Bilinearity in Spatiotemporal Integration of Synaptic Inputs

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Abstract

Neurons process information via integration of synaptic inputs from dendrites. Many experimental results demonstrate dendritic integration could be highly nonlinear, yet few theoretical analyses have been performed to obtain a precise quantitative characterization analytically. Based on asymptotic analysis of a two-compartment passive cable model, given a pair of time-dependent synaptic conductance inputs, we derive a bilinear spatiotemporal dendritic integration rule. The summed somatic potential can be well approximated by the linear summation of the two postsynaptic potentials elicited separately, plus a third additional bilinear term proportional to their product with a proportionality coefficient $\kappa$. The rule is valid for a pair of synaptic inputs of all types, including excitation-inhibition, excitation-excitation, and inhibition-inhibition. In addition, the rule is valid during the whole dendritic integration process for a pair of synaptic inputs with arbitrary input time differences and input locations. The coefficient $\kappa$ is demonstrated to be nearly independent of the input strengths but dependent on input times and input locations. This rule is then verified through simulation of a realistic pyramidal neuron model and in electrophysiological experiments of rat hippocampal CA1 neurons. The rule is further generalized to describe the spatiotemporal dendritic integration of multiple excitatory and inhibitory synaptic inputs. The integration of multiple inputs can be decomposed into the sum of all possible pairwise integration, where each paired integration obeys the bilinear rule. This decomposition leads to a graph representation of dendritic integration, which can be viewed as functionally sparse.

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Introduction

For information processing, a neuron receives and integrates thousands of synaptic inputs from its dendrites and then induces the change of its membrane potential at the soma. This process is usually known as dendritic integration [1–3]. The dendritic integration of synaptic inputs is crucial for neuronal computation [2–4]. For example, the integration of excitatory and inhibitory inputs has been found to enhance motion detection [5], regularize spiking patterns [6], and achieve optimal information coding [7] in many sensory systems. They have also been suggested to be able to fine tune information processing within the brain, such as the modulation of frequency [8] and the improvement of the robustness [9] of gamma oscillations. In order to understand how information is processed in neuronal networks in the brain, it is important to understand the computational rules that govern the dendritic integration of synaptic inputs.

Dendritic integration has been brought into focus with active experimental investigations (see reviews [1,10] and references therein). There have also been many theoretical developments based on physiologically realistic neuron models [11,12]. Among those works, only a few investigate quantitative dendritic integration rules for a pair of excitatory and inhibitory inputs [3,13] and there has yet to be an extensive investigation of the integration of a pair of excitatory inputs or a pair of inhibitory inputs. In this work, we propose a precise quantitative rule to characterize the dendritic integration for all types of synaptic inputs and validate this rule via realistic neuron modeling and electrophysiological experiments.

We first develop a theoretical approach to quantitatively characterize the spatiotemporal dendritic integration. Initially, we introduce an idealized two-compartment passive cable model to understand the mathematical structure of the dendritic integration rule. We then verify the rule by taking into account the complicated dendritic geometry and active ion channels. For time-dependent synaptic conductance inputs, we develop an asymptotic approach to analytically solve the cable model. In this approach, the membrane potential is represented by an asymptotic expansion with respect to the input strengths. Consequently, a hierarchy of cable-type equations with different orders can be
Author Summary

A neuron, as a fundamental unit of brain computation, exhibits extraordinary computational power in processing input signals from neighboring neurons. It usually integrates thousands of synaptic inputs from its dendrites to achieve information processing. This process is known as dendritic integration. To elucidate information coding, it is important to investigate quantitative spatiotemporal dendritic integration rules. However, there has yet to be extensive experimental investigations to quantitatively describe dendritic integration. Meanwhile, most theoretical neuron models considering time-dependent synaptic inputs are difficult to solve analytically, thus impossible to be used to quantify dendritic integration. In this work, we develop a mathematical method to analytically solve a two-compartment neuron model with time-dependent synaptic inputs. Using these solutions, we derive a quantitative rule to capture the dendritic integration of all types, including excitation-inhibition, excitation-excitation, inhibition-inhibition, and multiple excitatory and inhibitory inputs. We then validate our dendritic integration rule through both realistic neuron modeling and electrophysiological experiments. We conclude that the general spatiotemporal dendritic integration structure can be well characterized by our dendritic integration rule. We finally demonstrate that the rule leads to a graph representation of dendritic integration that exhibits functionally sparse properties.

integration, including excitatory-inhibitory, excitatory-excitatory and inhibitory-inhibitory inputs.

Our bilinear integration rule is derived from the two-compartment passive cable model. We then validate the rule in a biologically realistic pyramidal neuron model with active ion channels embedded. The simulation results from the realistic model are consistent with the rule derived from the passive cable model. We further validate the rule in electrophysiological experiments in rat hippocampal CA1 pyramidal neurons. All of our results suggest that the form of the bilinear integration rule is preserved in the presence of active dendrites.

As mentioned previously, there are thousands of synaptic inputs received by a neuron in the brain. We therefore further apply our analysis to describe the dendritic integration of multiple synaptic inputs. We demonstrate that the spatiotemporal dendritic integration of all synaptic inputs can be decomposed into the sum of all possible pairwise dendritic integration, and each pair obeys the bilinear integration rule (1), i.e.,

\[ V_S(t) = \sum_p V_{pE}^2(t) + \sum_q V_{qE}^2(t) + \sum_{i,j} k_{E}^{ij}(t) V_{E}^i(t) V_{E}^j(t) + \sum_{m,n} k_{N}^{mn}(t) V_{N}^m(t) V_{N}^n(t), \]

where \( V_S \) denotes the SSP, \( V_{pE}^2 \) denotes the \( p^{th} \) individual EPSP, \( V_{qE}^2 \) denotes the \( q^{th} \) individual inhibitory postsynaptic potential (IPSP), \( k_{E}^{ij}, k_{N}^{mn} \) are the corresponding proportionality coefficients with superscripts denoting the index of the synaptic inputs. We then confirm the bilinear integration rule (2) numerically using realistic neuron modeling. The decomposition of multiple inputs integration rule (2) leads to a graph representation of the dendritic integration. Each node in the graph corresponds to a synaptic input location, and each edge connecting two nodes represents the bilinear term for a pair of synaptic inputs given at the corresponding locations. This graph evolves with time, and is all-to-all connected when stimuli are given at all synaptic sites simultaneously. However, based on simulation results and experimental observations, we can estimate that there are only a small number of activated synaptic integration, or edges in the graph, within a short time interval. Therefore, the graph representing the dendritic integration can indeed be functionally sparse.

Finally, we comment that, in general, it is theoretically challenging to analytically describe the dynamical response of a neuron with dendritic structures under time-dependent synaptic conductance inputs. One simple approach to circumvent this difficulty is to analyze the steady state of neuronal input-output relationships by assuming that both the synaptic conductance and the membrane potential are constant [3,12]. Such analyses can be applied to study dendritic integration, but they usually oversimplify the description of the spatial integration, and fail to describe the temporal integration. Another approach to circumvent the difficulty is to study the cable model [14,15] analytically or numerically. For the subthreshold regime, in which voltage-gated channels are weakly activated, the dendrites can be considered as a passive cable. Along the cable, the membrane potential is linearly dependent on injected current input. This linearity enables one to use the Green’s function method to analytically obtain the membrane potential with externally injected current. In contrast, the membrane potential depends nonlinearly on the synaptic conductance input [12]. This nonlinearity greatly complicates mathematical analyses. Therefore, in order to solve the cable model analytically, one usually makes the approximation of...
constant synaptic conductance [16,17]. The approximation can help investigate some aspects of dendritic integration, however, the approximation in such a case is not sufficiently realistic because the synaptic conductances in vivo are generally time-dependent. On the other hand, one can study the dendritic integration in the cable model numerically. The compartmental modeling approach [14] enables one to solve the cable model with time-dependent synaptic inputs. This approach has been used to investigate many aspects of dendritic integration. For instance, it was discovered computationally that dendritic integration of excitatory inputs obeys a certain qualitative rule, i.e., EPSPs are first integrated nonlinearly at individual branches before summed linearly at the soma [18,19], which was verified later in experiments [20,21]. Clearly, the computational approach can help gain insights into various phenomena of spatiotemporal dynamics observed at the dendrites, however, a deep, comprehensive understanding often requires analytical approaches. Note that this point has also been emphasized in Ref. [22]. Here, our analytical asymptotic method can solve the cable model with time-dependent synaptic inputs analytically and reveal a precise quantitative spatiotemporal dendritic integration rule, as will be further illustrated below.

**Results**

We first study the dendritic integration of a pair of excitatory and inhibitory inputs (E-I), a pair of excitatory inputs (E-E), and a pair of inhibitory inputs (I-I) case by case. In each case, we first analytically derive the bilinear integration rule from the two-compartment passive cable model, and then validate the bilinear integration rule using the realistic model of a pyramidal neuron with both active channels and dendritic branches; we further validate the bilinear integration rule in electrophysiological experiments in rat CA1 pyramidal neurons. We then derive the bilinear integration rule for multiple excitatory and inhibitory inputs, and validate this rule in the simulation. Based on our bilinear integration rule for multi-inputs, we finally propose a graph representation of dendritic integration.

**Bilinear Rule for E-I Integration**

We begin to study the spatiotemporal dendritic integration of a pair of excitatory and inhibitory inputs. An analytical derivation of the bilinear integration rule is described in the section of Derivation of the Rule. The details of the cable model used in the derivation can be found in the section of Materials and Methods. The validation of the bilinear integration rule using the realistic neuron modeling and electrophysiological experiments is described in the section of Validation of the Rule. The spatial dependence of the coefficient $\kappa$ in the rule is described in the section of Spatial Dependence of $\kappa_{EI}$.

**Derivation of the rule.** Most neurons possess complicated dendritic morphology, however, for simplicity, we start to investigate the spatiotemporal dendritic integration rule with an idealized two-compartment passive cable model, in which a spherical soma is connected to an unbranched cylindrical dendrite with finite length $L$ and diameter $d$. The distance between a dendritic location and the soma is denoted by $x$. Given an excitatory input at location $x = x_E$ and at time $t = t_E$, and an inhibitory input at location $x = x_I$ and at time $t = t_I$, the membrane potential dynamics is governed by

$$ \frac{\partial v}{\partial t} = -g_L V - \sum_{q \in E,I} f_q g_q (t-t_q) \delta(x-x_q)(v-v_q) + \frac{d}{4 \pi \rho a} \frac{\partial^2 v}{\partial x^2}, \quad (3) $$

where $v$ is the membrane potential with respect to the resting potential on the dendrite, $c$ is the membrane capacitance per unit area, $\tau_a$ is the axial resistivity, and $g_L$ is the leak conductance per unit area. The excitatory and inhibitory input strengths $f_E$ and $f_I$ control the amplitude of EPSP and IPSP, respectively. The variables $g_E$ and $g_I$ denote the unitary excitatory and inhibitory conductances per unit area with their peak value normalized to unity [described by Equation (29)]. $g_E$ and $g_I$ are the corresponding reversal potentials, respectively. The values of the parameters in the model can be found in the section of Materials and Methods.

By assuming that one dendritic end is sealed and the other dendritic end connects to the spherical soma, the boundary conditions are given by

$$ \left. \frac{\partial v}{\partial x} \right|_{x=L} = 0, \quad (4) $$

$$ c \frac{\partial^2 v(0,t)}{\partial t^2} = -g_L V(0,t) - \frac{\pi d^2}{4S a} \frac{\partial v}{\partial x} \mid_{x=0}, \quad (5) $$

where $S$ is the surface area of the soma. The initial condition is simply set as

$$ v(x,0) = 0 \quad (6) $$

for a neuron at its resting state.

For the physiological regime, the corresponding synaptic input strengths, $f_E$ and $f_I$, are relatively small in the model [Equations (3)–(6)]. To be specific, for the amplitude of an EPSP less than $6mV$ and the amplitude of an IPSP less than $-3mV$, the corresponding strengths $f_E$ and $f_I$ are considered to be small. Therefore, we can represent the membrane potential as an asymptotic series in powers of $f_E$ and $f_I$ as follows:

$$ v(x,t) = \sum_{k=0}^{\infty} \sum_{m+n=k} f_E^m f_I^n v_{mn}(x,t). \quad (7) $$

Substituting Equation (7) into Equations (3)–(6), order by order, we can obtain its asymptotic solutions $v_{mn}(x,t)$. The solutions to the second order ($m+n \leq 2$) are described below (see the section of Materials and Methods for a detailed calculation). For the zeroth order, we have

$$ v_{00}(x,t) = 0. \quad (8) $$

The solution corresponds to the fact that the membrane potential response remains at its resting state when there is no stimuli presented ($f_E = 0, f_I = 0$). The first order excitation $O(f_E)$ is

$$ v_{10}(x,t) = G(x,x_E,t) \ast [g_E \delta(t-t_E)], \quad (9) $$

where ‘$\ast$’ denotes convolution in time, and $G(x,y,t)$ is the Green’s function of the cable equation given a $\delta$ impulse input (the analytical expression is presented in the section of Materials and Methods). Note that the input $g_E \delta(t_E)$ at $x_E$ can be viewed as the synaptic current when the local membrane potential is maintained at the resting state. The second order of excitation $O(f_E^2)$ is
where the expression of \( v_{10}(x_E,t) \) is given in Equation (9). Note that the input \(-g_{EI}v_{10}\) at \( x_E \) can be viewed as the synaptic current, which is the product of the local conductance \( g_{EI} \) with the first order local membrane potential \( v_{10} \). Similarly, we have the first and second order inhibition \( O(f_I) \) and \( O(f_I^2) \):

\[
v_{01}(x,t) = G(x,x_I,t) \ast [v_I g_I(t-t_I)],
\]

\[
v_{02}(x,t) = G(x,x_I,t) \ast [-g_I(t-t_I)v_{01}(x_I,t)].
\]

For the order of \( O(f_I f_E) \), we have

\[
v_{11}(x,t) = G(x,x_E,t) \ast [-g_{EI}(t-t_E) v_{10}(x_E,t)] + G(x,x_I,t) \ast [-g_I(t-t_I)v_{01}(x_I,t)].
\]

where \( v_{10}(x,t) \) and \( v_{01}(x,t) \) are given by Equations (9) and (11), respectively. On account of the fact that \( \varphi_E = 70mV \) (relative to the resting potential) is nearly an order of magnitude larger than \( |\varphi_I| = 10mV \), \( v_{11} \) in Equation (13) can be further simplified as

\[
v_{11}(x,t) \approx G(x,x_I,t) \ast [-g_I(t-t_I)v_{01}(x_I,t)],
\]

which indicates that the nonlinear integration effect mainly originates from the outward synaptic current, i.e., \( g_{EI}v_{10} \), induced by the first order EPSP measured at the inhibitory input site \( x_I \), i.e., \( v_{10}(x_I,t) \).

Numerical simulation of the cable model indicates that the second order asymptotic approximation is sufficiently accurate in capturing the model’s solution of physiologically realistic membrane potentials, as demonstrated in Fig. 1. Therefore, if only an individual inhibitory input is given [\( f_I = 0 \) in Equation (3)], the corresponding IPSP measured at the soma, denoted by \( V_I \), can be approximated by

\[
V_I(t) \approx \sum_{m=0}^{2} f_I^m v_{0m}(0,t).
\]

Similarly, if only an individual inhibitory input is given [\( f_E = 0 \) in Equation (3)], the corresponding IPSP measured at the soma, denoted by \( V_S \), can be approximated by

\[
V_S(t) \approx \sum_{n=0}^{2} f_E^n v_{0n}(0,t).
\]

If both the excitatory and inhibitory inputs are given at \( x_E \) and \( x_I \), the corresponding SSP measured at the soma, denoted by \( V_{SC} \), can be approximated as

\[
V_{SC}(t) \equiv V_S(t) - V_E(t) - V_I(t).
\]

From Equations (15), (16) and (17), we have

\[
V_{SC}(t) \approx f_E f_I v_{11}(0,t).
\]

If \( v_I \) is set to be at the resting potential, we can show that the value of \( V_I \) indicating hyperpolarization vanishes, while the value of \( V_{SC} \) stays nearly the same. Therefore, \( V_{SC} \) is mainly caused by the shunting effect and thus is referred to as the shunting component (SC). In our analysis, the SC is the leading order of the

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**Fig. 1. Asymptotic solutions of various orders for the two-compartment passive cable model.** Asymptotic solutions for (A) EPSP, (B) IPSP, and (C) SSP in comparison with numerical simulations of Equation (3). The blue dashed line is the first order approximation. The red circle is the second order approximation. The black solid line is the numerical solution of the full Equation (3). The stimuli are given at the location \( x_E = 240\mu m \) and \( x_I = 180\mu m \). Physiological parameters in the simulation can be found in the section of Materials and Methods.

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nonlinear integration between excitation and inhibition. If we further define the shunting coefficient $k_{EI}$ as

$$\kappa_{EI}(t; t_E, t_I, x_E, x_I) = \frac{V_{SC}}{V_E V_I}$$  \hspace{1cm} (20a)$$

$$\approx \frac{G(0, x_I, t) + [g_I(t-t_I) G(x_I, x_E, t_I) \ast g_E(t-t_E)] }{\epsilon_E G(0, x_E, t) + g_E(t-t_E) - G(0, x_I, t) \ast g_I(t-t_I)}$$  \hspace{1cm} (20b)$$

then $k_{EI}$ is nearly independent of the amplitude of EPSP and IPSP, because the input strengths $f_E$ and $f_I$, which determine the amplitudes of EPSP and IPSP, cancel each other in both the denominator and numerator in Equation (20b).

From Equation (20a), we have the following spatiotemporal dendritic integration rule

$$V_S(t) = V_E(t) + V_I(t) + \kappa_{EI}(t) V_E(t) V_I(t).$$  \hspace{1cm} (21)$$

The shunting coefficient $k_{EI}$ is nearly independent of the amplitude of EPSP and IPSP. In addition, $k_{EI}$ depends on the location of excitatory and inhibitory inputs $x_E$ and $x_I$. For a fixed pair of excitatory and inhibitory input locations, $k_{EI}$ is a function of both time $t$ and the arrival time difference between the excitatory and inhibitory input $\tau = t_E - t_I$, as illustrated in Fig. 2.

**Validation of the Rule.** As the bilinear integration rule (21) is derived from the idealized passive neuron model, we need to investigate its validity for a realistic neuron, which has active ion channels embedded in its tree-like dendrites.

We first perform the simulation of a biologically realistic pyramidal neuron with active channels (morphology shown in Fig. 2). The details of the model and the related computational method can be found in the section of Materials and Methods. The simulation results are summarized below.

For the case of concurrent inputs (Here, we use “concurrent” to denote the case when $t_E = t_I$), as shown in Fig. 3A, when the excitatory and inhibitory inputs are elicited concurrently at different locations on the dendritic trunk, the SSP is found to be always smaller than the linear sum of the EPSP and the IPSP when elicited separately. In this case, the bilinear integration rule (21) holds at the time $t'$ when the EPSP reaches its peak value. We can vary $f_E$ to control the amplitude of EPSP (less than $0.6 mV$) and vary $f_I$ to control the amplitude of IPSP (less than $-3 mV$). For fixed input strengths $f_E$ and $f_I$, we obtain the set of time courses of the EPSP, the IPSP, and the corresponding SSP. Using 9 sets of such data with different input strengths, we find that the SC amplitude $V_{SC}(t^*)$ depends linearly on the product of the EPSP and IPSP amplitudes, $V_E(t^*)V_I(t^*)$. The excellent linear fitting in Fig 4A shows that the slope $k_{EI}(t^*)$ is independent of the amplitude of EPSP and IPSP. This result is consistent with the experimental observation [3].

**Fig. 2. Description of $k_{EI}$ as a function of time $t$ and stimulus arrival difference $\tau$ for a fixed pair of excitatory and inhibitory input locations.** Left, a morphological plot of the realistic neuron model. The excitatory and inhibitory input locations are indicated by arrows. Right, (lower) an IPSP arrives at the soma earlier than an EPSP. The arrival times are indicated by vertical dashed lines. (upper) The shunting coefficient $k_{EI}$ remains at zero until the EPSP arrives at $t_E$. doi:10.1371/journal.pcbi.1004014.g002

**Fig. 3. An example of EPSP, IPSP, SSP, SC, and the corresponding linear sum.** (A) The EPSP and the IPSP are elicited concurrently. Here $t^*$ denotes the time when EPSP reaches its peak value. (B) The IPSP is elicited 20 ms before the EPSP. The results are obtained in the realistic pyramidal neuron model simulation which is described in detail in the section of Materials and Methods. The excitatory input is given at the location $x_E = 283 \mu m$ and the inhibitory input is given at the location $x_I = 151 \mu m$. doi:10.1371/journal.pcbi.1004014.g003
For the same case of concurrent inputs, we then calculate $\kappa_{EI}$ at any time $t$, instead of the peak time $t^*$. We compute $\kappa_{EI}(t)$ within the interval $t^* - \sigma < t < t^* + \sigma$, where $\sigma = 10\text{ms}$. We choose this $20\text{ms}$ interval because the amplitude of the EPSP is relatively large within that interval. As a consequence, we can avoid a small denominator in calculating $\kappa_{EI}(t)$ and improve the numerical accuracy. At each fixed time $t$, $\kappa_{EI}(t)$ is estimated by linear regression using the same 9 sets of data used to validate the bilinear integration rule at $t^*$. As demonstrated in Fig. 4B, at each time $t$, there is a small error bar for the slope $\kappa_{EI}$ estimation and the $R^2$ value is very close to 1. Both facts indicate an excellent linear fitting of $V_E(t)V_I(t)$ vs. $V_{SC}(t)$. Therefore, the shunting coefficient $\kappa_{EI}$ is nearly independent of the amplitude of EPSP ($V_E$) and IPSP ($V_I$) at any time. As expected, the error bar for the slope estimation increases dramatically far away from the peak time due to the fact that the numerical accuracy is low when EPSP and IPSP are small, in particular, when they approach zero. However, the SC amplitude in this case is sufficiently small, and can thus be neglected. Therefore, the bilinear integration rule can naturally be considered valid with $\kappa_{EI} = 0 \text{mV}^{-1}$.

For the case of nonconcurrent inputs, when the onset of the inhibitory input is 20ms earlier than that of the excitatory input (Fig. 3B), our numerical results show that the bilinear integration rule (21) still holds, as shown in Fig. 4C-D. The rule is also confirmed for any excitatory and inhibitory input locations arbitrarily distributed on the dendritic trees.

We next perform electrophysiological experiments to validate our bilinear integration rule (21). The details of the experimental procedure can be found in the section of Materials and Methods.

In experiments, the excitatory input is given at $\sim 100\mu\text{m}$ with the EPSP amplitude less than $8\text{mV}$ and the inhibitory input is given at $\sim 50\mu\text{m}$ with the IPSP amplitude less than $-3\text{mV}$. For the case of concurrent inputs, we found that $V_{SC}$ depends linearly on $V_EV_I$ at the time when EPSP reaches its peak, as shown in Fig. 4E, and at a non-peak time, as shown in Fig. 4F. Therefore, the slope $\kappa_{EI}$ is nearly independent of EPSP and IPSP amplitudes. For the case of nonconcurrent inputs, when the IPSP is elicited 20ms earlier than the EPSP, the linear relationship between $V_{SC}$ and $V_EV_I$ still holds, as shown in Fig. 4G-H, except that the value $R^2$ of the regression is smaller (0.77 to 0.81) than those in the concurrent case (0.90 to 0.99). Therefore, it can be seen from the above that, the bilinear integration rule (21) is confirmed in rat hippocampal CA1 pyramidal neurons.

Note that the bilinear integration rule is derived from an idealized passive neuron case. Interestingly, our results from the simulation and experiments demonstrate that the structure of the rule is preserved in the presence of both active channels and dendritic branches.

**Spatial dependence of $\kappa_{EI}$.** Although we have obtained the form of the bilinear integration rule (21), how the value of the shunting coefficient $\kappa_{EI}$ depends on the input location is difficult to analyze directly from its explicit form [Equation (20b)]. Here we investigate the spatial dependence of input location for $\kappa_{EI}$, which may partially reveal the way in which $\kappa_{EI}$ encodes spatial integration information.

In our previous study [23], a spatial rule for $\kappa_{EI}$ as a function of input locations has been proposed based on a theoretical analysis of a multi-compartment cable model. Under the situation when

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**Fig. 4. Dendritic integration of a pair of excitationary and inhibitory inputs.** (A–D) Simulation results with the excitatory input given at the location $x_E = 283\mu\text{m}$ and the inhibitory input given at the location $x_I = 151\mu\text{m}$. (A) The SC amplitude is plotted against the product of EPSP amplitude and IPSP amplitude, at the time when EPSP reaches its peak, i.e., $t = t^*$. (Note that $-V_{SC}$ and $V_EV_I$ are plotted). Varying $V_E$ less than $60\text{mV}$ and varying $V_I$ less than $-30\text{mV}$, it can be seen that $-V_{SC}$ increases linearly with $-V_EV_I$. (B) Dendritic integration in the time interval $t^* - \sigma < t < t^* + \sigma$, where $\sigma = 10\text{ms}$. (upper) $R^2$ for the goodness of the linear fitting of $V_{SC}$ vs. $V_EV_I$ at different times, (lower) The shunting coefficient $\kappa_{EI}(t)$ (in the unit of $\text{mV}^{-1}$) as the slope of the linear fitting is plotted at different times. The error bar indicates 95% confidence interval (The error bars are relatively small and are within the circles). The circle marked by red indicates the case in (A). (C–D) The same as (A–B) except that the IPSP is elicited 20ms before the EPSP. (E–H) Experimental results with the excitatory input given at the location $x_E \sim 100\mu\text{m}$ and the inhibitory input given at the location $x_I \sim 50\mu\text{m}$. (E–F) for concurrent inputs and (G–H) for nonconcurrent inputs that the IPSP is elicited 20ms earlier than the EPSP.

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Fig. 5. Shunting coefficient $k_{EI}$ in branched dendrites measured in experiments. The data marked by grey squares were collected from 7 neurons in our experiments, and lines connect data from the same neuron. The data marked by black squares are the average of the data marked by grey squares. The error bar indicates one standard deviation. In all figure panels, the locations of the inhibitory input ($I$) and excitatory inputs ($E_1$ and $E_2$) are marked by a blue dot and red dots, respectively. The I path is marked by green. (A) The inhibitory input $I$ at an oblique branch: $k_{EI}$ is nearly constant for two distal $E_1$ and $E_2$ on the same branch. (B) As in (A) except that $E_1$ and $E_2$ are more proximal than $I$. (C) The inhibitory input $I$ at the trunk: $k_{EI}$ is significantly different between $E_1$ and $E_2$, where $E_1$ is on the same branch as $I$ and $E_2$ is on a different branch. doi:10.1371/journal.pcbi.1004014.g005

the excitatory and inhibitory inputs are given concurrently, the spatial profile of $k_{EI}$ at the time when EPSP reaches its peak is characterized by the following spatial rule: For a fixed inhibitory input location, the I path (marked by green on the dendritic trees in Fig. 5) is defined as the path between the soma and the inhibitory input; Along the I path, $k_{EI}$ is predicted to increase as the distance between excitatory input location and the soma increases; for any branch (including the trunk) connecting to the I path, $k_{EI}$ is predicted to be constant for all excitatory input sites on the branch.

The prediction of this spatial $k_{EI}$ rule is consistent with our electrophysiological experimental results as shown in Fig. 5 (also see Ref. [3]). We next use the spatial $k_{EI}$ rule to explain these experimental results.

In Fig. 5A and 5B, an inhibitory input is given on an oblique branch and two excitatory inputs are given at two locations on the same oblique branch. The corresponding shunting coefficients $k_{EI}$ were estimated based on Equation (20a). In our experiment, no significant difference was found between the values of $k_{EI}$ when the two excitatory locations were both distal, as shown in Fig. 5A. This experimental observation can be easily understood by our rule: for two excitatory inputs on the same branch, $k_{EI}$ should be the same on such a branch.

In contrast, as shown in Fig. 5B, for two excitatory inputs at proximal locations, $k_{EI}$ was experimentally found significantly smaller for the excitatory input closer to the soma. This is consistent with our rule because $k_{EI}$ is predicted to be an increasing function of the distance between the excitatory input location and the soma for this case.

In Fig. 5C, an inhibitory input is given on the apical trunk and two distal excitatory inputs are given at either the trunk or a branch. For this case, the $k_{EI}$ values were found to be nearly constant in our experiment. This is the case in which the two branches where the two excitatory inputs are located connect to the I path with the same branching point. Therefore, this experimental observation can be understood through our rule that all $k_{EI}$ on the two branches are the same as the one at the branching point.

In Fig. 5D, an inhibitory input is given at an oblique branch and two distal excitatory inputs are given at different branches. For this case, the value of $k_{EI}$ for inhibitory and excitatory inputs located at the same branch was found in our experiment to be significantly larger than the case in which inhibitory and excitatory inputs are located at different branches.
asympotic series and solve it order by order to obtain the following bilinear integration rule:

\[ V_S(t) = V_{E1}(t) + V_{E2}(t) + \kappa_{EE}(t)V_{E1}(t)V_{E2}(t), \quad (23) \]

where \( V_{E1} \) and \( V_{E2} \) are EPSPs induced by two individual excitatory inputs, and \( V_S \) is the SSP when the two excitatory inputs are present. Similar to the case of a pair of excitatory and inhibitory inputs, the shunting coefficient \( \kappa_{EE}(t) \) only depends on the excitatory input locations and the input time difference. It does not depend on the EPSPs’ amplitudes. Here \( \kappa_{EE} \) will still be referred to as a shunting coefficient because the origin of the nonlinear integration for the paired excitatory inputs is exactly the same as that for the paired excitatory and inhibitory inputs from the passive cable model.

The bilinear integration rule (23) is found to be consistent with the numerical results obtained using the same realistic pyramidal neuron model as the one used in the section of Bilinear Rule for \( \kappa_{EE} \). For a pair of excitatory inputs with their locations fixed on the dendritic trunk, the rule holds when the amplitude of each EPSP is less than \( 2mV \). For the case of concurrent inputs, at the time \( t^* \) when one of the EPSPs reaches its peak value

\[ V_{SC}(t^*) = V_S(t^*) - V_{E1}(t^*) - V_{E2}(t^*) \]

is found to be linearly dependent of \( V_{E1}(t^*)V_{E2}(t^*) \), as shown in Fig. 6A. This linear relationship indicates \( \kappa_{EE} \) is independent of the amplitudes of the two EPSPs. In addition, as shown in Fig. 6B, the bilinear integration rule is numerically verified in the time interval \( t^* - \sigma < t < t^* + \sigma \), for \( \sigma = 10 \text{ms} \), within which the amplitude of EPSPs are relatively small. For the case of nonconcurrent inputs, the bilinear integration rule is also numerically verified in the same way, as shown in Fig. 6C–D.

In addition, we find that when the input strengths become sufficiently strong so as to make the depolarized membrane potential too large, i.e. \( V_{E1}V_{E2} > 5mV^2 \), there is a deviation from the bilinear integration rule (23). This deviation can be ascribed to the voltage-gated ionic channel activities in our realistic pyramidal neuron model. After blocking the active channels, the rule becomes valid with a different value of \( \kappa_{EE} \) for large EPSPs amplitudes, as shown in Fig. 7. However, we note that, regardless of input strengths, the amplitude of \( \kappa_{EE} \) is always two orders of magnitude smaller than the amplitude of SSP. Therefore, the integration of two excitatory inputs can be naturally approximated by the linear summation of two individual EPSPs, i.e. \( V_{SC} = 0mV \).

We then perform electrophysiological experiments with a pair of excitatory synaptic inputs to confirm the linear summation. As expected, the linear summation is also observed in our experiments for both concurrent and nonconcurrent input cases, as shown in Fig. 6E and 6F, respectively. Note that, the linear summation is also consistent with experimental observations as reported in Ref. [24].

Similarly, for a pair of inhibitory inputs, we can arrive at the following bilinear integration rule from the cable model:

\[ V_S(t) = V_{I1}(t) + V_{I2}(t) + \kappa_{II}(t)V_{I1}(t)V_{I2}(t), \quad (24) \]

where \( V_{I1} \) and \( V_{I2} \) are IPSPs induced by two individual inhibitory inputs, and \( V_S \) is the SSP when the two inhibitory inputs are present. Here, \( \kappa_{II}(t) \) is the shunting coefficient that is independent of the IPSPs amplitudes but is dependent on the input time difference and input locations. The above bilinear integration rule (24) is consistent with our numerical results using the realistic pyramidal neuron model, as shown in Fig. 8A–D. Our electrophysiological experimental observations further confirm this rule, as shown in Fig. 8E–H.

Fig. 6. Dendritic integration of a pair of excitatory inputs. (A–D) Simulation results with two excitatory inputs given at the location \( x_{E1} = 227 \mu m \) and \( x_{E2} = 233 \mu m \). (A) The SC amplitude is plotted against the product of the two EPSP amplitudes, at the time \( t^* \) when one of the EPSPs reaches its peak (Note that \( -V_{SC} \) is plotted). Varying \( V_{E1} \) and \( V_{E2} \) less than \( 2mV \), it can be seen that \( -V_{SC} \) increases linearly with \( V_{E1}V_{E2} \). (B) Dendritic integration in the time interval \( t^* - \sigma < t < t^* + \sigma \), where \( \sigma = 10 \text{ms} \). (upper) \( R^2 \) for the goodness of the linear fitting of \( -V_{SC} \) vs. \( V_{E1}V_{E2} \) at different times. (lower) The shunting coefficient \( \kappa_{EE}(t) \) (in the unit of \( mV^{-1} \)) as the slope of the linear fitting is plotted at different times. The error bar indicates 95% confidence interval (The error bars are relatively small and are within the circles). The circle marked by red indicates the case in (A). (C–D) The same as (A–B) except that one of the EPSPs is elicited \( 20 \text{ms} \) earlier than the other. (E–F) Our experimental result shows the nearly linear summation for (E) a pair of concurrent excitatory inputs and (F) nonconcurrent excitatory inputs with arrival time difference \( 20 \text{ms} \), when two excitatory inputs are given at the location \( x_{E1} = 50 \mu m \) and \( x_{E2} = 100 \mu m \).
simulation, all inputs are elicited starting randomly from 0 ms to 100 ms. In order to compare Equation (25) with the SSP simulated in the realistic neuron model, we first measure $k_{EE}$, $k_{EI}$, and $k_{II}$ pair by pair for all possible pairs. We then record all membrane potential traces $V_{E}^{i}$, $V_{E}^{j}$, ..., $V_{E}^{15}$ and $V_{I}^{1}$, $V_{I}^{2}$, ..., $V_{I}^{7}$ induced by the corresponding individual synaptic inputs. Our results show that the SSP measured from our simulation is indeed given by the bilinear integration rule (25), as shown in Fig. 9B and 9C. In contrast, the SSP in our numerical simulation deviates significantly from the linear summation of all individual EPSPs and IPSPs.

Graph Representation of Dendritic Integration

According to our bilinear integration rule (25), the dendritic integration of multiple synaptic inputs can be decomposed into the summation of all possible pairwise dendritic integration. Therefore, we can map dendritic computation in a dendritic tree onto a graph. Each dendritic site corresponds to a node in the graph and the corresponding shunting component is mapped to the weight of the edge connecting the two nodes. We refer to such a graph as a dendritic graph. The dendritic graph is an all-to-all connected graph if all stimuli are given concurrently (Fig. 10A). However, the dendritic integration for all possible pairs of synaptic inputs is usually not activated concurrently in realistic situations. For instance, if the arrival time difference between two inputs is sufficiently large, there is no interaction between them. The activated level of the nonlinear dendritic integration for a pair of synaptic inputs can be quantified by the SC amplitude—the weight of the edge in the graph. The simulation result shows that the number of activated edges at any time is relatively small on the dendritic graph (Fig. 10B–D), compared with the total number of edges on the all-to-all connected graph (Fig. 10A). Therefore, for the case of a hippocampal pyramidal neuron, the dendritic graph could be functionally sparse in time. The functional sparsity of a dendritic graph may also exist in neocortical pyramidal neurons. In vivo, a cortical pyramidal neuron receives about $10^4$ synaptic inputs [26]. Most of them are from other cortical neurons [27,28], which typically fire about 10 spikes per second in awake animals [29,30]. Thus, the neuron can be expected to receive $10^5$ synaptic inputs per second. The average number of synaptic inputs within 10 ms (membrane potential time constants in vivo) is $10^3$. The number of activated dendritic integration pairs within the 10 ms interval is $10^6$, which is relatively small compared with the total possible synaptic integration pairs $10^8$. Therefore, the activated integrations or edges in the dendritic graph within a short time window can be indeed functionally sparse ($10^{-2}$).

In general, the neuronal firing rates vary across different cell types, cortical regions, brain states and so on. Therefore, based on the above estimate, in an average sense, the graph of dendritic integration is functionally sparse.

Discussion

Our bilinear dendritic integration rule (21) is consistent with the rule previously reported [3], but is more general in the following aspects: (i) Our dendritic integration rule holds at any time and is not limited to the time when the EPSP reaches its peak value. (ii) The rule holds when the two inputs are even nonconcurrent. This situation often occurs because the excitatory and inhibitory inputs may not always arrive at precisely the same time. (iii) The form of the rule can be extended to describe the integration between a pair of excitatory inputs, a pair of inhibitory inputs, and even multiple inputs of mixed-types. The
Spatiotemporal integration rule holds in the subthreshold regime for a large range of membrane potential. When we derive the bilinear rule from the passive cable model, we assume that the spatiotemporal information of synaptic inputs interaction is coded in the shunting coefficient, which is a function of the input locations and input arrival time difference.
The bilinear integration rule (25) can help improve the computational efficiency in a simulation of neuronal network with dendritic structures. By our results, once the shunting coefficients for all pairs of input locations are measured, we can predict the neuronal response at the soma by the bilinear integration rule (25). By taking advantage of this, one can establish library-based algorithms to simulate the membrane potential dynamics of a biologically realistic neuron. An example of a library-based algorithm can be found in Ref. [37]. To be specific, based on the full simulation of a realistic neuron model, we can measure the time-dependent shunting coefficient as a function of the arrival time difference and input locations for all possible pairs of synaptic inputs and record them in a library in advance. For a particular simulation task, given the specific synaptic inputs on the dendrites, we can then search the library for the corresponding shunting coefficients to compute the neuronal response according to the bilinear integration rule (25) directly. In such a computational framework, one can avoid directly solving partial differential equations that govern the spatiotemporal dynamics of dendrites and greatly reduces the computational cost for large-scale simulations of networks of neurons incorporating dendritic integration.

**Materials and Methods**

**Ethics Statement**

The animal-use protocol was approved by the Animal Management Committee of the State Key Laboratory of
The Cable Model

We consider an idealized passive neuron whose isotropic spherical soma is attached to an unbranched cylindrical dendrite with finite length $l$ and diameter $d$. Each small segment in the neuron can be viewed as an RC circuit with a constant capacitance and leak conductance density \[11,38\]. The current conservation within a segment $[x,x+Ax]$ on the dendrite leads to

$$\frac{c\pi d Ax}{\partial t} = -g_L \pi d Ax_0 + I_{\text{syn}} + I(x) - I(x+Ax), \quad (26)$$

where $v$ is the membrane potential with respect to the resting potential of the dendrite, $c$ is the membrane capacitance per unit area, and $g_L$ is the leak conductance per unit area. Here, $I_{\text{syn}}$ is the synaptic current given by:

$$I_{\text{syn}} = - \sum_{q=E,I} \left( x + Ax \right) G_q dx(v-e_q), \quad (27)$$

where $G_E$ and $G_I$ are excitatory and inhibitory synaptic conductance per unit area and $e_E$ and $e_I$ are their reversal potentials, respectively. When excitatory inputs are elicited at $M_E$ dendritic sites and inhibitory inputs are elicited at $M_I$ dendritic sites, we have

$$G_q = \sum_{j=1}^{M_q} \sum_{i=1}^{\infty} f_i^q g_q(t-i^p_{ij})\delta(x-x^p_{ij}), \quad (28)$$

where $q=E,I$. For a synaptic input of type $q$, $f_i^q$ is the input strength of the $j^{th}$ input at the $i^{th}$ location, $t^p_{ij}$ is the arrival time of the $j^{th}$ input at the $i^{th}$ location, $x^p_{ij}$ is the $j^{th}$ input location. The unitary conductance is often modeled as

$$g_q(t) = N_q(e^{\frac{\tau_q}{2} t} - e^{\frac{-\tau_q}{2} t})\Theta(t) \quad (29)$$

with the peak value normalized to unity by the normalization factor $N_q$, and with $\tau_Q$ and $\tau_d$ as rise and decay time constants, respectively \[33\]. Here $\Theta(t)$ is a Heaviside function. The axial current $I(x)$ can be derived based on the Ohm’s law,

$$I(x) = \frac{\pi d^2 \hat{c} \nu}{4r_a \partial x}, \quad (30)$$

where $r_a$ is the axial resistivity. Taking the limit $Ax \rightarrow 0$, Equation (26) becomes our unbranched dendritic cable model,

$$\frac{\partial^2 \hat{c} \nu}{\partial t^2} = -g_L \nu - \sum_{q=E,I} G_q (v-e_q) + \frac{d \partial^2 \nu}{4r_a \partial x^2}, \quad (31)$$

In particular, for a pair of excitatory and inhibitory inputs with strength $f_E$ and $f_I$ received at $x_E$ and $x_I$, and at time $t_E$ and $t_I$, respectively, we have

$$\frac{\partial^2 \hat{c} \nu}{\partial t^2} = -g_L \nu - \sum_{q=E,I} f_q g_q(t-t_q)\delta(x-x_q)(v-e_q) + \frac{d \partial^2 \nu}{4r_a \partial x^2}. \quad (32)$$

Similarly, for a pair of excitatory or inhibitory inputs with strengths $f_{q1}$ and $f_{q2}$ received at $x_{q1}$ and $x_{q2}$, and at time $t_{q1}$ and $t_{q2}$ ($q=E,I$), respectively, we have

$$\frac{\partial^2 \hat{c} \nu}{\partial t^2} = -g_L \nu - \sum_{p=1,2} f_{q_p} g_{q_p}(t-t_{q_p})\delta(x-x_{q_p})(v-e_q) + \frac{d \partial^2 \nu}{4r_a \partial x^2}. \quad (33)$$

For the boundary condition of the cable model [Equation (31)], we assume one end of the dendrite is sealed:

$$\frac{\partial \hat{c} \nu}{\partial x} \bigg|_{x=l} = 0. \quad (34)$$

For the other end connecting to the soma, which can also be modeled as an RC circuit, by the law of current conservation, we have

$$c_S \frac{\partial \hat{c} \nu}{\partial t} = -g_L S \nu + I_{\text{dend}}, \quad (35)$$

where $S$ is the somatic membrane area, and $\nu^s$ is the somatic membrane potential. The dendritic current flowing to the soma, $I_{\text{dend}}$, takes the form of Equation (30) at $x=0$. Because the membrane potential is continuous at the connection point

$$\nu^s(t) = \nu(0,t), \quad (36)$$

we arrive at the other boundary condition at $x=0$:

$$c \frac{\partial \hat{c} \nu(0,t)}{\partial t} = -g_L \nu(0,t) + \frac{\pi d^2 \partial^2 \nu}{4Sr_a \partial x^2} \bigg|_{x=0}. \quad (37)$$

For a resting neuron, the initial condition is simply set as

$$\nu(x,0) = 0. \quad (38)$$

Green’s Function

In the absence of synaptic inputs, Equation (31) is a linear system. Using a $\delta$ impulse input, its Green’s function $G(x,y,t)$ can be obtained from

$$c \frac{\partial^2 G}{\partial t^2} = -g_L G + \frac{d \partial^2 G}{4r_a \partial x^2} + \delta(x-y)\delta(t), \quad (39)$$

with the following boundary conditions and initial condition,

$$c \frac{\partial G(0,y,t)}{\partial t} = -g_L G(0,y,t) + \frac{\pi d^2 \partial^2 G(x,y,t)}{4Sr_a \partial x^2} \bigg|_{x=0} \frac{\partial G(t)}{\partial x} \bigg|_{x=l} = 0, \text{ and } G(x,y,0) = 0. \quad (40)$$

For simplicity, letting $\tau = t/c$, $\xi = x \sqrt{4r_a/d}$, $\eta = y \sqrt{4r_a/d}$, $\lambda = l \sqrt{4r_a/d}$, the solution of Equation (39) can be obtained from the following system,
\[ \frac{\partial H}{\partial \tau} = -g_u H + \frac{\partial^2 H}{\partial z^2} + \delta(\zeta - \eta) \delta(\tau), \tag{40} \]

with rescaled boundary and initial conditions,

\[ \frac{\partial H(0, \eta, \tau)}{\partial \tau} = -g_u H(0, \eta, \tau) + \frac{\partial^2 H(\zeta, \eta, \tau)}{\partial z^2} \bigg|_{\zeta = 0}, \quad \frac{\partial H}{\partial z} \bigg|_{\zeta = \lambda} = 0, \quad \text{and} \quad H(\zeta, \eta, 0) = 0, \]

where \( \gamma = (\pi c^2/2S)(r_a d)^{-1/2} \). Taking the Laplace transform of Equation (40), we obtain

\[ \mathcal{L}H(\zeta, \eta, s) = \frac{A(\eta, s)e^{\sqrt{s + g_u}(\zeta - \eta)} + B(\eta, s)e^{\sqrt{s + g_u}(\lambda - \eta)} + e^{-\sqrt{s + g_u}(\zeta - \eta)}}{2\sqrt{s + g_u}}. \tag{41} \]

Combining the two boundary conditions \( (\partial B/\partial s) \) is thus eliminated), we have

\[ \mathcal{L}H(\zeta, \eta, s) = \left\{ \begin{array}{ll}
\frac{1}{\sqrt{s + g_u}}A(\eta, s)\cosh(\sqrt{s + g_u}(\zeta - \eta)) - \sinh(\sqrt{s + g_u}(\eta - \zeta)) & \text{for } \zeta \leq \eta, \\
\frac{1}{\sqrt{s + g_u}}A(\eta, s)\cosh(\sqrt{s + g_u}(\lambda - \zeta)) & \text{for } \zeta > \eta,
\end{array} \right. \tag{42} \]

where

\[ A(\eta, s) = \left( \frac{\sqrt{s + g_u} \sinh(\sqrt{s + g_u} \eta) + \sqrt{s + g_u} \cosh(\sqrt{s + g_u} \eta)}{\sqrt{s + g_u}} \right). \tag{43} \]

whose denominator is denoted as \( \zeta(s) \) for later discussions. For the inverse Laplace transform, we need to deal with singular points that are given by the roots of \( \zeta(s) = 0 \). It can be easily verified that these singularities are simple poles and \( \mathcal{L}H(\zeta, \eta, s) \) is analytic at infinity. Then \( \mathcal{L}H(\zeta, \eta, s) \) can be written as

\[ \mathcal{L}H(\zeta, \eta, s) = \sum_n H_n(\zeta, \eta)e^{-s/k_n}, \tag{44} \]

where \( H_n(\zeta, \eta) \) is a constant coefficient in the complex \( s \) domain, and \( s = -k_n \) are the singular points. Then taking the inverse Laplace transform of Equation (44), we obtain

\[ H(\zeta, \eta, \tau) = \sum_n H_n(\zeta, \eta)e^{-k_n \tau}. \tag{45} \]

Now we only need to solve \( k_n \) and \( H_n(\zeta, \eta) \) in Equation (45) to obtain the Green’s function of Equation (40). We solve the singular points \( s = -k_n \) first. Defining \( w_n = -i\sqrt{-k_n + g_u} \zeta \), \( \zeta(s) = 0 \) yields

\[ \tan(w_n) = -\frac{w_n}{\sqrt{2}}, \tag{46} \]

whose roots can be determined numerically. There are solutions for \( w_n \) with \((n - 1/2)\pi < w_n < (n + 1/2)\pi\) for \( n \geq 1 \) and \( w_0 = 0 \). Next, to determine the factors \( H_n(\zeta, \eta) \), we use the residue theorem for integrals. For a contour \( C_n \) that winds in the counter-clockwise direction around the pole \( s = -k_n \), and that does not include any other singular points, the integral of \( \mathcal{L}H(\zeta, \eta, s) \) on this contour is given by

\[ \int_{C_n} \mathcal{L}Hds = 2\pi i \left( \frac{1}{\mathcal{L}H(\zeta, \eta, s)} \right)^{-1}. \tag{47} \]

Using Equations (42–44) and (47), we obtain

\[ H_n(\zeta, \eta) = \frac{2}{\gamma \zeta + \gamma \lambda w_n} \left[ \sin(w_n(1 - \zeta/\lambda)) \cos(w_n(1 - \eta/\lambda)) \right]. \tag{48} \]

Asymptotic Analysis

We first consider the case when a pair of excitatory and inhibitory inputs are received by a neuron. Similar results can be obtained for a pair of excitatory inputs and a pair of inhibitory inputs. For the physiological regime (the amplitude of an EPSP being less than \( 2mV \) and the amplitude of an IPSP being less than \( -3mV \)), the corresponding required input strengths \( f_E \) and \( f_I \) are relatively small. Therefore, given an excitatory input at location \( x = x_E \) and time \( t = t_E \), and an inhibitory input at location \( x = x_I \) and time \( t = t_I \), we represent \( u(x, t) \) as an asymptotic series in the powers of \( f_E \) and \( f_I \),

\[ \nu = \sum_{k=0}^\infty \sum_{m+n-k} f_E^m f_I^n u_{mn}(x, t). \tag{51} \]

Substituting Equation (51) into the cable equation (31), order by order, we obtain a set of differential equations. For the zeroth-order, we have

\[ \frac{\partial v_{00}}{\partial \tau} = -g_u v_{00} + \frac{d}{4r_a} \frac{\partial^2 v_{00}}{\partial x^2}. \tag{52} \]

Using the boundary and initial conditions [Equations (34), (37), and (38)], the solution is simply \( v_{00} = 0 \).

For the first order of excitation \( \mathcal{O}(f_E) \), we have

\[ \frac{\partial v_{10}}{\partial \tau} = -g_u v_{10} + \frac{d}{4r_a} \frac{\partial^2 v_{10}}{\partial x^2} + g_v(t - t_E) \delta(x - x_E) e_E. \tag{53} \]

With the help of Green’s function, the solution can be expressed as

\[ v_{10} = G(x, x_E, t) \ast [e_E g_v(t - t_E)]. \tag{55} \]
here ‘*’ denotes convolution in time. For the second order of excitation $O(t_E^2)$, we have

$$c \frac{\partial v_{20}}{\partial t} = -g_L v_{20} + \frac{d}{4r_d} \frac{\partial^2 v_{20}}{\partial x^2} - g_E(t - t_E) \delta(x - x_E)v_{10}. \tag{56}$$

Because $v_{10}$ is given by Equation (55), the solution of Equation (56) is

$$v_{20} = G(x, x_E, t) \ast [-g_E(t - t_E)v_{10}(x_E, t)]. \tag{57}$$

Similarly, we can have the first and second order inhibitory solutions,

$$v_{01} = G(x, x_I, t) \ast [v_E g_I(t - t_I)], \tag{58}$$

$$v_{02} = G(x, x_I, t) \ast [-g_E(t - t_I)v_{10}(x_I, t)]. \tag{59}$$

For the order of $O(t_E t_I)$, we have

$$c \frac{\partial v_{11}}{\partial t} = -g_L v_{11} + \frac{d}{4r_d} \frac{\partial^2 v_{11}}{\partial x^2} - g_E(t - t_E) \delta(x - x_E)v_{01}$$

$$-g_I(t - t_I) \delta(x - x_I)v_{10}, \tag{60}$$

whose solution is obtained as follows,

$$v_{11} = G(x, x_E, t) \ast [-g_E(t - t_E)v_{01}(x_E, t)]$$

$$+ G(x, x_I, t) \ast [-g_I(t - t_I)v_{10}(x_I, t)]. \tag{61}$$

Numerical Simulation

For the numerical simulation of the two-compartment passive cable model [Equation (3)], the Crank-Nicolson method [39] was used with time step 0.01 $ms$ and space step 1 $\mu m$. Parameters in our simulation are within the physiological regime [3,12] with $c = 1mF/cm^2$, $g_L = 0.05nS/cm^2$, $E_E = 70mV$, $E_I = -10mV$, $S = 2827.4m^2$, $r_d = 100\Omega cm$, $l = 600\mu m$, $d = 1\mu m$, $\sigma_E = 5ms$, $\sigma_I = 7.8ms$, $\sigma_0 = 6ms$, and $\sigma_d = 18ms$. The time constants here were chosen to be consistent with the conductance inputs in the experiment [3].

The realistic pyramidal model is the same as that in Ref. [3]. The morphology of the reconstructed pyramidal neuron includes 200 compartments and was obtained from the Duke-Southampton Archive of neuronal morphology [40]. The passive cable properties and the density and distribution of active conductances in the model neuron were based on published experimental data obtained from hippocampal and cortical pyramidal neurons [18,19,34,41–50]. We used the NEURON software Version 7.3 [51] to simulate the model with time step 0.1 ms.

Hippocampal Slice Preparation and Electrophysiology

The experimental measurements of summation of EPSPs or IPSPs in single hippocampal CA1 pyramidal cells in the acute brain slice followed a method described in Ref. [3], with some modifications. A brief description of modified experimental procedure is as follows. Acute hippocampal slices (350 $\mu m$ thick) were prepared from Sprague Dawley rats (postnatal day 14–16), using a vibratome (VT1200, Leica). The slices were incubated at 34°C for 30 min before transferring to a recording chamber perfused with the ACSF solution (2 ml/min; 30–32°C). The ACSF contained (in mM) 125 NaCl, 3 KCl, 2 CaCl2, 2 MgSO4, 1.25 NaH2PO4, 1.3 sodium ascorbate, 0.6 sodium pyruvate, 26 NaHCO3, and 11 D-glucose, and was saturated with gas containing 95% O2 and 5% CO2 (pH 7.4). Whole-cell recording was made from the soma of CA1 pyramidal cells using glass micropipettes under an upright microscope (BX51WI, Olympus) equipped with the DIC optics and an infrared camera (IR-1000E, DAGE-MTI). The intra-micropipette solution contained (in mM) 145 K-glucocate, 5 KCl, 10 HEPES, 10 disodium phosphate, 4 Mg2+ATP, 0.3 Na2GTP, and 0.2 EGTA (pH 7.3), together with fluorescent dye Alexa Fluor 488 (20 $\mu M$, Invitrogen) to visualize the dendritic trees. Pipette resistance was about 3–4 $M\Omega$, and the access resistance during the whole-cell recording was normally less than 20 $M\Omega$. The same method for micro-iontophoretic application of extracellular glutamate or GABA at the apical dendrite of CA1 pyramidal cells was used to elicit rapid membrane depolarizations (EPSPs) and hyperpolarizations (IPSPs). For all three experimental configurations (EPSP-IPSP, EPSP-EPSP, and IPSP-IPSP summation), two micro-iontophoretic pipettes were placed at dendritic locations 100 $\mu m$ and 50 $\mu m$ from the soma, respectively, in particular for the EPSP-IPSP summation. GABA iontophoretic pipette was always placed at the more proximal location than glutamate iontophoretic pipette was placed. For each recorded cell, an electrode was placed at the soma to set the resting membrane potential to about $-60mV$ in order to obtain a driving force of $15–20mV$ for inhibitory GABA inputs. Electrical signals of individual and summed iontophoretic responses were amplified and filtered at 3 kHz (low pass) by a pach clamp amplifier (Multiclamp 700B, Molecular Devices), digitalized (100 kHz) by an AD-DA converter (Digidata 1440A, Molecular Devices), and acquired by a pClamp 10.3 (Molecular Devices) into a computer for further analysis.

Data Processing

In order to study the dendritic integration of a pair of excitatory and inhibitory inputs, for fixed input locations and strengths, a moving average technique with time lag 1 ms was first applied to smooth each individual trace of the EPSP, IPSP, and SSP recorded in our experiments. After smoothing, we measured the amplitudes of EPSP, IPSP, and SSP at different times, including those when EPSP reached its peak value, and denoted them by $V_{Ei}$, $V_{Ii}$, and $V_{Si}$, respectively. By varying the excitatory and inhibitory input strengths, we measured values of $V_{Ei}$, $V_{Ii}$ and $V_{Si}$. We then constructed a scatter plot of $-V_{Ei}V_{Ii}$ vs. $-V_{Si}$ for $-V_{Ei}V_{Ii} - V_{Si}$ at different times. We divided the range of $-V_{Ei}V_{Ii}$ into approximately 10 bins and averaged all the data points ($-V_{Ei}V_{Ii} - V_{Si}$) within each bin. The number of bins was chosen to ensure at least 8 data points were used for averaging. However, the qualitative results were not sensitive to the number of bins (e.g. from 6 bins to 16 bins). Using the Curve Fitting Toolbox in Matlab Version 7.14, we finally fitted the averaged data points by a linear function $V_{SC} = kEI V_{Ei} V_{Ii}$, from which the slope $k_{EII}$ was estimated together with its 95% confidence interval. For the dendritic integration of a pair of identical type, the same data processing procedure was followed.
Author Contributions
Conceived and designed the experiments: SL XhZ DZ DC. Performed the experiments: NI XhZ. Analyzed the data: SL NI XhZ DZ DC. Contributed reagents/materials/analysis tools: SL DZ DC. Wrote the paper: SL NI XhZ DZ DC.

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