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Controlling Complexity of Cerebral Cortex Simulations—II: Streamlined Microcircuits

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Recently, Markram et al. (2015) presented a model of the rat somatosensory microcircuit (Markram model). Their model is high in anatomical and physiological detail, and its simulation requires supercomputers. The lack of neuroinformatics and computing power is an obstacle for using a similar approach to build models of other cortical areas or larger cortical systems. Simplified neuron models offer an attractive alternative to high-fidelity Hodgkin-Huxley-type neuron models, but their validity in modeling cortical circuits is unclear.

We simplified the Markram model to a network of exponential integrate-and-fire (EIF) neurons that runs on a single CPU core in reasonable time. We analyzed the electrophysiology and the morphology of the Markram model neurons with eFel and NeuroM tools, provided by the Blue Brain Project. We then constructed neurons with few compartments and averaged parameters from the reference model. We used the CxSystem simulation framework to explore the role of short-term plasticity and GABA_B and NMDA synaptic conductances in replicating oscillatory phenomena in the Markram model. We show that having a slow inhibitory

H.H. ran the experiments, contributed to programming the simulator, and wrote the manuscript. V.A. programmed the CxSystem and wrote the manuscript. S.V. conceived the study, contributed to programming the simulator, and wrote the manuscript. Correspondence and requests for materials should be addressed to simo.vanni@helsinki.fi.

synaptic conductance (GABA_B) allows replication of oscillatory behavior in the high-calcium state. Furthermore, we show that qualitatively similar dynamics are seen even with a reduced number of cell types (from 55 to 17 types). This reduction halved the computation time.

Our results suggest that qualitative dynamics of cortical microcircuits can be studied using limited neuroinformatics and computing resources supporting parameter exploration and simulation of cortical systems. The simplification procedure can easily be adapted to studying other microcircuits for which sparse electrophysiological and morphological data are available.

1 Introduction

Recently, Markram et al. (2015) presented a digitally reconstructed rat somatosensory cortex microcircuit replicating several phenomena *in vivo* and *in vitro*. Their approach relied on high-fidelity, multicompartmental neuron models, leading to high computational requirements. In general, such detail is hard to validate due to the lack of experimental data and the computational complexity of detailed models. More important, increasing numbers of parameters impede interpretation of simulated data.

Biologically meaningful yet efficient neuron and synapse models exist, but their feasibility in modeling cortical microcircuits and systems has remained unclear. Integrate-and-fire (IF) models with reduced morphology offer an attractive alternative to multicompartmental Hodgkin-Huxley (HH) type models (Herz, Gollisch, Machens, & Jaeger, 2006; Hodgkin & Huxley, 1952). In addition to conceptual simplicity, they can be efficiently simulated on several optimized platforms (Brette et al., 2007; Tikidji-Hamburyan, Narayana, Bozkus, & El-Ghazawi, 2017). They include, among others, the leaky integrate-and-fire (LIF) model (Knight, 1972; Lapicque, 1907; Stein, 1965) and the exponential integrate-and-fire (EIF) model (Fourcaud-Trocme, Hansel, van Vreeswijk, & Brunel, 2003), which both have a single differential equation for describing membrane potential.

Although the reduced IF models seem simplistic, they should not be dismissed lightly. First, the computational demands of detailed models can be enormous. For example, the model of Hay and Segev (2015), composed of 150 detailed pyramidal cells, ran in a reasonable time when each neuron was simulated on a separate CPU core. Even with the current computing clusters, scaling such a network to cover any cortical system would be difficult. Second, the construction of high-fidelity models is demanding. Neurons are classified with increasing detail (Ascoli et al., 2008; DeFelipe et al., 2013; Spruston, 2008), and the number of distinct synaptic pathways grows with the number of neuron types squared. The characterization and the digital reconstruction of a cortical microcircuit are complex, and the existing data do not necessarily generalize across cortical areas or species (Luebke,

2017; Silberberg, Gupta, & Markram, 2002). Third, the IF models can be augmented with biologically meaningful mechanisms, such as simplified dendrites (Mel, 1994), short-term synaptic plasticity (Zucker & Regehr, 2002), or adaptation currents (Brette & Gerstner, 2005; Izhikevich, 2003). It is still unknown to what extent such augmentations allow reproduction of physiology without the costs of high-fidelity modeling.

Here, we study the feasibility of reduced IF models in modeling a cortical microcircuit. We have three specific aims: (1) the model components should be biologically meaningful, (2) the approach should be generic to enable exploration of less characterized microcircuits, and (3) the implementation should be computationally efficient. Our reference network is the Markram model, housing about 3×10^4 neurons and 37 million synapses between them (Markram et al., 2015). First, we reduce the complexity of the single-neuron models (step 1). Second, we reduce the number of cell types (step 2). We then use the CxSystem simulation framework (see the accompanying letter by Andalibi, Hokkanen, & Vanni, 2019, in this issue), built on top of the Brian2 simulator (Stimberg, Goodman, Benichoux, & Brette, 2014), to construct and simulate the microcircuit models. Finally, we augment the microcircuit models with short-term synaptic plasticity and GABA_B and NMDA receptor-mediated conductances. To summarize, our aim is to find a simplified model qualitatively replicating the Markram model behavior and to understand how different modeling choices affect the use of computational resources.

2 Methods

We use the CxSystem framework (see Andalibi et al., 2019, this issue) to numerically study the simplified models.

2.1 Simplified Models of the Neocortical Microcircuit. In step 1, we measure electrophysiological parameters from the digitally reconstructed neurons of the reference microcircuit to build the corresponding cell types with IF dynamics. We use the connectivity of the Markram model to build the network of cells with reduced dynamics. In step 2, we further simplify the microcircuit by decreasing the number of cell types from 55 to 17. We first describe these two steps and then introduce features of the model common to both steps. All data are from the Neocortical Microcircuit Collaboration (NMC) portal¹ unless otherwise explicitly stated. Table 1 summarizes our simplifications of the Markram model.

2.1.1 Step 1: Microcircuit with Reduced Dynamics and Simplified Compartmental Structure. Most cell types are modeled as point neurons. Their

¹<https://bbp.epfl.ch/nmc-portal/>.

Table 1: Simplifications to the Comprehensive Model of Markram et al. (2015).

Structure	Markram et al.	Simplified Models
Cell types		
Morphological	55	55 (step 1) or 17 (step 2)
Electrical	14	No separate types
Dendritic compartments		
Pyramidal cells	260 (mean)	2–5 (range)
Other cells	1	Soma only
3D structure	Real valued	Discrete layers
Ionic currents	13 (Hodgkin-Huxley model)	Leak
Receptor types	4	2–4
Synaptic dynamics	Stochastic	Deterministic
Synaptic placement	Specific	Stereotypical
Axonal conduction velocity	300 $\mu\text{m}/\text{ms}$	Uniform distribution 1.5–4.5 ms

membrane voltage, V , is described by the EIF model (Fourcaud-Trocmé et al., 2003):

$$C \frac{dV}{dt} = g_L \cdot (E_L - V) + \psi + I_{\text{tonic}} + I_{\text{synaptic}}$$
$$\psi(V) = g_L \Delta_T \exp\left(\frac{V - V_T}{\Delta_T}\right) \tag{2.1}$$

where C is membrane capacitance, g_L is leak conductance, and E_L is resting potential. When membrane potential is depolarized near threshold V_T , the spiking current, ψ , generates an action-potential-like upshoot with voltage sensitivity Δ_T . Voltage is then reset to V_{reset} . Tonic depolarization I_{tonic} is included to account for the missing excitatory drive and is expressed with respect to the rheobase current (default 95%).

We determine the parameters C , g_L , E_L , V_T , and V_{reset} by simulating current injection on model neurons. We analyze the voltage traces using the eFel library² (see Figure 1A). In the Markram model, there are 55 morphological cell types (m-types) which are further divided into electrical subtypes, totaling 207 morpho-electrical cell types (me-types). There are 1035 models available in the NMC portal, 5 for each me-type. We average the resulting parameters to produce a set of parameters for each me-type. We further take a frequency-weighted average over the electrical subtypes to produce a set of m-type parameters. Except for pyramidal cells, we use these derived m-type parameters in the step 1 simplification.

²<https://efel.readthedocs.io/>.

Figure 1: (A) One hyperpolarizing (with current I_e) and three depolarizing (one shown) current injections are used to derive parameters for the simplified non-pyramidal cell types. (B) Left: Morphological reconstructions of pyramidal cells are cut into pieces according to layer boundaries. Right: Membrane surface areas of the cut dendrites are used in the simplified pyramidal cell models. (C) Connection probabilities between the 55 cell types in the step 1 microcircuit. (D) Same as in panel C, but for the step 2 microcircuit after mapping the 55 Markram model cell types to a reduced set of 17 cell types.

Pyramidal cells (PCs) are modeled differently. They may have between three and seven isopotential compartments in one to six layers; the layer housing the soma also comprises one basal dendrite and the most proximal apical dendrite compartment. In addition, one to four apical dendrite

Table 2: Simplified Synaptic Placement on Pyramidal Cells.

Presynaptic Cell Class	Presynaptic Cell Types	Postsynaptic Compartment
Excitatory	PC, SS	Nearest dendritic compartment(s)
Inhibitory cell types		
Soma/AIS targeting	ChC, LBC, NBC, SBC	Soma
Distal dendrite targeting	MC	Most pial compartment
Dendrite targeting	BP, BTC, DBC, NGC	Nearest dendritic compartment(s)

Note: AIS = axon initial segment, PC = pyramidal cell, SS = spiny stellate, ChC = chandelier cell, LBC = large basket cell, NBC = nest basket cell, SBC = small basket cell, MC = Martinotti cell, BP = bipolar cell, BTC = bitufted cell, DBC = double bouquet cell, NGC = neurogliaform cell.

compartments may be connected to the proximal apical dendrite compartment, each layer housing one compartment.

We parameterize the pyramidal cell model using morphology data (see Figure 1B) and uniform passive parameters ($C = 1 \mu\text{F}/\text{cm}^2$, $g_L = 4.2 \cdot 10^{-5} \text{ S}/\text{cm}^2$). The reconstructed morphological neuron is placed with its soma in the middle of its layer in the vertical direction. Some neurons with extensive apical dendrites must be shifted downward to prevent their apical dendrite from traversing beyond L1. Each segment of the apical dendrite is assigned to a layer depending on its vertical coordinate, and the membrane surface area of the apical dendrite compartment in that layer is taken as the sum of these segments.

The basal dendrites are represented by a single compartment with an area that is the sum of the areas of all the basal dendrites. For layer 6 bipolar PCs, which exceptionally have two apical dendrites oriented toward opposite directions, we consider the apical dendrite oriented toward the white matter as belonging to the basal dendrites and increase the surface area of the basal dendrites accordingly.

We then use pathway data³ to create connections between the cell types. The connection probabilities are for seven hexagonally tiled microcircuits, but single-microcircuit synapse counts were kindly provided by the Blue Brain Project (Michael W. Reimann, personal communication). We do not take synaptic placement in the reference model into account but rather use fixed rules to choose which compartment on pyramidal cells is targeted (see Table 2).

The network is placed inside a cylinder of radius $210 \mu\text{m}$, with neurons spread randomly in each layer. To simulate a single whisker deflection, Markram et al. (2015) connected 60 thalamic fibers to 60 minicolumns in the center of the microcircuit and stimulated the network with one

³https://bbp.epfl.ch/nmc-portal/documents/10184/7288948/pathways_anatomy_factsheets_simplified.json.

synchronous spike. In line with this approach, we connect 60 fibers to L4 and L5 excitatory neurons in random locations within $92\ \mu\text{m}$ from the network center.

2.1.2 Step 2: Cell Type Reduction. Next, we reduce the 55 m-types of the Markram model to 17 cell types (the full table⁴ is available online). The reduced set of cell types represents the majority of cells in the cerebral cortex. Each of the cell types, eight excitatory and nine inhibitory, represents one to eight cell types in the Markram model.

The PCs are categorized according to their soma position and the extent of the apical dendrite oriented toward the cortex surface. However, the small population of L5 untufted pyramidal cells (UTPCs) (6.8% of L5 PCs) with a shorter apical dendrite is subsumed in the single L5 PC type. Layer 4 spiny stellates are included as a separate excitatory neuron population. We include the most prominent soma-targeting (basket cells, BCs) and dendrite-targeting inhibitory cell types (Martinotti cells, MCs), which together represent about 70% of all inhibitory cells (Markram et al., 2004). Moreover, by targeting the distal dendrites, Martinotti cell-mediated inhibition can have a distinct role in regulating pyramidal cells (Silberberg & Markram, 2007; Wang et al., 2004). Layer 1 contains a distinct set of interneuron types (Markram et al., 2015), and they are included as one aggregate cell type.

Neuron models are parameterized by taking frequency-weighted averages of the step 1 parameters. Although basket and Martinotti cell types in step 2 represent cell types other than basket or Martinotti as well, their step 2 neuron model parameters are derived only from step 1 basket and Martinotti cell parameters, respectively.

2.1.3 Synaptic Currents. We use conductance-based synaptic currents, I_{synaptic} . We compare three setups. First, we have one excitatory (AMPA) and one inhibitory (GABA_A) receptor, whose kinetics follow single-exponential decay. We then add two slow-acting receptors (NMDA, GABA_B), whose kinetics are described by separate rise and decay times (see Table 3). NMDA-mediated conductance has an extra voltage dependence due to the magnesium block (Jahr & Stevens, 1990). The magnesium level is fixed at a physiological concentration of 1.0 mM.

Synaptic weights are chosen from a random uniform distribution between $g \pm \frac{g}{2}$, where g is specified according to the pre- and postsynaptic neuron type (Markram et al., 2015; Figure S6). In vitro, the NMDA-to-AMPA peak conductance ratio varies between 20% and 770% (Myme, Sugino, Turrigiano, & Nelson, 2003); we fix a pathway-independent value of 40%. Similarly, the GABA_B-to-GABA_A peak conductance ratio is fixed at 20%.

⁴https://github.com/VisualNeuroscience-UH/CxSystem/blob/master/docs/supplementary_data/Mapping_cell_types.pdf.

Table 3: Parameters for the Synaptic Conductances.

Receptor	Model	E_{rev}	τ_{rise}	τ_{decay}	Peak Conductance
AMPA	Single exponential	0 mV	–	3.0 ms	1
NMDA	Bi-exponential	0 mV	0.3 ms	43 ms	$0.4 (\cdot w_{\text{AMPA}})$
GABA-A	Single exponential	–75 mV	–	8.3 ms	1
GABA-B	Bi-exponential	–93 mV	3.5 ms	260 ms	$0.2 (\cdot w_{\text{GABA-A}})$

Notes: The synaptic conductances are modeled using either single- or bi-exponential kinetics. “Peak conductance” indicates the relative value of the effective peak conductance to weight assigned in the model definition.

2.1.4 Calcium Dependency of Synaptic Efficacy. Validation procedures in Markram et al. (2015) emulated changes in the extracellular calcium concentration, which is associated with presynaptic vesicle release probability (Rozov, Burnashev, Sakmann, & Neher, 2001; Tsodyks & Markram, 1997). Since our synaptic model does not have stochastic release, we do the corresponding scaling to synaptic weights by

$$F(c) = \frac{C^4}{K_{1/2}^4 + C^4}, \quad (2.2)$$

where C is the extracellular calcium concentration and $K_{1/2}$ is the constant of calcium dependency (Rozov et al., 2001). Scaling is normalized to 1 at $C = 2.0$ mM. The calcium dependency is either steep ($K_{1/2} = 2.79$) or shallow ($K_{1/2} = 1.09$), with excitatory-excitatory synapses and synapses between excitatory neurons and Martinotti cells having a steep dependence in both directions, and synapses between excitatory cells and basket cells having a shallow dependence in both directions (Markram et al., 2015, Figure S11).

2.1.5 Short-Term Synaptic Plasticity. We augment the synapse model with short-term synaptic plasticity (STP) using the deterministic Tsodyks-Markram model (Markram, Wang, & Tsodyks, 1998; Tsodyks & Markram, 1997). For depressing synapses, the fraction of available resources R evolves according to the equation

$$\tau_d \frac{dR}{dt} = 1 - R, \quad (2.3)$$

where τ_d is the depression recovery time constant. Each spike decreases available resources R by $U \cdot R$, where U is the utilization constant, and increases the postsynaptic neuron’s synaptic conductance by $w \cdot U \cdot R$, where w is the connection weight. For facilitating synapses, the utilization factor is a dynamic variable u , which evolves according to

$$\tau_f \frac{du}{dt} = U - u, \quad (2.4)$$

where τ_f is the facilitation decay time constant and each spike increases u by $U \cdot (1 - u)$. Whenever short-term plasticity is included, the extracellular calcium level modulates the utilization factor U instead of the connection weight w .

The synapses from L5 PC to L5 MC neurons are facilitating with the time-constants taken from the Markram model ($\tau_f = 67$ ms, $\tau_d = 140$ ms, and $U = 0.09$), while all other synapses are depressing. All depressing synapses have the same time constant ($\tau_d = 670$ ms). The utilization factors are 0.5 and 0.25 for excitatory and inhibitory synapses, respectively, as for most connections in the Markram model (Markram et al., 2015, Table S6).

2.1.6 Background Input. Each neuron receives spontaneous noncorrelated Poisson-distributed excitation in relation to layer-wise averaged excitatory synapse counts. This estimate allows comparison with the Markram model, which has tuned spontaneous synaptic release rates between 0.01 and 0.6 Hz for excitatory synapses. In contrast to the Markram model, we use the same rate irrespective of the target cell type.

2.2 Analysis. To quantify global synchrony, we randomly sample cross-correlation (CC) between disjoint pairs ($M = 250$) of neurons:

$$CC_M = \frac{1}{M} \sum_{i,j} \frac{\text{cov}(S_i, S_j)}{\text{std}(S_i) \text{std}(S_j)}.$$

Here, cov is the covariance between two binned (3 ms) spike counts S_i and S_j . Simulations with $CC < 0.05$ are considered asynchronous. The oscillation frequency is the smallest nonzero frequency component of the Fourier transform of binned spike counts.

2.3 Simulation Time and Memory Use. We run simulations on a computing cluster,⁵ each node containing 16 CPU cores and at least 64 GB of memory. Each simulation runs on a single core; the network is not split between processors. Peak memory consumption is reported by the SLURM workload manager⁶ and only spikes are recorded. We run simulations in native Python with a time step of 0.1 ms.

⁵<https://research.csc.fi/taito-supercluster>.

⁶<https://slurm.schedmd.com/>.

3 Results

First, we describe the connectivity of the simplified network, which is common in all experiments. Then we describe the behavior of the network while cumulatively augmenting the synapse and the synaptic conductance models.

3.1 Connectivity between Cell Types. The step 1 simplification uses connection probabilities directly from the Markram model (see Figure 1C). As illustrated in Figure 1D, the connection probabilities of the step 2 microcircuit have an overall consistency with the Markram model. The step 1 simplification results in 1932 synaptic pathways, out of the 3025 possible pathways, between the 55 cell types. The step 2 simplification results in 272 synaptic pathways out of the 289 possible pathways, between the 17 cell types. Thus, the cell type reduction of step 2 results in an almost fully connected graph due to numerous small pathways between the step 1 cell types.

3.2 Dynamics of Spontaneous Behavior at High Calcium

3.2.1 EIF Model. When the E-I (excitatory-inhibitory) balance changes toward excitation, neural networks can shift from asynchronous to synchronous spiking (Brunel, 2000; Kumar, Schrader, & Rotter, 2008). Using the default values for synaptic weights (Markram et al., 2015, Table S6) and tonic depolarization of 95%, we search for a suitable level of inhibition. In the step 2 microcircuit, we drop the cell type-specific weights and use only the general E-E, E-I, I-E, and I-I weights. In our parameter exploration, we vary the weight of inhibitory synapses on excitatory cells (I-to-E weight), relative to the E-to-E weight. In the Markram model, this relative inhibition was 1.15. The second dimension in the parameter exploration is the rate of background input.

In the step 1 microcircuit, we observe high mean firing rates (see Figure 2A) and nonoscillatory behavior (see Figure 2B) with calcium concentration at 2.0. In the step 2 microcircuit, a similar picture is seen (see Figures 2C and 2D). The band of synchrony at 0.8 of relative inhibition is restricted to a few cell types and does not represent true global synchrony (data not shown).

3.2.2 Model Augmented with STP. Synaptic activity modulates weights via short-term synaptic plasticity (STP; Zucker & Regehr, 2002). Thus, we added STP and repeated the 2D parameter search. In the step 1 microcircuit, the mean firing rates show expected behavior (see Figure 2E), while some synchrony is seen with high levels of inhibition (see Figure 2F). In the step 2 microcircuit, mean firing rates (see Figure 2G) and synchrony (see Figure 2H) show a similar picture.

Figure 2: Mean firing rates and synchrony in different configurations. (A) The mean firing rate and (B) synchrony change in the step 1 EIF model when the strength of inhibition and the rate of background input are varied. (C,D) The same for the step 2 EIF model. (E–H) Step 1 and step 2 EIF + STP models. (I–L) The step 1 and step 2 models augmented with STP and the GABA_B conductance. (M–P) The step 1 and step 2 models augmented with STP, GABA_B, and NMDA.

3.3 Adding the Slow Inhibitory Conductance (GABA_B). Next, we add the slow GABA_B conductance. In a comparison to the step 1 EIF + STP model, the mean firing rates are significantly reduced (see Figure 2I). Global synchrony is seen with relative inhibition at 0.8, close to the reference value of 1.15 (see Figure 2J). In the corresponding step 2 model, mean firing rates behave similarly (see Figure 2K) and global synchrony is shifted to a lower level of relative inhibition (see Figure 2L).

3.4 Adding the Slow Excitatory Conductance (NMDA). We further add the slow NMDA conductance. Compared to the step 1 model augmented with STP and GABA_B, the mean firing rates are slightly higher (see Figure 2M). The increase in excitation leads to a narrower band of

synchrony (see Figure 2N). In the step 2 microcircuit, adding the NMDA conductance slightly increases the mean firing rates (see Figure 2O) and slightly shifts the band of synchrony to a higher level of relative inhibition (see Figure 2P).

3.5 Behavior in Low-Calcium State. Presynaptic vesicle release depends on calcium, and in vitro synaptic properties are typically investigated in higher-than-physiological calcium concentration to promote neurotransmitter release (Borst, 2010). Decreasing the calcium level from the high value of 2.0 mM to the physiological range (1.1–1.5 mM) shifts the E-I balance toward inhibition.

As synchrony seems to be particularly sensitive to relative inhibition, and not so much to the background rate, we fix the rate of background noise at 0.3 Hz. We then explore synchrony with varying levels of relative inhibition centered around 0.8, the level that most consistently produces oscillatory behavior. We restrict our analysis to the models augmented with STP and GABA_B, with and without NMDA, because these do not require additional parameter tuning.

We then reduce the calcium concentration. To compensate for the lack of excitatory drive due to the decrease in the calcium level, we increase the level of tonic depolarization to 100%.

In the step 1 model augmented with GABA_B, a narrow range of relative inhibition generates oscillatory behavior at calcium concentration 2.0, which switches to asynchronous behavior at lower levels of calcium (see Figure 3A). Representative raster plots before (see Figure 3B) and after (see Figure 3C) this phase transition show qualitatively different behavior. When NMDA is added, a similar picture emerges (see Figure 3D). Raster plots of configurations with the same parameters show analogous behavior in the synchronous (see Figure 3E) and the asynchronous state (see Figure 3F).

In the step 2 model augmented with GABA_B, asynchronous behavior emerges with higher levels of calcium (see Figure 3G). A raster plot of the synchronous state shows a qualitatively similar picture to the step 1 microcircuit (see Figure 3H). A raster plot of the asynchronous state is also similar (see Figure 3I). When NMDA is added, the synchronous state is more robust (see Figure 3J). Qualitatively, the synchronous (see Figure 3K) and the asynchronous state (see Figure 3L) show similar behavior.

3.6 Responses to Thalamic Stimulation in Low-Calcium States. Figures 4A, 4C, 4E, and 4G show the network responses to synchronized transient input, or “whisker deflection,” at low calcium configurations (1.5 mM) for the step 1 and step 2 models augmented with STP, GABA_B and with STP, GABA_B, and NMDA.

In step 1, the stimulus causes a brief, robust response in the thalamorecipient layers 4 and 5, while there are weaker responses in L2/3 and L6 (see

Figure 3: Spontaneous behavior at different levels of extracellular calcium. The background rate was fixed at 0.3 Hz. (A) EIF model augmented with STP and GABA_B. In the step 1 model, global synchrony exists in a narrow band of relative inhibition at high calcium concentration and disappears with decreasing calcium concentration, showing (B) synchronous spiking before and (C) asynchronous spiking after the phase transition. (D–F) The same for the step 1 model augmented with STP, GABA_B, and NMDA. (G–I) The step 2 EIF model augmented with STP and GABA_B. (J–L) The step 2 model augmented with STP, GABA_B, and NMDA. (B, C, E, F, H, I, K, and L) Relative inhibition at 0.55.

Figures 4A and 4C). For the model augmented with STP and GABA_B, these observations are confirmed by running 200 trials, of which representative poststimulus time histograms (PSTHs) are shown in Figure 4B. The model further augmented with NMDA shows qualitatively similar behavior (see Figure 4C), with the weaker responses of L2/3 and L6 becoming slightly more reliable (see Figure 4D).

Figure 4: Responses to thalamic stimulation in the low-calcium state (1.5 mM). (A) A representative trial showing the overall response in the step 1 model augmented with STP and GABA_B. (B) Over 200 trials, recorded individual neurons of different cell types generate spikes with different probability after a transient synchronous stimulus. (C–D) The same for the step 1 model augmented with STP, GABA_B, and NMDA. (E–F) The step 2 model augmented with STP and GABA_B. (G–H) The step 2 model augmented with STP, GABA_B, and NMDA. (A–H) Relative inhibition at 0.55 and calcium concentration at 1.5.

In step 2, both the STP + GABA_B model (see Figure 4E) and the STP + GABA_B + NMDA model (see Figure 4G) similarly show robust responses in the thalamorecipient layers. Interestingly, the L4 MCs show a strong response, which is not seen in the step 1 models, while responses in L5 and L6 become less reliable (see Figures 4F and 4H).

Figure 5: (A) Run time and (B) memory use for the step 1 (solid lines) and step 2 (dashed lines) models augmented with STP and GABA_B (light gray) and further with NMDA (dark gray). Run times for the step 2 microcircuits were roughly half of the run times of the corresponding step 1 microcircuits.

3.7 Simulation Time and Memory Use. We evaluate the computational cost of simulations at a high calcium level (configurations of Figure 2). The step 1 model with STP and GABA_B runs on average 20 minutes for each second of simulation (see Figure 5A, solid gray line). Addition of NMDA increases the run time by about 60% to about 32 minutes (see Figure 5A, solid black line). Run times of the step 1 EIF and EIF + STP models are between 20 and 30 minutes for each second of simulation.

The step 2 model with STP and GABA_B runs in about 40% of the time required for the corresponding step 1 model (see Figure 5A, dashed gray line). Further augmentation with NMDA increases the run time to 230% of the step 2 GABA_B augmented model, up to about 17 minutes per 1 second of simulation (see Figure 5A, dashed black line). This is still only about 55% of the run time of the corresponding step 1 model. The step 2 EIF and EIF + STP models both run about 14 minutes per 1 second of simulation.

The peak memory consumption was less than 2.6 GB for all the models in simulations up to 60 seconds (see Figure 5B). The EIF and EIF + STP models in both steps accumulate more spikes, and their memory consumption increases more steeply (data not shown). The step 2 models reduce memory consumption to about 80% of the corresponding step 1 models.

4 Discussion

4.1 The Behavior of the Simplified Models. We simplified a recently published detailed model of the rat somatosensory cortical microcircuit (Markram et al., 2015) in two steps: using simplified neuronal dynamics (step 1) and then, reducing the number of cell types (step 2). Our model

retained the original number of neurons and synapses. We studied two synapse models and three synaptic conductance models of varying complexity. Network-wide oscillations and their shift to asynchronous firing with reduced calcium concentration were seen in both steps whenever STP and GABA_B were included.

Synchronous behavior occurred at levels of relative inhibition of similar magnitude to that of the Markram model (about 1.15). Also, the shift to asynchronous firing occurred at a calcium concentration close to the level reported for the Markram model (about 1.3 mM). Exactly the same values were not achieved. The discrepancies were observed already in the step 1 microcircuit, suggesting that they require more complicated neuronal dynamics such as spike-frequency adaptation.

4.2 Computational Efficiency. We learned that adding the GABA_B synaptic conductance decreased the run times. This decrease was associated with a decrease in the mean firing rate (see Figure 2). Overall, increasing the synaptic complexity of the model had negligible effects on computational efficiency.

Similar to GABA at the network level, various voltage-gated potassium channels regulate neural activity in neuronal membranes (Hille, 2001). Thus, integrate-and-fire models with a single adaptation conductance, such as the adaptive exponential integrate-and-fire model (Brette & Gerstner, 2005), could have a similar effect on the computation time as observed in this study. In contrast, a minimal adapting Hodgkin-Huxley-type model includes a fast sodium conductance and at least two potassium conductances (Pospischil et al., 2008; Pospischil, Piwkowska, Bal, & Destexhe, 2011), requiring 12 additional dynamic variables compared to the EIF model. The computation time from these variables could outweigh any time savings obtained from the decreased spiking frequency in the network.

The aggressive cell type reduction we employed in step 2 resulted in only modest gains in terms of efficiency. Independent of whether a step 1 or a step 2 type approach is chosen, simulation of a more extensive microcircuit model would benefit from the ability to divide the network between several CPU cores for parallel processing.

We assume that reducing the number of pyramidal cell compartments from the average of 260 in the Markram model to 3 to 6 here reduced the computational costs in proportion to the number of compartments. Distinct compartments need separate state variables, increasing both the run time and the memory consumption.

4.3 Previous Work on Network Simplifications. Earlier, Rössert et al. (2016) emulated the synaptic dynamics of multicompartmental neurons with point neurons. They reproduced the calcium-dependent transition from asynchronous to synchronous spiking, as well as the stimulus response properties of the Markram model. However, their approach necessitates a separate state variable for each synapse, increasing the

computational demands significantly compared to our model, where conductances require only one state variable per compartment and synapse type (Brette et al., 2007). Moreover, we aimed at a conceptually parsimonious model, not merely an increase in computational efficiency.

Potjans and Diesmann (2014) used neurons with reduced morphology and IF membrane dynamics to study the spontaneous activity and the propagation of transient thalamic stimuli in the sensory cortex. Their model included point neurons with leaky integrate-and-fire dynamics and current-based synapses and was thus a more aggressive simplification than our model. Moreover, the Potjans-Diesmann model combined data from the rat visual and somatosensory cortices and the cat area 17, while we used a relatively complete data set from the rat somatosensory cortex. Most important, we aimed at operating in many biologically meaningful states, while the Potjans-Diesmann model was tuned to work only in vivo.

5 Conclusion

Simplifying assumptions about microcircuit components are useful for understanding and describing individual neurons while allowing larger circuits and systems. In terms of computational efficiency, having multiple cell types is not crucial, while the complexity of the neuron model is. The Markram model provides validation for high-fidelity modeling. However, it is yet to be systematically studied what sorts of questions can be answered without detailed neuron models and what questions allow the use of linear instead of nonlinear synaptic summation in dendrites.

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