

## FACETS

FP6-2004-IST-FETPI 15879

Fast Analog Computing with Emergent Transient States

## D13: Identification of Standardized Compartmental Topology for each Cell Type

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Report Preparation: Rajnish Ranjan, Shaul Druckmann, Albert Gidon, Yoav Banitt, Felix Schuermann, Henry Markram, Idan Segev, Wulfram Gerstner.

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Project Coordinator: Karlheinz Meier (Heidelberg)

Partners: U Bordeaux, CNRS (Gif-sur-Yvette, Marseille), U Debrecen, TU Dresden, U Freiburg, TU Graz, U Heidelberg, EPFL Lausanne, Funetics S.a.r.l., U London, U Plymouth, INRIA, KTH Stockholm



#### **DELIVERABLES TABLE**

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<sup>1</sup> R: Report; D: Demonstrator; S: Software; W: Workshop; O: Other – Specify in footnote

<sup>2</sup> Int.: Internal circulation within project (and Commission Project Officer + reviewers if requested)

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#### DELIVERABLE SUMMARY SHEET

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Title: Fast Analog Computing with Emergent Transient States

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Short description:

Biologically realistic single neuron modeling mainly depends on morphology, passive properties, ion channel combination, density and distribution. Here we report a modeling effort to replicate different electrical classes in detailed models of reconstructed excitatory and inhibitory neurons from the rat somato-sensory cortex. The robustness of these models is examined under different conditions including varying current stimulation, and changing morphology. We have observed that in most cases dendritic morphology does not strongly affect the electrical behavior.

Partners owning: 8b (EPFL – LNMC)

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# Single neuron modeling

## Introduction

Biologically realistic single neuron modeling mainly depends on morphology, passive properties, ion channel combination, density and distribution. It is quite challenging and sometimes technically very difficult to obtain these parameters experimentally. Therefore we have chosen a progressive approach where we start with a model with known parameters and successively integrate other experimental details as and when they are available. Here we report a modeling effort to replicate different electrical classes (Fig. 1) that were recently categorized under a standard nomenclature in the Petilla 2005 Convention [1].



### Figure 1

The first version of this model (Minimum Somatic model) includes detailed morphologies of different cell types from experiments, passive properties from the literature and six generic ion channels distributed only in the soma to generate different firing patterns [2]. Ion channel densities in the soma are explored using a hand made tool in NEURON [3] and initial results match gene expression data of different firing patterns. Work on an automatic fitting algorithm of ion channel densities is in progress and we aim to extend it for a greater number of ion channels as well as spatial distributions. The scope of this report goes beyond D13 as it includes not just compartment topology but also modeling of different electrical celltypes including ion channels in soma.

### Materials and methods Morphology

All neuron models begin with a structural framework, either assumed or based on an actual neuronal morphology. We use neuron morphology from cortical slices, obtained using Neurolucida software. To comprehensively recover morphology of a reconstructed neuron, the same is repaired using statistics of the complete part of the neuron [4]. In a preparatory step, the algorithm unravels the reconstructed neurons (correcting a shrinkage artifact) while maintaining their morphological structure (branches connectivity and angles). The application



Figure 2

then re-grows cut branches using the following approach: A 'probability cloud' inspired by the Sholl analysis is computed for the complete part of the neuron. The space is divided into concentric layers whose surfaces vary with the distance from the soma center. Bayesian statistics in each region between 2 layers are computed (e.g.: probability that a branch entering this region will end knowing that it is of order *i*). Using the statistical distributions in each region the branches are re-grown segment by segment. **Figure 2** shows one example of un-repaired and repaired neuron morphology.

### **Passive properties**

Informed estimates for membrane and cytoplasmic electric constants (Rm, Ra, Cm) are essential towards neuronal modeling. Although direct measurement of these parameters is difficult, experimental measurements combined with compartment models provide indirect estimates. Recent studies based on tight-seal whole cell recordings have generally arrived at estimates in the following ranges: Rm = 20-100 k $\Omega$  cm<sup>2</sup>, Cm = 0.5-1.5 $\mu$ F cm<sup>-2</sup>, Ra = 50-200  $\Omega$  cm.

### Compartmentalization

Approximating the cable equation by a series of compartments connected by resistors is known as compartmentalization. The main assumption in the compartmental approach is that small pieces of the neuron can be treated as isopotential elements, so that the essentially continuous structure of the neuron can be approximated by a linked assemblage of discrete elements. **Figure 3** shows a schematic diagram of a neuron divided into many isopotential compartments. Various strategies have appeared in the literature as aids to the use of judgment in choosing a spatial grid. We have used "d\_lambda rule" [3], which predicts the spatial grid based on the AC length constant  $\lambda_f$  computed at a frequency *f* that is high enough for transmembrane current to be primarily capacitive, yet still within the range of frequencies relevant to neuronal functions.



Figure 3

### Equations : No of compartments = $int((L/(0.1*lambda_f(100)) + 0.9)/2)*2 + 1$ lambda\_f(y) = 1e5\*sqrt(diam/(4\*PI\*y\*Ra\*Cm))

Following table describes relationship between morphological class, neuron size and number of compartments it is divided into.

Morph Type	Area(Sq Micron)	Total Length(Micron)	Number of
			compartments
L5CSPC	45589.32	16319.29	704
MC	12871.1	5901.92	202
DBC	8870.58	4483.76	194
LBC	19047.78	8466.30	368
BTC	8809.96	4529.04	204
ChC	5372.25	2797.9	118
NBC	9251.13	4293.49	156

### Ion channel model

The shape of an action potential depends upon kinetics of inward/outward ionic membrane currents. In recent years, numerous ionic membrane currents have been described [5]. These differ in principal carrier, voltage and time dependence, dependence on internal calcium and susceptibility to modulation by synaptic input and second messengers.

In our models we have used Na, K, A, CaT, CaP and KCa ion channels. These ion channels are implemented in NEURON using NMODL a high level language implemented for NEURON by Michael Hines [6].

Channel	E Rev	gates	Kinetics
Name	(mv)		
K+ (Basic	-72	n <sup>4</sup>	$\alpha = -0.01 * (Vm + 50)/(exp(-(Vm + 50)/10) - 1)$
potassium channel)			$\beta = 0.125 * \exp(-(Vm+60)/80)$
Na+ (Basic	55	M <sup>3</sup>	$\alpha = -0.1 * (Vm + 35)/(exp(-(Vm + 35)/10) - 1)$
Sodium			$\beta = 4 * \exp(-(Vm+60)/18)$
shannal)	55	Н	$\alpha = 0.07 * \exp(-(Vm+60)/10)$
channel)			$\beta = 1 / (\exp(-((Vm+30)/10)+1)))$
	-75	M <sup>3</sup>	minf =
			$(0.0761*(exp((Vm+94.22)/31.84))/(1+exp((Vm+1.17)/28.93)))^{(1/3)}$
A Channel			mtau = $(0.3632 + (1.158/(1 + \exp((Vm + 55.96)/20.12))))$
		Н	hinf = $(1/(1+\exp((Vm+53.3)/14.54))^{4})$
			htau = $(1.24 + 2.678/(1 + \exp((Vm + 50)/16.027)))$
		M <sup>2</sup>	minf = 1/(1 + exp(-((Vm + 57)/(6.2))))
T Type Co			mtau = (0.612+(1/(exp(-(Vm +132)/16.7)+exp((Vm +16.8)/18.2))))
T Type Ca		п	hinf = 1/(1 + exp(-((Vm + 81)/4)))
		11	htau = (28+exp(-(Vm +22)/10.5))
		M <sup>2</sup>	minf = 1/(1 + exp(-((Vm + 57)/(6.2))))
D Turna Ca			mtau = (0.612 + (1/(exp(-(Vm + 132)/16.7) + exp((Vm + 16.8)/18.2))))
P Type Ca		Н	hinf = 1/(1 + exp(-((Vm + 81)/4)))
			htau = (28 + exp(-(Vm + 22)/10.5))
	-72	n <sup>2</sup>	$ninf = 1.25*(10^8)*(cai)*(cai)/((1.25*(10^8)*(cai)*(cai))+2.5)$
KCa			$ntau = 1000/((1.25*(10^8)*(cai)*(cai)) + 2.5)$

Following table describes kinetics of each ion channels used in our models.

### Ion channel density/distribution

A serious problem in models that include a variety of ion channels spread non-uniformly across the neuron is the huge number of parameters available to describe channel densities. Therefore in the first version of this model (Minimum Somatic model) we have restricted our models to six ion channels distributed only in the soma. These ion channels are distributed using a hand made tool (Figure 4) in NEURON [3].

Using the six aforementioned ion channels, we fit both the density of channels and the specific form of the voltage dependency. We allow ourselves to do so for two reasons. Firstly, real neurons often have considerably more than just these six channels. Hence each channel in our selection might have to stand in for other non represented channels and as such cannot be expected to perform with the experimental parameters. Secondly, the values of the parameters of the voltage dependency of these channels are still under dispute among experimentalists.



The main idea behind Minimal Somatic model is to restrict the

Figure 4

number of free parameters. Work to replace this manual tool with automatic fitting algorithm is in progress and we aim to extend it for a large number of ion channels as well as for spatial distribution.

### **Observation**

In this preliminary phase we find that in most cases dendritic morphology does not strongly affect the electrical behavior. This is not surprising considering the current stage of modeling in which we use passive dendrites and an excitable soma whose size is quite similar across morphologies. This effective similarity is further enhanced by the nature of the dendritic arbors. The dendritic arbors of the various morphologies are as a rule not very large and not strikingly different from one another. Thus, one would expect a similar excitable zone burdened with a sink that does not differ wildly to exhibit qualitatively the same behavior.

### Results

We succeeded in simulating to a reasonable degree of accuracy all of these electrical classes (including bursting, long delayed, non-adapting behavior from almost flat depolarization) in detailed models of reconstructed excitatory and inhibitory neurons from the rat somatosensory cortex. The robustness of these models is examined under different conditions including varying current stimulation, changing morphology etc. Following result pages shows stimulus response of nine different models of electrical types (bAD, bFS, bNa, cAD, cFS, cNA, dNA, rBs, tBS) tested with different possible morphologies keeping ion channel densities same in the soma.

### References

[1] Petilla 2005 Convention <u>http://www.columbia.edu/cu/biology/faculty/yuste/petilla/petilla-webpages/Nomenclature/PetillaNomenclaturefinal.pdf</u>.

[2] Druckmann S., Gidon A., Banitt Y., Ranjan R., Toledo-Rodriguez M., Schuermann F., Markram H., Segev I., Conductance-based models capturing the firing repertoire of inhibitory interneurons in the neocortex, FENS vol.3, A037.20 (2006).

[3] Hines, M. L. & Carnavale, N. T. The NEURON simulation environment. Neural Comput. 9, 1179–1209 (1997).

[4] Riachi I., Anwar H., Schuermann F., Markram H., Repairing 3D morphological models obtained from in vitro morphological models obtained from in vitro experiments, FENS vol.3, A037.18 (2006).

[5] Hille B. Ion channels of excitable membranes Sunderland, MA: Sinauer (2001).

[6] Hines, M.L. and Carnevale, N.T. Expanding NEURON's repertoire of mechanisms with NMODL. Neural Computation 12:995-1007, 2000.

# bAD

**Burst adapting firing pattern Possible morphologies**: BTC, DBC, LBC, MC, NBC.

**Characteristics:** burst onset, 2 or more spikes, onset ISI<<steady state ISI. Figure 1 shows ion channels used to model this firing pattern. Figures 2-9 shows results for 3 different morphologies.



Figure 2 and 3 shows response of bAD model to step currents. **Amplitude of stimulus** Just above threshold (Fig. 2) 1.5 times threshold (Fig. 3)

**BTC cell** 

Figure 4 and 5 shows response of bAD model to SineSpec wave generated by using function w(x) =sin(exp(exp(x/5))). Ex.













NBC cell

Figure 6 and 7 shows response of cAD model in **Nest basket cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 6) 1.5 times threshold (Fig. 7)







LBC cell

Figure 8 and 9 shows response of bAD model in **Large basket cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 8) 1.5 times threshold (Fig. 9)





# <u>bFS</u>

Burst fast spiking Possible morphologies: SBC. Characteristics: Burst onset, 2 or more spikes, onset ISI<<steady state ISI, fast spiking, 100-500H. Figure 1 shows ion channels used to model this firing pattern. Figures 2-7 shows results for 2 different morphologies.



SBC cell

Figure 2 and 3 shows response of bFS model to step currents. **Amplitude of stimulus** Just above threshold (Fig. 2) 1.5 times threshold (Fig. 3)

Figure 4 and 5 shows response of bFS model to SineSpec wave generated by using function w(x) =sin(exp(exp(x/5))). Ex.













SBC cell

Figure 6 and 7 shows response of cAD model in **Small basket cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 6) 1.5 times threshold (Fig. 7)





# <u>bNA</u>

**Burst non adapting slow spiking. Possible morphologies**: BTC, DBC, LBC, SBC, BP, MC.

**Characteristics:** Burst onset, 2 or more spikes, no spike adaptation, slow spiking, <100Hz.

Figure 1 shows ion channels used to model this firing pattern. Figures 2-9 shows results for 3 different morphologies.



BTC cell

Figure 2 and 3 shows response of bNA model to step currents. **Amplitude of stimulus** Just above threshold (Fig. 2) 1.5 times threshold (Fig. 3)

Figure 4 and 5 shows response of bNA model to SineSpec wave generated by using function w(x) =sin(exp(exp(x/5))). Ex.













DBC cell Figure 6 and 7 shows response of bNA model in Double bouquet cell to step currents. Amplitude of stimulus Just above threshold (Fig. 6) 1.5 times threshold (Fig. 7)









Figure 8 and 9 shows response of bNA model in **LMartinotti cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 8) 1.5 times threshold (Fig. 9)





# <u>cAD</u>

**Continuous adapting firing pattern. Possible morphologies**: HC, CRC, PC, MC, BTC, DBC, BP, NGC, LBC, NBC, SBC, ChC.

**Characteristics:** Steady state ISI increases more than 20% in a 2 second train. Figure 1 shows ion channels used to model this firing pattern. Figures 2-9 shows results for 3 different morphologies.



L5CSPC cell

Figure 2 and 3 shows response of cAD model to step currents. **Amplitude of stimulus** Just above threshold (Fig. 2) 1.5 times threshold (Fig. 3)

Figure 4 and 5 shows response of cAD model to SineSpec wave generated by using function w(x) =sin(exp(exp(x/5))). Ex.



**Amplitude of stimulus** Just above threshold (Fig. 4) 1.5 times threshold (Fig. 5)

-100











MC cell

Figure 6 and 7 shows response of cAD model in **Martinotti cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 6) 1.5 times threshold (Fig. 7)



DBC cell

Figure 8 and 9 shows response of cAD model in **Double bouquet cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 8) 1.5 times threshold (Fig. 9)









# <u>cFS</u>

**Continuous fast spiking. Possible morphologies**: HC, CRC, LBC, SBC, NBC, ChC, MC, BTC, DBC. **Characteristics:** Non-adapting spiking, fast spiking, 100-500Hz. Figure 1 shows ion channels used to model this firing pattern. Figures 2-9 shows results for 3 different morphologies.







Figure 2 and 3 shows response of cFS model to step currents. **Amplitude of stimulus** Just above threshold (Fig. 2) 1.5 times threshold (Fig. 3)









![](_page_16_Figure_11.jpeg)

![](_page_17_Figure_0.jpeg)

NBC cell

Figure 6 and 7 shows response of cFS model in **Nest basket cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 6) 1.5 times threshold (Fig. 7)

![](_page_17_Figure_3.jpeg)

![](_page_17_Figure_4.jpeg)

![](_page_17_Picture_5.jpeg)

LBC cell

Figure 8 and 9 shows response of cFS model in **Large basket cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 8) 1.5 times threshold (Fig. 9)

![](_page_17_Figure_8.jpeg)

![](_page_17_Figure_9.jpeg)

# <u>cNA</u>

**Continuous non adapting firing pattern. Possible morphologies**: BTC, DBC, MC, BP, LBC, NBC, SBC. **Characteristics:** No spike adaptation, slow spiking, <100Hz. Figure 1 shows ion channels used to model this firing pattern. Figures 2-9 shows results for 3 different morphologies.

![](_page_18_Figure_2.jpeg)

![](_page_18_Picture_3.jpeg)

SBC cell

Figure 2 and 3 shows response of cNA model to step currents. **Amplitude of stimulus** Just above threshold (Fig. 2) 1.5 times threshold (Fig. 3)

Figure 4 and 5 shows response of cNA model to SineSpec wave generated by using function w(x) =sin(exp(exp(x/5))). Ex.

![](_page_18_Picture_7.jpeg)

![](_page_18_Figure_9.jpeg)

![](_page_18_Figure_10.jpeg)

![](_page_18_Figure_11.jpeg)

![](_page_19_Picture_0.jpeg)

BTC cell

Figure 6 and 7 shows response of cNA model in **Bitufted cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 6) 1.5 times threshold (Fig. 7)

![](_page_19_Figure_3.jpeg)

![](_page_19_Figure_4.jpeg)

![](_page_19_Picture_5.jpeg)

LBC cell

Figure 8 and 9 shows response of cNA model in **Large basket cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 8) 1.5 times threshold (Fig. 9)

![](_page_19_Figure_8.jpeg)

![](_page_19_Figure_9.jpeg)

# <u>dNA</u>

Delayed non adapting firing pattern. Possible morphologies: NGC, ChC. Characteristics: Delayed onset of spiking, no spike adaptation, slow spiking, <100H. Figure 1 shows ion channels used to model this firing pattern. Figures 2-5 shows results for different stimulus on a ChC cell.

![](_page_20_Figure_2.jpeg)

![](_page_20_Picture_3.jpeg)

**ChC cell** Figure 2 and 3 shows response of dNA model to step currents. **Amplitude of stimulus** Just above threshold (Fig. 2) 1.5 times threshold (Fig. 3)

Figure 4 and 5 shows response of dNA model to SineSpec wave generated by using function w(x) =sin(exp(exp(x/5))). Ex.

![](_page_20_Picture_6.jpeg)

![](_page_20_Figure_8.jpeg)

![](_page_20_Figure_9.jpeg)

![](_page_20_Figure_10.jpeg)

![](_page_20_Figure_11.jpeg)

# <u>rBS</u>

Repetitive bursting. Possible morphologies: Not known. Characteristics: Produces repetitive bursts riding on depolarization's. Figure 1 shows ion channels used to model this firing pattern. Figures 2-9 shows results for 3 different morphologies.

![](_page_21_Figure_2.jpeg)

![](_page_21_Picture_3.jpeg)

#### SBC cell

Figure 2 and 3 shows response of rBS model to step currents. **Amplitude of stimulus** Just above threshold (Fig. 2) 1.5 times threshold (Fig. 3)

Figure 4 and 5 shows response of rBS model to SineSpec wave generated by using function w(x) =sin(exp(exp(x/5))). Ex.

![](_page_21_Picture_7.jpeg)

Amplitude of stimulus Just above threshold (Fig. 4) 1.5 times threshold (Fig. 5)

-60

![](_page_21_Figure_9.jpeg)

![](_page_21_Figure_10.jpeg)

![](_page_21_Figure_11.jpeg)

 $\Lambda \Lambda \Lambda M M$ 

![](_page_22_Picture_0.jpeg)

**BTC cell** 

Figure 6 and 7 shows response of rBS model in **Bitufted cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 6) 1.5 times threshold (Fig. 7)

![](_page_22_Figure_3.jpeg)

![](_page_22_Figure_4.jpeg)

![](_page_22_Picture_5.jpeg)

LBC cell

Figure 8 and 9 shows response of rBS model in **Large basket cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 8) 1.5 times threshold (Fig. 9)

![](_page_22_Figure_8.jpeg)

![](_page_22_Figure_9.jpeg)

# <u>tBS</u>

![](_page_23_Figure_1.jpeg)

model this firing pattern. Figures 2-9 shows results for 3 different morphologies.

![](_page_23_Picture_3.jpeg)

MC cell

Figure 2 and 3 shows response of rBS model to step currents. **Amplitude of stimulus** Just above threshold (Fig. 2) 1.5 times threshold (Fig. 3)

Figure 4 and 5 shows response of rBS model to SineSpec wave generated by using function w(x) =sin(exp(exp(x/5))). Ex.

![](_page_23_Picture_7.jpeg)

**Amplitude of stimulus** Just above threshold (Fig. 4) 1.5 times threshold (Fig. 5)

![](_page_23_Figure_9.jpeg)

![](_page_23_Figure_10.jpeg)

Injected Current = 0.272461 nA 40

![](_page_23_Figure_12.jpeg)

![](_page_23_Figure_13.jpeg)

![](_page_23_Figure_14.jpeg)

![](_page_24_Picture_0.jpeg)

NBC cell

Figure 6 and 7 shows response of rBS model in **Nest basket cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 6) 1.5 times threshold (Fig. 7)

![](_page_24_Figure_3.jpeg)

![](_page_24_Figure_4.jpeg)

![](_page_24_Picture_5.jpeg)

SBC cell

Figure 8 and 9 shows response of rBS model in **Small basket cell** to step currents. **Amplitude of stimulus** Just above threshold (Fig. 8) 1.5 times threshold (Fig. 9)

![](_page_24_Figure_8.jpeg)

![](_page_24_Figure_9.jpeg)