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Research Article

The FitzHugh-Nagumo equations and quantum noise

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ABSTRACT

It is unclear whether quantum phenomena can be observed in brain recordings because of thermal noise causing decoherence, that is, quantum superpositions and entanglement quickly collapsing into classical, i.e. non-quantum states. This paper first demonstrates that neuronal noise of the Brownian motion type is mathematically equivalent to a wave-particle description of the kind predicted by a fundamental equation in quantum mechanics known as the Schrödinger equation. It then extends the considerations to the more realistic FitzHugh-Nagumo model which has been widely used to describe neuronal dynamics. This approach could provide new insights into the underlying mechanisms of brain function.

1. Introduction

Quantum mechanics is widely regarded as the most fundamental theory of nature, suggesting its applicability to even brain functions. However, the prevailing view is that quantum coherence is lost at the neuronal level due to the large size and complex environment of the neurons, a process known as 'decoherence' [1,2]. Each neuron is itself a massive and complex cell comprising a vast number of molecules, making it unlikely that quantum states could be maintained or measured across such a large scale. Neurobiological processes operate on much larger scales than those where quantum phenomena dominate. For example, action potentials are driven by ion exchanges across cell membranes that are well described by classical rather than quantum physics. Furthermore, cognitive functions, including memory, attention and sensory perception, typically involve neuronal populations interacting through electrochemical signals. While these might exhibit quantum effects, they might not scale up in a coherent way to affect brain activity at the population level. As a result, both physicists and neuroscientists have largely dismissed the relevance of standard quantum mechanics to neuronal processes. They use classical stochastic models as these are needed to explain brain data that show a large amount of variability [3–5,7]. This can be due to fluctuations in synaptic transmission, stochastic opening and closing of ion channels or changes in incoming input. Stochastic effects are then modelled as stochastic terms added to differential equations describing synaptic transmission, ion channel activity or incoming inputs [8]. Brain recordings include examples of stochastic variations in neuronal dynamics such as membrane potential fluctuations [9], irregular spike trains [10], fluctuating synaptic currents [11], trial to trial variability in response to stimuli [12], fluctuations in spike-triggered average [13], spike amplitude variability [14], variability in LTP measurements [15] and calcium dynamics [16], etc.

Neuronal models used to study these phenomena are based on stochastic differential equations, and predict effects that can be studied using classical physics. Such modeling studies indicate that stochastic noise may affect various neural processes, including information processing, spike timing reliability, stochastic resonance, firing irregularity, subthreshold dynamics, as well as the initiation and propagation of action potentials. This can be due to ion channel, synaptic, cellular or even mechanical and thermal noise and other factors like background network activity [5,6].

An alternative view is that quantum entanglement persists within microtubules and is central to consciousness, allowing for non-local connections and unique information processing capabilities in the brain, as suggested by Hameroff and Penrose [17–20]. They are shielded by Debye layers and actin gel among others [21]. This could protect mictotubule quantum coherence even at warm temperatures. While experimental evidence is limited, these ideas have sparked interesting discussions at the intersection of quantum mechanics, consciousness studies, and theoretical neuroscience.

Motivated by the mathematical equivalence between stochastic processes of the Brownian motion type and quantum mechanics shown by Nelson [22–24], we explore here yet another possibility, namely that the very noise that destroys quantum mechanical coherence in a neuron generates quantum-like coherence in its electromagnetic realm. This

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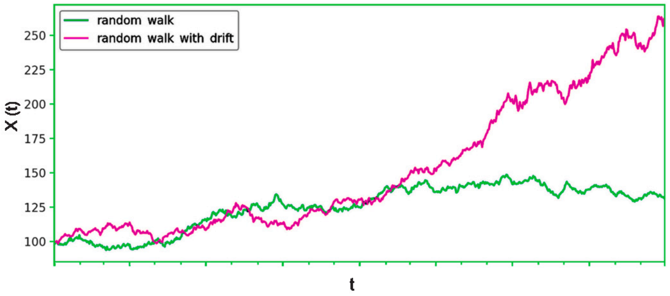

Fig. 1. Random walk with and without drift. The value $x(t)$ of the random variable $X(t)$, representing neural depolarization at time t, equals the last period's value plus a constant (a drift) and a white noise. The drift can be in the direction of the threshold (forward) or away from it (backward) and describes the generation of an action potential, once the threshold is reached.

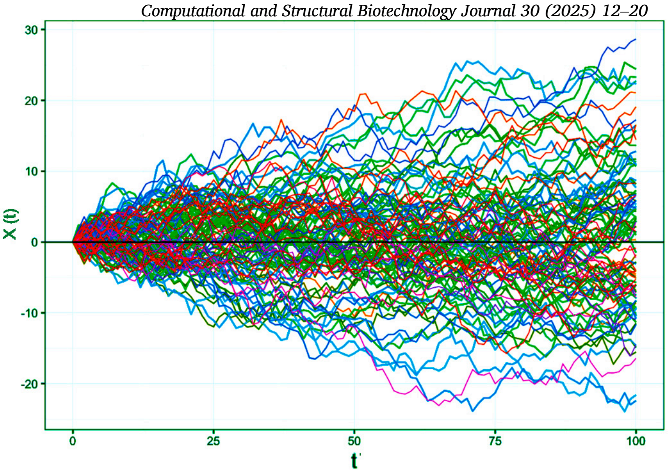

Fig. 2. Wiener process or gaussian random walk (Brownian motion) showing diffusion, i.e. the measure of the dispersion of $X(t)$ from its mean value zero increasing continuously with time. This can describe how neurons accumulate information before reaching the firing threshold.

has implications for how the brain processes information, the emergence of conscious experience, and the neural dynamics that result from this processing. These fundamental questions in biology can be explored through insights from quantum mechanics, of the sort presented here.

This approach, which can complement the use of classical models for other types of stochastic processes in neurons, can lead to novel insights and predictions that can be tested against real data.

In the next section, we will present the fundamental concepts and mathematical tools required to make our ideas more precise and investigate their implications.

2. 1D random walk model with drift for the spike activity of a single neuron

It would be helpful at this stage to introduce some technical terms which will be used in what follows. A stochastic process is a sequence of random variables whose values change over time in an uncertain way so that one knows the distribution of possible values at any point in time. Here we consider the neuron's membrane potential as a random variable. A Markov stochastic process is a particular type of stochastic process where only the current value of a variable is relevant for predicting the future movement, not past values. For neuronal data this is clearly a simplification as synaptic plasticity, refractory periods and mesoscale patterns of neuronal activity would need to be described by a correlated random walk. A random walk with and without drift is the stochastic process formed by successive summation of independent, identically (often normally) distributed random variables (Fig. 1). To describe neuronal dynamics resulting from the cumulative effect of several factors discussed above, like synaptic inputs, firing threshold, ion channel variability etc, we will assume a Wiener process. A Wiener process is a mathematical description of Brownian motion. It is a continuous time Markov process which is essentially a series of normally distributed random variables with zero mean such that the variances increase to reflect that it is more uncertain and hence more difficult to predict the value of the process after a longer period of time, a process called 'diffusion' (Fig. 2).

Let us now consider a simple 1D random walk model to describe neuronal dynamics and spike activity. For instance, the electrical state of polarization in the somatic and dendritic membrane can be modelled as a random variable representing the coordinate $Q(t)$ and executing a random walk, influenced by excitatory and inhibitory post-synaptic potentials (EPSPs and IPSPs), and moving back and forth along a straight line between a resting potential and a threshold of neuron firing [3,7]. Each incoming elemental EPSP (Excitatory Post Synaptic Potential) moves the random variable $Q(t)$ one unit toward the threshold, and each incoming elemental IPSP (Inhibitory Post Synaptic Potential) moves the random variable one unit away from the threshold (Fig.3). The motion toward the threshold will be called 'forward' motion and the motion away from the threshold 'backward' motion. If the average rate of incoming elemental EPSP and elemental IPSP are the same, there is an equal probability at any time that the random variable moves either a unit toward or a unit away from the threshold, i.e. there is no "bias toward" either input. Immediately after the random variable has attained the threshold and caused the production of an action potential, it returns to the resting potential, only to begin its random walk again. Such a model would be a simple random walk model.

In realistic physiological models, however, it would be far more reasonable to assume that there is some excess of either EPSP or IPSP inputs. Neuronal excitatory and inhibitory inputs are inherently unbalanced. This arises from several factors, including the dominance of glutamatergic over GABAergic inputs, the greater number of excitatory neurons compared to inhibitory ones, and similar structural considerations. As a result, the rates of EPSPs and IPSPs differ. Therefore, the probability for the random variable $Q(t)$ to move one unit 'forward' toward the threshold is different from the probability for it to move one unit away from the threshold, i.e. 'backward'. Considered as a diffusion process, the difference between these probabilities can be considered a "drift velocity", either toward or away from the threshold. The former is called the 'forward velocity' (usually denoted by b_f) and the latter the 'backward velocity' (denoted by b_b).

This phenomenon was formally demonstrated using a 'random walk model with drift' by Gerstein and Mandelbrot [3]. They obtained 'reasonably good agreement' between this model with drift and interval histograms as well as the joint density of successive interspike intervals of spiking data. We will now show that this 1D random walk model with drift is mathematically equivalent to a Schrödinger-like equation, indicating quantum-like behaviour of the neuron.

3. Nelson's method applied to single neurons

Our aim is to demonstrate that neuronal noise can exhibit coherence, stability and structure associated with quantum effects, a surprising example of 'order from disorder' [25]. We do this by showing first that the inherent stochastic nature of neural processes described by the 'random walk with drift' model (discussed in the previous section) is equivalent to a Schrödinger-like dynamics of neurons. Such a perspective offers a new framework for understanding brain function in terms of quantum-like processes. We do this by following Nelson's approach [22–24] and its further developments, in particular by Guerra and Morato [26] who used stochastic control theory to derive Nelson's results.

In this section we give a very simple sketch of Nelson's derivation, leaving the details to Appendix A. Let us start with a stochastic differential equation. Let the random variable q representing the membrane potential of a neuron move back and forth along a straight line, executing Brownian motion without friction. Then q follows the stochastic differential equation (SDE)

$$dq = b_f dt + \sigma dW_f. \tag{1}$$

Here, the first term is the usual velocity dependent term in deterministic mechanics, b_f representing the *mean forward* drift velocity (caused by EPSPs), and the second term is the stochastic term modelled by a forward Wiener process dW_f, σ denoting the square root of the diffusion coefficient. The diffusion coefficient, σ^2, describes the magnitude of the random fluctuation shown in Fig. 2 over time, and is determined by the physiological characteristics of the membrane.

Following Nelson [27], let us assume time reversal symmetry, i.e. symmetry of the processes under the transformation $t \to -t$. In classical mechanics, time reversal symmetry means simply reversing the sign of velocity: $v \to -v$. In stochastic mechanics, time reversal is more subtle because of the diffusion term. Under time reversal, the forward and backward velocities swap ($v_f \leftrightarrow v_b$). This implies that one process should map onto the other when the time axis is reversed. EPSPs bring neuronal depolarization closer to the firing threshold. If time were reversed, this movement would instead shift away from the threshold, precisely mirroring the typical effect of an IPSP in forward time. Consequently, the SDE for backward processes can be written in the form

$$dq = b_b dt + \sigma dW_b \tag{2}$$

where dW_b is the backward Wiener process. These SDEs ((1) and (2)) therefore describe the forward and backward stochastic processes in neurons caused by EPSPs and IPSPs respectively. There is thus an exact mathematical equivalence of stochastic processes in neural membranes modelled by Brownian motion and Nelson's stochastic mechanics.

We assume here that one can then define a *current velocity* as the sum of the forward and backward drift velocities,

$$v = \frac{1}{2}(b_f + b_b). \tag{3}$$

In deterministic mechanics this velocity can always be written in the form

$$v = \frac{1}{m}\frac{\partial}{\partial q}S \tag{4}$$

where S is a fundamental function called 'action' and m the inertia of a neuron, i.e. the tendency of its electrical potential to remain unchanged.

One can also define an *osmotic velocity* as the difference of the forward and backward velocities,

$$u = \frac{1}{2}(b_f - b_b). \tag{5}$$

It reverses sign under time reversal. Nelson showed that this velocity can be written in the form

$$u = \frac{\sigma}{2}\frac{\partial}{\partial q}\ln[\rho] \tag{6}$$

where ρ is the probability distribution of the random variable q. This relates the 'osmotic velocity' to diffusion and stochasticity. Hence, $u = 0$ for deterministic systems.

Having neatly separated the process into a deterministic part and a stochastic part, Nelson showed by a series of what he termed "miracles" that such a system can be mathematically mapped to the Schrödinger equation

$$i\hat{\hbar}\frac{\partial}{\partial t}\psi(q,t) = \left(-\frac{\hat{\hbar}^2}{2m}\partial_q^2 + V(q)\right)\psi(q,t) \tag{7}$$

where $\psi = \sqrt{\rho}\exp(iS/\hat{\hbar}) = \exp(\frac{1}{2}\ln\rho + iS/\hat{\hbar})$ and $\hat{\hbar} = m\sigma$. Guerra and Morato [26] showed that this equation extremizes the action in stochastic control theory.

Now, for neurons there are two possibilities: (a) $\hat{\hbar}$ depends on the type of neuron involved (its structure and function) or (b) it is a universal constant for all neurons. In either case, one has an equation for a single neuron that is exactly the Schrödinger equation in quantum mechanics except that the configuration space variable is replaced by the membrane potential q and the reduced Planck constant $\hbar$ is replaced by a neuronal constant $\hat{\hbar}$. We will show in Section 7 below how to determine $\hat{\hbar}$ from real data.

The wave function ψ describes the Markov process completely [28]:

$$\rho = |\psi|^2, \tag{8}$$

$$u = \frac{\sigma}{2}\frac{\partial}{\partial q}\ln[\rho] = \frac{\hat{\hbar}}{m}\partial_q \mathfrak{R}\ln\psi, \tag{9}$$

$$v = \frac{1}{m}\frac{\partial}{\partial q}S = \sigma\partial_q \mathfrak{I}\ln\psi. \tag{10}$$

This is the 'Nelson map'. It maps the probability distribution function and the current and osmotic velocities in single neurons to a wave function. In other words, it associates a stochastic process with diffusion to every solution of the Schrödinger-like equation (7). Note that the diffusion vanishes when the osmotic velocity u vanishes. In that case $\sigma m = \hat{\hbar} = 0$ and the system is classical. We will elaborate further on this in the next section.

This suggests that more realistic models of neuronal dynamics like the Hodgkin-Huxley (H-H) [29,30] and FitzHugh-Nagumo (FN) equations [31,32] may also be connected to a Schrödinger-like equation. We now proceed to show this.

4. Random walks and the Schrödinger equation for many variables

We have so far considered the basic stochastic mechanical theory of a neuron using a single random variable q. As shown by Gerstein and Mandelbrot [3], that is not realistic enough to deal with the known geometric complexity of synapses and of the somatodendritic membrane. Hence, the electrical state of these structures cannot be adequately described by a single state variable. Several variables are needed, and one must allow the state to vary over the surface of the neuron. The random walk will then take place in the same number of dimensions as the number of random variables.

There exist models of spiking neurons that use several random (also known as state) variables, like the 4D Hodgkin-Huxley (H-H) model [29] and its 2D variant, the FitzHugh-Nagumo model (FN) [31,32]. Here, we will establish a link between a two-state generalization of the theory presented above and the FN model. To do that we first need to extend our formalism to N state variables, which is quite straightforward. Having done that, we will demonstrate that the 2-state wave function corresponding to the Hamiltonian of the FN model with noise gives quantum corrections to the spiking rates calculated from the deterministic FN model. The wave function can then, in principle, be mapped to the underlying 2D stochastic processes (ρ, u, v) using the Nelson map (eqns (8), (9), (10)) for 2 state variables.

5. Generalization to N state variables

Just as one can write a N-particle Schrödinger wave function $\psi(x_1, x_2, \ldots x_N, t)$, one can also write a N-state neuron wave function $\psi(q,t), q = \{q_1, q_2, \ldots q_N\}$ where q is a set of generalized coordinates representing the state variables:

$$i\hat{\hbar}\frac{\partial}{\partial t}\psi(q,t) = \left(-\frac{\hat{\hbar}^2}{2m}\partial_q^2 + V(q)\right)\psi(q,t) \tag{11}$$

The Einstein summation convention has been used in writing this equation, i.e. $\partial_q^2\psi(q,t) = \sum_{i=q_1}^{i=q_N}\partial_{q_i}^2\psi(q_1, q_2, \ldots q_N)$. For notational simplicity, we have used the same m for all the state variables q_i.

By using the polar expression

$$\psi = \exp(R + iS/\hat{\hbar}) = \sqrt{\rho}\exp(iS/\hat{\hbar}) \tag{12}$$

in eqn (11) and separating the real and imaginary parts, the following coupled differential equations for the functions R and S can be derived [26,34]:

$$\frac{\partial S}{\partial t} + \frac{1}{2m}\left(\frac{\partial S}{\partial q}\right)^2 + V(q) + V_Q = 0, \;\; V_Q = -\frac{\hat{\hbar}^2}{2m}\left[\left(\frac{\partial R}{\partial q}\right)^2 + \frac{\partial^2 R}{\partial q^2}\right] \tag{13}$$

$$\frac{\partial R}{\partial t} + \frac{1}{2m}\left(R\frac{\partial^2 S}{\partial q^2} + 2\frac{\partial R}{\partial q}\frac{\partial S}{\partial q}\right) = 0. \tag{14}$$

The first equation is the Hamilton-Jacobi-Bellman equation for N variables. It is the classical Hamilton-Jacobi equation for N variables with an additional stochastic term V_Q which takes the form

$$V_Q = -\frac{\hat{\hbar}^2}{4m}\left[\frac{\partial_q^2 \rho}{\rho} - \frac{(\partial_q \rho)^2}{2\rho^2}\right] \tag{15}$$

in terms of $\rho = e^{2R}$. The second equation can also be written in terms of ρ as

$$\frac{\partial \rho}{\partial t} + \partial_q\left[\rho\frac{\partial_q S}{m}\right] = 0 \tag{16}$$

which is the continuity equation for N variables. These two coupled partial differential equations determine the underlying stochastic processes with N variables.

The term that couples these two equations is the stochastic term V_Q which vanishes when $\hat{\hbar} = 0$. In that case, the two equations become independent, i.e. the functions R and S evolve independently of each other. That is the case when the system is classical. In a quantum-like system, the amplitude $\sqrt{\rho}$ and the phase S of the wave function ψ (eqn (12)) get coupled, giving rise to interference and coherence.

The importance of Nelson's method lies in revealing the quantum-like features of stochastic processes of the Brownian type by mapping them to a wave function (12) which satisfies the Schrödinger equation (11). Without this crucial insight, coherence effects would lie hidden and the stochastic processes would appear to be classical.

Let $L(q, \dot{q})$ be the Lagrangian of a deterministic classical system with N variables from which one can construct the action

$$S(q) = \int L(q, \dot{q})dt \tag{17}$$

and the Hamiltonian

$$H(S) = \sum_{i=1}^{i=N} \frac{1}{2m_i}\frac{\partial S}{\partial q_i}\frac{\partial S}{\partial q_i} + V(q) := \frac{1}{2m}\left(\frac{\partial S}{\partial q}\right)^2 + V(q) \tag{18}$$

in terms of the action. The classical Hamilton-Jacobi equation is of the form

$$\frac{\partial S}{\partial t} + H(S) = 0. \tag{19}$$

On the other hand, if one uses the form (12) for $\psi(q)$ in the Schrödinger equation (11) and separates the real and imaginary parts, one gets, as we have just seen, the Hamilton-Jacobi-Bellman equation

$$\frac{\partial S}{\partial t} + H(S) + V_Q = 0 \tag{20}$$

with V_Q given by eqn (15), i.e. the classical and deterministic Hamilton-Jacobi equation with an additional stochastic term V_Q.

Now consider the momentum $p = mv$, v being the current velocity $\frac{1}{m}\partial_q S$. Then

$$\frac{dp}{dt} = \frac{d}{dt}\left(\frac{\partial S}{\partial q}\right) = \left(\frac{\partial^2 S}{\partial q^2}\right)\dot{q} + \frac{\partial}{\partial q}\left(\frac{\partial S}{\partial t}\right) \tag{21}$$

$$= \frac{\partial}{\partial q}\left[\frac{1}{2m}\left(\frac{\partial S}{\partial q}\right)^2 + \frac{\partial S}{\partial t}\right] \tag{22}$$

$$= -\partial_q[V + V_Q] \tag{23}$$

on using eqns (18), (20). This is Newton's second law with an additional stochastic term V_Q. Thus, V_Q gives 'non-classical' or quantum corrections to the classical equation of motion. It also shows that these corrections vanish when V_Q is independent of q. That is the case if ρ is independent of q. Now, notice that the osmotic velocity $u(q, t)$ (eqn (6)) vanishes if ρ is independent of q. Hence, the system behaves classically when the osmotic velocity vanishes, i.e. diffusion via Brownian motion vanishes. This is why the osmotic velocity is also called the 'quantum drift'.

In summary, *a non-vanishing neuronal constant $\hat{\hbar}$, and hence a non-vanishing stochastic potential V_Q and a non-vanishing osmotic velocity u, signal non-classical and quantum-like behaviour in Nelson's stochastic mechanics.*

Deterministic neuron models such as the H-H, FN or the 'integrate-and-fire' model typically generate a regular sequence of spikes. Spike trains of typical neurons *in vivo*, however, show a much more irregular behaviour, indicating noise [3,35]. The stochastic mechanics of single neurons developed in this paper is based on the existence of such noise, at least in part, as Brownian motion. Below, we will extend these considerations to a key model of brain dynamics known as the FitzHugh-Nagumo model.

6. The FitzHugh-Nagumo model

The FitzHugh-Nagumo model consists of two coupled differential equations including the membrane potential and a recovery variable [31,32]. The model has been widely used to study neuronal dynamics. Its applicability however, extends into other domains like cell division and physiology as well as population dynamics. We here use it to consider neuronal dynamics. The first equation describes the rapid changes in a neuron's membrane potential after a spike is generated, while the second equation describes the dynamics of the recovery variable and the dynamics of slower processes that restore the neuron to its resting state after excitation, typically modeling ion channel dynamics that inhibit or modulate the firing. The FitzHugh-Nagumo equations are as follows:

$$\frac{dq}{dt} = q - \frac{q^3}{3} - w + I, \tag{24}$$

$$\frac{dw}{dt} = \varepsilon(q + a - bw), \tag{25}$$

where q is the membrane potential (a deterministic variable, not a random variable in this model), w is the recovery variable, I is an external stimulus current that leads to excitation, ε, a, and b are parameters that control the model's dynamics. The nonlinear term in the first equation above describes rapid activation and deactivation. The parameter ε controls the time-scale of recovery (usually much slower than the membrane potential dynamics), while the parameters a and b determine the model's behaviour, adjusting the sensitivity and response of the recovery variable to changes in q. They determine threshold activation, spike duration, and recovery.

These equations are a simplification of the Hodgkin-Huxley equations [29] where the channel gating variables have been combined into one recovery variable, w, that represents the cumulative effects of ion channel inactivation and potassium increase that repolarizes the membrane.

If suitable noise terms are added to the FN equations, they describe variability in stimulus current, the opening and closing of sodium channels or slow dynamics associated with potassium channels. To incorporate such processes into the model, we replace the deterministic FN equations by

$$\frac{dq}{dt} = q - \frac{q^3}{3} - w + I + \xi_q(t), \tag{26}$$

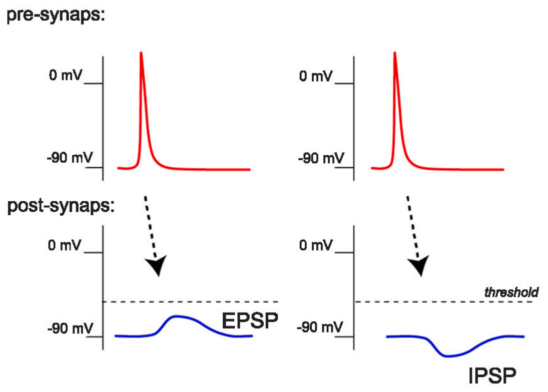

Fig. 3. The membrane potential's forward and backward movements corresponding to Excitatory (EPSP) and Inhibitory (IPSP) Post-Synaptic Potentials, respectively. Synaptic inputs create random fluctuations in depolarization modelled as a stochastic process.

$$\frac{dw}{dt} = \varepsilon(q + a - bw) + \xi_w(t) \tag{27}$$

where $\xi_v(t)$ and $\xi_w(t)$ are standard Wiener processes [33] representing additive channel noise due to randomly superimposed excitatory and inhibitory potentials (see Fig. 3). In their presence q is a random variable that performs a random walk with drift, considered in section 2. This suggests we can apply Nelson's method to this case.

It will be convenient for our purpose, though, to follow the converse of Nelson's method in this case, namely to first find the Schrödinger equation for this model, and then determine the underlying stochastic processes using the Nelson maps (8), (9), (10). We do this below by first constructing the Lagrangian $L(q, \dot q)$ (eqn (29)) for this model and from it the Hamiltonian $H(q, p)$ (eqn (35)). This classical Hamiltonian function is then converted to an operator $\hat H$ (eqn (37)) by using the canonical rule of writing the momentum p as an operator $-i\hat\hbar\partial_q$. This results, in the standard way, in a Schrödinger equation with a wave function $\psi(q,t)$ (eqn (38)). If this wave function is written in the polar form $\psi = \sqrt{\rho}e^{iS/\hat\hbar}$, then after separating the real and imaginary parts, the Schrödinger equation results, as we have seen before, in the Hamilton-Jacobi-Bellman equation which is the classical Hamilton-Jacobi equation with an additional stochastic term as in eqn (20) plus a continuity equation.

The equations (26) and (27) can be written as a second order equation

$$\ddot q = \left(1 - b\varepsilon - \frac{2q^2}{3}\right)\dot q + q\varepsilon\left(b - 1 - b\frac{q^2}{3}\right) - a\varepsilon + b\varepsilon + \dot I. \tag{28}$$

Consider the Lagrangian

$$L = \frac{1}{2}\dot q^2 + \frac{\varepsilon}{2}(b-1)q^2 - \frac{\varepsilon b}{12}q^4 - \frac{\varepsilon b}{2}w^2 \tag{29}$$

where q and w are generalized coordinates. We also define the Rayleigh dissipation function [36]

$$R_d = \left(\frac{1}{2} - \frac{b\varepsilon}{2} - \frac{2q^2}{6}\right)\dot q^2 + \frac{1}{2}\dot w^2 \tag{30}$$

and the generalized force

$$Q = \left(-a\varepsilon + b\varepsilon + \dot I\right). \tag{31}$$

Then the Euler-Lagrange equations with Q on the right hand side

$$\frac{d}{dt}\left(\frac{\partial L}{\partial \dot q}\right) - \frac{\partial L}{\partial q} - \frac{\partial R_d}{\partial \dot q} = Q, \tag{32}$$

$$\frac{d}{dt}\left(\frac{\partial L}{\partial \dot w}\right) - \frac{\partial L}{\partial w} - \frac{\partial R_d}{\partial \dot w} = \varepsilon(q + a) \tag{33}$$

yield the FN equations.

Notice that the Lagrangian L (eqn (29)) is a function of $\dot q$ but not of $\dot w$ which occurs only in the Rayleigh dissipation function R_d. Hence, using the Legendre transformation

$$H = \frac{\partial L}{\partial \dot q}\dot q + \frac{\partial L}{\partial \dot w}\dot w - L := p\dot q - L, \tag{34}$$

we get the Hamiltonian

$$H = \frac{1}{2}p^2 - \frac{\varepsilon}{2}(b-1)q^2 + \frac{\varepsilon b}{12}q^4 + \frac{\varepsilon b}{2}w^2 := \frac{1}{2}p^2 + V(q, w; a, \varepsilon, b) \tag{35}$$

where

$$V(q, w; a, \varepsilon, b) = -\frac{\varepsilon}{2}(b-1)q^2 + \frac{\varepsilon b}{12}q^4 + \frac{\varepsilon b}{2}w^2. \tag{36}$$

Then, in a representation in which q is an independent variable and $|\psi(q,t)|^2 dq$ is the probability that the system has coordinate between q and $q + dq$, the time evolution of the state function is governed by the equation of motion

$$i\hat\hbar\partial_t|\psi\rangle = \hat H|\psi\rangle, \quad \hat H = \frac{1}{2}\hat p^2 + V(q, w; a, \varepsilon, b) \tag{37}$$

where $\hat p = -i\hat\hbar\partial_q$. Time evolution of the state function $\psi(q,t) = \langle q|\psi\rangle$ where $|\psi(q,t)|^2 dq$ is probability that the system has coordinates between q and $q + dq$ is governed by the Schrödinger equation

$$i\hat\hbar\frac{\partial}{\partial t}\psi(q,t) = \left(-\frac{\hat\hbar^2}{2}\partial_q^2 + V(q, w; a, \varepsilon, b)\right)\psi(q,t). \tag{38}$$

Thus, the stochastic version of the FN equations can be rewritten as a Schrödinger equation. This suggests that predictions about variability in brain dynamics in the form of stochastic noise offered by these equations may also include noise due to quantum effects such as shot noise [37] as well as thermal fluctuations in ion channels [38].

7. Empirical determination of the neuronal constant $\hat\hbar$

The neuronal constant $\hat\hbar = m\sigma$ can be empirically determined by measuring (a) the diffusion coefficient $\sigma^2 := 2D = \langle q^2\rangle/\Delta t$ where $\langle q^2\rangle$ is the variance of $q = CV$, the randomly varying electrical potential of the membrane, and (b) the neuron inductance m. The neuron inductance has its origin in two sources, (i) the coil inductance of myelin and (ii) the piezoelectric effect of the cell membrane [39]. Myelin is the lipid-rich substance that surrounds nerve cell axons. Its primary role is to provide inductance in neuron systems. This inductance plays a significant role in the generation and propagation of neural signals.

In electromagnetism, an inductor is an electronic component for storing energy in the form of a magnetic field. However, biologists do not generally study an actual electrical circuit but an equivalent circuit in which an inductor is only a symbol for reproducing the voltage oscillations and resonance frequencies measured in electrophysiological tests. Since the voltage oscillations and resonance frequencies are typical characteristics of an LCR circuit, adding an inductor in the equivalent circuit becomes inevitable.

A large inductance was first measured on the squid giant axon [29], which is an unmyelinated nerve. Myelin sheaths can generate only a small inductance, far less than the measured value. Hence, this inductance cannot be associated with myelin. It has been proposed that the observed large value comes from an equivalent inductance generated by the piezoelectric effect of the cell membrane. For further details, the reader is referred to Ref [39].

Since present empirical evidence suggests that neurons have a large inductance m, it would be reasonable to expect that the neuronal constant $\hat\hbar$ has a large value too, unless σ turns out to be extremely small. Given the reasonably good agreement between the 'random walk with drift' model of neurons and the observed data [3], that seems unlikely. This lends considerable empirical support for the hypothesis that quantum-like effects play a non-negligible role at the level of neurons.

It remains to be seen, however, whether $\hat{\hbar}$ varies from one neuron type to another, or is a universal constant.

Another method could be to study subthreshold neural oscillations [40,41]. A simple equivalent circuit corresponding to subthreshold is an LC circuit [42,43]. The total energy of such a circuit is

$$U = \frac{1}{2}(CV^2 + LI^2) = \frac{1}{2}\left(\frac{C^2V^2}{C} + \frac{L^2I^2}{L}\right) \tag{39}$$

where C is the capacitance, L is the inductance, V is the voltage and I the current. This can be written in the form

$$\begin{aligned} H &= \frac{1}{2}\left(\frac{L^2I^2}{L} + \frac{C^2V^2}{C}\right) \\ &:= \frac{p^2}{2m} + \frac{\omega^2 Lq^2}{2} = \frac{p^2}{2m} + \frac{m\omega^2 q^2}{2} \end{aligned} \tag{40}$$

with $U = H$ (the Hamiltonian), $L = m$ (the mass), $q = CV$ (the coordinate), $I = CdV/dt = dq/dt$ (the velocity), $p = LI$ (the momentum) and $\omega = 1/\sqrt{LC}$ (the angular frequency). The identical formal structure of a mechanical and LC harmonic oscillator prompts us to postulate that the quantum mechanical description of the LC oscillator is in the form of a state vector $|\psi\rangle$. Then, in a representation in which q is an independent variable and $|\psi(q,t)|^2 dq$ is the probability that the oscillator has coordinate between q and $q + dq$, the time evolution of the state function is governed by the equation of motion

$$i\hat{\hbar}\partial_t|\psi\rangle = \hat{H}|\psi\rangle, \quad \hat{H} = \frac{\hat{p}^2}{2m} + \frac{1}{2}m\omega^2\hat{q}^2. \tag{41}$$

This corresponds exactly to the Schrödinger equation (7) with $\psi(q,t) = \langle q|\psi\rangle$, $\hat{p} = -i\hat{\hbar}\partial_q$, $V = m\omega^2 q^2/2$. We therefore conclude that the Schrödinger equation (7) with $V = m\omega^2 q^2/2$ describes the subthreshold oscillations of neurons.

Since we are interested in voltage oscillations, we need time-dependent solutions of (7) with $V = m\omega^2 q^2/2$. Such states are called ‘coherent states’ $|\alpha\rangle$ of the harmonic oscillator. They were first introduced by Schrödinger in 1926, and their theory was developed further by Glauber [44] and Sudarshan [45] in connection with laser optics. Their importance lies in the fact that they are ‘minimum uncertainty’ quantum states and closely approximate classical oscillators. One defines the ‘displacement operator’ $D(\alpha)$ as $D(\alpha) = e^{\alpha a^\dagger - \alpha^* a}$ where $\alpha = |\alpha|e^{i\phi}$ is a complex number. A coherent state $|\alpha\rangle$ is then defined as a displaced vacuum state $|0\rangle$,

$$|\alpha\rangle = D(\alpha)|0\rangle, \quad D(\alpha) = e^{\alpha a^\dagger - \alpha^* a}, \tag{42}$$

$$a|0\rangle = 0. \tag{43}$$

Using $\alpha(t) = \alpha e^{-i\omega t} = |\alpha|e^{-i(\omega t - \phi)}$, one can verify (see the Appendix B for details) that the expectation value of x in such a state is

$$\langle q\rangle = \sqrt{2}q_0|\alpha|\cos(\omega t - \phi) \tag{44}$$

where $q_0 = \sqrt{\frac{\hat{\hbar}}{m\omega}}$ is the width of the harmonic oscillator ground state which is a gaussian distribution. The uncertainties in position and momentum in such a state satisfy the relation $(\sigma_q)_0^2(\sigma_p)_0^2 = \hat{\hbar}^2/4$, showing they are minimum uncertainty states, i.e. states with minimum quantum uncertainty and hence closest to classical states.

Hence, the unequivocal prediction is that subthreshold neural oscillations should be sinusoidal with a scatter of $\hat{\hbar}^2/4$ around the classical values (Fig. 4). A measurement of the scatter will therefore determine the value of $\hat{\hbar}$. Future work should therefore investigate quantum-like fluctuations in subthreshold neural oscillations using, for example, high-resolution electrophysiological recordings, such as patch-clamp techniques [46,47], capable of detecting minute fluctuations in membrane potentials. Besides macroscale organization, these oscillations might also reflect microscopic effects of quantum-like origin. This follows from Nelson’s mapping and the correspondence between stochastic noise and the Schrödinger equation discussed above.

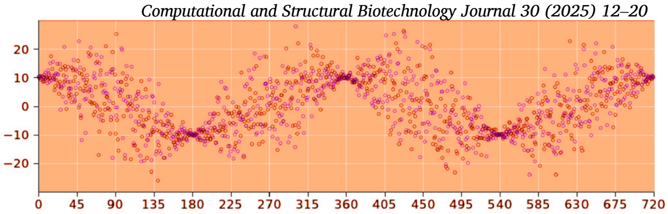

Fig. 4. Coherent state representation of the harmonic oscillator: the expectation value $\langle q\rangle$ as a function of time in the ground state of the harmonic oscillator, showing minimum uncertainty scatter points around a classical cosine wave.

Another possibility is to search for discrete stationary energy levels $E_n = (n + \frac{1}{2})\hat{\hbar}\omega$ of neurons described by a Schrödinger-like equation with a harmonic oscillator potential V implied by subthreshold oscillations (see Appendix B). These are solutions of the time-independent Schrödinger equation and should be observable during the quiescent or refractory periods of the neurons. The Helmholtz free energy F and the average energy $\langle E\rangle$ of a quantum harmonic oscillator are given by (see Appendix B)

$$F = \frac{\hat{\hbar}\omega}{2} + \frac{1}{\beta}\ln\left(1 - e^{-\beta\hat{\hbar}\omega}\right), \tag{45}$$

$$\langle E\rangle = \frac{\hat{\hbar}\omega}{2} + \frac{\hat{\hbar}\omega e^{-\hat{\hbar}\omega}}{1 - e^{-\beta\hat{\hbar}\omega}} \tag{46}$$

where $\beta = 1/kT$, T being the absolute temperature. These expressions show that both F and $\langle E\rangle$ tend to the zero-point energy as the temperature T tends to zero. These results are experimentally verifiable in principle and can be used to determine the value of $\hat{\hbar}$. If captured by electrophysiological methods, these energy levels would constitute direct evidence of non-classical and quantum-like effects in mesoscale neural dynamics.

8. Discussions

We first considered a 1D random walk model with drift of a single neuron (Section 2) and, using Nelson’s method of stochastic mechanics (Section 3), showed that it implies a Schrödinger-like equation in the space of the neuron’s state variable q. We then showed that the FN model of spiking neurons with noise (Section 6) also implies a Schrödinger-like equation. Both these models are known to correspond fairly well with the observed neuronal data.

Empirical evidence suggests that the neuronal constant $\hat{\hbar}$, the analog of the reduced Planck constant $\hbar$ in standard quantum mechanics, has a large value, indicating that quantum-like effects are non-negligible for neurons. Methods of empirically determining the constant will be found in Section 7.

Given that neural plasticity is often linked to the probabilistic nature of synaptic changes, our results suggest that quantum-like effects might influence how plasticity occurs in specific neural circuits.

Interestingly, ‘entangled states’ also exist in stochastic mechanics, and stochastic mechanics and quantum mechanics agree in predicting all observed correlations at different times. The reader is referred to the papers by Faris [48] and Petroni and Morato [49] for details. Looking for entanglement in neural systems is therefore another important area for further research, not only for its intrinsic value but also because entanglement is a key resource in quantum information processing, and it is important to find out whether the brain makes use of it, as conjectured [50]. Hameroff and Penrose have suggested that entanglement might involve quantum states in microtubules, dendrites and other parts of a neuron [17]. These would occur at a smaller scale than the one we consider here, the scale of a whole neuron. On the basis of the demonstrated equivalence of neuronal dynamics and Schrödinger-like behaviour, one would expect that the presence of non-classical correlations in neuronal fluctuations, akin to quantum entanglement, could be detected through cross-correlation analyses of simultaneous recordings from neighbouring neurons. Further work is required though to establish this, which goes beyond the scope of the present paper.

CRediT authorship contribution statement

Partha Ghose: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Dimitris A. Pinotsis:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A

The solutions $Q(t)$ of the stochastic differential equations (1), (2) are known to be continuous at all state points but nowhere differentiable. Hence, Nelson [27] suggested the following mean forward and backward differentials which we adopt:

$$D_f Q(t) = \lim_{\Delta t \to 0^+} E_t \left[\frac{Q(t+\Delta t) - Q(t)}{\Delta t} \right], \tag{47}$$

$$D_b Q(t) = \lim_{\Delta t \to 0^+} E_t \left[\frac{Q(t) - Q(t-\Delta t)}{\Delta t} \right] \tag{48}$$

where E_t denotes the expectation conditional on $Q(t) = q$. For differentiable curves $D_Q X(t) = D_b Q(t) = \dot{q} = v(t)$, the 'velocity' of the random variable. It follows that the drift coefficients in the forward and backward equations are given by

$$D_f(Q(t)) = b_f(Q(t), t), \quad D_b(Q(t)) = b_b(Q(t), t) \tag{49}$$

Then b_f is $D_f x(t)$, the *mean forward velocity*, and b_b is $D_b x(t)$, the *mean backward velocity* of the process. This amounts to a complete description of the motion, as in classical mechanics.

As is well known, the forward and backward SDEs lead to two Fokker-Planck equations for the probability density $\rho(x,t)$ of the random variable executing Brownian motion:

$$\frac{\partial}{\partial t}\rho(q,t) = -\frac{\partial}{\partial q}\left[b_f(q,t)\rho(q,t)\right] + \frac{\sigma^2}{2}\frac{\partial^2}{\partial q^2}\rho(q,t), \tag{50}$$

$$\frac{\partial}{\partial t}\rho(q,t) = -\frac{\partial}{\partial q}\left[b_b(q,t)\rho(q,t)\right] - \frac{\sigma^2}{2}\frac{\partial^2}{\partial q^2}\rho(q,t) \tag{51}$$

The negative sign of the noise term in the second (backward) equation is due to time reversal ($t \to -t$) which does not change the diffusion coefficient [51]. Adding these equations results in the continuity equation

$$\frac{\partial}{\partial t}\rho(q,t) + \frac{\partial}{\partial q}[v(q,t)\rho(q,t)] = 0 \tag{52}$$

with the *current velocity* defined by $v(q,t) = (b_f(q,t) + b_b(q,t))/2$. This displays the role of the current velocity in maintaining the probability distribution:

The difference of the forward and backward drifts $u(q,t) = (b_f(q,t) - b_b(q,t))/2$ is defined as the *osmotic velocity*. Subtracting the two Fokker-Planck equations results in

$$u(q,t) = \frac{\sigma}{2}\frac{\partial}{\partial q}\ln[\rho(q,t)] = \frac{\sigma}{2}\frac{\partial_q \rho}{\rho} = \sigma\frac{\partial R}{\partial q} \tag{53}$$

where $\ln\rho(q,t) = 2R(q,t)$. The coupled forward-backward stochastic differential equations for the position process can thus be written as

$$dQ(t) = (v(Q(t),t) + u(Q(t),t)) + \sigma dW_f(t), \tag{54}$$

$$dQ(t) = (v(Q(t),t) - u(Q(t),t)) + \sigma dW_b(t). \tag{55}$$

It follows from this that the current velocity is curl-free and can be written as

$$v(q,t) = \frac{1}{m}\frac{\partial}{\partial q}S(q,t) \tag{56}$$

where $S(q,t)$ is a scalar function which can be identified with the action.

Now, following Guerra and Morato [26], let us introduce the Lagrangian field

$$\mathcal{L} = \frac{1}{2}m(v+u).(v-u) - V(q) = \frac{1}{2}m(v^2 - u^2)(q,t) - V(q) \tag{57}$$

where $V(q)$ is the electrostatic potential, from which the action $S(q,t)$ can be constructed. The minus sign before u^2 is physically relevant; it means that the osmotic part of the action plays a role similar to an external potential V and is not a kinetic contribution. Using the variational principle, one can show that the main features of Nelson's stochastic mechanics can be derived from such an action. That is the justification for the form of the Lagrangian $\mathcal{L}$. As pointed out by Guerra [52], 'a physical justification for the assumed form of the stochastic Lagrangian seems to be a very difficult task, and surely it will involve new ideas about the origin of the underlying Brownian motion in stochastic mechanics'.

Using stochastic control theory and the current velocity as the control, Guerra and Morato showed that the following differential equations for the functions R and S extremize the action:

$$\frac{\partial S}{\partial t} + \frac{1}{2m}\left(\frac{\partial S}{\partial q}\right)^2 + V + V_Q = 0, \quad V_Q = -\frac{m\sigma^2}{2}\left[\left(\frac{\partial R}{\partial q}\right)^2 + \frac{\partial^2 R}{\partial q^2}\right], \tag{58}$$

$$\frac{\partial R}{\partial t} + \frac{1}{2m}\left(R\frac{\partial^2 S}{\partial q^2} + 2\frac{\partial R}{\partial q}\frac{\partial S}{\partial q}\right) = 0. \tag{59}$$

The first equation is the Hamilton-Jacobi-Bellman equation, i.e., the Hamilton-Jacobi equation with an additional stochastic term V_Q which takes the form

$$V_Q = -\frac{m\sigma^2}{4}\left[\frac{\partial_q^2\rho}{\rho} - \frac{(\partial_q\rho)^2}{2\rho^2}\right] \tag{60}$$

in terms of $\rho = e^{2R}$. It is the analog of the Bohm quantum potential [34]. The second equation can also be written in terms of ρ as

$$\frac{\partial\rho}{\partial t} + \partial_q\left[\rho\frac{\partial_q S}{m}\right] = 0 \tag{61}$$

which, using eqn (56) for the current velocity, is a continuity equation. These two coupled partial differential equations determine the stochastic process. These equations can be derived from the Schrödinger-like equation

$$im\sigma\frac{\partial}{\partial t}\psi(q,t) = \left(-\frac{m\sigma^2}{2}\partial_q^2 + V(q)\right)\psi(q,t) \tag{62}$$

by putting $\psi = \exp(R + iS/m\sigma) = \sqrt{\rho}\exp(iS/m\sigma)$ and separating the real and imaginary parts [26,34]. The argument q in the wave function $\psi(q,t)$ representing the value of the random variable $Q(t)$ of the neuron membrane plays the role of the spatial coordinate x and the coefficient σ plays the role of the factor $\hbar/m$ in standard quantum mechanics.

Bearing in mind that the stochastic processes which occur in neural membranes are entirely different from those in configuration space that give rise to standard quantum mechanics, it would be useful to introduce a new universal constant $\hat{\hbar} = m\sigma$ for neuronal media and rewrite the above equation in the form

$$i\hat{\hbar}\frac{\partial}{\partial t}\psi(q,t) = \left(-\frac{\hat{\hbar}^2}{2m}\partial_q^2 + V(q)\right)\psi(q,t) \tag{63}$$

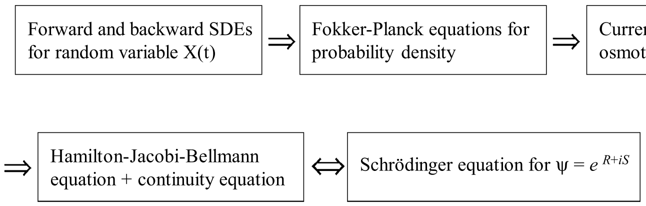

Fig. 5. Flow chart depicting the main mathematical steps used in deriving the Schrödinger equation from stochastic mechanics.

and treat it as the Schrödinger equation for single neurons. Like the Schrödinger equation in standard quantum mechanics, this equation will also ensure a novel level of stability and structure in the stochastic world of neurons.

Fig. 5 is a flow chart that summarizes the various mathematical steps used in deriving the Schrödinger equation in Nelson's stochastic mechanics.

Appendix B

When considering harmonic oscillators, it is convenient to introduce the ladder operators

$$a = \frac{1}{\sqrt{2m\omega\hat{\hbar}}}(m\omega q + i\hat{p}), \tag{64}$$

$$a^{\dagger} = \frac{1}{\sqrt{2m\omega\hat{\hbar}}}(m\omega q - i\hat{p}). \tag{65}$$

Using the commutation rule $[\hat{p}, q] = -i\hat{\hbar}$, one gets the commutation relation $[a, a^{\dagger}] = 1$, and

$$a^{\dagger}|n\rangle = \sqrt{n+1}|n+1\rangle, \tag{66}$$

$$a|n\rangle = \sqrt{n}|n-1\rangle, \tag{67}$$

$$a^{\dagger}a|n\rangle = n|n\rangle \tag{68}$$

where $n = 0, 1, 2, \ldots$ is an integer. The Hamiltonian operator can be written in the form

$$\hat{H} = \hat{\hbar}\omega\left(a^{\dagger}a + \frac{1}{2}\right) = \hat{\hbar}\omega\left(N + \frac{1}{2}\right) \tag{69}$$

where $N = a^{\dagger}a$ is the number operator. It then follows from the time-independent Schrödinger equation $\hat{H}\psi_n = E_n\psi_n$ that the energy eigenvalues are

$$E_n = \hat{\hbar}\omega\left(n + \frac{1}{2}\right). \tag{70}$$

The factor $\hat{\hbar}\omega/2$ is the 'zero-point energy' of neurons. The corresponding energy eigenfunctions are given by

$$\psi_n(q) = \frac{1}{\sqrt{n!}}(a^{\dagger})^n\psi_0(q) \tag{71}$$

with the ground state

$$\psi_0(q) = \left(\frac{m\omega}{\pi\hat{\hbar}}\right)e^{-\frac{m\omega q^2}{2\hat{\hbar}}} \tag{72}$$

which is a Gaussian distribution with width $q_0 = \sqrt{\frac{\hat{\hbar}}{m\omega}}$.

Now note that the coherent state can be written as

$$a|\alpha\rangle = \alpha|\alpha\rangle, \tag{73}$$

$$\langle\alpha|a^{\dagger} = \langle\alpha|\alpha^{*}, \tag{74}$$

$$\langle\alpha|a^{\dagger}a|\alpha\rangle = |\alpha|^2. \tag{75}$$

Using these results, one can compute the uncertainties in q and p:

$$(\sigma_q)^2 = \langle q^2\rangle - \langle q\rangle^2 = q_0^2\left(n + \frac{1}{2}\right), \tag{76}$$

$$(\sigma_p)^2 = \langle p^2\rangle - \langle p\rangle^2 = \frac{\hat{\hbar}^2}{q_0^2}\left(n + \frac{1}{2}\right), \tag{77}$$

and hence for the ground state ($n = 0$) $(\sigma_q)_0^2(\sigma_p)_0^2 = \hat{\hbar}^2/4$. For further details of coherent states the reader is referred to Ref [53].

The thermodynamic properties of the quantum harmonic oscillator can be calculated using the standard techniques of statistical mechanics. The partition function

$$Z = Tre^{-\beta\hat{H}} = \sum_{n=0}^{\infty} e^{-\beta E_n} = \sum_{n=0}^{\infty} e^{-\beta\left(n+\frac{1}{2}\right)\hat{\hbar}\omega} = \frac{1}{2}csch\left(\frac{\beta\hat{\hbar}\omega}{2}\right) \tag{78}$$

where $\hat{H}$ is the Hamiltonian operator. Hence

$$F = -\frac{1}{\beta}\ln Z = \frac{\hat{\hbar}\omega}{2} + \frac{1}{\beta}\ln\left(1 - e^{-\beta\hat{\hbar}\omega}\right), \tag{79}$$

$$\langle E\rangle = -\frac{\partial \ln Z}{\partial\beta} = \frac{\hat{\hbar}\omega}{2} + \frac{\hat{\hbar}\omega e^{-\hat{\hbar}\omega}}{1 - e^{-\beta\hat{\hbar}\omega}}. \tag{80}$$

Data availability

No data were created during this study.

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