epl A Letters Journal Exploring the Frontiers of Physics

April 2017

EPL, **118** (2017) 20001 www.epljournal.org
doi: 10.1209/0295-5075/118/20001

Generalized fluctuation-dissipation theorem as a test of the Markovianity of a system

Lucian Willareth[1], Igor M. Sokolov[1], Yael Roichman[2] and Benjamin Lindner[1,3]

[1] *Department of Physics, Humboldt Universität zu Berlin - Newtonstr 15, 12489 Berlin, Germany*
[2] *Raymond and Beverly Sackler School of Chemistry Tel Aviv University - Tel Aviv 6997801, Israel*
[3] *Bernstein Center for Computational Neuroscience - Haus 2, Philippstr. 13, 10115 Berlin, Germany*

received 23 March 2017; accepted in final form 30 May 2017
published online 20 June 2017

PACS 05.40.-a – Fluctuation phenomena, random processes, noise, and Brownian motion
PACS 87.18.Tt – Biological complexity: Noise in biological systems

Abstract – We study how well a generalized fluctuation-dissipation theorem (GFDT) is suited to test whether a stochastic system is not Markovian. To this end, we simulate a stochastic non-equilibrium model of the mechanosensory hair bundle from the inner ear organ and analyze its spontaneous activity and response to external stimulation. We demonstrate that this two-dimensional Markovian system indeed obeys the GFDT, as long as i) the averaging ensemble is sufficiently large and ii) finite-size effects in estimating the conjugated variable and its susceptibility can be neglected. Furthermore, we test the GFDT also by looking only at a one-dimensional projection of the system, the experimentally accessible position variable. This reduced system is certainly non-Markovian and the GFDT is somewhat violated but not as drastically as for the equilibrium fluctuation-dissipation theorem. We explore suitable measures to quantify the violation of the theorem and demonstrate that for a set of limited experimental data it might be difficult to decide whether the system is Markovian or not.

Introduction. – The equilibrium fluctuation-dissipation theorem (FDT) relates the response of an equilibrium system to an external perturbation to the spontaneous fluctuations of the system. The classical result reads [1]

$$S_{xx}(\omega) = \frac{2k_BT}{\omega}\Im(\chi_{xF}(\omega)), \tag{1}$$

where S_{xx} is the power spectrum of the variable $x(t)$ in the absence of external forcing, χ_{xF} is the linear response function (*i.e.*, its Fourier transform, the susceptibility) with respect to a weak external force $F(t)$, and $\Im(\cdot)$ denotes the imaginary part. The FDT can be used to determine the response function of the system from a measurement of its spontaneous power spectrum S_{xx}.

Another interesting implication of the theorem regards the distinction of equilibrium and non-equilibrium systems: the theorem provides a simple and model-free test whether a given system operates in thermodynamic equilibrium or not. If a system does not obey the theorem, it cannot be in equilibrium (a conclusion that, unfortunately, cannot be reversed). The latter idea has been applied in biological systems, for instance, in the mechanosensory hair bundle [2] and in cytoskeletal networks of biological cells [3]. Both systems show severe violations of the equilibrium FDT.

Despite the violation of the equilibrium FDT in non-equilibrium systems, there exist non-equilibrium generalizations of the theorem that are obeyed by systems, described by a set of variables $\bar{x}(t)$ with a steady-state probability distribution $P_0(\bar{x})$ and Markovian dynamics. Importantly, the set of variables $\bar{x}(t)$ constitutes a continuous-time Markov process (such a set will be said to give a complete Markovian description of the system's evolution). The generalized fluctuation-dissipation theorem (GFDT) was derived in the 1970s [4] (reviewed early in detail in [5]) but has more recently attracted renewed attention from a number of theoreticians [6,7] and experimenters [8,9]. To apply the theorem, a *conjugated variable* $z(\bar{x})$ is defined for a certain kind of perturbation $F(t)$ (which has not to be a force then). This variable is obtained from the following derivative with respect to a *static*

(time-independent) external perturbation F_0:

$$z(\bar{x}) = \frac{\partial}{\partial F_0} \ln P_0(\bar{x}; F_0)\Big|_{F_0=0}, \tag{2}$$

which can be also regarded as the derivative of an effective potential $\Phi(\bar{x}) = -\ln P_0$ with respect to the parameter F_0. For the observable $z(\bar{x})$ (essentially a nonlinear transformation of the original variables), the GFDT, connecting the spontaneous fluctuations of $z(t)$ and its response to a time-dependent forcing $F(t)$, reads

$$S_{zz}(\omega) = \frac{2}{\omega}\Im(\chi_{zF}(\omega)) \tag{3}$$

and is thus formally very close to the equilibrium FDT (even the missing factor of k_BT could be restored by rescaling the variable, but this is not common).

Because the theorem assumes the Markovianity of the underlying dynamics, it is suitable to test this property in non-equilibrium systems. Again, as for the distinction between equilibrium and non-equilibrium, the conclusion goes only one way: if a system does not obey the GFDT, the conclusion is permitted that the observed dynamics does not constitute a Markovian dynamics, *i.e.*, that the set of observables does not constitute the full set of variables necessary for a complete Markovian description. This holds true even if the dynamics *is* a (multidimensional) Markovian system but we use only a subset of variables to test the GFDT. This is so because a lower-dimensional projection of a Markovian system is generally non-Markovian. In summary, the violation of the GFDT is a sufficient but not a necessary condition for non-Markovianity.

The above-mentioned hair bundle system with its active properties [10–12] is an excellent test case for non-equilibrium statistical physics. There exist quantitatively accurate stochastic models of the single hair bundle [13,14], which have been used to model and analyze the response features of the basilar membrane [15–18], in the dynamics of which *coupled* hair bundles play an essential role. The GFDT was tested by Dinis *et al.* [9] for an isolated hair bundle from the bullfrog's sacculus. These authors were able to find a rough confirmation of the GFDT but also observed some deviations that were attributed to the limitations of the experimental accuracy and the computational approximations. However, Dinis *et al.* also raised the question if some degree of non-Markovianity may have affected their results.

Generally, the different limitations are difficult to disentangle in experiments on a biological system, which provides only a limited amount of data and is always prone to weakly non-stationary behavior. In this paper, we address how efficiently the GFDT can be used to test the Markovianity of the system. We employ the stochastic hair bundle model and use either both dynamical variables of the model (the full Markovian dynamics) or only the (experimentally accessible) position variable.

Model and measures. –

The hair bundle model and the conjugated variable. For studying the fluctuation-dissipation theorem, we use an established stochastic description of the hair bundle based on [13] in a simplified two-dimensional version [14,15] with the specific parameters from [18]. This model is given in terms of the hair bundles tip position X and the position of molecular motors, X_a, and reads

$$\begin{aligned} \lambda\dot{X} &= -K_{GS}(X - X_a - Dp_{\mathrm{op}}) - K_{SP}X + F(t) + \xi(t), \\ \lambda_a\dot{X}_a &= K_{GS}(X - X_a - Dp_{\mathrm{op}}) + F_{max}(Sp_{\mathrm{op}} - 1) + \xi_a(t). \end{aligned} \tag{4}$$

In the above equations, λ is the viscous friction parameter of the bundle, D the gating swing, K_{GS} the gating spring constant, K_{SP} the pivotal stiffness, $F(t)$ a (possibly time-dependent) force applied externally to the bundle's tip, F_{max} the maximal force that can be exerted by adaptation motors, S the feedback strength of the calcium concentration on motors. The equations above may look linear but they are not due to the function $p_{op} = p_{op}(X - X_a)$, which is the probability of the transduction channels to be open:

$$p_{op}(x) = \left[1 + \exp\left(\frac{N_e\Delta G + K_{GS}D^2/2 - K_{GS}Dx}{N_e k_B T}\right)\right]^{-1}, \tag{5}$$

where N_e is the number of transduction channels and ΔG is the energy difference between the open and the closed state of the channel. Finally, we note that $\xi(t)$ and $\xi_a(t)$ are independent white-Gaussian-noise sources with correlation functions $\langle\xi(t)\xi(t+\tau)\rangle = 2\lambda k_B T\delta(\tau)$ and $\langle\xi_a(t)\xi_a(t+\tau)\rangle = 3\lambda_a k_B T\delta(\tau)$. Because of active forces in the system due to molecular motors, the system is kept far from thermodynamic equilibrium and the hair bundle-model performs spontaneous noisy oscillations (see fig. 1(a), (b) for a sample trace) as seen also in the experiment [2,10]; for a detailed biophysical interpretation of the model, see [13].

The model has been used to study the effects of mechanical coupling of hair cells on signal transmission [15,16] and even was employed in a hybrid experiment, in which it was mechanically coupled to a real hair bundle [17]. Although originally developed for a specific type of hair bundle, namely the one in the sacculus of bullfrog, it has been generalized (by only modifying parameters) to hair bundles in other animals (including mammals) [14]. Analytical inspections of the model reveal that it is definitely beyond thermodynamic equilibrium and behaves as a relaxation oscillator [19]. Here we use the model as a reasonably simple description of a real-world system, for which the different kinds of (equilibrium and non-equilibrium) FDT have been experimentally tested [2,9].

In order to test the fluctuation-dissipation relation from eq. (3), first the conjugated variable $z(\bar{x})$ has to be determined. The steady-state probability density $P_0(X, X_a; F)$ is measured in the absence ($F(t) = 0$) and in the presence of a weak static force ($F(t) = F_0$). The stationary density

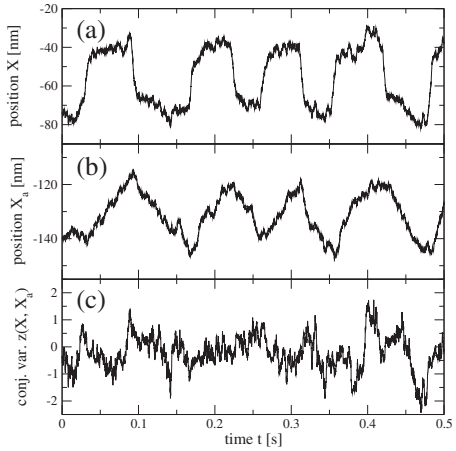

Fig. 1: Trajectories (sample traces) of the system variables ((a), (b)) and of the conjugated variable (c), determined via eq. (6). The two coupled stochastic differential equations (4) were simulated using a stochastic Euler method with a time step of $\mathrm{d}t = 0.1\,\mathrm{ms}$ and a time window of 1 s per trial (all other parameters are as in [18]).

for $F = 0$ is plotted in fig. 2(a) and reveals a crater-like shape with two pronounced peaks. This density is somewhat biased if the weak static force F_0 is applied (not shown). The negative logarithm of the density (shown in fig. 2(b)) can be regarded as an effective potential, although the relaxation oscillator described by eq. (4) is obviously *not* a potential system in the classical sense [1]. As an estimate of the conjugated variable for our specific system we can use

$$z(X, X_a) = -\frac{\partial}{\partial F_0}\Phi(X, X_a; F_0) \approx \frac{\ln P_0(X, X_a; F_0) - \ln P_0(X, X_a; 0)}{F_0}. \quad (6)$$

We note already at this point that a too large value of the bias force F_0 may lead later on to a violation of the GFDT, because the function $z(X, X_a)$ will not be the correct conjugated variable. We illustrate the dependence of z on X and X_a in fig. 2(c) and show a typical time course of the conjugated variable (extracted via eq. (6) from simulated time series $X(t), X_a(t)$) in fig. 1(c).

Spectral measures. Once we can determine time series of the conjugated variable $z(t)$ in a time window $t \in (0, T_w)$, we can measure its power spectrum:

$$S_{zz}(\omega) = \frac{\langle \tilde{z}(\omega)\tilde{z}(\omega)^* \rangle}{T_w}, \quad (7)$$

where $\langle\cdot\rangle$ indicates an ensemble average (different realizations of white Gaussian noise).

To verify the fluctuation-dissipation theorem from eq. (3) in the next step, the susceptibility has to be estimated. To this end, $F(t)$ is taken to be a band-limited white Gaussian noise with power only inside a specified

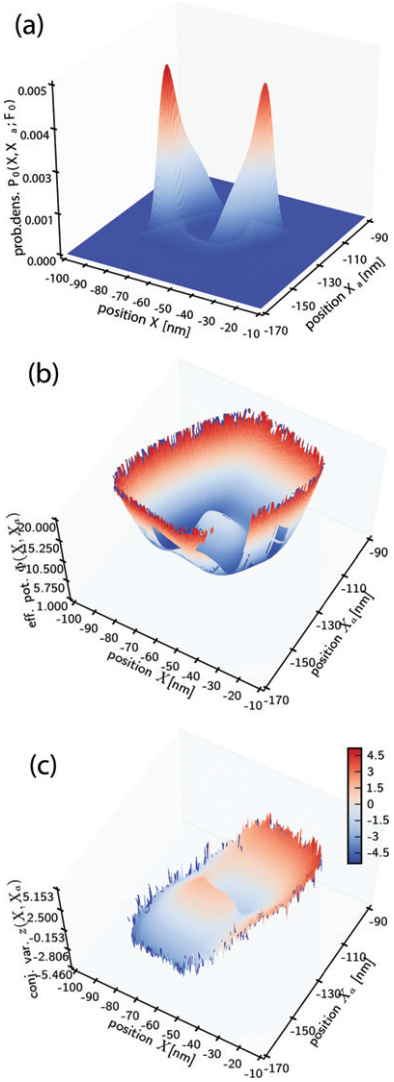

Fig. 2: (Colour online) (a) Probability density of the two-dimensional hair bundle dynamics. The probability density is measured for $F(t) = 0$ and $F(t) = F_0$. Both densities display roughly the same shape but are slightly shifted with respect to each other. (b) The effective potential $\Phi(X, X_a) = -\ln[P_0(X, X_a)]$. (c) The conjugated variable, approximated by the two probability densities for $F = 0$ and $F = F_0$ using eq. (6).

frequency band:

$$S_{FF}(f) = 2\varepsilon^2/f_c, \quad \text{for } |f| < f_c. \quad (8)$$

Here, ε is by definition the standard deviation of the external perturbation and the cut-off frequency f_c is set to 30 Hz. Single realizations of the stochastic force are created drawing random numbers in the Fourier domain and transforming the resulting random spectrum to the time domain [20]. Applying these $F(t)$ to the hair bundle and measuring the cross-spectrum between the force and the conjugated variable

$$S_{zF} = \frac{\langle \tilde{z}(\omega)\tilde{F}^*(\omega) \rangle}{T_w} \quad (9)$$

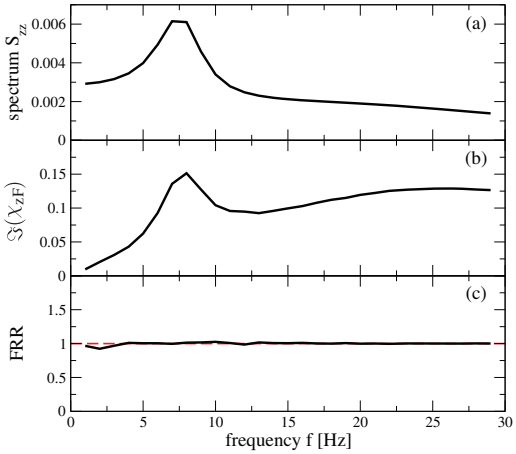

Fig. 3: (Colour online) The generalized fluctuation-dissipation theorem (GFDT) is tested on the conjugated variable $z(X, X_a)$. From the spectrum of spontaneous fluctuations $S_{zz}(\omega)$ (a) and the systems response to a small external perturbation quantified by the imaginary part of the susceptibility $\Im(\chi_{zF}(\omega))$ (b), the fluctuation-response ratio (FRR) is determined as a function of frequency (c). The theoretically correct ratio is FRR = 1 (red dashed line). Parameters: $F_0 = 0.1\,\mathrm{pN}$, $\epsilon = 0.05$, number of realizations $= 10^7$.

the susceptibility is given by

$$\chi_{zF}(\omega) = \frac{S_{zF}(\omega)}{S_{FF}(\omega)}. \tag{10}$$

Of course, we again should use values of the stimulation standard deviation ε as small as possible, because the GFDT involves only the linear response. Too small values, though will result in a very noisy estimate of the susceptibility, which is, of course, likewise undesirable.

With the power spectrum and the susceptibility available the generalized fluctuation-dissipation theorem from eq. (3) can be tested. To this end, one usually computes the *fluctuation-response ratio* (FRR), which is expected to be equal to one whenever the GFDT holds true:

$$\mathrm{FRR}_z = \frac{\omega S_{zz}(\omega)}{2\Im(\chi_{zF}(\omega))}. \tag{11}$$

Deviations from unity can occur in numerical estimation of this ratio even when the system itself should exactly obey the theorem. Reasons are limitations i) of the averaging ensemble (insufficient statistics); ii) in the correct estimation of the conjugated variable (finite static force for estimating $P_0(X, X_a; F_0)$); iii) in the correct estimation of the susceptibility, *i.e.*, the system's linear response (any finite-amplitude force $F(t)$ will evoke both linear and nonlinear response contributions because our system is nonlinear). An interesting question is whether we can distinguish the caused deviations from others that are due to a potential non-Markovianity of the system.

Verification of the generalized FDT in the hair bundle model. – In fig. 3 we show results from numerical simulations of the spectral measures. Both spontaneous power spectrum and susceptibility of the conjugated variable reveal peaks around 8 Hz, similar to the statistics seen for the variable X in experiment [2] and theory [13]. In particular, the FRR shown in fig. 3(c) confirms the GFDT with a satisfying accuracy. This agreement does not emerge easily but results from a very large averaging ensemble and small values of the static bias force (needed to determine the conjugated variable $z(X, X_a)$) and of the stimulus standard deviation ε (needed for determining the susceptibility).

In experiments, typically, we have fewer data than we used in the extensive numerical simulations for fig. 3. Hence, even when the system obeys the GFDT, deviations may occur because of the three reasons mentioned above. As a measure of how well the GFDT is obeyed, we use the integrated squared deviation between denominator and numerator of the FRR and normalize it by the integral over squared denominator:

$$\Delta^2 = \frac{\int_0^{f_c} \left(\omega S_{zz}(\omega) - 2\Im(\chi_{zF}(\omega))\right)^2 \mathrm{d}\omega}{\int_0^{f_c} \left(2\Im(\chi_{zF}(\omega))\right)^2 \mathrm{d}\omega}. \tag{12}$$

This can be interpreted as a relative error and is used to illustrate that a faithful adjustment of external parameters such as F_0 and ε is necessary for a quantitative confirmation of the GFDT. For instance, if the external random force is too strong (high values of ε in eq. (8), leading to an inaccurate estimate of the linear response function), the mean-square deviation stagnates after the number of trials reaches some characteristic value, *i.e.*, further averaging does not improve the results. Naively, one may expect that the measure decays without bound with increasing averaging ensemble sizes but this is only true if at the same time the values of F_0 and ε are lowered as well.

We illustrate this in fig. 4(a), where we plot Δ^2 *vs.* the number of realizations (*i.e.*, the size of the averaging ensemble) for three different values of the stimulus strength ε. The dependence is certainly non-trivial. For a thousand of realizations, for instance, the strongest signal will lead to the smallest deviation. Here the measurement noise in the numerical determination of the susceptibility is smallest and this is the dominant contribution to Δ^2 at this point. If we, however, have a much larger averaging ensemble ($N = 10^7$), the relation between the curves is reversed and the smallest signal amplitude yields the smallest deviation between the different spectral measures that should be equal according to the GFDT.

In experiments, one often has a long time window of data, which is typically split into N different trials (realizations) of length T_w. The length of the time window sets the frequency resolution of the spectral measures ($\Delta f = 1/T_w$), and thus has to be chosen such that the relevant time scales in the system can be resolved. In fig. 4(b) we show results for $T_w = 0.1\,\mathrm{s}$ (resolution 10 Hz) and $T_w = 10\,\mathrm{s}$ (resolution 0.1 Hz) in addition to the standard value of $T_w = 1\,\mathrm{s}$ used in fig. 4(a). With the very short time window and a 10 Hz resolution, we are unable to

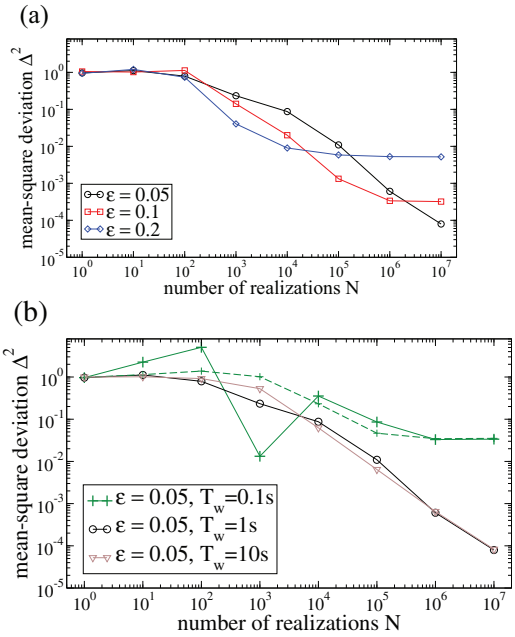

Fig. 4: (Colour online) Quantification of the deviations from the GFDT. The mean-square deviation, eq. (12), is shown as a function of the number of trials, N, (realizations) used to compute the spectral measures. (a) Effect of stimulus amplitude, ϵ ($T_w = 1\,\mathrm{s}$). Ideally, Δ^2 should decay to zero as N increases in the linear response regime. However, larger values of ϵ lead to a partly nonlinear response and thus even in the limit of many trials, we observe small remaining deviations from the GFDT for the large ϵ. Contrariwise, at a smaller number of trials ($N < 10^4$), a larger amplitude might be better, because it leads to a less noisy numerical estimate of the susceptibility. (b) Effect of the length of the time window of the single trial, T_w ($\epsilon = 0.05$). Longer time windows ($T_w = 10\,\mathrm{s}$, brown triangles) result in a refined frequency resolution but do not change much the deviation from the GFDT (black circles are close to brown triangles). A too short time window ($T_w = 0.1\,\mathrm{s}$, green plus), however, leading to a too coarse frequency resolution, results in a drastic increase of the deviations. In addition, because the averaging effect of the frequency integration is reduced (we sum over fewer frequency bins), fluctuations strongly increase. The dashed green line indicates an average over ten repetitions of the procedure and is closer to the expected monotonic drop with increasing N.

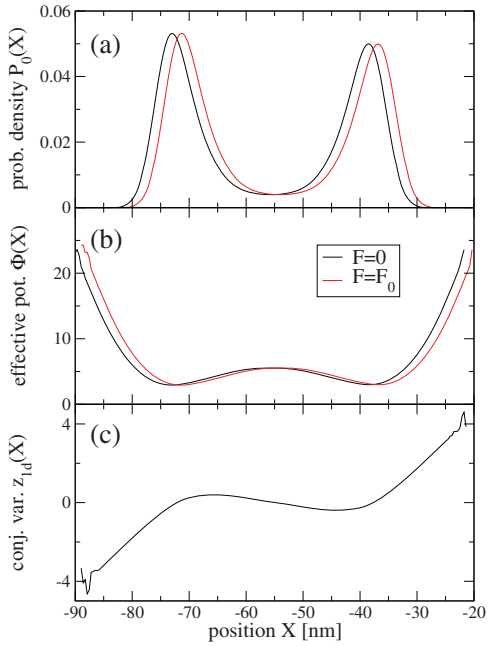

Fig. 5: (Colour online) Determination of the conjugated variable neglecting the position of the adaptation motors X_a. (a) In the first step the probability densities are measured for two small external bias forces, *e.g.*, $F(t) = 0$ (black line) and $F(t) = F_0$ (red line). (b) The effective potential. (c) The approximation from eq. (6) is applied to compute the conjugated variable $z_{1d}(X)$.

capture all the relevant time scales of the system (oscillation frequency is around 8 Hz) and thus the error saturates at a non-vanishing level even in the limit of a large number of realizations. In addition, because we integrate over a few points only, the averaging effect of the frequency integration is weak and thus strong fluctuations in the curve emerge that can be reduced by further averaging (dashed line). In contrast to these observations, a further increase of the time window to $T_w = 10\,\mathrm{s}$ does not change the statistics much, compared to the standard window size of $T_w = 1\,\mathrm{s}$. In summary, this illustrates that, in the interest of a correct statistics but also a maximal number of realizations, experimental data sets should be subdivided into windows of sufficient length (covering the relevant time scales) but not excessive length (which would lead to a reduced number of trials N).

In our numerical approach, we deal by assumption with a (two-dimensional) Markovian system. In experiments on real hairbundles, however, only one of the variables (the bundle's tip position, $X(t)$) is accessible [9]. Even if one could measure the motor variable, it is uncertain, that the experimental system is completely Markovian. Put differently, we cannot be sure that all dynamical variables are captured and that all fluctuations are sufficiently well described by white noise (a precondition for the driven system to be Markovian). How does an omission of one Markovian variable affect the results when testing the GFDT?

Neglecting the second variable —a non-Markovian test case. – In fig. 5 we apply the procedure of extracting the conjugated variable to the time series $X(t)$ alone —ignoring the motor variable completely. This is exactly the situation in the experiment (unless one attempts to extract the hidden variable by other means as done in [9]).

We first estimate the probability densities for a vanishing and a small non-vanishing value of the static bias force (black and red lines in fig. 5(a), respectively). We again interpret the logarithm appearing in the definition of the conjugated variable as an effective potential (fig. 5(b)); this potential is bistable in accordance to the bimodal probability density of the relaxation oscillator.

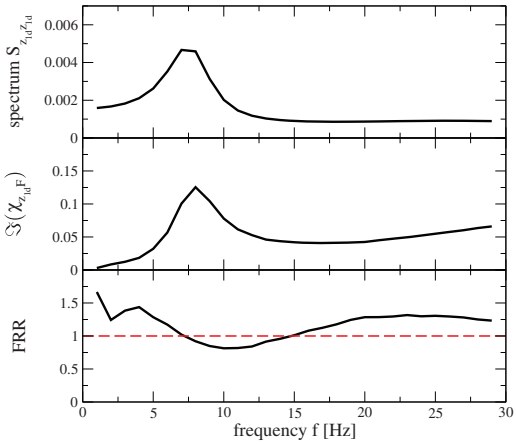

Fig. 6: (Colour online) Testing the GFDT for the reduced (non-Markovian) system, in which the motor variable is neglected. After the determination of the conjugated variable in fig. 5 the spontaneous fluctuations and the systems response can be measured and compared using the FRR. The fluctuation-response ratio shows moderate deviations from unity (red dashed line), *i.e.*, the GFDT is somewhat (but not drastically) violated.

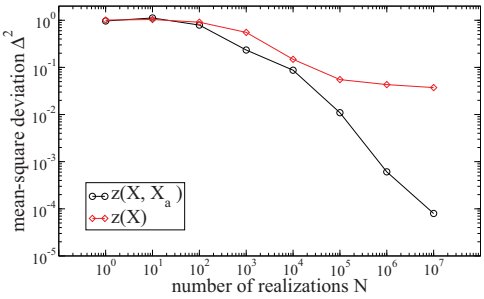

Fig. 7: (Colour online) The mean-square deviation from eq. (12) for the two-dimensional conjugated variable $z(X, X_a)$ and the one-dimensional $z(X)$. The two-dimensional conjugated variable confirms the GFDT. The neglection of the second Markovian variable leads to persistent deviations in the FRR from one (saturation), which is interpreted as a violation of the GFDT.

We finally take the difference between the two potentials as the estimate of the derivative, giving us an approximation $z_{1d}(t) = z_{1d}(X(t))$ of the true conjugated variable $z(t) = z(X(t), X_a(t))$. In the following, the trials of the hair bundles tip $X(t)$ are transformed into trials of the approximated conjugated variable $z_{1d}(t)$ and for the latter variable we can then determine the spontaneous power spectrum (for $F(t) \equiv 0$) and the susceptibility (from the cross-spectrum in the presence of the white-noise stimulus $F(t)$). In fig. 6 we show the resulting spectra and the fluctuation-response ratio.

We recall that if we use the deflection variable $X(t)$ itself in order to compute the FRR, *i.e.*, if we test the equilibrium FDR, then this function attains very large and, for low frequencies, even negative values [2,9]. In contrast to these strong deviations from unity, the variable $z_{1d}(t)$ shows only moderate deviations from one, and these are also only seen, if a sufficiently large averaging ensemble is used. This is surprising given the drastic reduction from two to one dimension and the qualitative difference between those: a first-order differential equation driven by white Gaussian noise cannot show the oscillatory behavior that is the hallmark of the stochastic relaxation oscillator under investigation. Remarkably, the FRR is close to one for a frequency close to the oscillation frequency of the hair bundle. The deviations from unity seen in the surrounding frequency bands are difficult to interpret. We also note that the deviations that we see with our simple procedure are still of the same order of magnitude as the deviations that were obtained in [9] (typically, $0.5 < \mathrm{FRR} < 1.5$), where the authors tried to reconstruct the unobservable Markovian dimension by different means.

Considering finally the mean-square deviation for the non-Markovian test case (see fig. 7), we find that it is difficult to distinguish between finite-size (measurement noise) constraints and the effect of non-Markovianity up to ensemble sizes of $N = 10^4$. Only if we go to the excessive number of ten million realizations, we observe a saturation in the mean square deviation that we unequivocally can ascribe to the neglect of the second variable. Given the intrinsic limitations of doing prolonged experiments on organelles like the hair bundle, such numbers of trials will rarely be feasible.

Summary. – In the present paper, we have demonstrated that the generalized fluctuation-dissipation theorem is obeyed by a stochastic biophysical model of the sensory hair bundle. We have inspected the numerical effects of limited averaging, finite-amplitude estimates of the conjugated variable and finite-amplitude of the time-dependent driving.

For the present model we could, moreover, study, whether an omission of one of the two variables in the procedure would lead to a substantial violation of the generalized fluctuation-dissipation theorem. Such a violation might be expectable, because considered in only one dimension, the stochastic relaxation-oscillator–like dynamics exhibited by the system cannot be in any way the outcome of a one-dimensional Markovian system. However, we found only a moderate deviation of the fluctuation-response ratio from one. This is in marked contrast to the strong violation of the equilibrium FDR, *i.e.*, the same relation when we use the original bundle position instead of its nonlinear transform. The deviations are also of the same order of magnitude as the deviations in the experiments on hair bundles from the bullfrog's sacculus once a reconstruction of the hidden second variable was incorporated in the estimate of the fluctuation-response ratio.

In principle, the GFDT can be used to test the Markovianity of a set of variables. Our results, however, show that this might be in many cases more difficult than previously thought and finite-size deviations of different kinds

might dominate the test results instead of the absence or presence of the Markov property.

REFERENCES

[1] Risken H., *The Fokker-Planck Equation* (Springer, Berlin) 1984.

[2] Martin P., Hudspeth A. J. and Jülicher F., *Proc. Natl. Acad. Sci. U.S.A.*, **98** (2001) 14380.

[3] Mizuno D., Tardin C., Schmidt C. F. and MacKintosh F. C., *Science*, **315** (2007) 370.

[4] Agarwal G. S., *Phys. Lett. A*, **38** (1972) 93.

[5] Hänggi P. and Thomas H., *Phys. Rep.*, **88** (1982) 207.

[6] Prost J., Joanny J.-F. and Parrondo J. R., *Phys. Rev. Lett.*, **103** (2009) 090601.

[7] Gomez-Solano J. R., Petrosyan A., Ciliberto S., Chetrite R. and Gawedzki K., *Phys. Rev. Lett.*, **103** (2009) 040601.

[8] Mehl J., Blickle V., Seifert U. and Bechinger C., *Phys. Rev. E*, **82** (2010) 032401.

[9] Dinis L., Martin P., Barral J., Prost J. and Joanny J. F., *Phys. Rev. Lett.*, **109** (2012) 160602.

[10] Martin P., Bozovic D., Choe Y. and Hudspeth A. J., *J. Neurosci.*, **23** (2003) 4533.

[11] LeMasurier M. and Gillespie P. G., *Neuron*, **48** (2005) 403.

[12] Hudspeth A. J., *Neuron*, **59** (2008) 530.

[13] Nadrowski B., Martin P. and Jülicher F., *Proc. Natl. Acad. Sci. U.S.A.*, **101** (2004) 12195.

[14] Tinevez J., Jülicher F. and Martin P., *Biophys. J.*, **93** (2007) 4053.

[15] Dierkes K., Lindner B. and Jülicher F., *P. Natl. Acad. Sci. U.S.A.*, **105** (2008) 18669.

[16] Lindner B., Dierkes K. and Jülicher F., *Phys. Rev. Lett.*, **103** (2009) 250601.

[17] Barral J., Dierkes K., Lindner B., Jülicher F. and Martin P., *Proc. Natl. Acad. Sci. U.S.A.*, **107** (2010) 8079.

[18] Dierkes K., Jülicher F. and Lindner B., *Eur. Phys. J. E*, **35** (2012) 37.

[19] Clausznitzer D., Lindner B., Jülicher F. and Martin P., *Phys. Rev. E*, **77** (2008) 041901.

[20] Billah K. and Shinozuka M., *Phys. Rev. A*, **42** (1990) 7492.