Fast-slow Variable Dissection with Two Slow Variables Related to Calcium Concentrations: A Case Study to Bursting in a Neural Pacemaker Model

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Fast-slow variable dissection with two slow variables related to calcium concentrations: A case study to bursting in a neural pacemaker model

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Abstract Neuronal bursting is an electrophysiological behavior participating in physiological or pathological functions and a complex nonlinear alternating between burst and quiescent state modulated by slow variables. Identification of dynamics of bursting modulated by two slow variables is still an open problem. In the present paper, a novel fast-slow variable dissection method with two slow variables is proposed to analyze the complex bursting in a 4-dimensional neuronal model to describe bursting associated with pathological pain. The luminal (C_{lum}) and intracellular (C_{in}) calcium concentrations are the slowest variables respectively in the quiescent state and burst duration. Questions encountered when the traditional method with one low variable is

used. When C_{lum} is taken as slow variable, the burst is successfully identified to terminate near the saddle-homoclinic bifurcation point of the fast subsystem and begin not from the saddle-node bifurcation. With C_{in} chosen as slow variable, C_{lum} value of initiation point is far from the saddle-node bifurcation point, due to C_{lum} not contained in the equation of membrane potential. To overcome this problem, both C_{in} and C_{lum} are regarded as slow variables, the two-dimensional fast subsystem exhibits a saddle-node bifurcation point, which is extended to a saddle-node bifurcation curve by introducing C_{lum} dimension. Then, the initial point of burst is successfully identified to be near the saddle-node bifurcation curve. The results present a feasible method for fast-slow variable dissection and deep understanding to the complex bursting behavior with two slow variables, which is helpful for the modulation to pathological pain.

Keywords Bifurcation · Bursting · Fast-slow variable dissection · Calcium concentration

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1 Introduction

Identification of nonlinear dynamics of neuronal electrical behavior is very important for understanding the functions of nervous system [1-6]. Neuronal bursting is a complex nonlinear electrical behavior related to fast and slow variables, which participates many kinds of physiological functions, pathological functions, and even brain diseases [7-9]. For example, bifurcations of bursting have been identified to participate information coding [10-14] in blood pressure and pathological pain. In an animal model of injured nerve fiber to investigate the pathological pain [15], or called neuronal pacemaker, many complex bursting patterns containing period-

ic, chaotic, and stochastic patterns, have been observed in the electrophysiological experiment [16]. Modulated by potassium or calcium concentrations, the bursting patterns exhibit complex bifurcations, which is related to information coding of firing patterns instead of neural firing frequency [12, 13]. Recently, different bursting patterns have been build relationships to spreading depression (SD) and seizure (SZ) [17-20] and respiratory function [21-24]. The bursting in lateral habenula (LHb) has been related to depression [25]. Bursting activity related to autapse in pyramidal neuron is associated with coincidence detection [26]. Identification of bursting dynamics has been an important issue of the nonlinear dynamics [27-30].

Typical bursting exhibits alternation behavior between burst and quiescent state, which is modulated by fast and slow variables [1, 22, 31-35]. In neurophysiology, the fast variables are mainly related to the membrane potential and sodium or potassium channel, and the slow variables are often associated with calcium concentrations. The minimal theoretical model to describe bursting is always composed of the three variables. For example, in the famous Chay model and Hindmarsh-Rose model, except for a slow variable, there are two fast variables comprising fast subsystem whose differential equations contain the slow variable [36-38]. The bursting dynamics can be well explained with a feasible method which is called the fast-slow variable dissection [1, 39]. With the slow variable regarded as bifurcation parameter, the fast subsystem often exhibits spiking behavior and resting state, and bifurcations between both behaviors. The bursting behavior exhibits relationships to the bifurcations and behaviors of fast subsystem. In general, the burst correspond to the spiking behavior, and the quiescent state to the resting state. Furthermore, the transitions between two behaviors within burst are associated with the bifurcations between two behaviors of the fast subsystem, respectively. Correspondingly, a bursting pattern is named with the two bifurcations, and many bursting behaviors are classified into different patterns with such a classification method. For example, for the well-known "Fold/Homoclinic" bursting pattern, the former and latter bifurcations is associated with the beginning and ending phases of the burst. The dynamics of bursting with one slow variable has been successfully analyzed with fast-slow variable dissection [7, 39-47].

In many real nervous systems, the bursting patterns are related to two or more slow variables. For example, both intracellular and luminal calcium concentrations are slow variables for many nervous system such as the injured nerve fiber [14], pyramidal neuron of CA1 region of hippocampus [48], neuron of Pre-Bötzinger

(PB) complex [21, 23, 41, 49-53], and β -cell [54]. At least three cases of two slow variable can be found from theoretical models. For case-1, two slow variables exhibit very different time scales. The representative corresponds to β -cells with two slow variables. One is much slower than the other. Therefore, when the fast-slow variable dissection is performed, the slowest one is taken as a constant and the other slow one is regarded as the bifurcation parameter. The dynamics of complex bursting can be explained to a certain extent. Case-2 corresponds to two variables with approximate time scale. The pyramidal neuron of CA1 region of hippocampus related to SD or SZ [55-57] belongs to case-2. Both potassium and sodium concentrations are slow variables, and two slow variables exhibit nearly approximate time scale. For such a theoretical model with two slow variables with nearly equaling time scale, question was encountered when the fast-slow variable dissection with one slow variable is performed. For either of two slow variables taken as bifurcation parameter, the bifurcation points between the spiking and resting state of the fast subsystem mismatch the transition points between the burst and quiescent state of the bursting, as reported in Ref. [58]. To overcome this problem, fast-slow variable dissection with two slow variables is proposed, with both low variables (potassium and sodium concentrations) regarded as bifurcation parameters of the fast subsystem. The codimension-1 bifurcation curves in the parameter plane of potassium and sodium concentrations are acquired. The dynamics of bursting is identified according to the codimension-1 bifurcation curves intersected with the trajectory of bursting. The bursting for SD is related to the Hopf bifurcation, and for SZ is related to saddle-node bifurcation. For the case-2, the equations of the fast subsystem contains both slow variables of potassium and sodium concentrations.

Except for case-1 and case-2, the two slow variables are intracellular calcium concentration (C_{in}) and luminal calcium concentration (C_{lum}) for case-3, and the representative contains the model for neurons in Pre-Bötzinger (PB) complex [51-53] and a 4-dimensional theoretical model to describe the bursting of injured nerve fiber. For the 4-dimensional theoretical model, the variables V and n are considered to describe the membrane potential and the gating dynamics of potassium channel, respectively, except for the variables C_{in} and C_{lum} . The differential equations to describe dynamics of fast subsystem V and n do not contain the variable C_{lum} , and the differential equation of C_{lum} does not contain the variables V or n . Such dependence between V , n , and C_{lum} is popular for the bursting models with two slow variables C_{in} and C_{lum} [51-53]. There-

fore, the fast-slow variable dissection methods with two slow variables used to β -cell in Ref. [54] and to SZ or SD in Refs. [58] cannot directly used to identify dynamics of bursting associated with two slow variables, C_{in} and C_{lum} , due to that the fast subsystem of V and n does not contain C_{lum} . When the fast-slow variable dissection is performed to analyze the dynamics of case-3 bursting patterns with two slow variables, questions arise in two aspects.

(1) If C_{lum} is regarded as slow variable, differential equations to describe V , n , and C_{in} form the fast subsystem. The differential equations of V and n (not contain the variable C_{lum}) and the differential equation of C_{lum} (not contain V and n) become uncoupling. How to acquire the dynamics of the fast subsystem including the bifurcations becomes a problem.

(2) If both C_{lum} and C_{in} are taken as slow variables, how to acquire the bifurcations of the fast subsystem composed of equations of V and n in double-parameter plane (C_{in} , C_{lum}) is a problem, due to that the equations of fast subsystem do not contain C_{lum} . Therefore, identification of dynamics of bursting modulated by C_{in} and C_{lum} is still open question.

To answer the questions mentioned above, the bursting modulated by C_{in} and C_{lum} in pacemaker model to describe dynamics in the injured nerve fiber is studied in the present paper. The variable C_{in} is identified to be the slowest variable in the quiescent state and C_{lum} is the slowest variable in the burst duration. A feasible process to perform the fast-slow variable dissection with two slow variables C_{in} and C_{lum} is proposed. The dynamics of the bursting is acquired by three manners of the fast-slow variable dissection, with C_{in} , C_{lum} , and both C_{in} and C_{lum} taken as slow variables, respectively. Firstly, when C_{lum} is taken as slow variable, the termination phase of burst is identified to correspond to the saddle-homoclinic bifurcation of the fast subsystem (V , n , C_{in}), while the initial phase mismatches the saddle-node bifurcation, due to that C_{lum} instead of C_{in} is the slowest variable in burst duration. Secondly, when C_{in} is chosen as slow variable, the initiation phase of burst is close to the saddle-node bifurcation point of fast subsystem (V , n , C_{lum}) in C_{in} direction but far from the saddle-node point in C_{lum} direction, due to the uncoupling between the differential equations of V and n and the equation of C_{lum} . Thirdly, to overcome this problem, both C_{in} and C_{lum} are regarded as the slow variables. Due to that the saddle-node bifurcation with respect to C_{in} is independent of C_{lum} (the equations of V and n not containing C_{lum}) in the fast subsystem, the saddle-node bifurcation point is extended to a saddle-node bifurcation curve by introducing the dimension of C_{lum} , with the values of the saddle-node point along

C_{lum} -axis unchanged. Then, the burst is identified to begin from a point near the saddle-node curve, and C_{lum} value of the begging point is determined by not the fast subsystem but the full system. Last, a comprehensive viewpoint of dynamics of the bursting is presented by comparisons between dynamics acquired with the three manners of fast-slow variable dissection. These results present deep understanding for the complex dynamics underlying the bursting behavior of pacemaker model, which is helpful to modulate the bursting related to pathological pain, and a novel feasible performing process for fast-slow variable dissection with two slow variables related to calcium concentrations, which can be extensively utilized to analyze the bursting of other models with slow variables C_{in} and C_{lum} .

The rest of the present paper is organized as follows. Section 2, 3, and 4 present the model and method, results, and conclusion, respectively.

2 Model and Method

2.1 Model

The neuronal pacemaker model is proposed based on the electrophysiology experimental results of the injured nerve fiber (or called neural pacemaker) [11, 12, 14-16] and the Chay model, which exhibits complex bursting behaviors and bifurcations from bursting to spiking patterns. The differential equations of the four-dimensional pacemaker model are described as follows:

$$\frac{dV}{dt} = -g_i m_\infty^3 h_\infty (V - v_i) - g_{kv} (V - v_k) n^4 - g_{kc} \frac{C_{in}}{1 + C_{in}} (V - v_k) - g_l (V - v_l) \quad (1)$$

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n} \quad (2)$$

$$\frac{dC_{in}}{dt} = \frac{m_\infty^3 h_\infty (v_c - V) - k_c C_{in}}{\tau_c} + \frac{k_{rel} C_{in}}{k_{erc} + C_{in}} (C_{lum} - C_{in}) - k_{erp} C_{in} \quad (3)$$

$$\frac{dC_{lum}}{dt} = -\frac{k_{rel} C_{in}}{k_{erc} + C_{in}} (C_{lum} - C_{in}) + k_{erp} C_{in} \quad (4)$$

where the variable V describes the membrane potential, n describes the activation probability of voltage-active potassium K^+ channel, C_{in} is the intracellular concentration of Ca^{2+} , and C_{lum} is the luminal calcium concentration in the endoplasmic reticulum. The

parameters g_i , g_{kv} , g_l , and g_{kc} are the corresponding maximal conductance for Na^+ , voltage-active K^+ , leakage, and intracellular concentration dependent K^+ ions, respectively. And the parameters v_i , v_k , v_l , and v_c are the equilibrium potentials corresponding to the Na^+ , voltage-active K^+ , leakage, and intracellular concentration dependent K^+ ions. The functions h_∞ , m_∞ , and n_∞ are the inactivation probability of the Na^+ channel, the activation probability of the Na^+ channel, and the steady-state value of the second variable n , respectively. More details about the model refer to Refs. [14,30,36].

The equations of the functions are as follows:

$$\begin{aligned} h_\infty &= \frac{\alpha_h}{(\alpha_h + \beta_h)}, m_\infty = \frac{\alpha_m}{(\alpha_m + \beta_m)}, n_\infty = \frac{\alpha_n}{(\alpha_n + \beta_n)}, \\ \alpha_h &= 0.07e^{-0.05V-2.5}, \beta_h = \frac{1}{1+e^{-0.1V-2}}, \\ \alpha_m &= 0.1 \frac{25+V}{(1-e^{-0.1V-2.5})}, \beta_m = 4e^{-\frac{50+V}{18}}, \\ \alpha_n &= 0.01 \frac{20+V}{(1-e^{-0.1V-2})}, \beta_n = 0.125e^{-\frac{30+V}{80}}, \\ \tau_n &= 0.1 \frac{1}{\lambda_n(\alpha_n + \beta_n)}. \end{aligned}$$

The unit of membrane potential is mV, the unit of time is ms, and the unit of conductance is mS. In the present paper, $v_i = 100$ mV, $v_k = -75$ mV, $v_l = -40$ mV, $g_i = 1800$ mS, $g_{kv} = 1700$ mS, $g_{kc} = 16$ mS, $g_l = 7$ mS, $k_c = 3.3/18$, $\tau_c = 1.0$, $\lambda_n = 237.3$, $k_{erp} = 15$, $k_{rel} = 0.3$, and $k_{erc} = 0.5$. The parameter v_c is regarded as the bifurcation parameter.

2.2 Methods

The four-dimensional pacemaker model is solved using the 4th-order Runge–Kutta integration method and time step is 0.001 ms. If the upstroke of the membrane potential reaches -30.0 mV, a spike is thought to appear. The bifurcations are acquired using the software XPPAUT 8.071 [59].

3 Results

3.1 Bursting patterns and bifurcations

The theoretical model exhibits various bursting patterns and spiking patterns at different v_c values. For example, period-4 bursting appears when $v_c = 110$ mV, as shown in Fig. 1(a). The burst and a long quiescent state alternate. With decreasing v_c , the interspike intervals (ISIs) of the firing exhibit a complex bifurcation process, as depicted in Fig. 1(b). Such a bifurcation process has been observed in the experiments [11, 12, 14]. The bursting behaviors include the chaotic and periodic bursting patterns such as period-1, -2, $\dots$, -11, $\dots$, and even -17. In the present paper, the period-11 bursting for $v_c = 80$ mV is chosen as representative, as shown in Fig. 2(a1).

3.2 C_{in} and C_{lum} are slow variables in quiescent state and burst durations, respectively

The variables V , n , C_{in} , and C_{lum} for period-11 bursting are depicted in Fig. 2(a1), (b1), (c1), and (d1), respectively. And the derivatives dV/dt , dn/dt , dC_{in}/dt , and dC_{lum}/dt are shown in Fig. 2(a2), (b2), (c2), and (d2), respectively. The blue and red stars represent the termination and initiation phases of the burst, respectively. During the quiescent state, dC_{in}/dt (green) is closer to zero than that of dV/dt (black), dn/dt (red), and dC_{lum}/dt (blue), as shown in Fig. 3(a). In the burst duration, the value of dC_{lum}/dt (blue) is closer to zero than that of dC_{in}/dt (green), dV/dt (black), and dn/dt (red), as illustrated in Fig. 3(b). C_{in} exhibits the slowest variation during the quiescent state and C_{lum} manifests the slowest variation in the burst duration. Therefore, C_{in} and C_{lum} are alternative slow variables within a period of the bursting.

3.3 The question encountered when fast-slow variable dissection is performed

Due to that C_{in} is the slowest variable in the quiescent state and C_{lum} is the slowest variable in burst duration, the fast-slow variable dissection is performed in 3 manners in the present paper:

(1) C_{lum} is taken as the slow variable, and equations to describe variables V , n , and C_{in} form the fast subsystem;

(2) C_{in} is chosen as the slow variable and equations of variables V , n , and C_{lum} are composed of the fast subsystem;

(3) C_{lum} and C_{in} are regarded as the slow variables and equations to describe the variables V and n are fast subsystem contains.

It should be noticed that a characteristic of the model makes it difficult to perform the fast-slow variable dissection to bursting. Both of Eq. (1) and Eq. (2) do not contain the variable C_{lum} . Both of variables V and n are not contained in Eq. (4), and the differential equation of C_{lum} (Eq.(4)) is only determined by the variable C_{in} and the C_{lum} itself, as shown in Eq. (4). Therefore, no direct relationship between slow variable C_{lum} and fast variables V and n . Such a characteristic of the model makes it difficult to perform the fast-slow variable dissection to the bursting for the manners 2 and 3, which is introduced when the problem is encountered.

Fig. 1 The dynamics of firing patterns in the theoretical model. (a) The period-4 bursting for $v_c = 110$ mV; (b) A complex bifurcation process with respect to v_c .

Fig. 2 The variables (left) and the corresponding derivatives (right) for the period-11 bursting when $v_c = 80$ mV. (a1) V ; (a2) dV/dt ; (b1) n ; (b2) dn/dt ; (c1) C_{in} ; (c2) dC_{in}/dt ; (d1) C_{lum} ; (d2) dC_{lum}/dt . Blue and red stars represent the termination and initiation phases of the burst.

Fig. 3 Derivatives of variables V (black), n (red), C_{in} (green), and C_{lum} (blue) of the period-11 bursting when $v_c = 80$ mV. (a) During the quiescent state; (b) During the burst. Blue and red stars represent the termination and initiation phases of the burst, respectively.

3.4 Burst terminates at saddle-homoclinic bifurcation: manner 1

The equations of three variables V , n , and C_{in} form the fast subsystem, which are described as follows:

$$\frac{dV}{dt} = -g_i m_\infty^3 h_\infty (V - v_i) - g_{kv} (V - v_k) n^4 - g_{kc} \frac{C_{in}}{1 + C_{in}} (V - v_k) - g_l (V - v_l) \quad (5)$$

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n} \quad (6)$$

$$\frac{dC_{in}}{dt} = \frac{m_\infty^3 h_\infty (v_c - V) - k_c C_{in}}{\tau_c} + \frac{k_{rel} C_{in}}{k_{erc} + C_{in}} (C_{lum} - C_{in}) - k_{erp} C_{in} \quad (7)$$

where C_{lum} is the bifurcation parameter. With respect to C_{lum} , the equilibrium point curve of the subsystem (V, n, C_{in}) is called curve E1 in the present paper, as depicted in Fig. 4. The projection of E1 in (V, C_{in}) and (n, C_{in}) space are illustrated in Fig. 4(a) and (b), respectively. The projection of E1 exhibits a Z-shaped curve containing three branches. The middle branch representing a saddle intersects the lower one representing a stable node forms a saddle-node bifurcation point labeled as SN1 (red diamond).

For the fast subsystem (V, n, C_{in}) , there exists a stable limit cycle. The projection of E1 (red), maximal (LCU1, upper pink curve) and minimal (LCL1, lower pink curve) values of the cycle, and bursting trajectory (cyan) on (C_{lum}, V) plane are depicted in Fig. 5(a). The part around the trajectory (cyan) of bursting is enlarged, as depicted in Fig. 5(b). A saddle-homoclinic bifurcation point emerges when the limit cycle contacts with the middle branch, which is labeled as SH1 (blue diamond). The bursting trajectory (cyan) evolves in clockwise, as shown by the black arrow. The results

in the (C_{in}, n) and (C_{lum}, C_{in}) planes are similar, as illustrated in Fig. 5(c) and (d). Therefore, the burst is identified to terminate at the SH1 point.

After the SH1 point, the behavior of bursting runs down to the lower branch of curve E1, i.e. the stable node, and runs along the lower branch. After running across the SN1 point, the trajectory goes through a relative long distance, and then runs up to the limit cycle (pink) to form the burst with 11 spikes. Therefore, the burst begins not at the SN1 point but a point (red star) far away from the SN1 point in C_{lum} distance. For convenience, the projection of the equilibrium curve E1 (red curve), the maximal (LCU1, upper pink curve) and minimal (LCL1, lower pink curve) value of the limit cycle, and bursting trajectory (cyan) in (C_{lum}, C_{in}, V) space are shown in Fig. 6, which exhibits three characteristics:

- (1) The burst terminates at the SH1 point (blue star nearly overlap with blue diamond);
- (2) The amplitude of limit cycle (pink) is consistent with those of the burst;
- (3) The burst begins not at the SN1 point but a phase after SN1 point (the red star is far away from the red diamond).

Due to that the C_{lum} is the slowest variable in the burst duration, therefore, the dynamics of the termination phase of burst can be explained with the dynamics of fast subsystem with C_{lum} taken as slow variable. This is the cause that the burst terminates at the SH1 point and the amplitude of the burst is consistent with that of the stable limit cycle. In addition, due to that C_{lum} is not the slowest variable during the quiescent state, therefore, the quiescent state terminates not at the SN1 point (red diamond), i.e. the burst begins not from the SN1 point. Therefore, the dynamics of termination phase of the quiescent state and initiation phase of the burst should be studied in the fast subsystem (V, n, C_{lum}) with C_{in} taken as the bifurcation parameter in

Fig. 4 The values of equilibrium point curve (E1) of the fast subsystem (V , n , C_{in}) change with respect to the parameter C_{lum} . (a) (V , C_{in}) values; (b) (n , C_{in}) values. SN1 (saddle-node bifurcation, red diamond) represents the intersection between the lower branch and the middle branch.

Fig. 5 Fast-slow variable dissection with C_{lum} taken as slow variable. (a) Dynamics of fast subsystem (V , n , C_{in}) in (C_{lum} , V) plane. The projection of equilibrium point curve E1 (red Z-shaped curve), stable limit cycle with maximal (LCU1, upper pink curve) and minimal (LUL1, lower pink curve) values; SN1 (red diamond) and SH1 (blue diamond) represents the saddle-node bifurcation and saddle-homoclinic bifurcation point, respectively. Blue and red stars represent the termination and initiation phases of the burst; (b) Trajectory of period-11 bursting (cyan) plotted with Fig. a around SN1 and SH1; (c) Projection of bursting trajectory (cyan) and dynamics of fast subsystem (V , n , C_{in}) in (C_{lum} , n) plane; (d) Projection of bursting trajectory (cyan) and dynamics of fast subsystem (V , n , C_{in}) in (C_{lum} , C_{in}) plane.

the following paragraphs, due to that C_{in} is the slowest variable during the quiescent state.

$$\begin{aligned} \frac{dV}{dt} = & -g_i m_\infty^3 h_\infty (V - v_i) - g_{kv} (V - v_k) n^4 \\ & - g_{kc} \frac{C_{in}}{1 + C_{in}} (V - v_k) - g_l (V - v_l) \end{aligned} \quad (8)$$

3.5 Possible saddle-node bifurcation for the beginning phase of burst: manner 2

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n} \quad (9)$$

In the present subsection, C_{in} is chosen as slow variable, and the equations of other three variables V , n , and C_{lum} combine to form the fast subsystem, which is described as follows:

$$\frac{dC_{lum}}{dt} = -\frac{k_{rel} C_{in}}{k_{erc} + C_{in}} (C_{lum} - C_{in}) + k_{erp} C_{in} \quad (10)$$

The difficulty introduced in subsection 3.3 is encountered when fast-slow variable dissection analysis

Fig. 6 Fast-slow variable dissection for manner 1. The projection of equilibrium point curve E1 (red), stable limit cycle with maximal (LCU1, upper pink curve) and minimal (LCL1, lower pink curve) values, and the trajectory of the period-11 bursting (cyan) in the (C_{lum}, C_{in}, V) space. SN1 (red diamond) and SH1 (blue diamond) represent the saddle-node and saddle-homoclinic bifurcation points, respectively.

is performed for the manner 2. Either of Eqs. (8) and (9) does not contain the variable C_{lum} . Therefore, the Eqs. (8) and (9) of variable V and n are independent of C_{lum} , and the Eq. (10) of the variable C_{lum} is independent of variables V or n . However, Eqs. (8) and (9) are dependent of C_{in} , and Eq. (10) is dependent of C_{in} . Therefore, Eqs. (8) and (9) are uncoupled to Eq. (10), although their dynamics are determined by the same parameter C_{in} .

For the equilibrium point corresponding to a fixed C_{in} of the fast subsystem, the equilibrium point of Eqs. (8) and (9) is acquired as $(V(C_{in}), n(C_{in}))$ and for Eq. (10) is $C_{lum}(C_{in})$, and then the equilibrium point $(V(C_{in}), n(C_{in}), C_{lum}(C_{in}))$ of the fast subsystem for Eqs. (8-10) is formed. With respect to C_{in} , $(V(C_{in}), n(C_{in}), C_{lum}(C_{in}))$ form the equilibrium curve (navy) of the fast subsystem (Eqs. (8-10)), called equilibrium curve E2 (navy) in the present paper, as illustrated in Fig. 7. The projection of the curve E2 in the (C_{lum}, C_{in}, V) and (C_{lum}, C_{in}, n) space are depicted in Fig. 7(a) and (b), respectively. Both projections of E2 exhibit a Z-shaped curve. A saddle-node bifurcation point appears as the middle branch (saddle) intersects with the lower branch (stable node), which is labeled as SN2 (red dot).

However, the Eqs. (8) and (9) (V and n) exhibit a stable limit cycle, which is independent of Eq. (10) (C_{lum}), due to Eqs. (8) and (9) and Eq. (10) are uncoupled. The projection of E2 (navy), maximal (LCU2, upper blue curve) and minimal (LCL2, lower blue curve) values of the limit cycle are depicted in Fig. 8(a). A saddle-homoclinic bifurcation point emerges when the limit cycle intersects with the saddle (middle branch),

which is labeled as SH2 (blue dot). The enlargement of Fig. 8(a) plotted with the trajectory of period-11 bursting (cyan) forms Fig. 8(b), and the projection on (C_{in}, n) plane is illustrated in Fig. 8(c). In addition, the projection on the (C_{lum}, C_{in}) space is depicted in Fig. 8(d). Three characteristics can be found from Fig. 8(b)-(d), which are introduced as follows:

(1) The burst begins from the SN2 point in V , n , and C_{in} directions (red star and red diamond are very close in Fig. 8(b) and (c)) instead of C_{lum} direction (red star is far from the red diamond in C_{lum} direction), which shows that the burst possibly begins and the quiescent state possibly terminates at the saddle-node bifurcation. The mismatch between the trajectory (navy) of the bursting and the SN2 point (red diamond) of the fast subsystem in C_{lum} direction is induced by the uncoupling relationship between Eqs. (8-9) and Eq. (10).

(2) The amplitude of the limit cycle, especially the minimal value (lower blue), is not consistent with (higher than) that of the burst, as illustrated in Fig. 8(b) and (c).

(3) The burst is identified to terminate not at the SH2 point (the blue star is very far from the blue diamond).

In summary, the amplitude of the stable limit cycle is inconsistent with that of the burst, and the burst does not terminate at the SH2 point, due to that C_{in} is not the slowest variable in burst duration. The burst is identified to begin from the saddle-node bifurcation point in the V and n directions except for the C_{lum} direction, due to that the C_{in} is the slowest variable in the quiescent state and the uncoupling characteristic between differential equation of variable C_{lum} and differential equations of variables V and n . To acquire more comprehensive and deep understanding to the beginning phase of the burst, the fast-slow variable dissection analysis with both C_{in} and C_{lum} taken as slow variables (manner 3) to bursting is performed.

3.6 Comparisons of dynamics between fast subsystem (V, n, C_{in}) and (V, n, C_{lum})

To be compared with the dynamics between the fast subsystem (V, n, C_{in}) and (V, n, C_{lum}) , the equilibrium point curve E1 (red curve), SN1 (red diamond), and SH1 (blue diamond) of the fast subsystem (V, n, C_{in}) , and the curve E2 (navy curve), SN2 (red dot), and SH2 (blue dot) of the fast subsystem (V, n, C_{lum}) are illustrated in Fig. 9(a). The maximal (upper) and minimal (lower) values of the stable limit cycle of the fast subsystems (V, n, C_{in}) (pink) and (V, n, C_{lum})

Fig. 7 The values of equilibrium curve (E2, navy) of the fast subsystem (V , n , C_{lum}) change with respect to the parameter C_{in} . (a) (V , C_{lum}) values; (b) (n , C_{lum}) values. SN2 (saddle-node bifurcation, red dot) represents the contact point between the middle and lower branches.

Fig. 8 Fast-slow variable dissection with C_{in} taken as the slow variable (manner 2). The projection of equilibrium point curve E2 (navy), stable limit cycle with maximal (LCU2, upper blue curve) and minimal (LUL2, lower blue curve) values, and trajectory (cyan) of period-11 bursting on different planes. (a) (C_{in} , V) plane; (b) Enlargement of Fig. (a); (c) (C_{in} , n) plane; (d) (C_{in} , C_{lum}) plane. SN2 (red dot) and SH2 (blue dot) correspond to the saddle-node and saddle-homoclinic bifurcation points, respectively. Blue and red stars represent the termination and initiation phases of the burst, respectively.

(blue) are plotted with Fig. 9(a) to form Fig. 9(b). Fig. 9(c) represents the enlargement of Fig. 9(b) and the trajectory (cyan) of the period-11 bursting. Fig. 9(d) is the enlargement of a part of Fig. 9(c).

As depicted in Fig. 9, the dynamics of the fast subsystem (V , n , C_{in}) are different from those of the fast subsystem (V , n , C_{lum}). For example, the curve E1 (red curve) is different from E2 (navy curve), SN1 (red diamond) is different from SN2 (red dot), and SH1 (blue diamond) is different from SH2 (blue dot). In addition, the amplitudes (pink and blue) of the limit cycle are different. Furthermore, the SH1 (blue diamond) instead of SH2 is associated with the termination phase (blue star) of burst, and the amplitude (upper and lower pink) of the limit cycle for manner1 instead of manner 2 (upper

and lower blue) matches that of the burst (cyan). However, SN2 (red dot) is related to the beginning phase (red star) at the V , n and C_{in} directions except for the C_{lum} direction, and SN1 (red diamond) is very far from the beginning phase of the burst (red star). Therefore, the bifurcation associated with the initiation phase of the burst is acquired by manner 3 of fast-low variable dissection method (C_{in} and C_{lum} taken as slow variables) and the relationships of the dynamics between different fast subsystems are identified in the following paragraphs.

Fig. 9 The relationships between the bursting trajectory (cyan) and the dynamics of the fast subsystems (V, n, C_{lum}) and (V, n, C_{in}) in (C_{in}, C_{lum}, V) space. (a) The equilibrium point curve E1, bifurcation point SN1, and SH1 of the fast subsystem (V, n, C_{in}) and E2, SN2, and SH2 of the fast subsystem (V, n, C_{lum}) ; (b) The maximal (upper) and minimal (lower) values of the stable limit cycle of the fast subsystems (V, n, C_{in}) (pink) and $((V, n, C_{lum}))$ (blue) are plotted with Fig. 9(a); (c) Enlargement of Fig. (b) around the trajectory of bursting (cyan); (d) Enlargement of Fig. (c). E1 (red curve) and E2 (navy curve) represent the equilibrium point curve, SN1 (red diamond) and SN2 (red dot) represent the saddle-node bifurcation, and SH1 (blue diamond) and SH2 (blue dot) represent the saddle-homoclinic bifurcation point. LCU1 (upper pink curve) and LCU2 (upper blue curve) represent the maximal values of the limit cycle, respectively. LUL1 (lower pink curve) and LUL2 (lower blue curve) represent the minimal values of the limit cycle, respectively. Blue and red stars represent the termination and initiation phases of the burst.

Fig. 10 The bifurcations of two-dimensional fast subsystem (V, n) with respect to C_{in} . (a) The bifurcation of (V, n) of equilibrium point (olive curve), and the maximal (LCU, upper green curve) and minimal (LUL, lower green curve) values of the stable limit cycle, respectively; (b) The projection of Fig. (a) on (C_{in}, V) plane; (c) The projection of Fig. (a) on (C_{in}, n) plane. H (black circle), SN (red circle), and SH (blue circle) represent the Hopf, saddle-node, and saddle-homoclinic bifurcations, respectively.

3.7 Saddle-node bifurcation for the beginning phase of the burst: manner 3

In this subsection, both C_{in} and C_{lum} are taken as the slow variables, and the fast subsystem is the first two equations, which is shown as follows:

$$\begin{aligned} \frac{dV}{dt} = & -g_i m_\infty^3 h_\infty (V - v_i) - g_{kv} (V - v_k) n^4 \\ & - g_{kc} \frac{C_{in}}{1 + C_{in}} (V - v_k) - g_l (V - v_l) \end{aligned} \quad (11)$$

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n} \quad (12)$$

The fast subsystem contains the parameter C_{in} , but does not contain the parameter C_{lum} . Therefore, the bifurcations of the fast subsystem are dependent of C_{in} , but independent of C_{lum} . For the fast subsystem, the bifurcations are depicted in Fig. 10. A Z-shaped curve of equilibrium of (V, n) appears, called E in the present paper, as shown by olive curve in Fig. 10(a). A Hopf bifurcation point labeled as H (black circle) emerges on the upper branch. A stable limit cycle with maximal (LCU, green curve) and minimal (LCL, green curve) values emerges via the Hopf bifurcation point. When the limit cycle contacts with the middle branch, a saddle-homoclinic bifurcation called SH point (blue circle) emerges. The lower branch and the middle branch of the equilibrium curve intersect and then a saddle-node bifurcation labeled as SN (red circle) appears. The projection of the curve E on (C_{in}, V) plane and on (C_{in}, n) plane is depicted in Fig. 10(b) and 10(c), respectively.

The dynamics of the fast subsystem Eqs. (11) and (12) (not containing C_{lum}) is independent of C_{lum} , as shown in (V, n, C_{in}) space in Fig. 10(a). Therefore, the dynamics for the fast subsystem cannot be build a relationship to the trajectory (cyan) of period-11 bursting in C_{lum} direction. To overcome such a problem, the dynamics shown in Fig. 10 can be extended by the introduction of the dimension C_{lum} . With changing C_{lum} , the (V, n, C_{in}) along C_{lum} -axe remains unchanged. For example, for the projection of E on (C_{in}, V) plane (olive curve in Fig. 10(b)), after introducing the dimension C_{lum} and with (C_{in}, V) value along the C_{lum} -axe unchanged, a surface in (C_{lum}, C_{in}, V) space which is extended from the curve E forms, as shown in Fig. 11(a), which is called S here. Corresponding to the curve E which has upper, middle, and lower branches, the surface S is also composed of the three branches, called S_U , S_M , and S_L , respectively. The surface is vertical to the plane (C_{in}, V) . Such a surface exhibits relationships to the trajectory of period-11 bursting in (C_{lum}, C_{in}, V) space.

Similarly, the saddle-node bifurcation point depicted in Fig. 10(b) can be extended to a curve vertical to the plane (C_{in}, V) , which is called SNc, as shown by the dashed yellow curve in Fig. 11(a). Due to the equations of fast subsystem (V, n) do not contain the parameter C_{lum} , the C_{lum} value for the saddle-node bifurcation cannot be acquired in the fast subsystem (V, n) . Therefore, the SNc curve exhibits fixed values of V , n , and C_{in} along the C_{lum} -axe.

Furthermore, the curves of maximal (green curve) and minimal (green curve) values of the stable limit cycle in Fig. 10(b) can be extended to surfaces upper and lower to the upper branch of S surface S_U , which is called L_U and L_L , respectively, as shown by the upper and lower olive surfaces in Fig. 11(b). The intersection between the surface L_L and the middle branch of S surface S_M forms an SH curve (solid yellow curve), which is called SHc. The SHc curve (bold yellow curve) is the extension of the SH point in Fig. 10. The enlargement of Fig. 11(b) around the SNc (dashed yellow) and SHc (solid yellow curve) is shown in Fig. 11(c). Furthermore, Fig. 11(c) around the middle and lower branches of S surface S_M and S_L is enlarged, as shown in Fig. 11(d). These figures are helpful for understanding period-11 bursting in (C_{lum}, C_{in}, V) space.

The relationship between the period-11 bursting and dynamics of the fast subsystem (V, n) in (C_{lum}, C_{in}, V) space can be acquired from Fig. 12. The trajectory (cyan) of period-11 bursting and the dynamics such as bifurcation curves and surfaces of the fast subsystem are illustrated in Fig. 12(a). A part of Fig. 12(a) is enlarged and is depicted in Fig. 12(b), and Fig. 12(c) is the back of Fig. 12(b). After running across the middle branch S_L at a certain point near the saddle-node curve SNc (dashed yellow curve), the quiescent state of the bursting terminates and the burst begins, as shown by the red star. Therefore, the period-11 bursting begins from the saddle-node bifurcation in the (C_{lum}, C_{in}) space indeed, as shown in Fig. 12(b). The result shows that the termination phase of the quiescent state, i.e. the initiation phase of the burst, is related to the saddle-node bifurcation. However, the C_{lum} values for the bifurcations cannot be acquired in the fast subsystem (V, n) , due to that the equations of fast subsystem (V, n) do not contain the variable C_{lum} , which is the cause that the burst begins from the SNc curve with fixed values of V , n , and C_{in} (exclusive C_{lum} value). In addition, the termination phase (blue star) of burst is far from the SHc curve (solid yellow), which shows that the burst terminates not at the SHc curve. The amplitude of the limit cycle (L_U and L_L) does not match that of the burst.

Fig. 11 The extended surface and bifurcation curves by introducing a dimension C_{lum} for the fast subsystem (V, n). (a) The equilibrium surface S (olive surface) composed of upper (S_U), middle (S_M), and lower (S_L) branches and saddle-node bifurcation curve SNc (dashed yellow curve); (b) Fig. (a) plotted with the extended surface of maximal (L_U , upper green surface) and minimal (L_L , lower green surface) values of limit cycle and the SHc curve (solid yellow curve); (c) The enlargement of Fig. (b) in C_{in} direction; (d) The enlargement of Fig. (b) in V direction.

Fig. 12 The fast-slow variable dissection to period-11 bursting (cyan) with (C_{lum}, C_{in}) taken as slow variables (manner 3). The surfaces of equilibrium and stable limit cycle and bifurcation curves are the same as Fig. 11. (a) The framework of dynamics in (C_{lum}, C_{in}, V) space; (b) The enlargement of Fig. (a) around the middle branch (S_M) and low branch (S_L) of equilibrium surface S ; (c) The Fig. (b) shown in a different angle (back of Fig. (b)). The dashed yellow curve and the solid yellow curve represents the saddle-node curve SNc and SHc curve SHc . The red and blue stars represent the initiation and termination phases of the burst, respectively. L_U (upper green surface) and L_L (lower green surface) represent the extended surface of maximal and minimal value of limit cycle, respectively.

In summary, the burst of period-11 bursting begins from the saddle-node bifurcation curve SNc of the fast subsystem (V, n) . However, the burst terminates not at the SHc of the fast subsystem (V, n) or the SH2 of the fast subsystem (V, n, C_{lum}) , but at the SH1 of the fast subsystem (V, n, C_{in}) . In the following paragraphs, the comparisons of dynamics between different fast subsystems are presented.

3.8 Comparison between the dynamics of fast subsystems (V, n) and (V, n, C_{in})

The surface of equilibrium point S, the saddle-node bifurcation curve SNc (dashed yellow curve), and the saddle-homoclinic bifurcation curve SHc (bold yellow curve) for the fast subsystem (V, n) are shown in Fig. 13(a). The equilibrium curve E1 and saddle-node bifurcation point SN1 (red diamond) of (V, n, C_{in}) are plotted with Fig. 13(a) to form Fig. 13(b). The equilibrium point of the fast subsystem (V, n, C_{in}) is a subset of those of the fast subsystem (V, n) , and the saddle-node bifurcation point of the fast subsystem (V, n, C_{in}) is a subset of saddle-node bifurcation curve SNc of the fast subsystem (V, n) , therefore, the equilibrium curve E1 is on the equilibrium surface S, and SN1 point is on the SNc curve (dashed yellow curve).

Fig. 13 (c) represents Fig. 13(b) plotted with The extended surface of maximal (L_U , upper green surface) and minimal (L_L , lower green surface) values of the fast subsystem (V, n) , and the stable limit cycle with maximal (upper pink curve) and minimal (lower pink curve) values and the saddle-homoclinic bifurcation point SH1 (blue diamond). Fig. 13(d) is the enlargement of Fig. 13(c), showing that the SH1 point (blue diamond) of the fast subsystem (V, n, C_{in}) is not located on the curve SHc (solid yellow curve) of the fast subsystem (V, n) . In addition, the amplitude of limit cycle of the fast subsystem (V, n, C_{in}) , i.e. LCU1 and LCL1, is not consistent with that of the extended surfaces of stable limit cycle L_U and L_L , due to that the L_L surface of the fast subsystem (V, n) contains the SHc curve rather than LCL1 (minimal value of limit cycle) of the subsystem (V, n, C_{in}) .

The trajectory (cyan) of the period-11 bursting is plotted with the dynamics of the fast subsystems (V, n) and (V, n, C_{in}) , as depicted in Fig. 14. Fig. 14(b) represents the enlargement of Fig. 14(a), and Fig. 14(c) is the enlargement around the SNc (dashed yellow curve) and SHc (solid yellow curve) of Fig. 14(b), and 14(d) is the back of Fig. 14(c). It can be found that the burst begins from the saddle-node bifurcation curve SNc (dashed yellow curve) of the fast subsystem (V, n) , as illustrated in Fig. 14(c). However, the initial phase of burst (red

star) and the SN1 point (red diamond) of fast subsystem (V, n, C_{in}) have the nearly equaling values in C_{in} , which is not presented in Fig. 5, although they have different values in C_{lum} . The burst begins not from the SN1 point (red diamond) of the fast subsystem (V, n, C_{lum}) , due to C_{in} is not the slowest variable during burst. As can be found from Fig. 14(b), the maximal (upper pink curve) and minimal (lower pink curve) values of the burst (cyan) correspond to maximal (upper pink curve) and minimal (upper pink curve) values of the limit cycle of the fast subsystem (V, n, C_{lum}) , respectively. More importantly, the burst terminates at the SH1 point (blue diamond) of the fast subsystem (V, n, C_{lum}) instead of SH curve SHc (solid yellow curve) of the fast subsystem (V, n) , as depicted in Fig. 14(b-d).

3.9 Comparison between the dynamics of fast subsystem (V, n) and (V, n, C_{lum})

The surface of equilibrium point S, the saddle-node bifurcation curve SNc (dashed yellow curve), and the saddle-homoclinic bifurcation curve SHc (bold yellow curve) for the fast subsystem (V, n) are shown in Fig. 15(a). Fig. 15(b) represents Fig. 15(a) plotted with the equilibrium curve E2 (navy) and saddle-node bifurcation point SN2 (red dot) of the fast subsystem (V, n, C_{lum}) . Similarly to Fig. 13, the curve E2 (navy) is on the surface S, and the SN2 point (red dot) is on the SNc curve (dashed yellow curve). Fig. 15(c) represents Fig. 15(b) plotted with the stable limit cycle with maximal (upper blue curve) and minimal (lower blue curve) value and the saddle-homoclinic bifurcation point SH2 (blue dot) of the fast subsystem (V, n, C_{lum}) and the extended surface of maximal value (L_U , upper green surface) and minimal value (L_L , lower green surface) of stable limit cycle of the fast subsystem (V, n) . Fig. 15(d) represents the enlargement of a part of Fig. 15(c). The SH2 point (red dot) of the fast subsystem (V, n, C_{lum}) is on the curve SHc (solid yellow) of the fast subsystem (V, n) , due to that the curve is extended from the point. And the LCU2 and LCL2 curve are on the L_U and L_L branches of surface S, respectively, due to that the surfaces are extended from the corresponding curves.

The trajectory (cyan) of the period-11 bursting is plotted with the dynamics of the fast subsystem (V, n) and (V, n, C_{lum}) , as depicted in Fig. 16. Fig. 16(b) is the enlargement of Fig. 16(a), Fig. 16(c) represents the further enlargement of Fig. 16(b) around the SNc (dashed yellow curve) and SHc (solid yellow curve) curves, and Fig. 16(d) is the back of Fig. 16(c). The burst begins from the saddle-node bifurcation curve SNc (dashed yellow curve) of the fast subsystem (V, n) ,

Fig. 13 The comparison of dynamics between fast subsystem (V, n) and (V, n, C_{in}) . (a) The equilibrium surface S , the saddle-node bifurcation curve SNc (dashed yellow curve), and the saddle-homoclinic bifurcation curve SHc (solid yellow curve) of fast subsystem (V, n) ; (b) Fig. (a) plotted with the equilibrium curve $E1$ (red curve) and saddle-node bifurcation point $SN1$ (red diamond) of fast subsystem (V, n, C_{in}) ; (c) Fig. (b) plotted with limit cycle with maximal ($LCU1$, upper pink curve) and minimal ($LCL1$, lower pink curve) values and saddle-homoclinic bifurcation point $SH1$ (blue diamond) of fast subsystem (V, n, C_{in}) , and the extended surfaces of maximal value (L_U , upper green surface) and minimal value (L_L , lower green surface) of the limit cycle of the fast subsystem (V, n) ; (d) Enlargement of a part of Fig. (c).

Fig. 14 The comparison of fast-slow variable dissection between manner 1 (C_{lum} taken as slow variable) and 3 (both C_{in} and C_{lum} taken as slow variables). (a) The trajectory (cyan) of period-11 bursting, dynamics of the fast subsystem (V, n) including the equilibrium surface S (S_U , S_M , and S_L), the saddle-node bifurcation curve SNc (dashed yellow curve), and the saddle homoclinic bifurcation curve SHc (solid yellow curve), and dynamics of the fast subsystem (V, n, C_{in}) containing the limit cycle ($LCU1$ and $LCL1$, pink), equilibrium curve $E1$ (red curve), saddle-node bifurcation $SN1$ (red diamond), and saddle-homoclinic bifurcation point $SH1$ (blue diamond) of the fast subsystem (V, n, C_{in}) ; (b) Enlargement of Fig. (a); (c) The enlargement of Fig. (b) in a different angle; (d) Fig. (c) shown in a different angle (the back of Fig. (c)). The red and blue stars represent the initiation and termination phases of the burst, respectively.

Fig. 15 The comparisons of dynamics between fast subsystem (V, n) and (V, n, C_{lum}) . (a) The equilibrium surface S , the saddle-node bifurcation curve SNc (dashed yellow curve), and the saddle-homoclinic bifurcation curve SHc (solid yellow curve) of the fast subsystem (V, n) ; (b) Fig. (a) plotted with the equilibrium curve $E2$ (navy) and saddle-node bifurcation $SN2$ (red dot) of the fast subsystem (V, n, C_{lum}) ; (c) Fig. (b) plotted with the limit cycle with maximal (upper blue curve) and minimal (lower blue curve) values and saddle-homoclinic bifurcation $SH2$ (blue dot) of the fast subsystem (V, n, C_{lum}) , and the extended surface of maximal value (L_U , upper green surface) and minimal value (L_L , lower green surface) of the limit cycle of the fast subsystem (V, n) ; (d) The enlargement of Fig. (c).

as shown in Fig. 16(c). The initial point of the burst (red star) and the $SN2$ point (red dot) of the fast subsystem (V, n, C_{lum}) have nearly equaling values for C_{in} but different values for C_{lum} . The burst terminates not at the $SH2$ point (blue circle) of the fast subsystem (V, n, C_{lum}) or the saddle-homoclinic bifurcation curve SHc (solid yellow curve) of the fast subsystem (V, n) , as illustrated in Fig. 16(b) and (d). As depicted in Fig. 16(b), the maximal and minimal values of the burst (cyan) do not correspond to those of the limit cycle (upper and lower blue curves) of the fast subsystem (V, n, C_{lum}) . All these results further show that the termination of burst cannot be explained with the fast subsystem (V, n) or (V, n, C_{lum}) .

3.10 The comparison of the results between three manners

The surfaces, bifurcation curves, bifurcation points of three fast subsystems, and the trajectory of period-11 bursting around the saddle-node bifurcation curve SNc are depicted in Fig. 17(a). Fig. 17(b) represents the back of Fig. 17(a). The largest amplitudes of burst are not shown here due to that they are introduced clearly in the previous subsections. The relationships between these surfaces, curves, and points mentioned above can

be clearly found from Fig. 17, and the dynamics of 3 fast subsystems are also listed in Table 1. Fig. 17(c) and (d) represent the dynamics related to the begging and ending phases of the burst from front and back sides, respectively.

There are two most important points about the dynamics of the period-11 bursting, which is described as follows:

(1) The burst begins from a certain point on the saddle-node curve SNc (dashed yellow curve) of the fast subsystem (V, n) , as illustrated in Fig. 17(a). The C_{lum} of the point cannot be acquired from the fast subsystem due to that the fast subsystem (V, n) does not contain the C_{lum} , which is an important characteristic for the model containing C_{in} and C_{lum} . The C_{lum} influences the dynamics of the bursting via the modulations of C_{lum} to C_{in} . The C_{in} , V and n values of the termination point is determined by the fast subsystem. Correspondingly, the burst begins not at the saddle-node bifurcation $SN2$ of the fast subsystem (V, n, C_{lum}) due to the uncoupling between the equation of C_{lum} and equations of V and n . In addition, the burst starts not at the saddle-node bifurcation $SN1$ of the fast subsystem (V, n, C_{in}) , due to that C_{lum} is not the slowest variable during the quiescent state. The results show that the initial phase of the burst can be explained with the fast

Fig. 16 The comparison of fast-slow variable dissection between manner 2 (C_{in} taken as slow variable) and 3 (both C_{in} and C_{lum} taken as slow variables). (a) The trajectory (cyan) of period-11 bursting equilibrium surface, the dynamics of fast subsystem (V, n) including the saddle-node bifurcation curve SNc (dashed yellow curve), and the saddle-homoclinic bifurcation curve SHc (solid yellow curve), and the dynamics of the fast subsystem (V, n, C_{lum}) containing the equilibrium curve E2 (navy curve), stable limit cycle (LCU2 and LCL2, blue), saddle-node bifurcation point SN2 (red dot), saddle-homoclinic bifurcation point SH2 (blue dot) of the fast subsystem (V, n, C_{lum}); (b) Enlargement of Fig. (a); (c) Enlargement of Fig. (b); (d) Fig. (c) shown in a different angle (the back of Fig. (c)). The red and blue stars represent the initiation and termination phases of the burst, respectively.

Table 1 The dynamics of 3 fast subsystems

	Slow variables		
	C_{lum}	C_{in}	(C_{in}, C_{lum})
Equilibrium point	E1 curve	E2 curve	S surface (Containing E1 and E2)
Saddle-node bifurcation	SN1 point	SN2 point	SNc curve (Containing SN1 and SN2)
Saddle-homoclinic bifurcation	SH1 point	SH2 point	SHc curve (Not containing SH1, containing SH2)
Limit cycle	LCU1 curve	LCU2 curve	L_U surface (Not containing LCU1 curve, containing LCU2 curve)
	LCL1 curve	LCL2 curve	L_L surface (Not containing LCL1 curve, containing LCL2 curve)

subsystem (V, n), i.e. the fast-slow variable dissection analysis with two slow variables C_{lum} and C_{in} related to the calcium concentrations.

(2) The burst terminates at the saddle homoclinic bifurcation point SH1 (blue diamond) of the fast subsystem (V, n, C_{in}), and the amplitude of the limit cycle (pink) matches that of the burst, as depicted in Fig. 17(c) and (d), which shows that the burst dynamics can be explained with the dynamics of the fast subsystem (V, n, C_{in}), due to C_{lum} is the slowest variable during

the burst. Therefore, when C_{in} is taken as slow variable or both C_{in} and C_{lum} are chosen as the slow variables, the burst dynamics cannot be well explained, which is the cause that the burst terminates not at the saddle-homoclinic bifurcation point SH2 of the fast subsystem (V, n, C_{lum}) or the saddle-homoclinic bifurcation curve SHc of the fast subsystem (V, n).

Fig. 17 The comparisons between 3 manners of fast-slow variable dissection to period-11 bursting. (a) The trajectory of period-11 bursting (cyan), the beginning phase (red star) and termination phase (blue star) of burst, and the dynamics for fast subsystem (V, n, C_{in}) (equilibrium point curve E1 (red curve), saddle-node bifurcation point SN1 (red diamond), saddle-homoclinic bifurcation point SH1 (blue diamond), minimal value of limit cycle LCL1 (lower pink curve)), for fast subsystem (V, n, C_{lum}) (equilibrium point curve E2 (navy curve), saddle-node bifurcation point SN2 (red dot), saddle-homoclinic bifurcation point SH2 (blue dot), minimal value of limit cycle LCL2 (lower pink curve)), and for fast subsystem (V, n) (middle and lower branches of extended equilibrium point surface S_M (olive surface) and S_L (olive surface), saddle-node bifurcation curve SNc (dashed yellow curve), saddle-homoclinic bifurcation curve SHc (solid yellow curve), and minimal value of extended surface of stable limit cycle L_L (lower green surface)); (b) The Fig. (a) shown in a different angle; (c) The bifurcations related to the beginning (red star) and ending (blue star) phases of burst in Fig. (a); (d) Fig. (c) shown in a different angle (the back of Fig. (c)).

4 Conclusion

Identification of nonlinear dynamics of bursting which participates physiological or pathological functions is very important for the nonlinear dynamics as well as the neuroscience [1-6, 60-62]. The dynamics of bursting modulated by one slow variable has been well explained with bifurcations acquired by the fast-slow variable dissection [1, 22, 27-29]. At present, identification of bursting dynamics modulated by two slow variables is an open problem. Recently, two case of bursting modulated by two slow variables are studied [54,58]. In the present paper, the dynamics of bursting modulated by the third cases of two slow variables, the calcium concentrations (C_{in} and C_{lum}), is acquired in a four-dimensional model to describe a neural pacemaker related to pathological pain. The results exhibit significances in the following 3 aspects.

Firstly, a feasible process to perform fast-slow variable dissection is proposed to analyze the dynamics of bursting modulated by slow variables C_{in} and C_{lum} . The problems encountered when traditional process of fast-slow variable dissection method with two slow vari-

ables is performed to analyze the bursting dynamics is overcome by introducing the dimension C_{lum} , due to that the fast subsystem does not contain C_{lum} . Such a method can be extensively employed to analyze bursting patterns modulated by C_{in} and C_{lum} in other nervous system or neuronal model such as PB complex and β -cells [23, 36, 53, 54]. Such a method is different from the fast-slow variable dissection to bursting with two slow variables used in Ref. [54] (case-1) and Ref. [58] (case-2), due to that the characteristics of the slow variables or the relationship between the slow variables are different.

Secondly, the initial phase of burst is identified with the novel method of fast-slow variable dissection. The burst is identified to begin from the saddle-node bifurcation curve of the two-dimensional fast subsystem (V, n). However, the termination phase mismatches the saddle-homoclinic bifurcation curve of the subsystem (V, n), due to that C_{in} is much slower than C_{lum} in quiescent state.

Last, the burst is identified to terminate at the saddle-homoclinic bifurcation point of the fast subsystem (V, n, C_{in}) with C_{lum} taken as bifurcation parameter, due

to that C_{lum} is the slowest variable in the burst duration. One on hand, the present paper shows that the combination of 3 manners of fast-slow variable dissection more effective than one manner. On the other hand, the deep understanding to the complex bursting is helpful for the modulation to the bursting patterns related to pathological pain.

Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

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