Statistical Physics of Biocomplexity

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With 5 Figures

Abstract

Biology and physics share common ancestors. The progress of methods of statistical physics and the developments of new physical tools and various ingenious experimental techniques have triggered dramatic progress for the field of biophysics. Likewise, the two fields fertilized each other repeatedly over the last decades. Most importantly, the complexity of biophysics inspired new developments in physics and chemical physics. In this contribution, we focus on some recent problems that attracted the interest of many statistical physicists. Biological cells contain nanoscale machineries that exhibit a unique combination of high efficiency, high reliability and recognition features and self-assembly properties. Most importantly, these biological machines transport material and perform work in a noisy environment. Here, we will elaborate on the constructive role of noise for the amplification and enhanced detection of weak information-carrying signals (Stochastic Resonance in Biology) and directed transport of vesicles and the like (Brownian Motors in Biology). Quantum statistical physics enters the biological complexity at the interface of electronic transport processes and the interaction with light. In this context, physicists and chemists have become increasingly interested in the electronic properties of the »molecule of life«, the DNA. We will comment on the present hot debate whether quantum electronic transport in DNA behaves more like a good molecular wire or whether DNA behaves more like an insulator.

Zusammenfassung

Die beiden Naturwissenschaften Biologie und Physik teilen gemeinsame Interessen: In den letzten Jahrzehnten konnten sich beide Disziplinen immer wieder gegenseitig stimulieren. Der Fortschritt der Biophysik profitiert in hohem Maße von den Methoden der statistischen Physik und von neuen physikalischen Entwicklungen und Technologien. Umgekehrt inspirierte die Vielseitigkeit der Biophysik neue Richtungen in der Physik und der physikalischen Chemie. In diesem Artikel konzentrieren wir uns auf aktuelle Probleme, die insbesondere unter statistischen Physikern auf ein reges Interesse gestoßen sind: Wenige Nanometer große Proteine fungieren in biologische Zellen als Maschinen und vereinigen dabei eine einzigartige Kombination von hoher Effizienz, hoher Zuverlässigkeit, und der Fähigkeit zur Selbstorganisation und Steuerung. Sie transportieren biologisches Material und verrichten physikalische Arbeit in einer thermisch verrauschten Umgebung. Die konstruktive Rolle des Rauschens für die Verstärkung und Detektierung schwacher Signale (Stochastische Resonanz in der Biologie) und für den gerichteten Transport (biologische Brownsche Motoren) werden diskutiert. Die Beschreibung des elektronischen Transports oder der Wechselwirkung mit Licht erfordert sogar quantenphysikalische Ansätze in der Biologie. So interessieren sich Physiker und Chemiker für die elektronischen Eigenschaften des »Moleküls des Lebens«, der DNA. In diesem Zusammenhang soll auf die heiß geführte Debatte eingegangen werden, ob der quantenmechanische elektronische Transport in DNA sich wie in einem guten molekularen Draht oder eher wie in einem Isolator verhält.

1. Introduction

The field of biology underwent dramatic changes in recent years. With the progress and development of new experimental techniques the areas of modern biology and modern physics have fertilized each other repeatedly. One such area involves high-resolution microscopy techniques: Starting from the invention of a first microscope

by Zacharias JANSSEN (1588–1630), and the first documentation in form of a book by Robert HOOKE (1635–1703) the first high resolution microscope was built by the Dutchman Antoine VAN LEEWENHOECK (1632–1723). His invention led him to observe bacteria and other micro-organisms. The early 19th century brought further progress with prominent input from Physics. It was the theory of microscopic resolution by Ernst ABBE (1840–1905), in particular his insight into improving resolution via a high »numerical aperture« (n sin a_l) by use of a high refraction index material which enabled considerable further progress. The modern age of microscopy arrived with the development of the electron microscopy by Ernst RUSKA (1906–1988) in 1932. This instrument has a resolution of ca. 50 nm, i. e. it became possible to gain insight into the architecture of individual cells and proteins. Finally, the progress culminated with the construction and working of the scanning tunnelling microscope (STM), that can provide atomic resolution, by the pioneers Gerd BINNIG and Heinrich ROHRER at IBM during the portentous night of march 16, 1981. The further efforts focused on atomic size imaging techniques for insulating materials. The result has been the construction of the atomic force microscopy (AFM) by BINNIG et al. (1986).

Another root to the progress of molecular biology involves Brownian motion theory as pioneered independently from each other by Marian VON SMOLUCHOWSKI and Albert EINSTEIN. SMOLUCHOWSKI has been working passionately on the theory of Brownian motion since 1900. He, however, delayed the publication of his theoretical findings because he also planned experiments to verify his calculations. After seeing EINSTEIN'S (1905) paper in the *Annalen der Physik* he consequently also published his results in 1906 in the same journal.

It is fair to say that Brownian-motion-related phenomena have decisively stimulated many new developments and advances for statistical physics over the last fifty years. As a matter of fact, the field is still very much alive with pioneering contributions covering the physics on the micro-scale and even the nano-scale in situations where novel physics on the quantum level and /or far from thermal equilibrium are ruling the transport behaviour.

One of the greatest challenges in the field of molecular biophysics involves the elucidation of the principles by which the nano-scale machineries in biological cells perform their work with such high efficiency, high adaptability to changing environmental conditions and high reliability. Above all, these biological motors must perform all of these functions in the face of inescapable thermal noise that is often much greater than the energy input that we can use to direct their operation. For this reason many physicists are working to understand the elementary mechanisms by which biological motors operate. An important insight is that thermal noise is most likely incorporated as an essential element for controlled motion by biological motors, giving rise to the term »*Brownian Motor*« (BARTUSSEK and HÄNGGI 1995, HÄNGGI and BARTUSSEK 1996, ASTUMIAN 1997, JÜLICHER et al. 1998, REIMANN and HÄNGGI 2002). For a most comprehensive review, which in addition provides a wealth of references for this timely research area, we refer the interested reader to the recent *oeuvre* by REIMANN (2002).

From everyday experience, noise is usually thought of as the enemy of order rather than as a constructive influence. In nonlinear systems that possess some sort of threshold, however, random noise can assume a beneficial role in enhancing the detection of weak sensory signals. This phenomenon, termed *Stochastic Resonance* (MOSS 1991, WIESENFELD and MOSS 1995, GAMMAITONI et al. 1998, HÄNGGI 2002) does find useful applications in physical, biological and biomedical contexts.

Certain biological systems may even use this effect for optimizing function and behaviour (see below).

Statistical quantum physics enters such prominent biological areas as photosynthesis. Clearly, the laws of quantum electron-transfer dynamical processes do in fact determine the mechanism by which sun light is harvested by cells. Most importantly, the structure of proteins and particularly the molecule of life, DNA, which plays a pivotal role as the carrier of genetic information in all living species do obey the laws of quantum mechanics. The structures are by no means fixed but do wobble and shake due to the influence of thermal and non-thermal noise forces. In this context, the question of charge transport in DNA has attracted much enthusiasm within the scientific communities of physics, chemistry and biology. Notably, the potential of DNA with its unique assembly properties, unparalleled recognition features, stability, adaptability and optical qualities together with its electronic properties are far too tempting for not being considered as a prime species for molecular electronics (DEKKER and RATNER 2001).

In the following we elucidate the useful and serviceable role of statistical physics for the description of three salient problems of biocomplexity: These are the phenomena of Brownian motors in biology (Section 2) the phenomenon of Stochastic Resonance (SR, Section 3) and the issue of electronic motion in DNA (Section 4).

2. Brownian motors in biology

Parallel to the impressive progress in nanotechnology and the advances in the study and manipulation of small scale biological systems we can witness a tremendous activity in the theoretical understanding of small-scale non-equilibrium transport devices, including a discussion of both the fundamental issues and the limits of the application of the second law of thermodynamics (HÄNGGI and BARTUSSEK 1996, ASTUMIAN 1997, JÜLICHER et al. 1998, REIMANN and HÄNGGI 2002, REIMANN 2002). Brownian motors and Stochastic Resonance have been at the forefront of this new scientific wave; this is mainly due to their intimate connection from the viewpoint of the physics which is at work in these corresponding biological problems.

2.1 Brownian Motor: Proof of principle

Following the reasoning of REIMANN et al. (1996) a simple example of a Brownian motor is depicted in Figure 1, where micron sized particles move on an asymmetric saw-tooth etched structure, e. g., on a glass slide. Because of the asymmetry of the structure, fluctuations in time between cold and hot temperature cause the particles to move, on average, to the right. In accordance with the second law of thermodynamics we note, however, that the net transport is zero whenever the temperature is held fixed. The directed motion arises because the cycling in time between cold and hot feeds energy into the system from a hot reservoir and dissipates it to a cold reservoir. In the example, the particles are the »motors« – the elements that undergo directional translation. The fuel is the energy supplied by heating and cooling the device. This simple model in Figure 1 illustrates the three main ingredients necessary for a »Brownian motor« (HÄNGGI and BARTUSSEK 1996, ASTUMIAN 1997, REIMANN and HÄNGGI 2002): (i) symmetry breaking, (ii)

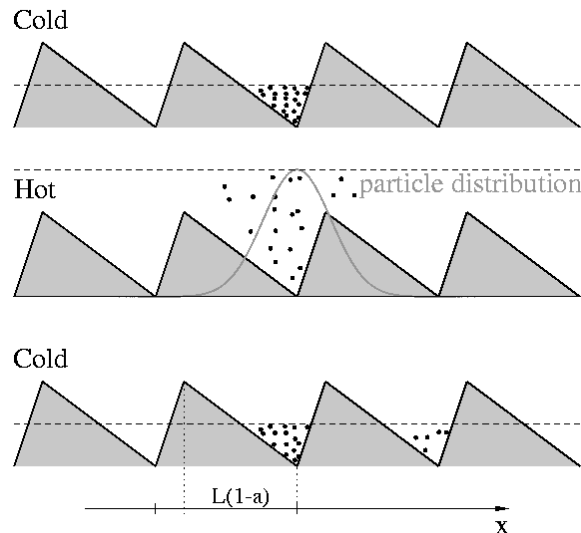energy input and (iii) thermal noise. Without any one of these the Brownian motor mechanism fails.

Fig. 1 Following the temperature-Brownian motor scheme by REIMANN et al. (1996) consider non-interacting particles in a viscous medium moving on an asymmetric saw-tooth potential of period L and height V subject to a temperature that fluctuates in time between »hot« and »cold« ($T \in T_{cold}, T_{hot}$). For simplicity let $V/(k_B T_{hot}) \ll 1$, and $V/(k_B T_{cold}) \gg 1$. The dashed line indicates the level $2k_BT$ below which ca. 95 % of the particles are found at any given time. When the temperature is cold, the particles are pinned at a potential minimum. Then, when the temperature is increased, the particles effectively do not »feel« the potential and begin to diffuse. When the temperature is cold again, any particles that have diffused the short distance aL, with a < ½, to the right are caught in the well to the right, any particles that have diffused the long distance $(1-a)L$ towards the left are caught in the well to the left, and the rest are pinned again in the original well from which they started. Because the chance for a particle to diffuse the short distance aL during the time when the temperature is hot is much greater than the chance to diffuse the long distance $(1-a)L$, net motion to the right is induced by strong temperature fluctuations. Optimally the system should remain hot long enough for the particles to diffuse the short distance, but not the long distance. The time in the cold state is less critical since pinning the particles is a predominately deterministic process that will be much faster than the diffusive motion.

The scheme in Figure 1 mimics a Brownian motor first proposed by BUG and BERNE (1987) working at Columbia University in New York and AJDARI and PROST (1992) working at the ESPCI in Paris; see also JÜLICHER et al. (1998). The latter researchers in Paris envisioned a situation where turning on and off an asymmetric electric potential would provide a means for separating particles based on diffusion coefficients yielding a so called *flashing* Brownian motor device. Such a scheme has been realized experimentally in several different ways (REIMANN 2002). A most pivotal feature is the rectification property of such Brownian motors. For any *fixed* temperature and an external negative tilt, the particles will move downhill on average. The numerically evaluated load curve, see Figure 2, instead depicts that the opposite is true within an entire interval of negative bias forces when additionally the device is now periodically cycled between two temperatures: Surprisingly indeed, the particles are moving uphill on average, thereby performing work against an external load. In particular, a finite velocity results at zero external load force. Moreover, one needs a finite negative force, the so termed *stall force*, before the average directed motion comes to a standstill.
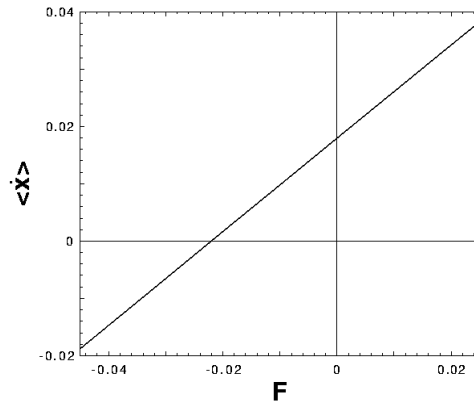
Fig. 2 Numerically determined time- and ensemble-averaged particle current in the long-time limit versus an external applied constant force for a temperature-Brownian motor depicted in Figure 1. Notwithstanding a not too large force pulling the particles to the left, the particle move uphill towards the right side. At a finite negative force, the so-called stall force, the average directed motion of the particle becomes reversed. After REIMANN and HÄNGGI (2002).

2.2 From Brownian motors to molecular motors

The principle of such Brownian motor physics is seemingly at work for molecular motors. Nature uses both, linear and rotary molecular motors that transport a variety of biological cargo and propel cells. This rationale of molecular motors in biology is widespread: It is known that such motors drive the replication of DNA, its transcription into messenger RNA as well as, e. g., the injection of DNA into bacteria by bacteriophage (BUSTAMANTE et al. 2000). The latter motor is the strongest presently known molecular motor: It stalls at an amazingly large force of 55 pico-Newton. Yet another astounding rotary motor is the ATPase synthease (the enzyme that uses the H^+-gradients to produce adenosin triphosphate (ATP) – the energy source that powers most molecular motors) which turns at a speed of up to around 4 Hz generating up to 3 ATP molecules per revolution. Notably, we produce and consume every day about half of our body weight in ATP. In all these cases the thermal fluctuations are truly tumultuous and are readily used in pushing stochastically particles over activation barriers. All these motors work in a strong viscous medium (very low Reynolds numbers), i. e. the stochastic motion is strongly overdamped: The situation that cells and bacteria meet is that of a human swimming in very sticky honey. This is also why nature has optimally solved the problem of locomotion under such conditions by use of motors that employ a rotating helical tail, or beating flagella.
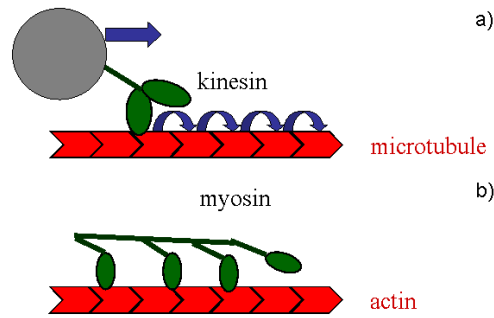
Fig. 3 Sketches of microtubules and actin filaments from the basic scaffolding of cells are depicted. The motor proteins kinesin and myosin are responsible for material transport and muscle motion. a) A kinesin molecule transports cargo along the microtubules by alternate binding and unbinding of the two heads. b) Muscle contractions are caused by aggregated myosin molecules. The motor heads of the myosin filament can bind to the actin filaments. Unbound heads fluctuate freely around their equilibrium positions. By preferentially binding at an angle in a forward direction directed motion occurs.

In the following we discuss only linear motors, cf. Figure 3, which move tangentially along a periodic structure of cytoskeletal filaments. The motor proteins are divided into families by sequence similarities. Myosin-II and myosin-V motors move on actin filaments and operate the contraction of muscles; kinesin and dyenin motors transport cargo along microtubules. These proteins use the chemical energy obtained from the hydrolysis of ATP which is then transformed into mechanical work by the assistance of tempestuous thermal fluctuations. As such the motion becomes a stochastic process and the key issue in this scenario refers to the problem of the strength of coupling between chemical and mechanical degrees of freedom in this non-equilibrium stochastic process. Important challenges address issues such as (i) the role of weak vs. a tight mechano-chemical coupling, (ii) what is the average energy input per cycle, (iii) what is the efficiency, and (iv) what is the degree of cooperativity among the motors in the process of directed transport.

First ideas of how molecular motors work were put forward by Sir Andrew HUXLEY (1957) in his landmark paper on the contraction of muscles, cf. Figure 3(b). It idealizes the myosin-II heads being anchored in the myosin filaments of a sacromer as harmonic springs with two states. In the bound state the motor heads form a crossbridge between the neighbouring myosin and actin filaments; in the unbound state the heads fluctuate freely around their equilibrium positions. Directed motion now occurs when the head binds preferentially at an angle in a forward direction and unbinds after completion of the work. Binding of the head is followed by a backward shift of the actin filament. These spatially asymmetric binding and unbinding rates consequently rectify the thermal fluctuations of the motor head, i. e. this model is an example for a Brownian motor. The myosin-II motors are so termed *nonprocessive* motors with a small duty ratio. The latter refers to the ratio of the average time spent in the bound state and the bound-plus-

unbound time interval. Being so, the myosin-II motors must work in groups in order to perform the task. In turn, this feature allows for a fast contraction in response to an external load. A molecular motor that walks over long distances before it detaches and gets lost, possesses consequently a high duty ratio; such motors, like kinesin or myosin-V are termed *processive*. The stochastic nature of the motors is a key ingredient allowing for asymmetric forward versus backward rates; indeed, thermal noise is truly essential in overcoming the various activation steps (HÄNGGI et al. 1990). The cooperativity of motor molecules has far reaching consequences: the statistical mechanical treatment of the coupling among the motors can give rise to fascinating phenomena such as phase transitions, normal and anomalous hysteretic behaviour, absolute negative mobility and spontaneous oscillatory behaviours, to name but a few (JÜLICHER et al. 1998, REIMANN 2002).

The walking of the processive motor kinesin mimics closely the Brownian motor scenario depicted with Figure 3(a). The microtubule is built up periodically with the constituent protein »tubulin«. This is a dimer consisting of two quite similar globular proteins, a-tubulin and ß-tubulin about 4 nm in diameter and 8 nm long. This asymmetric structure mimics the asymmetric potential profile in Figure 1. Each two-headed kinesin comprises a microtubule binding site as well as an ATP-binding site, termed the ATP-binding-pocket, see Figure 3(a). Each head can bind and hydrolyze ATP on its own. The chemical reaction cycle consists of the following main four steps. Step 1: the motor is interacting with the environment and is attached to the microtubule at a ß-tubulin binding site with no ATP bound to the ATP-pocket. Step 2: The head binds one ATP out of the environment in its ATP-binding pocket. Step 3: The ATP is broken up into adenosine diphosphate (ADP) and inorganic phosphate (the power stroke). In doing so, ca. 20 kT are gained in energy. Step 4: The inorganic phosphate is for a short time (thus implying a high duty ratio) released from the ATP-binding pocket and at the same time the kinesin motor typically detaches and undergoes Brownian motion, cf. the second part in Figure 1. Transition into state 1: ADP is released. The affinity to the binding site increases with the result that after some free diffusion one head will bind preferentially in forward direction again to the microtubule. Typically, a kinesin motor can cover a distance of a few µm with a velocity of ca. 1 µm/sec at 10 mM ATP concentration before it looses contact with the microtubule filament. Therefore, a single kinesin molecular motor makes hundreds of unidirectional 8-nanometer steps without detaching from, or freely sliding along the microtubule on which it moves (processive motor). Moreover, it possesses a stall force of ca. 5 pico-Newton. Note also that the two heads coordinate their actions: One head always stays attached and the power stroke energy release of the front head seemingly triggers the rear head to swing forward. How does the forward motion take place? Is it in a hand-over-hand like fashion or more like that of an inchworm (or a caterpillar)? Very recent experiments (HUA et al. 2002) seem to favour an inchworm-like scenario. This would disprove the previously accepted picture that the enzyme's two heads alternately and symmetrically step over each other along the microtubule. Yet, there are still some other schemes thinkable which are still consistent with the present experimental knowledge (ASTUMIAN and DERENYI 1999). In any case, the Brownian motor mechanism is at work in all these different mechanisms.

Modern statistical physics clearly is able to provide the necessary tools to describe such non-equilibrium biological transport in terms of Brownian motion theory within coupled flashing potential landscapes (HÄNGGI and BARTUSSEK

1996, ASTUMIAN 1997, JÜLICHER et al. 1998, REIMANN 2002). Clearly, the mere use of a rate description already implies that noise-activated escape events do play an important role in biological transport mechanisms; i. e. a pure deterministic picture can never fully cover the complete story behind microbiological locomotive schemes.

3. Biological Stochastic Resonance

In everyday life, noise is generically viewed as being of harmful influence in detecting and transferring information. In contrast, Stochastic Resonance (SR) (MOSS 1991, MOSS 1994, WIESENFELD and MOSS 1995, GAMMAITONI et al. 1998, HÄNGGI 2002) refers to a situation where the mere addition of random noise to the dynamics improves a system's sensitivity to discriminate weak information carrying signals. Thus, this phenomenon constitutes yet another example where random perturbations play a beneficial role. Because of its generic nature, this phenomenon boasts universal applications extending from classical and quantum physics to chemistry, engineering, and in recent years, also in biology and biomedicine.

3.1 Introduction to SR

The mechanism of SR works as follows: Consider a particle sitting in one well of a symmetric double well potential – let us say, a marble in an egg carton. A gentle force (periodic or aperiodic) tilts the whole system forth and back. This perturbation may be looked upon as an information carrying signal that is acting on the nonlinear system. Under the influence of this weak force the marble simply rolls around in the bottom of the well. Now, if its movement is detected only when it jumps into the neighbouring well, this weak signal will go unnoticed. Adding noise to the system – by rocking randomly the egg carton up and down – will, *a priori,* only mask the weak perturbation further. In fact, however, under some suitable conditions just the opposite is true. The weak signal together with the noise will allow the ball to occasionally exit into the neighbouring well. Now the theory of SR (GAMMAITONI et al. 1998) says that these exit events do not occur completely at random, but become correlated with the weak signal. An increasing noise level – correlated with the input signal – enhances the chance for excursions over the barriers. Since these large jump events dominate the response of the system, the small input signal is enlarged. One the other hand, too much noise will deteriorate the coherence of the signal assisted, noise-induced crossings. These barrier-crossing events expose an element of nonlinear system dynamics by which random noise can benefit faint signals by boosting them in a correlated manner over a threshold. The noise-enhanced output response is, therefore, fairly regular with only small fluctuations. From this perspective we find that SR is a cooperative phenomenon in which a weak, coherent input entrains ambient noise.
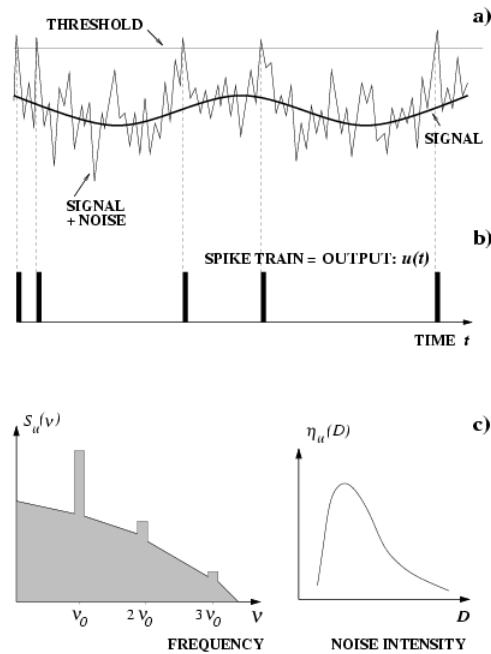
Fig. 4 Threshold stochastic resonance: a) Neuronal-like dynamics detect those events that rise above some threshold value (the thin top line). A weak, periodic subthreshold signal (thick line) can therefore be detected only if its dynamics are assisted by noise (noisy trace). A crossing event occurs most likely when the weak signal assumes its peak value. b) Upward-directed crossing events trigger a firing of spike-train dynamics, u(t). c) The power spectrum $S_u(?)$ of the output dynamics is depicted on the left-hand side; superimposed on a typical broadband background the spectrum features sharp peaks at multiples of the driving frequency $?_0$. The spectral power amplification, see the right-hand side in part c), exhibits the typical SR signature of a bell-shaped resonance versus increasing noise intensity D. The peak value is assumed at an optimal dose of noise for which the periodically modulated threshold crossing rate approximately synchronizes the signal with the firing events.

A typical characteristic of SR consists in its anomalous amplification of input signals by noise. The response itself serves thus as a natural measure of SR. In particular, for a periodic input signal the spectral power amplification (JUNG and HÄNGGI 1989, JUNG and HÄNGGI 1991) evaluates the ratio between the spectral power of the output at the driving frequency and the total power of the input signal. This amplification criterion undergoes a resonance-like behaviour: it increases *vs.* increasing noise intensity (regime of SR) until it reaches an optimal maximum, and then falls off; hence the term SR, see Figure 4. The spectral power amplification quantifier also yields a criterion of synchronization between the input signal and the noise-activated output dynamics. Note that the effect of SR is *not* a resonance phenomenon for the rate of the weak signal and noise-assisted escape dynamics: The time-averaged rate increases monotonically with both, increasing noise strength and perturbation intensity. Moreover, as a function of increasing driving frequency this time-averaged rate of escape starts out from a plateau-behaviour and then decreases monotonically; i. e. no common resonance peak feature is detected for the rate of escape, see JUNG and HÄNGGI (1989) and JUNG (1989). Another common approach to characterize SR is the signal-to-noise ratio (SNR)

(MCNAMARA and WIESENFELD 1989). This latter quantity is formed from the ratio obtained from the output spectral power at the driving frequency and the background power spectrum, multiplied by the experimental bin-width, of the driven stochastic dynamics at the driving frequency. Unlike the spectral power amplification, however, this quantifier does, in leading order of the signal strength, not depend on the driving period; consequently, it cannot be related to a synchronization measure. Another indirect measure of SR, which is often used by biologists, is the residence time probability distribution or inter-spike interval histogram. The corresponding measure is composed of a set of separated peaks that vary in width and separation upon increasing the noise intensity. Moreover, the characterization of noise-assisted transduction of realistic, broad-band type biological input-signals typically necessitates the introduction of complexity measures that are based on entropy related concepts, like the mutual information, the Kullback entropy, the rate of information gain and diverse cross-correlation measures (GAMMAITONI et al. 1998, ANISHCHENKO et al. 1999, HÄNGGI 2002).

Since its discovery in early 1981, the phenomenon of SR has been demonstrated repeatedly with diverse applications in chemistry, physics and the technical sciences (GAMMAITONI et al. 1998). SR in biology started with benchmark publications in the early nineties wherein the authors discovered SR in sensory neurons that have been subjected to external noise (BULSARA et al. 1991, LONGTIN et al. 1991, CHIALVO and APKARIAN 1993). In a series of experiments the group of Frank MOSS (DOUGLAS et al. 1993, WIESENFELD et al 1994, PEI et al. 1996) and several other groups as well, convincingly established the effect of SR in a variety of biological systems (HÄNGGI 2002).

Sensory neuronal systems are ideally suited to exhibit SR: they are intrinsically noisy and they do operate as threshold systems, cf. Figure 4. In these neuronal systems a propagating action potential upon reaching the threshold triggers a firing (voltage) spike, which is being followed by a quiescent time interval during which no firing events occur. In this context, a prominent question concerns the role of the internal noise of the sensory systems. Moreover, does the biological system intrinsically use noise-enhanced signal detection, via SR, to optimize its operational function? A promising first evidence that SR occurs with internal noise has been shown by PEI et al. (1996) where the internal noise may be varied by altering the light intensity that falls on the photoreceptive areas of crayfishs' hair cells which sense hydrodynamic flows.

3.2 Biological SR on the Subcellular Level: SR in Ion Channels

Ever since the discovery of SR, the Holy Grail of biological SR-related research has been the validation of the premise that mother nature has adapted, during evolution, to use intrinsic ambient noise for the optimization of sensory transduction on its most fundamental level: the ion channels. Presumably, SR has its origin in the stochastic properties of ion channel clusters that are located inside a receptor cell membrane. For an artificial system of ion channels which is composed of a parallel array of the peptide alamethicin, BEZRUKOV and VODYANOY (1995) have found evidence that SR does in fact occur. This result provokes the challenge whether SR in biology is rooted as a collective effect in finite assemblies of natural ion channels or whether SR can occur already within a single ion channel. In recent work, however, it was demonstrated theoretically that SR in a single Shaker potassium channel can indeed occur if the parameters for

operation are located within a regime where the channel is predominantly dwelled in the closed state (GOYCHUK and HÄNGGI 2000). This result is not only of interest on its own, but also impacts prominent applications that involve manipulations on the nanoscale, such as the design of a single-molecular biosensor. Where does SR originate from and what is its relevance in biological systems? Membrane patches that are able to exhibit an excitable dynamics must contain ion channels of at least two different kinds – such as potassium and sodium channels. The mean field model of HODGKIN and HUXLEY (1952) for voltage gated ion channels, when subjected to *external* noise, clearly exhibits in its firing dynamics the signature of SR (GAMMAITONI et al. 1998). More challenging, however, is the question of whether this biological system, if amended by a leakage current due to chloride ions and internal noise that originates from the random fluctuations of stochastic opening and closing of individual channels, is capable to exhibit SR. The intrinsic fluctuations within a given assembly of ion channels scale inversely with its system size. Indeed, the SNR of the spiking dynamics has recently been demonstrated to exhibit SR, which is solely due to internal noise (JUNG and SHUAI 2001, SCHMID et al. 2001). The SNR increases with increasing system size until it assumes a peak value at an optimal area of the assembly of ion channels, cf. Figure 5(a). Notice that this SR-behaviour mimics SR for the amplification in Figure 4(c); but now with the noise intensity being read from right-to-left. Above the optimal area, the SNR decreases with increasing size. Only the addition of external noise will again restore the SR behaviour in this regime (see Figure 5(b)). Put differently, there exists an optimal size for which ambient internal noise is beneficial for the functionality of ion channel patches. For sub-optimal, small sizes of ion channel assemblies, the addition of (external) noise (which simulates even smaller patch-areas) will thus only degrade the transduction behaviour. Moreover, there exists an internal noise-induced coherence phenomenon for which the spiking activity assumes for an optimal patch size a »most rhythmic« activity in the absence of any external input-signal that stems solely from spontaneous internal ion channel noise (JUNG and SHUAI 2001, SCHMID et al. 2001). These findings yield support to the conjecture that SR, in fact, is biologically significant. Likewise, the observed SR in biological systems is most likely rooted in a collective property of globally coupled ion channel assemblies.
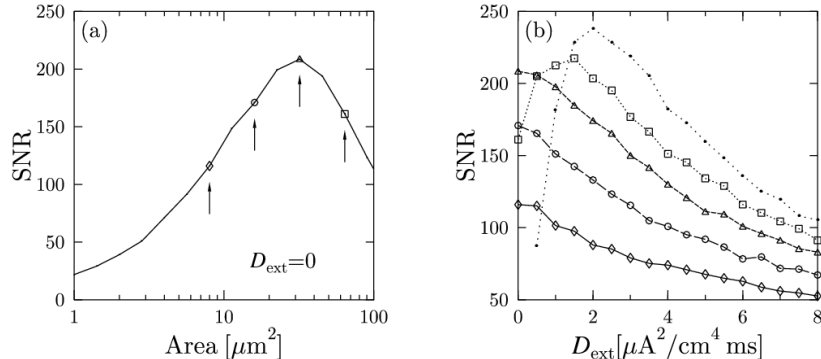

Fig. 5 (a) SNR data for a stochastic Hodgkin-Huxley modelling of an assembly of sodium and potassium ion channels and additional leakage channels for an external sinusoidal subthreshold stimulus of amplitude $1.0\,\mu\mathrm{Acm}^2$ and angular driving frequency of $0.3\,\mathrm{ms}^{-1}$ (SCHMID et al. 2001). One observes intrinsic SR for a weak stimulus versus solely internal noise. The internal noise intensity decreases with increasing area of the membrane patch. (b) If additional, external noise, $D_{\mathrm{ext}} ? 0$, is applied for the

system sizes marked by the arrows in (a), one finds the SNR behaviour for the corresponding membrane size versus D_{ext}. Notice that adding noise to small assemblies below optimal size only deteriorates the transduction behaviour further. In clear contrast, however, for above-optimal sizes the addition of noise yields the conventional SR behaviour. For comparison, the situation for infinite size (i.e. the mean field limit) with zero internal noise is depicted by the dotted line through the thin dots.

3.3 Biomedical benefits from SR

A most appealing feature of SR is the fact that it holds promise for the good of mankind, where numerous physiological functions are marked by threshold behaviours. For example, several disorders of the nervous system are caused by increased sensory thresholds, which lead to a reduced firing rate in the corresponding neurons. Experimental results (COLLINS et al. 1996, RICHARDSON et al. 1998) have offered hope that SR will find its way into applications that are beneficial for mankind in providing some means for the possible cure of, for example, a disordered person's balance, a patient's locomotion and other physiological functions. COLLINS et al. (1996) could establish several experimental SR procedures in order to improve a patient's tactile sensation by employing an optimal dose of mechanical or electrical noise to successfully detect subthreshold stimuli. The human visual perception system (RIANI and SIMONOTTO 1995, SIMONOTTO et al. 1997) and the human blood pressure regulatory system, the so termed »baroreflex system« (HIDAKA et al. 2000) offer yet other examples for biomedical benefits via the phenomenon of SR.

4. Electronic Transport in DNA

The molecule of life, DNA, plays a pivotal role in biology for the storage and the propagation of genetic material. Recently, DNA has moved into the limelight as a possible candidate for long range electronic motion. Unlike other proteins such as cytochromes and the photosynthetic reaction centre, DNA is not an ideal electron transfer species. There is also little evidence for the role of DNA-assisted charge migration in biological function and performance. So, why is there so much excitement about DNA being possibly a good conductor? First, the DNA with its p-electron system of four bases (guanine [G], cytosine [C], adenine [A], thymine [T]) stacked upon each other resembles certain »molecular metals«. Second, there are biological implications which pertain to radiation-induced damage, where radical reactions with nucleobases occur. These may be followed by charge migration processes that result in inter-strand and intra-strand chemical reactions which in turn lead to mutations. Most of all, however, DNA with its unique assembly properties, unparalleled recognition features, stability and optical properties make DNA a most potential candidate for the timely area of molecular electronics. It may be used as a toolkit component in building molecular architectures composed of molecular biosensors, molecular switches, molecular memory elements and molecular rectifiers and the like. Needless to say, that theoretical and experimental DNA assisted charge transport issues have attracted much attention recently (DEKKER and RATNER 2001). According to some recent experiments by physicists with a bundle of DNA of ca. 10 nm in length (FINK and SCHÖNENBERGER 1999), DNA conducts well with ~ 1 mega-Ohm of resistance. Others (KASUMOV et al. 2001) even claim that DNA can conduct charge with

virtually no resistance at room temperature; moreover, at extreme low temperatures DNA possibly even exhibits a supercurrent (KASUMOV et al. 2001). In contrast, researchers at Delft University of Technology have shown by a series of reproducible experiments with poly(dG)-poly(dC) DNA of 10–40 nm in length that DNA behaves like a good insulator with a resistance larger than 10^{12} Ohm (PORATH et al. 2000, DEKKER and RATNER 2001). This result is corroborated in recent experiments of the Princeton group (ZHANG et al. 2002) by two-probe current *vs.* voltage measurements with micron based (lambda)-DNA molecular wires bound to two gold electrodes (by incorporating thiol-modified nucleotides into both DNA ends) embedded in a buffer solution. The result is that (lambda)-DNA indeed behaves as an insulator possessing at room temperature a specific resistance ? $> 10^6$ Ohmcm. These latter experimental studies are fully consistent with recent electron transfer studies in DNA: Physical chemists have convincingly demonstrated (MEGGERS et al. 1998, GIESE et al. 2001) that long-range electron transfer in DNA occurs either via »thermal hopping« when G-C pairing sites are involved, or via coherent superexchange (i. e. no energy is exchanged with the molecule and environment) when A-T base pairs must be overcome. In the latter case the reaction rate decreases exponentially with the distance between donor and acceptor.

A satisfactory theoretical treatment of the overall electron (hole)-transport process is still lacking. In particular, this unique combination of incoherent hopping and coherent electron transfer mechanisms calls for a unified treatment that consistently accounts for the effects of coherence and dissipation on the same basis as it had been put forward for the thermally assisted tunnelling escape rate (the quantum-Kramers turnover theory) for reactions that occur in condensed phases, see HÄNGGI et al. 1990.

The transport mechanism of DNA when sandwiched between electrodes seems not settled yet. A whole series of mechanisms have been proposed for the problem of bridged hole-transport in DNA: These range from band-like transport, to incoherent hopping, to polaron mechanisms and fluctuation-induced electron transfer. On the bridge itself, however, the dominant mechanisms are, as mentioned above, coherent tunnelling and thermal, tunnelling assisted hopping events. The confusingly many different claims that range from well-insulating behaviour to metal-like and even to the support of superconducting currents may indicate that the parameter range of DNA is indeed extremely huge. The differences might be due to the role of a differing sequencing, the role of solvation on hole motion, differing ambient surroundings such as experiments in liquids, air or vacuum, the structural form of the DNA probe and, in particular, the electrode-DNA molecule interface. As a consequence, the community urgently is in need of careful and reproducible verifications of the different existing experiments and all the seemingly conflicting findings before final conclusions can be drawn.

5. Summary and outlook

In this article we have discussed the role of modern statistical physics in describing a selection of complex biological phenomena. We elucidated the ubiquitous role of noise for the transduction of biological information, the transport of biological cargo, energy and charge and the function of biological cellular systems. The pursuit of Brownian motor theory, Stochastic Resonance and electron transfer

theory into the biological and medical domain is very exciting and promising. Indeed, this change of focus from physical sciences towards life sciences carries a great potential and causes us to rethink and refine some of our usual concepts and issues. The lesson to be learned from all these examples is that noise does provide a useful task for biological activity rather than being a hindrance. It would seem strange when nature would not have taken advantage of the benefits of the naturally occurring boisterous fluctuations, rather than beating it. There exist many other cases, such as, e. g., the migration of ligands in proteins (ALBERDING et al. 1978, FRAUENFELDER and WOLYNES 1985, FRAUENFELDER and MCMAHON 2001), protein folding and the like, where the methods of modern statistical physics are salient and essential in order to account reliably for the jiggling- and wiggling-behaviours of biomolecules characterizing biocomplexity. The ultimate goal must be to be able to describe the physical and chemical laws governing the structure, the dynamics and the function of biological materials. At present times, however, we are still far away from being able to provide biology with major predictive power. On the contrary, physics has repeatedly learned fundamental principles and concepts from biological phenomena, and it certainly will continue to do so in the future! In this spirit we (as communicated to us by Hans FRAUENFELDER) may also quote here Stan ULAM:

»Ask not what physics can do for biology, ask what biology can do for physics.«

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