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Letter to Editor

Geometric phase shifts in biological oscillators

HIGHLIGHTS

- It is not well understood how cell division events affect biological oscillations.
- I demonstrate that a geometric phase shift may arise during the cell cycle.
- This can perturb circadian control and cause asynchrony between cells.

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ABSTRACT

Many intracellular processes continue to oscillate during the cell cycle. Although it is not well-understood how they are affected by discontinuities in the cellular environment, the general assumption is that oscillations remain robust provided the period of cell divisions is much larger than the period of the oscillator. Here, I will show that under these conditions a cell will in fact have to correct for an additional quantity added to the phase of oscillation upon every repetition of the cell cycle. The resulting phase shift is an analogue of the geometric phase, a curious entity first discovered in quantum mechanics. In this letter, I will discuss the theory of the geometric phase shift and demonstrate its relevance to biological oscillations.

1. Introduction

Rhythmic cycles of gene expression underpin oscillatory processes that occur in biology with periods ranging from several years to a fraction of a second (Goldbeter, 1996). At the cellular level, oscillatory phenomena are controlled by molecular regulators that form a network of positive or negative feedback loops (gene circuits). Positive and negative regulators, which increase and decrease gene expression respectively, are usually protein factors whose activities are in turn regulated during transcription, or at a later, post-translational stage. For example, transcription factors CLOCK and BMAL1 regulate the levels of mRNA in the mammalian circadian clock (Reppert and Weaver, 2002), and the E3 ubiquitin ligase Mdm2 controls oscillations of the tumour suppressor p53 (Lahav et al., 2004). Computational and mathematical methods have been used to study these mechanisms (reviewed in Goldbeter, 2002) since understanding how biological oscillations function on the molecular scale is essential for explaining the dynamics of a cell. In addition, today's research needs to address how the loss of circadian control contributes to disease at the level of an organism.

In a recent article, Gonze (2013) questioned the robustness of molecular oscillations that occur concomitantly with the cell cycle. It was pointed out that most circadian clock and gene circuit models do not satisfactorily account for discontinuities in the cellular environment, since biological oscillations must also perpetuate across repetitive cell divisions (Elowitz and Leibler, 2000; Mihalcescu et al., 2004). Adopting a numerical approach, Gonze demonstrated the influence of cell cycle-related effects on two popular non-linear oscillators, the Repressilator model (Elowitz and Leibler, 2000) and the Goodwin (1965) model. He found that although robustness diminishes for smaller periods of the cell cycle, oscillations remain relatively robust provided that the period of the cell division is much larger than the period of the oscillator (Gonze, 2013).

It is the purpose of this letter to describe an effect that manifests itself on a clock (from now on 'clock' will refer to any general circadian clock or gene circuit) exactly when the oscillation is considered most robust by the analysis of Gonze. More precisely, an effect that arises when the period of the cell cycle is large compared to the period of oscillations, causing the cellular environment to change *adiabatically* with respect to the molecular components of the clock. Under these conditions, a classical analogue of the quantum geometric phase, Hannay's angle, may be realised in a given clock system and require the cell to correct for an additional quantity added to the phase of oscillation upon every repetition of the cell cycle. Here, I will discuss the theory of geometric phase shifts and their relevance to biological systems, suggest under what conditions they may be detected, and derive Hannay's angle for two different versions of the Goodwin model.

2. The classical geometric phase shift

Existence of the geometric phase shift in quantum mechanics was first noted by Berry (1984) and almost immediately realised to

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be a *holonomy* also present in other dynamical systems (Simon, 1983; Berry, 1985; Hannay, 1985). A holonomy is an intrinsic property associated with any curved space, the classical example being the holonomy of the unit sphere. This holonomy is realised if one is to take a vector tangential to the sphere at a given starting point (think of a pen held on the surface of a volleyball) and then transport it around a closed loop on the surface, keeping the vector parallel to the direction of transport at every point. After completing the closed path the vector returns to its original point, but will be rotated with respect to the direction it was pointing at the beginning of the journey. The angle of rotation is proportional to the area of the surface bounded by the path and scales with the size of the loop. It does not depend on the time taken to complete the cycle.

In Hamilton's formulation of conservative mechanics, the equations of motion describing the time evolution of a system are derived from the Hamiltonian H. This is a function of generalised coordinates Q, momenta P, and some constant parameters denoted by R. Oscillatory systems trace out an ellipse of area $2\pi I$ in (Q, P) phase space, and so it is convenient to make a canonical change of coordinates to action-angle variables (I,θ) so that the equations of motion become

$$\frac{d\theta}{dt}=\frac{\partial H}{\partial I}=\text{const}=\omega_0,\quad \frac{dI}{dt}=-\frac{\partial H}{\partial \theta}=0. \tag{1}$$

Action-angle variables are particularly useful because frequencies ω_0 of the oscillation can be obtained without ever having to solve the equations of motion.

Hannay (1985) asked what would be the effect of making the parameters dependent on time, so that the vector R is slowly transported around a closed loop in parameter space (slow with respect to the period of oscillations). By the assumption of adiabaticity, the period $\tau : R(t)=R(t+\tau)$ would be much larger than the period of a single orbit in (Q, P) phase space, and although the path changes as the parameters are varied, the area I enclosed by that path would remain the same. It turns out that after such a time τ, the angle variable θ is given by the anticipated dynamical term (arising from the fact that θ is continually making orbits around the curve in phase space) plus an additional term $\Delta\theta$ depending only on the circuit in parameter space and not the duration of the process:

$$\theta(\tau)=\theta(0)+\int_0^\tau \omega_0\,dt+\Delta\theta. \tag{2}$$

For an adiabatic excursion, $dI/dt=0$, but now the equation of motion for θ is given by

$$\frac{d\theta}{dt}=\frac{\partial H}{\partial I}+\frac{dR}{dt}\left\langle\frac{\partial H}{\partial R}\right\rangle, \tag{3}$$

where the angled brackets denote the contained quantity averaged over a single period. Consequently, Hannay's angle is given by

$$\Delta\theta=\int_0^\tau \frac{dR}{dt}\left\langle\frac{\partial H}{\partial R}\right\rangle dt=\oint\left\langle\frac{\partial H}{\partial R}\right\rangle dR. \tag{4}$$

The fact that the additional phase angle $\Delta\theta$ had lain undiscovered in classical mechanics for more than a century came as a great surprise to modern physicists. Together with Berry's phase it arises as a purely geometric effect of making a non-trivial loop in parameter space and is closely related to the example of the sphere described above. Shortly after its discovery, Kepler and Kagan (1991) and Kagan et al. (1991) demonstrated that time-independent geometric phase shifts also occur in dissipative systems, such as the Belousov–Zhabotinsky chemical reaction, which cannot be described by a Hamiltonian.

Realising geometric phase shifts that are present in dissipative systems has deep implications for biology, which by its very nature is a complicated chemical process operating far from equilibrium. The geometric phase shift would become relevant to a biological oscillator if there exists a mechanism that transports parameters describing the cellular environment around a closed loop in parameter space. Remarkably well-suited to this task, the cell cycle provides a natural way in which the environment changes adiabatically before returning to an initial state after each cell division event. Every repetition of the cell cycle causes variations in degradation, transcription and translation rates (usually assumed to be constant in oscillator models) that could give rise to a geometric phase shift in the oscillations of a molecular clock. In the next section I will demonstrate this to indeed be the case.

3. Geometric phase shifts induced by the cell cycle

In the first half of this section I will derive an exact expression for Hannay's angle corresponding to a simple version of the Goodwin model. In doing so, one finds an interesting relationship to be satisfied between expression and degradation rates when $\Delta\theta$ is to contribute to the phase of an oscillation. In the second half I will consider a more complicated Goodwin model involving protein–protein interactions for which the existence of a geometric phase shift will be demonstrated through numerical simulation. This second Goodwin model cannot be described by a Hamiltonian, and is therefore an example of a dissipative process common to many biological systems.

Goodwin (1965) proposed several models for different biological oscillators, the simplest of which can be described by a Hamiltonian H, a function of mRNA concentration X and protein concentration Y. The linearised version of this model is

$$\frac{dX}{dt}=-\frac{\partial H}{\partial Y}=\frac{a}{A}(1-kY)-b,\quad \frac{dY}{dt}=\frac{\partial H}{\partial X}=\alpha X-\beta, \tag{5}$$

where the degradation rates b,β and expression rates a, A, k, α are understood to make up a set of constant parameters R on which H depends. Goodwin used this system of equations to describe a closed negative feedback loop that exhibits oscillatory behaviour under the correct choice of R.

To account for cell cycle effects in the linear Goodwin model it is necessary to make degradation and expression rates vary periodically in time. That is, $R(t)=R(t+\tau)$, where τ is the time taken to complete one round of the cell cycle. This means the equations become notoriously difficult to solve for arbitrary parameters. However, after making the substitutions

$$\alpha=\frac{1}{M},\quad \frac{\alpha}{\beta}=\mu,\quad \alpha\frac{ak}{A^2}=\omega^2,\quad \frac{a}{A}-b-\frac{d}{dt}\frac{\alpha}{\beta}=F, \tag{6}$$

the Hamiltonian $H(t)$ transforms into

$$H(t)=\frac{1}{2M}(X^2+\omega^2M^2Y^2)-\left(\frac{d\mu}{dt}+F\right)Y-\frac{\mu}{M}X, \tag{7}$$

which is the Hamiltonian of a classical harmonic oscillator for which action-angle variables (I,θ) are known (Song, 2000). A second order equation of motion (independent of X) can be obtained for Y, and is satisfied by a linear combination of a particular solution Y_p and two linearly independent solutions Y_1, Y_2 of the homogeneous equation. Defining $\rho=\sqrt{Y_1^2+Y_2^2}$ and $\Omega=M(\dot{Y}_1Y_2-Y_1\dot{Y}_2)$, where the dot denotes differentiation of a solution with respect to time, it can been shown that (I,θ) are given by the relations

$$I=\frac{1}{2\Omega}\left[\frac{\Omega^2}{\rho^2}(Y-Y_p)^2+M\frac{d\rho}{dt}(Y-Y_p)-\rho(X-MY_p-\mu)^2\right], \tag{8}$$