Systematic mapping between dendritic function and structure

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Abstract
For many classes of neurons, the relationship between computational function and dendritic morphology remains unclear. To gain insights into this relationship, we utilize an inverse approach in which we optimize model neurons with realistic morphologies and ion channel distributions (of $I_{KA}$ and $I_{CaT}$) to perform a computational function. In this study, the desired function is input-order detection: neurons have to respond differentially to the arrival of two inputs in a different temporal order. There is a single free parameter in this function, namely, the time lag between the arrivals of the two inputs. Systematically varying this parameter allowed us to map one axis of function space to structure space. Because the function of the optimized model neurons is known with certainty, their thorough analysis provides insights into the relationship between the neurons’ functions, morphologies, ion channel distributions, and electrophysiological dynamics. Finally, we discuss issues of optimality in nervous systems.

Keywords: Single neuron computation, function–structure relation, dendrites, neural computation, input order detection, genetic algorithm

Introduction
Neurons come in many sizes and shapes. There is a wide variety of different neuronal morphologies in the brains of different animal species (Bullock and Horridge 1965; Niewenhuys et al. 1998), in different brain regions of one species (Shepherd 1998), or even in the same brain region (Markram et al. 2004). The diversity of neural cell types is larger in animals with more complex behavior.
(Bullock and Horridge 1965). These observations suggest that different neural morphologies give rise to the different computational functions of neurons. Indeed, the relationship between dendritic morphology and the computations performed by neurons are known for a few classes of neurons. An example is the class of the coincidence-detector neurons in the nucleus laminaris of the avian auditory brainstem (Agmon-Snir et al. 1998; Carr et al. 2005). However, in most classes of neurons, the structure–function relationship is much less understood. Even though a wealth of knowledge about the physiology and morphology of some of these neurons is established, the computational functions (i.e., the input–output transformations) that they potentially and actually perform are not known.

A related issue is how the presence and distribution of voltage-gated (active) conductances on dendrites affects the function of a neuron. Heterogeneous distributions of a number of conductances are known to exist and their influence on some possible computational functions is established: for example, the normalization of excitatory postsynaptic potential (EPSP) waveforms by spatial gradients of $I_h$ (Magee 1998; Magee 1999), the reduction of EPSP (Ramakers and Storm 2002), and the action potential amplitude (Hoffman et al. 1997) by $I_{KA}$ and the boosting of EPSPs by distally located $I_{CaT}$ (Schiller et al. 1997). But to date, there is no general rule or heuristic explaining the emergence of computational function from dendritic morphology, active dendritic properties, and the interaction of the two. This study aims to contribute to the understanding of this emergence of function from structure.

We have recently developed a theoretical approach to automatically find dendritic morphologies optimized for a given computation (Stiefel and Sejnowski 2007). In this inverse approach, the researcher specifies a computational function to be performed by a model neuron, and the optimized morphology that allows for this computation is analyzed. Our methodology contrasts studies in which a model is designed to represent naturally occurring neurons in the fact that the functions of our model neurons are known with certainty. Therefore, the analysis of the morphological and physiological features of our optimized model neurons contributes significantly to the understanding of function–structure relationship in neurons.

The present study is an extension of the previous study, and is enhanced in four ways. First, to generate model neurons we use a different, stochastic morphogenetic algorithm that potentially produces more structural complexities and results in more realistic model neurons. Second, distributions of active conductances are included. Third, we optimize model neurons for a range of temporal intervals (5–30 ms) between inputs, thus mapping a range of function parameters onto a range of neuronal morphologies. Fourth, in the present study we perform a detailed analysis of the underlying electrophysiology and the neuronal dynamics that arise on the optimized structure. Moreover, we analyze how the structure relates to the desired function of input-order detection.

The inverse approach can be used in two distinct ways. First, it can serve as a “hypothesis tester”. When a type of neuron is believed to be capable of performing a certain computational function, model neurons are optimized for this function. If the morphologies of the optimized model neurons resemble the real neurons, the belief in the hypothesis about the function–structure relationship is strengthened. Second, the inverse approach can also be used in an exploratory manner, in which
case the model neurons are optimized for a function of theoretical interest. In this way, the inverse approach can serve as a “hypothesis pump”. It then may or may not generate neuronal models with morphological similarities to known neural cell types. If a similarity is found, this will be an indication of a possible function of the real neuron. In this study, the inverse approach is used as a hypothesis pump, i.e., we aim at finding quantitative rules describing the structure–function relationship for an abstract but potentially crucial computational task of input-order detection. The aim of the present study is not to investigate a known biological system, and the inverse approach is thus not used as a hypothesis tester.

**Methods: Outline of the inverse approach**

**Workflow**

Our goal was to find the model neurons optimized for performing a specific computational function, input-order detection. For that purpose, we used a genetic algorithm (GA) (Mitchell 2001) to optimize multi-compartmental neuron models which perform this function.

We adopted the following workflow: In GAs, an initially random population of parameter sets (termed “genomes”) is created. The parameter sets are then used by a morphogenetic algorithm to generate neuronal structures. These neuronal structures are, in turn, used to construct multi-compartmental models that contain conductance distributions and synapses. Simulations of these compartmental models are used to assess how well they are performing the desired function (termed “fitness”). Subsequently, the GA used the fitness information to enrich the next generation of the population with parameter sets encoding high-performing neurons. This optimization procedure was carried out iteratively to obtain optimized model neurons, competent to perform input-order detection. Finally, the morphologies and simulated electrophysiological dynamics of these neurons were analyzed.

**Fitness function**

In this study we systematically investigated the relationship between a class of computational functions and the neural structures including active electrical properties optimized for performing the desired function. Specifically, we investigated input-order detection, the capability of a neuron to react differentially to two temporal permutations at the arrival of synaptic inputs. The synaptic inputs arrive at two different sets of synapses (here left and right) and are separated by a time lag $\Delta t$. An ideal input-order detector will react as strongly as possible to the activation of the synapses in the temporal order $\text{left} \rightarrow \Delta t \rightarrow \text{right}$, but as weakly as possible to $\text{right} \rightarrow \Delta t \rightarrow \text{left}$. This function is similar (but not equivalent) to a Reichardt motion detector, a neuronal device capable of determining the direction of a moving percept (Egelhaaf et al. 1989; Haag et al. 2004). It is also similar to the functions already investigated by Rall (1964) in passive dendritic trees. We picked this task because it is straightforward (it can be described in a short equation), but interesting for three reasons. Firstly, input-order detection has been proposed
to be important for information processing in the cortex (VanRullen et al. 2005). Secondly, it is also similar to the computation performed by a Reichardt motion detector. Thirdly, it is a time-critical function, which makes it attractive as an object of study, as there is a continued experimental and theoretical interest in time-critical processing capabilities of nervous systems (Singer 1999). The function of input-order detection has a single free parameter, namely the time lag($\Delta t$) between the arrivals of the two sets of inputs. We varied $\Delta t$ over a range of values and addressed a number of questions: (1) Is there a systematic variation in the morphologies of the neurons optimized for input-order detection with increasing $\Delta t$? (2) Is the electrophysiological principle for performing this task conserved across these neurons? (3) What role can voltage-gated conductances (A-type K$^+$ and T-type Ca$^{2+}$) play in performing the computational task under investigation, and how do they interact with the passive properties of the dendritic morphology?, and (4) How do the results of the GA-mediated optimization compare to predictions for an optimized morphology derived from dendritic cable theory (see Supplementary material)?

**Methods: Implementation details**

In the following subsections, we give a detailed description of the different components required by the inverse approach we follow: (1) the generation of morphologies, (2) the multi-compartmental simulations, (3) the fitness assessments, (4) the GAs, (5) the analysis of morphologies, and (6) the analytic model of input-order detection.

An analytical treatment of a simplified model equally performing input-order detection and an explanation of the meaning of “optimization” in this context is presented in the Supplementary material.

**Generation of morphologies**

Neuronal morphologies are generated by means of a stochastic and recursive algorithm based on Burke’s algorithm (Burke et al. 1992). We refer to this algorithm as morphogenetic algorithm (in contrast to the GA used for optimization). The morphogenetic algorithm uses statistical information about morphological features in the form of parametric density distributions. By recursively sampling values from these density distributions and by combining the sampled values, we can generate a virtual neuronal morphology. More specifically, one set of sampled values gives rise to a single dendritic segment. So, in each recursive step of the algorithm, a dendritic segment is added and the algorithm decides whether to terminate, bifurcate, or prolong the current segment. The decision is made by sampling from additional parametric density distributions. The parameters of the required density distributions are what we call the basic parameters, and are listed in Table I. It is these parameters that are subject to optimization as explained later.

Figure 1 schematically illustrates the morphogenetic algorithm. The algorithm starts the generation of a neuron with a spherical soma (of constant diameter, 25 µm). The next step is the sampling of values for the initial stem diameter, stem
segment length, and rotation and elevation angles for the stem. Using these values, the first segment of a dendritic tree is added to the soma. Afterwards, the algorithm iteratively extends this tree. It first decides whether to terminate the branch based on comparing a random number to the termination probability. Additionally, the dendrite is always terminated when the path length to the soma is greater than 2000 m or the current diameter drops below 0.15 m; these limitations are motivated by biological realism. If the dendrite does not terminate, the algorithm samples a value for the rotation and elevation angles and adds another segment. Then, a stochastic decision is made whether to bifurcate. If so, the algorithm samples values for the diameters of the daughter branches (from a Gaussian function with $\mu = \text{parent diameter}/2$, $\sigma = 0.05$), and branching angles for both daughter branches. This choice of daughter branch diameters somewhat limited the search space, and making the parent/daughter branch diameter ratio a parameter of the GA is one of the future improvements of this algorithm.

The algorithm is then iterated until all branches have terminated. Except for the stem diameter, all diameters are computed instead of sampled. The parameters underlying the density distributions from which the exact values are sampled are given in Table I.

The number of dendritic branches is limited between 2 and 4. This is done in order to limit the search space, and thus, to increase the effectivity of the optimization procedure. While input-order detection is, in principle, possible with a single dendrite, this will inevitably lead to sub-optimal performance with the arrangement of synapses used here. Essentially, the solutions found when only one dendrite was allowed contained a short, thick dendrite which soon gave rise to

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial value</th>
<th>Drawn from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem elevation</td>
<td>$\mu = U(-80, 80), \sigma = 10$</td>
<td>Gaussian</td>
</tr>
<tr>
<td>Stem rotation</td>
<td>$\mu = U(0, 360), \sigma = 10$</td>
<td>Gaussian</td>
</tr>
<tr>
<td>Stem diameter</td>
<td>Uniform (0.2, 10)</td>
<td>Constant</td>
</tr>
<tr>
<td>Segment length</td>
<td>Uniform(5, 30)</td>
<td>Gaussian</td>
</tr>
<tr>
<td>Branch rotation</td>
<td>$\mu = G(0, 8), \sigma = 10$</td>
<td>Gaussian</td>
</tr>
<tr>
<td>Branch elevation</td>
<td>$\mu = G(0, 8), \sigma = 10$</td>
<td>Gaussian</td>
</tr>
<tr>
<td>Taper rate</td>
<td>$-0.125$</td>
<td>Constant</td>
</tr>
<tr>
<td>Bifurcation probability</td>
<td>$\alpha = U(0, 4) + 1, \beta = U(90, 170)$</td>
<td>Scaled $\gamma$</td>
</tr>
<tr>
<td>Termination probability</td>
<td>$\alpha = U(0, 4) + 1, \beta = U(5, 50)$</td>
<td>Cumulative $\gamma$</td>
</tr>
<tr>
<td>$I_{\text{KA}}$ stem density</td>
<td>U(0, 0.08), range [0, 0.2]</td>
<td>Constant</td>
</tr>
<tr>
<td>$I_{\text{KA}}$ tapering rate</td>
<td>U(0.85, 1.15)</td>
<td>Constant</td>
</tr>
<tr>
<td>$I_{\text{CaT}}$ stem density</td>
<td>U(0, 0.0001), range [0, 0.02]</td>
<td>Constant</td>
</tr>
<tr>
<td>$I_{\text{CaT}}$ tapering rate</td>
<td>U(0.85, 1.15)</td>
<td>Constant</td>
</tr>
</tbody>
</table>

The bifurcation and termination probabilities are drawn from conditional distributions dependent on the path length from the soma. The bifurcation probability uses a $\gamma$-distribution which is scaled so that the peak equals $p = 0.8$. The termination probability uses a cumulative $\gamma$-function with extra constraints motivated by biology so that a dendritic branch has to terminate either when the path length to the soma is greater than 2000 $\mu$m or the current diameter drops below 0.15 $\mu$m. These functions are heuristically chosen as they are often used to describe neuroanatomical data (Burke et al. 1992; Ascoli et al. 2001).
Figure 1. Morphogenetic algorithm used for the generation of neural morphologies. 
(a) Flow-diagram of the algorithm. The algorithm starts from a soma and attaches a dendrite for every block of parameters in the genome. Initially, an initial orientation for the dendrite is sampled. Then, the algorithm iteratively decides whether to elongate, bifurcate or terminate the dendrite. A dendrite is also terminated if it grows in length > 2000 µm or in diameter < 0.15 µm. (b) Assembly of a dendritic tree. The numbers correspond to the steps in (a). (c) Insertion of active conductances and synapses, performed after the assembly of the dendritic tree. The synapses are inserted if the dendrite grows through a sub-region of space termed “dendritic zone”.

(a) Genome + Seed
Make a soma
For all dendrites

For each dendrite:
Sample segment length
and initial stem
elevation, rotation, diameter

Add a segment
Sample taper rate,
elevation, rotation

Terminate
branch?
Yes
No

Yes
Bifurcate?
No

Finished

(b) 1 2,3,4,6 3,4,6
2,3,4,6
3.5,x

3.5, x

(c) Synaptic
zone
two branches growing into the left and right target zones, respectively (not shown). This arrangement is electrotonically very similar to a soma with two dendrites. When neurons with one to four dendrites were allowed, the neurons resultant of the optimization nevertheless contained more than one dendrite. Equally, we deemed that more than four branches were unnecessary for integrating two groups of synaptic inputs and excluded this possibility.

The diameters, synapses, and conductances are inserted after the generation of the 3D-branching patterns. First, the diameters (except for the stem diameter) are computed recursively as follows: $d_i = d_{i-1} \times \text{taper rate}$, where $d_i$ is the diameter of the current segment and $d_{i-1}$ the diameter of the parent segment. Second, the synapses are inserted in every segment that crosses through a region between 170 and 190 $\mu$m below or above the soma; these regions correspond to the right and left synaptic groups in the input-order detection task. For every 5 $\mu$m of the dendritic segment, one synapse is inserted. By convention, we call the top layer where synapses are inserted the right, and synapses in the bottom layer the left. The taper-rate, the location of the synapses, and the passive electrical properties (which are also required to perform electrophysiological simulations) were kept constant. Third, the conductances are inserted in a manner analogous to the dendritic diameter. An initial density is assigned to the stem of the dendritic tree, and the density of the next segment is computed by multiplying the density of the previous segment with a constant value. This constant factor is contained in the genome and therefore also subject to optimization. Depending on the relationship of this constant to the segment length, the resulting distribution of active conductances can be constant, linear, sub- or supra-linear as a function of the dendritic path length.

The choice for spatially restricted 2D synaptic zones is motivated twofold. First, there is biological evidence that axons project into specific areas in which synapses occur between dendrites and axons (Van Horck et al. 2004). Frequently synapses of one pathway are formed onto neurons only in a subspace of the space filled by the nucleus or cortex these neurons are a part of. An example is the entorhinal afferents to the hippocampus, which only synapse to the distal apical dendrites (in the superficial layer of the hippocampus) of the hippocampal pyramidal neurons (Johnston and Amaral 2004).

Second, for the sake of the simulation, we fixed all experimental parameters except for the time lag $\Delta t$. Only by fixing all other parameters, we are confident that the observed effects can be attributed to the desired computational function and the systematic sweep over the free parameter.

However, while we are confident that this placement of synapses is biologically realistic, we are aware that this is a relatively strong constraint and that there are alternative rules of synapse placement. An example is the precise targeting of cortical pyramidal neurons’ axon hillocks by axo-axonic interneurons (Somogyi et al. 1998). Therefore, we also developed a method of synapse-placement in which we placed the synapses on the dendrites in a manner analogous to the ionic conductances. For each dendrite, one parameter specified the initial synaptic density and one parameter the value this density was multiplied with at the beginning of each new segment. As in the case of the ionic conductances, this allowed for a sub-linear, linear, or supra-linear gradients of synaptic densities as a function of the path length from the soma. The number of synapses in
a dendritic segment was determined by rounding the density value, and synapses were spaced evenly. The unitary conductance of each synapse was set to 20% of the value in the other simulations (0.1 nS) to allow a finer graduation of synaptic conductances.

Next to the passive model neurons, we also optimized model neurons containing active conductances. These model neurons included an A-type potassium current \( I_{KA} \) and a T-type calcium current \( I_{CaT} \), or both. We chose \( I_{KA} \) as a representative of the large class of potassium currents present in neurons\(^2\). In addition, its inactivation over time makes it an interesting current to investigate in the context of a time-critical task, like input-order detection. \( I_{KA} \) has been implicated in the dendritic integration of EPSPs (Ramakers and Storm 2002) and back propagation of action potentials and has been termed a “dendritic shock absorber” (Hoffman et al. 1997).

We also chose \( I_{CaT} \) as a representative of a large class of neural currents, depolarization activated, and depolarizing currents shaping the electrophysiological properties of neurons. As the A-type potassium current, the T-type calcium current inactivates over time and thus is an interesting candidate for influencing a time-critical task. This current is involved in neural dynamics such as the dendritic integration of EPSPs (Schiller et al. 1997) and oscillatory activity (Huguenard and Prince 1994).

**Multi-compartmental simulations**

The neuronal morphologies created in this way are then translated into multi-compartmental models. The dendrites are divided into small compartments assumed to be isopotential for the sake of the simulation (Rall 1995). These compartments were simulated by a set of coupled ordinary differential equations:

\[
c_m \frac{dV_n}{dt} = g_l(V - E_l) + g_a \Delta V_{n-1} + g_a \Delta V_{n+1}
\]

where \( c_m \) is the membrane capacitance, \( V_m \) the membrane potential of the compartment \( n \), \( g_l \) the leak conductance, \( E_l \) the leak reversal potential, and \( g_a \) the axial resistance. The number of compartments was set to 1 per 5 \( \mu \)m (rounded up toward the next odd number). In segments with a synapse, the following term was added to the right-hand side of the previous equation:

\[
\left( e^{-\frac{t}{\tau_2}} - e^{-\frac{t}{\tau_1}} \right) g_{syn}(V - E_{syn})
\]

where \( \tau_1 \) and \( \tau_2 \) are the synaptic time constants and \( g_{syn} \) is the maximum conductance of the synapse. During the simulations, all synapses of each group (left and right) were activated simultaneously.

When active conductances were included in the model, an additional term was present:

\[
g_{Km} h(V - E_K),
\]

\[
\frac{dm}{dt} = \frac{m - m_\infty}{\tau_m},
\]

and an exponential dependence of \( \alpha \) and \( \beta \) on the voltage and a temperature correction factor. The parameters and model description files for \( I_{KA} \) and \( I_{CaT} \) were
taken from (Migliore et al. 1995), and were originally designed to describe the currents in hippocampal CA3 neurons. The parameter values for these equations are given in Table II. The equations describing the multi-compartmental models were solved numerically with the fixed time-step Cranck–Nicholson algorithm (time-step = 0.025 ms) or the adaptive time-step CVode algorithm (error < 10^{-5}) using NEURON 5.9 (Carnevale and Hines 2006).

Fitness assessment

Our aim was to optimize neurons for the computational task of input-order detection. As mentioned before, the model neuron should react as strongly as possible to the activation of two groups of synapses in a temporal order, but as weakly as possible in the inverse order. This ability can be expressed quantitatively by means of the following fitness function $F$; larger values are better.

$$
F = \begin{cases} 
-1 \times \frac{M_{rl}}{M_{lr}} & \text{while } \frac{M_{rl}}{M_{lr}} > 0.9 \\
100 - 10 \times \frac{M_{rl}}{M_{lr}} - \alpha \left( \sum l / \sum l_0 \right) & \text{otherwise}
\end{cases}
$$

With, $M_{lr}$ the compound EPSP amplitude in the preferred order, $M_{rl}$ in the nonpreferred order, $\sum l$ the the sum of all the dendritic lengths, $\sum l_0$ the minimum required dendritic length for two dendrites to reach the synaptic zones on both sides, and $\alpha$ is a weighing factor.

The ratio $M_{rl}/M_{lr}$ has to be as small as possible and results in higher values for $F$. At the beginning of the optimization process, the achieved input-order detection (expressed in $M_{rl}/M_{lr}$) is high. To guide the optimization process, we first optimize for a reasonably good performance, which we define as a ratio $M_{rl}/M_{lr} \leq 0.9$. While the performance is not sufficiently (i.e., $M_{rl}/M_{lr} > 0.9$), the fitness function returns a negative value which goes to zero when improving. Only when a reasonably good performance is achieved, the full fitness function is used and a positive value is

<table>
<thead>
<tr>
<th>Electrophysiology</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Simulated time</td>
<td>50 or 200 ms</td>
</tr>
<tr>
<td>Integration step</td>
<td>0.025 ms or adaptive</td>
</tr>
<tr>
<td>$R_a$</td>
<td>100 $\Omega$ cm</td>
</tr>
<tr>
<td>$C_m$</td>
<td>0.8 $\mu$F cm$^2$</td>
</tr>
<tr>
<td>$r_{syn}$</td>
<td>on: 0.2 ms off: 1 ms</td>
</tr>
<tr>
<td>$V_m$ initial</td>
<td>$-70$ mV</td>
</tr>
<tr>
<td>$g_{pas}$</td>
<td>0.00002 pS $\mu$m$^{-2}$</td>
</tr>
<tr>
<td>$E_{pas}$</td>
<td>$-70$ mV</td>
</tr>
<tr>
<td>$g_{syn}$</td>
<td>0.5 nS per synapse (1 synapse 5 $\mu$m dendrite in the synaptic zones)</td>
</tr>
<tr>
<td>$T$</td>
<td>37$^\circ$C (correction factor for conductance kinetics)</td>
</tr>
</tbody>
</table>

The active parameters can be found in Migliore et al. 1995 and were obtained from ModelDB (http://senselab.med.yale.edu/modeldb/).
returned for \( F \) (which approaches +100). The full fitness function penalizes for larger structures while still optimizing for better (lower) \( M_{rl}/M_{lr} \). Without this two-stage fitness assessment, the optimization algorithm would optimize the size of the structure without optimizing for the desired function. Hence, the rationale behind splitting optimization in two stages is that first a reasonably well-performing solution has to be found before optimizing an additional feature (the size of the neuron). This is done to keep the optimization procedure from getting stuck in local optima early in the search and is a common practice with evolutionary algorithms (Torben-Nielsen 2007).

Additionally, several heuristics were included in order to avoid trivial or biologically implausible solutions. The dendritic structures were required to have a minimum of 15 segments, one bifurcation, and one synapse on both sides. A proportional penalty was given to structures that failed to meet these requirements and they were not tested in a physiological simulation. Also, the left and right EPSP amplitudes were required to be at least 2 mV at the soma and within a factor of four of each other. In the optimization runs with active conductances additional constraints were added to obtain plausible results: soma membrane potentials higher than 25 mV (\( V_m > -45 \) mV) were not allowed to avoid spikes, and, \( V_m \), soma had to be nonincreasing during the last five time-steps of the simulation. This was done to make sure that the fitness function was judging EPSPs, and not oscillatory or intrinsically excitatory potentials.

**Genetic algorithm**

We employed GAs for the optimization of model neuron morphologies. GAs were chosen as an optimization method because they are proven to be powerful in problems with large and rough solution spaces (Koza 1992; Boers and Sprinkhuizen-Kuyper 2001; Mitchell 2001). These algorithms exploit the principle of survival of the fittest. Candidate solutions to a certain problem (individuals, neuron models in this study) are encoded in individual parameter sets. First, a population is initialized with random genomes. Then every individual (phenotype) is generated from its genome and tested for performance (fitness) in the task under consideration, input-order detection. The fitness function (see above) assigns a fitness value to each individual. The individuals with the highest fitness value in a population are then used to construct a new population from the old one. This is done in two steps: selection and the introduction of variation. Subsequently, the process starts again with the generation and testing of individuals (Figure 2). We will now describe each of these stages in more detail.

Neural morphologies are encoded in parameter sets of 9- to 13-tuples, each of which corresponding to the basic parameters of the morphogenetic algorithm (Table I) for a single dendritic tree. Since the number of dendritic trees was limited between two and four, each genome contained minimally 18 (2 \( \times \) 9) to maximally 52 (4 \( \times \) 13) parameters. Individual genomes were generated from these parameters by the morphogenetic algorithm described above.

After the evaluation of the numerical simulations, we used \([\mu, \lambda]\) selection (Black 1996). In this method, \( \mu \) is the population size and \( \lambda \) is the number of individuals selected for the next generation. The best \( \lambda \) individuals are selected and used to
make a new generation. By means of reproduction and mutation, \( \lambda \) offspring are generated from \( \mu \) parents.

Variation is introduced into the genomes by two different genetic operators: crossover and mutation. Single-point crossover creates a descendant from two parent genomes. A descendant’s genome will consist of exactly one part from both parents. When the size of the parent genomes is unequal, the descendant’s genome’s length will be equal to the longer of the two. The crossover point is chosen randomly.

Mutation is the pseudo-random modification of an individual’s genome before it is included in the new population. We employed three different mutation strategies. First, argument mutation modifies a parameter by subtracting or adding...
a small number. This was done by drawing a random sample from a Gaussian
distribution with $\mu = \text{current value}$ and $\sigma = 0.05$ truncated by two standard
deviations on both sides. The second mutation strategy is the introduction of
a pseudo-random dendritic tree. The third mutation strategy deletes a complete
tree. When introducing new parameters, a new $n$-tuple (9 to 13-tuple, Table I) was
pseudo-randomly generated from the default values and added to the existing
genome. Each $n$-tuple contained the parameters necessary for the construction of
exactly one dendritic tree originating from the soma. For example, in the case of
passive neurons, a genome with 18 parameters would code for a neuron with two
dendritic trees. After the addition of nine more parameters, the new genome, now
containing 27 parameters, would code for a neuron with three dendritic trees.
Parameter deletion and introduction therefore have to occur in groups of nine
(for passive neurons; in groups of 11 or 13 in the case of neurons with active
conductances) in order for the genome to make sense to the morphogenetic
algorithm.

As a result of the genetic operators, the new population consisted of modified
descendants of the best performing individuals of the previous generation. The
iteration of this procedure with 200 individuals for 650 generations gave rise
to neural morphologies optimized for performing the task specified in the fitness
function. The parameters used in the GA were chosen on a heuristic basis to achieve
the convergence of neural morphologies and are given in Table III.

**Analysis of morphologies**

We analyzed the morphologies of the optimized model neurons for features constant
across all neurons and for features varying with $\Delta t$ the neuron was optimized for.
We measured 17 morphological features for the complete dendritic tree, the
dendritic trees having synaptic inputs on either side, summing to $3 \times 17$ features.
In addition, we recorded another nine global features (Table IV) thus summing
to a total of 60 morphological features describing each optimized neuron. Table IV
lists the recorded features.

These features were then systematically analyzed using two statistical techniques:
Pearson correlations, and Monte-Carlo sensitivity analysis (Helton et al. 2004).
The former is used to identify correlations between features (task-specific, in common for all the neurons performing input-order detection), while the latter is used to identify systematic variation of features with varied $\Delta t$ (time-specific, specific for neurons doing input-order detection with a given $\Delta t$). These can be applied to pairs of features or pairs of linear combinations of specific features. Both methods are explained below.

**Pearson-correlation matrices.** A linear correlation between pairs of features can be computed with the Pearson product-moment correlation (or short, Pearson correlation). Thus, it can be investigated if two features have the tendency to

<table>
<thead>
<tr>
<th>Feature number</th>
<th>Feature name</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$f_{d-x}$</td>
<td>Fractal dimension of tree $x$</td>
</tr>
<tr>
<td>2</td>
<td>$n_{o-stems-x}$</td>
<td>Number of stems of tree $x$</td>
</tr>
<tr>
<td>3</td>
<td>$n_{o-terms-x}$</td>
<td>Number of terminal tips of tree $x$</td>
</tr>
<tr>
<td>4</td>
<td>$L_{-tot-x}$</td>
<td>Total length of tree $x$</td>
</tr>
<tr>
<td>5</td>
<td>$bi_{ffs-x}$</td>
<td>Number of bifurcations of tree $x$</td>
</tr>
<tr>
<td>6</td>
<td>$L_{-biff-x}$</td>
<td>Average inter-bifurcation length of tree $x$</td>
</tr>
<tr>
<td>7</td>
<td>$Cnt_{-btn-x}$</td>
<td>Average dendritic contraction of tree $x$. Contraction is computed as the ratio of the Euclidean distance to a terminal tip divided by the path length.</td>
</tr>
<tr>
<td>8</td>
<td>$Path_{-vs-distance-x}$</td>
<td>Contraction reformulated from tree $x$</td>
</tr>
<tr>
<td>9</td>
<td>$Frg$</td>
<td>Average fragmentation of tree $x$. Fragmentation is defined as the number of compartments in a segment</td>
</tr>
<tr>
<td>10</td>
<td>$D_{-term-x}$</td>
<td>Average dendritic diameter computed over all terminal segments of tree $x$</td>
</tr>
<tr>
<td>11</td>
<td>$D_{-all-x}$</td>
<td>Average dendritic diameter computed over all segments of tree $x$</td>
</tr>
<tr>
<td>12</td>
<td>$L_{-term-x}$</td>
<td>Average segment length of the terminals of tree $x$</td>
</tr>
<tr>
<td>13</td>
<td>$Order_{-x}$</td>
<td>Average order of bifurcation points in tree $x$</td>
</tr>
<tr>
<td>14</td>
<td>$TropismF_{-x}$</td>
<td>Average soma-tropism factor of tree $x$. The tropism factor is defined as the ratio of the segment length divided by the distance traveled away from the soma (of that segment)</td>
</tr>
<tr>
<td>15</td>
<td>$L_{-Segments-x}$</td>
<td>Average segment length of tree $x$</td>
</tr>
<tr>
<td>16</td>
<td>$L_{-path-avg-term-x}$</td>
<td>Average path length from the soma to the terminal tips of tree $x$</td>
</tr>
<tr>
<td>17</td>
<td>$L_{-dist-avg-term-x}$</td>
<td>Average Euclidean distance from the soma to the terminal tips of tree $x$</td>
</tr>
</tbody>
</table>

1–17 measured for the complete tree, and the left and right dendrites.

<table>
<thead>
<tr>
<th>Feature number</th>
<th>Feature name</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>$\Delta t$</td>
<td>Time interval between two pulses</td>
</tr>
<tr>
<td>53</td>
<td>$Ratio$</td>
<td>Resulting ratio as defined in the fitness function</td>
</tr>
<tr>
<td>54</td>
<td>$totSyn$</td>
<td>Total number of synapses in a neuron</td>
</tr>
<tr>
<td>55</td>
<td>$synLeft$</td>
<td>Number of synapses in the left subtree</td>
</tr>
<tr>
<td>56</td>
<td>$synRight$</td>
<td>Number of synapses in the right subtree</td>
</tr>
<tr>
<td>57</td>
<td>$psL$</td>
<td>Average path length to the synapses in the left subtree</td>
</tr>
<tr>
<td>58</td>
<td>$psR$</td>
<td>Average path length to the synapses in the right subtree</td>
</tr>
<tr>
<td>59</td>
<td>$diamL$</td>
<td>Average stem diameter of the left subtree</td>
</tr>
<tr>
<td>60</td>
<td>$diamR$</td>
<td>Average stem diameter of the right subtree</td>
</tr>
</tbody>
</table>
decrease or increase together; or whether the two features behave in opposite
direction where one is increasing while the other is decreasing. Formally, the
Pearson correlation is defined as follows (assuming nS samples).

\[
r(X, Y) = \frac{\sum_{i=1}^{nS} (x_i - \bar{x})(y_i - \bar{y})}{\left[\sum_{i=1}^{nS} (x_i - \bar{x})^2\right]^{1/2} \left[\sum_{i=1}^{nS} (y_i - \bar{y})^2\right]^{1/2}}
\]

here, \( r(X, Y) \) is on the range \([-1, 1]\) with positive values indicating that \( X \) and \( Y \) increase/decrease together, and negative values indicating that \( X \) and \( Y \) move away from each other. In addition to analyzing the correlation between two features \( X \) and \( Y \), we also investigate the correlation between \( \Delta t \) and the ratio between all features, i.e., \( X \) is set to \( \Delta t \) and \( Y = \text{feature1/feature2} \). This way, we can investigate the potential trend between the time lag and combinations of two other features. The Pearson correlation thus elucidated if any correlations of morphological features or correlations of ratios formed by these features are preferentially found in model neurons optimized for input-order detection, i.e., which correlations of morphological features are necessary for performing this computational task.

Monte-Carlo sensitivity analysis. We also wanted to investigate whether specific features of the optimized neurons varied as a function of \( \Delta t \). Generally, such a tendency can be discovered by fitting a curve to the values of the feature of interest against \( \Delta t \). Unfortunately, the small number of data points (four for each \( \Delta t \)) caused by the large requirements of processor time for obtaining each point did not allow for straightforward curve-fitting techniques. Therefore, we used Monte-Carlo sensitivity analysis to compensate for the small number of data points. In this technique, it is assumed that the obtained results are normally distributed and surrogate data points are generated by sampling from a normal distribution fitted to the observed data. Thus, for each \( \Delta t \), a new point was sampled from these distributions and a curve was fitted. A great number of curves were generated this way. The goodness-of-fit (i.e., signal-to-noise ratio) of all generated curves compared to the original curve determined the confidence in the original fit. When the fit was good, the slope of the curve could be used to identify morphological tendencies as a function of \( \Delta t \).

We used standard polynomial curve fitting, specifically the first (linear) and the second (quadratic) polynomial. The higher order polynomials would evidently give rise to better fits, but the results would be unreliable due to the low sample size. Goodness-of-fit was determined by taking the signal-to-noise ratio of the slope, or the actual values of the sampled data.

Results

We optimized model neurons for performing input-order detection with a series of intervals (\( \Delta t = 5–30\) ms, in 5 ms steps) between the arrival of the inputs in the preferred and non-preferred temporal order. The model neurons had an elaborate dendritic morphology, and either had passive membrane properties or contained an A-type potassium current (\( I_{KA} \)), a T-type calcium current (\( I_{CaT} \)), or both.
These models of optimized but artificial neurons were of a conceptually opposite type of the neurons modeled after naturally occurring neurons; normally, a neuron's structure is known, but its function unknown. In contrast, the function of our optimized model neurons is known with certainty. For each of them, we analyzed the morphology and the electrophysiological dynamics underlying the function.

We found morphological features and current distributions constant across all neurons and systematically varying with $\Delta t$. We also found passive and active electrophysiological dynamics conserved across all neurons and systematically varying with $\Delta t$. In the “Supplementary material” we present an approach using dendritic cable theory to predict the theoretically optimal performance. With this approach we demonstrated the near-optimality of the numerically obtained optimized neuron models. In the next subsections, we present the results obtained by the (1) passive model neurons, (2) model neurons containing $I_{KA}$, (3) model neurons containing $I_{CaT}$, and (4) model neurons containing both $I_{KA}$ and $I_{CaT}$.

**Passive model neurons**

We initially optimized neurons with passive membrane properties. The resulting morphologies are all illustrated in Figure 3. Note that this figure is intended to give a global overview of all optimized neurons. More detailed illustrations of the optimized model neurons are presented in later figures. We also encourage the reader to inspect the 3D morphologies and conductance distributions using the provided NEURON simulations (see Supplementary material).

The passive model neurons are illustrated in the left column of Figure 3. A common feature of all the optimized neurons was that the two groups of synapses were localized on different dendritic trees. In a quarter of cases, the synapses were

![Figure 3. Morphological features of neurons optimized for input-order detection. Best performing neurons from four optimization runs for six different $\Delta t$'s. Shown (columns from left to right) are passive neurons and neurons containing $I_{KA}$, $I_{CaT}$, and $I_{KA}$ and $I_{CaT}$. The blue and red circles represent the left and right synapses. Conductance densities are color-coded ($I_{KA}$, left, 0–0.22 pS $\mu$m$^{-2}$, $I_{CaT}$, right, 0–0.0022 pS $\mu$m$^{-2}$).](image-url)
located only on one dendrite for each group. All evolved neurons (active and passive) had a single left branch and only 16% of the neurons had more than one dendritic branch receiving input from the right side. Almost half of the neurons (41%) had an additional short dendritic tree devoid of synapses. While such configurations, with synapses restricted to only parts of the dendrites, are not typically found in nature, they make sense in the context of a neural model performing a single task. The situation we are dealing with here is akin to a model of a CA1 pyramidal neuron responding to the Schaffer collateral inputs to its apical dendrites, without taking other excitatory or inhibitory inputs into account.

Visually, the evolved morphologies appear realistic and resemble certain types of hippocampal interneurons (Figure 4). Their contraction rates (Euclidean distance to a terminal tip/path length, a measure of the dendritic curvature) are comparable in range to those of spinal cord motor neurons and cerebellar granular neurons (Table V).

In order to quantify the morphological features present in all neurons and the morphological tendencies emerging when the neurons were optimized for increasing $\Delta t$, we used Pearson correlation matrices (Figure 5a) and Monte-Carlo sensitivity analysis (Figure 5b) on all morphological parameters and all ratios of two parameters. We found that the ratio of length/diameter of the dendrites carrying the left synapses strongly decreased with increasing $\Delta t$ (Figure 5c). Furthermore, we found that in all neural input-order detector models, the ratio of the number of synapses between the two groups (activated first/second) was relatively constant at value ($#left \approx 2 \times #right$, Figure 5d).
These correlations were, however, only a fraction of the total correlations or tendencies found. The large number of trivial correlations was caused by the simplicity of the evolved neurons: the overall morphological blue-print was one thick and short dendrite, one thin and long dendrite, and one extra dendrite devoid of synaptic inputs functioning as extra current sink. As a result of this observed

Table V. Contraction rates of the artificial passive model neurons generated in this study, rat hippocampal granule neurons and cat spinal cord motor neurons.

<table>
<thead>
<tr>
<th>Neuron models, this study</th>
<th>Rat hippocampal granule neurons</th>
<th>Cat spinal cord motor neurons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>0.6</td>
<td>0.62</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.999</td>
<td>1</td>
</tr>
<tr>
<td>Mean</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.007</td>
<td>0.05</td>
</tr>
</tbody>
</table>

The contraction rate is the Euclidean distance to the tip of the dendrite divided by the path distance, and a measure of dendritic curvature. The morphologies of the real cells were retrieved from the NeuroMorpho.org repository.

Figure 5. Morphological analysis of optimized passive input-order detector model neurons. (a) Covariance matrix of the morphological features of these optimized neurons. Feature numbers correspond to Table IV. (b) Gaussian resampling of the ratio as a function of $t/C_1$. (c) Number of left and right synapses as a function of $t$. (d) Length/diameter of the dendrite carrying the left synapses as a function of $t$.

These correlations were, however, only a fraction of the total correlations or tendencies found. The large number of trivial correlations was caused by the simplicity of the evolved neurons: the overall morphological blue-print was one thick and short dendrite, one thin and long dendrite, and one extra dendrite devoid of synaptic inputs functioning as extra current sink. As a result of this observed
simplicity, many correlations were trivial; a substantial part (20 out of 60) of the morphological features were always correlated to each other because they are constant. In addition to these trivial correlations and tendencies, we also found a number of correlations that had no clear functional relevance. For instance, in optimized passive neurons there is a strong correlation between the order of the whole tree and the number of bifurcations on the left tree; a description of these is omitted. The morphological features and correlations observed for the passive neurons held for the active neurons as well.

After the morphological analysis of the optimized neurons, we focused on their functional characteristics and we assessed the performance which is determined by the ratio between the amplitude of the EPSP in preferred direction divided by the amplitude of the EPSP in the other order. Hence, higher values are better. The best performance of all passive model neurons was obtained for a $\Delta t$ of 20 ms at a ratio of 1.45 between the EPSPs evoked in the preferred and nonpreferred order (Figure 9a). The poorest performance was observed at a $\Delta t$ of 5 ms with a ratio of 1.22.

How do the morphological features found in the model neurons contribute to the computation of input-order detection? A common pattern of electrophysiological activity was observed in all the optimized neurons (Figure 6). In the preferred temporal order, the left synapses on the thin dendrite were activated first. Due to the

![Diagram](image)

Figure 6. Electrophysiological dynamics of passive neurons performing input-order detection. (a) Morphology and synapse location of the best-performing neuron (out of four optimizations) for input-order detection with $\Delta t=15$ ms. (b) EPSPs at the sites of the synapses (left, right) and at the soma (center) when activated in the preferred (top) and the nonpreferred (bottom). The colors of the voltage traces correspond to the groups of synapses activated to cause the EPSPs.
length and low diameter of the left dendrite, the EPSP evoked by its synapses was significantly low-pass filtered on its path to the soma. Therefore, the peak voltage of this EPSP was delayed for an interval close to $\Delta t$ the neuron was optimized for. In this way, the second EPSP, evoked by the right synapses, started close to the peak of the first EPSP, thus maximizing the compound EPSP's amplitude. If the EPSPs were evoked in the inverse order, right before left, the right EPSP was not low-pass filtered nearly as much, and the left EPSP, evoked $\Delta t$ later, started below its peak on its downward slope. From there, the left EPSP rose to a voltage just under the peak of the right EPSP. Thus, the compound EPSP did not reach a peak higher than the peak of the right EPSP alone. Therefore, the computation was based on two aspects of the neural dynamics: One was the ($\Delta t$ dependent) difference in low-pass filtering by the dendrites carrying the left and right EPSPs. The other was the difference in the amplitudes of the EPSPs, adjusted so that the left EPSP did not rise higher than the right EPSP when following it. These two aspects of neural dynamics were based on two corresponding features of the neural morphology, the high (and $\Delta t$ dependent) length/diameter ratios of the dendrites carrying the left synapses and the relation between the numbers of left and right synapses (Figure 5c and d).

The extra dendrite devoid of synapses effectively added surface area to the soma and made it a larger current sink. Optimized model neurons with this seemingly redundant dendrite were poorer input-order detectors with this dendrite removed.

Even though a number of individual parameters remained relatively constant or changed systematically as a function of $\Delta t$, the dynamics involved in input-order detection nevertheless resulted from the complex interplay between several emergent features. Most importantly, in all neurons, the left dendrites were stronger low-pass filters than the right dendrites, both with respect to amplitude attenuation and the phase shift. The precise interplay between the effect of the dendritic low-pass filtering on the time to peak and amplitude of the EPSPs and the initial EPSP amplitude (due to the number of synapses) gave rise to the optimal performance in input-order detection.

We also tested the tuning of these neurons by taking the best performing neurons from each optimization run. Each of these neurons was optimized for input-order detection at one $\Delta t$ between the activation of the left and the right groups of synapses. We now tested each of these neurons for input-order detection for all $\Delta t$'s, ranging from 0.1 to 45 ms (in steps of 0.1 ms). In fact, all neurons performed best within 2.5 ms (mean: $\pm 0.85$ ms) of the $\Delta t$ they were optimized for (Figure 7).

One set of simulations was run with the synapse-placement method in which we inserted the synapses not when the dendrites entered a target location, but as determined by parameters directly subjected to optimization by the GA. This was done order by order to assess how much of an influence the method of inserting synapses has on the outcome of the optimizations. When optimizing neurons for input-order detection at $\Delta t = 10$ ms, the resulting morphologies qualitatively resembled the neurons we obtained in simulation where the location of synapses was constant and not optimized (Figure 8). Each of them equally had at least one thick and one thin dendrite, and the synapses activated first in the preferred order were preferentially placed on the thin dendrite. Thus, the same electrophysiological principle, differential low-pass filtering, was employed to perform spike-order detection.
However, there were some minor differences in the dendritic morphologies: The synapses activated first/second in the preferred order were mainly, but not exclusively placed on the thick/thin dendrites, and they were distributed along the whole length of the dendrites. The dendrites were not oriented at an angle around 180° away from each other, as they were not required to extend into juxtaposed synaptic zones. These morphological features do not (dendrite orientation) or only moderately (relaxed synapse placement) influence the electrophysiological dynamics, which we deemed similar enough to the neurons’ obtained with the

Figure 7. Input-order detector performance (EPSP ratio with left/right inputs activated first, normalized to peak performance) of neurons optimized for Δt’s from 5 to 30 ms. Each neuron was tested for input-order detection a range of Δt’s, from 0 to 45 ms (step size 0.1 ms, x-axis). The Δt’s the neurons were optimized for is indicated above the plot.

Figure 8. Passive neurons optimized for spike-order detection with Δt = 10 ms, with synapse placement directly subject to the optimization. Synapses were inserted according to densities encoded in each of the neurons’ parameter sets.
zone-based method of inserting synapses. Therefore we continued to use the latter method only in the remainder of this study.

These results confirm and extend the insights gained in a previous study with simpler, equally passive, model neurons (Stiefel and Sejnowski 2007). In the next stage of this study, we included active currents in the repertoire of the model neurons we optimized.

Model neurons containing an A-type potassium current

The A-type potassium current, $I_{KA}$, is an inactivating, hyperpolarizing current with a half-activation voltage around value $-55 \text{ mV}$ (Hille 2001). We next investigated how the inclusion of this current in the repertoire of the GA would influence the structure of the neurons optimized for input-order detection. Thus, in addition to optimizing neural morphology, we also optimized the distribution of $I_{KA}$ conductances.

The morphology of the optimized neurons containing $I_{KA}$ was qualitatively similar to the morphologies of the passive neurons but some quantitative differences were observed (Figure 3, second column). While only 25% of the passive neurons had more than two branches, most neurons containing $I_{KA}$ (75%) had an extra dendrite devoid of synaptic inputs. As in the passive neurons, these dendrites acted effectively to increase the effect of the soma as current sinks. Additionally, in most cases the membranes of the dendrites devoid of synapses contained a significant amount of $I_{KA}$ conductance. Removing these dendrites reduced the neuronal performance in input-order detection.

The most important observation is that while passive neurons performed poorly for fast $\Delta t$’s (5 and 10 ms) the introduction of $I_{KA}$ significantly increased the performance for these $\Delta t$’s while the results for slower $\Delta t$’s remained unchanged (Figure 10a). The optimized neurons for fast $\Delta t$’s contained the highest conductance allowed by the morphogenetic algorithm ($0.2 \text{ S cm}^{-2}$), almost uniformly distributed over the thick dendrite. This way, the EPSP resulting from the first pulse in the nonpreferred order will have a shorter half-width, as the decaying phase will be “shaved off” (the decay was accelerated) by $I_{KA}$. Therefore, when the synapses were activated in the nonpreferred order, the second EPSP started at a lower initial voltage as compared to the same neuron without $I_{KA}$ and the compound EPSP will sum to a lower maximum (Figure 9a and c). For slower $\Delta t$’s (>15 ms), the first EPSP will decay sufficiently fast due to its passive properties and no active shortening of the EPSP is required. Hence, the optimized neurons for slower $\Delta t$ hardly contained any $I_{KA}$ conductance. These results demonstrate a qualitative difference in the conductance distributions of neurons optimized for quantitatively different variants of one computational function. As in the case of the passive neurons, these neurons performed input-order detection best close to the $\Delta t$’s they were optimized for. However, the discrepancy was somewhat larger and always negative (mean: $-6.4 \text{ ms}$). The removal of $I_{KA}$ lead to a shift of the optimal performance to slower $\Delta t$’s, (+13.4 ms relative to the optimized $\Delta t$), consistent with the role of this current in speeding up the decay of the EPSP evoked second in the preferred order (Figure 10b).
Model neurons containing a T-type calcium current

The T-Type calcium current, $I_{\text{CaT}}$, is an inactivating, depolarizing current with a half-activation voltage around value $-40 \text{ mV}$ (Hille 2001). We next investigated how the inclusion of this current in the model neurons influences the outcome of the optimizations for input-order detection.

As observed in the previous simulations, the neurons had a thin and a thick dendrite carrying the left/right synapses, respectively. In some cases neurons had an extra dendrite devoid of synapses, carrying additional $I_{\text{CaT}}$ and acting as a current sink.

Compared to the performance of the passive and $I_{\text{KA}}$ containing neurons, the neurons optimized for slower $\Delta t$'s performed better (Figure 10a). For slower $\Delta t$'s, the thin and long dendrite contained a lot of conductance strongly localized around the sites of the synaptic inputs (i.e., the GA found an exponential distribution for the current density, Figure 3, third column). The localized $I_{\text{CaT}}$ conductance is activated by the first EPSP in the preferred order and the resulting depolarization amplifies and temporally extends the EPSPs. Consequentially, the second EPSP will start almost exactly at the peak of the first EPSP which results in a high-amplitude compound EPSP (Figure 9b and d). For faster $\Delta t$'s, a sustained first pulse will have less of a functional advantage, as passive filtering alone can sufficiently
extend the EPSP. The clustering of $I_{CaT}$ conductances in the left dendrite is thus observed to a lower degree in neurons optimized for faster $\Delta t$’s. This tendency is, however, not as strong as the lack of $I_{KA}$ in the opposite set of dendrites in the previous simulations. In most cases, a smaller amount of $I_{CaT}$ was present in the dendrite carrying the synapses preferentially activated first in neurons optimized for faster $\Delta t$’s. Also, the best neuron optimized for $\Delta t = 10$ ms contains a high amount of conductance in the thick dendrite (carrying the synapses preferentially activated second) acting as a booster of EPSP amplitude. This discontinuity in function–structure mapping indicates that several neural solutions are possible for the computational task under question, especially when the inclusion of an active current leads to more degrees of freedom (Goldman et al. 2001; Golowasch et al. 2002).

Again, we tested the performance of each optimized model neuron for a range of $\Delta t$’s, ranging from 0.1 to 45 ms. The $\Delta t$ of optimum performance was not as tightly coupled to the $\Delta t$’s the neurons were optimized for, but typically slower (mean: +16.9 ms). Even though the model neurons were the best found by the GA for their respective $\Delta t$’s, $I_{CaT}$ nevertheless improved the performance at slower

![Graph](image-url)

**Figure 10.** Input-order detection as a function of $\Delta t$ and active currents. (a) Summary of all the achieved performance levels. (b) Model neuron containing $I_{KA}$ optimized for input-order detection at $\Delta t = 5$ ms and tested at $\Delta t$’s, from 0 to 45 ms (step size 0.1 ms). The achieved ratio is plotted as a function of the $\Delta t$ tested. Gray line: achieved ratio in a neuron with the same morphology, but devoid of $I_{KA}$. (c), (d) Equivalent plots for optimized model neurons containing $I_{CaT}$ and $I_{CaT}$ and $I_{KA}$.
\( \Delta t \)'s even more. This divergence was more pronounced for faster \( \Delta t \)'s (<15 ms), while it was only \(-0.1\) ms for \( \Delta t = 25\) ms. Inversely to the observations in optimized neurons containing \( I_{KA} \), the removal of \( I_{CaT} \) after successful optimization with this current led to an optimal performance at faster \( \Delta t \)'s \((-7.3\) ms relative to the optimized \( \Delta t \), Figure 10c). This observation is consistent with the role of this current in slowing down the decay of the EPSP activated first in the preferred order.

**Model neurons containing both an A-type potassium current and a T-type calcium current**

In many real neurons, a multitude of currents interact in the integration of EPSPs in the dendrites (Migliore and Shepherd 2002). To investigate these interactions, we optimized neurons for input-order detection, which contained both \( I_{KA} \) and \( I_{CaT} \) in their dendrites. Based on our previous results, we expected that the \( I_{KA} \) would be involved in improving the neurons optimized for faster \( \Delta t \)'s, while \( I_{CaT} \) would be involved in improving the neurons optimized for slower \( \Delta t \)'s. To our surprise, the performance of the optimized neurons for every \( \Delta t \) was higher than in the simulations with only a single active conductance, which indicates a synergistic effect between the \( I_{KA} \) and \( I_{CaT} \) (Figure 10). This increase in performance was highest for \( \Delta t \)'s of more than 10 ms. In these cases, the performance was increased by both having \( I_{KA} \) conductances in the thick dendrite to decrease the compound EPSP in the nonpreferred order, and, \( I_{CaT} \) in the thick dendrite to boost the compound EPSP in the preferred order (Figure 3, right column). Interestingly, when comparing the passive neurons with those containing both active conductances, there was no performance increase for \( \Delta t = 10\) ms. This points toward the passive parameters being already very well suited to perform input-order detection with this time interval.

The best optimized neurons containing both active conductances display a wider variety of branching patterns. Possibly an elaborated morphology is required to allow for the required physiological complexities to perform the input-order detection task. Contrary to the case of the neurons optimized with \( I_{CaT} \) alone, the \( \Delta t \) with the optimum performance was locked to the \( \Delta t \) these neurons were optimized for (mean: \( \pm 4.2\) ms). Consistent with the result of the optimizations with only individual active currents, the removal of \( I_{KA} \) shifted the optimal \( \Delta t \) to slower values, the removal of \( I_{CaT} \) to faster values (Figure 10d).

**Discussion**

**Significance**

In this study, we optimized dendritic trees of model neurons for performing the function of input-order detection with a range of temporal intervals. The inclusion of variable and spatially heterogeneous densities of \( I_{KA} \) or \( I_{CaT} \) further improved the performance of these model neurons. This contributes to the understanding of dendritic computation and structure–function relationship in several ways, by showing that: (1) a systematic variation of the desired computation (changing \( \Delta t \)'s) leads to a systematic change in the morphologies of the optimized neurons.
This function to structure mapping is discontinuous: In optimized neurons, in response to quantitative variation of the desired computation (changing $\Delta t$'s), the distributions of $I_{KA}$ and $I_{CaT}$ are qualitatively different ($I_{KA}$ is prominent at faster $\Delta t$'s, $I_{CaT}$ at slower $\Delta t$'s). (3) $I_{KA}$ and $I_{CaT}$ were distributed in a different manner (gradients/hot-spots) according to their different interactions with passive membrane properties. (4) We also improved a method (Stiefel and Sejnowski 2007) for matching neuronal structure to function by improving the realism and complexity of the morphogenetic algorithm and including spatially heterogeneous active conductances. We expect this method to be useful in the future for the elucidation of a variety of function–structure relationship, especially in the light of ever increasing computer hardware resources.

In contrast to the previous work, which had focused on optimized wiring efficiency (Chen et al. 2006; Cuntz et al. 2007), we investigated the dendrites optimized for electrophysiological computations. We speculate that both biological needs shape the neural dendrites.

Electrophysiological and morphological principles involved

All neurons carried the synapses activated first in the preferred order on a long and thin dendrite, second in the preferred order on a short and thick dendrite. When optimizing passive neurons, we observed a constant relationship between the numbers of synapses in the two groups. We also observed a systematic variation of the length/diameter ratio of the thinner dendrite as a function of $\Delta t$. When optimizing for neurons containing $I_{KA}$ or $I_{CaT}$ on their dendrites, we still observed these trends, as well as additional ones.

When optimizing neurons with $I_{KA}$, this conductance was distributed differently in neurons optimized for a faster (5–15 ms) or a slower $\Delta t$ (20–30 ms). In the first case, the thick dendrite contained a large amount of $I_{KA}$ conductance along its entire length, while the other dendrites contained very little of it. The latter trend did not hold, however, for neurons optimized for longer $\Delta t$'s, where $I_{KA}$ played only a minor role. Thus, a quantitative change in the parameters of the computation to be performed led to a quantitatively different type of neurons.

Despite the fact that neurons with $I_{KA}$ or $I_{CaT}$ in their dendrites performed better than passive neurons, the morphological features of the dendrites were quantitatively similar. Thus, the active properties supplemented the computation performed by the passive properties. Removal of $I_{KA}$ shifted the optimal $\Delta t$ of the input-order detection task to longer intervals. The opposite happened when $I_{CaT}$ was removed: Then the optimal $\Delta t$ was shifted to shorter intervals. The neurons were transformed from input-order detectors specialized for $\Delta t$ to such detectors specialized for $\Delta t + 13.4$ ms and $\Delta t - 7.3$ ms, respectively. This shift in the temporal integration window is reminiscent of the effects of neuromodulators such as acetylcholine and dopamine on neurons, which influence the expression of active conductances on the dendrites (McCormick 1989; Seamans and Yang 2004). These effects are believed
to influence the computational functions of neurons, just as the removal or addition of $I_{KA}$ or $I_{CaT}$ did in our artificially created neurons.

An interesting difference between the distribution of $I_{KA}$ and $I_{CaT}$ was that $I_{KA}$ was spread out along the dendrite, while $I_{CaT}$ was concentrated at the site of the synaptic contacts. We argue that this is because $I_{KA}$ sharpens the EPSP waveform, and thus acts against passive dendritic filtering, whereas $I_{CaT}$ extends the EPSP waveform and acts in concert with it. Thus, $I_{KA}$ has to continuously counteract the dendritic low-pass filtering and must thus be present along the whole length of the dendrite. In contrast, the local patch of $I_{CaT}$ initially leads to a widening of the EPSP, which is then further flattened by passive dendritic properties on its path to the soma. Therefore $I_{CaT}$ is present only locally, which aids the specificity of its effect. Depolarizing and hyperpolarizing currents are thus principally different in their optimal dendritic distributions required for input-order detection, and possibly for other time-critical tasks as well. This observation is in accordance with the experimental findings and theoretical arguments, which have shown and proposed continuous distributions, often gradients, of many hyperpolarizing currents, such as $I_{KA}$ (Hoffman et al. 1997), $I_{KM}$ (Shah et al. 2002), $I_{leak}$ (Stuart and Spruston 1998), and $I_{H}$ (Stuart and Spruston 1998; Magee 1999). In contrast, to our knowledge, “hot spots” have only been reported or theorized of depolarizing currents such as $I_{Na}$ and $I_{Ca}$ (Traub and Llinás 1979; Tucker and Fettiplace 1995; Nevian et al. 2007).

In the case of the passive neurons, we have shown that the morphologies found by the GA are in the vicinity of the theoretically obtainable global optimum (see Supplementary material).

All of these morphological properties, conductance distributions, and resulting electrophysiological dynamics were found completely automatically by the optimization algorithm. They are completely emergent, as none of them was explicitly specified by us in the fitness function.

The way to connect these theoretical insights about morphology and electrophysiology necessary for performing a given computational function to experimental knowledge about neurons is to compare them to the artificial neurons obtained here. In this study, this was done by visually matching them to cortical bipolar interneurons (Figure 4). Predictions from the similarity between these classes of neurons are that (1) they are likely to be input-order detectors, (2) if present, depolarizing currents (like $I_{CaT}$) will be preferentially located on the thick dendrites, and (3) if present, hyperpolarizing currents (like $I_{KA}$) will be preferentially located on the thin dendrites.

In the future, we aim to establish a quantitative, algorithmic comparison between the optimized artificial neurons and reconstructed neurons from the brains of animals. After successful optimizations, an algorithm will scan neural morphology databases for similarities in dendritic structure.

**Function to structure mapping**

By optimizing model neurons for quantitative variants of a computational function, we have established a systematic mapping from an axis of function space to an axis of neural structure space. The axis runs along an increasing $\Delta t$ of the input-order detection function and maps onto four subspaces of neural structure-space,
which are passive neurons, and neurons containing $I_{KA}$, $I_{CaT}$, or both. The mapping onto the neurons containing $I_{KA}$ contains a discontinuity between 15 and 20 ms, as this current is much less important above 15 ms. The function–structure mapping we found is present in two forms: One is a lookup-table composed of the optimized neural morphologies the GA found. The other is a set of regularities derived from the analysis of these neurons, which can also be understood as rules for the construction of input-order detectors with a given optimal $\Delta t$. As we cannot exclude that a number of complexities and interdependencies between the morphological parameters escaped our analysis, the lookup-table is an inherently more precise function–structure mapping.

An important point in this context is that many neurons are likely not to perform only a single computation, but, depending on the context or neuromodulatory state, perform multiple computations. Moreover, these computations might be performed concurrently in different parts of the dendritic tree. Such multi-tasking within one structure is inherently difficult to grasp by human intuition alone, and we plan to make this one of the next topics we study with the inverse function–structure approach used here.

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Notes

[1] We use “model neurons” and “neurons” interchangeably in order to improve readability.

[2] $I_h$, in terms of its effect, also belongs in this class. While potassium currents are hyperpolarizing and depolarization activated, $I_h$ is a depolarizing and hyperpolarization activated. Because they have opposing activation and opposing effects, the result of both currents is similar.

[3] The GA nomenclature overlaps with the nomenclature of genetics. However, GAs are used here purely as an optimization procedure, not a model for genetics and biological evolution.
References


Supplementary material

Program code and simulation results

The simulation-program code and a package featuring the results of our optimizations are available from the authors upon request or from the Yale Senselab Model Database (http://senselab.med.yale.edu/modeldb/).

We encourage researchers to perform their own optimization runs using the simulation code. The code is all written in the Java programming language and requires Java and NEURON (http://www.neuron.yale.edu/neuron/) to be installed. A “readme” file is included in the zipped archive which explains how to reproduce or modify the simulations presented here.

The model neurons resultant from the optimizations presented in this article are provided in a package of NEURON-code. When executing “FUNCTION to STRUCTURE.hoc” a pull-down menu appears which allows the user to load any optimized model neuron (Δt 5–30 ms, omitting/including IKA and/or ICaT). When
loading the neuron, the task of input-order detection is simulated and the input and transfer impedances are automatically computed. The user can display the neuron’s morphology and conductance distributions with NEURON’s “model view” utility.

**Model neuron impedances**

The filter properties of the dendrites can be described by their frequency-dependent resistances, or impedances. Any signal originating in the dendrites, like an EPSP, will be shaped by these impedances. We can distinguish the input impedance (the transformation of the signal at the site of the synapses) and the transfer impedance (the transformation occurring on the path to the soma). Furthermore we can distinguish between filtering by the dendrites of the amplitude (the signal will be attenuated) and the phase (the signal will be delayed). These impedances interact with the number of placement of the synapses to enable the model neurons to act as input-order detectors. In Figure S1 we show the impedances of a passive and two active neurons (containing $I_{KA}$ and $I_{CaT}$). In the case of the neurons with active properties, we also show how the impedances change if the active conductances are removed.

**Analytic model of input-order detection**

**Aim.** Due to the finite number of generations and the numerical nature of the GA-based optimization, we cannot state with absolute certainty that the resulting model neurons were at or close to the global optimum. Therefore, we use the linear cable theory to find an analytical formulation for the morphology of a simplified neuron optimally performing input-order detection. We restrict ourselves to models involving only two dendrites, with synaptic input at their ends only. The dendrites are modeled using the linear cable theory. We consider a model composed of two standard lumped soma models. We assume that the depolarization measured at the soma is a linear sum of contributions from the two dendrites. The derivation of the model is largely based on equations from Tuckwell (2005a). Despite being simplified mathematical models, they can give a good indication how close our numerically optimized neurons are to the true optima for the desired computational function of input-order detection.

Here, we present the two-step mathematical construction of the analytical model. First, we show the “two semi-infinite cables” model, and then the “ball and stick” model. Subsequently, it is shown how to numerically evaluate the model to find the optimal values.

We use dimensionless time and length, $T = t/\tau_m$, $X = x/\lambda$, normalized by the time and space constants: $\tau_m = r_m c_m$.

**Two semi-infinite cables.** In terms of the dimensionless quantities $X$ and $T$, the cable equation for an infinite cable with no applied current is:

$$\frac{\delta V(X, T)}{\delta T} = \frac{\delta^2 V(X, T)}{\delta X^2} - V(X, T)$$
Figure S1. Frequency-dependent filter properties and their alterations in the presence of $I_{KA}$ and $I_{CaT}$. (a) passive model neuron (optimized for $\Delta t = 15$ ms) (b) model neuron containing $I_{KA}$ (optimized for $\Delta t = 5$ ms). (c) Model neuron containing $I_{CaT}$ (optimized for $\Delta t = 30$ ms). Right: Input impedance at the site of the synapses (thick lines) and transfer impedances from the synapses to the soma (thin lines as a function of frequency of the left (blue) and right (red) dendrites. Left: Morphology, synapse location and color coded $I_{KA}$ (0–0.22 pS $\mu m^{-2}$) and $I_{CaT}$ conductance density (0–0.0022 pS $\mu m^{-2}$).
We make use of the Green’s function for a semi-infinite cable, sealed at $X = 0$ (Equation 5.67 in Tuckwell (2005a)):

$$G(X, Y, T) = H(T) \frac{e^{-T}}{\sqrt{4\pi T}} \left[ \frac{e^{-(X-Y)^2}}{4T} - \frac{e^{-(X+Y)^2}}{4T} \right]$$

where $H()$ is the Heaviside function and $Y$ the normalized distance to the site of the current injection. Instantaneously, injecting a finite charge into the end results in a depolarization proportional to $G(X, 0, T)$. Let us approximate the depolarization measured at an electrotonic distance $l$ from the sealed end of a dendrite by $G(l, 0, T)$. Then the total depolarization measured resulting from synaptic inputs (current injections) induced at dimensionless times $T_1$ and $T_2$ at the ends of two dendrites of electrotonic lengths $l_1$ and $l_2$ with strengths in the ratio $1: \omega$ can be written as:

$$V_s(l_1, T_1, l_2, T_2, \omega, T) \propto G(l_1, 0, T - T_1) + \omega G(l_2, T - T_2)$$
The ratio of maximum depolarization for the cases of $T_1 = T_2 - \Delta T$ (synaptic input is first induced at the end of dendrite 1 and then, after a dimensionless time $\Delta t = \Delta t/\tau_m$, at the end of dendrite 2) and $T_1 = T_2 + \Delta T$ (the reverse) is:

$$R_i(l_1, l_2, \Delta T, w, T) = \frac{\max_{t>0} V_i(l_1, 0, l_2, \Delta T, w, T)}{\max_{t>0} V_i(l_1, \Delta T, l_2, 0, w, T)}$$

Note that this ratio depends only upon the electrotonic lengths of the dendrites, not on the length or diameter separately. If we denote the lengths of the dendrites by $L_1$ and $L_2$ and the respective diameters by $d_1$ and $d_2$, then we have:

$$l_z = \frac{L_z}{\lambda_z} = 2\sqrt{G_mR_i} \left( \frac{L_z}{d_z} \right)$$

where $R_i$ is the axial resistance and $z \in \{1, 2\}$. This model suffers from the fact that the synaptic input is modeled by a $\Delta$ function in time. Additionally, the induced voltages have no upper bound (they do not saturate). These assumptions are only viable if the dendrites are long and thin. The model is therefore useful, but restricted to cases with long, thin dendrites (or, to be more precise, large electrotonic lengths).

We drew two conclusions from the derivations pertaining to the semi-infinite cables. First, the ratio of the maximum depolarizations (i.e., voltage amplitudes), $R_i$, is a function of $l_1/\sqrt{d_1}$ and $l_2/\sqrt{d_2}$ only and particularly not of $L_1$, $d_1$, $L_2$, or $d_2$ separately. Therefore we will present the results of the numerical evaluations on 2D plots having axis: $l_1/\sqrt{d_1}$ and $l_2/\sqrt{d_2}$. Second, a more complex model is required to approximate performance as input-order detection of model neurons. We thus progress to a more complex ball and stick model to model the input-order detection function.

**Ball and stick model.** The response at a soma, at one end of a finite cable of electrotonic length $l$ and with sealed other end, to a current proportional to $H(T) T e^{(-aT)}$ is (Equation (6.122) in Tuckwell (2005))

$$V_l(l, d, T) \propto H(T) \sum_{n=0}^{\infty} \frac{A_n(l, d)}{1 + \lambda_n(l, d)^2 - a} \times \left[ T e^{(-aT)} - \frac{e^{(-aT)}}{1 + \lambda_n(l, d)^2 - a} + \frac{e^{(-T(1+\lambda_n(l, d)^2))}}{1 + \lambda_n(l, d)^2 - a} \right]$$

where $A_0(l, d) = \gamma(d)/(1 + \gamma(d)l)$,

$$\gamma(d) = \frac{d^{5/2}}{2d^2 \sqrt{G_mR_i}}$$

$d_s$ is the diameter of the soma (assumed to be spherical),

$$A_n(l, d) = \frac{2\gamma(d)}{\sin[\lambda_n(l, d)]} \left( \frac{\gamma(d)}{\lambda_n(l, d)} - \lambda_n(l, d)/l \right) + \cos[\lambda_n(l, d)]l(2 + \gamma(d)/l)$$

for $n > 0$, $\lambda_0(l, d) = 0$, and $\lambda_n(l, d) = x_n(l, d)/l$ for $n > 0$, where the $x_n(l, d)$ are subsequent positive roots of the equation $\tan(x) = -x/\gamma(d)/l$ (Table 6.1 of Tuckwell (2005)).
Once again, we compute the weighted sum:

\[ Vl(l_1, d_1, T_1, l_2, d_2, T, w, T) \propto Vl(l_1, d_1, T - T_1) + wVl(l_2, d_2, T - T_2) \]

and the ratio

\[ R(l_1, d_1, l_2, d_2, \Delta T, w, T) = \frac{\max_{t > 0} Vl(l_1, d_1, 0, l_2, d_2, \Delta T, w, T)}{\max_{t > 0} Vl(l_1, d_1, \Delta T, l_2, d_2, 0, w, T)} \]

but this time there is an explicit dependence on \( d_1 \) and \( d_2 \) due to the presence of a soma in the model. Thus, we can use the ball and stick model to derive the performance, and the appropriate dendritic segment lengths and diameters.

**Numerical evaluation.** The values used for \( C_m, G_m, \) and \( R_i \) were identical to those used for the numerical solution of the ODEs in the multi-compartmental model. Also, \( d = 25 \mu m, a = 80 \) so that we have \( \tau_m = 40 ms \) and \( \lambda(d) = 1118 \mu m^{1/2} \). The synaptic input current of the ball and stick model is proportional to \( T e^{(-aT)} \) for positive dimensionless time \( (T > 0) \) and has its peak at 0.5 ms. The dimensionless \( \gamma \) appearing in the ball and stick model has the approximate value of \( 1.789 d^{3/2} \mu m^{-3/2} \) for a dendrite of diameter \( d \). For a fixed \( \Delta T \), and defining and, we now have computed values of:

\[ R_{\Delta T}(e_1, e_2) = \max_{T, d_1, d_2, w} R_i\left(\frac{e_1\sqrt{d_1}}{\lambda_1}, \frac{e_2\sqrt{d_2}}{\lambda_1}, \Delta T, w, T\right) \]

for given values of \( e_1 \) and \( e_2 \) in the interval \((65.320 \mu m^{1/2}, 2062.761 \mu m^{1/2})\). The maximum was taken over values of \( T \) with constant step size \( t_s = (100 ms \) per \( \tau_m)/2000 \) (corresponding to 0.2 ms per step) from \( t_s \) to \((2000 - 1) \times t_s \) (corresponding to times up to 100 ms), and values of \( d_1 \) and \( d_2 \) which were both within the interval \((0.15 \mu m, 10 \mu m)\). Also the lengths and were kept in the interval \((200 \mu m, 800 \mu m)\). For the diameters \( d_1 \) and \( d_2 \), a geometric progression with common ratio close to unity was used. This ensured that the coverage was finer for smaller diameters. \( w \) was restricted to \([0.5, 2] \), these limits coming from a consideration of the effects of saturation caused by inserting too many synapses in a small region of a dendrite (and supported by simulations performed using NEURON in which we added even more synapses to the end of a dendrite while measuring the response at the soma). Once we had an approximate global maximum over these values of \( T, d_1, d_2, \) and \( w \), we then performed a local optimization over \( d_1, d_2, \) and \( w \) (while still remaining within the limits described above and using the same set of \( t \) values). As a result, our optimizations of \( R_{\Delta T}(e_1, e_2) \) and the corresponding fitness landscapes (as illustrated in Figure 10) can be considered (i) to be accurate, and (ii) to represent the optimal performance of this simplified model of a input-order detector.

**Analytical predictions.** So far, we have used numerical methods combined with GAs to find neurons optimized for input-order detection. The methodology can, however, not guarantee to find model neurons at, or close to the global optimum for this task. To determine the value and location of this global optimum, we used an approach based on analytically calculating EPSP amplitudes in a simplified
model neuron. The systematically calculated ratios of the compound EPSP amplitudes constitute the fitness landscapes for input-order detection.

The simulation of the model as described in the supplementary material results in fitness landscapes which are illustrated in Figure 10. In these fitness landscapes the performance as input-order detector is shown with respect to two axes; the $x$-axis denotes $e_1$ while the $y$-axis denotes $e_2$. These terms stand for a more complex term composed from the length of the dendritic segment up to the synapses in one dendrite divided by the average diameter of the dendrite up to the synapses (i.e., $L_x/\sqrt{d_x}$, where $x$ stands for either the left or right dendritic tree). The shown landscapes are actually a projection of three axis $e_1$, $e_2$ and $w$ onto the plane. The $w$ axis is discarded in the plots because it has only a minor influence on the landscape. The different symbols on the landscape represent the performances of all optimized model neurons. In all of these landscapes, there is a single ridge with the best performances that goes upright from bottom left. The amplitude of the ridge increased for longer $\Delta t$, and the peak is always found for higher $e_1$ coupled with lower $e_2$. In terms of structural properties this means that the left dendrite should have a high ratio between the dendritic length up to the synapses and the average dendritic diameter up to the same location ($L_l/\sqrt{d_l}$) in combination with a low ratio of similar structural properties in the right dendritic tree (i.e., $L_r/\sqrt{d_r}$). This is exactly what the optimized neuron models suggest. The performances of the optimized neuron models are all close to the optimal solution predicted by the analytical model. A difference is observed in the exact location of (i) the performance of the model neurons and (ii) the optimal performance computed with an analytical model. This difference is caused by two reasons. First, the analytical model is purely passive. Thus, a difference with the active model neurons is inevitable. Second, the projection of the triplet $e_1$, $e_2$ and $w$ onto a 2D plane causes some information (e.g., exact location) to be lost. Nevertheless, the model indicates that the morphologies found by the GA are likely to be close to the single global optimum for neural morphologies performing input-order detection.

General comments on optimization using GAs in the context of neuroscience. We use a number of methods commonly unfamiliar to neuroscientists, and want to share some general remarks on their strengths and weaknesses in this section. Particularly, since we use a numerical (GA based) approach for the optimizations of neural morphologies, the question arises as to how we know that they are at, or close to, global optima. The answer is that for principal reasons we cannot be certain, but we have several reasons to believe so. These reasons are the convergence with a second (analytical, see the Section “Analytic model of input-order detection”) approach and the known capabilities of GAs. Furthermore, we argue for the usefulness of very good, but not globally optimal solutions in biology.

Convergence with the analytical approach. The analytical approach we pursued (see the Section “Analytic model of input-order detection”) found solutions very similar to the GA-based optimizations. Thus, a strength of our approach to optimization is our use of two fundamentally different algorithms. One uses an essentially exact method to solve an approximate problem, the other uses an approximate method to solve what is essentially the exact problem. The basic idea is simple: It is better to
ask two strangers for directions than to ask one stranger twice. Our analytic model of input-order detection is a highly simplified model of a neuron with two dendrites. It is the simplicity of the model, both in terms of the dimensionality of the search space and also smoothness of the fitness function in this space, which allows us to scan the entire search space for an optimal solution.

**GAs as standard tools.** Genetic algorithms are the standard for problems with high-dimensional and rough fitness landscapes, such as the problem we address (Coello et al. 2002). While they are powerful optimization tools which have been successful for a multitude of problems, they are not guaranteed to find global optima.

Instead, GAs find local or global optima. True global optima can only be identified using global bounds on values of the fitness function, such as its derivatives. Running such a standard algorithm with different starting configurations would then produce a list of optima. In this case, it might in principle make sense to perform the optimization more than once, but it would not make sense to attempt to make error estimates (and draw error bars) on the basis of the output list of local optima. The global optimum may be the best of them or it may not be. The remaining local optima are not necessarily representative or even informative of the global optimum, just as hills in northern India tell us little about the peak of Mount Everest. Furthermore, our actual fitness function is not a closed mathematical expression which might be analyzed as we choose. Rather, our fitness function is defined solely in terms of the outputs of a software package. We are unable to bound or even compute derivatives. Since an optimum is defined in terms of vanishing derivatives, we are in fact forced to use approximate methods to approach even a local optimum.

Thus, our GA is of a different nature. It is a simulation-based direct search method (Kolda et al. 2003), for which very little is known about convergence to the true global optimum, given that our actual fitness function is not even continuous in our case, largely due to our use of a recursive morphogenetic algorithm to specify topology. On the other hand, this approach does have the great advantage of allowing small changes in the parameters to correspond to great leaps in search space, and this gives us confidence that our algorithm will not easily fall into the trap of premature convergence (Fogel 1994). Since our algorithm simply terminates after a fixed number of iterations, we would have no means of estimating error were it not for our analytic model. The fact that the best approximate solutions of the GA are close to the global optimum of the analytic model means that we have reasons to believe that these best approximate solutions are in fact close to the global optimum with respect to some suitably defined metric. It is unlikely that running the GA over and over again will produce any significant improvement in the output in a reasonable amount of time (Aldous and Vazirani, 1994).

**Optimization and biology.** In summary, while we have no certainty that the model neurons we obtained are indeed global optima, we have several reasons to believe that they are at least close to them. We also believe that this amount of optimization is sufficient for our purposes.

This is the case because in biology, we are always dealing with populations, and not with idealized types. The eventual goal of our approach is to compare
the optimized artificial neurons to populations of neurons, with a range of morphologies. It is not its goal to compare the artificial neuron to the pyramidal neuron or the bipolar interneuron. The question is whether an artificial neuron lies within a population of real neurons. The answer will be almost the same for artificial neurons which are at, or just close to, the global optimum morphology for performing a certain computation. Thus, we conclude that the amount of optimization we obtained is sufficient to draw conclusions about neural function–structure relationship.

References


