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Geometry and dynamics of activity-dependent homeostatic regulation in neurons

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Abstract

To maintain activity in a functional range, neurons constantly adjust membrane excitability to changing intra- and extracellular conditions. Such activity-dependent homeostatic regulation (ADHR) is critical for normal processing of the nervous system and avoiding pathological conditions. Here, we posed a homeostatic regulation problem for the classical Morris-Lecar (ML) model. The problem was motivated by the phenomenon of the functional recovery of stomatogastric neurons in crustaceans in the absence of neuromodulation. In our study, the regulation of the ionic conductances in the ML model depended on the calcium current or the intracellular calcium concentration. We found an asymptotic solution to the problem under the assumption of slow regulation. The solution provides a full account of the regulation in the case of correlated or anticorrelated changes of the maximal conductances of the calcium and potassium currents. In particular, the solution shows how the target and parameters of the regulation determine which perturbations of the conductances can be compensated by the ADHR. In some cases, the sets of compensated initial perturbations are not convex. On the basis of our analysis we formulated specific questions for subsequent experimental and theoretical studies of ADHR.

Keywords

Activity-dependent homeostatic regulation; Morris-Lecar model; Central pattern generators; Neuronal dynamics; Mathematical modeling

1 Introduction

Neurons demonstrate remarkable and vitally important durability whether they are involved in sensory perception, motor control, or higher level information processing. They function reliably, in some cases over decades, adjusting to turnover of the ion channel proteins determining membrane excitability, organism growth, and other changing conditions, including those caused by injuries and insults (Marder and Goaillard 2006). Multiple physiological mechanisms make this durability possible. Those include neuronal and synaptic plasticity (Davis and Bezprozvanny 2001; Marder and Prinz 2002; Turrigiano and Nelson 2004; Davis 2006; Nelson and Turrigiano 2008), glial cell activity (Fellin et al. 2006), and others. Here, we focus on a neuron's self-regulation of its "target" activity, or activity-dependent homeostatic regulation (ADHR).

The physiological mechanisms of ADHR are complex. There are at least three potential sources of complexity. First, homeostatic plasticity may interact with mechanisms of learning (Marder

et al. 1996; Turrigiano 1999); while learning changes neuronal responses, homeostatic regulation tends to stabilize them. Second, experiments and modeling show that the target of regulation is not one but many parameter sets for which the neuronal activity is the same (MacLean et al. 2003; Prinz et al. 2003; Prinz et al. 2004a; MacLean et al. 2005; Marder and Goaillard 2006; Olypher and Calabrese 2007, 2009). Finally, as suggested by control theory applications to homeostatic regulation in biological systems, ADHR can be intrinsically complex to ensure the robustness of the regulation with respect to variations of the parameters of the regulation, such as for example parameters of activity sensors (El-Samad et al. 2005; Gunay and Prinz 2009). Existing models of ADHR (LeMasson et al. 1993; Liu et al. 1998; Golowasch et al. 1999; Zhang and Golowasch 2007) mimic experimental data, however, the validity and limitations of these models are poorly understood.

Our study was motivated by experimental and modeling studies of ADHR in the neurons of the crustacean pyloric network. This small network with identified neurons (Fig. 1(a)) provides one of the best studied examples of homeostatic regulation. Under normal conditions, the network produces a regular triphasic rhythmic pattern. Permanent blockade of the neuromodulatory inputs that are normally present in the system (Fig. 1(b)) shuts down the network. However, within a few days the network recovers its rhythmic pattern in the continued absence of neuromodulators (Luther et al. 2003; Khorkova and Golowasch 2007; Zhang and Golowasch 2007; Zhang et al. 2008). It has been shown that ionic conductances of individual neurons change in the course of recovery (Mizrahi et al. 2001; Thoby-Brisson and Simmers 2002; Khorkova and Golowasch 2007). The mechanisms underlying these changes are as yet unidentified. Ca^{2+} is likely to play a critical role in the activity-dependent regulation. For example, periodic depolarization of inferior cardiac neurons of the crab *Cancer borealis* upregulates the transient outward current, I_A . Blocking of the Ca^{2+} influx by extracellular Cd^{2+} eliminates the increase of the I_A current density (French et al. 2002).

To better understand general properties of ADHR, we posed and solved a prototypical homeostatic regulation problem for a classical Morris-Lecar (ML) neuronal model (Morris and Lecar 1981). We did not strive to accurately reproduce experimental findings. Our goal was to better understand the regulation problem from the mathematical point of view. Such analysis should advance further theoretical studies of ADHR because even explicitly posing a regulation problem is a challenge (cf. (Zhang and Golowasch 2007)). We also asked how the target of ADHR, initial perturbations to ionic conductances, and parameters of the regulation determine the success or failure of ADHR. We solved the ADHR problem for the ML model and answered the above questions by developing the approach of LeMasson et al. (1993) based on the separation of fast dynamics of the neuron membrane potential and ion channel gating variables from slow dynamics of the regulated neuronal parameters. On the basis of our results, we formulated specific testable questions for subsequent experimental and theoretical studies that should advance our understanding of ADHR.

Parts of this work have been published previously in abstract form (Olypher and Prinz 2008).

2 Results

2.1 A problem of homeostatic regulation in the Morris-Lecar model

Consider the Morris-Lecar model in the following dimensionless form (Rinzel and Ermentrout 1998):

$$\begin{cases} \frac{dv}{dt} = I - 0.5(v+0.5) - g_K w(v+0.7) - g_{Ca} m_\infty(v-1), \\ \frac{dw}{dt} = (w_\infty - w)/\tau. \end{cases} \quad (1)$$

Here v is the membrane potential, w is the activation of the potassium current, I is the external current, g_{Ca} and g_K are the maximal conductances of the calcium and potassium currents. In this study, we considered $g_{Ca} \in [0,3]$ and $g_K \in [0,5]$. The steady state functions w_∞ and m_∞ , and the time constant τ are given by the expressions $w_\infty = 0.5(1 + \tanh((v-0.1)/0.145))$, $m_\infty = 0.5(1 + \tanh((v + 0.01)/0.15))$, $\tau = [\varphi \cdot \cosh((v - 0.1)/0.29)]^{-1}$. In what follows, $I=0.3$, $\varphi=0.333$.

To formulate a problem of activity-dependent homeostatic regulation it is necessary to define the target of the regulation. From a physiological point of view, ADHR should maintain a functional state of the neuron. We assumed that system (1) functions properly when it has stable periodic dynamics. Such dynamics in the ML model may correspond to regular spiking or bursting in biological neurons (Izhikevich 2007).

To define the target of the regulation more precisely, we considered the domain of g_{Ca} and g_K values for which the ML model has stable periodic dynamics. The borders of the domain are formed by the points where system (1) experiences Andronov-Hopf bifurcations (Guckenheimer and Holmes 1983). The border of the oscillatory domain to the left of point G (Fig. 2) is formed by the points where system (1) experiences a supercritical Andronov-Hopf bifurcation. When this border is crossed from left to right, the stable steady state (equilibrium) transforms into the stable periodic state (limit cycle). The amplitude of periodic oscillations gradually increases from zero with the distance from the border. The border of the oscillatory domain to the right of point G is formed by the points where system (1) experiences a subcritical Andronov-Hopf bifurcation. When this border is crossed from right to left, the stable steady state becomes unstable. All the trajectories now converge to the stable periodic state (limit cycle). The amplitude of the corresponding periodic oscillations is not small even immediately after the bifurcation (Fig. 2(b)). To the right of the oscillatory domain, there is a domain of bistability (an opaque stripe), where system (1) either oscillates or is quiescent depending on the initial conditions (Fig. 2(c), third and fourth panels from the top). The domain of bistability in Fig. 2(a) is bounded to the right by the points where system (1) has a limit cycle fold bifurcation. When the line of the limit cycle fold bifurcation is crossed from left to right, the stable limit cycle collides with the unstable limit cycle and both annihilate (Fig. 2(b)).

Oscillations in (1) are characterized by different time-averaged values $\langle I_{Ca} \rangle$ of the calcium current $I_{Ca} = g_{Ca}m_\infty(v - 1)$ (Fig. 2(a)). Let the target oscillatory state be identified by a particular value $\langle I_{Ca} \rangle^*$ of $\langle I_{Ca} \rangle$. The condition $\langle I_{Ca} \rangle = \langle I_{Ca} \rangle^*$ defines not one but multiple points (g_{Ca}, g_K) belonging to the intersection of the isoline $\langle I_{Ca} \rangle = \langle I_{Ca} \rangle^*$ with the oscillatory domain. Further constraints, for example on the period of oscillations, could significantly reduce the set of g_{Ca} and g_K values for which system (1) exhibits the target behavior (Fig. 3). However, experimental and modeling data show that in the living pyloric system functional states are characterized by multiple sets of distinct parameter values (Prinz et al. 2004a; Goaillard and Marder 2006). Accordingly, the only requirement for a target oscillatory regime in our analysis was $\langle I_{Ca} \rangle = \langle I_{Ca} \rangle^*$.

To complete the formulation of the problem of ADHR it is necessary to define perturbations, P , for which the regulation should compensate. Let the “intact” system be in the target, functional and stable state before a perturbation. Some perturbations can affect dynamical variables v and w but not the parameters of the system. In such cases, the internal dynamics return the system to its original dynamical state. This is what constitutes the stability of the state. Regulation of parameters is not required in this case. We did not consider perturbations of v and w in this study. We focused instead on perturbations of g_{Ca} and g_K that push system (1) out of the target state and terminate oscillations. Precise description of P is a part of the solution to the problem of ADHR.

ADHR in system (1) should readjust g_{Ca} and g_K to get the system back to the target state. We assume that the readjustment starts immediately after the end of the perturbation. Solving the regulation problem means finding regulation dynamics of g_{Ca} and g_K such that, in time, system (1) regains its functional state after any perturbation from P . We assume that the regulation has the form $dg_{Ca}/dt = f_{Ca}(t)$ and $dg_K/dt = f_K(t)$; thus the problem is finding appropriate functions f_{Ca} and f_K . We show below that in accord with intuition the choice of f_{Ca} and f_K determines the perturbations P for which the regulation works. Conversely, the choice of P determines which f_{Ca} and f_K provide a solution to the ADHR problem.

We considered a simple model of control as in (LeMasson et al. 1993):

$$\begin{cases} \frac{dg_{Ca}}{dt} = \alpha_{Ca} (I_{Ca} - \langle I_{Ca} \rangle^*), \\ \frac{dg_K}{dt} = -\alpha_K (I_{Ca} - \langle I_{Ca} \rangle^*), \end{cases} \quad (2)$$

where the absolute values of α_{Ca} , α_K are the rate constants. Here, the calcium current, I_{Ca} , is considered as a correlate of the intracellular Ca^{2+} concentration, $[Ca]$; below, we analyze a regulation explicitly based on $[Ca]$. The absolute values of the parameters α_{Ca} and α_K in Eq. (2) are assumed to be small to correspond to slow (on the scale of days) changes in the conductances. Under this assumption, the system of Eqs. (1), (2) splits into the “fast” subsystem (1) and the “slow” subsystem (2). In the fast subsystem, g_{Ca} and α_K can be approximately considered as constants. In the slow subsystem, fast changes of the right-hand sides of the equations, caused by fast dynamics, can be averaged out. The split of the system into the fast and slow subsystem allows for a geometric solution to the problem (1), (2).

2.2 Geometric solution to the problem of homeostatic regulation in the Morris-Lecar model

An approximate solution to the formulated problem can be obtained with the help of a protractor and a ruler (Fig. 4). Indeed, Eq. (2) imply that the point $(g_{Ca}(t), g_K(t))$ moves along a straight line

$$g_K = -\frac{\alpha_K}{\alpha_{Ca}} (g_{Ca} - g_{Ca,0}) + g_{K,0} \quad (3)$$

where $g_{Ca,0} = g_{Ca}(0)$ and $g_{K,0} = g_K(0)$. The point $(g_{Ca}(t), g_K(t))$ moves along the line (3) starting from the point $(g_{Ca,0}, g_{K,0})$ until it reaches the isoline $I_{Ca} = \langle I_{Ca} \rangle^*$. Note that in the target oscillatory regime, I_{Ca} oscillates around $\langle I_{Ca} \rangle^*$ so that the equality $I_{Ca} = \langle I_{Ca} \rangle^*$ holds only in the temporal average. Conductances g_{Ca} and g_K oscillate as well, though the amplitudes of oscillations are small because α_{Ca} and α_K are small; for example in Fig. 4(b), the amplitudes of oscillations of g_{Ca} and g_K are approximately equal to 0.003.

The regulation (2) is successful only if line (3) crosses the target isoline $I_{Ca} = \langle I_{Ca} \rangle^*$ in the domain of oscillations. This necessary condition constrains P to a stripe formed by all the lines with the slope $-\alpha_K/\alpha_{Ca}$ crossing the target isoline. As we show below, in some cases the geometry of P can indeed be as simple as a stripe, but in other cases it can be more complex.

For further analysis, it is useful to consider the dynamics of the conductances g_K and g_{Ca} in the time-averaged system (2). Given that g_K is determined by g_{Ca} according to (3), it is sufficient to consider only one equation from (2),

$$\frac{dg_{Ca}}{dt} = \alpha_{Ca} (\langle I_{Ca} \rangle - \langle I_{Ca} \rangle^*) \quad (4)$$

with the calcium current I_{Ca} substituted with its time-averaged value $\langle I_{Ca} \rangle$. $\langle I_{Ca} \rangle$ does not depend on the membrane potential v because of the averaging. It is known that solutions to (4) are close to solutions to (2) when α_{Ca} and α_K are small, which is the case here (Guckenheimer and Holmes 1983). A steady state $\langle I_{Ca} \rangle = \langle I_{Ca} \rangle^*$ in Eq. (4) is stable if α_{Ca} is positive and $d\langle I_{Ca} \rangle / dg_{Ca}$ is negative. When $\langle I_{Ca} \rangle^* = -0.25$ and $\alpha_K = -0.01$, $\alpha_{Ca} = 0.005$, all the points of the target isoline inside the oscillatory domain are stable. This can be established just by noticing that the color for $\langle I_{Ca} \rangle$ is darker to the left of the isoline than to the right of the target isoline $\langle I_{Ca} \rangle = -0.25$ (Fig. 5(a)). Thus in this example, P consists of all the points outside the domain of oscillations that belong to the lines with slope $-\alpha_K/\alpha_{Ca}$ crossing the target isoline.

Figure 5(b) provides an example where two pieces of the target isoline form the border of P . Here $\langle I_{Ca} \rangle^* = -0.75$, $\alpha_{Ca} = 0.005$, $\alpha_K = 0.05$. Potential elements of P are the points between the two dashed lines below the border of the oscillatory domain. Any line with the slope -10 inside this area crosses the isoline $\langle I_{Ca} \rangle^* = -0.75$ at two points. In the upper point, $d(\langle I_{Ca} \rangle) / dg_{Ca} < 0$. Hence the upper point is stable. In the lower point $d(\langle I_{Ca} \rangle) / dg_{Ca} > 0$. Hence, the lower point is unstable. The “unstable” piece of isoline $\langle I_{Ca} \rangle^* = -0.75$ limits P from below.

Finally, Fig. 5(c) provides an example where the set P is not convex. In this example, $\langle I_{Ca} \rangle^* = -0.5$, $\alpha_{Ca} = 0.005$, $\alpha_K = -0.0147$. Potential elements of P are the points between the two dashed lines below the border of the oscillatory domain. Some lines with the slope $-\alpha_K/\alpha_{Ca} = 2.94$ inside this area cross the isoline $\langle I_{Ca} \rangle^* = -0.5$ at three points; the middle point lies in the area of bistability of the ML model. Analysis of the sign of $d(\langle I_{Ca} \rangle) / dg_{Ca}$ in these points show that the middle point is unstable while the two other points are stable. As a result, P in this case is a relatively small and nonconvex set.

Remarks—First, the geometric solution considered here is an asymptotic one. The smaller coefficients α_{Ca} and α_K are the better the geometric solution approximates the exact solution. For large values of α_{Ca} and α_K corresponding to fast conductance regulation, geometric considerations based on Fig. 2 are inappropriate. For example, for $\alpha_{Ca} = \alpha_K = 2.5$, $g_{Ca,0} = g_{K,0} = 2$, and $\langle I_{Ca} \rangle^* = -0.25$ the system (1), (2) does not converge to an oscillatory solution at all (Fig. 6). Instead, it converges to a stable steady state in which $I_{Ca} = -0.25$ (Fig. 6(b1)). The steady state values of conductances are $g_{Ca} = 3.43$ and $g_K = 0.57$. These values of conductances are well inside the oscillation domain (black cross in Fig. 6(a)). Why, then, does the system not oscillate? The explanation is that for large values of α_{Ca} and α_K the changes of g_{Ca} and g_K are not slow. As a result, the ML model with constant conductances g_{Ca} and g_K does not approximate the dynamics of Eq. (1) with the conductances evolving according to Eq. (2). Consequently, the bifurcation diagram and isolines of $\langle I_{Ca} \rangle$ in Fig. 2 become inapplicable. Interestingly, for just slightly slower regulation $\alpha_{Ca} = \alpha_K = 2.25$ the solution of system (1), (2) does converge to a stable oscillatory regime (Fig. 6(b2)). The finding of the exact values of α_{Ca} and α_K for which regulation (2) brings the system to oscillations required bifurcational analysis of the full system (1), (2) which was beyond the scope of the current study, in which we constrained ourselves to studying slow ADHR only.

Second, for appropriate initial perturbations, regulation can be achieved by changing only one conductance. Indeed, a general form of Eq. (3) is $\alpha_{Ca}(g_K - g_{K,0}) + \alpha_K(g_{Ca} - g_{Ca,0}) = 0$. For example, when $\alpha_K = 0$, g_{Ca} changes along the line $g_K \equiv g_{K,0}$, and the border for P is parallel to the axis g_{Ca} .

Third, regulation (2) is robust. It is robust in that there is no need to finely tune coefficients α_{Ca} and α_K to achieve the control goal. The values of these coefficients can vary over wide ranges. Each choice of α_{Ca} and α_K however changes the domain of perturbations P compensated by the regulation (Fig. 4(b) and (c)).

Finally, similar geometric considerations hold in the case when conductances are regulated in proportion to the product of the difference $I_{Ca} - \langle I_{Ca} \rangle^*$ and the conductances themselves:

$$\begin{cases} \frac{dg_{Ca}}{dt} = \alpha_{Ca} (I_{Ca} - \langle I_{Ca} \rangle^*) g_{Ca}, \\ \frac{dg_K}{dt} = -\alpha_K (I_{Ca} - \langle I_{Ca} \rangle^*) g_K. \end{cases} \quad (5)$$

In this case, not the conductances themselves but their logarithms are constrained to a line

$$\ln(g_K) = -\frac{\alpha_K}{\alpha_{Ca}} (\ln(g_{Ca}) - \ln(g_{Ca,0})) + \ln(g_{K,0}).$$

The approximate solution to (1), (4) can be also found with the help of a protractor and a ruler. In this case, however, it must be done in the plane $(\ln(g_{Ca}), \ln(g_K))$.

2.3 Details of transitions to the target regime during slow regulation are determined by specific bifurcations in the fast subsystem

As we have shown above, the regulation (2) for system (1) can be a success when g_{Ca} and g_K correlate and when g_{Ca} and g_K anti-correlate, though for different perturbations. Can both cases occur in the living neuron? The knowledge of details of transitions to the target regime during the recovery could help to answer this question.

In the case of the ML model, considered here, correlated changes of g_{Ca} and g_K lead to oscillations predominantly through a supercritical bifurcation in the fast system, while anti-correlated changes of g_{Ca} and g_K lead to oscillations predominantly through a subcritical bifurcation in the fast system. This is a consequence of the geometry of the bifurcational diagram and the isolines of $\langle I_{Ca} \rangle$. Do these two transitions to oscillations look differently in system (1), (2)?

Simulations show that the transitions are quite distinct though smeared by the slow regulation. Figure 7 illustrates the case with $\langle I_{Ca} \rangle^* = -0.25$, $\alpha_K = \alpha_{Ca} = 0.005$ and $\alpha_K = \alpha_{Ca} = 0.00005$, and initial values of g_{Ca} and g_K at the line $g_K = 3.5 - g_{Ca}$. Figure 7(a) shows that the slow increase of g_{Ca} and decrease of g_K lead to a slow increase of the amplitude of oscillations, completely in accord with the intuition on a transition to oscillations through a supercritical Andronov-Hopf bifurcation (Fig. 2(b)). The transition to oscillations through a subcritical Andronov-Hopf bifurcation does not happen through a sudden emergence of oscillations as it would be the case in the classical ML model (Fig. 2(b)). Instead, the amplitude increases gradually (Fig. 7(b)). However, the increase of the amplitude is much more rapid compared to the transition to oscillations through the supercritical Andronov-Hopf bifurcation. After the rapid increase, the amplitude starts to decrease, in accord with the amplitude map (Fig. 3(b)). In the case of the supercritical Andronov-Hopf bifurcation the amplitude increases monotonically. Finally, a slower rate of the regulation slows down the changes of the amplitude in both cases.

We see that assumptions on regulation and initial perturbations predict specific details of the transition to oscillations. Vice versa, the knowledge of the transition informs on the location of the transition and hence, possible regulation and initial perturbations.

2.4 “Bouting” in the Morris-Lecar model with homeostatic regulation of ionic conductances

In what follows we provide an example of how specific details of regulation in living neurons can be mimicked and explored in a model using the knowledge of the geometry and dynamics of the regulation.

When the pyloric network in crabs recovers from the termination of modulatory input, the recovery is accompanied by episodic bouts of the network activity (Luther et al. 2003). During each bout of activity the neurons of the network burst in the triphasic pattern of the pyloric rhythm for some time, and then become silent again. The full recovery with regular uninterrupted bursting occurs after a number of bouts.

We hypothesize that isolated AB and PD neurons that form the pacemaker kernel of the pyloric network (Miller and Selverston 1982) also exhibit bouts of activity during their recovery. The above analysis of system (1), (2) suggests that these bouts of neuronal activity could occur because of repetitive entries into and exits out of the domain in the space of parameters where these neurons burst. What regulation could lead to “bouting” in the ML model?

Regulation (2) is not sufficient to mimic bouting. Indeed, bouting implies repetitive and significant increases and decreases of the calcium conductance g_{Ca} . If g_{Ca} is driven by (2) then as we showed earlier, the average value of g_{Ca} changes monotonically until $\langle I_{Ca} \rangle$ reaches $\langle I_{Ca} \rangle^*$ (Fig. 4(b) and (c)). To overcome this limitation, we considered a more complex regulation involving intracellular calcium concentration $[Ca]$ (here and below $[Ca]$ refers to the cytosolic concentration of Ca^{2+} ; see Section 3 for further details):

$$\begin{cases} \frac{dg_{Ca}}{dt} = -\alpha_{Ca} ([Ca] - \langle [Ca] \rangle^*), \\ \frac{dg_K}{dt} = \alpha_K ([Ca] - \langle [Ca] \rangle^*), \\ \frac{d[Ca]}{dt} = -\gamma I_{Ca} - [Ca]/\tau_{Ca}. \end{cases} \quad (6)$$

The target of the regulation (6) is a specific average value of $[Ca]$, $\langle [Ca] \rangle^*$; γ , α_K , α_{Ca} , and τ_{Ca} are positive constants such that the dynamics in (6) is much slower than the dynamics in (1). When $\gamma=0.01$, $\alpha_K=0.01$, $\alpha_{Ca}=0.01$, $\tau_{Ca}=98.4$, $\langle [Ca] \rangle^*=0.48$, $g_{Ca,0}=2$, $g_{K,0}=1.5$, the dynamics of system (1), (6) exhibits bouts of oscillations (Fig. 8). According to the first two equations in (6) and Eq. (3), conductances g_{Ca} and g_K move along the line

$$g_K = -(g_{Ca} - 2) + 1.5 \quad (7)$$

The line (7) crosses the target isoline $\langle [Ca] \rangle^*=0.48$ in the domain of bistability. The isoline is not shown. It is slightly left to the isoline $\langle I_{Ca} \rangle^*=-0.5$ because the third equation of (6) implies that in the limit when g_{Ca} and g_K do not change on average, $\langle I_{Ca} \rangle = -\langle [Ca] \rangle / (\tau_{Ca}\gamma)$. Hence, $\langle [Ca] \rangle^*=0.48$ corresponds to the value $\langle I_{Ca} \rangle^*=-0.49$. The point of the intersection of (7) and the isoline $\langle [Ca] \rangle^*=0.48$ (black cross in Fig. 8(a)) is a stable steady point for the equation $dg_{Ca}/dt = -\alpha_{Ca}(\langle [Ca] \rangle - 0.48)$ because $d(\langle [Ca] \rangle)/dg_{Ca}$ is positive in this point. Bouting occurs because the dynamics of $[Ca]$ is slightly slower than the dynamics of the conductances. This gives the system (7) some inertia, which first brings the point $(g_{Ca}(t), g_K(t))$ to the oscillatory domain and then pulls it back to the silent domain (Fig. 8(b)). When the point $(g_{Ca}(t), g_K(t))$ returns back, oscillations are prolonged because of the bistability (Figs. 2(b) and 8(c)). Because of the slow drift of the point $(g_{Ca}(t), g_K(t))$ up the line (7), at a certain moment of time $(g_{Ca}(t), g_K(t))$ is not able to reach the silent domain, and this is the moment of complete recovery, i.e. transition to uninterrupted oscillations. If the point $(g_{Ca}(t), g_K(t))$ did not drift into the side of the oscillatory domain but change periodically the resulting dynamics

would correspond to the mechanism of periodic elliptic bursting described by Rinzel and Ermentrout (1998; see their Fig. 7.10)

The observed bursting was sensitive to the parameters of regulation (6). For example, when τ_{Ca} increased from 98.39 through 98.41 the number of bouts decreased from 30 to 13. When $\tau_{Ca}=100$, so that the rates of dynamics of the conductances and $[Ca]$ in (7) are equal, bouts of oscillations in (1), (6) did not converge to normal, uninterrupted oscillations.

As in the case of system (2), the fast/slow analysis allows us to determine the set of initial conditions P which are compensated by control (6). Fast changes of I_{Ca} based on fast changes of the membrane potential v can be averaged over in system (6) with $\langle I_{Ca} \rangle$ substituting for I_{Ca} :

$$\begin{cases} \frac{dg_{Ca}}{dt} = -\alpha_{Ca} ([Ca] - \langle [Ca] \rangle^*), \\ \frac{d[Ca]}{dt} = -\gamma \langle I_{Ca} \rangle - [Ca]/\tau_{Ca}. \end{cases} \quad (8)$$

Straightforward analysis shows that system (8) has a stable steady state in which g_{Ca} is the solution to the equation $-\gamma \langle I_{Ca} \rangle (g_{Ca}) - \langle [Ca] \rangle^*/\tau_{Ca} = 0$ and $[Ca] = \langle [Ca] \rangle^*$. The eigenvalues, λ_1 and λ_2 , of the system's Jacobian in the steady state conform to the equalities $\lambda_1 + \lambda_2 = -1/\tau_{Ca}$, $\lambda_1 \lambda_2 = -\alpha_{Ca} d(\langle I_{Ca} \rangle)/dg_{Ca}$. Hence, for positive τ_{Ca} , α_{Ca} , γ the eigenvalues λ_1 and λ_2 are both negative when $d(\langle I_{Ca} \rangle)/dg_{Ca}$ is negative along the line

$g_K = -\frac{\alpha_K}{\alpha_{Ca}} (g_{Ca} - g_{Ca,0}) + g_{K,0}$ (see Eq. (3)), and accordingly the target steady state is stable. It is easy to check that $d(\langle I_{Ca} \rangle)/dg_{Ca}$ is negative in most of the cases. Exceptions are provided by a small set of regulations with $\alpha_K > \alpha_{Ca}$ and particular values of $\langle [Ca] \rangle^*$ as in the example in Fig. 5(c), where $d(\langle I_{Ca} \rangle)/dg_{Ca}$ is positive in the magenta portion of the isoline.

3 Discussion

We have presented a theoretical and computational solution to a prototypical problem of a slow activity-dependent homeostatic regulation (ADHR) for the Morris-Lecar (ML) model. The solution reveals geometric and dynamic properties of activity-dependent homeostatic regulation (ADHR). In particular, we showed explicitly how the activity target, initial perturbations to ionic conductances, and parameters of the conductance regulation determine the success or failure of ADHR. Our approach is quite general and can be applied to more complicated neuronal models. It is based on the slowness of the regulation compared to the neuronal dynamics, and the assumption that a complex regulation of neuronal parameters is approximated by a linear combination of a fixed number of regulatory mechanisms.

Our approach is similar to that of LeMasson et al. (1993). The main difference is that to gain deeper insight into the mathematical properties of ADHR, we considered perturbations of the conductances only, but not perturbations of reversal potentials of ionic currents as in (LeMasson et al. 1993). Accordingly, the domain of ionic conductances where our model had periodic oscillations was not affected by perturbations. We also advanced the analysis of the regulation by exploiting the well-known bifurcational properties of the ML model. The choice of the ML model was convenient but not critical; XPPAUT (Ermentrout 2002) and CONTENT software packages (Kuznetsov et al. 1996) allow to perform a bifurcational analysis for quite complex neuronal models (Cymbalyuk et al. 2002; Fernandez et al. 2007).

3.1 Geometry arising from a limited number of control mechanisms: low-dimensional manifolds linking the initial and target values of regulated parameters

The geometric analysis in this study exploited a general fact that neuronal parameters varying in the course of ADHR belong, with some accuracy, to low-dimensional linear manifolds. The linearity of these manifolds follows from a natural assumption that the regulated parameters $g_i = g_i(t)$, $i=1, \dots, m$, are controlled by a linear superposition of several regulating mechanisms $f_j = f_j(t)$, $j=1, \dots, n$:

$$\begin{cases} \frac{dg_1}{dt} = a_{11}f_1 + a_{12}f_2 + \dots + a_{1n}f_n, \\ \vdots \\ \frac{dg_m}{dt} = a_{m1}f_1 + a_{m2}f_2 + \dots + a_{mn}f_n; \end{cases}$$

here a_{ij} are constants. Such linearization can be an acceptable approximation to the actual mechanism of regulation (cf. Liu et al. 1998). The dimension of the linear manifold that contains the g_i 's does not exceed the number of the regulating mechanisms; the exact value is equal to the rank of the matrix $A = (a_{ij})$. For example, in the model of ADHR in (Liu et al. 1998) $m=7$, $n=3$, and the dimension of the manifold was equal to three. Our work shows examples of one-dimensional manifolds.

The concept of a linear manifold containing regulated parameters naturally extends to the case when the changes of parameters are proportional to parameters themselves, as in Eq. (5). In this case linear manifolds contain not the parameters but the natural logarithms of the regulated parameters. Interestingly, correlations between the logarithms of conductances but not between conductances themselves were indeed observed in stomatogastric neurons (J. Golowasch, personal communication).

One-dimensional manifolds of regulated parameters can be found in earlier models of ADHR, sometimes without explicit mention. For example in the model of ADHR in (Liu et al. 1998), the maximal conductances of the currents with slow dynamics, namely the calcium-dependent and transient potassium currents, and a hyperpolarization-activated current, belong to a line. The dimension of the manifold is equal to one because of particular values of the coefficients of the linear combination of regulating mechanisms (Eq. (3) and Table 1 in (Liu et al. 1998)). For close values of the coefficients, one-dimensional manifolds can be considered as initial approximations. In another model of ADHR, the maximal conductances of a calcium, $\overline{G_{Ca}}$, and potassium, $\overline{G_K}$, current were the only two regulated conductances (Zhang and Golowasch 2007). In that model, $\overline{G_{Ca}}$ was inversely proportional to $\overline{G_K}$. In other words, the logarithms of $\overline{G_{Ca}}$ and $\overline{G_K}$ belonged to a straight line with a slope -1 .

Recent experimental data support the possibility that certain subsets of regulated parameters can belong to one-dimensional manifolds and accordingly be subject to a common control. Schulz et al. (2007) have found multiple correlations between the expression levels of mRNA's corresponding to certain ion current channels in stomatogastric (STG) neurons of the crab. As a result, the levels of expression concentrate near a line segment in the space of mRNA expression levels (Fig. 4(b) in (Schulz et al. 2007)). That could mean that all cells have the same regulatory mechanism which started to control mRNAs from the same initial values. Different locations along the line in the space of mRNA expression levels then might mean that this mechanism acted with different intensity in different animals. As in the case with conductances, the levels of mRNA expression not necessarily change monotonically in time. Pairwise correlations between parameters have also been observed for STG neuronal models by brute force exploration of the parameter space of the model (Prinz et al. 2008).

A necessary condition for the success of ADHR is the intersection of the manifold with the regulated parameters, M_{RP} , with the domain of parameters where the neuron has the target activity. As we have noted recently, the target domain is generically a smooth manifold, at least locally (Olypher and Calabrese 2007). For the ML model considered, this was a portion of the isoline corresponding to a specific value of the averaged calcium current or the averaged intracellular calcium concentration. As we showed here, the target domain can be at least partially identified by constructing a bifurcation diagram (Fig. 2). Bifurcation diagrams can be built for quite complex neuronal models using XPPAUT (Ermentrout 2002) and CONTENT software packages (Kuznetsov et al. 1996) (see e.g., (Cymbalyuk et al. 2002; Fernandez et al. 2007)). These packages allow the identification and localization of bifurcation boundaries for three simultaneously varied parameters at most. This limitation reflects the increasing complexity of bifurcation analysis with the increase of the number of simultaneously varied parameters (Arnold et al. 1994). ADHR may involve simultaneous change of more than three parameters. For example, four ionic conductances changed significantly in the course of functional recovery of stomatogastric neuron (Khorkova and Golowasch 2007). However, even in the case of more than three regulated parameters, the border of the target domain will mostly consist of hypersurfaces determined by simple bifurcations as in Fig. 2, where the most complex bifurcation determines only one point, G, of the border. A geometric description of the target domains for data coming from brute force exploration of parameter spaces (Prinz et al. 2003; Prinz et al. 2004a) is an open problem (Taylor et al. 2006). Some description can be obtained computationally by finding convex hulls of the appropriate parameter subsets (Barber et al. 1996).

As we have explicitly shown in the case of the ML model, the efficiency of the control is strongly determined by the set of perturbations this control is supposed to compensate. This is the third key component of the ADHR geometry, along with M_{RP} and the domain of target values of the regulated parameters. We found that for some parameters of the regulation (2), the set of perturbations, P , that can be compensated by the regulation, has complex geometry (Fig. 5(c)). Complex geometry of P such as in Fig. 5(c) seems incompatible with the experimentally observed robustness of ADHR. Future experiments should explore how specific perturbations tolerated by neurons are.

We also found that perturbations determine specific transitions to the target state of the neuron. In our model, some perturbations led to slow increase of the oscillation amplitude while others led to rapid increase of the oscillations during the transition from the quiescent state. This is why experimental studies of how the recovery depends on specific perturbations will be important for revealing the mechanisms of ADHR.

Our model shows that depending on perturbations, the conductances of the potassium and calcium currents should either correlate (Fig. 5(a) and (c)) or anti-correlate (Figs. 4(a) and 5 (b)) for the success of the regulation. Experimental data on the functional recovery of stomatogastric neurons shows correlated changes of ionic conductances only (MacLean et al. 2003; MacLean et al. 2005; Khorkova and Golowasch 2007; Schulz et al. 2007). Our results thus raise an important question: whether the model does not account for specific genetic and epigenetic mechanisms favoring correlated over anti-correlated changes of the conductances, or whether living neurons do not recover from perturbations which would require anti-correlated changes of the conductances.

3.2 Dynamics of homeostatic regulation: slow and fast subsystems

In this work, we exploited a separation of activity-dependent homeostatic regulation into slow and fast processes. We considered all the endogenous neuronal dynamics as fast compared to slow changes of parameters in the course of regulation. The averaging method provides a tool for the effective exploration of the fast and slow subsystems separately. This method has proved

to be useful in many problems of neuronal activity such as for example the analysis of bursting (Rinzel and Ermentrout 1998); see also recent results on analysis of the persistent states of activity (Cressman et al. 2009; Ullah et al. 2009).

Provided the ratio of characteristic times of the fast and slow subsystems is low, as is the case for slow ADHR, the solution to the averaged system well approximates the exact solution in two main cases: when the fast subsystem has a stable steady state (Tikhonov's theorem) or a stable periodical regime (Pontryagin-Rodygin's theorem) (see (Izhikevich 2007)). It is well known that near the state transitions the accuracy of averaging requires special consideration. Our analysis of the averaged systems (4) and (8) was in agreement with the simulations. It suggests that the accuracy remained reasonable even in the presence of state transitions.

Dynamics of ADHR typically involve transitions of neuronal dynamics from one state to another. As we showed, these transitions are associated with bifurcations of the fast subsystem during the slow evolution of the regulated parameters. Specific bifurcations mean specific parameter changes in specific locations of the parameter space. Such information narrows the domain of the initial perturbation of neuronal parameters and the way parameters are regulated. Our study shows that although the characteristic behavior of the fast subsystem during bifurcations can be smeared by the slow dynamics of regulated neuronal parameters, different bifurcations can still be distinguishable (Fig. 7). Intracellular recordings of neurons when they start to recover their functional spiking activity, and bifurcational analysis of adequate neuronal models can specify transitions between dynamical states of the neurons during ADHR.

A perhaps even more feasible way of exploring details of transitions would be using dynamic clamp (Prinz et al. 2004b). Our analysis, and the model of the pyloric network pacemaker AB neuron (Zhang et al. 2008) predict that even the variation of one conductance can be sufficient for ADHR. In the experiment, one could selectively block various currents in isolated STG neurons after decentralization, and then add the blocked currents with the dynamic clamp (see, e.g. (Sorensen et al. 2004; Olypher et al. 2006)). A slow increase of the conductance of the blocked current could lead to the recovery of the neuron. In this way, one might explore transitions to the functional state of the neuron in great detail, and accurately assess the role of the current by comparing the original value of conductance and the value sufficient for the recovery of the neuron.

Further theoretical analysis of ADHR should benefit from control theory (Fradkov and Pogromsky 1998). The theory provides an adequate framework for the problem of ADHR. For example, regulation (6) can be considered as an integral feedback control of the rate of conductance changes driven by the difference between the current calcium concentration in the neuron and the target value of the concentration (cf. (El-Samad et al. 2002)).

3.3 Potential homeostatic regulation mechanisms in living neurons

We showed that even in our simple model of ADHR there are multiple ways of activity-dependent homeostatic regulation. Subcellular mechanisms underlying such regulation in living neurons are a subject of intense research. At least some of these mechanisms may involve Ca^{2+} -dependent signaling networks that transform the changes of membrane depolarization into transcriptional activity in the nucleus (Fields et al. 2005). Signaling in these networks depends on Ca^{2+} -dependent molecules, including Ca^{2+} /calmodulin-dependent protein kinases, which ultimately act upon intra-nuclear targets. Spatio-temporal changes in Ca^{2+} depend on the calcium influx through channels in the neuronal membrane, fluxes through intracellular compartments such as endoplasmic reticulum and mitochondria, and release and uptake from internal Ca^{2+} stores. All these processes are potential targets of regulation. For example, maintenance of the endoplasmic reticulum Ca^{2+} concentration was at the core of homeostatic regulation in a recent modeling study by (Zhang and Golowasch 2007; Zhang et al. 2008).

Activity-dependent calcium regulation is likely important for ADHR not only in individual neurons but also in neuronal networks because variations of calcium concentration link intrinsic and synaptic plasticity (Petersen and Verkhratsky 2007; Nelson and Turrigiano 2008).

Agents other than calcium might be also involved in ADHR. For example, the extracellular concentration of tumor necrosis factor alpha (TNF- α) correlates with neuronal activity (Stellwagen and Malenka 2006). Another study reports a calcium-independent long-lasting increase of neuronal excitability in Aplysia (Kunjilwar et al. 2009). Finally, not only ionic conductances but parameters of the current activation and inactivation kinetics can be regulated. For example (McAnelly and Zakon 2000) have reported a coregulation of sodium inactivation and potassium activation time constants in the electric organ cells of weakly electric fish. Further experimental and theoretical work is necessary to elucidate various mechanisms of activity-dependent homeostatic regulation in neurons.

Our study suggests the following steps for the theoretical analysis of slow ADHR in neurons. 1) Select two neuronal parameters, say P1 and P2, which are assumed to change most during the regulation. 2) On the basis of experimental data identify the target dynamical state of the neuron. 3) Define a neuronal model whose parameters include P1 and P2. Use bifurcational analysis to determine the domain in the plane (P1, P2) where the model has target dynamics. 4) Choose a functional and its value(s) which might correspond to the target dynamics; in the present study, the average value of the calcium current was such a functional. 5) If neuronal dynamics during ADHR change qualitatively then determine bifurcations in the bifurcational diagram which are most consistent with the changes. These bifurcations constrain the initial values of P1 and P2 and the trajectory of the point (P1, P2). 6) Consider possible approximations of the (P1, P2) trajectory by lines in Cartesian or logarithmic coordinates. For such approximations, the simplest control mechanism would be a proportional control where the derivatives of the parameters P1 and P2 are proportional to the difference between the momentary and target value of the functional as in (2), or to the product of the difference and the parameter as in (5). 7) Check if such model matches with the experiment and what are the predictions of the resulting model of ADHR.

4 Methods

The Morris-Lecar model was simulated with the Matlab (MathWorks, Natick, MA) solver `ode15s` with the absolute and relative tolerances equal to 10^{-8} . The initial conditions for most of the simulations were the same: $v(0) = -0.1$, $w(0) = 0$. Except for the bistability domain, initial values were of no importance because of the global stability of dynamical regimes.

In all simulations, the first 100 units of time were considered as an interval sufficient for stabilization of the pattern and were discarded. For the analysis we used the next 100 units of time, T . Low variability of the period in this range confirmed the convergence to a stable regime. Time-averaging for the calcium current, $\langle I_{Ca} \rangle$, was performed by integrating the values of the current over T and dividing by 100. This averaging interval included more than ten oscillations given the period of oscillations did not exceed ten (see Fig. 3(a)). For the integration, we used the trapezoid method with the integration step 0.01. In Figs. 2(a) and 3, g_{Ca} varied from 0 to 3 with step 0.1 and g_K varied from 0 to 5 with step 0.1. For these simulations we used a high-performance Emory University cluster with 256 nodes. To generate smooth and colored diagrams in the plane of g_{Ca} and g_K we used the Matlab function *surf*. For the bistability domain, we did not calculate the time-averaged values of the calcium current, $\langle I_{Ca} \rangle$. Bifurcation diagrams were generated with the packages XPPAUT (Ermentrout 2002) and CONTENT (Kuznetsov et al. 1996).

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Abbreviations

ADHR	activity-dependent homeostatic regulation
ML	model Morris-Lecar model
STG	stomatogastric

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Fig. 1.

The stomatogastric ganglion of crustaceans as a model system for studying activity-dependent homeostatic regulation in neurons. **(a)** Schematic of the pyloric network and its typical pattern of activity. All synapses in the circuit are inhibitory. **(b)** Location of the stomatogastric ganglion (STG), within the stomatogastric nervous system. Decentralization by cutting the stomatogastric nerve (stn) terminates modulatory input to STG neurons. AB, anterior burster interneuron; PD, pyloric dilator neuron; LP, lateral pyloric neuron; PY, pyloric neuron; Ach, acetylcholine (PD only); Glu, glutamate (all but PD)

Fig. 2.

Average calcium current $\langle I_{Ca} \rangle$ in the plane of g_{Ca} and g_K and bifurcational diagram for the Morris-Lecar model (1). **(a)** In the interior of the parabolic-like curve system (1) has stable oscillations (“Oscillations”). The points on the left (right) border of the oscillatory domain are the points of a super- (sub-) critical Andronov-Hopf bifurcation. At point G these bifurcations coalesce. In the opaque stripe, system (1) converges to an oscillatory regime or a steady state depending on the initial conditions. In the rest of the area, system (1) has a stable steady state. Dashed white line marks $g_K = 3$. The colorcode and isolines are for $\langle I_{Ca} \rangle$. **(b)** Maximal and minimal values of the membrane potential v for $g_K = 3$ and $g_{Ca} \in [0, 3]$. Stable steady state (solid line), unstable steady state (dashed line), stable limit cycle (filled circles), unstable limit cycle (open circles). AHsup, Andronov-Hopf supercritical bifurcation; AHsub, Andronov-Hopf subcritical bifurcation; limit cycle fold, limit cycle fold bifurcation. **(c)** Limit behavior of v and $\langle I_{Ca} \rangle$ for g_K and g_{Ca} corresponding to open circles in (A): $g_{Ca} = 0.12, 0.68, 1.44, 1.44, 2.63$ (from top to bottom); in all the cases $g_K = 3$. For $g_{Ca} = 1.44$ (a point in the area of bistability) two sets of initial conditions were used: $v(0) = 0.07, w(0) = 0.4$ (third panel counting from the top), and $v(0) = 0.1, w(0) = 0.5$ (fourth panel counting from the top); v (thick line), and I_{Ca} (thin line); dashed line stands for 0; $t = 0$ corresponds to $t = 100$ in simulations (see Section 4)

Fig. 3. Characteristics of the stable dynamic regimes in the Morris-Lecar model (1) for different values of g_{Ca} and g_K . (a) Period and (b) amplitude of oscillations, (c) maximal membrane potential, (d) minimal membrane potential. The borders of the dynamic regimes are the same as in Fig. 2. All entities are dimensionless

Fig. 4.

A simple activity-dependent homeostatic regulation mechanism in the ML model with negative correlation between the potassium and calcium conductances. Regulated conductances g_{Ca} and g_K are constrained to a line with the slope -1 . The target value of the average calcium current $\langle I_{Ca} \rangle^*$ is equal to -0.25 ; $\alpha_K = \alpha_{Ca} = 0.005$. (a) Trajectories of the point $(g_{Ca}(t), g_K(t))$ during regulation for different initial values $(g_{Ca,0}, g_{K,0})$ (triangle, square, and circle). Control (2) returns the system to an oscillatory regime with $\langle I_{Ca} \rangle^* = -0.25$ for all initial values between the dashed lines. Arrows show the directions of the evolution of $(g_{Ca}(t), g_K(t))$. The set of perturbations which are compensated by regulation (2) is in green. (b–d): Time-dependence of the membrane potential v (top), conductances g_{Ca}, g_K (middle), and I_{Ca} (bottom). (b) $g_{Ca,0}=0.2, g_{K,0}=5$; triangle in (a). (c) $g_{Ca,0}=2, g_{K,0}=2$; square in (A). (d) $g_{Ca,0}=1, g_{K,0}=1$; circle in (A). Control (2) does not restore oscillations though the target $\langle I_{Ca} \rangle^* = -0.25$ is achieved. Red dashed line: $I_{Ca} = -0.25$

Fig. 5.

Examples of perturbations of the conductances g_{Ca} and g_K compensated by the regulation (2). The sets of perturbations which are compensated by regulation (2) are in green. **(a)** $\langle I_{Ca} \rangle^* = -0.25$, $\alpha_{Ca} = 0.005$, $\alpha_K = -0.01$. **(b)** $\langle I_{Ca} \rangle^* = -0.75$, $\alpha_{Ca} = 0.005$, $\alpha_K = 0.05$. **(c)** $\langle I_{Ca} \rangle^* = -0.5$, $\alpha_{Ca} = 0.005$, $\alpha_K = -0.0147$. Stable (attracting) points in the target isolines are in white, unstable (repelling) points are in magenta. Arrows show the directions of the evolution of $(g_{Ca}(t), g_K(t))$.

Fig. 6.

Inapplicability of the geometric method for fast regulation of conductances. **(a)** Color coding and isolines of the average calcium current $\langle I_{Ca} \rangle$ are as in Fig. 2. The two trajectories of the point $(g_{Ca}(t), g_K(t))$ during the regulation (2) with $\langle I_{Ca} \rangle^* = -0.25$ starting from the initial values $g_{Ca,0} = g_{K,0} = 2$ (square) for different rate constants (see **b**) are visually indistinguishable (straight line). Black cross: $g_{Ca} = 3.43$ and $g_K = 0.57$. **(b)** Traces of the membrane potential v (top panel), g_{Ca} and g_K (middle panel), and I_{Ca} (bottom panel). **(b1)** Dynamics of the system (1), (2) converges to the steady state with $g_{Ca} = 3.43$ and $g_K = 0.57$ (black cross in **(a)**) and $I_{Ca} = -0.25$ when $\alpha_{Ca} = \alpha_K = 2.5$. **(b2)** For slightly slower rates of regulation, $\alpha_{Ca} = \alpha_K = 2.25$, dynamics converges to the limit cycle with $\langle I_{Ca} \rangle = -0.25$ and average values of g_{Ca} and g_K close to 3.43 and 0.57 respectively. Notice that the limit values of conductances lay within the oscillatory domain and far from the isoline $\langle I_{Ca} \rangle = -0.25$ of the ML model. Red dashed line in bottom panels of **b**: $I_{Ca} = -0.25$

Fig. 7.

Transitions to the oscillatory state in the Morris-Lecar model (1) with regulation (2). Conductances g_{Ca} and g_K for all moments of time belong to the line $g_K = 3.5 - g_{Ca}$; $\langle I_{Ca} \rangle^* = -0.25$. **(a)** Transition through the supercritical Andronov-Hopf bifurcation; initial values of the conductances $g_{Ca,0} = 0.431$, $g_{K,0} = 3.069$. **(b)** Transition through the subcritical Andronov-Hopf bifurcation; initial values of the conductances $g_{Ca,0} = 1.005$, $g_{K,0} = 2.495$. Faster ($\alpha_K = \alpha_{Ca} = 0.005$; gray) or slower ($\alpha_K = \alpha_{Ca} = 0.00005$; black) regulation implies faster or slower transition, respectively

Fig. 8.

Bouts of oscillations prior to complete recovery in the Morris-Lecar model (1) with regulation (6). **(a)** Bifurcational diagram and color coded values of the average calcium current for system (1). Black straight line is the trajectory of the point $(g_{Ca}(t), g_K(t))$ starting from $g_{Ca,0}=2$, $g_{K,0}=1.5$ (black square); in the course of the regulation $(g_{Ca}(t), g_K(t))$ sets to the point $(1.08, 2.42)$ (black cross). The target value of the intracellular calcium concentration, $[Ca]$, is 0.48; it is close to the isoline $\langle I_{Ca} \rangle = -0.5$ (see the text for details); $\alpha_{Ca}=0.01$, $\alpha_K=0.01$. **(b)** Time-dependence of the membrane potential v (top), conductances g_K (solid line), g_{Ca} (dashed line) (middle), and $[Ca]$ (bottom) corresponding to **(a)**. The target value of $\langle [Ca] \rangle$ is 0.48 (red dashed line); **(c)** Expanded interval of time marked in gray in **(b)**. Solid black line marks the value of g_{Ca} at which the fast system experiences a subcritical Andronov-Hopf bifurcation. Notice that

the oscillations continue for greater values of g_{Ca} (up to the dashed line) because of the bistability in the Morris-Lecar model for these values of g_{Ca} and g_K (cf. Fig. 2(b)).