoscopic pore or cavity, the number of molecules is low, and the interactions between them are strong such that the collective behavior of molecules dominates the dynamics, and equilibrium thermodynamics is not applicable (Schumacher et al., 2005; Roduner, 2006; Goettmann and Sanchez, 2007). As a result, properties of the absorbed material may differ dramatically compared with those in bulk. For instance, the melting and freezing points can shift as a function of the pore size (Alba-Simionesco et al., 2006), as was experimentally shown in the case of water absorption (Schreiber et al., 2001).

A case of particular interest is the effect of confinement on catalytic activity. Porous solids are known

to display catalytic properties; however, the relation between pore size and catalytic activity is not well-established (Goettmann and Sanchez, 2007). Depending on the confining volume, the efficiency of a catalyst may vary, such that the catalytic activity is optimal at a certain intermediate confining volume. Unlike microporous materials such as zeolites, it is quite difficult to isolate the role of confinement in the kinetics of catalysis reactions happening inside mesoporous materials. Nevertheless, the results of several experiments suggest that confinement within the pores of mesoporous materials is correlated with the catalytic properties (Iwamoto et al., 2003; Raja et al., 2003; Thomas et al., 2003). Two relatively recent experiments that report pore size dependence of catalytic activity is due to Tanchoux and coworkers who investigated the catalytic isomerization of 1-hexene in mesoporous aluminosilicates (Pariente et al., 2006; Tanchoux et al., 2009).

Although the typical pore size of metal organic frameworks is a few nanometers at most, they are usually synthesized as a large 3D periodic array of pores, which is certainly macroscopic. With newly developed synthesis methods, it has become possible to produce metal organic frameworks with controlled growth direction and size (Lin et al., 2009; Li et al., 2010). Currently the smallest frameworks measure a few tens of nanometers on one side; for instance, as shown in recent works of Kitagawa and coworkers, illustrated in Figure 3A (Tsuruoka et al., 2009; Diring et al., 2010). Further decrease in the framework size while maintaining high crystallinity will bring these materials to the mesoscopic realm. In the near future, it will be very interesting to see if novel effects show up due to the mesoscopic nature of these samples.

DNA origami is a recently developed technique which allows the fabrication of mesoscopic structures with DNA molecules (Rothemund, 2006). As the sequence of nucleotides in a DNA molecule can be controlled almost exactly, it is possible to design structures formed from them with great precision. Recently, it was shown that structures constructed from DNA can help us visualize and understand some of the mesoscopic biological phenomena, which is often impossible to observe in conventional experiments. Using DNA origami technique, Sugiyama and coworkers designed a mesoscopic frame in which two single molecules of DNA can be simultaneously placed (Endo et al., 2010a,b; Sannohe et al., 2010). They showed that this configuration makes it possible to observe interactions involving DNA at the single molecule level. Within a DNA frame, it is not only possible to isolate the interaction between single DNA molecules, but also to monitor them closely. By using fast-scanning atomic force microscopy (AFM) technique, the group reported results on the time evolution of these processes with up to 1 s time resolution, unusually quick for conventional AFM measurements. By taking advantage of these techniques, quite recently, Endo et al. (2010a,b) probed the dynamics of DNA methylation and repair, and Sannohe et al. (2010) visualized the formation of a G-quadruplex (see Figure 3B and 3C), which is a four-stranded DNA structure (Burge et al., 2006) that also draws attention from drug industry (Wong et al., 2009). A common finding in these studies is that the amount of tension in a DNA strand is crucial for its function such that loose strands appear to be more active.

In material science, the significance of mesoscopic features in fabricated materials and mesoscale modeling has been appreciated slightly longer than in life sciences, as emphasized in relatively early reviews on the subject (Stoneham and Harding, 2003; Antonietti and Ozin, 2004), where interested readers can find additional examples for materials that rely on mesoscopic features for their function.

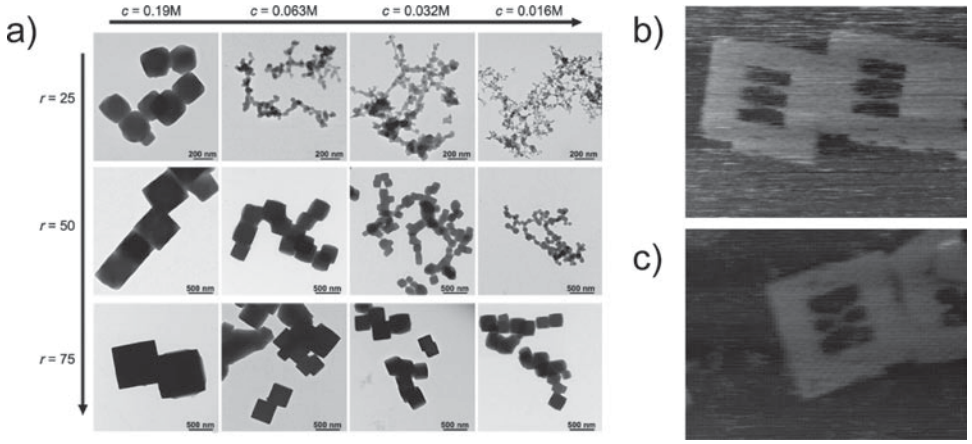

Figure 3. (A) Transmission electron microscopy images of nano–meso–micro-sized porous coordination polymers produced in the study by Diring et al. The quantities *r* and *c* correspond to the ratio of dodecanoic acid (which regulates the growth) to benzene-1,3,5-tricarboxylic acid (which is necessary to synthesize the framework) and the initial concentration of benzene-1,3,5-tricarboxylic acid, respectively. Reprinted with permission from Diring et al. (2010). Copyright (2010) American Chemical Society. (B, C) AFM images of DNA frames containing two double-stranded DNA molecules. In (B) K-ions are absent and the DNA molecules are separated, whereas in (C) K-ions are present and G-quadruplex formation is clearly observed. The size of the images is 300 × 225 nm. Reprinted in part with permission from Sannohe et al. (2010). Copyright (2010) American Chemical Society.

Concluding remarks and future outlook

Over the past few decades it has become increasingly clear that complex systems such as a living cell cannot be fully understood by examining the frozen structures alone (Frauenfelder et al., 2003; Yanagida et al., 2007). In order to reveal the functions of small structures such as organelles in a cell, we desperately need to gather information about the time evolution of the system by employing state of the art experimental techniques. In this review, we tried to give the reader an idea about how the dynamics of small systems is like, from the point of view of different research fields. By providing examples of mesoscopic phenomena from physics, biology and chemistry, we discussed the characteristic properties of the mesoscopic regime, and how the functions of a small system are related to its mesoscopic nature. Although much work needs to be done to clarify the mechanisms, the evidence we bring into focus in this review suggests that cellular processes as diverse as transport of cargo by molecular motors, regulation of gene expression, spatiotemporal organization of molecules in the cytoplasm and the plasma membrane, charge transport during photosynthesis are all strongly connected to the mesoscopic nature of cellular machinery.

Once more, we would like to emphasize that the salient feature of a mesoscopic system is its probabilistic nature. Whether it is the sample-to-sample variance of conductivity in metals, or the state of a molecular motor on a microtubule, mesoscopic systems are characterized by probability distributions. Therefore, the theories that aim to make predictions on the properties of these systems need to bridge stochastic processes with experimentally observable quantities. Fortunately, the progress in this field has been remarkable, as we discussed under the title of fluctuation theorems, and more and more predictions are becoming amenable to experimental verification.

By combining the efforts made in different disciplines, it will become easier to solve challenging problems, especially in life sciences. With regard to our discussion on porous materials, we believe that new generations of these flexible materials may also help us understand biologically functional structures by mimicking them, in a primitive way. These materials provide an excellent playground to observe the effects of confinement on a small number of interacting molecules. As we discussed throughout this review in several different contexts, confinement effects of similar nature are also important for the functions of the components of the cell. However it is extremely difficult to study them in vivo as we mentioned in our discussion of the effects of confinement on the organization and activity of molecules in the cell membrane. In the near future, development of single molecule microscopy techniques alternative to FRET, along with advanced data analysis methods could greatly help probing molecular interactions *in vivo*.

One of the challenges that living organisms face is being able to evolve new functions while successfully keeping their integrity. Cells certainly possess a robust machinery as they can stay alive during sudden changes in environment. At the same time, they need to be flexible enough to occasionally, and quite randomly, undergo changes that can modify their functions at evolutionary timescales. In order to elucidate the process of evolution, we therefore need to understand how a cell responds to fluctuations in the environment. In the light of our discussions throughout this article, we argue that it is the mesoscopic nature of the components of a cell that enables it to be stable and flexible at the same time; for mesoscopic architectures such as a chromosome can have rich dynamics while being simple in structure. Recently, both theoretical and preliminary experimental studies have been carried out to reveal the relation between fluctuations in gene expression and adaptability (Hill and Zhang, 2004; Ito et al., 2009). With the use of advanced techniques that allow the researchers to monitor the time-dependent expression of even weakly expressed genes at single cell level, we hope that the functional role of fluctuations in gene networks and evolutionary processes will be better understood in the near future.

We anticipate that in the near future, our understanding of small systems, especially living systems, will improve enormously, as more and more researchers recognize the patterns in the messy and nonlinear mesoworld.

Acknowledgements

I would like to thank Akihiro Kusumi for many helpful discussions during the preparation of this review article, and I am grateful for valuable comments from Peter Carlton, John Heuser, and Norio Nakatsuji.

Declaration of interest

The research in author's laboratory was financially supported by the World Premier International Research Center (WPI) Initiative of the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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Editor: Michael M. Cox