Temporal Integration by Stochastic Recurrent Network Dynamics With Bimodal Neurons

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1Laboratory for Neural Circuit Theory, RIKEN Brain Science Institute, Saitama; 2Corporate Research Group, Fuji Xerox Co., Ltd., Kanagawa; 3Department of System Neuroscience, Tokyo Metropolitan Institute for Neuroscience; and 4Brain Science Research Center, Tamagawa University, Tokyo, Japan

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Okamoto H, Isomura Y, Takada M, Fukai T. Temporal integration by stochastic recurrent network dynamics with bimodal neurons. J Neurophysiol 97: 3859–3867, 2007. First published March 28, 2007; doi:10.1152/jn.01100.2006. Temporal integration of externally or internally driven information is required for a variety of cognitive processes. This computation is generally linked with graded rate changes in cortical neurons, which typically appear during a delay period of cognitive task in the prefrontal and other cortical areas. Here, we present a neural network model to produce graded (climbing or descending) neuronal activity. Model neurons are interconnected randomly by AMPA-receptor–mediated fast excitatory synapses and are subject to noisy background excitatory and inhibitory synaptic inputs. In each neuron, a prolonged afterdepolarizing potential follows every spike generation. Then, driven by an external input, the individual neurons display bimodal rate changes between a baseline state and an elevated firing state, with the latter being sustained by regenerated afterdepolarizing potentials. When the variance of background input and the uniform weight of recurrent synapses are adequately tuned, we show that stochastic noise and reverberating synaptic input organize these bimodal changes into a sequence that exhibits graded population activity with a nearly constant slope. To test the validity of the proposed mechanism, we analyzed the graded activity of anterior cingulate cortex neurons in monkeys performing delayed conditional Go/No-go discrimination tasks. The delay-period activities of cingulate neurons exhibited bimodal activity patterns and trial-to-trial variability that are similar to those predicted by the proposed model.

INTRODUCTION

Graded neuronal activity that steadily increases or decreases during a delay period is typically seen in the prefrontal cortex when animals are anticipating sensory cues (Rainer et al. 1999), motor responses (Hoshi et al. 2000), or rewards (Watanabe 1996). In addition, such a graded activity may provide neural substrates for decision making (Barraclough et al. 2004; Brody et al. 2003; Constantinidis et al. 2002; Hanes and Schall 1996; Hernández et al. 2002; Lo and Wang 2006; Mazurek et al. 2003; Shadlen and Newsome 2001; Takeda and Funahashi 2002), invariant recognition of stimulus sequence (Hopfield and Brody 2001), and perception of interval timing (Durstewitz 2003; Kitano et al. 2003; Leon and Shadlen 2003; Reutimann et al. 2004). It is widely accepted that delay-period activity of prefrontal neurons may be generated by reverberating synaptic input (Goldman-Rakic 1995) and the graded activity was modeled by recurrent networks with slow synapses (Wang 2002), special wiring patterns, or neuron-dependent activation thresholds (Miller et al. 2003; Seung et al. 2000), as well as by single-neuron mechanisms (Durstewitz 2003). The mechanism underlying graded neuronal activity or, more generally, temporal integration of an external input has been the focus of extensive investigation.

Here, we propose a recurrent neural network of stochastic neurons as a model for neural mechanisms for temporal integration. In the network, spike-triggered afterdepolarizing potentials enable the model neurons to exhibit distinct firing states, a baseline firing state, and an elevated firing state in the presence of an external input. Then, driven by this input, the neurons show transitions between these two states in a temporally organized manner. If we appropriately tune the weight of uniform recurrent synapses and the variance of background input, the number of neurons in the elevated firing state changes slowly at an external input-dependent speed to yield a graded population activity. The present temporal integration mechanism differs from the previously proposed deterministic mechanisms using bistable neurons (Koulakov et al. 2002) or bistable dendritic compartments (Goldman et al. 2003; Lowenstein and Sompolinsky 2003; Teramae and Fukai 2005). The present stochastic model does not assume any mechanism that relies on differences between individual processing units, such as neuron-dependent activation threshold. All neurons, and even recurrent synapses, can be identical. From trial to trial, stochastic noise recruits neurons sequentially for graded activity in a randomized order.

We examined the validity of the proposed mechanism by analyzing the graded activity recorded previously from the anterior cingulate cortex (ACC) of monkeys performing delayed Go/No-go discrimination tasks (Isomura et al. 2003). The ACC, which engages in motor (Isomura and Takada 2004; Shima and Tanji 1998), cognitive (Botvinick et al. 2004; Brown and Braver 2005; Greene et al. 2004; Shidara and Richmond 2002), and emotional (Bishop et al. 2004) functions, receives major inputs from the prefrontal and limbic cortices (Dum and Strick 1993). These inputs might be integrated during the Go/No-go discrimination tasks. The graded neuronal activity in ACC displayed bimodal frequency distributions and large trial-to-trial variability analogous to those predicted by the present model, suggesting that it has a biological reality.
METHODS

Recurrent network model

Typically, we used a network of 500 excitatory and 100 inhibitory neurons. Each excitatory neuron projects to 10% of randomly chosen other excitatory neurons and to all inhibitory neurons, whereas each inhibitory neuron projects to all excitatory neurons, but not to other inhibitory neurons. We subsequently show the mathematical details of the present network model. The values of parameters are listed in a separate subsection.

The membrane potential dynamics of an excitatory neuron is described by leaky integrate-and-fire neuron models as $C(dV/dt) = -G_L(V - V_L) - I_{AMPA} - I_{GABA} + I_{ext} + I_{BG}$, where $C$ is the membrane capacitance, and $G_L$ and $V_L$ represent the conductance and reversal potential of leak current, respectively. When $V$ reaches threshold $V_T$, the neuron generates a spike. Then, $V$ is reset to $V_{reset}$ and is clamped at this voltage during a refractory period. Each postsynaptic spike triggers $Ca^{2+}$ entry into the cell body and raises the concentration of intracellular $Ca^{2+}$. The time course of the $Ca^{2+}$ concentration is given as $d[Ca^{2+}]/dt = -[Ca^{2+}]/\tau_{Ca} + \Delta_C \delta(t - \tau_C)$, where $\tau_C$ denotes the time at which the postsynaptic neuron fires. Then, $Ca^{2+}$-dependent cationic current generates a depolarizing potential that follows the spike generation. The current is modeled as $I_{Ca} = g_{Ca}(V - V_{Ca})(Ca^{2+})^4\theta(V)/asps, where $Ca^{2+}$ is known to be abundant in cortical neurons (Haj-Dahmane and Andrade 1997; Okada et al. 1999).

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)–receptor-mediated recurrent synaptic input is described as $I_{AMPA} = g_{AMPA}(V - V_{AMPA}) \sum_n p_n$, where the sum is taken over presynaptic neurons. When the nth presynaptic neuron fires, the gating variable $p_n$ is instantaneously increased by $r_n(1 - p_n)$ with $r_n = 0.5$; otherwise, it obeys $dp_n/dt = -p_n/\tau_{AMPA}$. We describe γ-amino butyric acid type A (GABA_A)–receptor-mediated synaptic input from inhibitory neurons in a similar way: $I_{GABA} = g_{GABA}(V - V_{GABA}) \sum_n q_n d_n/\tau_{GABA}$ and $d_n = q_n - r_n(1 - q_n)$ at each presynaptic spike. $I_{ext}$ represents an external input, which may represent internally or externally driven information that should be integrated during a delay period. $I_{ext}$ is depolarizing during climbing activity, whereas $I_{ext} = 0$ during descending or spontaneous activity. To terminate a climbing activity, we apply a transient hyperpolarizing current at the end of the delay period (the downward arrow in Fig. 3A, top). To induce a descending activity, we apply a transient depolarizing current that lifts the neuronal activity to a prerequisite level at the beginning of the delay period (the upward arrow in Fig. 4A, top).

$I_{BG}$ represents the net background synaptic input from external neuron pools: $I_{BG} = \mu + I_{E} + I_{I}$, where $\mu$ is a constant and $I_{E}$ and $I_{I}$ represent excitatory and inhibitory inputs mediated by AMPA and GABA_A receptors, respectively. They are described as $I_{E} = -g_{E}(E - V_{AMPA})$ and $I_{I} = -g_{I}(I - V_{GABA})$. The gating variables obey $d_{E}/dt = -E/\tau_{AMPA} + X_{E}/\tau_{AMPA}$, where $X_{E}$ and $X_{I}$ represent independent Poisson processes of the rates $R_{E}$ and $R_{I}$, respectively. The constant bias $\mu$ is introduced for the convenience in adjusting the firing rate of spontaneous activity in the baseline state (typically ~1–3 Hz), although, in principle, we could do this without $\mu$ by adjusting the values of $G_{E}, G_{I}, R_{E},$ and $R_{I}$. The bistability of the neuron model was assessed under the “frozen” condition, in which $I_{AMPA} = I_{GABA} = 0$ and $I_{BG}$ is replaced with its average, that is, the fluctuating components are eliminated: $I_{R} = I_{E} + I_{I} \rightarrow -G_{R}g_{R}(V - V_{AMPA}) - G_{R}g_{R}(V - V_{GABA})$.

The membrane potential dynamics of an inhibitory neuron are described as $C(dV/dt) = -g_{L}(V - V_L) - I_{AMPA} + I_{BG}$, where $I_{BG}$ for the background synaptic input modeled similarly in the case of excitatory neurons. We include the inhibitory neurons to make the present network model realistic. However, these neurons do not play a crucial role in the proposed mechanism of temporal integration.

Parameter values

In the excitatory neuron model, $C = 0.5 \text{ nF}$, $G_L = 0.025 \mu \text{s}$, $V_L = -70 \text{ mV}$, $V_n = -52 \text{ mV}$, and $V_{reset} = -62 \text{ mV}$. The refractory period was 4 ms. The AMPA-receptor–mediated synaptic current was modeled with $\tau_{AMPA} = 5 \text{ ms}$, $V_{AMPA} = 0 \text{ mV}$, and $r_n = 0.5$. A suitable range of the maximum conductance of recurrent synapses depends on the network size. Unless otherwise stated, we set $G_{AMPA} = 0.02 \text{ nS}$ at excitatory-to-excitatory as well as excitatory-to-inhibitory AMPA synapses. We modeled the $Ca^{2+}$–dependent cationic current with $G_{Ca} = 6 \text{ nS}$, $V_{Ca} = -35 \text{ mV}$, and $K_{Ca} = 1 \mu \text{M}$ (Aoyagi et al. 2002; Kang et al. 1998), and the intracellular calcium dynamics with $\tau_{Ca} = 70 \text{ ms}$ and $\Delta_{Ca} = 1.3 \mu \text{M}$ (Wang 1999). The background synaptic input to each excitatory neuron was modeled with $G_E = G_I = 0.7 \text{ nS}$ and $R_E = R_I = 1.8 \text{ kHz}$. The constant bias was adjusted as $\mu = 0.2 \text{nA}$.

In the inhibitory neuron model, $C = 0.2 \text{ nF}$, $G_L = 0.02 \mu \text{s}$, $V_L = -65 \text{ mV}$, $V_n = -52 \text{ mV}$, and $V_{reset} = -60 \text{ mV}$. The refractory period was 2 ms. In GABA_A–receptor–mediated inhibitory-to-excitatory synapses, $G_{GABA} = 10 \text{ nS}$, $V_{GABA} = -80 \text{ mV}$, $r_n = 0.5$, and $G_{GABA} = 0.02 \text{nS}$. The background synaptic input to an inhibitory neuron was modeled with $G_{E} = G_I = 0.35 \text{nS}$ and $R_E = R_I = 1.8 \text{ kHz}$. The constant bias was adjusted as $\mu = 0.5 \text{nA}$.

Consecutive firing-rate distribution

We examined whether graded neuronal activity might consist of bimodal rate changes detectable by using the consecutive firing-rate distribution. We first chose a target period to analyze the spike trains of a single neuron. The distribution visualized how the firing rate of a neuron was distributed during the target period, which did not necessarily involve sufficiently many spikes. In this study, the typical interval of the target period was 500 to 600 ms. We divided the target period into consecutive 200- or 300-ms-long intervals, allowing a 100- or 150-ms overlap between the neighboring intervals, respectively. Then, in each trial we calculated the firing rates averaged over each of these intervals. For instance, if the target period is 500 ms long and the interval is 200 ms long, the period can be divided into four consecutive intervals consisting of 0–200, 100–300, 200–400, and 300–500 ms. If spike trains of a given neuron are available for 20 trials, we may obtain (4 × 20 = 80) samples of the firing rate. Constructing a normalized distribution of these samples of firing rate gives the consecutive firing-rate distribution.

The temporal length of each interval sets the resolution of the rate changes detectable by the consecutive firing-rate distributions. If the resolution should be <5 Hz, the interval should be >200 ms. We must, however, make the interval sufficiently small compared with a delay period, to see how the rate distributions evolve during that period. Within these conflicting demands, an interval of 200–300 ms usually yielded excellent results.

The consecutive rate distribution played a major role in the statistical tests of the present study. The distribution of the instantaneous firing rate (i.e., the inverse interspike intervals) is given as $p_{\nu}(s) = (\lambda/s) \exp(-\lambda/s)$ for a Poisson spike train of rate $\lambda$. Then, we can derive the following rate distribution for a nonstationary Poisson spike train with the mean rate increasing steadily from $\lambda_{min}$ to $\lambda_{max}$

$$p_{\nu}(s; \lambda_{min}, \lambda_{max}) = (\lambda_{max} - \lambda_{min})^{-1} \int_{\lambda_{min}}^{\lambda_{max}} p_{\nu}(s) d\lambda$$

$$= (\lambda_{max} - \lambda_{min})^{-1} [(1 + \lambda_{max}/\nu) \exp(-\lambda_{max}/\nu) - (1 + \lambda_{min}/\nu) \exp(-\lambda_{min}/\nu)]$$

The corresponding consecutive firing-rate distribution should approximately coincide with this. This formula demonstrates that the rate distribution would have a single peak near at a frequency of $(\lambda_{max} - \lambda_{min})/2 \ln(\lambda_{max} - \lambda_{min})$ (see Fig. 2D), if spike trains exhibit
graded rate changes in each trial. This fact was used in the statistical
tests to discriminate the two hypotheses proposed for graded activity
of ACC neurons.

Statistical test

In experiments, the consecutive firing-rate distributions of climbing
or descending activity exhibited prominent troughs, which possibly
imply that the neurons underwent discontinuous rate changes (see Fig.
2, C and F). Indeed, these troughs cannot be consistent with the
hypothesis that the graded activity constitutes truly graded activities in
the individual trials (see Fig. 2, A and E). Rather, the troughs represent
statistically significant deviations from the predictions of this hypoth-
esis. To prove this, we calculated the distribution expected for the
firing rate \( \nu \), hypothesizing that graded activity represented the aver-
age of single-trial Poisson spike trains with such a graded rate change
as indicated by the peristimulus time histogram (PSTH). We divided the
time axis of graded activity into \( B \) consecutive bins of width \( \Delta \),
which was typically 200 or 300 ms, and derived how many such bins
might contain \( \Delta \) spikes in each spike train. Let \( \lambda_k \) be the average
firing rate in the \( b \)th bin of the PSTH. On the preceding hypothesis,
the probability of finding \( k \) spikes in the \( b \)th bin of a single-trial spike
train is \( \pi_{k,b} = e^{-\lambda_b}(\lambda_b)^k/k! \). Then, the probability of finding \( n_k \)
spikes in the bin that contain \( k \) spikes is \( P_b(n_k) = \sum_s \cdots \sum_s p_{b,s}(s_2) \cdots p_{b,s}(s_k) \), where \( p_{b,s}(l) = \pi_{s,b}k \) and
\( p_{b,s}(0) = 1 - \pi_{s,b} \), and the sum is taken under the constraint \( s_1 + s_2 + \ldots + s_B = n_k \). By using the generating function \( g_s(u) = \sum_{m=0}^{\infty} u^m P_b(m) = \Pi_{s=1}^{B} [ \pi_{s,b} + (1 - \pi_{s,b}) ] \), we can obtain the average and variance of \( n_k \) as \( \mu_s = \delta g_s(u) / \delta u |_{u=1} = \sum_{b=1}^{B} \pi_{s,b} \) and
\( \sigma^2_s = \delta^2 g_s(u) / \delta u^2 |_{u=1} = \sum_{b=1}^{B} \pi_{s,b}^2 - \sum_{b=1}^{B} \pi_{s,b} \), respectively. We
then plotted \( \mu_s \) as a function of \( \nu \), which gives the firing-rate
distribution for the observed graded activity on the hypothesis that the
neuron exhibits a truly graded rate change in single trials (Fig. 6, G-I,
gray thick curves).

Thus obtained rate distribution in general has a single peak at some firing rate \( \hat{\nu} \) (or some spike count \( k = \hat{\Delta} \nu \)). Therefore we performed
statistical tests of the actual bin count at this firing rate. Assuming that
the count obeys a Gaussian distribution with mean \( \mu_s \) and variance \( \sigma^2_s \),
we calculated the \( z \)-score to examine whether the difference between
the actual and expected counts is statistically significant. Furthermore,
we performed a \( t \)-test, in which the variance in the number of bins
containing \( k \) spikes was calculated from the trial-to-trial fluctuations
around \( \mu_s \). This test enables us to examine the hypothesis of truly
graded single-neuron activity allowing the trial-to-trial variations in
the slope of graded rate changes. We note that the coefficient of
variation (CV) values calculated from background or task-unrelated
activities of several ACC neurons ranged from 0.73 to 1.02 with an
average value of 0.91. This justifies the use of Poisson spike trains in
the preceding statistical analysis.

Behavioral tasks and electrophysiological recordings

Two female Japanese monkeys (Macaca fuscata) were trained to
perform self-paced, delayed conditional Go/No-go discrimination
(Konorski-type) tasks using spatial (location) and nonspatial (color)
visual cues, as previously described (Isomura et al. 2003). Briefly, the
task started once the monkeys pressed a key and fixated on a fixation
square on the CRT monitor. In the spatial-discrimination task, location-
related visual cues were displayed (300 ms) on either the left or the
right side of the fixation square (at 1 and 2.5 s after the start.
Subsequently, a go signal was displayed at the fixation position 4 s
after the start. Thus each trial had two delay periods, 1.3–2.5 and
2.8–4.0 s, during which the visual cues were not present. If the two
visual cues appeared in the same position, the monkeys had to release
the key (Go trials) and if they appeared in different positions, the
monkeys had to keep pressing the key until the fixation square
disappeared 5 s after the start (No-go trials), to get a drop of juice as
reward. In the nonspatial-discrimination task, color-related visual
cues, blue and red squares, were displayed at the position of the
fixation square instead of the location-related visual cues and the two
cues in the same or different colors indicated the Go or No-go trials,
respectively. The spatial- and nonspatial-discrimination tasks were
alternately changed after every correct trial and therefore the monkeys
were able to assume a task type (location or color) in advance. Go
and No-go trials were systematically randomized within each of the
spatial and nonspatial conditions. During the Go/No-go discrimination
tasks, single-unit activity was recorded from the CMAd (area 24c),
CMAd (area 6c), and CMAv (area 23c) on the side contralateral to the
hand used for key pressing. All experiments were carried out in
accordance with the Guide for the Care and Use of Laboratory
Animals (National Institutes of Health 1996) and the Guideline for
Care and Use of Animals (Tokyo Metropolitan Institute for Neuro-
science 2000).

RESULTS

Bimodal response of single excitatory neurons

We first clarify the bimodal response properties of the single
excitatory neurons. Figure 1A (top) shows the response of a single
excitatory neuron to a brief depolarizing input in the absence of external and
control input. In the simulation, we eliminated the fluctuating components of the background syn-
aptic input, keeping its mean ("frozen" condition; see Meth-
ods). An action potential triggers Ca \(^{2+}\) entry through the
voltage-dependent Ca \(^{2+}\) channels, which in turn activates
Ca \(^{2+}\)-dependent cation current to induce an afterdepolarizing
potential. However, the afterdepolarizing potential is not large
enough to produce regenerative spike discharge and thus the
membrane potential returns the resting level (Fig. 1A, bottom). If we apply a weak constant external input \( I_{ext} \), the neuronal
response turns to be bistable (Fig. 1A, bottom). That is, the
depolarizing pulse induces a regenerative spike generation
until it is suppressed by a hyperpolarizing input. Because of
this bistability, if we introduce the fluctuating components of background synaptic input, the neuron repeats distinct periods of baseline and elevated firing states (Fig. 1B, top). As illustrated
by the shaded epochs ([Ca \(^{2+}\)] \( > \) 2 \( \mu \)M), we can detect the transitions between the bimodal states by monitoring the
concentration of intracellular Ca \(^{2+}\) (Fig. 1B, bottom).

The consecutive firing-rate distribution (see Methods) showed a
peak at low frequencies (<10 Hz) and another broad peak at
higher frequencies (20–30 Hz) (Fig. 1C). As \( I_{ext} \) is increased,
the peak at higher frequencies grows whereas that at lower frequencies
decays (Fig. 1D), implying that the probability for the transition from the baseline to elevated firing state is increased with \( I_{ext} \). As we will see later, this property allows us to
control the slop of graded activity by changing \( I_{ext} \).
Hz) and an elevated firing state (30 Hz) in a network of binary units (Fig. 2C). This mechanism works well when the occurrence of each transition is equally probable at an arbitrary time point during a delay period. The consecutive rate distributions of the different graded-activity types exhibited quite different profiles (Fig. 2, E and F). Most characteristically, the distribution obtained from the stepwise rate changes in single neurons exhibits a trough near the peak of the distribution obtained from the truly graded rate changes. Thus the rate distribution enables us to examine which type of graded activity given spike trains are more likely to represent.

**Graded activity in recurrent neural networks**

We then constructed a recurrent network consisting of 500 excitatory neurons and 100 inhibitory neurons (see METHODS). In the network model, excitatory neurons receive excitatory and inhibitory recurrent synaptic inputs, excitatory and inhibitory background synaptic inputs, and an external input to induce graded activity. Inhibitory neurons receive synaptic input from excitatory neurons as well as excitatory and inhibitory background synaptic inputs. Each excitatory neuron projects to 10% of randomly chosen other excitatory neurons and to all inhibitory neurons, whereas each inhibitory neuron projects to all excitatory neurons, but not to other inhibitory neurons. We note that the temporal integration performance was relatively independent of the connectivity of synapses. In the present model, the averaged rate distribution of the activity in the recurrent network is influenced by the connectivity of synapses, and thus the distribution becomes bimodal (Fig. 2D, E).
the presence of the background synaptic inputs, the excitatory neurons in the network showed a low- (~5 Hz) and a high-frequency (~10–30 Hz) firing state, respectively. Below, we demonstrate that our network model actually exhibits the type of graded activity proposed in Fig. 2C.

Depending on stimulus protocols, excitatory model neurons show climbing or descending activity in the simulations of the network. A constant depolarizing input applied to these neurons induced climbing activity, which was obtained either by averaging spike trains of a single neuron over repeated trials (Fig. 3A) or by averaging spike trains of a neuron ensemble in a single trial (Fig. 3B). In each trial, climbing activity was terminated by a brief inhibitory input. We constructed the consecutive firing-rate distributions of the climbing activity from the spike trains obtained in repeated trials. In Fig. 3C, we calculated the distributions in three different periods to show the time evolution of the firing rate. The distributions resembled the rate distribution for stepwise-changing Poisson spike trains, but differed remarkably from that of gradually increasing Poisson spike trains (Fig. 2, E and F). The distributions, especially the one in an intermediate period of the simulated delay period, showed clear bimodal peaks. We could construct a similar bimodal profile of the rate distributions using spike trains of multiple neurons in a single simulation trial (Fig. 3D).

Thus both trial- and ensemble-averaging procedures yielded similar climbing profiles, high variability in spike trains, and consecutive rate distributions. It is noted that the individual neurons significantly changed the order of activation from trial to trial (Fig. 3E). In fact, there was no a priori preferable order of activation among different neurons in the stochastic dynamics of the present uniform network, which consists of identical neurons interconnected by recurrent synapses of equal weights (Fig. 3F). This explains why spike trains were highly variable from trial to trial in the present model.

The network model exhibited descending activity if excitatory neurons were raised to the elevated firing state by a brief external input. As in climbing activity, averaging either spike trains of a single neuron over repeated trials (Fig. 4A) or spike trains of a neuron ensemble in a single trial generated descending activity (Fig. 4B). This activity terminated automatically when the activities of all excitatory neurons returned to the baseline level. The consecutive firing-rate distributions of descending activity showed clear bimodal peaks that indicate bimodal state transitions (Fig. 4, C and D). The temporal order of deactivation of the neurons changed significantly from trial to trial without a preferable order (Fig. 4, E and F).

The temporal profile of graded activity depended on several parameters in the model. In particular, the intensity of background input and the weight of recurrent synapses exerted significant influences on the network performance. Climbing activity grew at a nearly constant rate within adequate ranges of the values of these parameters and the slope of the climbing activity was modifiable by the intensity of a depolarizing external input. These properties were preserved if the noise intensity and the synaptic weight were tuned roughly within ±5 and ±10% of the optimal values, respectively (Fig. 5A1). However, the growth of population activity rapidly decelerated with time if recurrent connections were too weak (Fig. 5A2) or noise intensity was too strong (Fig. 5A3), or both (Fig. 5A6). By contrast, graded activity was accelerated excessively when the synaptic weight was too strong (Fig. 5A4) or the noise intensity was too weak (Fig. 5A5), or both (Fig. 5A8). The network model could tolerate the tuning errors if the two errors were correlated (Fig. 5, A7 and A9). These results imply that the climbing activity in this network model requires an adequate balance between the noise intensity and the synaptic weight. We can show similar results in the descending activity, where the intensity of a hyperpolarizing input modifies its slope (Fig. 5B).

Graded delay-period activity of ACC neurons

We tested the validity of the temporal integration with bimodal neuronal firing states using the data recorded from the anterior cingulate cortex. Anterior cingulate neurons of monkeys performing multitrial reward schedule tasks exhibited multimodal firing-rate distributions across trials and mixtures
of a few Poisson distributions well represented a substantial proportion of the neuronal responses (Shidara et al. 2005). These results encouraged us to examine graded activity of ACC neurons. As subsequently demonstrated, results of our data analysis exhibited a surprising similarity to those of the present computational model.

The data set previously recorded from the monkey ACC contained 20 neurons that showed obvious climbing (n = 7) or descending (n = 13) activity during a delay period (Isomura et al. 2003). In this study, we primarily analyzed the activity of these neurons. Among the 20 cells, five cells showing climbing activity and 11 cells showing descending activity displayed the consecutive firing-rate distributions with clear bimodal peaks. Figure 6 shows typical examples of graded activity and their consecutive firing-rate distributions. The PSTHs representing the trial-averaged activity of single neurons display steady increases (Fig. 6A) or decreases (Fig. 6, C and E) during a delay period. In all examples, the trial-to-trial variability of temporal spiking patterns is quite significant during the period of graded rate changes. The rate distributions of each neuron exhibit bimodality, which is manifested by a trough between their low- and higher-frequency portions (Fig. 6, B,D,F). The higher-frequency portion grows with time in climbing activity, whereas it decreases gradually in descending activity.

We tested whether Poisson spike trains with gradually changing firing rates (i.e., the hypothesis illustrated in Fig. 2A) might consistently account for the consecutive firing-rate distributions of ACC neurons. To this end, we constructed the firing-rate distribution from the PSTH of graded activity of each ACC neuron. Examples of such rate distributions are displayed in Fig. 6, G–I for the three ACC neurons shown previously. If the rate change in a single trial has a profile similar to that of the PSTH—that is, if the above hypothesis is true—the consecutive firing-rate distribution will exhibit a
showed a rich spectrum of frequency components times activity shown in accelerated increase at times activity shown in J peak (see METHODS). We note that the peaks were generally located near the troughs of the consecutive firing-rate distributions of the above 3 neurons were calculated in the entire periods of graded activity. Solid and dashed curves display the average and SE, respectively, of the bin counts predicted from the hypothesis that the graded activity consists of truly graded components. Results of our statistical tests confirmed the statistical significance of the deviations. In total, 16 cells exhibited clear bimodal rate distributions. Among them, the deviations were statistically significant in all five cells showing climbing activity in both z-score and t-test (P < 0.05). The remaining 11 cells displayed descending activity and the troughs were statistically significant in nine or ten cells in z-score or t-test, respectively (P < 0.05). Thus, graded activity of ACC neurons gives spike trains, PSTHs, and the firing-rate distributions that are consistent with those obtained by simulations of the present network model.

We noticed that climbing activity of ACC neurons often displayed modulations of higher-frequency components at the late stage of a delay period. Figure 6J shows such an example for the climbing activity presented in Fig. 6A. The frequency components >20 Hz reflected the accelerated rate increase at times >3.4 s in the PSTH of this neuron. Similarly, Fig. 6K displays the firing-rate distribution during the initial epoch of the descending activity shown in Fig. 6C. The frequency components >40 Hz originated from the epoch of a steeper rate decrease at times <3 s in the PSTH. These results may suggest that the rate of the elevated firing state undergoes continuous modulations or that the ACC neurons might have more than two modes of firing states.

**DISCUSSION**

**Slow temporal integration by stochastic bimodal neurons**

Graded neuronal activity, which gradually increases or decreases typically during a delay period of cognitive task, is generally considered to represent temporal integration of information relevant to behaviors. We have proposed a novel form of temporal integration in a uniform recurrent network of stochastic bimodal neurons. In this network, stochastic neural dynamics recruits an ensemble of neurons for integrating an external input in single trials. The mechanism does not require N-methyl-d-aspartate (NMDA)–receptor-mediated slow recurrent synapses because the stochastic transitions between the bimodal neuronal states are slow enough to integrate input in a range of hundred milliseconds to seconds. A formal mathematical theory for this stochastic mechanism was developed in our previous paper (Okamoto and Fukai 2001; Sakai et al. 2006). Interestingly, the proposed mechanism gives no prescribed temporal order of activation to each neuron.

Our analysis of previously recorded data (Isomura et al. 2003) revealed that graded delay-period activity of ACC neurons exhibits bimodal neuronal responses analogous to those predicted by the network model. It was reported that activity of ACC neurons displayed bimodal firing-rate distributions across different trials of cognitive task (Shidara et al. 2005). Bimodal or, more generally, multimodal firing state might be the method by which ACC neurons encode information. However, the experimental data available for the present analysis were limited, so the results need to be confirmed by further experiments. By contrast, graded activity might constitute truly graded activity of individual neurons, the hypothesis used in several previous models of graded activity (Durstewitz 2003; Miller et al. 2003; Wang 2002). Prefrontal neurons display graded delay-period activity in decision making (Barracough et al. 2004; Constantinidis et al. 2002; Takeda and Funahashi 2002).
in which an internal signal representing subject’s confidence level may start growing until it reaches a certain criterion for decision (Hanes and Shall 1996; Maimon and Assad 2006; Reddi and Carpenter 2000; Usher and McClelland 2001). The prefrontal cortex of the monkey performing a parametric working memory task (Brody et al. 2003) and the posterior parietal cortex of the monkey performing a duration discrimination task (Leon and Shadlen 2003) also exhibit graded activity. It seems intriguing to investigate whether and how the mechanism of temporal integration may differ in different cortical regions using the multiunit recording technique.

**Physiological origin of bimodal neuronal responses**

Our model used the spike afterdepolarizing potential induced by voltage-dependent Ca	extsuperscript{2+} current and Ca	extsuperscript{2+}-dependent cation current to generate bimodal neuronal responses. Several other mechanisms can generate a similar bimodal response (Gruner et al. 2003; Loewenstein et al. 2005). For instance, the NMDA-receptor-mediated synaptic current provides a mechanism of bistability (Lisman et al. 1998). Spontaneous membrane potential fluctuations might be another possible source of bimodality in cortical neurons. In vivo and in vitro cortical neurons display membrane potential fluctuations between a depolarizing UP and a resting DOWN state (Anderson et al. 2000; Bazhenov et al. 2002; Cossart et al. 2003; Ikegaya et al. 2004; Peterson et al. 2003; Shu et al. 2003; Steriade et al. 2001; Stern et al. 1997). Although these fluctuations exhibit irregular oscillating patterns in anesthetized animals, they might temporarily be organized in behaving states. However, whether the two-state fluctuations appear in an awake or a behaving animal remains controversial (Kitano et al. 2002; Peterson et al. 2003; Steriade et al. 2001).

**Relation to previous models**

Several models of neural integrator networks were previously proposed in the literature (Cannon et al. 1983; Galiana and Outerbridge 1984) for temporal integration. Seung et al. (2000) and Miller et al. (2003) showed that a special class of finely tuned recurrent networks produces a continuous attractor state useful for temporal integration. Later, this fine-tuning was relaxed by using bistable neurons or bistable dendritic compartments (Goldman et al. 2003; Koulakov et al. 2002). Because of the specific wiring structures or the neuron-specific activity thresholds, these models will activate neurons in an approximately fixed order with small trial-to-trial jitters arising from biological noise. By contrast, our model has essentially no preferable order of activation among neurons. We also note that our model does not require the perfect stability of bimodal states because stochastic noise destabilizes such states.

Models with slow synaptic transmissions also produce gradually climbing or descending neuronal activity (Brody et al. 2003; Wang 2002). Because spike trains in these models are highly variable, these models may display spike raster similar to that of our model. However, the inspection of firing-rate distributions will enable us to discriminate the two types of network models (Fig. 1). Single neurons can also perform temporal integration of stimuli (Durstewitz 2003; Egorov et al. 2002; Fransen et al. 2006; Loewenstein and Sompolinsky 2003; Teramae and Fukai 2005). Depending on the detailed cellular mechanisms, such neurons presumably produce a continuous or a multi-stepwise-graded rate change.

Mongillo et al. (2003) proposed another type of recurrent neural network model that may be consistent with the results of the present analysis of graded activity in the ACC. They considered two-state transitions in synaptic activity triggered by stochastic noise. Unlike the present model, their model generates bimodal responses of the entire network through recurrent excitation, so all neurons in the network exhibit coherent two-state transitions. Nevertheless, the trial average of single-cell activity displays a graded profile because the time of the coherent transition changes at random across trials. In addition, the model neurons exhibit bimodal rate distributions similar to those analyzed in this study. Although the model by Mongillo et al. does not serve as a neural integrator in single trials, the bimodal firing-rate distributions revealed in the ACC neurons do not exclude their model. Further discriminations between their model and ours require multiunit recordings and single-trial–basis analyses of graded activity.

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