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Modelling of photo-thermal control of biological cellular oscillators

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Abstract

We study the transient dynamics of biological oscillators subjected to brief heat pulses. A prospective well-defined experimental system for thermal control of oscillators is the peripheral electroreceptors in paddlefish. Epithelial cells in these receptors show spontaneous voltage oscillations which are known to be temperature sensitive. We use a computational model to predict the effect of brief thermal pulses in this system. In our model thermal stimulation is realized through the light excitation of gold nanoparticles delivered in close proximity to epithelial cells and generating heat due to plasmon resonance. We use an ensemble of modified Morris-Lecar systems to model oscillatory epithelial cells. First, we validate that the model quantitatively reproduces the dynamics of epithelial oscillations in paddlefish electroreceptors, including responses to static and slow temperature changes. Second, we use the model to predict transient responses to short heat pulses generated by the light actuated gold nanoparticles. The model predicts that the epithelial oscillators can be partially synchronized by brief 5 – 15 ms light stimuli resulting in a large-amplitude oscillations of the mean field potential.

I. INTRODUCTION

In neuroscience, the control of cellular dynamics is traditionally performed by electrical stimulation or by various pharmacological agents. For example, control of neuronal oscillations by application of electrical stimuli to specific brain areas was suggested to suppress abnormal large-scale oscillations observed in Parkinsonian patients [1, 2]. A recent revolutionary technique, called optogenetics, utilizes light stimulation of cells whose membranes include light-sensitive cation channels "inserted" by genetic modification [3, 4]. Yet another alternative is to employ metallic nanoparticles (NPs) or nanocrystals attached to a cell or even to specific proteins and stimulated by light or magnetic field. In particular, NPs of noble metals are notorious for effective heat generation by the light excitation of plasmon resonance [5]. Photothermal effect in metal NPs has many potential applications in biomedical research including photothermal therapy, sensing, imaging, actuation and drug release [6–12].

Oscillations of the membrane potential of a biological cell are temperature sensitive due to temperature-dependent conductivity and kinetics of ion channels in the cell's membrane [13]. For example, oscillatory responses of sensory hair cells are highly temperature sensitive [14]. Temperature variations can modulate rhythms of hippocampal field activity in the brain [15]. Light-activated metallic NPs are capable of delivering brief heat pulses, and thus represent an attractive technique for control of cellular dynamics and oscillations. Indeed, we expect that a temperature increase may raise the frequency of voltage oscillations of a cellular system. Furthermore, a short thermal stimulus may also reset the phase of oscillations changing the collective dynamics [16]. Several recent experimental studies demonstrated the possibility of thermal control of cellular dynamics using metallic NPs in *in vitro* preparations of single or cultured cells [17–19]. Here we model an experiment in which gold NPs are used as actuators to control oscillations in an *in vivo* preparation of peripheral electroreceptors in paddlefish.

Electroreceptors (ERs) are peripheral sensory organs in the skin, sensitive to weak voltage gradients in water. ERs are hair cell - sensory neuron receptors, similar to those for the senses of hearing and balance. ERs in paddlefish are organized in clusters of 3 – 30 pores mainly on the frontal appendage, called the rostrum. Each skin pore leads into a short canal, ~200 μm deep and 30–400 μm in internal diameter, which ends in a sensory epithelium consisting of ~1000 sensory hair cells along with support cells [20]. Sensory cells in the epithelium, each ~10 μm long and 5–7 μm in diameter, are cellular transducers for external weak electrical signals. Epithelial cells exhibit spontaneous voltage oscillations at ~26 Hz at 22°C that are temperature sensitive [21]. These oscillations can be recorded directly from an ER canal in the form of a mean field potential in an intact *in vivo* preparation [21]. Gold (Au) NPs can be easily delivered to the natural cavities formed by ER canals and used as nanoheaters upon excitation by the laser light of appropriate resonant wavelength. In this paper we simulate such an experiment. We develop a simple model of epithelial oscillations using an ensemble of Morris-Lecar systems with temperature scaling coefficients. We use experimental data on static temperature sensitivity of ERs from [21] to tune the model parameters. We then calculate brief temperature changes in water due to heat generated by Au NPs complex in response to a short laser pulse and study collective response of epithelial oscillators.

II. MODEL

In our model Au NPs are delivered to a pore of the ER cluster on the rostrum of the paddlefish. NPs form a thin layer above apical surfaces of epithelial cells at the bottom of the canal (Fig. 1). Laser pulse directed into the canal excites plasmon resonances in Au NPs resulting in a brief heat pulse which then affects voltage dynamics of the ensemble of epithelial cells. The model neglects the light absorption by tissue and water. This is justified if green or near infrared light is used, as at 500 – 1100 nm wavelength the light absorbance of tissue and water is several order of magnitudes smaller than that of Au NPs [22, 23].

We assume that the Au NPs complex is a cylinder of uniform density n_{NP} , of radius R_0 and height h (Fig. 1). Furthermore, we assume that a medium surrounding the Au NPs complex is uniform with thermal properties of water. With these assumptions, the dynamics of the

local temperature change $\mathcal{T}(t, \mathbf{r})$ as a function of the position $\mathbf{r}$ and time t is given by the conventional heat transfer equation,

$$\rho c \frac{\partial \mathcal{T}(t, \mathbf{r})}{\partial t} = \kappa \nabla^2 \mathcal{T}(t, \mathbf{r}) + q(t, \mathbf{r}), \quad (1)$$

where ρ , c and κ are the mass density, specific heat and thermal conductivity of water, respectively. In Eq.(2) $q(t, \mathbf{r})$ is the local heat source due to light dissipation in Au NPs given by [24],

$$q(t, \mathbf{r}) = \begin{cases} C_{\text{abs}} \Phi(t) n_{\text{NP}} & \mathbf{r} \text{ within NPs complex,} \\ 0 & \text{otherwise,} \end{cases} \quad (2)$$

where C_{abs} is the absorption cross section of a single NP and $\Phi(t)$ is the incident light flux. The light flux, $\Phi(t)$, is a rectangular pulse with duration τ_L and the peak magnitude Φ_0 . The initial and boundary conditions are $\mathcal{T}(t_0, \mathbf{r}) = 0$ and $\mathcal{T}(t, \pm\infty) = 0$, where $t_0 = 0$ is the onset of the light pulse. The local temperature is then $T(t, \mathbf{r}) = T_0 + \mathcal{T}(t, \mathbf{r})$, where $T_0 = 22^\circ\text{C}$ is the ambient (room) temperature. The heat transfer equation (2) is solved by the standard method of Green's functions [25],

$$\mathcal{T}(t, \mathbf{r}) = \begin{cases} q_0 z t \left(\frac{\pi}{\mathcal{D}t} \right)^{\frac{3}{2}} \int_{-1}^1 du \int_0^1 \eta d\eta \int_0^{2\pi} d\phi \sqrt{\frac{\pi}{B_1}} \text{erfc} \sqrt{B_1}, & 0 < t < \tau_L \\ q_0 z \tau_L \left(\frac{\pi}{\mathcal{D}\tau_L} \right)^{\frac{3}{2}} \int_{-1}^1 du \int_0^1 \eta d\eta \int_0^{2\pi} d\phi \sqrt{\frac{\pi}{B_2}} \left(\text{erf} \sqrt{\frac{B_2}{t/\tau_L - 1}} - \text{erf} \sqrt{\frac{B_2}{t/\tau_L}} \right), & t > \tau_L \end{cases} \quad (3)$$

$$B_1(t, \mathbf{r}, \eta, u, \phi) = \frac{R_0^2}{4\mathcal{D}t} \left\{ (\eta \cos \phi - x/R_0)^2 + (\eta \sin \phi - y/R_0)^2 + \frac{z_0^2}{R_0^2} (u - z/z_0)^2 \right\},$$

$$B_2(t, \mathbf{r}, \eta, u, \phi) = \frac{R_0^2}{4\mathcal{D}\tau_L} \left\{ (\eta \cos \phi - x/R_0)^2 + (\eta \sin \phi - y/R_0)^2 + \frac{z_0^2}{R_0^2} (u - z/z_0)^2 \right\},$$

where x, y are coordinates on a plane which is the distance z below the center of the NPs complex, $\mathcal{D} = \kappa/(\rho c)$ is thermal diffusivity of water, $z_0 = h/2$ and

$q_0 = (C_{\text{abs}} n_{\text{NP}} \Phi_0 R_0^2) / (\rho c (2\pi)^3)$. The integrals in Eqs. (3) were taken numerically using the Simpson method.

$N = 1000$ epithelial cells are distributed uniformly on a disk of radius $R_c = 100 \mu\text{m}$, forming epithelial layer located $z = 10 \mu\text{m}$ below the Au NPs complex (Fig. 1). Cells are electrically uncoupled [20]. Voltage oscillation of a cell is modelled by modified Morris-Lecar (ML) equations [26], mimicking ionic currents of the cell's basolateral membrane [27]. The model describes dynamics of the membrane potential $V(t, \mathbf{r})$ of a cell located at a position $\mathbf{r}$ in the epithelial layer,

$$C_r \frac{\partial V}{\partial t} = -\alpha(T)[g_{Ca} m_\infty(V)(V - V_{Ca}) + g_K w(V - V_K) + g_L(V - V_L)] + I_0 + \xi_r(t), \quad (4)$$

$$\frac{\partial w}{\partial t} = \beta(T) \frac{w_\infty - w}{\tau_w(V)}, \quad m_\infty(V) = \frac{1}{2} \left[1 + \tanh \left(\frac{V + 1.2}{18} \right) \right],$$

$$w_\infty(V) = \frac{1}{2} \left[1 + \tanh \left(\frac{V - 2}{30} \right) \right], \quad \tau_w(V) = \cosh^{-1} \left(\frac{V - 2}{60} \right).$$

In Eqs.(4) slow variable $w(t, \mathbf{r})$ describes activation of potassium (K) ion channels. The parameters of the ML system were tuned to replicate collective epithelial oscillations in paddlefish ERs [21]. The cell membrane capacitance, C_r , was drawn randomly for each cell from the continuous uniform distribution in the range 10 – 12 pF to account for spatial inhomogeneity; $V_{Ca} = 120$ mV, $V_K = -84$ mV, $V_L = -60$ mV are equilibrium potentials for calcium, potassium and leak channels, respectively; $g_{Ca} = 4.4$ nS, $g_K = 8$ nS, $g_L = 1.7$ nS are maximal values of conductances of corresponding channels; $I_0 = 112$ pA is a constant current which sets the fundamental frequency of oscillators. Currents $\xi_r(t)$ are zero mean Gaussian white noise sources independent across the cells ensemble, $\langle \xi_r(t) \xi_r(t + \tau) \rangle = 2D\delta(\tau)$ with the intensity $D = 200$ kHz(pA)². In the absence of noise each ML system was in a regime of limit cycle oscillations.

The temperature dependence was introduced using a standard approach of rescaling the conductances and kinetics of corresponding ion channels [13, 28, 29]. The scaling factors $\alpha(T)$ for conductances and $\beta(T)$ for kinetics of potassium ion channels in (4) are

$$\alpha(T) = Q_{10,\alpha}^{(T-T_0)/T_0}, \quad \beta(T) = Q_{10,\beta}^{(T-T_0)/T_0}, \quad (5)$$

where $Q_{10,\alpha}$, $Q_{10,\beta}$ are the so-called Q_{10} temperature coefficients. The temperature T in (5) can be treated as a parameter of the model for simulation of static temperature responses, or can be a function of time, e.g. solution of the heat transfer equation (3), to study responses to dynamical (i.e. time-dependent) temperature variations. In our model the temperature coefficients were $Q_{10,\alpha} = 1.2$ and $Q_{10,\beta} = 2.7$ which provided excellent correspondence with experimental data on static and dynamic temperature sensitivity of epithelial oscillations in paddlefish ERs (Results). Stochastic ML equations (4) were integrated numerically using the Euler-Maruyama method [30] with the time step of 10^{-3} ms.

To study the collective dynamics of epithelial cells we calculated the mean field potential, i.e. mean voltage across the ensemble of cells: $\langle V(t) \rangle_r = (1/N) \sum_r V(t, \mathbf{r})$, where the sum is taken over N cells in the ensemble. We note that the mean field $\langle V(t) \rangle_r$ corresponds to *in vivo* recording of spontaneous epithelial oscillations of Ref. [21]. To assess transient responses due to dynamic temperature variations we extracted instantaneous phases and frequencies of individual oscillators and then calculated ensemble averaged instantaneous frequency, $\langle f(t) \rangle_r$ and the order parameter $\gamma(t)$. Instantaneous phase of a cell at a spatial

position $\mathbf{r}$, $\psi(t, \mathbf{r})$, was estimated from a sequence times $\{t_k(\mathbf{r})\}$ at which the cell's voltage crossed a level of +20 mV with a positive slope [31],

$$\psi(t, \mathbf{r}) = 2\pi \frac{t - t_k(\mathbf{r})}{t_{k+1}(\mathbf{r}) - t_k(\mathbf{r})} + 2\pi k, t_k(\mathbf{r}) < t < t_{k+1}(\mathbf{r}), \quad (6)$$

where $t_{k+1}(\mathbf{r}) - t_k(\mathbf{r}) = \mathcal{P}(t, \mathbf{r})$ is the instantaneous period. The ensemble averaged instantaneous frequency and the order parameter were calculated as

$$\langle f(t) \rangle_{\mathbf{r}} = 1 / \langle \mathcal{P}(t, \mathbf{r}) \rangle_{\mathbf{r}}, \quad \gamma(t) = |\langle \exp[i\psi(t, \mathbf{r})] \rangle_{\mathbf{r}}|. \quad (7)$$

In the context of our study the time-dependent order parameter is also known as the resetting index [32] which measures how tightly the phases of oscillators are time locked to a stimulus. $\gamma(t)$ varies from 0 (no phase resetting) to 1 (perfect phase reset across the ensemble of oscillators).

III. RESULTS

Figure 2 shows a sample path of the mean voltage fluctuations and its statistics at a constant room temperature, $T = 22^\circ\text{C}$. With the parameters listed in the previous section, the model reproduced quantitatively epithelial oscillations of paddlefish ERs. As expected, the fluctuations are Gaussian, characterized by a peak in the power spectral density at the fundamental frequency, f_e , and its higher harmonics. To test how well the model reproduced *static* temperature sensitivity we varied the temperature T as a parameter and then calculated the peak frequency f_e of the *steady state* mean field oscillations. The result shown in Fig. 3(a) demonstrates excellent correspondence with the experimental data.

The time-dependent ensemble averaged oscillation frequency calculated from the model simulations shown in Fig. 3(b) followed the temperature trace [Fig. 3(c)] and was in excellent agreement with the experimental data. The results above show that the model reproduced quantitative details of thermal sensitivity of epithelial oscillations in paddlefish ERs. Next, we model an experiment in which the temperature of epithelial oscillations was changed *dynamically* by administering a flow of warm water to a cluster of canals on the rostrum of paddlefish (cf. Fig. 10A in [21]). In this experiment the temperature was raised from 22°C to 28°C and then dropped back to 22°C by stopping the flow of warm water. In numerical simulations we took the temperature trace $T(t)$ from this experiment and applied it uniformly to all ML oscillators.

Since the epithelial cells are electrically uncoupled, the temperature dependence through the coefficients α and β is the only factor that may introduce spatio-temporal correlations among the cells. Presumably a short, e.g. less than a period long, temperature pulse of large enough magnitude can reset phases of epithelial oscillators leading to their transient synchronization. Light-activated Au NPs are capable of delivering heat almost instantly [33–35] so that dispersion of the resulting temperature gradient is solely due to finite heat conductivity of a medium. In the following we provide calculations for commercially available Au NPs of 50 nm in diameter each. The NPs density was taken as $n_{\text{NP}} = 2.5 \times 10^{12} \text{ cm}^{-3}$. Cylindrical NPs complex had the radius $R_0 = 50 \text{ }\mu\text{m}$ and the height $h = 10 \text{ }\mu\text{m}$. The Au

NPs complex was activated by a green laser with the wavelength $\lambda = 530$ nm. For this wavelength the absorption cross section of a single 50 nm NP is $C_{\text{abs}} = 6.2 \times 10^{-11} \text{ cm}^2$ [24]. Activation of the Au NPs complex by 5 – 15 ms pulses of green light with the peak flux of $\Phi_0 = 380 \text{ W/cm}^2$ resulted in large temperature pulses of 10 – 14 °C in magnitude at the bottom of epithelial layer as shown in Fig. 4(a).

Transient responses of epithelial cells to heat pulses generated by NPs complex were modelled by incorporating the solution of inhomogeneous heat equation (3) into the ensemble of stochastic ML systems (4). Brief photo-activated heat pulses resulted in large-amplitude transient oscillations of the mean field shown in Fig. 4(b). Before the heat pulse, membrane potentials of individual cells were uncorrelated and the resultant mean field potential was small. Brief temperature raise due to heat generated by light-activated Au NPs acted as a common stimulus for oscillators increasing their frequencies and resetting their phases as indicated by rapid increase of the order parameter (resetting index) $\gamma(t)$ in Fig. 4(c). During and after the heat pulse, the cells became partially synchronized, leading to large-amplitude oscillations of the mean field potential shown in Fig. 4(b). Indeed this photo-thermally induced synchronization faded away as the cells were not coupled. The duration of the laser pulse can be optimized to reach a maximal response as indicated in Fig. 4(b,c). In the example shown, the maximal response occurred for $\tau_L = 12$ ms. Shorter or longer light pulses resulted in weaker responses characterized by smaller amplitudes of the mean field and by smaller values of the order parameter γ . This example demonstrates that brief temperature gradients generated by light-activated NPs can control the collective dynamics of cellular oscillators.

IV. CONCLUSIONS

We have developed a framework for modelling of control of biological cellular oscillators by brief heat stimuli. We modelled oscillatory epithelial cells in peripheral electroreceptors in paddlefish as an example of a well-defined and experimentally accessible system in which temperature control can be performed in *in vivo* settings. The plasmonic photothermal effect of light stimulated gold nanoparticle was used to form brief spatially localized heat pulses. We showed that with realistic physical parameters the nanoheater complex generated heat enough to raise the temperature by 10 – 14 °C, resulting in brief (millisecond level) temperature pulses. These thermal stimuli were common for the population of uncoupled cellular oscillators and were able to synchronize them transiently, eliciting large amplitude responses of the ensemble averaged voltage (mean field potential). Although phases of individual epithelial cells are hard if not impossible to measure in an electro-physiological experiment, the collective voltage oscillations are recorded routinely and correspond to the mean field potential, $\langle V(t) \rangle_r$, in our model. Thus, our modelling study provides experimentally testable predictions on photo-thermally induced transient synchronization.

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FIG. 1.

(Color online) Schematic drawing showing single canal of an electroreceptor cluster. Epithelial cells are at the bottom of the canal. In our theoretical model optically excited gold nanoparticles ensemble (Au NPs) are above the epithelial layer. Au NPs heater is a uniform cylinder 100 μm in diameter and 10 μm in height. The distance between the Au NP heater and the bottom of the epithelial cell layer is 10 μm . The drawing is not to scale.

FIG. 2.

Spontaneous epithelial oscillations at room temperature, $T = 22^\circ\text{C}$. (a): Two seconds segment of the mean voltage oscillations from an ensemble of 1000 cells each modelled by stochastic Morris-Lecar system. (b): Probability density function (p.d.f.) of the mean field oscillations (circles) and the Gaussian p.d.f. with the standard deviation of 0.895 mV (solid line). (c): Power spectral density (PSD) of epithelial oscillations.

FIG. 3.

(Color online) (a): Static temperature dependence of the frequency of epithelial oscillations. Circles show experimentally measured frequency of epithelial oscillations for $n = 54$ electroreceptors taken from Fig. 9B of Ref. [21]. Solid (red) line shows the peak oscillation frequency from numerical simulation of the model of 1000 stochastic Morris-Lecar systems with parameters given in the text. (b): Dynamic response of the model to a slow temperature raise shown in panel (c). Circles show experimentally measured frequency of epithelial oscillations from an electroreceptor taken from Fig. 10A of Ref. [21]. Solid (red) line shows the mean instantaneous frequency, $\langle f(t) \rangle_{\mathbf{r}}(7)$, from numerical simulation of the model.

FIG. 4.

(Color online) Response of epithelial oscillators to the heat pulse from light-activated Au NPs. Au NPs complex was activated by a rectangular laser pulse of three different durations τ_L , 5 ms, 12 ms and 15 ms, indicated in the figure legend. Laser pulse was administered at $t_0 = 200$ ms. (a): Temporal dependence of spatially averaged temperature at the bottom of the epithelial cells. (b): Ensemble averaged voltage (mean field potential) versus time, $\langle V(t) \rangle_r$. (c): The order parameter, $\gamma(t)$ (7).