Itinerant Dynamics of Class I* Neurons Coupled by Gap Junctions

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Abstract. Although it is generally recognized that " interneurons generate a variety of synchronous inhibitory rhythms in the neocortex··· " (J. R. Gibson *et al.*) and they " may play a key role in coordinating cortical activity··· "(M. Galarreta & S. Hestrin), little is known how they behave in the *in vivo* neocortex. A salient property of some interneuron systems in the neocortex is that they are coupled by gap junctions (GJs) - a kind of electrical couplings very intensively between the same type of interneurons. In our previous studies, we reported the theoretical possibility that a class of neuron systems may exhibit spatio-temporal chaos when they are coupled by GJs, while the individual neurons, when isolated, exhibit only simple repetitive firings. This dynamics is emergent, and unveils only when cells are coupled by GJs. Mathematically, this phenomenon could be an expression of chaotic itinerancy among pseudo-attractors (or, *attractor ruins*). In view of the ubiquity of GJs - there are *at least* five distinct interneuron systems coupled by GJs in the six layers of the neocortex, and in view of the significance of the concept of chaotic itinerancy in memory dynamics we give in this lecture a review about general property and collective dynamics of GJ-coupled neuronal systems.

1 Introduction

1.1 Background

Recent physiological data recognizes the massive presence of gap junctions (GJs) among interneuorns in the neocortex, which poses serious questions about the organization of neocortex, the possible role of interneurons in neocortical rhythm generations and the role of interneurons in cognitive functions. In our previous studies (Nakano *et al.*, 2003 [21]; Fujii and Tsuda, 2004 [8]), we reported the theoretical possibility that a class of neuron systems may exhibit spatio-temporal chaos when they are coupled by GJs, while the individual neurons, when isolated, exhibit only simple repetitive firings under injected background currents. This dynamics is emergent, and unveils only when cells are coupled by GJs. Mathematically, this phenomenon could be an expression of *chaotic itinerancy* among pseudo-attractors (or, *attractor ruins*), which could be characterized as transiently synchronized states. In view of the ubiquity of GJs - there are *at least* five distinct interneuron systems coupled by GJs in the six layers of the neocortex, and in view of the significance of the concept of chaotic itinerancy and transient synchrony in memory dynamics (Tsuda and Fujii [32], *this issue*), we give in this lecture a review about general property of collective dynamics in GJ-coupled neuronal systems. The emphasis here is on the itinerant behavior made by model neuron systems of *realistic* cortical neurons.

Gap junctions exist in, as mentioned in the above, at least *five* distinct interneuron systems in the six layers of the neocortex. Among FS (fast spiking) neurons in the layer 2/3, among FSs and among LTS (low threshold spiking) neurons in the layer 4, among FSs in the layer 5/6. Recently, a new member joined to this GJ-coupled interneuron groups: multipolar bursting (MB) interneurons in the layer 2/3. (Blatow *et al.*, 2003 [1].) Gap junctions are not only ubiquitous, but *massive* ([9], [10], [29]). They form distinct networks, and some of them possess chemical synaptic connections, too. Although it is generally believed that " a (gap junction-coupled) network of FS cells in the neocortex may play a key role in coordinating cortical activity··· " (M. Galarreta & S. Hestrin, 1999 [9]), or " interneurons generate a variety of synchronous inhibitory rhythms in the neocortex··· "(J. R. Gibson *et al.*, 1999 [10]), little is known how those interneurons collectively behave when coupled by GJs in a massive way. In view of the fact that various distinct interneuron systems are involved in GJ couplings, one may be led to ask such general questions as: what kind of ionic channel properties or, what kind of nonlinearity in mathematical terms may lead to what kind of collective dynamics when they are coupled by GJs? In particular, one may ask what kind of neuronal processes may give rise to such an emergent chaotic dynamics ? These questions, together with their possible role in cognitive functions, have not been well understood from both mathematical and physiological points of view.

We may also envisage possible relations with some dynamical phenomena observed in the neocortex, e.g., transient synchrony and fluctuation in local field potentials (LFP) ([11]). See, also discussions in Tsuda and Fujii [32].

1.2 Gap Junctions in the Neocortex - a Quick Review

It is already three decades ago that the presence of gap junctions in primates neocortex was firstly reported ([28]). Very recently it is generally recognized that the GJs are really *massive* and *ubiquitous* in the neocortex - but only among interneurons. (See, e.g., [1], [9], [10] and [29]).

1. GJ couplings exist in the layers 2/3, 4, and 5/6. In the layer 2/3, there are two distinct systems: FS and MB interneurons. MBs may send chemically-induced spikes to FSs, but not *vice versa* (Blatow *et al.* [1], 2003). The layer 4 has two distinct GJ-coupled systems: FS and LTS-systems. The two systems may also be coupled by gap junctions each other, but the couplings are not so dense ([9], [10], [29]). The layers 5/6 include a GJ-coupled FS interneuron system.

2. GJ-couplings are neuron type specific within the same type of neurons, with an exception: FS-LTS in the layer 4.

3. Connectivity within a neuron group is not fully understood, but connections are massive. For example, (although there are some inconsistency among known data), one may say that the GJ couplings are far more massive (or, at least not less) than synaptic connections, although functions of the two " couplings/connections " as well as connectivity are *not* equal. See, [9], [10] and [29]. Interplay of those two connection systems should play important roles in neocortical rhythm genesis.

   In view of its dense GJ-couplings, an interneuron system, if it is GJ-coupled, may better be regarded primarily as *a GJ-coupled system.* Chemical connections may play their role on the basis of the intrinsic " rhythms " induced by GJs.

4. Origins of EPSPs (projected on GJ systems): some evidence exits that they are fed in a feed forward manner, but details are largely unknown yet, including the possibility that they might receive some top down " signals " from other cortical areas etc. Dantzker and Callaway. ([5]) reported that both the FS interneurons and pyramidal cells (PYR) in the layer 1/2 are fed from the layer 4 in a parallel way. It appears that FSs do not receive (at least strong) EPSPs from PYRs of the same layer, while PYRs are inhibited by these FSs. There are other interneuron groups (probably, with no GJ couplings) which receive excitatory inputs from PYRs. This gives some idea about the general organization of PYR-FS cell interactions. Whether and how this GJ-coupled FS interneuron system receives inputs from other cortical/non-cortical areas as " top down " or " control " signals is not known.

2 Single Cell Behavior of Class I Cells - Some Examples

2.1 Historical Background

Hodgkin pointed out in 1948 that there exist two classes of " neurons " (actually, " axons "). In his paper of 1948 [15] (before he published the famous paper describing the Hodgkin-Huxley (HH) equations) he wrote that class I " axons are capable of repetition over a wide range of frequencies, varied smoothly over a range of about 5-150 impulses per sec. ", and class II " axons usually give a train of impulses of frequency 75-150 /sec which was relatively insensitive to changes in the strength of the applied current ".

Rogawski commented in his review ([25], 1985) that the difference of the dynamic range property, that is, of spike firing characteristic, originates from the presence of I_A -current, a transient slowly inactivating potassium current. I_A is an outward potassium current, differs from the rectifying K^+ current I_K, in several important aspects, i.e., in its kinetics, in that it activates at more hyperpolarized level of membrane potential, and blocked by 4-AP, less sensitive to TEA (a blocker of I_K). I_A does not exist in squid axons on which the HH model is based. He stressed that this fact provides the basis of the class I characteristic of the most of cortical neurons.

It was Connor and his coworkers ([4], 1971; [3], 1977) who studied the " class I " neurons with I_A channel from model-theoretic standpoints. They derived Hodgkin-Huxley type equations with six variables, two among them coming from additional activation/inactivation states of the I_A-current. Based on the Connor's work, Rose and Hindmarsh ([26], 1989) reduced the Connor equations into two-dimensional equations with the spirit to approximate the six variable equations by a simpler system, and still keeping explicit relations to the original ionic currents. Similar attempts have been made to the original HH equations by, e.g., Rinzel ([23]) and others. Wilson ([33a,b], 1999) presented two-variable equations similar to the Rose-Hindmarsh equations to qualitatively approximate" essential dynamics " of neocortical class I and II neurons.

The argument of Rogawski ([25]) may be controversial in a few aspects. After his review appeared, it become recognized that there are *at least* two I_A-currents: I_{As} (or, I_D) I_{Af}, with difference in kinetics, activation/inactivation level and sensitivity to 4-AP. Rogawski's arguments may have been based on these two currents in a mixed-up way. Next, the class I property does not necessarily comes from I_A-currents. For example, the Morris-Lecar model, which was designed to " model " the crustacean neurons, with only Ca^{++} and K^{+} channels included, may have the class I property. We note, however, that it is generally recognized that most of cortical neurons are of class I (see, e.g., Cauli, [2]) in the sense of Hodgkin. But the ionic currents responsible to their class I characteristic appear to be not fully understood.

The concept of *class* I/II of neurons may be better understandable in a mathematical context. Namely, the difference of dynamic behavior between these two classes is attributed to that of generation mechanism of action potentials: *homoclinic bifurcations* (class I), and *subcritical Hopf bifurcations* (class II). In this respect, we note two points. Firstly, the *homoclinic* bifurcations do not mean a unique concept if viewed from a dynamical systems standpoint. As we shall see later, one may observe *saddle-node on a limit cycle bifurcations* for the Connor neuron family, and *saddle separatrix loop bifurcations* typically seen in the Morris-Lecar neurons in their class I regime. (See, also, Izhikevich [17].) This taxonomy, identified by the orbits in the phase plane and the bifurcation diagram, appears subtle, but it will affect the nature of collective behavior when coupled by GJs. The second note is that the HH model itself is of class II in most of biologically appropriate parameter values. It is reasonable to assume that a Hopf singularity (i.e., bifurcation point) is built-in in the HH equations, and in fact it can be observed numerically.

Although the concept of " class " of neurons and that of bifurcations as well do *not* depend on the number of variables, we proceed our arguments based primarily on a reduced form of two-variables, where the first variable, say V, may represent the membrane potential, and the second one, R, the " recovery " variable representing an activation state of, e.g., some potassium channels in a generalized sense [23], [26]. With the injected current strength being denoted by

i, the single cell equation may be written as:

$$\begin{cases} \tau_V \dfrac{dV}{dt} = f(V,R) + i \\ \\ \tau_R \dfrac{dR}{dt} = g(V,R) \end{cases} \tag{1}$$

All the ion channel characteristics are“ condensed ”in the nonlinearity of the functions of f and g here - but only in an approximate sense. The correspondence between the original ionic channel-based equations of HH-type and (1) is not one-to-one, but many-to-one. Note also that if one considers to describe a more general dynamic behavior of single cells like “ bursting ”, “ adaptation ”, etc. which are observed in pyramidal cells, or regular spiking interneurons and so on, one need to add *at least* another one variable to represent “ slow ” dynamics. However, in this lecture we restrict our discussions to equations of the type (1), and focus on the collective behavior of such cells coupled by GJs, rather than detailed dynamics of single isolated cells.

2.2 Class I and II Neurons in Two-variable Models

Let us begin with the two-variable model of the form (1). We denote by $\mathcal{N_V}$ and $\mathcal{N_R}$ the nullclines of the V and R equations: $\mathcal{N_V} = \{\ (V,R)\ |\ f(V,R){+}i{=}0\ \}$ and $\mathcal{N_R} = \{(V,R)\ |\ g(V,R){=}0\ \}$, respectively. $\mathcal{N_V}$ and $\mathcal{N_R}$ correspond to the sets of points in *(V,R)*-space where $\dfrac{dV}{dt} = 0$ and $\dfrac{dR}{dt} = 0$ hold, respectively. Within the framework of two-variable reduced model of the form (1), $\mathcal{N_V}$ takes a *cubic-like* form in most cases. On the other hand, the form of $\mathcal{N_R}$ characterizes the neuron property. As we shall give particular examples, the class I neurons are characterized by *quadratic-like* $\mathcal{N_R}$'s, and the class II neurons by *essentially linear* $\mathcal{N_R}$'s.

The FitzHugh-Nagumo (FHN) model ([7], [20]) is one of the most known *class II* “ neurons ”, which has an inclined *I-shaped* $\mathcal{N_R}$. Since $\mathcal{N_V}$ is *essentially* cubic, the point of intersections of $\mathcal{N_V}$ and $\mathcal{N_R}$ shifts according to the level of the injected current i, taken as a *bifurcation parameter.* For class II neurons, the intersection of the two nullclines is (in most cases) unique, and the nature of the intersection changes from a stable *node* (two real negative eigenvalues) to an unstable *spiral.* (i.e., a pair of complex conjugate eigenvalues with positive real parts). Between those two states, there appears a pair of pure imaginary eigenvalues which correspond to a Hopf bifurcation point.

For the convenience of later discussions, we introduce a few models of class I and II in explicit forms in the following.

Example 1. Morris-Lecar model – Regime I and II

Although the Morris-Lecar equation was firstly introduced to model crustacean neurons with Ca^{++} and K^{+} channels, it has frequently been used as a *theoretical* model. (Rinzel-Ermentrout [24], Izhikevich [17].) This ML model can be both of class I and II depending on its parameters.

$$\begin{cases} \dfrac{dV}{dt} = -g_{Ca} m_{\infty}(V)(V-1) + g_K R(V-V_K) + g_L(V-V_L) + i \\[2ex] \dfrac{dR}{dt} = q[R_{\infty}(V) - R]/\tau_R(V) \end{cases}$$

where

$$\begin{bmatrix} m_{\infty}(V) = [1 + tanh\{(V-V_a)/V_b\}]/2 \\ R_{\infty}(V) = [1 + tanh\{(V-V_c)/V_d\}]/2 \\ \tau_R(V) = 1/\cosh\{(V-V_c)/(2V_d)\} \end{bmatrix} \tag{2}$$

with

$$\begin{bmatrix} V_a = -0.01, V_b = 0.15, g_{Ca} = 1.0, g_K = 2.0 \\ g_L = 0.5, V_K = -0.7, V_L = -0.5, q = 1.15 \end{bmatrix}$$

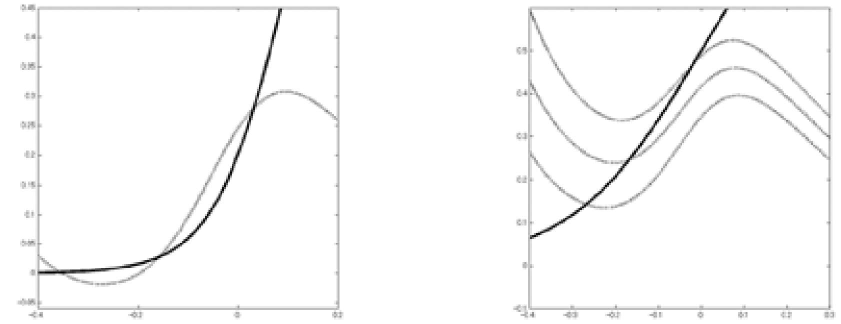

Fig. 1: Two regimes of the Morris-Lecar model Two nullclines are drawn in the phase (V, R)-space. (*Left*) Class I regime: $V_c = 0.1$, $V_d = 0.145$, q = 1/3; $i = 0.083$ (*Right*) Class II regime: $V_c = 0$, $V_d = 0.3$, q=0.2; $i = 0.2;0.3;0.4$

Fig.2 shows the orbit in the phase space in the case of Class I regime at the saddle separatrix loop bifurcation where the unstable and stable manifolds make a closed loop, i.e., a homoclinic orbit. As the current-level i increases, this loop splits from the saddle. Since the new born loops are close enough to the saddle, their period is very large just after they split from the saddle. This is the class I formation mechanism of spikes in the Morris-Lecar I case. Although this may provide an example of *class I* characteristic in Hodgkin's sense, those " spikes " are actually small membrane potential *oscillations* in a depolarized state.

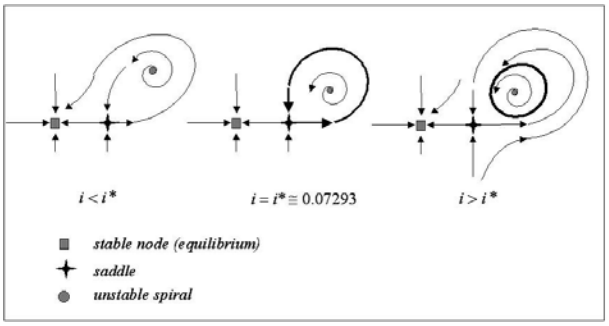

Fig. 2: Phase diagram of the Morris-Lecar model in Class I regime. The diagrams illustrate the birth of a *saddle separatrix loop bifurcation.* The left diagram shows the orbits when the current i is below the bifurcation point. As i increases, the unstable and the stable manifolds from the saddle (the *cross* mark) form a closed loop, i.e., *a homoclinic orbit (center).* Then, the loop splits from the saddle and forms a limit cycle (*right*).

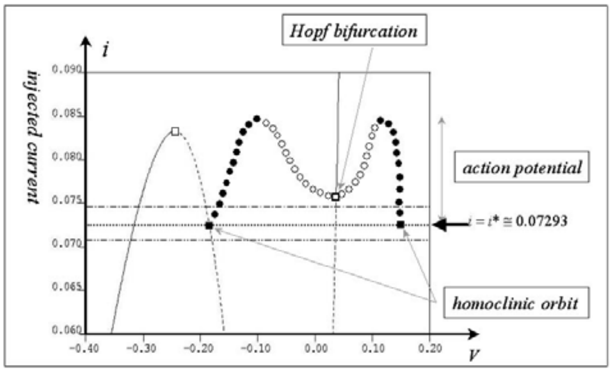

Fig. 3: Bifurcation diagram of the Morris-Lecar model in Class I regime. At the critical current value i=i*, there appears a homoclinic orbit. Filled circles indicate bifurcated stable branch of " spikes ", while the open circles are an unstable branch of spikes.

Example 2. A model of Connor-Rose-Hindmarsh (CRH) family

The Rose and Hindmarsh model based on the Connor equations is also written in the form of (1), where $\mathcal{N}_{\mathcal{R}}$ takes a *quadratic-like* U-shape. Let us consider (1) with the nonlinearity in the form of (3), following the formulation of Rinzel [23] and Wilson (1999, [33a]):

$$\left\{ \begin{array}{l} f(V,R) = -m_{\infty}(V)(V - V_{Na}) - g_K R(V - V_K) \\ g(V,R) = -R + R_{\infty}(V) \end{array} \right. \tag{3}$$

Nakano *et al.* ([21], 2003) considered a class I model of the form (1), (3), where

$$\left[\begin{array}{l} m_{\infty}(V) = 5.36 + 17.04V + 16.9V^2, R_{\infty}(V) = 1.29V + 0.53 + 3.3(V + 0.18)^2, g_K = 11.0 \\ V_{Na} = 0.48, V_K = -0.95, \tau_V = 1.0, \tau_R = 2.4 \end{array} \right. \tag{4}$$

which is a modified version of Wilson's Class I model (1999, [33a]). Eqs.(1), (3), (4) have an unstable *spiral* instead of the unstable *node* in the Wilson model. See, Fig.4.

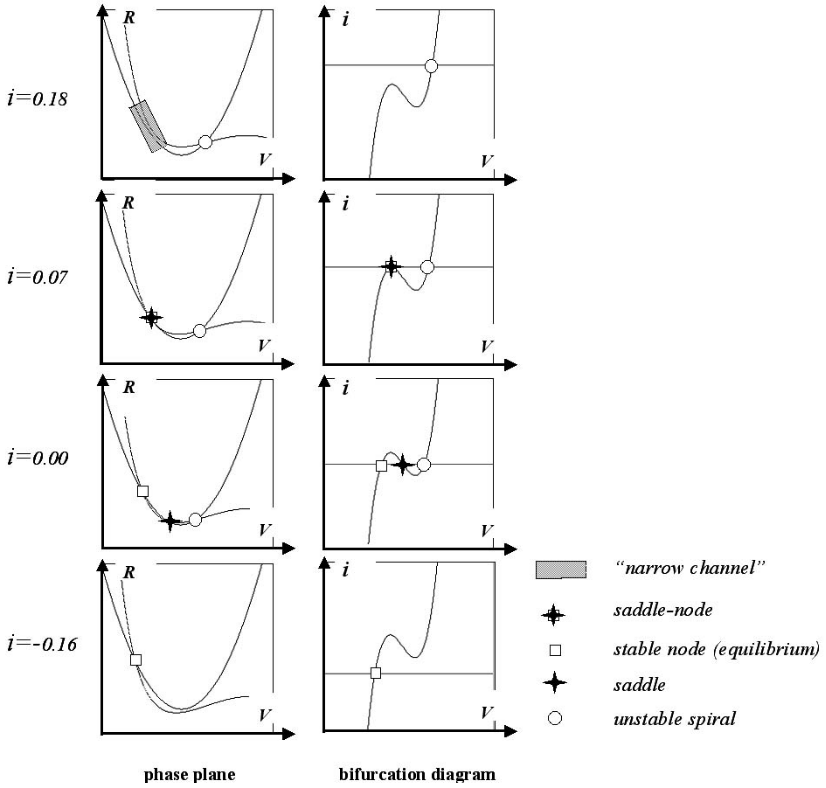

Fig. 4: Phase diagram of the Connor-Rose-Hindmarsh model. As the injected current i increases from the rest state, the nullclines become to have three intersections, i.e., a *stable node* (an equilibrium), a *saddle* and an *unstable spiral.* Then, the stable node and the saddle collide at a critical current value, where a homoclinic orbit appears from the saddle-node. See, also Fig.5. This is the *seed* of action potentials with the period $= \infty$. Note that after the current i traverses the saddle-node bifurcation point, there appears a " narrow channel " between the two nullclines.

The number of intersections of $\mathcal{N}_{\mathcal{V}}$ and $\mathcal{N}_{\mathcal{R}}$ varies from one to three, and then again back to one for such neurons when the current level i increases from the rest state. There appears a *saddle-node* bifurcation point at the critical level of i where the saddle and the node collide as is shown in Fig. 4 when $i = 0.07$. The salient property of the reduced Connor family is that as the injected current i traverses the saddle-node bifurcation point, there appears a *narrow channel* between $\mathcal{N}_{\mathcal{V}}$ and $\mathcal{N}_{\mathcal{R}}$. See, the top picture of Fig.4, at $i = 0.18$. Rose and Hindmarsh [26] emphasized that this is a consequence of the presence of I_A-current. Fig.5 illustrates how a saddle-node bifurcation yield a homoclinic orbit in the phase plane.

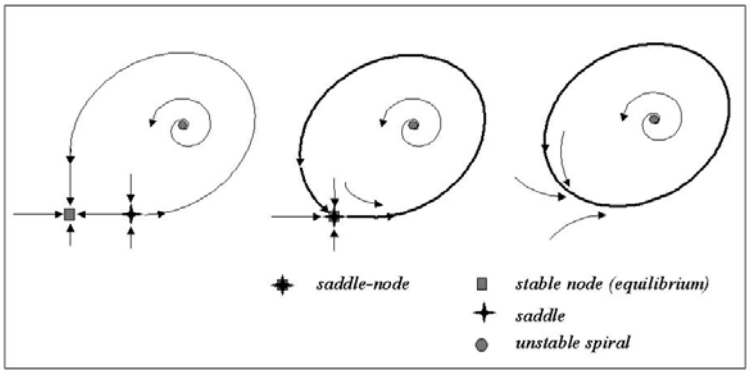

Fig. 5: Formation of limit cycles at a saddle-node bifurcation point for the Connor-Rose-Hindmarsh neuron. (*left*) There are two heteroclinic orbits from the saddle to the node (*left*), one of which becomes a large *homoclinic* orbit when the saddle and the node collide (*center*). Then, as the saddle-node disappears, the remaining closed loop turns into a limit cycle (*right*).

For the purpose of comparison, Nakano *et al.* ([21]) also considered a class II neuron model by Wilson (1999, [33a]) with a linear nullcline $\mathcal{N}_{\mathcal{R}}$.

$$\left[\begin{array}{l} m_\infty(V) = 17.81 + 47.71V + 32.63V^2, \\ R_\infty(V) = 1.35V + 1.03, \\ g_K = 26.0, V_{Na} = 0.55, \\ V_K = -0.92, \tau_V = 0.8, \tau_R = 1.9 \end{array}\right. \tag{5}$$

Fig.6 shows instantaneous spike rates as functions of injected current strengths for the class I (Eqs. (1), (3) and (4)) and class II (Eq. (5)) models. The lower box indicates the class I firings as the current increases.

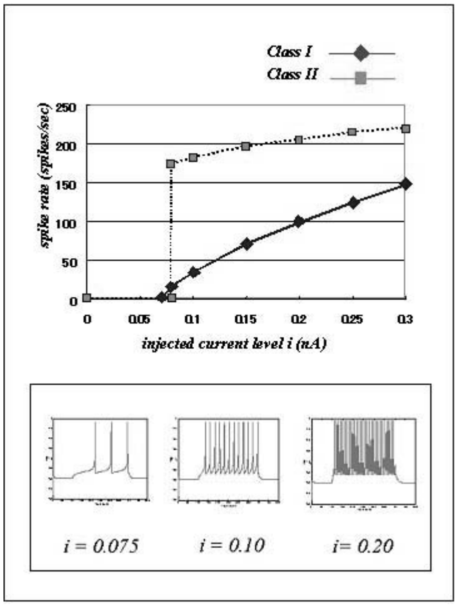

Fig. 6: Spike frequency characteristics of class I and II neurons (*top*) and the class I spike generation of a class I model due to Eqs. (1), (3) and (4) (*bottom*).

3 Class I vs. Class II Neurons under GJ Couplings - a Zoology

In this section we give a zoology of spatio-temporal dynamics emerged by GJ-coupled system of neurons of class I and II. The aim here is to understand the variety of potential dynamics *intrinsic* to class I and II neuronal systems that may emerge when coupled by GJs. With this in mind, we examine the GJ-coupled dynamics under a simple situation: under uniform GJ-couplings without synaptic connections, i.e., with no internal irregularity of the network structure and with no external fluctuation of injected currents. This may help us to know the nature of intrinsic coupled dynamics: the difference between cells of class I and II, between two prototypes of the class I neurons etc..

For instance, Nakano *et al.* [21] have shown that the modified Connor-Rose-Hindmarsh system, i.e., Eqs. (1), (3) and (4) with nearest neighbor couplings exhibits extensive spatio-temporal chaos under a spatially and temporally constant injected current which puts the system near the saddle-node critical level. As is shown in the previous section (Fig.6), those neurons show only repetitive firings when isolated. Han *et al.* [12a,b] reported that the Morris-Lecar model in the class I regime exhibits *dephasing* of oscillations under all-to-all couplings.

In the actual cortex GJ couplings are obviously not uniform, and the spatial connectivity is not fully understood. There are also chemical synapses among interneurons which may exert inhibitory effects on the network dynamics. Potential and emergent dynamics intrinsic to GJ-coupled systems we introduce here may provide a basis for the study of interplay of the GJ-induced dynamics with those synaptic interactions, and interneuron-PYR neuron interactions. Note that the FS-PYR structural configuration mentioned in Sect. 2.1 (Dantzker and Callaway [5]) may justify our strategy to study as a first step the intrinsic dynamics of interneurons.

We first summarize the results of numerical works done by Nakano *et al.*[21] in the following. Then, we discuss the collective dynamics of ML systems.

3.1 Gap Junction Couplings

Gap junctions are assumed to take the following form according to Schweighofer *et al.* [27].

For j =1,...,N;

$$\begin{cases} \tau_V \dfrac{dV_j}{dt} = f(V_j, R_j) + I_j + J_j \\ \tau_R \dfrac{dR_j}{dt} = g(V_j, R_j) \end{cases} \tag{6}$$

where I_j's stand for injected background currents (which are assumed to be constant in time and space in this simulation), while J_j's represent the currents induced by gap junction couplings:

$$J_j = cc \sum_{nb_j} (V_{nb_j} - V_j), (nb_j \quad \in \ \textit{coupled neigbor cells}) \tag{7}$$

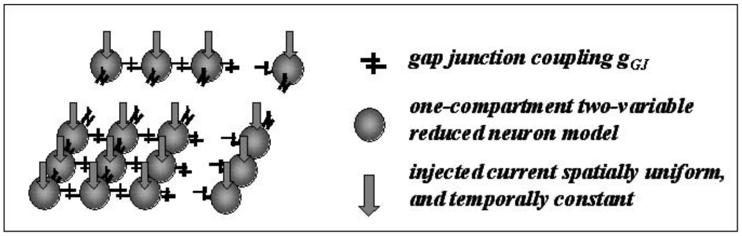

Fig. 7: The configurartion of GJ-couplings considered. Neurons are arranged as a two (or, one) dimensional array. GJ-couplings are either 4 or 8 (or, 2) nearest neighbor-couplings. Coupling conductances g_{GJ}'s are assumed to be constant.

Here, g_{GJ} is a coupling constant, which is assumed to be identical for all connections in the present simulation. When the system is two (one)-dimensionally lined up with four (two) neighbors coupling, this is the nearest neighboring coupling equivalent to a linear *discrete* diffusion process. For cells at the boundaries, the couplings are only with the inner cells according to the definition by Eq.7. (Usually, this is referred to as the Neumann boundary condition.)

A note about the coupling term J_j's. Scheweighofer *et al.* ([27]) formulated the GJ-coupling term with a mild nonlinearity. However, since we found no *qualitative* difference at least from collective dynamics standpoints, we simply assume the linear discrete GJ effects (7) throughout this lecture.

3.2 Chaos in Two Class I Systems

a. Nakano *et al.* model - a member of the Connor-Rose-Hindmarsh family

The model defined by Eqs. (1), (3) and (4) of class I neuron of the Connor-Rose-Hindmarsh family exhibits extensive spatio-temporal chaos with, even spatially and temporally constant, injected currents near or over the saddle-node critical point. In general, this GJ-coupled classI system has several typical dynamical patterns: synchronous repetitive firings, periodic *metachronal*[1] firings, and spatio-temporal chaos as well as synchronous resting state, depending on the GJ conductance and the background current level. Note that chaos appears very robustly with regard to the background current strength, the strength of GJ conductance and even the coupling structure. See, Figs.8, 9 and 12 below. The maximal Lyapunov exponents are positive in such cases. Individual cells exhibit extensive fluctuations both in phase and magnitude.

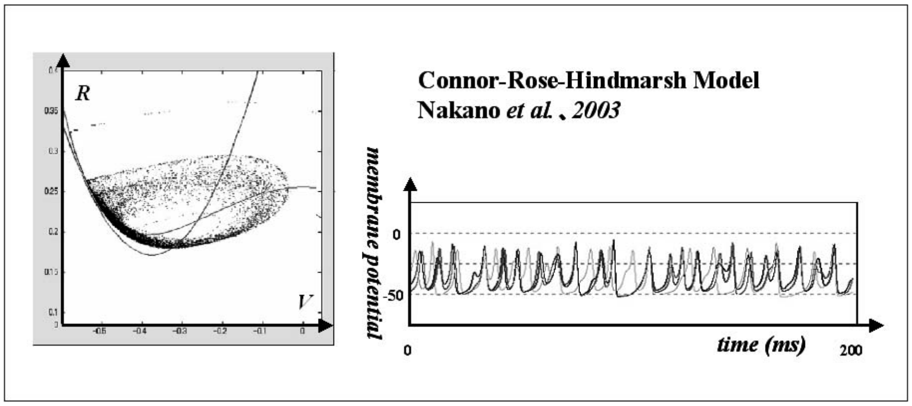

Fig. 8: Chaotic dynamics in the phase plane and the membrane potentials of three representative neurons among 10x10 GJ-coupled system of Eqs. (1), (3) and (4).

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[1] A *metachronal* wave is a wave produced by successive phase shifts of neighboring neurons' activity like the movement of centipedes or cilium and flagella.

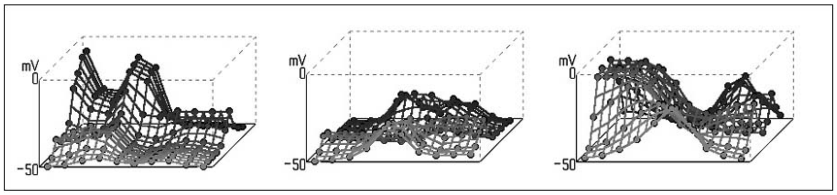

Fig. 9: The snapshots of GJ-coupled class I neuron systems of Eqs. (1), (3) and (4).

b, Morris-Lecar Model in Class I Regime

The Morris-Lecar model has a parameter range of class I regime. Han *et al.* ([12a,b]) have observed *dephasing* of oscillations under all-to-all couplings. In our nearest neighbor couplings, we can also observe alternation of phases of small amplitude oscillations at a *depolarized* potential level. Also the orbit intermittently itinerates around the saddle equilibrium. Although a snapshot of the spatial pattern appears to be similar to the Connor family, the dynamics in the phase plane of individual cells seems very different in that the orbit oscillates around the limit cycle in a " depolarized " state and never turns back to the rest state. See, Fig.10.

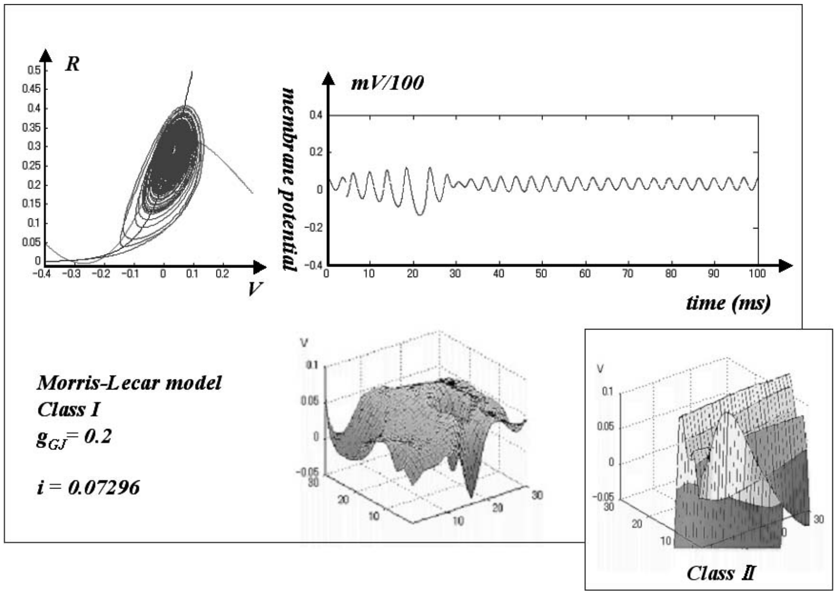

Fig. 10: Behavior of GJ-coupled Morris-Lecar model in regime I. The saddle separatrix bifurcation occurs approximately at $i = 0.07293$. The class II regime, on the other hand, has plane traveling waves (*right*).

3.3 Gap Junction-coupled Class I and Class II Dynamics

We show some typical spatio-temporal patterns exhibited by class I and II neurons. The first row of Fig.11 below shows the chaotic dynamics of 80x80, 4-neighbor coupled Class I neurons. The next two rows indicate both class II model behaviors with the same configuration as the above case. Since Class II equations originate as models of action potential propagations in axons, it is natural that they exhibit traveling waves or spiral waves when they are coupled by GJs in a one- or two dimensional array. This appears in the third row, while they exhibit also complicated spatially non-uniform periodic patterns as in the second row. Morris-Lecar equations of regime II show plane traveling waves. (See, Fig 10.)

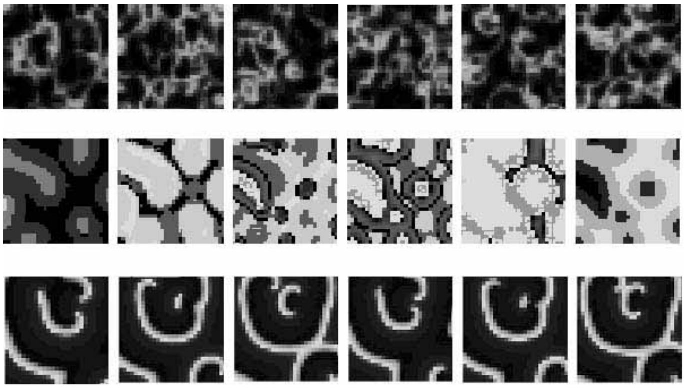

Fig. 11: Typical spatio-temporal patterns of Class I neurons defined by Eqs. (1), (3) and (4) (*top*), and class II neurons Eqs. (1), (3) and (5) (*center* and *bottom*).

3.4 Spatial Scales of Chaotic Patterns

Fig.12 (a), (b) show snapshots of membrane potential contours made by 80x80 coupled Connor family neurons Eqs.(1), (3) and (4), with increasing gap junction conductance g_{GJ}. This shows how *robustly* spatio-temporal chaos appears; it appears in a wide range of parameters near the saddle-node bifurcation points, and even for far larger injection currents if g_{GJ} is smaller. Fig.12 (a), (b) are the cases for 4- and 8-nearest neighbor couplings. Also, the size of spatial patterns become larger when the coupling g_{GJ} is set stronger.

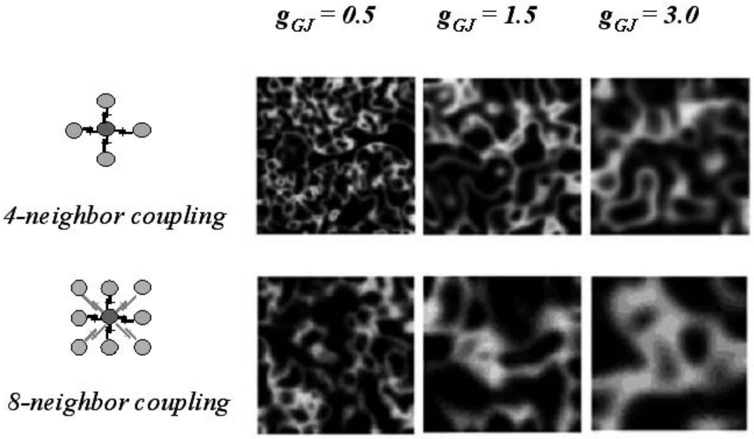

Fig. 12: Snapshots of contours of membrane potentials of 80x80 class I* neurons. (a) (top) 4nearest neighbor couplings (b) (bottom) 8-nearest neighbor couplings The gap junction strength g_{GJ} is, from left to right, 0.5, 1.5 and 3.

4 Class I* - Essential Nonlinearity

We have introduced the basic possibility that there is some class of neurons in the Connor-Rose-Hindmarsh family, which emerges spatio-temporal chaos when they are coupled by GJs under a certain level of background currents. The aim of this section is to consider the question: what is the essence of the nonlinearity of the model which may induce chaotic behavior when coupled by GJs?

4.1 Class I*

We define a neuron class, say I*, in an abstract setting, which includes (a part of) the class I neurons of Connor type. Let I* denote a subclass of class I neurons, in which there is an open interval $\mathcal{I} = (i^*,\ i^{**})$ of injected currents such that for all $i \in \mathcal{I}$, it holds that

1. there is a family of closed orbits $\mathcal{O}(i)$ with periods $\mathit{\Pi}\ (i)$ such that
$$\lim_{i \to i*} \mathit{\Pi}(i) = +\infty$$
2. a *narrow channel* appears between the two nullclines for $i > i^*$, and
3. an unstable *spiral* fixed point exists inside the orbit $\mathcal{O}(i)$.

The second condition implicitly assumes that the channel has a finite “ length ” and the “ width ” of the channel changes proportionally to $\mathit{\Delta} i = i\text{-}i^*$, i.e., the excess of current over the critical current i^*. We note that during when an orbit is passing inside the “ narrow ” channel, the “ neuron ” undergoes the repolarizing process from the hyperpolarizing state. Since the orbit is close enough to the two nullclines during that period, the recovery proceeds very slowly with the speed proportional to Δi.[2] The period of an action potential discharge drastically affected by fluctuations of the current near i^*, and lengthens or shortens according to the magnitude of Δi, i.e., the *width* of the channel.

The last condition claims that the closed orbit $\mathcal{O}(i)$ is *filled in* by infinitely many spiral orbits. Note that we assume the class I property in the sense of Hodgkin as stated in the first condition, but not necessarily a homoclinic bifurcation, although the latter is a natural situation in most neuron models.

We hypothesize that class I* neurons, when coupled by gap junctions, exhibit extensive spatio-temporal chaos in some parameter regions[3] [4] as its emergent property of coupled systems.

4.2 Models with Class I* Essential Nonlinearity

It is not difficult to construct simple models of class I*. For instance, the readers can easily see that a model with a cubic $\mathcal{N}_{\mathcal{V}}$ and a quadratic $\mathcal{N}_{\mathcal{R}}$ can be in the class I* with appropriately chosen parameters. The first example is our one (μ-)parameter family.

μ -model:

$$\begin{cases} \dfrac{dx}{dt} = -y + f(x) + i \\[2ex] \dfrac{dy}{dt} = -y + g(x) \end{cases} \tag{8}$$

with

$$f(x) = -\mu x^2 (x - \frac{3}{2}), \; g(x) = \mu x^2$$

The μ -family possesses necessary and sufficient features to express class I* neurons, and hence the essential minimum. This minimum model for the Connor equations may have a similar position which the FitzHugh-Nagumo model has to the Hodgkin-Huxley equations in a mathematical sense, but not in an electrical sense. A note should be added with regard to the Hindmarsh and Rose model ([14b], 1984) which has one slow variable and two-variables, introduced to simulate bursts in hippocampal cells. As Kaas and Petersen ([18], 1987) and

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[2] One might think that even for a system without a narrow channel, orbits may proceed very slowly near the“ ruin ”of a saddle-node. In fact, this makes the system to behave as class I in the sense of Hodgkin. However, the claim for finite length of the channel is the key property for class I* property.

[3] There are neurons of class I, but not belong to class I*. Also, some class I neurons in Connor family may not be of class I*.

[4] We should also choose an appropriate set of the time constants τ_V and τ_R.

Hansel and Sompolinsky (1992, [13]) worked out, a *single neuron* of the three-variable Hidmarsh-Rose model exhibits a chaotic behavior for a limited interval of injected current. Interestingly, if the third slow variable is omitted, the remaining equations for the two-variables are within the class I* family, and have essentially the same nonlinearity as the μ-family. Thus, the essence of the chaos genesis for the three-variable Hindmarsh-Rose model appears to be in its class I* property, where slow oscillations serve as a midwife. For the two-variable Connor family the current inflow/outflow from neighboring cells through GJs plays the role of unveiling the intrinsic chaos.

Piecewise Linear Class I* Model

We can define a class I* piecewise linear model, with a saw teeth shaped, cubic-like $\mathcal{N}_{\mathcal{V}}$ and quadratic-like $\mathcal{N}_{\mathcal{R}}$. This may provide a theoretical model that possesses the essence of the class I* property. See, Fig.13.[5] This simple model yields spatio-temporal chaos typically observed in class I* family. See, Fig.14.

$$
\left[\begin{array}{ll}
f(x) = \begin{cases} -\phi_L x - (\phi_0 + \phi_L)\ell, & x < -\ell \\ \phi_0 x, & \mid x \mid \leq \ell \\ -\phi_R x + (\phi_0 + \phi_R)\ell, & x > +\ell \end{cases} & \\
 & \\
g(x) = \begin{cases} -\psi_L(x-\alpha) + \beta, & x \leq \alpha \\ +\psi_R(x-\alpha) + \beta, & x > \alpha \end{cases} & \\
\text{with} & \\
\phi_L \quad = 1.42, \phi_0 = 1, \phi_L = 1.42, \ell = 1.1; & \\
\psi_L \quad = 1.4, \psi_R = 3.2, \alpha = -0.8, \beta = -1.6 &
\end{array}\right. \tag{9}
$$

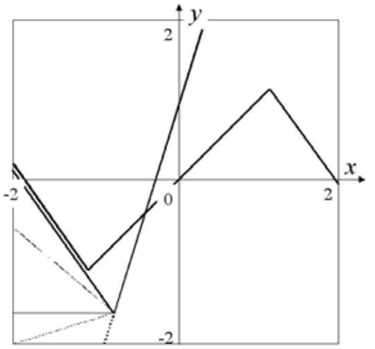

Fig.13: This model is obtained just by replacing the quadratic and cubic functions in μ-model by piecewise linear functions. By modifying parameters, one can obtain piecewise linear versions of class I*. Moreover, one can metamorphose the model continuously from class I*, class I without narrow channel, Morris-Lecar and even to class II neurons. The thick solid lines correspond to a class I* nonlinearity (Eq.9), which yields a spatio-temporal chaos typical in class I* family. See, Fig. 14.

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[5] The piecewise linear model metamorphoses continuously to models of a variety of other classes, e.g., piecewise linear versions of class I*, class I *without* narrow channel, Morris-Lecar and even class II neurons by changing a few parameters in the model.

5 Itinerant Dynamics in Class I* GJ-coupled Systems

We have discussed some aspects of the genesis of spatio-temporal chaos which may be intrinsic to class I* neuron models. In this section, we turn to the question of the nature of such global dynamics. One of the authors (I.T.) has argued that memory dynamics in the brain could be characterized as *chaotic itinerancy*, typically observed in high-dimensional dynamical systems. Chaotic itinerancy is addressed as a transitory and sometimes " nonstationary " dynamics. The dynamical orbits once approach one of " quasi-attractors " (or, " attractor ruins ") and stay for sometime with a certain distribution, and escape there and approach to other ruins. This transitory dynamics continues without external perturbations. Here the quasi-attractors may be possible to define in terms of the concept introduced by Milnor ([19]). Chaotic itinerancy is characterized by the presence of many near-zero Lyapunov exponents, slow decay of correlations/ (mutual) information, history (path)-dependent transition, no ergodicity, nonconvergence or an extremely slow convergence of near-zero and/or even the largest Lyapunov exponents in some case. See, Tsuda ([30]-[32]) for more details.

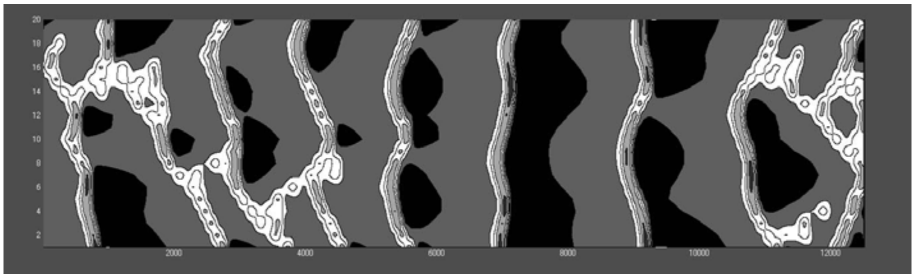

Fig14: Contour map of membrane potentials of 20 neurons of class I* piecewise linear neurons coupled with the two neighbors by gap junctions with $g_{GJ} = 0.2$. The vertical and horizontal directions indicate respectively the neuron positions, and the time (0 - 250 msec). Each neuron receives a constant injected current without any external fluctuations. No structural irregularity exists in this model. (From Fujii and Tsuda [8], 2003.).

Figure 14 shows a contour map of the time series of membrane potentials observed in the GJ-coupled piecewise linear class I* neurons. It appears that no classical attractors exist in the system, and we observe *metachronal* waves which chaotically repeat creations and annihilations. If a *metachronal* wave with a short time lag could be viewed as a *synchronized state*, Figure 14 and other examples, including the μ-family, of our numerical results may indicate the presence of *transient synchrony* - chaotic alteration of *synchronized* and *desynchronized* states; the alternation is chaotic both in its timing and spatio-temporal patterns.[6]

Based on numerical studies, we propose that these transitions can be described as chaotic itinerancy. Further studies on mathematical mechanism of the chaotic transitions are necessary for understanding the global itinerant dynamics observed in class I* family.

6 Concluding Remarks

We have demonstrated in this lecture a theoretical possibility that gap junction-coupled neuron systems may emerge spatio-temporal chaos, if they possess a certain kind of nonlinearity, which is basically induced from ionic channel properties of the cell. We have shown a zoology of spatio-temporal patterns which neurons of class I* and II could exhibit as their intrinsic dynamics.

We then characterized the neuron property as class I* which may lead neurons to emerge spatio-temporal chaos when coupled by GJs. This classification is based on models with two-variables. The essential nonlinearity of class I* is summarized as: the presence of narrow channel and a spiral fixed point, together with the presence of a homoclinic orbit due to a saddle-node bifurcation in a generalized sense. We have given two simple theoretical models of class I* nonlinearity.

Through numerical studies, we hypothesize that those spatio-temporal chaos can be described as chaotic itinerancy itinerant among quasi-attractors (or, *attractor ruins*), which are characterized as synchronous states of groups of neurons. The global dynamics are thus expressed as transitory dynamics between synchronous and desynchronous states. In a word, *synchrony within chaos* should be the direction for further investigation. Mathematical mechanisms of emergent chaos in high-dimensional systems are, however, far from fully understood, the results here are mostly through numerical studies, and many statements presented here are only in a form of hypothesis. To understand the mathematical mechanism of the transitory dynamics in class I* GJ-systems we need further studies.

Physiological meaning of the principal condition for class I* nonlinearity, i.e, the existence of narrow channel is not trivial, though Rose and Hindmarsh ([26]) emphasized that it is a consequence of I_A-currents based on the Connor formulations ([4]). See, also the arguments of Rogawski ([25]). In this respect, since so many distinct interneurons, FS, LTS and MB cells, are involved in GJ couplings in the neocortex, physiological study about ionic channel properties, as well as efforts in mathematical modelings should be crucial.

We proposed ([32]) the i*nhibitory chaotic field hypothesis*, suggesting the relation of the hypothetical transitory dynamics of interneuron systems to the observed neocortical LFP (local field potential) fluctuations. This says that the origin of the LFP fluctuations and stimulus-dependent transient synchrony, firstly observed and claimed by Gray [11] as the indicator of *feature binding*, is the itinerant chaos exhibited in gap junction-coupled interneuron systems consisting of class I* neurons. It should be noted, however, that chaotic fluctuations of inhibitory interneurons in cortical layers, are not

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[6] In our numerical data we generally observe the dimension gap, i.e., the Lyapunov dimension (an approximation of the Haussdorf dimension of a chaotic attractor) is bigger than the topological dimension by more than one. This dimension gap stems from a large number of negative Lyapunov exponents with a small absolute value. This brings about distributed attractors in phase space.

directly reflected in LFP. It should be a result of interplay of GJ-coupled neuron systems and pyramidal systems. About further discussions on possible cognitive functions of itinerant interneuron dynamics, please refer to our another paper (Tsuda and Fujii [32] , *this issue*).

Although many questions remain open, we hope that our study may provide a new scope for the study of neocortical dynamics and its cognitive role.

Acknowledgments

The authors would like to express their special thanks to the other members of the Dynamical Brain Group (" Gang of Five "), Prof. M. Tsukada (Tamagawa University), Prof. K. Aihara (the University of Tokyo) and Prof. S. Nara (Okayama University). They also thank to H. Yokoyama, M. Nakano, M. Ibuki (Kyoto Sangyo University) for the calculations of dynamics of various models and bifurcation structures. The first author (H.F.) was supported by the Advanced and Innovational Research Program in Life Sciences, while the second author (I.T.) was partially supported by Grant-in-Aid no. 12210001 on priority areas (C), Advanced Brain Science Project, both from Ministry of Education, Culture, Sports, Science and Technology, the Japanese Government.

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