Fractional differentiation by neocortical pyramidal neurons

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Neural systems adapt to changes in stimulus statistics. However, it is not known how stimuli with complex temporal dynamics drive the dynamics of adaptation and the resulting firing rate. For single neurons, it has often been assumed that adaptation has a single time scale. We found that single rat neocortical pyramidal neurons adapt with a time scale that depends on the time scale of changes in stimulus statistics. This multiple time scale adaptation is consistent with fractional order differentiation, such that the neuron’s firing rate is a fractional derivative of slowly varying stimulus parameters. Biophysically, even though neuronal fractional differentiation effectively yields adaptation with many time scales, we found that its implementation required only a few properly balanced known adaptive mechanisms. Fractional differentiation provides single neurons with a fundamental and general computation that can contribute to efficient information processing, stimulus anticipation and frequency-independent phase shifts of oscillatory neuronal firing.

In response to the sudden change of a stimulus, the firing rate of many neurons undergoes a quick, large change followed by slower adaptation to steady state. First described over 75 years ago, this adaptation causes the spike rate to accentuate changes in the input rather than constant values, and in this sense the neuronal response resembles a derivative of the input. In general, neural systems adapt to a change in stimulus statistics, which may serve to maintain maximal information transmission. Recently many neural systems have been shown to respond adaptively to changes not just in mean input, but also in input variance or contrast, higher-order moments and correlation structure. In several systems, it has also been shown that the time scale of firing-rate adaptation is not static, but depends on the stimulus, for example, the duration of stimulus steps (B. Wark, A.L.F. and F. Rieke, unpublished data).

The extent to which such adaptation of neural systems results from a property of the neural circuit or whether it is a property of single neurons is often unclear. Neocortical neurons have adaptive processes that modify mean firing rate over time scales ranging from tens of milliseconds to tens of seconds and have been implicated in single neuron adaptation to stimulus statistics. But for single neurons, the time course of firing-rate adaptation is often taken to be fixed, or at least independent of the history of change in stimulus statistics.

The mean and variance of fluctuating inputs to cortical neurons can be modulated by changes in input synchrony, changes in network excitability resulting from changes in brain state or by stimulus properties. Here, we found that the firing rate in single rat neocortical pyramidal neurons adapted to such changes with multiple time scales, as revealed by corresponding time scales of change in stimulus statistics. We found that these multiple time scales are a signature of a more general property; the neuron’s firing rate encodes slowly varying stimulus statistics through fractional order differentiation. This gentle form of differentiation emphasizes change in the stimulus while preserving low-frequency information and produces a power law response to sudden stimulus transitions. The fractional differentiation model captures the firing rate response to a stimulus with complex, time-varying statistics. This operation can be biophysically implemented through a balance of only a few known adaptive mechanisms.

Fractional differentiation provides single neurons with a form of adaptation in which no single time scale is preferred; these dynamics may tune the effective time scale of adaptation to the time scales of the stimulus. This operation expands our understanding of the basic processing capabilities of single neurons to the encoding of changes in stimulus statistics over behaviorally relevant time scales in the range of seconds to tens of seconds.

RESULTS
We made recordings from 55 neocortical pyramidal neurons using sharp (n = 49) and whole-cell patch (n = 6) electrodes (see also Supplementary Data and Discussion online). All were layer 2-3 (L2-3) neurons of the rat sensorimotor cortex, except for three of the patch-recorded neurons, which were from layer 5; the results were not distinguishable from those from L2-3. We probed the dynamics of the firing rate with a range of stimulus dynamics.

Multiple time scales of adaptation in single neurons
The responses of L2-3 pyramidal neurons in acute neocortical slices were recorded using sharp intracellular electrodes. The neurons were driven with square wave current stimuli, which alternated periodically,
with cycle period $T$, between two values (Fig. 1a), and with filtered Gaussian noise whose s.d. alternated periodically between two values as the mean remained constant (Fig. 1b). Generally, the binned spike rates adapted upward after a step decrease and downward after a step increase (Fig. 1c; see Methods). Although the time course of adaptation was not necessarily exponential, we fitted the averaged firing rates for each half cycle by a single exponential to determine an effective adaptation time scale for both the low and high mean or variance conditions. As $T$ increased, the effective adaptation time constant $\tau$ increased proportionally for both the noiseless step stimuli (Fig. 1e) and the noisy stimuli with a step change in variance (Fig. 1f), thus showing history-dependent adaptation to be a property of a single neocortical neuron.

The close-to-linear stimulus dependence of the adaptation time scale suggests that the observed rate adaptation was generated by a scale-invariant (no preferred time scale), multiple time scale process rather than by a single exponential mechanism. This is consistent with power-law dynamics, as has been observed in some primary sensory receptors. Power-law response to a step is one example of an input-output relationship for a system implementing fractional order differentiation. We tested whether the adaptive mechanisms of single neurons allow them to function as fractional differentiators of the somatic input current.

Fractional differentiation (see also Supplementary Equations online) is a linear operation that can be written in the time $t$ or frequency $f$ domain as

$$r(t) = k h(t) * x(t) + n_0 \Rightarrow R(f) = k H(f)X(f) + n_0 \delta(f)$$

where $r(t)$ is the firing rate response to a time-varying input $x(t)$, $h(t)$ is the fractional differentiating filter in the time domain and $H(f)$ is the Fourier-transformed filter in the frequency domain (Fig. 2). The constants $k$ and $n_0$ account for the filter gain and the overall mean firing rate; these constants can be fixed by the mean and s.d. of the observed firing rate. In the frequency domain, the filter $H(f)$ is $(2\pi f)^\alpha$, where $\alpha$ is the order of fractional differentiation. If a neuron functions as a fractional differentiator, the gain of the frequency response will be proportional to $(2\pi f)^\alpha$ and each frequency component of the rate response will have a frequency-independent phase lead of $\alpha \pi/2$ with respect to the stimulus (see Methods and Supplementary Equations). For comparison, a single exponential filter leads to a frequency-dependent gain of $\exp(-2\pi f T)$ and phase of $\alpha \pi/2$. If these conditions hold, the order $\alpha$ of fractional differentiation can be determined from the gain-frequency relationship and phase leads. For example, when $x(t) = \sin(2\pi ft)$, then the fractional derivative with order $\alpha$ is $\frac{d^\alpha}{dt^\alpha} \sin(2\pi ft) = (2\pi f)^\alpha \sin(2\pi ft + \frac{\pi \alpha}{2})$. Finally, fractional differentiation differs from integer order differentiation in that it is non-local. Although integer order differentiation depends instantaneously on the input function, the result of fractional differentiation depends on the history of the stimulus, as seen in the slow (power-law) decay of $h(t)$ with time (as in Fig. 2a).

Single neurons as fractional differentiators

We tested this functional model of the neuronal response through linear analysis. We recorded firing-rate responses of L2-3 neurons to injected sine wave (noiseless) currents and sine-modulated noise (constant mean) (Fig. 3a,b). Although previous work has focused on...
sudden stimulus changes and response characterization for high input frequencies (∼1–1,000 Hz)\(^{18,29}\), we focused on low-frequency responses (∼0.03–1 Hz), for which stimulus periods are large compared with typical interspike intervals.

The average gain over all neurons in response to sine wave current and sine wave–modulated noise decreased with increasing \(T\) in a power law–like manner (Fig. 3c). The exponent \(x\) can be determined from the slope of the gain-period relationship on a log-log curve. In response to both sine wave current and sine wave noise, the phase leads were close to frequency independent (Fig. 3d) and the value of \(x\) extracted from the phase shift was consistent with that estimated from the gain. The increased phase lead response to sine wave currents for \(T = 1–2\) s may reflect a voltage-dependent activation of a conductance with a power law–like manner (Fig. 3c). We found the response of a neuron to square wave–current stimuli for three different frequencies (\(8, 16, 32\) s) to be similar to a power law with exponent \(x\), as seen from the log-log gain curves; the slope of the best-fit line is \(-\alpha\). (d) In response to sine-wave current, the phase lead was frequency independent for \(T = 1–32\) s (\(n = 8\), one-way ANOVA, \(F_{1,28} = 1.63, P = 0.204\)) with mean 11.9° (\(x = 0.13\)) and was frequency independent in response to sinusoidally modulated noise for \(T = 1–32\) s (\(n = 11\), one-way ANOVA, \(F_{5,60} = 0.51, P = 0.766\)) with mean 12.3° (\(x = 0.14\)). Error bars represent standard error.

Figure 3 The gain of the neuronal firing response can be described by a power law and the phase lead is frequency independent. (a,b) Sine–wave current (a) or sinusoidally modulated noise (b) was injected and elicited a sinusoidal response (60 bins per period) with a phase lead with respect to the stimulus (see also Supplementary Fig. 6 online). Data are from two example neurons. (c) The average gain of the response decreased with period \(T\) (\(n = 8\) and 11 for sine-wave currents and sine-modulated noise, respectively), similar to a power law with exponent \(x\), as seen from the log-log gain curves; the slope of the best-fit line is \(-\alpha\). (d) In response to sine-wave current, the phase lead was frequency independent for \(T = 4–32\) s (\(n = 8\), one-way ANOVA, \(F_{1,28} = 1.63, P = 0.204\)) with mean 11.9° (\(x = 0.13\)) and was frequency independent in response to sinusoidally modulated noise for \(T = 1–32\) s (\(n = 11\), one-way ANOVA, \(F_{5,60} = 0.51, P = 0.766\)) with mean 12.3° (\(x = 0.14\)). Error bars represent standard error.

Figure 4 Neuronal response to sine-wave noise envelopes is similar when periods \(T = 4, 8, 16\) and 32 s are presented simultaneously (with phases \(\phi = 0, 1, 2\) and 3 rad) or individually. (a) The stimulus noise envelope is a sum of four sine waves; the amplitude of the neuronal response can be obtained from the Fourier transform of spike responses. Data are from an example neuron. (b,c) Gain curves were similar (\(n = 12\), two-way ANOVA, \(F_{1,88} = 0.02, P = 0.902\), b), as were phase leads (\(F_{1,88} = 1.37, P = 0.245\), c). For individually presented sine-wave noise, the mean phase lead was 13.1° (\(x = 0.14\)) and for the sum of sine-wave noise, the mean was 11.9° (\(x = 0.13\)). Error bars represent standard error.
periods (Fig. 5a), which we overlaid with the predicted response derived from the linear filter with amplitude and exponent \( a \) derived from the sinusoidal experiments (as in Fig. 3c). We also determined the response to a more complex stimulus in which the s.d. changed periodically between three different values (Fig. 5b). This induced upward adaptation when the stimulus stepped from the high to the medium variance and downward adaptation when the step was from the low to the medium variance. Given appropriate scale factors, these dynamics were well captured by the fractional differentiator model without fitting (see Methods).

Thus, the dynamics of neuronal responses to complex stimuli were well predicted by the differentiating filter. We then least-squares fit the square wave responses (Fig. 1c,d) with the response predicted by equation (1) using the parameter \( a \). In this case, the best \( a \) was found for each neuron in response to square wave current or square noise. For square wave current and noise, \( a \) was 0.163 (s.d. = 0.034) and 0.137 (s.d. = 0.048), respectively (Fig. 5c). The difference in error between fitting each curve using an exponential form and fitting all with a single fractional-differentiating filter was small. For square-wave current, the difference in the mean of the absolute error was 0.18 Hz per bin, whereas the difference was 0.06 Hz per bin for square-wave noise, where errors were slightly smaller with exponential fitting. Differences in squared errors were significant for square-wave noise (two-way ANOVA, \( F_{1,5938} = 7.94, P = 0.005 \)), but not for square-wave current (two-way ANOVA, \( F_{1,2864} = 2.92, P = 0.087 \)). Thus, scale-invariant fractional differentiation provides an accurate description of the data, with fewer parameters, compared with fitting separate exponential time scales.

We then compared the value of \( a \) as estimated in eight ways (Fig. 5c). The overall mean was 0.15 (s.d. = 0.06). These data show that the neuronal firing-rate response to time-varying stimulus statistics is compactly approximated as fractional differentiation of order 0.15.

Implementation of fractional differentiation

It remains unclear how power-law dynamics are implemented biologically, although previous theoretical work suggests several possibilities\(^{25,26,30–32}\). For single neurons, several mechanisms are known to underlie rate adaptation, including slow sodium-channel inactivation\(^{18}\) and after-hyperpolarization (AHP) currents\(^{16,17,19,20}\), which decay with a mixture of time scales\(^{33}\). Because slow AHP (sAHP) currents are distinct from the spike-generating mechanism, in contrast with slow sodium inactivation, it is relatively straightforward to manipulate these currents experimentally. We experimentally manipulated sAHP currents, as we expected that these currents contribute to the adaptation time scales as measured by the phase lead; increasing sAHP currents should increase phase leads, whereas decreasing sAHP currents should decrease phase leads.

Figure 6 Fractional differentiation depends on a balance of multiple adaptation mechanisms with different time scales. Artificially increasing or pharmacologically blocking sAHP currents led to opposite changes in phase leads. (a) sAHP currents were added to patch-clamped neurons (\( n = 6 \)) using dynamic clamp (1-ms pulse, \( \tau = 3 \) s, \( \Delta G = 0.05 \) nS per spike, –100 mV reversal potential). Without the artificial sAHP conductance, phase leads were frequency independent (one-way ANOVA, \( F_{3,30} = 1.60, P = 0.190 \)). With the artificial sAHP conductance, phase leads were strongly frequency dependent (\( F_{3,30} = 7.48, P = 0.000 \)). The two conditions were significantly different (two-way ANOVA, \( F_{1,60} = 27.9, P = 0.000 \)) and phase leads increased for \( T = 4–16 \) s. (b) Application of \( \alpha \)-methyl-5-HT reduced sAHP currents with \( \tau \approx 1 \) s by 63% (s.d. = 13%), as measured 450–550 ms after a train of 30 spikes at 50 Hz from a pre-train membrane potential set to –65 mV by injection of positive holding current. Drug application (\( n = 10 \)) altered phase leads (two-way ANOVA, \( F_{1,108} = 9.39, P = 0.003 \)) by reducing them for \( T = 4–16 \) s. Error bars indicate standard error and asterisks indicate significant differences (paired t tests, \( P < 0.05 \)).
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First, we artificially added a sAHP conductance with a decay \( \tau = 3 \) s
to patch-clamped neurons (L2-3 and L5) using spike-triggered current clamp (Fig. 6a and Supplementary Fig. 1 online). Without the artificial conductance, phase leads were frequency independent, but with the artificial conductance, phase leads increased for \( T = 4-16 \) s with a frequency dependence consistent with a previous study\(^{34}\). Thus, the addition of a sAHP conductance disturbed the balance of underlying adaptive mechanisms.

Next, again using sharp electrodes (L2-3 neurons), we pharmacologically partially blocked the early sAHP current \( (\tau \sim 1 \) s) using the 5-HT\(_2\) receptor agonist z-methyl-5-HT (refs. 6, 7), reducing it by 63% (s.d. = 13%) (see Fig. 6 and Supplementary Figs. 2 and 3 online). This manipulation decreased phase leads for \( T = 4-16 \) s (Fig. 6b). However, the magnitude of the pharmacologically induced reduction of the sAHP was only weakly correlated with the magnitude of reduction in phase leads (Pearson correlation coefficients were 0.51, 0.21 and 0.33 with \( P \) values of 0.13, 0.55 and 0.36 for \( T \) values of 4, 8 and 16 s, respectively). On the basis of this and previous data showing that other mechanisms also contribute to spike-frequency adaptation\(^{18,19}\), we do not believe that sAHP currents are solely responsible for the observed phase leads. Rather, it is probable that a combination of mechanisms gives rise to fractional differentiation in these neurons. Here, we have shown that manipulating the sAHP current affects phase leads, as expected if this current at least partially underlies multiple time-scale adaptation.

We examined whether a few AHP currents with different time constants are sufficient to generate the observed multiple time-scale adaptation. To examine this, we first added 2–3 AHP currents to a standard, single-compartment Hodgkin-Huxley model neuron with no slow adaptive processes and then added two time scales of slow sodium inactivation (Fig. 6a; see Supplementary Methods online). AHP currents were added with time constants that roughly spanned the range of observed sAHP currents in neocortical pyramidal neurons\(^{20}\).

The amplitudes of these currents were precisely balanced with respect to one another to approximate fractional differentiation. For slow sodium inactivation, we augmented sodium current dynamics with slow inactivation gates having two time scales and with kinetics as measured in neocortical neurons\(^{15}\).

These models showed multiple time scales of adaptation (Fig. 7a) and approximately frequency-independent phase leads (Fig. 7b), as was observed in the real neurons (Figs. 1 and 3). The observation that only a few adaptive processes can underlie rate adaptation over a wide range of time scales is consistent with theoretical analysis showing that a single adaptive process affects the neuronal response over a wide range of frequencies\(^{34}\). Together, these results demonstrate that fractional differentiation can be implemented biophysically with known adaptive mechanisms.

DISCUSSION

Although single neurons respond to current fluctuations on very short time scales\(^{15}\), the mean firing rate can be considered to encode slowly varying statistical properties of the stimulus\(^{4}\) or the stimulus envelope\(^{34}\), acting as an additional channel of information\(^{37}\). We found that the dynamics underlying spike-rate adaptation to stimulus steps in single cortical neurons functionally approximate fractional differentiation. This provides a general model for the firing-rate response to time-varying stimulus statistics or envelope encoding. Far from simply accommodating to a new state, these adaptive dynamics convey detailed information about stimulus components. Furthermore, this rate response is a linear function of the stimulus mean or envelope. Although extracting a stimulus envelope requires a nonlinear operation\(^{38}\), here the dynamics of spike generation and adaptation provide this operation, while retaining the neuron’s ability to represent high-frequency fluctuations. We considered responses to variations in mean and variance separately. Further work is required to evaluate the encoding of simultaneous and potentially correlated change in both statistics.

We have focused on the slower time scales that are relevant for time-varying firing rates. One could combine this approach with methods of capturing fast time-scale dynamics (for examples, see refs. 38,39) to give a model that captures both specific stimulus components causing single spikes and slower-varying components relevant for the firing rate. The simplest possibility is that the rate dynamics \( \dot{r}(t) \) act as a multiplicative gain on the fast dynamics of spike generation. Consider, for example, the case of a slowly time-varying s.d. \( \sigma(t) \). For a given \( \sigma \), the occurrence of single spikes is determined by a gain function \( g_\sigma \), which acts on the input after convolution with a filter \( f_\sigma \). Decomposing the input into an envelope and a fast-varying component as \( \sigma(t)\eta(t) \), this multiplicative model for the spike probability is

\[
P(\text{spike}|\sigma(t)\eta(t)) = r(\sigma(t))g_\sigma(f_\sigma * \eta(t)),
\]

where the rate \( r \) is determined by the envelope \( \sigma(t) \), as we have explored here. Such a description may hold true when there is a separation of time scales between the short time-scale action of \( f_\sigma \) and \( g_\sigma \) and the slowly time-varying stimulus parameter \( \sigma \), and allows for changes in the instantaneous coding of inputs resulting from statistical properties of the stimulus, such as gain normalization\(^{5}\).

Previous work has shown that slow adaptation currents in neocortical neurons have multiple time scales\(^{16,17,18,20}\). One study\(^{19}\) found that in vitro data from rat L5 pyramidal neurons could be modeled by a leaky integrate-and-fire (LIF) model neuron modified to include two
spike-dependent adaptation currents and one facilitation current. The average fitted time constants for these currents were 48 ms, 5.8 s and 580 ms, respectively. As a result of the facilitating current, this modified LIF model\(^\text{19}\) does not generate results consistent with fractional differentiation. However, a modified LIF model with an early sAHP current (\(\tau = \sim 1\) s)\(^\text{20}\) instead of a facilitating current can give results similar to ours (Fig. 7). As the LIF and Hodgkin-Huxley models can give similar results, it is likely that the fractional differentiation model does not depend on the details of spike generation. Other mechanisms of adaptation, such as slow sodium inactivation, cannot be readily implemented in an LIF model.

A fractional differentiator has a power-law response to stimulus steps. Power law responses have been observed in a range of neural systems, from single ion channels\(^\text{15}\) to cognitive behavior\(^\text{32,40}\). The presence of power-law adaptation to a step and fractional differentiation are not synonymous; it is possible to have a power law response without the frequency-independent phase property of the fractional differentiator. Fractional order dynamics have been observed in the vestibular-ocular system\(^\text{30,41,42}\) and in the fly motion sensitive neuron H1 (ref. 43). However, these results were from neural systems rather than from single neurons. A range of mechanisms may contribute to fractional order dynamics and power laws, including circuit\(^\text{30}\) and synaptic\(^\text{40}\) mechanisms, geometrical properties of cells\(^\text{25}\) and dendrites\(^\text{43}\), and the multiple inactivation states of sodium channels\(^\text{31}\).

Our results show that this computation can be carried out by single cortical neurons and can be implemented by known adaptation mechanisms in a spatially restricted region of the neuron.

Unlike a full derivative, fractional differentiation enhances responses to stimulus change, but does not entirely remove information about very low-frequency stimulus fluctuations. Retaining information about both the signal magnitude and the signal rate-of-change is a property of fractional order derivatives that leads to dependence on stimulus history. Unlike integer order derivatives, fractional orders are non-local. We found the fractional order (\(z\)) to be \(\sim 0.15\). This gentle differentiation may reflect a requirement for the neural system to encode only a modest amount of rate-of-change information by a single neuron. Increasing the effective value of \(z\) beyond 0.15 could be accomplished by a neural circuit through the sequential adaptation effects of multiple neurons and intervening synaptic dynamics\(^\text{30,44}\).

We found that the fractional differentiation model for spike rate changes holds true over time scales from \(\sim 1–30\) s, a range that is behaviorally relevant for fluctuations in input statistics. It has been suggested that fractional order differentiation may be an important property of motor control systems that compensates for fractional order integration dynamics of muscle and tissue, resulting from their viscoelastic properties\(^\text{43}\). Here, we found that single neurons in the sensory-motor cortex have this property. This kind of rate encoding may also allow neurons to process information efficiently by matching response time scales to input time scales\(^\text{45}\) or to temporally decorrelate, or whiten, the stimulus envelope\(^\text{46}\). The power-law form of the gain may be related to the typical power-law spectra of natural stimuli\(^\text{47,48}\), which would facilitate stimulus whitening. The constant phase shift allows phase to be modulated independently of frequency, which may be important for the interaction of neocortical neurons with slow oscillatory frequencies in the brain\(^\text{39}\).

Finally, representing an input’s derivative could allow neural circuits to predict future stimuli, similar to a Taylor approximation\(^\text{44}\).

Our results suggest that fractional differentiation is a fundamental and elementary computation of L2-3 neocortical pyramidal neurons and provides a general model of the response of adapting neocortical neurons to time-varying stimuli. These intrinsic dynamics provide a substrate for a form of short-term memory, retaining stimulus information over the intermediate time scales of seconds to tens of seconds. Although we focused on L2-3 neurons distributed throughout the sensorimotor cortex, we found similar results among a small sample of L5 neurons. Fractional differentiation may be a general property of adapting neurons in the neocortex. A subset of L5 neurons show minimal slow firing-rate adaptation\(^\text{7}\) and these cells may not show fractional differentiation. Although it may seem surprising that these dynamics have not been discovered previously, it is probable that the experiments that would have revealed these dynamics were not carried out at the slow time scales investigated here. The appearance of these dynamics in single neurons and our ability to disrupt them suggest that adaptation currents and slow sodium inactivation, among other adaptive mechanisms, may be finely tuned to contribute these multiple time scales. This tuning may achieve a balance between providing rate-of-change information and preserving a continuous response in the face of negative feedback.

METHODS

Preparation of cortical slices. We deeply anesthetized 5–12-week-old Sprague Dawley rats in a chamber filled with 4% isoflurane in oxygen and quickly decapitated them. The rostral, caudal and ventral portions of the brain were removed and the remaining block was attached to the stage of a Vibratome tissue slicer (TPI) using cyanoacrylate glue (Loctite 404; Loctite) and immersed in ice-cold cutting solution containing 220 mM sucrose, 3 mM KCl, 1 mM CaCl\(_2\), 5 mM MgCl\(_2\), 26 mM NaHCO\(_3\), 1.25 mM NaH\(_2\)PO\(_4\) and 10 mM d-glucose. The cutting solution was bubbled with 95% O\(_2\)/5% CO\(_2\) to maintain pH at 7.4. Coronal slices (300 \(\mu\)m thick) were cut (\(\sim 1\) mm to \(\sim 1\) mm relative to bregma) and transferred to a holding chamber filled with artificial cerebrospinal fluid containing 125 mM NaCl, 3 mM KCl, 2 mM CaCl\(_2\), 2 mM MgCl\(_2\), 26 mM NaHCO\(_3\), 1.25 mM NaH\(_2\)PO\(_4\) and 20 mM d-glucose, bubbled with 95% O\(_2\)/5% CO\(_2\). The temperature of the holding chamber was maintained at 34 °C for \(\sim 60\) min and then allowed to cool to approximately 22 °C.

Recording. Slices were transferred to a recording chamber and perfused at \(\sim 2 \text{ ml min}^{-1}\) with warmed artificial cerebrospinal fluid (\(\sim 33 \pm 1^\circ\text{C}\)). For pharmacological experiments, the control recording solution also contained 6,7-dinitroquinoxaline-2,3(1 H,4 H)-dione (20 \(\mu\)M), 3,3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (5 \(\mu\)M) and picrotoxin (100 \(\mu\)M) to block AMPA/kainate, NMDA and GABA\(_\text{A}\) receptors, respectively. Recordings were obtained from cells in L2-3 (sharp electrodes) and L2-3 and L5 (whole-cell patch electrodes) in the dorsal neocortex \(\sim 1-4\) mm from the midline using an Axoclamp 2-A amplifier (Molecular Devices) in continuous bridge mode. Sharp electrodes were filled with 3 M KCl and had resistances of \(\sim 60-100\) MΩ. Patch pipettes were filled with solution containing 127 mM KCH\(_2\)SO\(_4\), 10 mM myo-inositol, 2 mM MgCl\(_2\), 5 mM KCl, 10 mM HEPES, 0.02 mM EGTA, 6 mM sodium phosphocreatine, 2 mM Na\(_2\)ATP and 0.5 mM Na\(_2\)GTP, pH 7.2–7.3. Access resistances during whole-cell recording were \(\sim 10-20\) MΩ. Data were filtered at 10 kHz and sampled at 10–20 kHz using ITC-16 and ITC-18 data acquisition boards (Instrutech). Data acquisition was controlled by custom macros written in Igor Pro (WaveMetrics).

Current stimuli. Single neurons were stimulated with time-varying current stimuli in current clamp. Square waves were generated to switch between values of 1 and 2 with a range of oscillation periods. Similarly, standard sine waves were generated to vary between 1 and 2 with a range of periods. A positive holding current was applied to depolarize each neuron to within 10% of rheobase, near the threshold for firing. The basic periodic waveforms were scaled by a factor between 50 and 250 pA, chosen individually for each cell such that the neuron fired throughout the stimulus block. In trials using noise stimuli, the simple periodic waveforms were multiplied by exponentially filtered (1-ms time constant) Gaussian white noise to give periodically modulated noise, with a s.d. given by the square or sine wave. To produce current stimuli, these noise sequences were again shifted using a positive holding current to near rheobase and scaled as described above. During the
noise stimuli, this scaling produced membrane-potential fluctuations with s.d. of ~2–8 mV. These stimulus sets were presented in blocks with periods T = 1, 2, 4, 8, 16 and 32 s, where each period was presented for 96 s, giving a total stimulus length of 576 s, following which periods were presented in reverse order. On every individual cycle repetition, the particular noise sequence differed. Finally, modulated noise stimuli were created where the modulation envelope was generated as a sum of sinusoids. Four sine waves with periods T = 4, 8, 16 and 32 s and phase shifts ϕ = 0, 1, 2 and 3 rad were summed and the result was used to multiply a Gaussian white-noise sequence as above. In this case, the block length was 192 s. Control blocks consisting of individual sine waves with T = 4, 8, 16 and 32 s and block length 96 s were presented to the same cells. Stimuli were scaled before injection, as described above.

Cell-acceptance criteria and firing rates. Neurons were considered to be healthy and stable if their resting membrane potential was <−70 mV, spikes were >65 mV in height, and the resting membrane potential and rheobase (the current at which the neuron first began to spike) did not fluctuate by more than 10% between stimulus blocks (except during pharmacological or dynamic clamp manipulations). Spike times were recorded when the membrane potential crossed ~10 mV and reached its peak, and subsequent upward crossings within 2 ms were not considered. Time-varying firing rates were found by taking a histogram of spike times modulo the cycle period.

Fitting exponentials to firing rates. Firing-rate time courses (as in Fig. 1a,b) were least-squares fit with the two-parameter exponential A exp(−t/T), where the steady state was defined to be the last three bins of each half period and 30 bins were used for each period. Cells for the square-wave (n = 8) and square-noise (n = 11) experiments were included if firing was >1 Hz throughout and firing rates did not show upward adaptation after a step increase. Upward adaptation in the high condition was observed in ~10% of neurons and was usually seen in cells with unusually high firing rates, signs of poor cell health or unstable recordings. Thus, experiments showing this type of response were excluded from the present analyses. Exponential T’s were not considered if the amplitude of the exponential relaxation, A, was less than 10% of the steady-state firing rate. This criterion excluded 14 of the total 228 measurements of T.

Fitting sine waves to firing rates. The amplitude and phase lead of the response with respect to the stimulus were found by least-squares fitting the mean firing-rate response of each neuron, determined, as done previously, by taking a histogram of spike times, with sin(2πf + ϕ), with the two parameters A and ϕ. Identical results were obtained via Fourier transform of the firing-rate response, represented as a vector of zeros and ones designating bins in which there was not or was a spike; the dominant frequency amplitude and corresponding phase were easily identified. The gain for each T was found by dividing A by the stimulus scaling factor used for a given neuron, which ranged from 50–250 pA. For the sum of sines experiment, a vector of zeros and ones to signify no spike or spike, respectively, was created with a sampling rate of 500 Hz; amplitudes and phases were found from the Fourier transform of this vector, with results nearly identical to those from the least-squares fitting of the mean firing-rate histogram, or from the Fourier transform of the histogram. Neurons were included if at least four blocks (12.8 min) of data in response to the sum of sines stimulus were obtained, so that phases could be determined with sufficient accuracy. Neurons were excluded if they did not fire throughout T.

Fitting square-wave data with fractional differentiator responses. The shapes of the firing-rate curves were fit with the response that a fractional differentiator with order α has to a square-wave stimulus. The fractional-differentiating filter was found as follows. In the frequency domain, the filter was defined as A(2πf)α for frequencies ~900/T to 9000/T with Af = 0.01/T. In the time domain, this filter was convolved with step functions of period T with a sample rate of 1.920/T, using only the result computed without the zero-padded edges. Neighboring bins of this finely sampled response were averaged to match the bin number of the firing-rate responses. As we simply wished to evaluate the exponent α for the population, we fixed the amplitude A by normalizing each response such that input and output had the same mean and s.d. For each experiment, which consisted of six periods, the single best α was found by least-squares fitting to the firing-rate response. Thus, fitting responses from a single experiment required three parameters (α plus normalization of mean and variance) instead of 36 parameters (six parameters for two exponential fits per T), as was done previously.

Using dynamic clamp to add AHP currents. When the membrane potential crossed ~10 mV, a pulse generator injected a 1-ms negative current pulse into a resistor-capacitor circuit, the voltage, VEC, of which relaxed with a 3-s time constant. The resistor-capacitor circuit provided input to a custom-made analog dynamic-clamp circuit that produced an output GAHP(Vmembrane = EK), where GAHP = kVEC = 0.05 nS per spike and EK = −100 mV. This was summed with the stimulus current.

Biophysical modeling. The single-compartment, conductance-based Hodgkin-Huxley model neuron20 was used with standard parameters (Supplementary Methods), except as noted. For each AHP current, an additional current, or term, was added to the equation for dV/dt of the form −G_\text{AHP}(V − E_{\text{rest}}), where a was incremented by one after each spike and decayed according to dA/dt = −1/τ, with τ = 0.3, 1 and 6 s, and GAHP = (0.05, 0.006 and 0.004)GAHP with the time scales as indicated. To implement slow sodium inactivation with two time scales, two extra gating variables, s1 and s2, were added to the sodium current so that it became: GSNaβ(Vmembrane − EK). The kinetics for these additional gating variables were: d\phi/dt = k(\phi1(1 − s) − βs), with \phi1 = 0.001 exp(-50/\phi2) and βs = (0.001/\phi2)k. The term was used to modify the time constant \tau = (\phi2/2) τs of s. Specifically, given these kinetics, \tau is voltage dependent with a peak of ~2,300 ms at −50 mV, tapering off to ~500 ms by 0 mV. To approximate AHP currents with time constants of 0.3 s and 6 s (as in Fig. 7), \tau was set equal to 2/0.3 and 2/6, respectively. Equations were solved numerically using fourth-order Runge-Kutta integration with a fixed time step of 0.05 ms and spike times were identified as the upward crossing of the voltage trace at −10 mV (resting potential = −65 mV) separated by more than 2 ms. For these data, the mean of the exponentially filtered (\tau = 1 ms) Gaussian white-noise stimulus was 5.5 μA cm−2 and the s.d. of the square and sine waves varied between 20 and 32 μA cm−2.

Magnitude and phase of a fractional differentiating filter. Because complex numbers can be written in terms of amplitudes and phases, the response R(f) to a signal X(f) = C_f exp(iθ_f) through a fractional differentiating filter may be written as

\[ R(f) = |(i2\pi f)^\alpha X(f)| = (2\pi f)^\alpha |X(f)|, \]

where it can be seen that the magnitude of R(f) is (2\pi f)^\alpha C_f and the phase of R(f) has a frequency-independent phase shift of \pi αT. If the signal x(t) is a step function, the resulting response after the step will be a power-law decay, as the Fourier transform of a power law is a power law.

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS
All authors conceived of and designed the experiments. B.N.L. and M.H.H. performed the experiments. B.N.L. analyzed the data, performed the modeling and wrote the initial draft. All authors revised the paper.
Responses averaged across (a) 8 neurons in response to sine wave current and (b) 11 neurons in response to sine wave noise for a given period. In both cases a phase lead is observed, where the dotted black line is a sine wave with zero phase. Phase leads increased during the dynamic clamp condition for $T = [4 \ 8 \ 16]$ sec. These data are summarized in Figure 5a.

**Figure S1:** Phase leads increased during the dynamic clamp condition for $T = [4 \ 8 \ 16]$ sec. These data are summarized in Figure 5a.

**Figure S2:** Reduction of the sAHP by $\alpha$-methyl-5-HT. For each trace, the magnitude of the early sAHP current ($I_{sAHP}$) was approximated by taking the mean membrane voltage at 450-550 msec and subtracting the resting membrane voltage before the train of 30 action potentials at 50-Hz. For clarity, spikes have been removed.

- Reduction of the sAHP by $\alpha$-methyl-5-HT. For each trace, the magnitude of the early sAHP current ($I_{sAHP}$) was approximated by taking the mean membrane voltage at 450-550 msec and subtracting the resting membrane voltage before the train of 30 action potentials at 50-Hz. For clarity, spikes have been removed.
Phase leads decreased, on average, after application of α-methyl 5-HT. For each neuron ($n = 10$), the fraction of the control phase lead ($\phi_{AfterDrug}/\phi_{BeforeDrug}$) for $T = [4\ 8\ 16]$ sec remaining after drug application was plotted against the fraction of the sAHP remaining ($DV_{AfterDrug}/DV_{BeforeDrug}$).

**Figure S3:** Phase leads decreased, on average, after application of α-methyl 5-HT. For each neuron ($n = 10$), the fraction of the control phase lead ($\phi_{AfterDrug}/\phi_{BeforeDrug}$) for $T = [4\ 8\ 16]$ sec remaining after drug application was plotted against the fraction of the sAHP remaining ($DV_{AfterDrug}/DV_{BeforeDrug}$).
Figure S4: Normalized average firing rate responses show a similar shape regardless of period. Firing rates from 8 neurons averaged for a given period in response to the (a) low and (c) high condition of square-wave currents. Similar results for 11 neurons are seen in response to the (b) low and (d) high conditions of square-wave noise.

Figure S5: Using fixed bin widths yielded similar results as Figures 1c and 1d in response to (a) square-wave current and (b) square-wave noise. Here, the inverse of each inter-spike-interval was used to find a firing rate estimate using 50 msec bins, and the resulting firing rate estimates were fit with exponentials as described previously.
Responses averaged across (a) 8 neurons in response to sine wave current and (b) 11 neurons in response to sine wave noise for a given period. In both cases a phase lead is observed, where the dotted black line is a sine wave with zero phase.

**Figure S6**: Responses averaged across (a) 8 neurons in response to sine wave current and (b) 11 neurons in response to sine wave noise for a given period. In both cases a phase lead is observed, where the dotted black line is a sine wave with zero phase.
Supporting Online Materials

Methods

The following equations comprise the standard HH model (Hodgkin and Huxley, 1952; Koch, 1999; Dayan and Abbott, 2001; Gerstner and Kistler, 2002):

\[
\frac{dV}{dt} = \frac{1}{C} \left( I_{in} - \frac{G_{Na} m^3 h V}{C} - \frac{G_{K} n^4 V}{C} - \frac{G_{Leak} V}{C} \right)
\]

\[
\frac{dn}{dt} = \frac{n (1-n)}{\tau_n} - \frac{n}{\tau_n}
\]

\[
\frac{dm}{dt} = \frac{m (1-m)}{\tau_m} - \frac{m}{\tau_m}
\]

\[
\frac{dh}{dt} = \frac{h (1-h)}{\tau_h} - \frac{h}{\tau_h}
\]

where steady-state gating values, such as \(n\), are equal to \(\frac{1}{1 + \exp(-V/V_\text{th})}\).

Standard parameters for HH are:

\[
G_{Na} = 120, \quad G_{K} = 36, \quad G_{Leak} = 0.3 \text{ mS/cm}^2; \quad E_{Na} = 50, \quad E_{K} = -77, \quad E_{Leak} = -54.4 \text{ mV}; \quad C = 1 \text{ µF/cm}^2.
\]

Data and Discussion

Physiological properties of neurons recorded. For 45 of the sharp electrode recordings, the resting membrane potential was \(-86 \pm 5\) mV, the rheobase was \(0.47 \pm 0.21\) nA, and the input resistance, calculated using the steady-state current needed to depolarize the cell from rest to just below rheobase, was \(67 \pm 25\) M\(\Omega\) (mean \(\pm\) SD). For the patch recordings, three cells were in layer 2/3 and had resting membrane potentials of \([-80, -87, -88]\) mV, rheobases of \([0.28, 0.34, 0.51]\) nA, and chord resistances of \([20, 27, 32]\) M\(\Omega\); three cells were in layer 5 and had resting membrane potentials of \([-72, -75, -77]\) mV, rheobases of \([0.35, 0.37, 0.70]\) nA, and chord resistances of \([63, 59, 46]\) M\(\Omega\).

Effect of data binning on adaptation measures for square-wave current and square-wave noise. For each \(T\), the time-dependent mean firing rate of each neuron was determined from a histogram of spike times with 30 bins; because equal time was spent on each \(T\) and we were looking for a single exponential time constant to describe adaptation, we used a fixed number of bins rather than a fixed time interval for each bin. When the mean firing rates from each neuron were averaged and normalized, it was evident that the shape of the average response was similar over the tested range of \(T\) (Figure S1). Although a bin width of \(1/30\) \(T\) masks exponentials with \(\tau < \sim 0.01\) \(T\), in the present studies we observed exponential relaxation of firing rate with \(\tau \sim 0.1\) \(T\). To investigate whether our results were substantially biased by using 30 bins for each \(T\), the firing rate for each neuron was also found using the inverse of each inter-spike interval (ISI), sampled at 500 Hz and down-sampled to a bin width of 50 msec. The results obtained (Figure S2) were similar to Figures 1c and 1d, despite inherent sampling and edge biases. For the modeling data (Figures 6a and 6b), when data sets were large, fixed bin width and fixed bin number gave nearly identical results.
Phase leads decreased, on average, after application of \(-\text{methyl 5-HT}\). For each neuron \((n = 10)\), the fraction of the control phase lead \((\text{"AfterDrug"}/\text{"BeforeDrug"})\) for \(T = [4\ 8\ 16]\) sec remaining after drug application was plotted against the fraction of the sAHP remaining \((D_{V\text{AfterDrug}}/D_{V\text{BeforeDrug}})\).

**Supplementary Equations: Filtering with a fractional differentiator**

We provide here a more detailed outline of the mathematics underlying fractional differentiation (Miller and Ross, 1993; Podlubny, 1999; Kleinz and Osler, 2000; Sokolov et al., 2002; Oldham and Spanier, 2006), which has already been presented in the main text. We suggest that a single cortical neuron transforms mean current input and the envelope of modulated current noise into mean firing rate in a manner that has the general properties of fractional differentiation. We first clarify the specific filtering properties of fractional differentiation. It is convenient to express fractional differentiation in the frequency domain rather than in the time domain. In the frequency domain, a linear operator such as fractional differentiation is expressed as a filter, or transfer function. Recall that any function in the time domain can be transformed into the frequency domain \((\omega = 2\pi f)\) and back into the time domain using the following Fourier transforms:

\[
X(\omega) = \int_{-\infty}^{\infty} e^{-i\omega t} x(t) dt
\]

\[
x(t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} e^{i\omega t} X(\omega) d\omega
\]

so that

\[
x(t) \leftrightarrow F X(\omega).
\]

The first derivative with respect to time in the time domain can be written in the frequency domain as

\[
\frac{d}{dt} x(t) \leftrightarrow F (i\omega) X(\omega).
\]

Therefore, the \(n\)th derivative of \(x(t)\) can be written as

\[
x^{(n)}(t) \leftrightarrow F (i\omega)^n X(\omega).
\]

(1)

Mathematically, \(n\) is not restricted to be an integer, and indeed Eq. (1) can be used to define fractional differentiation in the frequency domain for any real \(n\); when \(n\) is negative, then Eq. (1) describes
fractional integration. To emphasize that \( n \) may be non-integer, from here onward we use \( \alpha \) instead of \( n \) to designate the order of the fractional derivative.

In general, a linear, time-invariant system that filters an input \( x(t) \) with a filter \( h(t) \) and gives an output \( r(t) \) can be expressed via convolution as:

\[
 r(t) = h(t) * x(t) = \int_{-\infty}^{\infty} h(t-\tau) x(\tau) d\tau .
\]  

(2)

In the frequency domain, convolution becomes multiplication, and so Eq.(2) becomes:

\[
 R(\omega) = H(\omega) X(\omega).
\]

From Eq. (1), the filter for fractional differentiation is

\[
 H(\omega) = (i\omega)^{\alpha}.
\]

Thus, if \( x(t) \) is some time-varying input variable (specifically, here we have considered the mean or SD of a time-varying current injected into the soma) and \( r(t) \) is the neuron’s response as measured by its mean firing rate, then the neuron’s computation can be modeled as:

\[
 r(t) = \frac{d^{\alpha}}{dt^{\alpha}} x(t),
\]

where the parameter \( \alpha \) is the fractional order, or, in the frequency domain,

\[
 R(\omega) = (i\omega)^{\alpha} X(\omega).
\]  

(3)

Because \( X(\omega) \) is in general a complex number, it can be rewritten in its polar form in terms of its magnitude \( C_{\omega} \) and phase \( \theta_{\omega} \):

\[
 X(\omega) = |X(\omega)| \exp(i \angle X(\omega)),
\]

where

\[
 |X(\omega)| = \sqrt{X_R^2(\omega) + X_I^2(\omega)} = C_{\omega}
\]

\[
 \angle X(\omega) = \arctan \left( \frac{X_I(\omega)}{X_R(\omega)} \right) = \theta_{\omega},
\]

where \( X_R(\omega) \) and \( X_I(\omega) \) are the real and imaginary parts of \( X(\omega) \), respectively, and \( C_{\omega} \) and \( \theta_{\omega} \) denote the magnitude and phase of the component at frequency \( \omega \). From Euler’s formula,

\[
 \exp(ix) = \cos x + i \sin x,
\]

and noticing that:

\[
 \exp \left( i \frac{\pi}{2} \right) = \cos \frac{\pi}{2} + i \sin \frac{\pi}{2} = i,
\]

we can now write Eq. (3) as:

\[
 R(\omega) = (i\omega)^{\alpha} X(\omega)
 = \omega^{\alpha} \exp \left( i \frac{\alpha \pi}{2} \right) C_{\omega} \exp(i\theta_{\omega})
 = \omega^{\alpha} C_{\omega} \exp \left( i\theta_{\omega} + i \frac{\alpha \pi}{2} \right).
\]  

(4)

Eq. (4) shows two properties: the magnitude of \( R(\omega) \) is \( \omega^{\alpha} C_{\omega} \) and \( R(\omega) \) has a frequency-independent phase shift of \( \alpha \pi/2 \).
Response characteristics of a fractional differentiating filter
A particular output of this operation that has experimental relevance is the response to step stimuli. Here, we compute how a fractional differentiator should respond to this kind of stimulus. If the input $x(t)$ is the Heaviside step function, such that $x(t)=0$ for $t<0$ and $x(t)=1$ for $t\geq 0$, then the input in the frequency domain is

$$X(\omega) = \frac{1}{i\omega} + \pi \delta(\omega).$$

Ignoring the constant $\pi$ when $\omega=0$, which means that our result will need to be shifted by some average value, we then have:

$$H(\omega)X(\omega) = (i\omega)^{\alpha} = (i\omega)^{\alpha-1}.$$

Given the definition of the gamma function as:

$$\Gamma(k) = \int_0^\infty \lambda^{k-1} e^{-\lambda} d\lambda,$$

by setting $\lambda=i\omega t$ and $d\lambda=i\omega dt$, one finds:

$$\left((i\omega)^{-k}\right)^{-1} = \frac{1}{\Gamma(k)} \int_0^\infty t^{-k} e^{-i\omega t} dt.$$

Then, by letting $\alpha=1-k$,

$$H(\omega)X(\omega) = \frac{1}{\Gamma(1-\alpha)} \int_0^\infty t^{-\alpha} e^{-i\omega t} dt,$$

where the right hand side is proportional to the Fourier transform of $t^{-\alpha}$ with $0<\alpha<1$ as the order of the fractional differentiator. Thus, a fractionally differentiating neuron will respond to a step function with a power law $t^{-\alpha}$. In summary, here are three properties of the response of a fractional differentiator with order $\alpha$:

1. Its magnitude in the frequency domain is $\omega^{\alpha} \mathcal{C}_\omega$.
2. Its phase shift in the frequency domain is $(\alpha\pi)/2$.
3. Its time-dependent response to a step increase is proportional to $t^{-\alpha}$.

Form of the fractional differentiating filter in the time domain
The form of the fractional differentiating filter in the time domain is

$$h(t) = \mathcal{F}^{-1}[H(\omega)] = \frac{1}{2\pi} \int_{-\pi}^{\pi} (i\omega)^{\alpha} \exp(i\omega t) d\omega.$$

Using the following approximation for the delta function with finite range of frequencies (Arfken and Weber, 1995),

$$\delta_n(t) = \frac{\sin nt}{\pi t} = \frac{1}{2\pi} \int_{-\pi}^{\pi} \exp(i\omega t) d\omega,$$

the form of the filter is

$$h(t) = _a D_t^\alpha \left[ \delta(t) \right],$$

where fractional differentiation can be defined as (Podlubny, 1999; Oldham and Spanier, 2006):

$$_{a}D^\alpha f(t) = \frac{1}{\Gamma(1-\alpha)} \frac{d}{dt} \int_0^t (t-\tau)^{-\alpha} f(\tau) d\tau, \quad (0 \leq \alpha < 1).$$

For discrete time from $0$ to $t$,

$$h(t) = \frac{1}{\Gamma(1-\alpha)} \frac{d}{dt} \int_0^t (t-\tau)^{-\alpha} \frac{\sin nt}{\pi t} d\tau, \quad (0 \leq \alpha < 1).$$
Methods
The following equations comprise the standard HH model (Hodgkin and Huxley, 1952; Koch, 1999; Dayan and Abbott, 2001; Gerstner and Kistler, 2002):

\[
C \frac{dV}{dt} = -G_{Na} m^3 h (V - E_{Na}) - G_K n^4 (V - E_K) - G_{Leak} (V - E_{Leak}) + I
\]

\[
\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,
\]

\[
\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m,
\]

\[
\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h,
\]

\[
\alpha_n (V) = \frac{0.01(V + 55)}{1 - e^{-0.1(V + 55)}} \quad \beta_n (V) = 0.125 e^{-(V + 65)/80},
\]

\[
\alpha_m (V) = \frac{0.1(V + 40)}{1 - e^{-0.1(V + 40)}} \quad \beta_m (V) = 4 e^{-(V + 65)/18},
\]

\[
\alpha_h (V) = 0.07 e^{-(V + 65)/20} \quad \beta_h (V) = \frac{1}{1 + e^{-0.1(V + 35)}},
\]

where steady-state gating values, such as \(n_{\infty}\), are equal to \(\alpha / (\alpha + \beta)\). Standard parameters for HH are: \(G_{Na} = 120\), \(G_K = 36\), and \(G_{Leak} = 0.3\) mS/cm\(^2\); \(E_{Na} = 50\), \(E_K = -77\), and \(E_{Leak} = -54.4\) mV; and \(C = 1 \mu F/cm^2\).
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