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Received 17 Jul 2016 | Accepted 9 Jan 2017 | Published 10 Mar 2017

DOI: 10.1038/ncomms14566

OPEN

Theory of optimal balance predicts and explains the amplitude and decay time of synaptic inhibition

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Synaptic inhibition counterbalances excitation, but it is not known what constitutes optimal inhibition. We previously proposed that perfect balance is achieved when the peak of an excitatory postsynaptic potential (EPSP) is exactly at spike threshold, so that the slightest variation in excitation determines whether a spike is generated. Using simulations, we show that the optimal inhibitory postsynaptic conductance (IPSG) increases in amplitude and decay rate as synaptic excitation increases from 1 to 800 Hz. As further proposed by theory, we show that optimal IPSG parameters can be learned through anti-Hebbian rules. Finally, we compare our theoretical optima to published experimental data from 21 types of neurons, in which rates of synaptic excitation and IPSG decay times vary by factors of about 100 (5–600 Hz) and 50 (1–50 ms), respectively. From an infinite range of possible decay times, theory predicted experimental decay times within less than a factor of 2. Across a distinct set of 15 types of neuron recorded *in vivo*, theory predicted the amplitude of synaptic inhibition within a factor of 1.7. Thus, the theory can explain biophysical quantities from first principles.

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Synaptic inhibition approximately counterbalances excitation on a millisecond timescale^{1–15}. Although balanced inhibition has advantages^{16–20}, it is not known what constitutes optimal balance. We recently proposed that perfect homeostatic balance is momentarily achieved when the peak of an EPSP is exactly at spike threshold, so that whether a spike does or does not occur will depend on the slightest variation in the amplitude of the excitatory postsynaptic conductance (EPSC)²¹. This would maximize the information that ‘spike’ or ‘no spike’ conveys about EPSC amplitude.

If correct, the theory should explain and predict biophysical properties. There is a wealth of data showing that IPSC mediated by GABA_A and glycine receptors have decay time constants that vary from 1 to at least 50 ms across diverse types of neurons, and a lot is known about the biophysical basis of this diversity²². But why should a specific synapse have the specific IPSC decay time that it does? Why should decay times vary across synapses? A good theory should explain the specific decay times and their variability from fundamental principles.

The proposed goal of homeostatic balance is to maximize the causal and informational link between EPSC amplitude and spike generation. In other words, a spike should accurately ‘measure’ EPSC amplitude. Like any other measurement, this requires comparison to a reference. A balance scale measures weight in almost perfect analogy to the way that membrane voltage and spikes measure EPSC (Fig. 1a,b). The angle of the arm (membrane voltage) depends on the difference between the new and unknown weight of interest on one side (EPSC) and a known reference weight on the other (IPSC and all other factors that counteract depolarization). If the balance scale has a binary output (spike or no spike), that output indicates only whether the new weight (EPSC) is more (spike) or less (no spike) than the reference (IPSC). Measurement is most accurate when perfect balance is attained (EPSP peak at spike threshold), and this is the homeostatic ideal.

Balance is difficult to achieve because EPSC vary dynamically across a large range of amplitudes and on a timescale of a millisecond or less. Balance requires that inhibition is dynamically adjusted to predict EPSC amplitude, analogous to continually adjusting the reference weight in anticipation of a new weight being placed on the balance scale. We have therefore referred to this process as ‘predictive homeostasis’²¹, and it is related to principles of ‘predictive coding’^{23–25}. It is ‘homeostatic’ insofar as the parameters of inhibition (synaptic strength, decay time and so on) are adjusted through negative feedback (for example, anti-Hebbian plasticity) to drive membrane excitability towards an intermediate target (optimal balance), and it is ‘predictive’ insofar as these parameters are determined in advance to counterbalance the expected future amplitude of excitation.

A useful example is a thalamocortical neuron of the lateral geniculate nucleus (LGN) recorded during viewing of a movie (Fig. 1c)²⁶. As expected for effective homeostatic balance, many of the large retinogeniculate EPSPs cause spikes and many do not (~50% on average across neurons)^{27–30}, indicating that spike generation is highly sensitive to the precise amplitude of retinogeniculate EPSC. Retinogeniculate EPSC are the proximate cause of all spikes, which signify evidence against light in this OFF-type neuron (Fig. 1c). In addition, there are two types of IPSC that convey evidence of opposite polarity (Fig. 1d)^{26,31–33}. ‘Homeostatic IPSC’ convey evidence of the same polarity as EPSC (evidence for EPSC amplitude, which is evidence against light in this example), whereas ‘opponent IPSC’ convey evidence against EPSC amplitude. Opponent IPSC are anti-correlated (out of phase) with EPSC (since simultaneous evidence for and against light in the same small receptive field is unusual) and thus they tend to cause hyperpolarization (Fig. 1c,d)^{26,34}. In contrast, homeostatic IPSC occur at nearly the same time as EPSC, and thus suppress EPSC amplitude. Homeostatic IPSC are consistently delayed from EPSC onset by

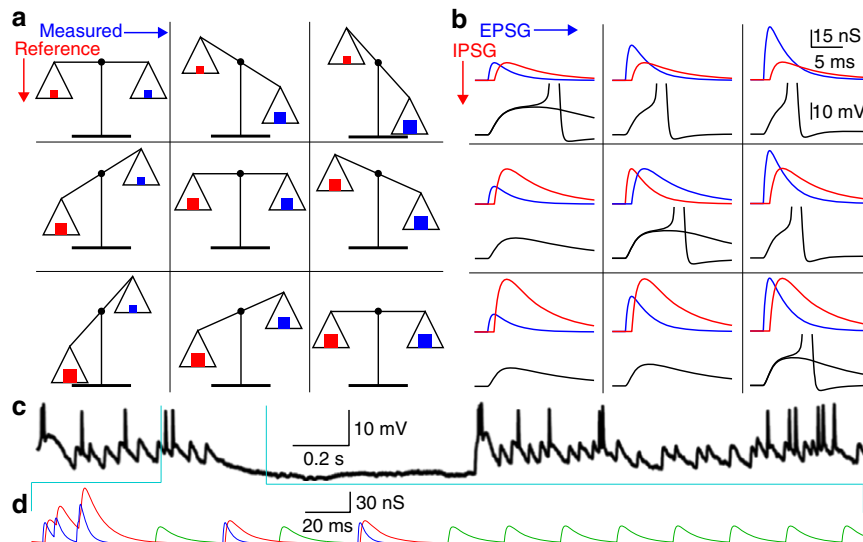


Figure 1 | Illustration of theory by analogy to a balance scale for measuring weight. (a) Each of the nine configurations of the balance scale are analogous to the corresponding combinations of EPSC, IPSC and membrane voltage in **b**. When EPSC amplitude exceeds the counterbalance provided by the IPSC and all other factors that counteract depolarization, an AP is generated (depolarized phase of AP not shown). Perfect homeostatic balance is achieved when EPSC peak is exactly at AP threshold (diagonal from top left to bottom right; since an AP is equally likely to occur or not occur, we have shown overlaid traces with and without AP). The illustrated EPSC and IPSC amplitudes were chosen only for convenience. **(c)** Membrane voltage in a thalamocortical neuron in cat LGN during viewing of a naturalistic movie (reprinted from ref. 26, copyright 2007, with permission from Elsevier). **(d)** Estimates of the amplitude and timing of retinogeniculate EPSC (blue), homeostatic IPSC (red) and opponent IPSC (green) that contribute to the membrane voltage in **c** during the period indicated (cyan lines). Estimates were based on experimental observations (Supplementary Tables 1 and 2)^{26,28,29,31}, but our primary purpose here is only to illustrate that homeostatic and opponent IPSC are ‘in’ and ‘out’ of phase with EPSC, respectively.

1 ms in LGN (due to a dendrodendritic synapse)³¹. Despite their opposing information content, homoeostatic and opponent IPSPG have similar amplitudes and decay times in LGN³¹.

Our present focus is homoeostatic IPSPG, which are likely to be more prevalent than opponent IPSPG since not all neurons have an ‘opponent neuron’. Through computer simulations of a simple and generic model neuron, we identified the IPSPG decay time constant (τ) and mean peak amplitude (I) that are optimal given a particular temporal pattern of EPSPG. We found that these optimal IPSPG closely match experimental data.

Results

Single-compartment model. We began with a single-compartment model having only a constant ‘leak’ conductance (G_L , reversal at -70 mV), and IPSPG that always followed EPSPG by 1.0 ms. In initial simulations, our model neuron did not have action potentials (AP), and ‘spike threshold’ was -50 mV. Although conductance amplitudes naturally vary from one synaptic event to another, our interest was the contribution of postsynaptic strength, which changes more slowly. Thus unitary mean peak amplitudes (I and E) were constant over time in each simulation. We usually refer to the ratio of amplitudes ‘ I/E ,’ where ‘ I ’ was the parameter of interest and ‘ E ’ a constant (30 nS standard).

For each EPSPG we measured ‘distance from optimality’ (Fig. 2a), which we called a ‘residual’ (Methods)²¹. For a given ensemble of EPSPG, optimal IPSPG parameters were taken to be those that minimized the mean squared residual (MSR).

Fixed intervals between pairs of EPSPG. We start with the simplistic but illustrative example of a pair of EPSPG separated by a fixed interval, with inhibition provided only by G_L . G_L corresponds to the special case of an IPSPG in which τ approaches infinity and amplitude approaches zero. Since excitation can be approximately counterbalanced by G_L alone, we need to understand why neurons have ‘fast IPSPG’.

MSR is naturally a U-shaped function of G_L , with G_L that minimizes MSR being optimal (Fig. 2b). For long intervals (no temporal summation), optimal G_L causes the peak of each EPSPG to be exactly at threshold (MSR = 0). For short intervals, temporal summation of EPSPG requires greater G_L to counter-balance excitation, but optimal G_L cannot eliminate residuals (Fig. 2a,b). The first EPSPG will be sub-threshold (too much inhibition) and the second super-threshold (too little inhibition). A dynamic inhibitory conductance that is stronger at the time of the second EPSPG could better balance excitation. Indeed, adding an IPSPG further reduced MSR (compare minima in Fig. 2b,c). For long intervals with no temporal summation, synaptic and leak conductances could fully substitute for one another, but for short intervals a single combination was optimal (Fig. 2d).

Optimal IPSPG are larger and faster at higher EPSPG frequency.

We identified optimal IPSPG parameters given inter-EPSPG intervals randomly drawn from geometric distributions (time unit of 1.0 ms) with mean rates of 1–800 Hz. With EPSPG of 30 nS, G_L of 10 nS was near optimal (based on systematically varying G_L , I , τ and frequency), and this combination defined our ‘standard model’.

Although many combinations of I/E and τ approximately balanced excitation, there was one combination that was optimal for each EPSPG frequency (Fig. 3a–d). MSR was a smooth function of τ over 1–120 ms, and optimal G_L resulted in MSR just slightly greater than τ of 120 ms (Fig. 3d). Therefore we are quite confident that we identified the one optimal τ from the infinite range of possibilities.

We illustrate two τ (2.2 and 26 ms) that were optimal at 400 and 5 Hz, respectively (with I/E optimized in all four cases) (Fig. 4). Relative to optimal and slow τ at 5 Hz, excessively fast decay resulted in sub-threshold EPSPGs that tended to be smaller (since I/E was too high), and super-threshold EPSPGs that tended to be larger (since faster IPSPG decay resulted in slower EPSPG decay and thus greater temporal summation). At 400 Hz, τ that

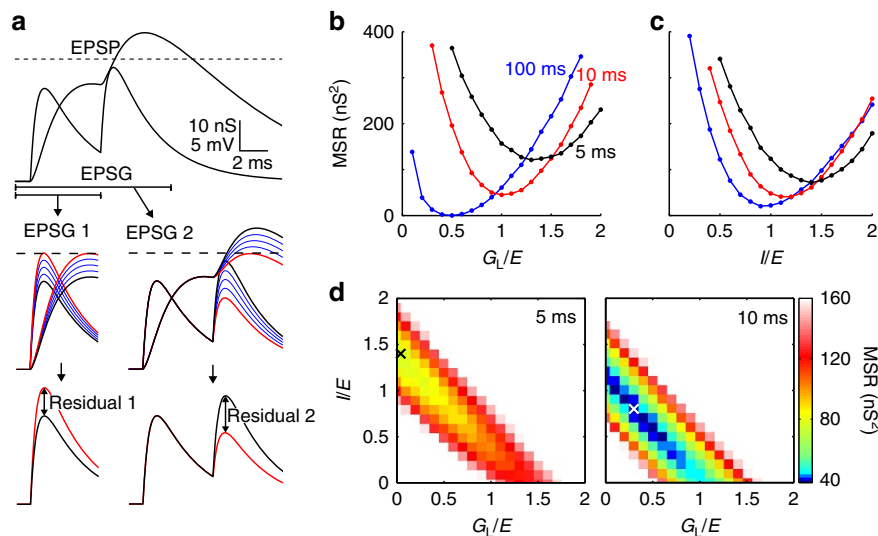


Figure 2 | Optimal inhibition in relation to EPSPG interval. (a) Method of measuring ‘residuals’. Top, two EPSPG and the resulting EPSP. Dashed line indicates -50 mV, the ‘spike threshold’ in these simulations without AP. Middle, ‘test EPSPG’ (blue) were injected at the time of ‘real EPSPG’ (black) to find the ‘threshold EPSPG’ (red) that caused an EPSP with its peak to be nearest to threshold (in other words, EPSPG amplitude was varied, but this ‘test variation’ was only to find spike threshold, and had no influence on ‘real’ voltage at the time of subsequent EPSPG). Bottom, the residual was the difference in peak amplitudes between threshold and real EPSPG. The residual depended on current and past but not future synaptic events; thus residual 1 in this example (left) was found in simulations in which EPSPG 2 did not occur. (b) MSR as a function of the ratio of G_L to E (30 nS) for two EPSPG separated by 5 (black), 10 (red) and 100 ms (blue) in the absence of synaptic inhibition ($I/E = 0$). (c) As in b, but showing MSR as a function of I/E ($\tau = 10$ ms, $G_L = 0.1$ nS). (d) Heat plots of MSR as a function of both G_L/E and I/E for inter-EPSPG intervals of 5 (left) and 10 ms (right). ‘X’ indicates minimum MSR.

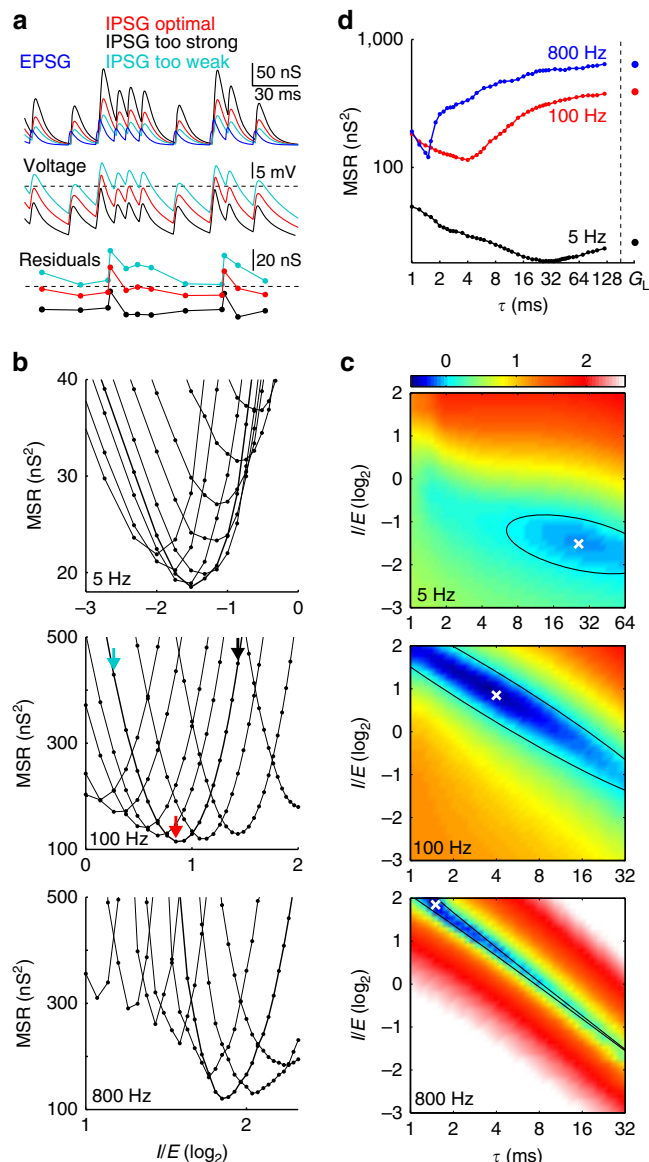


Figure 3 | Finding optimal IPSG with random EPSP intervals.

(a) Conductances (top), voltages (middle) and residuals (bottom) for the case that I/E was too strong (black), too weak (cyan) and near optimal (red) for EPSP (blue) at 100 Hz. Dashed lines indicate -50 mV (spike threshold) and residual of zero. The sign of residuals was chosen so that positive residuals corresponded to EPSP peaks more positive than -50 mV. (b) For each value of τ , MSR as a function of I/E for EPSP at 5, 100 and 800 Hz (top to bottom). Thicker lines indicate τ that minimized MSR. Arrows indicate values of I/E shown in a. (c) Heat plots of MSR (same data as b). For each EPSP frequency, MSR was divisively normalized by the MSR obtained with no IPSG and only optimal G_L (see below). Black ellipses indicate IPSG parameter values that resulted in MSR equivalent to optimal G_L in the absence of IPSG. 'X' indicates minimal MSR. (d) MSR as a function of τ for EPSP at 5 (black), 100 (red) and 800 Hz (blue). I/E was optimized for each τ , and thus each data point corresponds to the minimum of one function in b. At far right is MSR with no IPSG and only optimal G_L (25.6, 389.4 and 638.0 nS at 5, 100 and 800 Hz, respectively), which corresponds to an IPSG with infinitely slow τ .

was too slow resulted in IPSG that were substantially out of phase with EPSP, resulting in periods of excessive depolarization and hyperpolarization (Fig. 4a, right). Interestingly, EPSP had earlier peak latencies and faster decay with optimal versus suboptimal τ

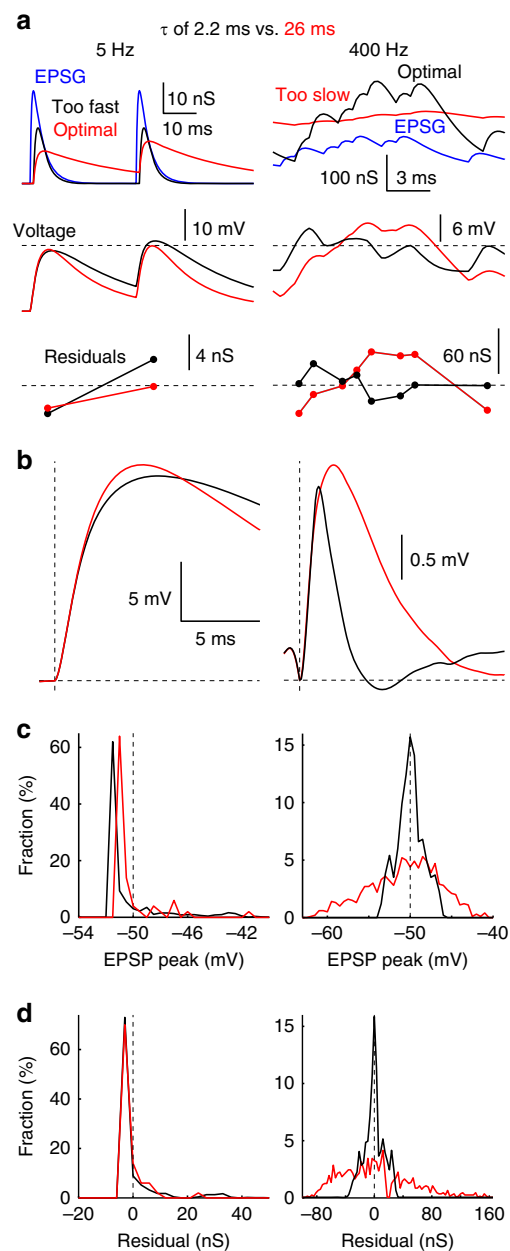


Figure 4 | Comparison of optimal and suboptimal IPSG decay times.

(a-d) τ of 2.2 (black) and 26 ms (red) at EPSP frequencies of 5 (left) and 400 Hz (right). I/E was optimized in all four cases, whereas τ of 26 and 2.2 ms were optimal at 5 and 400 Hz, respectively. (a) Examples of EPSP and IPSG (top), voltage (middle), and residuals (bottom). (b) EPSP-triggered average EPSPs. (c) Histograms of EPSP peaks. Dashed lines indicate 'spike threshold' of -50 mV; EPSP peaks positive of -50 mV were designated as positive residuals. (d) Histograms of residuals.

at both 5 and 400 Hz, demonstrating that faster voltage dynamics are favoured by either fast or slow IPSG depending on EPSP frequency (Fig. 4b). This helps to explain how optimal τ was near optimal in minimizing spike latency and variability (see below).

As EPSP rate increased from 1 to 800 Hz, optimal I/E increased and τ decreased (Fig. 5a,b). Even with optimal IPSG parameters, homeostasis was not as well maintained at high frequencies (MSR was greater), although it was maintained better with optimal IPSG than with only optimal leak conductance (Fig. 5c).

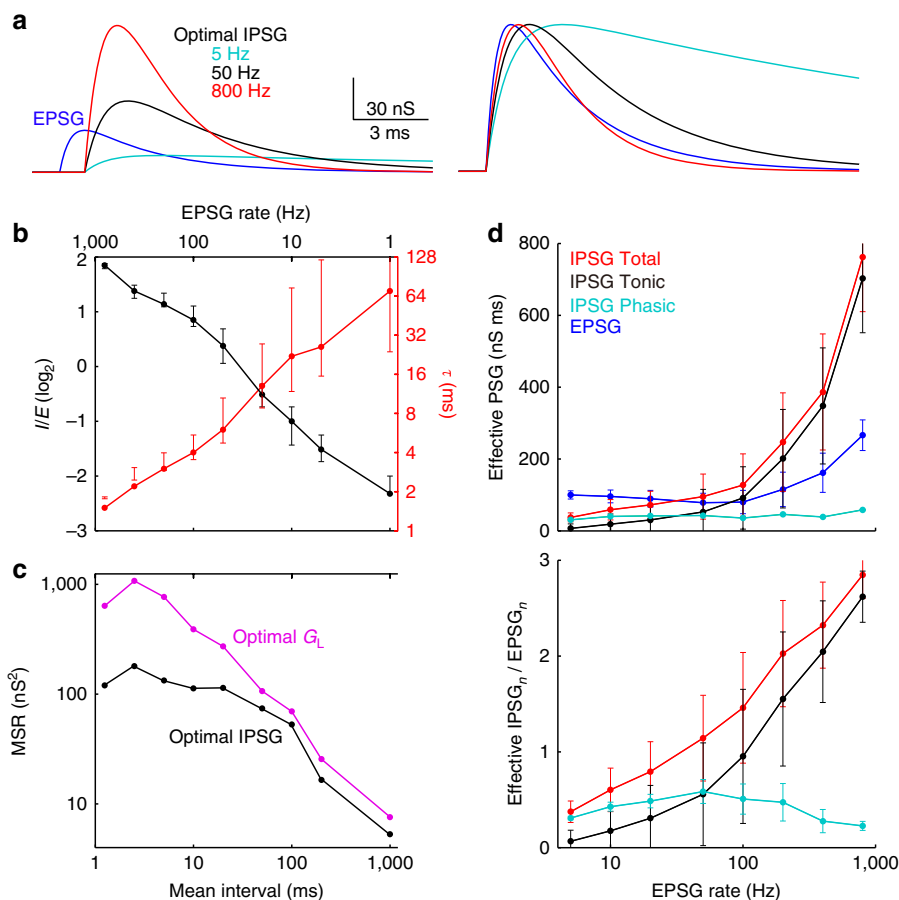


Figure 5 | Optimal IPSG parameters depend on EPSP frequency. (a) Optimal IPSG for EPSP at 5 (black), 50 (green) and 800 Hz (red). Right, same as left but with EPSP (blue) and IPSP onsets aligned and peaks normalized. (b) Optimal I/E (black) and τ (red) as a function of mean EPSP interval (bottom axis) and frequency (top axis), with log-log coordinates. Bars indicate the parameters necessary to increase MSR by 10% above the minimum achieved by optimal parameters. (c) MSR as a function of frequency with optimal IPSP (black) and G_L (magenta). (d) Tonic and phasic postsynaptic conductances (PSG). To estimate the ‘effective PSG’ that influenced the causal link between EPSP and spike generation, we found the mean spike latency at each frequency (5.0–1.7 ms at 5–800 Hz) and we integrated each PSG from EPSP onset to mean latency. The effective PSG was averaged (mean \pm s.d.) across all synaptic events (top), or the ratio of effective IPSP to EPSP at the time of each event was averaged across all synaptic events (bottom). The ‘total IPSP’, but not EPSP, was split into tonic and phasic components.

Tonic and phasic components of IPSP. Whether $EPSP_n$ causes a spike will depend on both the ‘phasic’ $IPSP_n$, as well as the ‘tonic’ component contributed by summation of $IPSP_{n-1}$, $IPSP_{n-2}$ and so on. We estimated these components by integrating conductances from EPSP onset to mean spike time (5.0–1.7 ms at 5–800 Hz). The tonic IPSP increased with frequency and was larger than the phasic IPSP at 100 Hz and above (Fig. 5d), despite optimal IPSP being larger and decaying faster at higher frequencies. Thus one effect of optimization is to counteract the natural tendency of the tonic component to overwhelm the phasic component as frequency increases.

In our standard model (above), both tonic and phasic components made significant contributions to suppressing spikes, and thus optimization of IPSP depended on both components. However, phasic inhibition was reduced in a model with much greater membrane conductance, especially at high frequencies (due to decreased spike latency). This flattened the relations of optimal I/E and τ to frequency (see below). The relations became flatter still when we eliminated all phasic inhibition in this high-conductance model by increasing the delay from EPSP to IPSP onset ($E-I$ delay) from 1.0 to 2.0 ms (optimal τ was 7.0, 3.0 and 6.0 ms at 5, 100 and 800 Hz; optimal I/E was 0.9 at 800 Hz, less than any other frequency).

Influence of additional parameters. We modified our standard model to examine a variety of additional factors (Figs 5–7; Supplementary Figs 1–2). Although each was influential, none fundamentally altered the dependence of optimal I/E and τ on EPSP frequency that was observed with our standard model (Fig. 5b,c; Supplementary Results).

Our standard model was simplified in using unitary EPSP and IPSP that were of constant amplitude over time. However, variability *in vivo* is much less than one would expect given typical conditions in brain slices³⁵. Under naturalistic conditions at the calyx of Held, EPSC at 40 Hz had a coefficient of variation (CV) of 8% (ref. 36). We performed additional simulations with unitary synaptic conductance amplitudes having the same mean (30 nS) but CVs of 15 and 79%, with normal and log-normal distributions, respectively (Fig. 6a,b) (in the latter case, the standard deviation corresponded to 15–60 nS, a factor of 2 from the mean). EPSP and IPSP varied independently (although we would expect moderate covariance under natural conditions). Relative to our standard model, the lesser variance had virtually no effect on optimal IPSP parameters, whereas larger variance with a skewed distribution decreased the amplitude and more than doubled the decay time at all but the highest frequencies (Fig. 6c). MSR increased with variance, as expected (Fig. 6d).

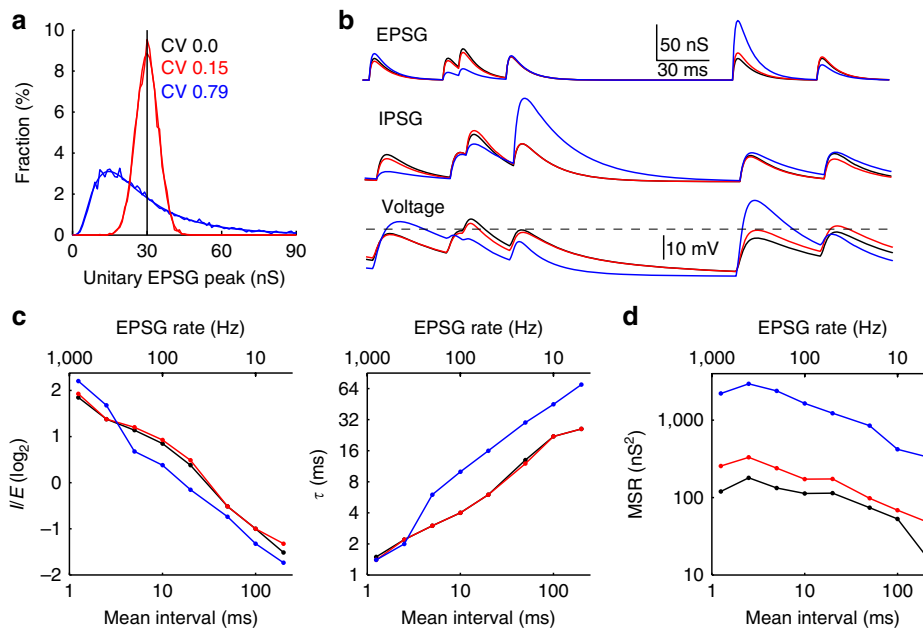


Figure 6 | Effect of independent variance in unitary EPSP and IPSP amplitudes. (a) Unitary EPSP had no variance (black, standard condition), or were randomly sampled from a normal distribution with CV of 0.15 (red, $\sigma = 4.5$ nS) or from a log-normal distribution with CV of 0.79 (blue, $\sigma = 23.6$ nS, corresponding to a factor of 2 from the mean). Smooth functions are probability distributions and jagged functions are frequency histograms of 1,000 and 10,000 PSG for normal and log-normal distributions, respectively. The mean EPSP was 30 nS for each distribution, whereas the mean IPSP was determined by the parameter I/E . (b) Examples of EPSP, IPSP and voltage (top to bottom) for the three distributions (all simulations utilized the same random sample of PSG intervals). (c) Optimal I/E (left) and τ (right) as a function of EPSP frequency for each amplitude distribution. (d) MSR increased with variance.

It is interesting to note that log-normal or similarly skewed distributions of biophysical properties are common³⁷, and our log-normal condition may be relevant to cortical neurons and others in which synchronous activation of smaller numbers of synapses is presumably more common than larger numbers, resulting in a skewed distribution of EPSP and EPSP amplitudes^{38,39}.

As another step towards more realistic and complex patterns of EPSP, we considered alternating periods of EPSP at 10 and 100 Hz (Supplementary Fig. 2 and Supplementary Results). Even when 100 Hz occurred only 9% of the time (0.1 s of each 1.1 s period; 18 Hz average, with equal average numbers of EPSP at each frequency), optimal parameters were still more similar to those optimal for 100 than 10 Hz. Thus, brief periods of high frequency have a disproportionately large influence with respect to optimal IPSP, suggesting that our randomized rates may be most comparable to rates achieved in real neurons during periods of mild or moderate stimulus-evoked excitation rather than long-term average excitation (Supplementary Results).

We optimized I/E and τ with alternative parameters for membrane conductance, $E-I$ delay, and chloride equilibrium potential (E_{Cl^-}), both with (Fig. 7) and without AP (Supplementary Fig. 1). Although each of these factors had a significant influence, their effects were generally small relative to the effect of EPSP frequency, which still favoured larger and faster IPSP at higher frequencies. Homeostasis was promoted (MSR was minimized) by addition of AP, low conductance and a brief $E-I$ delay, although these factors mattered less at low EPSP frequencies (Fig. 7, bottom). E_{Cl^-} had a smaller influence on MSR, but -70 mV was near optimal (Fig. 7, bottom). The influence of each factor is described in detail in Supplementary Results.

Learning optimal IPSP amplitude and decay time. From theory one can logically derive anti-Hebbian rules through which a neuron could learn which inhibitory inputs best maintain

homeostasis given a particular pattern of EPSP^{21,40}. Here we show that optimal IPSP can be learned through anti-Hebbian rules (Fig. 8a).

Learning was based only on the local IPSP and the presence or absence of a spike. A spike following IPSP onset was evidence that the inhibitory synapse was too weak, and therefore it was strengthened, whereas absence of a spike had the opposite effect. We tested three learning rules (Methods). Rule 1 was simple and was applied to a neuron with a single inhibitory synapse with τ pre-specified to be optimal. Rules 2 and 3 were implemented in a neuron with nine inhibitory synapses, each with a distinct decay time (1.5–50 ms) (Fig. 8b). These rules associated spikes with local synaptic ‘eligibility’, which depended on ‘activity’ that varied from one synapse to another due to the influence of local τ on temporal summation (Fig. 8c).

Total inhibition was initially too weak, and all weights increased until approximate $E-I$ balance was attained and nearly half of EPSP caused AP (Fig. 8d). Thereafter, some synapses weakened and others strengthened until IPSP parameters were nearly the same as those that were optimal in minimizing MSR (Fig. 8a). Interestingly, rules 2 and 3 performed better than the simpler rule 1 in minimizing MSR, despite the fact that optimal τ was assigned with rule 1. When EPSP rate switched from 800 to 5 and back to 800 Hz, near optimal parameters were learned in each case, demonstrating that learning of optimal parameters did not depend on the choice of initial weights (Fig. 8e).

Spike probability and timing. As expected, both spikes and spike failures were common with optimal IPSP. With our simple learning rule 1, spike probability (ratio of spikes to EPSP) was almost exactly 1/2 for all EPSP frequencies, whereas for learning rule 2 and minimization of MSR it was less, especially at low frequencies (Fig. 9a). This is explained by asymmetries that are more pronounced at low EPSP frequencies (Fig. 4c,d; Supplementary Fig. 3 and Supplementary Results).

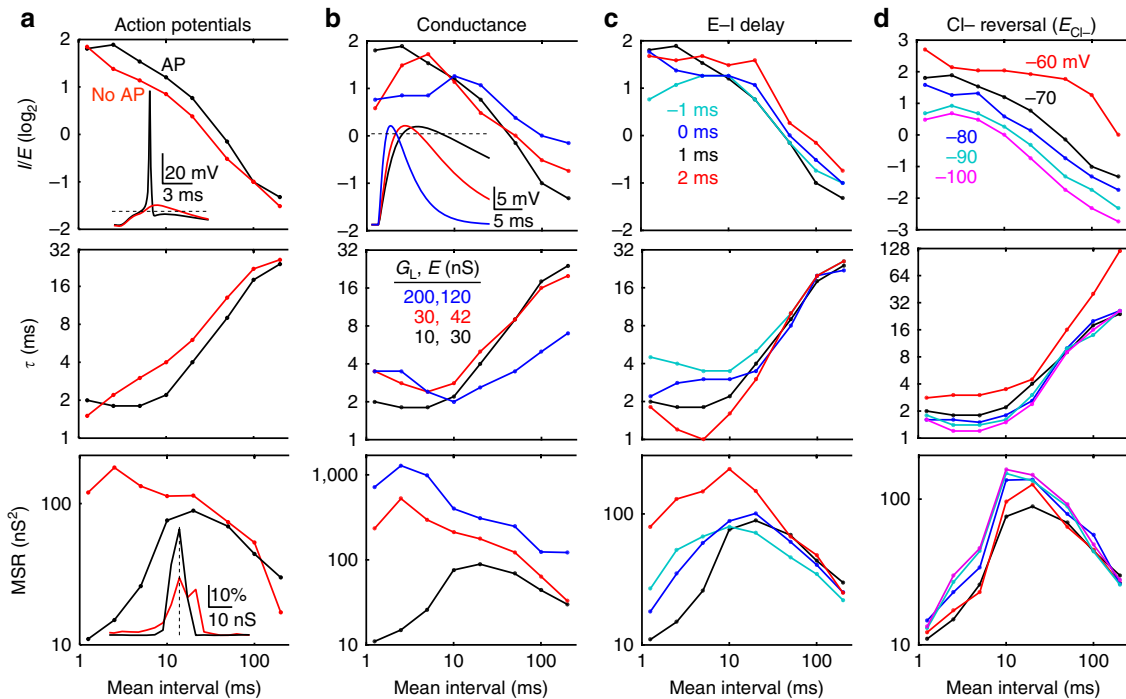


Figure 7 | Influence of additional factors. Optimal I/E (top), τ (middle), and MSR (bottom) as a function of mean EPSP interval. **(a)** Our standard model with (black) and without (red) AP. Data without AP is the same as Fig. 5b,c; data with AP is repeated in **b-d** for comparison. Top inset, sample voltage responses to EPSP at 50 Hz with optimal IPSPG. Bottom inset, distribution of residuals at 800 Hz. Dashed lines in insets correspond to -50 mV (top) and zero residual (bottom). **(b)** Membrane conductance was low (black; $E = 30$ nS, $G_L = 10$ nS), medium (red; $E = 42$ nS, $G_L = 30$ nS) and high (blue; $E = 120$ nS, $G_L = 200$ nS). The three combinations of E and G_L were chosen so that from resting membrane potential of -70 mV, an EPSP would cause an EPSP with peak near -48 mV in the absence of IPSPG and AP (inset at top). **(c)** $E-I$ delays of -1 (cyan), 0 (blue), 1 (black) and 2 ms (red). **(d)** IPSP reversal potentials (E_{Cl-}) of -60 (red), -70 (black), -80 (blue), -90 (cyan) and -100 mV (magenta).

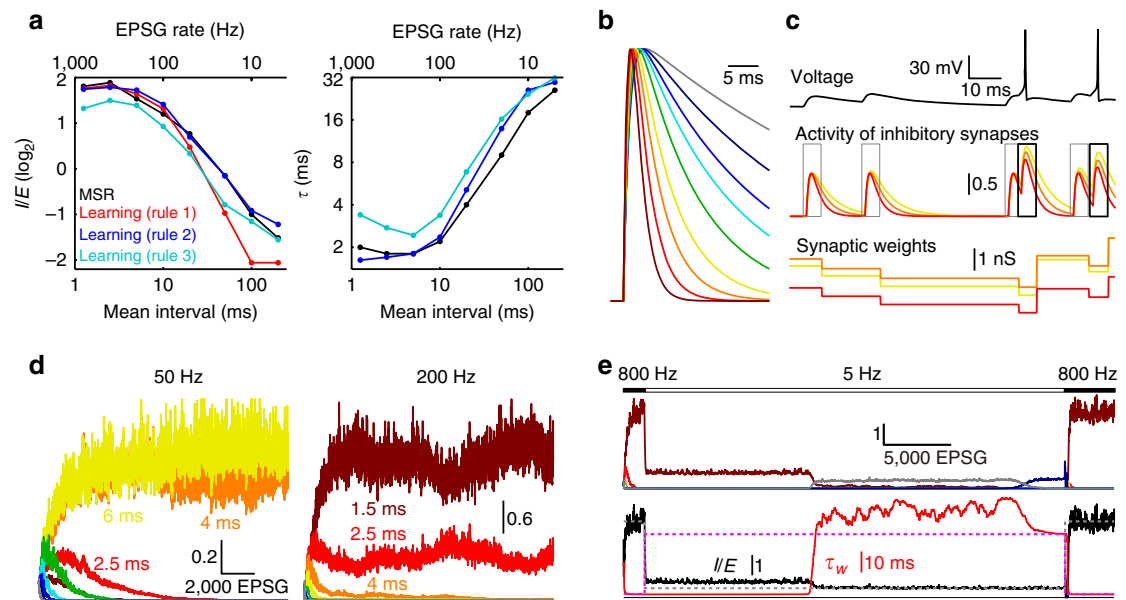


Figure 8 | Learning optimal IPSP parameters. **(a)** I/E (left) and τ (right) as a function of mean EPSP interval for learning rules 1 (red), 2 (blue), 3 (cyan) and for minimization of MSR (black; same as Fig. 5b). With learning, ' τ ' is a weighted average across the nine synapses (except rule 1). All simulations were performed with AP. **(b)** Normalized IPSPG for each of the nine synapses (τ of 1.5–50 ms). Colour code is maintained in **b-e**. **(c)** Illustration of learning rule 2. From top to bottom, voltage, activity and synaptic weights (τ of 2.5, 4.0 and 6.0 ms) with EPSPG at 50 Hz, selected from a time early in learning, after approximate $E-I$ balance had been attained but before weights were substantially differentiated. Rectangles indicate periods in which activity was averaged to find eligibility; thick black indicates spike occurrence. **(d)** Weight of each synapse (w_i/E) as a function of EPSP number at 50 and 200 Hz for rule 2. All weights were initially equal. **(e)** In a separate simulation with rule 2, EPSPG frequency was switched from 800 to 5 and then back to 800 Hz. Top, analogous to **d**, except that the learning rate was 2.5 times greater and weights are shown as a moving average with bin size of 50. Bottom, I/E and weighted τ . Dashed horizontal lines indicate I/E (grey) and τ (magenta) that were learned by rule 2 in **a**.

Although IPSPs preserve spike timing^{2,41}, our criteria for optimality is based only on ‘if’ and not ‘when’ a spike occurs. ‘If’ is more important here, given that our theory and model insures that a spike can only occur within a few milliseconds after onset of an EPSP. Nonetheless, even within this brief window, it is desirable for spike latencies to be short and precise. For τ of 1–32 ms, all with optimal I/E , each EPSP was always followed by

0 or 1 AP (prior to onset of the next EPSP), and τ that was optimal in minimizing MSR was nearly optimal in minimizing both the mean and standard deviation of AP latency (Fig. 9b,c). Thus optimization of IPSPG with respect to spike occurrence may also optimize spike timing.

Comparison of theory to experiment. Figure 10a compares predictions of optimal IPSPG from theory with experimental data. Each of the 21 red circles represents the published average τ from a single type of neuron (Supplementary Table 1), and our estimate of the typical EPSP input rate of that type of neuron under conditions of mild activation (Supplementary Methods). If theory explained all variability in τ , all experimental data would lie on the identity line (Fig. 10b), and the root mean squared error (r.m.s.e.) would correspond to a factor of 1. The actual data deviated from the predictions of theory by a factor of 1.9 for simulations with AP in our standard model (with learning rule 2 or minimization of MSR) (Fig. 8a). Across 20 model neurons (Fig. 7, Supplementary Fig. 1), r.m.s.e. ranged from a factor of 1.8, in the standard model without AP, to 3.1 for the model with the highest conductance and AP.

How accurate is a factor of 2 or 3? A prediction based on the mean of the 21 experimental τ (9.4 ms) was off by a factor of 3.2, and linear regression by a factor of 1.7. Compared to these, the evidence favoured our model by factors of 10^4 and 10^{-2} , respectively (Methods). However, although predictions based on statistics provide a familiar and useful reference, they are not appropriate comparisons. Beyond the fact that statistics do not explain data, our theory and model did not use any knowledge of τ in deriving predictions (except in the case of learning, where τ was specified to be between 1 and 50 ms). Since we are unaware of any alternative theory that predicts τ , we compare our results to the ‘null hypothesis’. What is the chance that our predictions would be within a factor of 2 given no knowledge of τ ? Any τ is possible, with a leak conductance being the limiting case of ‘infinite τ ’. As an approximation, we can assume bounds of 1 ms and 1 year, and precision of 1 ms. With no additional knowledge, logic requires that all possible τ are equally probable. The probability of ‘randomly drawing’ τ between 5 and 20 ms (within a factor of 2 from the mean of 10 ms) is 4.8×10^{-10} . This number is rather arbitrary, but its derivation shows that the match of theory and data is not a coincidence.

Estimation of natural EPSP rates is difficult for a variety of reasons. Although we provide detailed justification for our estimate in each of the 21 types of neuron (Supplementary Methods), uncertainty in these estimates limits confidence in the conclusions drawn from Fig. 10a,b. However, we would expect that the error in our estimates is approximately a factor of 2 (for example, if we estimate 20 Hz, the true rate is probably between 10 and 40 Hz), much less than the factor of 100 that distinguishes neurons with the fastest and slowest EPSP and spike rates (average EPSP rates were 3.7 Hz in locus coeruleus⁴², and > 500 Hz in medial superior olive in the absence of acoustic stimulation⁴³). Therefore uncertainty in our estimates of EPSP rates does not substantially detract from our conclusion that theory can explain variability in IPSPG decay times across neurons.

However, we can entirely avoid the difficulty of estimating natural EPSP rates if we instead focus on the important but lesser challenge of explaining only the typical or average IPSPG decay time. In other words, why are IPSPG decay times on the order of 10 ms across many types of neurons? If we assume that 50 Hz is the median EPSP rate across real neurons, theory predicts optimal τ to have a median value of 5.1 ms (rule 2 in Fig. 8a), whereas the median across the 21 neurons was 7.0 ms. With this prediction of 5.1 ms, the error (r.m.s.e.) is a factor of 2.8, approximately twice that observed using EPSP rates as an

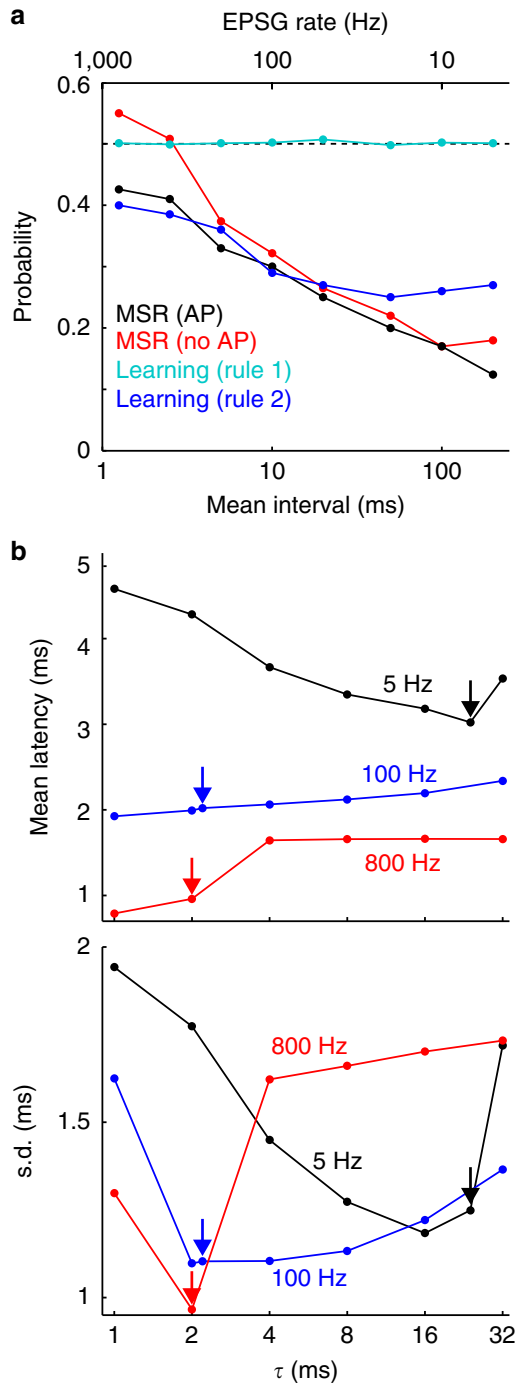


Figure 9 | Spike probability and timing. (a) Ratio of total spikes to EPSP as a function of mean EPSP interval, with IPSPG that minimized MSR in the absence (red) or presence (black) of AP, and after learning according to rule 1 (cyan) and 2 (blue). (b) Mean AP latency (top) and s.d. (bottom) from EPSP onset as a function of τ (with optimal I/E) for EPSP rates of 5 (black), 100 (blue) and 800 Hz (red). Arrows indicate τ that minimized MSR.

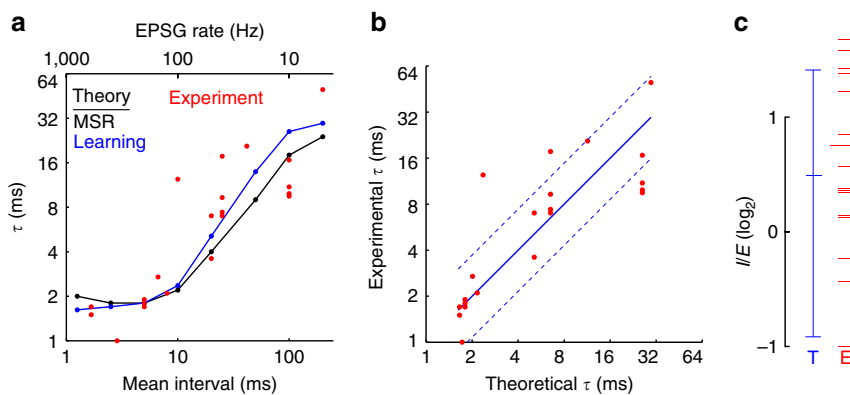


Figure 10 | Comparison of theoretical optima with experimental data. (a) Experimentally measured average τ and estimate of typical EPSP rate for 21 types of neurons (red) (Supplementary Table 1 and Supplementary Methods) compared to predictions based on theory (black and blue, same as Fig. 8a). (b) Experimental data (circles) and theoretically optimal τ (identity line). Prediction of theory was based on linear interpolation between data points in a. Dashed lines indicate r.m.s.e., which corresponds to a factor of 1.9. (c) I/E predicted to be optimal by theory (left; at 10, 40 and 100 Hz, from bottom to top, based on rule 2 in Fig. 8a) and observed experimentally (right; longer line is the mean). Experimental data ($n=15$) were mostly from cortical pyramidal neurons ($n=12$), especially primary auditory cortex ($n=8$), but was distinct with respect to neuronal type, cortical layer, species or laboratory (Supplementary Table 2 and Supplementary Methods).

explanatory factor across neurons (1.9; see above). Therefore the probability of observing this match between theory and experiment doubles, but is only 10^{-9} . Theory provides a remarkably accurate prediction of typical IPSP decay times, even if we disregard estimates of EPSP rates.

Theory also correctly predicted the mean and range of I/E observed in adult animals *in vivo* (Fig. 10c, Supplementary Table 2). Whereas cortical pyramidal neurons were excluded from measures of τ , they constituted 12 of 15 measures of I/E (Supplementary Tables 1 and 2, Supplementary Methods). We did not attempt to estimate EPSP rates for each of these types of neurons, but we would expect them to be 10–100 Hz, with 40 Hz being our single best guess. For 40 Hz, theory (rule 2; Fig. 8a) predicts optimal I/E to be 1.4, with a range from 10 to 100 Hz of 0.53–2.66 (Fig. 10c, left). The experimental mean was 1.7 with range of 0.5–3.2 (Fig. 10c, right). The 15 measures of I/E deviated from the estimate of 1.4 with a r.m.s.e. corresponding to a factor of 1.7.

Ideally we would like to have estimates of EPSP rates, τ , and I/E in a single type of neuron. We were only able to get such estimates in thalamocortical neurons of LGN and cerebellar granule cells (40 and 50 Hz, 7.0 and 7.4 ms, 1.1 and 1.1, respectively)^{31,44,45} (Supplementary Tables and Supplementary Methods). Measurements in both cell types agree with our estimate of optimality (at 50 Hz, 5.1 ms and 1.5).

Explaining slow IPSP decay in cochlear bushy cells. In bushy cells of the ventral cochlear nucleus (VCN), τ is substantially slower than predicted by our standard model (12.4 versus 2.2 ms) (Fig. 10a, Supplementary Table 1). Unlike our standard model, there is little or no phasic IPSP in bushy cells (spike latency is prior to onset of IPSP, 1–2 ms after EPSP onset) as a result of large and fast EPSP and high membrane conductance^{41,46–48}. In contrast, phasic IPSP may be present in neighbouring T-stellate cells of VCN, since they have slower EPSP and lower conductance⁴⁹. Likewise they have much faster IPSP decay (1.0 ms) that is close to that predicted by our standard model (Fig. 10a, Supplementary Table 1)⁴¹.

We further examined the same high-conductance model as above ($E=120$ nS, $G_L=200$ nS; Fig. 7b) at 100 Hz but with AP. Optimal τ remained fast (1.8 ms, $I/E=2.2$), but phasic inhibition remained despite the high conductance (35% of AP occurred after IPSP onset at 1.0 ms). Increasing $E-I$ delay to 2.0 ms eliminated all phasic inhibition and resulted in optimal IPSP that were

slower ($\tau=9$ ms, $I/E=1.1$). Next, we made EPSP kinetics ~ 10 -fold faster to match those in bushy cells (which required increasing E to 270 nS to maintain EPSP peak; see Fig. 7b inset), while keeping our standard $E-I$ delay of 1.0 ms. Phasic inhibition was absent and optimal τ was 34 ms ($I/E=0.1$). Thus refining our model to better mimic bushy cells resulted in a more accurate prediction of their slow IPSP decay.

Discussion

Although the field of neurobiology has measured many biophysical properties, it generally lacks an explanation of why those properties are what they are. Why should the IPSP decay time constant be 1.0 ms in T-stellate cells of VCN⁴¹? Why is it at least eight fold slower in neighbouring bushy cells^{41,48}? Although advantages have been found for one set of IPSP parameters over another^{19,20,41}, we are not aware of any previous predictions of exact optimal values. We used theory and computer simulations to find the IPSP amplitude and decay time that provides the optimal homeostatic counterbalance to excitation. We further demonstrated that optimal IPSP parameters could be learned through anti-Hebbian rules. Most remarkably, our predictions closely match experimental observations of decay times across 21 types of neuron.

Together with recent experiments^{50,51}, we have tested a theory of the information contributed to membrane voltage by synapses and ion channels^{21,40,52,53}. The theory extends a long line of research relating neuronal function to quantitative principles of information^{23,24}. The central idea is illustrated by a balance scale, in which the challenge of measurement is to accurately predict and counterbalance the unknown weight of interest. It was proposed long ago that synaptic inhibition provides the appropriate counterbalance to excitation²³, and there is strong supporting evidence²⁵. However, it has not been known exactly what constitutes optimal balance (or ‘gain control’). To find this requires a theory that specifies the ideal homeostatic balance, including the period of time over which that balance should be achieved. Since most theories focus on firing rates or spike patterns (rather than single spikes), optimal $E-I$ balance has usually been defined over periods that are long compared to IPSP decay times^{16,17,19,20}. Any particular level of balance over a long time period (for example, a target firing rate over 20 ms) can be achieved with multiple combinations of IPSP decay time and peak amplitude. Thus theories focused on longer time periods are poorly suited for distinguishing IPSP amplitude from decay time,

and we are not aware of any studies of $E-I$ balance that have systematically varied them. In contrast, our theory specifies the optimal $E-I$ balance at the time of a single EPSP and the spike it may cause. Because of this fine timescale, the exact IPSP time course matters, and we can identify a single combination of amplitude and decay time that is optimal (Fig. 3).

The predictions of theory closely matched experimental measures of IPSP amplitude and decay time. One's attention is naturally drawn to the fact that theory correctly predicted the slope of τ in Fig. 10a, but much more remarkable is that it predicted the actual value of τ (y offset) within a factor of 2. Indeed, one might mistakenly guess that we 'fit the data' in some way. It is easy to accurately predict data given statistics from the same data, and neuroscientists have had knowledge of IPSP decay times for many years. However, theory should explain and predict data based on principles that are independent of the data. The accuracy of our predictions is remarkable because we did not use any knowledge of τ in predicting τ . Without knowledge of τ , and in the absence of any formal theory, or intuition, there is no reason to believe that fast decay should be better than slow decay (the extreme limit of slow IPSP decay corresponds to a constant 'leak' conductance). Our prediction was within a factor of 2 despite an infinite range of possible decay times. Although one could question our estimates of natural EPSP rates in the 21 neurons, the error in prediction increased only to a factor of 2.8 when we did not utilize these estimates as a predictive factor, which is still slightly more accurate than the factor of 3.2 for a prediction based on the mean decay time across the 21 neurons. Thus, if we disregard our estimates of natural EPSP rates (Fig. 10a,b), then we cannot claim to have explained variability in IPSP decay across neurons, but we can still claim to have explained the typical or average IPSP decay time.

Theory was also able to predict the mean and range of experimentally measured ratios of peak synaptic inhibition to excitation (Fig. 10c). We had data on both I/E and τ for only 2 of the 21 neurons (cerebellar granule cells and thalamocortical neurons), and theory accurately predicted the combination of parameter values in those neurons (see Results).

As a test of theory, the present results apply more to neurons that receive few rather than many strong excitatory synapses. For a variety of reasons we did not include cortical pyramidal neurons among the 21 types of neurons from which we obtained IPSP decay times (Supplementary Methods). The greatest difficulty is that the presence of a large number of excitatory synapses make it possible to generate many patterns of synaptic excitation, and yet we have little knowledge of the actual patterns. The knowledge we do have indicates that synchronous but temporally sparse excitation causes large and discrete EPSPs, at least in some cortical pyramidal neurons^{38,39}. Although our standard model had large and discrete EPSPs, it lacked the variability that would be expected in a neuron with many excitatory synapses. However, limited results from an alternative model, having the high variance and skewed distribution of EPSP amplitudes that might be expected in a cortical pyramidal neuron, led to qualitatively similar conclusions (Fig. 6).

Despite our confidence in the theory, we were surprised by how well it predicted the experimental data given our neuronal model. The theory specifies that optimality should depend on numerous factors that contribute to membrane excitability, yet our model neuron was simple and generic, with a single electrical compartment and no active intrinsic properties (or only AP). Our intention was to mimic a typical neuron, and in principle such a generic 'average model' may be the best single model for explaining variance in IPSP across diverse neurons. However, a more detailed model should produce a more accurate prediction with respect to a particular neuron. The largest error of our

standard model occurred with bushy cells of VCN, in which τ is more than five fold slower than predicted (Fig. 10a,b)^{41,48}. When we eliminated phasic inhibition to better mimic bushy cells, optimal τ was slower and more similar to that found in bushy cells. Thus the relatively small errors in prediction based on our simple model may be reduced further through detailed models of specific types of neuron.

Evidence for the theory would be further strengthened if it can correctly predict additional parameters of inhibition, and especially combinations of multiple parameters. For example, multiple specializations speed conduction through inhibitory pathways so that $E-I$ delay is brief or even negative^{3,11,14,31,49,54}, consistent with our results (Fig. 7c, bottom). In layer 6 of auditory cortex, one neuronal population has negative $E-I$ delay and large I/E (-1.6 ms and 3.0), whereas another population has the opposite combination ($+1.6$ ms and 0.6)¹¹. Neurons in the medial superior olive are of particular interest because they are exceptionally fast. They receive EPSP at over 500 Hz (ref. 43), have fast IPSP decay (1.7 ms), negative $E-I$ delay (-0.4 ms), and unusually negative E_{Cl-} (-90 mV)^{14,55-57}. At the opposite end of the spectrum are neurons of the inferior olive, which fire at about 2 Hz (ref. 58) and have exceptionally slow IPSP decay⁵⁹.

A combination of physiology and simulations could be used to test the theory's ability to predict multiple IPSP parameters over the course of development, or in response to direct manipulation of EPSP patterns (for example, at the retinotectal synapse¹³). Membrane properties become faster over development, including the rate of IPSP decay⁵⁶. The present results suggest that faster IPSP decay could result from anti-Hebbian learning in response to an increasing prevalence of brief EPSP intervals over the course of development (whether or not average rates increase).

Real neurons have numerous conductances that were lacking in our models, and we have proposed that many of these work to maintain homeostatic balance as described here for IPSP^{21,40}. Like phasic IPSP, some low-threshold K^+ channels activate during the rising phase of EPSP (for example, $Kv1$) and complement IPSP in keeping EPSP peak close to spike threshold¹⁴. The theory should predict the properties of voltage-gated ion channels as it did IPSP. For example, the theory correctly predicted the experimental observation that T-type calcium channels are homeostatic in counterbalancing opponent IPSP in thalamocortical neurons of LGN⁵⁰. The more general theory proposes differences between sensory and motor neurons, and it correctly predicted evidence that T-type calcium channels are not homeostatic but cause bursts of spikes in motor thalamus⁵¹. In addition to predicting the properties of a type of neuron, theory may also be useful in explaining variability in ion channel parameters across neurons of the same type, particularly by indicating which combinations of ion channel parameters work in a concerted manner to maintain near optimal homeostatic excitability^{60,61}.

Anti-Hebbian rules have previously been shown to optimize the amplitude of synaptic inhibition to maintain sensitivity of spikes to synaptic excitation and sensory stimuli^{25,62,63}. Here we have shown for the first time that anti-Hebbian rules could enable simultaneous learning of optimal IPSP decay times as well as amplitudes, as predicted by theory^{21,40} (Fig. 8). Thus adjustment of IPSP parameters could restore homeostatic excitability within minutes following a change in the temporal pattern of EPSP²⁵. By providing a plausible mechanism for dynamic optimization, our results with learning strengthen our conclusion that IPSP are optimized for homeostatic balance in accord with theory.

Methods

Model neuron. We simulated a single-compartment neuron using NEURON software (version 7.3)⁶⁴. The model neuron had a membrane of $24,058 \mu\text{m}^2$ and

capacitance (C_m) of 0.24 nF ($1 \mu\text{F cm}^{-2}$), as previously described⁶⁵. It included a leak conductance (G_L), EPSP (g_{Exc}) and IPSP (g_{Inh}). Simulations with AP also included a Hodgkin–Huxley-type, voltage-dependent sodium conductance (g_{Na}) and potassium conductance (g_K). In simulations with AP, the dynamics of the membrane potential (V) were governed by equation (1).

$$C_m \frac{dV}{dt} = g_{\text{Na}} m^3 h (E_{\text{Na}} - V) + g_K n^4 (E_K - V) + g_{\text{Leak}} (E_{\text{Leak}} - V) + g_{\text{Exc}}(t)(E_{\text{Exc}} - V) + g_{\text{Inh}}(t)(E_{\text{Inh}} - V) \quad (1)$$

Reversal potentials (E) for each conductance were 50, -90 , -70 , 0 and -70 mV, respectively. In some simulations, the IPSP reversal potential (E_{Inh}) had other values (Fig. 7d). The time unit for simulations was 0.1 ms in simulations with AP, and 0.25 ms without AP.

Synaptic conductances. Post-synaptic conductances (PSG) were intended to mimic those mediated by AMPA-type glutamate receptors and GABA_A/glycine receptors. They followed the form of equation (2).

$$\text{PSG} = e^{-t/\tau_{\text{decay}}} - e^{-t/\tau_{\text{rise}}} \quad (2)$$

where $t = 0$ at the onset of the conductance, τ_{rise} is the rise time constant, and τ_{decay} is the decay time constant. For EPSP, these were 0.45 and 3.0 ms, respectively. For IPSP, τ_{rise} was 0.9 ms, whereas IPSP decay time (τ) was varied between 1 and 160 ms. In our standard model, IPSP onset always followed EPSP onset by 1.0 ms.

Action potentials. We designed AP to be simple and brief. By making AP brief we were able to measure residuals for every EPSP. Another reason for using simple and brief AP is that AP in real neurons activate a diversity of conductances, which typically cause an after-hyperpolarization lasting at least a few milliseconds. We expect that these conductances are homeostatic and work synergistically with IPSP^{21,37}. Although it is of interest to investigate how these conductances interact with IPSP, we avoided this issue by having a single K⁺ conductance with rapid decay.

We modified the parameters of a previous model (available from ‘NEURON ModelDB’)⁶⁵. The absolute refractory period was < 1.0 ms, which was the minimum interval between EPSP and enabled us to measure a residual at the time of each EPSP (every EPSP in our simulations at 800 Hz was able to evoke an AP if it was sufficiently large). AP duration at half of peak amplitude was 0.2 ms, and G_{K^+} at 0.5 ms after AP peak was 6 nS, 0.1% of its maximum and 60% of our standard G_L .

AP thresholds were adjusted to be near -50 mV, which was designated as ‘spike threshold’ in simulations without AP. The mean maximal sub-threshold EPSP (measured in response to ‘threshold EPSP’ as part of our method of finding residuals) was -52.3 , -50.5 and -50.0 mV with EPSP at 5, 100 and 800 Hz, respectively, in simulations with optimal IPSP.

Ensemble of EPSP. In our standard model, each EPSP was of identical unitary amplitude ($E = 30$ nS). EPSP amplitude was larger in some simulations (Fig. 7b) and variable in others (Fig. 6). The most critical variable was the mean interval between EPSP. Except in simulations in which an ‘ensemble’ consisted of only 2 EPSP (Fig. 2), EPSP ensembles were generated by randomly sampling from geometric interval distributions (the discrete analogue of an exponential distribution) with a discrete unit of 1.0 ms. Thus an EPSP interval could be 1.0, 2.0, 3.0 ms and so on. Mean EPSP frequencies varied from 1 to 800 Hz (mean intervals of 1,000 to 1.25 ms). Although EPSP intervals were randomly sampled at each frequency, sampling was only performed once for each frequency. Thus the same sequence of intervals was used for every simulation of a given frequency (Figs 3a and 6b).

MSR was found with ensembles of 1,000 EPSP for each combination of parameters and at each frequency, and for each neuronal model. However, 5,000 EPSP were used in the case of our standard model at 5 Hz. Testing with 4,000 additional EPSP did not result in any change to optimal parameter values relative to 1,000 EPSP, but slightly reduced MSR (18.6–16.6 nS²). With log-normal variance in unitary PSG, we used 10,000 to sufficiently sample the larger space of both amplitudes and intervals. The number of EPSP tested with learning was chosen to reach stable synaptic weights (Fig. 8d) (see below).

Residuals and MSR. At the time of each EPSP, we measured ‘distance from optimality’ as previously described²¹. We refer to this distance as a ‘residual.’ After finding the ‘real’ voltage in response to an EPSP ensemble, we performed additional test simulations to find how much larger or smaller each EPSP would need to have been in order for the EPSP peak to reach exactly to spike threshold (Fig. 2a). Critically, the n th residual depended on membrane properties at the time of EPSP _{n} , including IPSP _{n} , but it did not depend on EPSP _{$n+1$} and other future events (Fig. 2a). Therefore, to find the n th residual, the voltage and conductance up to the n th synaptic event was kept for the test simulation, but later EPSP and IPSP were discarded. Test EPSP were injected with onset at the time of the real EPSP _{n} , making it larger or small as needed so that the peak of the test EPSP was as near as possible to spike threshold (AP threshold, or -50 mV in simulations

without AP). The increment of test EPSP was 0.3 nS. This increment determined the precision with which we estimated the threshold EPSP and residual. In simulations without AP, the peak of the ‘threshold EPSP’ was 50 ± 0.01 mV (mean \pm s.d.).

The residual was defined as the negative of the difference between the ‘threshold EPSP’ and the ‘real EPSP’. For display purposes only, we used the negative of this difference so that positive residuals corresponded to EPSP peaks that were positive of -50 mV (Figs 3a and 4a,d, Supplementary Fig. 3c). For a given ensemble of EPSP, the optimal IPSP parameters were taken to be those that minimized the MSR.

In simulations without AP, occasionally there were cases in which membrane voltage was above ‘spike threshold’ of -50 mV at the time of EPSP onset. This almost never occurred at low EPSP frequencies, but it occurred with 18.7% of EPSP at 800 Hz in our standard model with optimal IPSP parameters. In such cases, the threshold EPSP should bring the EPSP to -50 mV, but the EPSP had no peak in this case and the voltage trajectory continued downwards. This creates a problem for measuring the residual. To measure the residual, we defined the ‘threshold EPSP’ to be the EPSP that caused the mean voltage at 1–3 ms after EPSP onset to be nearest to -50 mV.

To find optimal parameter values, τ was tested across a range of 1–50 ms, but up to 120 ms in Fig. 3d, and 160 ms with E_{Cl^-} of -60 mV (Fig. 7d). For values of τ that were near optimal in minimizing MSR, we tested increments of 0.1 ms at 1–2 ms, 0.2 ms at 2–3 ms, 0.5 ms at 3–5 ms, 1.0 ms at 5–16 ms, 2.0 ms at 16–50 ms and 10.0 ms at 50–160 ms, although less in some instances. Values of I/E that were near optimal for a given τ were tested in increments of 0.1 ($\Delta I = 3$ nS) for τ of 1–22 ms, and 0.05 for larger τ . However, for 5, 100 and 800 Hz with our standard model (Fig. 3d), increments were 0.01 for τ above 14 ms.

Learning. Since our goal was only to demonstrate the feasibility of anti-Hebbian learning, we made little effort to optimize the learning rules, or to make them realistic in all respects. For simplicity, learning occurred following each synaptic event, rather than in real time.

We tested three rules. Rule 1 was simple and was applied to a neuron with a single inhibitory synapse. It lacked a dynamic ‘presynaptic’ term and thus was not ‘associative’ in a meaningful sense. IPSP decay time was pre-specified to be optimal for the EPSP frequency, and thus the only objective was to learn the optimal homeostatic value of I/E . Learning with rule 1 occurred following each synaptic event (n) according to equation (3).

$$w_{n+1} = w_n + \alpha v_n \quad (3)$$

The learning rate α was 0.6 nS per synaptic event. The weight of the inhibitory synapse (w) increased or decreased depending on whether an AP did ($v = 1$) or did not occur ($v = -1$) during the ‘spike period,’ which was -0.5 to 4.5 ms from IPSP onset, or prior to onset of the next IPSP if the next IPSP occurred within < 4.5 ms. The synaptic weight was updated at the end of the spike period, and thus w_n was effective from 4.5 ms after IPSP _{n} to 4.5 ms after IPSP _{$n+1$} (Fig. 8c).

Rules 2 and 3 addressed the greater challenge of learning IPSP decay time as well as amplitude. The model neuron had nine inhibitory synapses, each having synchronous activation 1.0 ms after each EPSP, but with a distinct decay time ($\tau = 1.5$ –50 ms; Fig. 8b). The IPSP at synapse ‘ i ’ and time ‘ t ’ depended on synaptic weight ($w_{i,t}$) and activity ($u_{i,t}$) (equation (4)).

$$\text{IPSG}_{i,t} = w_{i,t} u_{i,t} \quad (4)$$

‘Activity’ was analogous to ‘presynaptic activity’ in conventional associative rules, and corresponds to the time course of GABA_A or glycine receptor activation (unitary activity at each synapse had a peak of 1), whereas the ‘weight’ can be understood as the number of receptors at the synapse. The IPSP is decomposed into ‘weight’ and ‘activity’ so that the regulation of weight (learning, or induction of plasticity) can be independent of weight (memory, or expression of plasticity). (This could occur if there are GABA_A receptors that regulate learning but do not allow current to pass.)

Learning at the time of a synaptic event should depend on the information available about the causal relation between inhibitory activity and spike generation. The ‘eligibility’ for learning ($\bar{u}_{i,n}$) was the average synaptic activity during the period -1 to 4.0 ms from IPSP onset (0–5 ms from EPSP onset), or until the onset of the subsequent IPSP if it occurred in < 4.0 ms (indicated by rectangles in Fig. 8c). The spike period during each synaptic event was also 5.0 ms in duration, but was delayed by 0.5 ms from the eligibility period. Although this was a minor detail, the principle was to account for the causal delay expected between inhibitory activity and spike generation. Defining eligibility and spikes in these rather long periods was simplistic, and as a consequence, learning sometimes depended in part on inhibitory activity that occurred just after a spike. This would not occur in a more realistic model, which could have used an exponentially decaying eligibility trace.

Weights were updated at the end of the spike period according to rule 2 (equation (5)) or 3 (equation (6)).

$$w_{i,n+1} = (2^v - (2^v - 1)e^{-\alpha \bar{u}_{i,n}}) w_{i,n} \quad (5)$$

$$w_{i,n+1} = w_{i,n} + \alpha \bar{u}_{i,n} v_n / \tau_i \quad (6)$$

The learning rate α was 60 and 0.9 nS per synaptic event in learning rules 2 and 3, respectively. Learning with rule 2 was faster at stronger synapses (as measured in nS), but had no direct dependence on decay time. In contrast, learning with rule 3 had no dependence on synaptic weight, but was inversely proportional to τ and was thus slower at synapses with slower decay.

Simulations of learning were run until synaptic weights stabilized. We used 2,000 synaptic events for rule 1, 15,000 with rules 2 and 3 (Fig. 8d), and 35,000 synaptic events for 'reversal learning' (Fig. 8e). The 'learned parameter values' (Fig. 8a) were found by averaging across the last 100 synaptic events. For comparison to our standard parameters I/E and τ (Fig. 8a), the total phasic peak IPSP amplitude T across all synapses was the sum of the weights (w_i) across the nine synapses, and 'weighted τ ' was the weighted sum of the decay time constants across the nine synapses, where the weights were the synaptic weights (w_i).

Statistical analysis. Although it is not a fair comparison (see Results and Discussion), we compared the evidence for our model of τ to two other models, one based on the mean τ across the 21 types of neurons, and the other based on linear regression of the 21 τ on EPSP frequency. The 'odds' are defined as the ratio of the probability of the data given one model to the probability of the data given the other model, which corresponds to the evidence favoring one model over another⁶⁶. We assumed that errors were normally distributed, and that the parameter σ was equivalent to the r.m.s.e. calculated from the model and sample data. Since it follows that the errors were conditionally independent, the probability of the 21 data points was the product of the 21 probabilities. The probability of the data was 10^4 times greater given the predictions of our model relative to the prediction based on the mean τ , and thus the evidence for our model was 10^4 times greater. The evidence favoured linear regression over our model by a factor of ~ 100 .

Data availability. Code and additional parameter values used in the NEURON model are available from the authors upon request.

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Acknowledgements

We thank Larry Trussell, Gary Westbrook, Mike Wehr and Gerard Borst for helpful discussions. Research was supported by a grant to C.D.F. from the National Research Foundation of Korea (2015-R1A2A2A01004185).

Author contributions

J.K.K. performed simulations, analysed data, and made figures. C.D.F. and J.K.K. designed simulations, collected published data from the literature, and wrote the manuscript.

Additional information

Supplementary Information accompanies this paper at <http://www.nature.com/naturecommunications>

Competing financial interests: The authors declare no competing financial interests.

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How to cite this article: Kim, J. K. & Fiorillo, C. D. Theory of optimal balance predicts and explains the amplitude and decay time of synaptic inhibition. *Nat. Commun.* **8**, 14566 doi: 10.1038/ncomms14566 (2017).

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