SI Appendix

SI Methods

Hippocampal slice preparation Transverse hippocampal slices (300 - 350 μm thick) were prepared from Sprague Dawley rats (postnatal day 16 - 21) in ice-cold artificial cerebrospinal fluid (ACSF) with a vibratome (model 3000, Vibratome, St. Louis, MO), and maintained at 34°C for 0.5 hr and then at room temperature (22 - 26°C). The ACSF contained (in mM): 119 NaCl, 3 KCl, 2 $CaCl_2$, 1 $MgSO_4$, 1.25 NaH_2PO_4, 26 $NaHCO_3$, and 20 glucose, and was saturated with 95% O_2 and 5% CO_2 (pH 7.4). The animal use protocol was approved by the Animal Care and Use Committee of Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences.

Electrophysiology and iontophoresis Electrophysiology experiments were performed in a submerged recording chamber that was perfused with ACSF (~ 2 ml/min) at 30 - 32°C. Neurons were visualized with an upright microscope (BX51WI, Olympus) equipped with an infrared camera (IR-1000, DAGE-MTI, Michigan City, IN). Whole-cell recording was made from the soma of CA1 pyramidal neurons. Recording pipettes were filled with the internal solution that contained (in mM): 130 K-gluconate, 7 KCl, 1 $MgCl_2$, 10 HEPES, 10 phosphocreatine, 3 MgATP, 0.3 $Tris_2GTP$ and 0.1 EGTA (pH 7.3). Fluorescent dye Alexa Fluor 488 was loaded into the cell through the recording pipette to visualize the dendritic tree. Whole-cell recording pipettes had a resistance of 2.5 - 3.5 MΩ and during the recording the access resistance was normally smaller than 20 MΩ. Electrical signals were amplified and filtered at 1 KHz by a patch-clamp amplifier (Axopatch 200B, Molecular Devices, Union City, CA), digitalized by a DIGIDATA board (Model 1322A, Molecular Devices), acquired and analyzed by pClamp 9

(Molecular Devices) in a computer.

The iontophoretic method followed that described previously (1), with some modifications. The sharp iontophoretic pipette was filled with 150 mM glutamate (pH 8.0, adjusted with NaOH) or 350 mM GABA (pH 3.5, adjusted with HCl) and had a resistance of 150 - 300 MΩ. The pipette tip was coated with Sylgard-184 (Dow Corning, Midland, MI) to reduce the pipette capacitance. Both the holding current (1.5 - 2.0 nA) and iontophoretic current (10 - 100 nA, with a duration of 0.2 - 1.0 ms) were applied through a Multiclamp 700A amplifier (Molecular Devices) and the pipette capacitance was compensated by a built-in function of the amplifier. A Master-8 stimulator (AMPI, Israel) was used to control the duration, amplitude and onset timing of the iontophoretic current. The iontophoretic responses were highly sensitive to the proximity of the pipette tip to the dendrite, but were reproducible for a given location (Fig. S1*A*,*B*). For the response kinetics, the averaged 10-90% risetime for glutamate and GABA iontophoretic responses were 8.2 ± 1.7 ms and 13.8 ± 2.8 ms (mean ± SD, n = 10), respectively, similarly to those of electrically evoked natural EPSP (6.7 ± 2.5 ms) and IPSP (11.4 ± 3.5 ms, mean ± SD, n = 10). In both experiments and simulations, the driving force (the difference between the reversal potential and resting membrane potential) for the inhibitory input was fixed at -10 mV, in order to allow comparison of results from various experiments. Each measured response was averaged from 10 - 15 trials. All chemicals were from Sigma-Aldrich except that Alexa Fluor 488 was from Invitrogen.

Realistic neuronal modeling The reconstructed CA1 pyramidal neuron included 200 compartments and was obtained from Duke-Southampton Archive of neuronal morphology (2). The passive cable properties and the density and distribution of active conductances in the model

cell were based on published experimental data obtained from hippocampal and cortical pyramidal cells. The source code for our simulation model is available on the web (http://www.ion.ac.cn/laboratories/zhangxiaohui/).

For active conductances, the model neuron included voltage-gated sodium conductance g_{Na}, the delayed rectifier potassium conductance g_{Kd}, two variants of A-type potassium conductance g^{p}_{KA} and g^{d}_{KA} [applied to the proximal (< 100 μm) and distal (> 100 μm) dendrites, respectively], and the hyperpolarization-activated conductance g_h. It also contained AMPA, NMDA, $GABA_A$ and $GABA_B$ receptors, with kinetic properties described previously (3-5). AMPAR, NMDAR and $GABA_AR$ followed a first order kinetics of transmitter binding to the postsynaptic receptors□$dR/dt = Alpha * [T]* (1-R) - Beta*R$, where R is the fraction of open receptors, *Alpha* and *Beta* are forward and backward rate constants for transmitter binding, and [T] is the transmitter concentration. The postsynaptic current is given by: $I_{syn} = g * (V - E_{rev})$, where V is the postsynaptic potential, E_{rev} the reversal potential, and g the synaptic conductance. For AMPAR and $GABA_AR$, $g = g_{max} * R$, where g_{max} is the maximum synaptic conductance and for NMDAR, $g = (g_{max} * R)/(1 + 0.33 * [Mg^{2+}] * exp(- (0.06*V)))$, where $[Mg^{2+}]$ is the extracellular magnesium concentration. For $GABA_BR$, the kinetic equations are $dR/dt = K_1 * [T] * (1-R) - K_2 * R$ and $dG/dt = K_3 * R - K_4 * G$, where K_1 and K_2, similar to *Alpha* and *Beta*, are forward and backward transmitter binding rate, K_3 and K_4 the rate constants of G protein production and decay□G is the fraction of activated G proteins; $g = g_{max} * G^n / (G^n + K_D)$, where K_D is the dissociation constant of potassium channel. The parameters used in the four types of receptors are largely the same as previous reports (3-7), with minor adjustments to match the results from our iontophoretic experiment. Moreover, the resting membrane resistance R_m was set to be non-uniform along the dendritic tree (8). Sodium channels were distributed with a largely constant

density along the somatodendritic axis (9). The A-type potassium channels differed in their kinetics between the proximal and distal populations, and their density increased progressively by more than 6-fold from the soma to a distance of 350 μm along the apical trunk (10, 11). The density of hyperpolarization-activated cationic current (I_h) increased by more than 6 folds from the soma to the distal dendrites (12). The distribution of AMPA receptors was set with a gradient along the dendrite to achieve a distance-dependent scaling property (13-16). Based upon the above experimental results, the parameters used in the model were set as follows: the peak sodium conductance g_{Na} = 30 mS/cm^2 in the soma and dendrites, g_{Na} = 60 mS/cm^2 in the axon; g_{Kd} = 5 mS/cm^2 (uniform distribution); $g^p_{KA}(d) = g^{p0}_{KA} * (1 + d/70)$, if the distance from the soma $d \leq 100$ μm; $g^d_{KA}(d) = g^{d0}_{KA} * (1 + d/70)$, if $100 < d \leq 350$ μm; and $g^d_{KA}(d) = 6.5 * g^{d0}_{KA}$ if $d > 350$ μm, where $g^{p0}_{KA} = g^{d0}_{KA}$ = 5 mS/cm^2; $g_h(d) = g_{h0} + 9 * g_{h0}/[1.0 + exp((300 - d)/50)]$, where g_{h0} = 20 μS/cm^2; the ratio of maximal NMDAR conductance to AMPAR conductance was of the form $r_{N/A} = 0.6 / (1 + d/300)$ for the dendrite located in the *stratum radiatum* and the ratio of $GABA_BR$ to $GABA_AR$ was set as 0.6.

The passive biophysical properties include: $R_m = R_{m0} + (R_{m1} - R_{m0}) / [1.0 + exp(-(d - 300)/50)]$, where R_{m0} = 60 kΩcm^2 and R_{m1} = 20 kΩcm^2; R_i = 80 Ωcm; C_m = 1 μF/cm^2. The temperature was 34ºC and the resting membrane potential was -70 mV. Reversal potentials were set as: E_{Na} = +55 mV, E_K = -90 mV, E_h = -30 mV, $E_{AMPA} = E_{NMDA}$ = 0 mV, E_{GABA_A} = -80 mV, E_{GABA_B} = -90 mV.

SI Theoretical Analysis

To investigate the theoretical basis of the empirically derived arithmetic rule, we applied the two port analysis developed by Koch (1999) to a passive dendritic tree. In this analysis, the time-dependent aspects were not considered. The somatic voltage response (V_{se}) to the

individual excitatory input at location *e* can be written as:

$V_{se} = K_{es} g_e (E_{re} - V_e^e)$, and $V_e^e = K_{ee} g_e (E_{re} - V_e^e)$

Where V_e^e is voltage change from resting potential and K_{ee} is the input resistance at location *e*, K_{es} is the transfer resistance between location *e* and the soma, E_{re} is the difference between the reversal potential for the excitatory synaptic current and the resting membrane potential, and g_e is the excitatory synaptic conductance. Solving the above two equations, we arrive at

$$V_{se} = \frac{K_{es} g_e E_{re}}{1 + K_{ee} g_e} \quad (1)$$

Likewise, for the inhibitory input we obtained

$$V_{si} = \frac{K_{is} g_i E_{ri}}{1 + K_{ii} g_i} \qquad (2)$$

For the somatic response to coincident excitatory and inhibitory inputs, we obtained

$V_s = K_{es} g_e (V_e - E_{re}) + K_{is} g_i (V_i - E_{ri})$,

where $V_e = K_{ee} g_e (E_{re} - V_e) + K_{ie} g_i (E_{ri} - V_i)$ and $V_i = K_{ii} g_i (E_{ri} - V_i) + K_{ei} g_e (E_{re} - V_e)$

The solution of the above equations can be expressed as (17):

$$V_s = \frac{K_{es} g_e E_{re} + K_{is} g_i E_{ri} + (K_{es} K_{ii} - K_{is} K_{ie}) g_i g_e E_{re} + (K_{is} K_{ee} - K_{es} K_{ie}) g_e g_i E_{ri}}{1 + K_{ee} g_e + K_{ii} g_i + (K_{ee} K_{ii} - K_{ie}^2) g_e g_i} \qquad (3)$$

$K_{ee} g_e$, $K_{ii} g_i$, $K_{ie} g_e$, and $K_{ie} g_i$ have magnitudes on the order of $10^{-2} \sim 10^{-1}$, and satisfy the conditions $K_{ee} g_e << 1$, $K_{ii} g_i << 1$ and $(K_{ee} K_{ii} - K_{ie}^2) g_e g_i << 1$. Thus, Equations (1-3) can be reduced by Taylor series expansion to yield

$V_{se} \approx K_{es} g_e E_{re} (1 - K_{ee} g_e) \approx K_{es} g_e E_{re}$

$V_{si} \approx K_{is} g_i E_{ri} (1 - K_{ii} g_i) \approx K_{is} g_i E_{ri}$

$$V_s \approx V_{se} + V_{si} - K_{ei}(\frac{1}{K_{es}E_{ri}} + \frac{1}{K_{is}E_{re}})V_{se}V_{si}$$

By defining $k = -K_{ei}(\frac{1}{K_{es}E_{ri}} + \frac{1}{K_{is}E_{re}})$, we obtained $V_s \approx V_{se} + V_{si} + kV_{se}V_{si}$. This equation has the same form as the empirically derived arithmetic rule, for which V_s, V_{se} and V_{si} correspond to Sum, EPSP and IPSP, respectively, in our empirically obtained arithmetic rule. Considering that $E_{ri} << E_{re}$ and K_{es} and K_{is} are of the same order of magnitude, *k* is reduced to

$$k \approx \frac{K_{ei}}{K_{es}(-E_{ri})} \qquad (4)$$

Note that E_{ri} is the difference between the reversal potential of the inhibitory current and the resting membrane potential, a value fixed at -10 mV in the simulations and experiments in the present study. The unit of *k* is mV^{-1}.

The transfer resistance between locations A and B (K_{AB}) can be calculated by dividing the voltage change in location B by the magnitude of the injected current in location A. The K_{AB} value is smaller for more distant A and B. A qualitative analysis of Equation (4) for a given *i* location is as follows:

(i) When *e* is proximal to *i* : K_{ei} becomes smaller and K_{es} becomes larger with increasing *e*-*i* distance, leading to a decreasing *k* with increasing *e*-*i* distance.

(ii) When *e* is distal to *i* : K_{ei} and K_{es} decrease concurrently with increasing *e* distance from the soma, leading to a largely constant *k* for distal *e*.

Further simulation was carried out according to Equation (4), and the results (Fig. S5) indeed support the above qualitative analysis and agree with the asymmetric *k* profile found in both realistic modeling and experiments (Fig. 3).

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