

Rigorous results of nonequilibrium statistical physics and their experimental verification

L P Pitaevskii

DOI: 10.3367/UFNe.0181.201106d.0647

Contents

1. Introduction	625
2. Rigorous results of nonequilibrium statistical physics	626
2.1 Bochkov–Kuzovlev and Jarzynski equalities; 2.2 Crooks reversal relations; 2.3 How many times does an experiment need to be repeated to verify the Jarzynski equality?	
3. Experimental verification of the theory	628
3.1 Experiment with a torsion pendulum; 3.2 Experiments with ribonucleic acids	
4. Conclusion	632
References	632

Abstract. Rigorous relations of nonequilibrium statistical physics are discussed. An arbitrary system brought into a strongly nonequilibrium state by an external time-dependent impact is considered. Based on the Hamiltonian formalism of classical mechanics, the Bochkov–Kuzovlev equality, the Jarzynski equality, and Crooks reversal relations valid for fluctuations in the work done on a system are derived. Verification of these equalities in mechanical experiments with a torsion pendulum and biological objects (folded ribonucleic acids) is described.

1. Introduction

I dedicate this paper to the memory of my senior friend V L Ginzburg.¹ When I began attending his seminar, I was amazed at the universality of his interests. The participants in the seminar discussed a very wide range of issues. VL listened with great interest to the reports touching on many different topics, and his comments and questions were, as a rule, very nontrivial. The present paper is not quite usual either. It deals with some very crucial issues of modern theoretical physics, but the theory expounded in it has been verified most precisely in experiments carried out in a quite a

¹ This paper was to be reported at the session of the Physical Sciences Division of the Russian Academy of Sciences (RAS) dedicated to V L Ginzburg, which I unfortunately could not attend. (Materials of this session are published in the present journal issue on p. 633.)

L P Pitaevskii P L Kapitza Institute for Physical Problems, Russian Academy of Sciences,
ul. Kosygina 2, 119334 Moscow, Russian Federation,
INO-CNR BEC Center and Dipartimento di Fisica, Università di Trento,
I-38123 Povo, Trento, Italy
E-mail: lev@science.unitn.it

Received 18 April 2011

Uspekhi Fizicheskikh Nauk 181 (6) 647–654 (2011)

DOI: 10.3367/UFNr.0181.201106d.0647

Translated by Yu V Morozov; edited by A Radzig

different branch of science — molecular biology. I believe it represents the mainstream development paradigm for our science. Such a situation would certainly have drawn the attention of Vitaly Lazarevich and he might have been pleased by it.

As known, statistical physics of the equilibrium state based on the Gibbs distribution provides a comprehensive description of the phenomena being observed. Knowing the Hamiltonian of a system, $H(p, q)$, one can calculate its free energy (see, for instance, Ref. [1])

$$F(T, V) = -k_B T \log Z, \quad (1)$$

where Z is the partition function defined as

$$Z = \int \exp(-\beta H(p, q)) d\Gamma, \quad \beta = \frac{1}{k_B T}, \quad (2)$$

and derive thermodynamic identities. Here, $d\Gamma$ is the number of states in the phase space volume element

$$d\Gamma = \frac{d^3 p_1 \dots d^3 p_N d^3 q_1 \dots d^3 q_N}{(2\pi\hbar)^{3N}}, \quad (3)$$

and N is the number of atoms in the system. In this way, the microscopic substantiation of equilibrium thermodynamics is given. The phase space distribution function takes the form $\exp[\beta(F - H(p, q))]$. In other words, the probability that the system resides in the phase space volume element $d\Gamma$ is

$$d\mathcal{P} = \exp[\beta(F - H(p, q))] d\Gamma. \quad (4)$$

[I am reasoning in terms of the classical (to be precise, quasi-classical) statistical physics that rather accurately describes the experiments discussed in Sections 2, 3. The reader will find some remarks on the quantum formulation of the problem in the Conclusion (Section 4).]

A different situation is encountered in the statistical physics of nonequilibrium processes or physical kinetics.

Although the kinetic equation describing the nonequilibrium behavior of a rarified gas was derived by L Boltzmann as early as 1872, there are still very few exact results applicable to arbitrary systems in arbitrary nonequilibrium states. A major leap forward was the discovery by L Onsager in 1931 of the symmetry principle for kinetic coefficients describing the behavior of a system under the influence of a small external perturbation [2, 3]. This theory was further developed by H B Callen and T A Welton [4], who proved in 1951 the fluctuation-dissipation theorem relating fluctuations in a system to dissipation under the effect of a small external perturbation.

The situation began to change in the late 1970s after the pioneering publications of G N Bochkov and Yu E Kuzovlev, who obtained rigorous equalities for fluctuations in an arbitrary system brought into a strongly nonequilibrium state by an external time-dependent impact [5–8]. In their time, this far-reaching work did not attract the attention it deserved, probably due to the difficulties encountered in its experimental verification (I shall dwell on the causes behind these difficulties below). It was appreciated later when researchers took a fresh look at the problem and more general equalities were obtained. In my opinion, the results of C Jarzynski [9] and G E Crooks [10, 11] are very important, and I shall rely on them henceforth. Their theoretical predictions have been validated in interesting—even if scarce—experiments performed thus far.

2. Rigorous results of nonequilibrium statistical physics

2.1 Bochkov–Kuzovlev and Jarzynski equalities

Let us consider a thermally isolated macroscopic (i.e., consisting of a large number of particles) system. Let external forces deliver work to the system. Then, its Hamiltonian will depend on parameter λ that is, in turn, a time-dependent one, $H = H(p, q, \lambda(t))$. Let us further assume that the work done on the system is small compared with its total energy. This condition can be realized in a natural way if the work is done on a small part of the system (subsystem), e.g., on the contents of a small cylinder with a movable piston (Fig. 1). Let parameter λ be constant and equal λ_0 up to an instant $t = 0$. Then, at $t = 0$, the system resides in thermodynamically equilibrium state with temperature $T = 1/(k_B\beta)$. However, this macroscopic state corresponds to a variety of states of a system with given initial values of momenta p and coordinates q .

Let the system have momenta and coordinates p_0, q_0 at an initial instant $t = 0$ when its energy is $H(p_0, q_0, \lambda_0) \equiv H_0$. The system moving in phase space in accordance with laws of classical mechanics will pass into a certain state p_f, q_f by the time t_f , and its energy will be $H(p_f, q_f, \lambda(t_f)) \equiv H_f$. The work

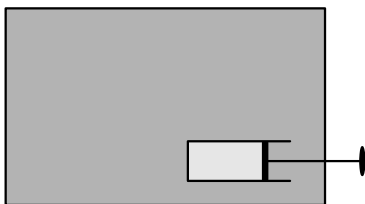


Figure 1. Schematic of the imaginary experiment.

done on the system² is given by

$$W = \int_0^{t_f} \frac{\partial H}{\partial \lambda} \frac{d\lambda}{dt} dt = H(p_f, q_f, \lambda(t_f)) - H(p_0, q_0, \lambda(0)). \quad (5)$$

However, the statistical sense is attributed to average work

$$\langle W \rangle = \langle H(p_f, q_f, \lambda(t_f)) - H(p_0, q_0, \lambda(0)) \rangle, \quad (6)$$

with averaging over the results of the experiment performed repeatedly with the same dependence $\lambda(t)$.

The central point of the theory expounded here is that the quantity $\langle \exp(-\beta W) \rangle$ rather than $\langle W \rangle$ needs to be considered. The system having been in equilibrium at $t = 0$, its distribution function is $\exp[\beta(F_0 - H_0)]$, where F_0 is the free energy at the initial instant³ $t = 0$. According to the definition of the average, one has

$$\begin{aligned} \langle \exp(-\beta W) \rangle &= \int \exp[\beta(F_0 - H_0)] \exp[-\beta(H_f - H_0)] d\Gamma_0 \\ &= \exp(\beta F_0) \int \exp(-\beta H_f) d\Gamma_0. \end{aligned} \quad (7)$$

The main point of the proof is that the Jacobian of the transformation from variables p_0, q_0 to variables p_f, q_f is unity in accordance with the Liouville theorem (see Ref. [12, par. 46]; therefore, $d\Gamma_f$ can be substituted for $d\Gamma_0$:

$$\langle \exp(-\beta W) \rangle = \exp(\beta F_0) \int \exp(-\beta H_f) d\Gamma_f. \quad (8)$$

As a result, we arrive at the ‘Jarzynski equality’ [9]:

$$\langle \exp(-\beta W) \rangle = \exp(-\beta \Delta F), \quad \Delta F = F_f - F_0, \quad (9)$$

where F_f is the equilibrium free energy calculated with the Hamiltonian H_f at temperature T . It should be emphasized that F_f is by no means the free energy of the system at the moment t_f when the system is generally speaking out of equilibrium. However, if parameter λ remains (not necessarily) constant for $t > t_f$, the system sooner or later come to equilibrium, while its temperature, owing to the large size of the system and the small energy imparted to it, will not change. Then the free energy of the system will finally equal F_f .

If the final and initial values of parameter λ coincide, $\lambda(t_f) = \lambda(0)$, i.e., in the case of a cyclic process, then $\Delta F = 0$ and equality (9) reduces to the Bochkov–Kuzovlev equality [5, 6]

$$\langle \exp(-\beta W) \rangle = 1. \quad (10)$$

² The question of the definition of work is actually an intricate one, as illustrated by a simple example. Let us consider the static problem of an oscillator in an external field λ : $H(q, \lambda) = q^2/2 - \lambda q$. Minimization gives $q = \lambda$; as λ changes from zero to λ_f , the Hamiltonian H changes from 0 to $-\lambda_f^2/2$. Then, if the work is defined by relationship (5), $W \equiv W^{\text{incl}} = -\lambda_f^2/2$. Bear in mind that, in our definition, the change in the second term in H is included in the work; hence, the superscript *incl.* However, a different formulation of the problem is equally feasible in which the energy of the subsystem is taken to be $q^2/2$, and the second term is related to the system doing work. Then, work $W^{\text{excl}} = \lambda_f^2/2$. Because the second term in H fluctuates, W^{incl} and W^{excl} have different statistical properties. The former definition of work is adopted in Ref. [9] and in the present paper, and the latter was used in Refs [5, 6].

³ The assumption that the system obeyed the Gibbs distribution at the initial instant of time implies that it was in contact with a bigger thermal reservoir before heat insulation.

Equations (9), (10) look very simple. However, they prove rather unusual on closer examination. Recall firstly the known properties of the work $\langle W \rangle$. If parameter λ changes adiabatically slowly, i.e., time t_f is large compared with all relaxation times in the system, the process is reversible and isothermal. In this case, one has

$$\langle W \rangle = \Delta F \tag{11}$$

(see Ref. [1, par. 15]).

If parameter λ changes rapidly, the entropy of the system increases. In this case, ‘usual’ statistical physics tells us only that

$$\langle W \rangle > \Delta F . \tag{12}$$

Here, however, we immediately encounter a paradox. Let the subsystem on which work is done (gas in the cylinder) be large enough, i.e., contain $N_s \gg 1$ particles, and the work $\langle W \rangle$ be on the order of the subsystem’s energy, i.e., $\propto N_s$. Then, fluctuations of $\langle W \rangle$ are relatively small, $|\delta W|/\langle W \rangle \sim 1/\sqrt{N_s}$, and can naturally be neglected in equation (9), which can be rewritten as $\exp(-\beta\langle W \rangle) \approx \exp(-\beta\Delta F)$. Hence, the relation $\langle W \rangle \approx \Delta F$ that is in obvious conflict with inequality (12) because the work in a nonequilibrium process may be different from ΔF by several-fold.

The solution to this paradox is very nontrivial. The fact is that large work fluctuations acquire significance in equality (9) in the nonequilibrium case, when W fortuitously takes small values compared with $\langle W \rangle$. Such fluctuations are very rare, but they make an important contribution due to the exponential dependence of $\langle \exp(-\beta W) \rangle$ on W . To understand the type of fluctuations in question, let us consider our cylinder and assume the process in it to be a two-fold compression of the gas. At what fluctuation will the compression work be small? If all molecules of the gas are gathered by fluctuations in the half of the cylinder where we wish them to be, no work whatever will be needed. But the experiment will have to be endlessly repeated till the ‘right’ fluctuation occurs (see Section 2.3 for the estimation of the number of required repetitions). It is such fluctuations that contribute to Eqns (9), (10). I think that these equations are the first exact relations of statistical physics in which large fluctuations make a definitive contribution. Certainly, this peculiarity of equalities (9), (10) hampers their verification on macroscopic objects, which probably explains why the first studies were not properly appreciated. Today, the situation has changed. Mesoscopic objects are playing an increasingly greater role in physics and technology, and the studies mentioned acquire progressively greater importance.

To conclude this section, it is worth noting that formula (9) leads to inequality (12). The inequality $\langle \exp x \rangle \geq \exp \langle x \rangle$ may be used for the proof. However, this does not mean that we thus proved the entropy increment law, because we postulated that the system would eventually come into equilibrium at temperature T .

Equality (9) may be utilized to calculate the first fluctuation correction to ΔF . To this end, let us rewrite the equality as

$$\Delta F = -k_B T \log \langle \exp(-\beta W) \rangle , \tag{13}$$

represent the work in the form $W = \langle W \rangle + \delta W$, and expand (13) with respect to δW , restricting ourselves to a quadratic

term. As a result, one arrives at

$$\Delta F \approx \langle W \rangle - \frac{\beta \langle (\delta W)^2 \rangle}{2} . \tag{14}$$

This expression was obtained by Hermans [13] with the help of a usual fluctuation–dissipation theorem.

2.2 Crooks reversal relations

The equalities derived in Section 2.1 are based on the fact that the system of interest moves in phase space in accordance with Hamilton’s equations and therefore satisfies the Liouville theorem. Other important relationships can be obtained bearing in mind the reversibility of the equations of motion (G E Crooks [10, 11]). Henceforth, I shall follow paper [14].

In order to obtain these relationships, the ‘direct’ process in which parameter λ changes in accordance with the $\lambda^A(t)$ law should be considered along with the ‘reverse’ process in which $\lambda = \lambda^R(t) \equiv \lambda^A(t_f - t)$. In other words, $\lambda^R(t)$ runs through $\lambda^A(t)$ values in the reverse order, from $\lambda(t_f)$ to λ_0 . Let our system be in thermodynamic equilibrium before the onset of the direct process. Let us again choose a trajectory $p_0 q_0 \rightarrow p_f q_f$ in the phase space in which the work W is delivered. According to formula (4), the probability of doing such a work is given by

$$d\mathcal{P}^A = \exp [\beta(F_0 - H(p_0, q_0, \lambda_0))] d\Gamma_0 . \tag{15}$$

Let us consider the reverse process in which parameter λ varies according to $\lambda = \lambda^R(t) \equiv \lambda^A(t_f - t)$. At $t = 0$, the system resides in equilibrium at the parameter value λ_f . Let us now consider the trajectory of the system in the phase space with initial conditions $p, q = -p_f, q_f$ at $t = 0$. Because the Hamiltonian H exhibits symmetry with respect to the change in the sign of time, namely

$$H(-p, q) = H(p, q) , \tag{16}$$

the Hamiltonian at the initial moment will be equal to H_f , and the probability of this initial state takes on the form

$$d\mathcal{P}^R = \exp [\beta(F_f - H_f)] d\Gamma_f . \tag{17}$$

Next, variables $(-p, q)$ in the ‘reverse’ trajectory will clearly run in the reverse order over the same values as (p, q) in the direct trajectory (Fig. 2):

$$(p^R, q^R)_{(t)} = (-p^F, q^F)_{(t_f-t)} . \tag{18}$$

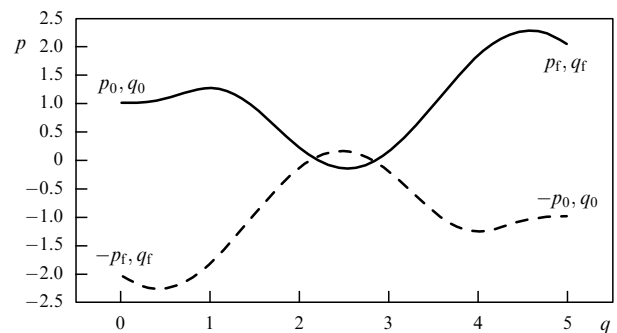


Figure 2. Schematic representation of direct (solid curve) and reverse (dashed curve) trajectories in phase space.

Accordingly, the values of momenta and coordinates at $t = t_f$ will be equal to $-p_0, q_0$, and the Hamiltonian is H_0 ; hence, the work delivered is $H_0 - H_f = -W$.

Combining Eqns (15) and (17) and taking account of the Liouville theorem, we arrive at the sought Crooks equation for the probability distribution of direct and reverse trajectories:

$$\frac{d\mathcal{P}^A(W)}{d\mathcal{P}^R(-W)} = \exp[\beta(W - \Delta F^A)]. \quad (19)$$

In a reversible process, the probabilities are equal and $W = \Delta F$ in accordance with relationship (11). However, these probabilities may prove equal in a nonequilibrium process, too, for a certain value of the work W . This value gives the difference between the energies of two equilibrium states. Equation (19) holds true in the absence of a magnetic field that breaks time symmetry of H . Therefore, for this equation to be correct in the presence of a magnetic field, probabilities (19) should be calculated for its opposite directions.

It should be noted that the value of $W_d = W - \Delta F$ has the sense of energy dissipation in a given realization of the process. It is referred to as dissipated work. The mean value of this work is positive: $\langle W_d \rangle \geq 0$, but in certain realizations of the process W_d may be negative. Equality (9) can be written out in terms of W_d as

$$\langle \exp(-\beta W_d) \rangle = 1. \quad (20)$$

Let us show that equation (9) directly follows from equation (19). To this effect, Eqn (19) should be rewritten as

$$\exp(-\beta W) d\mathcal{P}^A(W) = \exp(-\beta \Delta F) d\mathcal{P}^R(-W)$$

and integrated over the entire phase space. Taking into account that $\int d\mathcal{P}^R(-W) = 1$, it gives equality (9).

2.3 How many times does an experiment need to be repeated to verify the Jarzynski equality?

As mentioned in Section 2.1, rare fluctuations with work values significantly smaller than $\langle W \rangle$ contribute to the mean value of $\langle \exp(-\beta W) \rangle$ for a sufficiently large system. To find what these work values are, both direct and reverse processes need to be considered [14]. The probability distribution of different experimental realizations of the direct process, $d\mathcal{P}^A = \exp[\beta(F_0 - H_0)] d\Gamma_0$, has a sharp peak in the phase space region close to the hypersurface corresponding to the mean energy value, $H_0(p_0, q_0, \lambda_0) = \langle E_0 \rangle$. We denote this region by Γ_{Typ}^A . As a result, the overwhelming majority of realizations of the experiment will give the ‘typical’ value of work in the vicinity of $\langle W^A \rangle$. The distribution determining the average $\langle \exp(-\beta W) \rangle$ is $\exp(-\beta W) \exp[-\beta(F_0 - H_0)] d\Gamma_0$. It has a maximum in the still unknown phase space region Γ_{Dom}^A responsible for the dominant contribution to integral (7). The same transformations as in the derivation of this equation lead to

$$\begin{aligned} \exp(-\beta W) \exp[-\beta(F_0 - H_0)] d\Gamma_0 \\ = \exp[-\beta(F_0 - H_f(p_f, q_f, \lambda_f))] d\Gamma_f. \end{aligned} \quad (21)$$

The expression on the right-hand side of this equality is proportional to the initial equilibrium distribution for the reverse process, having a maximum near $\langle W^R \rangle$. This means

that the main contribution to $\langle \exp(-\beta W^A) \rangle$ comes from the values close to the typical value $\langle W^R \rangle$ of the work for the reverse process. By analogy, one finds

$$\Gamma_{\text{Dom}}^A = (\Gamma_{\text{Typ}}^R)^*, \quad (22)$$

where superscript $*$ denotes the change of the signs of all momenta.

Now, we can calculate the probability \mathcal{P} that the value of W in a given realization of the experiment will be on the order of W_{Dom} . Then, the quantity $\mathcal{N} = 1/\mathcal{P}$ stands for the number of realizations (to an order of magnitude) of the experiment needed to satisfy equality (9). Let us consider the direct process. The probability of finding the value from Γ_{Dom}^A in a given realization of the experiment is given by

$$\begin{aligned} \mathcal{P}^A &= \int_{\Gamma_{\text{Dom}}^A} \exp[-\beta(F_0 - H_0)] d\Gamma_0 \\ &= \int_{\Gamma_{\text{Typ}}^R} \exp[-\beta(W^R + \Delta F^A) - \beta(F_f - H_f)] d\Gamma_f. \end{aligned} \quad (23)$$

In this transformation, we utilized the Crooks equality (19), as well as formulas (16) and (22). Let us take into account that $W \approx \langle W^R \rangle$ in the small integration domain Γ_{Typ}^R in the last integral. It allows for the substitution $W \rightarrow \langle W^R \rangle$. The remaining integral is roughly equal to unity, by definition of Γ_{Typ}^R . Thus, $\mathcal{P}^A \approx \exp[-\beta(\langle W^R \rangle + \Delta F^A)]$ or, after the introduction of dissipated work $\langle W_d \rangle = \langle W^R \rangle + \Delta F^A$, one finds

$$\mathcal{N} = \frac{1}{\mathcal{P}} \approx \exp(\beta \langle W_d \rangle). \quad (24)$$

In other words, the number of necessary realizations of the experiment is determined by an energy dissipation but, oddly enough, in the reverse process. Clearly, the theory under consideration implies that experiments should be performed with energy dissipation on the order of several $k_B T$, which requires small but not necessarily mesoscopic systems; practically speaking, they must be such so as to ensure the observation of Brownian motion. However, the necessity of multiple measurements creates difficulties. The system’s properties (i.e., its Hamiltonian) may change during such repetitions, e.g., as a result of material fatigue.

Notice that the above formulas also hold for the reverse process with the substitution $A \leftrightarrow R$.

3. Experimental verification of the theory

3.1 Experiment with a torsion pendulum

Let us begin the discussion of the experimental verification of the theory from a direct and demonstrative experiment reported by Douarche, Ciliberto, Petrosyan, and Rabbiosi [15]. Their experimental device (Fig. 3) was a Brownian torsion pendulum composed of a bronze strip (length 10 mm, width 0.75 mm, thickness 50 μm , and mass 5.9×10^{-3} g) and a glass mirror with a gold surface (length 2.25 mm, width 7 mm, thickness 1.04 mm, and mass 4.02×10^{-2} g) glued in the middle of the strip. The elastic torsional stiffness of the strip was $C = 7.50 \times 10^{-4}$ N m rad $^{-1}$, the moment of inertia of the suspension $I = 1.79 \times 10^{-10}$ kg m 2 , and the eigenfrequency of pendulum oscillations in a vacuum $f_0 = 326.25$ Hz. The pendulum was enclosed in a cell filled with a viscous fluid

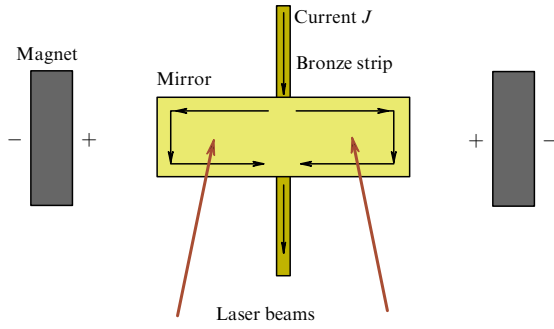


Figure 3. Torsion pendulum to check the Jarzynski equality. Schematic of an experimental setup [15].

to increase friction and ensure thermal contact. As a result, the eigenfrequency decreased to $f_0 = 213$ Hz. Relaxation time of the liquid oscillator in the presence of the fluid and in a vacuum was $\tau_{\text{relax}} = 23.5$ and 666.7 ms, respectively. Notice that the device had macroscopic dimensions altogether.

The role of parameter λ in this experiment was played by the moment M of forces applied to the pendulum. It was created by means of electric current J delivered through the strip to the two coils glued behind the mirror. The whole device was positioned between analogous poles of two permanent magnets; due to this, the flowing current created the moment $M \propto J$. The mirror was illuminated by two laser beams, their interference making possible the measurement of the pendulum rotation angle θ . The moment M of forces varied in experiment up to a certain maximum value M_{max} over time τ . In each realization of the experiment, the work W was calculated for the direct and reverse processes using formula (5) reduced to

$$W = - \int_0^{\tau} \dot{M} \theta dt. \quad (25)$$

The multiple repetition of the experiment allowed the probability distributions of W to be determined. They are shown in Fig. 4 for two different parameters of the process (see cases 1 and 3 in the table). In this experiment, ΔF could be calculated in advance: if $M_0 = 0$, then

$$\Delta F_{\text{calc}} = - \frac{M_{\text{max}}^2}{2C}, \quad (26)$$

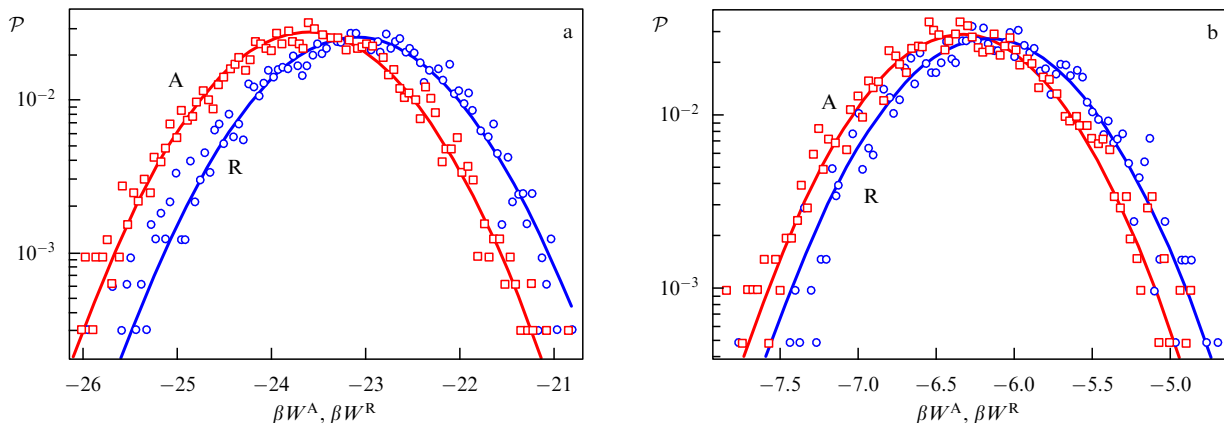


Figure 4. Probability distributions of direct (W^A , circles) and reverse (W^R , squares) processes Nos 1 (a) and 3 (b) (see table) [15].

Table. Results of measurements for five implementations of the torsion pendulum experiment.*

No.	τ/τ_{relax}	M_{max}	$-\beta\Delta F_{\text{calc}}$	$-\beta\Delta F^A$	$\beta\Delta F^R$	$-\beta\Delta F_{\times}$	$\beta \Delta F_{\text{cycl}} $
1	8.5	11.9	23.8	24.1	24.5	24.1	1.0
2	0.85	6.1	6.1	5.6	6.1	6.2	1.0
3	3.5	6.1	6.1	6.1	6.3	5.7	0.4
4	2.8	4.2	2.7	2.6	2.8	2.2	0.3
5	4.2	1.2	0.22	0.23	0.24	0.22	0.04

* The ratio of the time of experiment to the relaxation time, τ/τ_{relax} , and the maximum moment M_{max} of forces in terms of [pN m] units are presented. The cell was filled with a viscous fluid. The value of ΔF_{calc} was calculated by Eqn (26). ΔF^A and ΔF^R were found by using the measured work values to calculate ΔF according to the Jarzynski equality (9) for the direct and reverse processes, respectively. The value of ΔF_{\times} was determined by Eqn (19) from the intersection of work probability distribution curves for the direct and reverse processes. Theoretically, the last three values must coincide with ΔF_{calc} . The quantity ΔF_{cycl} characterizes a change of the free energy calculated from Eqn (9) for a cyclic process. Theoretically, it must be zero.

because in an equilibrium isothermal process only the elastic energy of the pendulum varies. The results of measurements under different experimental conditions are presented in the table.

Clearly, the results of this laborious experiment are in satisfactory agreement with the theory. However, the linear oscillator for which the difference ΔF between the free energies is known beforehand cannot be regarded as a sufficiently general system. Moreover, the observed fluctuations of the work obeyed the Gaussian distribution within the accuracy of the measurement. This means that large fluctuations, the account of which is the most nontrivial part of the theory, made no substantial contribution in the above experiments.

3.2 Experiments with ribonucleic acids

3.2.1 DNA and RNA. It turned out that experiments with natural microscopic springs created in the course of the evolution of living organisms enable extraction of much more useful information than those with artificially prepared working substances. Such springs are represented by ribonucleic acids (RNA) and deoxyribonucleic acids (DNA) playing the key role in the storage and transfer of genetic information.

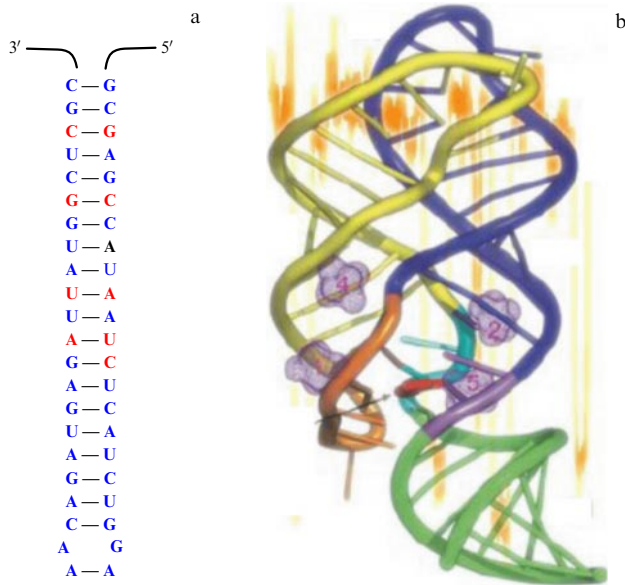


Figure 5. (a) The structure of an RNA segment from *Tetrahymena thermophila* ribosomes [16]. Capital letters denote nitrogenous bases. (b) Folded RNA [17].

RNA and DNA are similar in their overall structure. They comprise two long helical strands of organic compounds — nitrogenous bases. The two individual strands of DNA are folded into a double helix, whereas the single strand of typical RNA folds in a hairpin loop fashion. Figure 5a shows the RNA P5abΔU segment structure for unicellular infusoria *Tetrahymena thermophila*. This RNA segment (with modifications) was utilized in experiments [16].

We are interested in the mechanical properties of this RNA macromolecule. To begin with, it should be emphasized that such a molecule, if left to its own resources, tends to fold into itself (Fig. 5b). However, such a folded molecule can be straightened like a spring by applying a stretching force to its free ends. This implies that some work needs to be done. Notice that such natural springs are characterized by high quality. While the straightening energy may be on the order of several $k_B T$ (at room temperature), a much higher energy is required to rupture the molecule, guaranteeing the conservation of genetic information.

3.2.2 Experimental setup. A few studies reported thus far were designed to verify the theory under discussion in experiments with the use of RNA molecules [16, 18–21]. We shall consider here experiments [16, 19, 20] that yielded the most detailed information (see also the interesting popular article [22]). Figure 6 depicts the setup employed in these experiments. Measurements of fluctuations of the work needed to unfold and refold the single-stranded RNA molecule call for having a device performing such deformation. The parameters to be measured are the displacement of the molecule's ends and the force acting on them.

First and foremost, it turned out that the length of a RNA segment chosen for the measurement (ca. 20 nm) was too short to be manipulated straightforwardly.⁴ Therefore, flanking DNA 'handles' had to be attached to the two free

⁴ Specifically, the distance between the beads must be large enough, so that the effect of van der Waals interaction can be neglected.

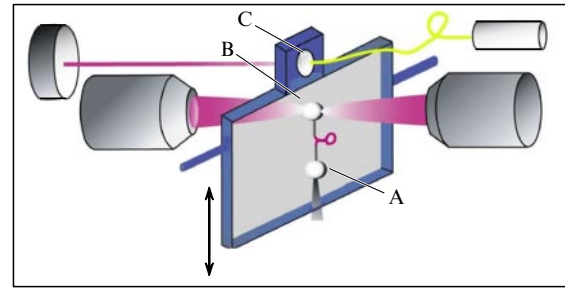


Figure 6. Experimental setup [19]: A — the bead attached to the cell; B — the bead held in the optical trap, and C — the lens of the laser level gauge.

ends of the RNA molecule by means of specific enzymes. The free ends of the DNA segments were in turn glued to polystyrene beads 2,000–3,000 nm in diameter. The RNA strand tethered to the beads was immersed in an aqueous solution within a transparent cell. The lower bead anchored on a glass micropipette was rigidly coupled to the cell, while the upper one was confined by an 'optical trap', i.e., in the focus of two oppositely directed laser beams that pulled in the dielectric material of the bead. The position of the cell was varied with the help of a piezoelectric device (actuator), while the upper end of the DNA glued to the upper bead remained virtually motionless. The displacement was governed by a level gauge consisting of a laser, whose beam was delivered through a lightguide to the lens in the upper part of the cell, and a detector. In this way, RNA stretching could be measured. The measurement of the force encountered greater difficulties that were overcome by a trick described in the study by Smith, Cui, and Bustamante [23].

Let the RNA unfolding force be applied to the upper bead. It will displace the bead in the optical trap in the vertical direction, but the displacement will be too small to be measured. However, it is possible to directly evaluate the force by measuring the light intensity distribution behind the beam-focusing lens. The momentum transferred from the RNA to the bead must be carried away by the light scattered from the bead. The momentum carried away per unit time in the direction \mathbf{n} in the solid angle $d\omega_n$ is equal to $\Delta P = (n_1/c) I(\mathbf{n}) d\omega_n/4\pi$, where $I(\mathbf{n})$ is the radiation intensity in this angle, and n_1 is the refraction coefficient of the fluid within the cell. Projection of ΔP on the focal plane is $\Delta P_\perp = (n_1/c) I(\mathbf{n}) d\omega_n/4\pi \sin \theta_1$, where θ_1 is the angle with respect to the optical axis at which the beam leaves the lens focus. It follows from the equations of geometric optics that such a beam leaves the lens at distance r_\perp from the axis, described by the equation $r_\perp = R_L n_1 \sin \theta_1$, where R_L is the lens focal distance. The law of energy conservation asserts that $I(\mathbf{n}) d\omega_n/4\pi = J(\mathbf{r}_\perp) d^2 r_\perp$, where $J(\mathbf{r}_\perp)$ is the energy of radiation leaving the lens per unit area, and $d^2 r_\perp$ is the area on the plane behind the lens through which the light from the solid angle $d\omega_n$ passes. Elimination of $\sin \theta_1$ from these equations and their integration yield the force acting on the bead:

$$\mathbf{f}_\perp = \frac{1}{c} \int J(\mathbf{r}_\perp) \frac{\mathbf{r}_\perp}{R_L} d^2 r_\perp. \quad (27)$$

Thus, the force can be evaluated from the intensity distribution of the light passing through the lens, which is measured by the detector. Notice that the role of the external

parameter λ in these experiments is played by the displacement of the end of the RNA molecule rather than the moment of forces, as in torsion pendulum experiments.

3.2.3 Discussion of experimental results. Let us first discuss the orders of magnitude of the values with which an experimenter has to be concerned. The maximum unfolding of the molecules was 50–250 nm, and the maximum unfolding force amounted to 15–20 pN. Slow and fast deformations corresponding to a reversible process were effectuated at a rate on the order of 1–5 and 30–50 pN s⁻¹, respectively.

The order of magnitude of work values in these experiments varied in a range of (50–200) $k_B T$, and dissipated work amounted to 50 $k_B T$. The unfolding of the molecules was viewed as a direct process, and the refolding as a reverse one; hence, notations U and R in the figures.

Equality (9) was checked up in Ref. [20] by comparing the ΔF value calculated using this equality with an independently measured value.⁵ Special experiments were designed to find ΔF in which average work $W_{A,rev}$ was measured during slow, i.e., reversible, deformation of the molecule. This work coincided with ΔF . For the RNA modification used in this experiment, $\Delta F = 60.2 \pm 1.6 k_B T$. The fast deformation experiments with a rate of 34 and 52 pN s⁻¹ were also carried out. Two estimates of ΔF were obtained, one using equality (9) (with the resultant value denoted by W_{JE}) and the other from the ‘fluctuation–dissipation’ equality (14) (the resultant value denoted by W_{FD}). The results of comparisons are given in Fig. 7. Obviously, W_{JE} coincides with ΔF within the accuracy of the experiment, whereas W_{FD} and especially $W_A \equiv \langle W \rangle$ are essentially different from it.

The setup described in Ref. [20] was used later [16] to verify the Crooks equality (19) in experiments with various RNA molecules. Figure 8 presents the results of unfolding and refolding experiments using an RNA segment of human immunodeficiency virus (this object is known to undergo nonequilibrium deformation at a rate convenient for the purpose of experiment). The value of W at the point of intersection of the curve describing the direct and reverse processes determines ΔF (in the present case, $\Delta F = 110.3 k_B T$). Notice that the coincidence point is independent of the deformation rate, in agreement with equation (19). Actually, this method for determining ΔF has

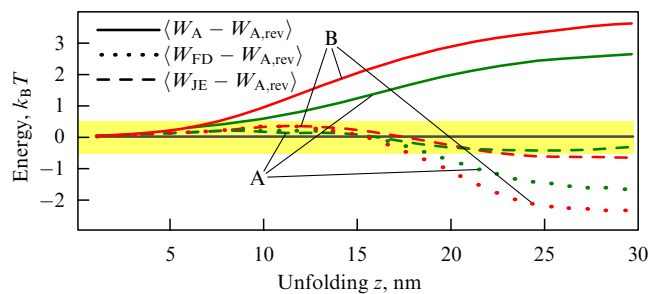


Figure 7. Comparison of different $\Delta F \equiv W_{A,rev}$ estimates (see the text). Curve A — experiment with the deformation rate of 34 pN s⁻¹, and curves B — with the deformation rate of 52 pN s⁻¹ [20].

⁵ In this experiment, deformation was produced at a constant pressure. Due to this, ΔF was practically identical with the change in the molecule’s Gibbs thermodynamic potential $\Delta\Phi$.

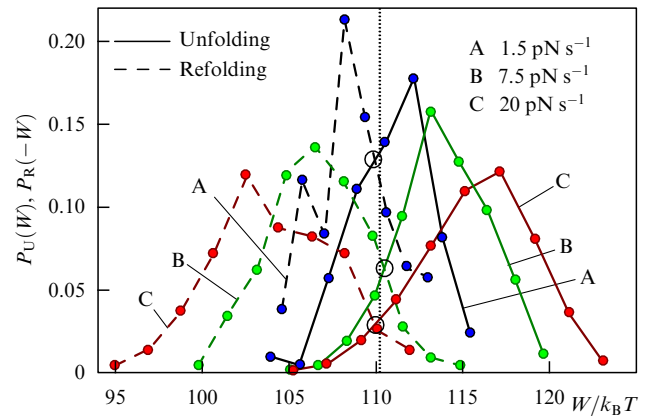


Figure 8. Work probability distributions for RNA unfolding (U) and refolding (R). Curves A, B, and C correspond to the different deformation rates shown in the figure [16]. Curve A — the result of 130 repetitions of deformation for three molecules, curve B — 380 repetitions for four molecules, and curve C — 700 repetitions for three molecules (total: 10 experiments). Circles indicate intersection points of curves U and R. The corresponding W value gives the free energy difference ΔF .

practical implications, since too large a relaxation time may hamper the achievement of thermodynamic equilibrium.

Of great interest are experiments in which a high degree of departure from equilibrium was reached. In this case, the work distribution function was broad and essentially non-Gaussian, with long tails. These experiments were performed using the RNA of wild-type and mutant strains of *Escherichia coli*. The results are demonstrated in Fig. 9. In either case, the regions where curves U and R overlap were small, while dissipated work was large, especially for mutants. Two wild-type and five mutant molecules were subjected to deformation 900 and 1200 times, respectively. The inset to Fig. 9 shows the values of $\log [P_U(W)/P_R(-W)]$ corresponding to $W/k_B T$ in accordance with the Crooks reversal relation. The slope of the experimental curve, 1.06, is in excellent agreement with the theory.

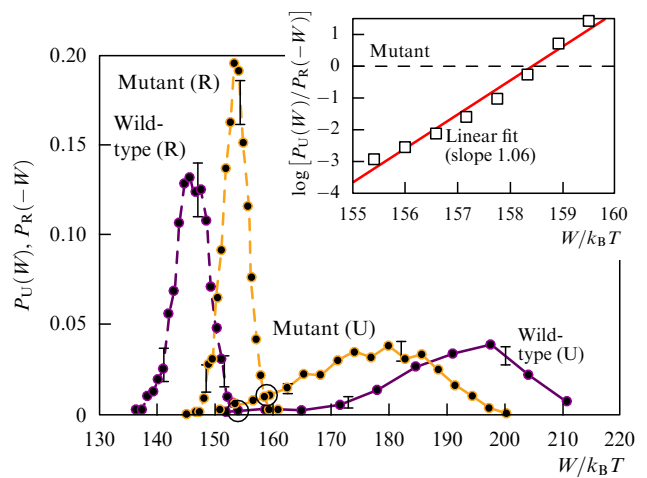


Figure 9. Work probability distributions for unfolding (U) and refolding (R) RNA of wild-type and mutant *E. coli* [16]. Circles indicate intersection points of curves U and R, and give the free energy difference ΔF . The inset: logarithm of the right-hand side of the Crooks equality found from the data obtained with a mutant strain. The slope of the experimental curve, 1.06, is in a good agreement with the theoretical value of 1.

4. Conclusion

I have discussed in the present article only one of the possible formulations of a problem in nonequilibrium statistical physics, namely that of fluctuations in a system driven away from thermodynamic equilibrium by a time-dependent external impact. My choice is dictated first and foremost by the fact that the theory of interest is rather simple and can be verified in relatively simple experiments. However, this is not the sole possible formulation of the problem. For example, the rather general relations have been obtained in the practically important problem of fluctuations in stationary but far-from-equilibrium systems [24]. In this paper, I discussed only real experiments. However, there are many studies devoted to the verification of analytical relations in numerical simulations. Sometimes, such calculations give evidence of the existence of new exact relations.

I purposely presented all conclusions in the framework of classical statistical physics. Their generalization for the quantum regime encounters difficulty. A key notion in the classical theory is that of the trajectory in phase space along which the work is calculated. This notion makes no sense in quantum mechanics; furthermore, it is impossible to introduce the work operator because the work cannot be measured in a one-shot manner. The correct quantum definition of work has the form $W = E_f - E_0$, where E_0 and E_f are the energy values measured at moments $t = 0$ and $t = t_f$ in one and the same realization of the process. Based on this definition, Campisi, Hänggi, and Talkner proved the quantum version of equalities (9)–(10) (see Ref. [25]). A rather detailed discussion of the quantum approach to the phenomena under consideration can be found in the work of Esposito, Harbola, and Mukamel [26].

I believe quite enough has been said to convince the reader that nonequilibrium statistical physics is an important area of theoretical and experimental research. Its significance is increasing every day, in parallel with the development of nanoscale physics. Nonequilibrium statistical physics is beginning to find applications even in such a field as quantum informatics (see, for instance, Ref. [27]). It has proved equally useful for physicochemical research in biology.

I am grateful to I R Arkhipova for the discussions on the section addressing biological issues.

References

- Landau L D, Lifshitz E M *Statisticheskaya Fizika* (Statistical Physics) Ch. 1 (Moscow: Fizmatlit, 2001) [Translated into English (Oxford: Pergamon Press, 1980)]
- Onsager L *Phys. Rev.* **37** 405 (1931)
- Onsager L *Phys. Rev.* **38** 2265 (1931)
- Callen H B, Welton T A *Phys. Rev.* **83** 34 (1951)
- Bochkov G N, Kuzovlev Yu E *Zh. Eksp. Teor. Fiz.* **72** 238 (1977) [*Sov. Phys. JETP* **45** 125 (1977)]
- Bochkov G N, Kuzovlev Yu E *Zh. Eksp. Teor. Fiz.* **76** 1071 (1979) [*Sov. Phys. JETP* **49** 543 (1979)]
- Bochkov G N, Kuzovlev Yu E *Physica A* **106** 443 (1981)
- Bochkov G N, Kuzovlev Yu E *Physica A* **106** 480 (1981)
- Jarzynski C *Phys. Rev. Lett.* **78** 2690 (1997)
- Crooks G E *Phys. Rev. E* **60** 2721 (1999)
- Crooks G E *Phys. Rev. E* **61** 2361 (2000)
- Landau L D, Lifshitz E M *Mekhanika* (Mechanics) (Moscow: Fizmatlit, 2001) [Translated into English (Oxford: Pergamon Press, 1980)]
- Hermans J J *Phys. Chem.* **95** 9029 (1991)
- Jarzynski C *Phys. Rev. E* **73** 046105 (2006)
- Douarche F et al. *Europhys. Lett.* **70** 593 (2005)
- Collin D et al. *Nature* **437** 231 (2005)
- Chugunov A, <http://biomolecula.ru/content/218>
- Hammer G, Szabo A *Proc. Natl. Acad. Sci. USA* **98** 3658 (2001)
- Liphardt J et al. *Science* **292** 733 (2001)
- Liphardt J et al. *Science* **296** 1832 (2002)
- Greenleaf W J et al. *Science* **319** 630 (2008)
- Bustamante C, Liphardt J, Ritort F *Phys. Today* **58** (7) 43 (2005)
- Smith S B, Cui Y, Bustamante C *Meth. Enzymology* **361** 134 (2003)
- Gallavotti G, Cohen E G D *Phys. Rev. Lett.* **74** 2694 (1995)
- Campisi M, Hänggi P, Talkner P *Rev. Mod. Phys.* **83** 771 (2011); arXiv:1012.2268
- Esposito M, Harbola U, Mukamel S *Rev. Mod. Phys.* **81** 1665 (2009)
- Sagawa T, Ueda M *Phys. Rev. Lett.* **102** 250602 (2009)