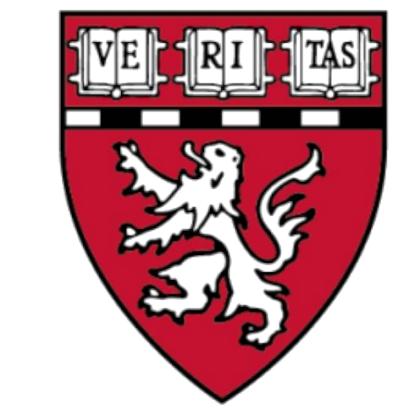


# Towards a detailed mechanistic model of human cortical microcircuits that accurately predicts the cellular- and circuit-level effects of TMS



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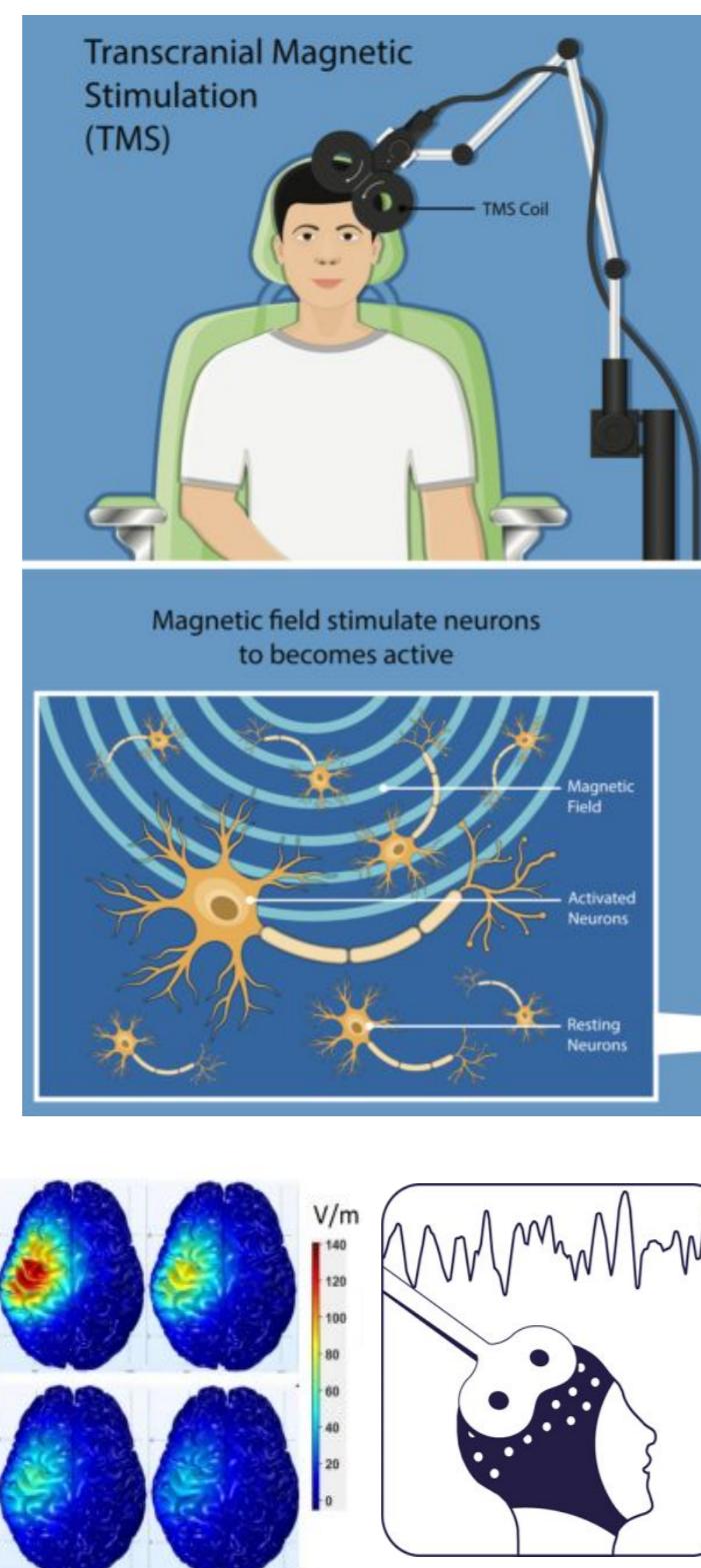
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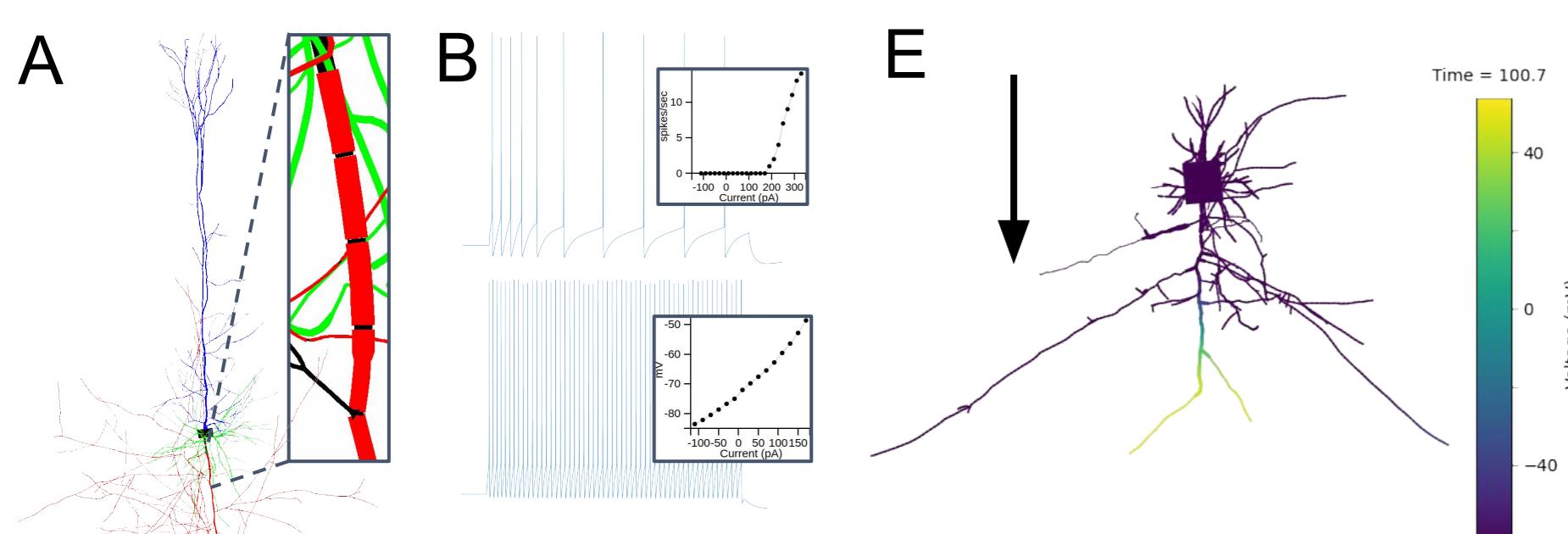
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## Transcranial magnetic stimulation (TMS)

- TMS is a non-invasive neuromodulation technique which alters activity in a relatively small brain region<sup>1</sup>. An electromagnetic coil generates strong electric fields in the brain, which can be used to treat a range of neurological conditions<sup>2</sup>.
- Simulations can help in predicting the TMS effect with strong intensity and frequency avoiding side effects in patients.
- How TMS affects brain circuit dynamics remains an unsolved problem<sup>3</sup>.
- Realistic human brain model is missing.
- Only mechanistic biophysical simulation of brain circuits can generate accurate predictions at the molecular, cellular and circuit scales; simulate LFP and EEG recordings and TMS stimulation effects.
- Simulations can be used to inform TMS optimal parameters for each clinical condition providing greater efficiency in personalized treatments.



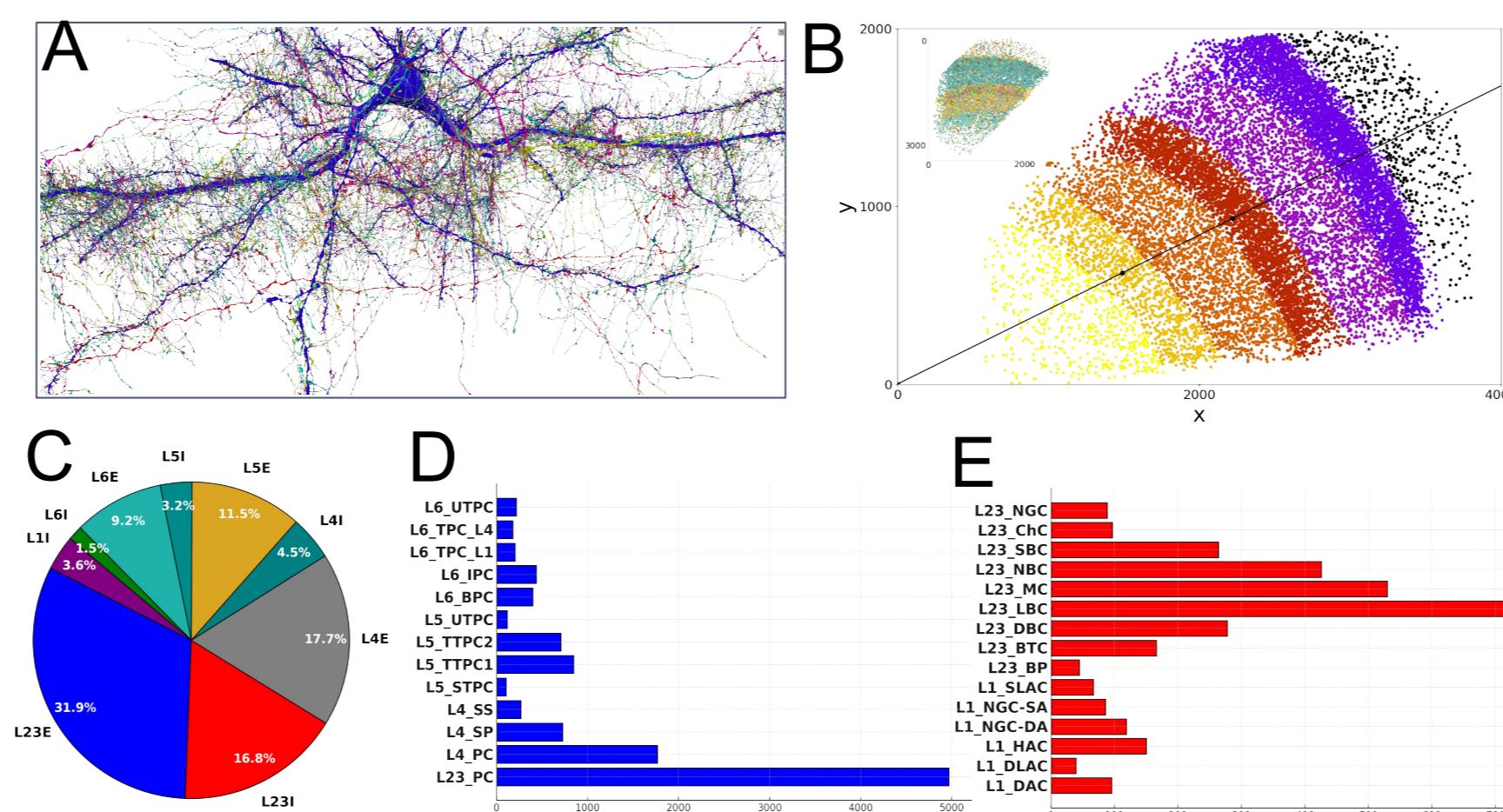
## Neurons, axons, and TMS pulse



**Figure 1 - Morphology and TMS response of full reconstructed neurons with detailed axons.** (A) Exemplar human neuron model with morphology and biophysics adapted from rat. Apical dendrites (blue), basal dendrites (green), soma (black), and axon (red with black nodes). (B) Exemplar rescaled human cell traces simulation (Exc and Inh, under 300 pA square pulse) and V-I and F-I curves from Allen Brain Atlas recordings ([celltypes.brain-map.org](http://celltypes.brain-map.org), ID569844159). (C) Subthreshold dynamic under TMS with uniform E-field and 10 V/m, voltage traces recorded in response to a 1 ms biphasic pulse. (D) Suprathreshold dynamic under TMS, the same as C but with 100 V/m. (E) All sections V at time 100.7 ms of D. (F) LFP of D.

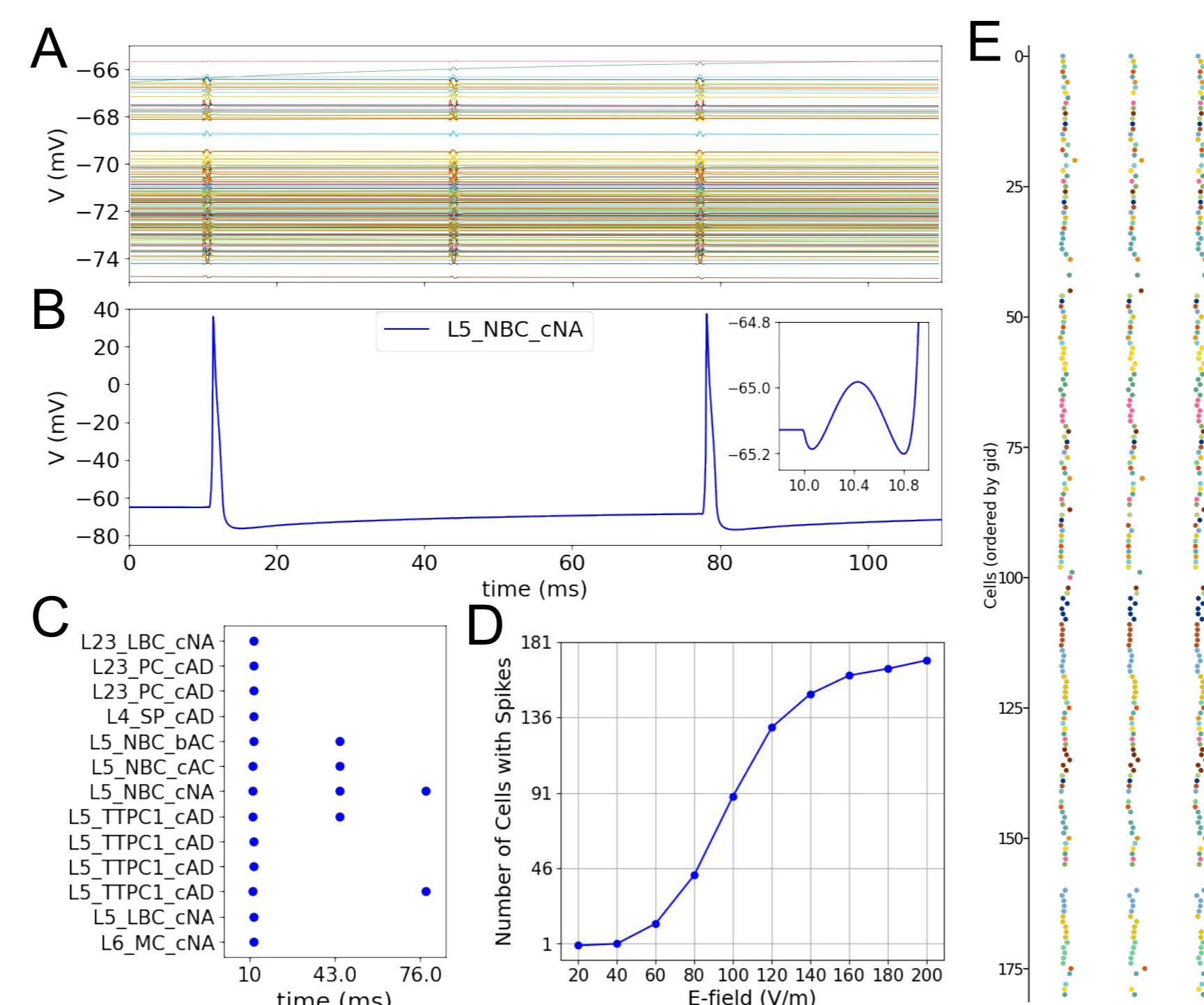
## Human cortex and Network model

We extended a previous model<sup>3</sup> including 55 morphological types, 207 morpho-electrical types, and 1035 morphologies. Distance dependence connection rules, synaptic background stimulation and short-term plasticity were included to reproduce *in vivo* like firing patterns<sup>4</sup>. The neurons were distributed based on electron microscopy reconstruction of human cortex fraction<sup>5</sup>. Using a high level python interface NetPyNE and NEURON simulator, we simulated the intra and extracellular voltages of all sections over all neurons. The simulations provide the firing activity, voltage traces, and LFPs as outputs; these can be compared with EEG recordings during TMS sessions.



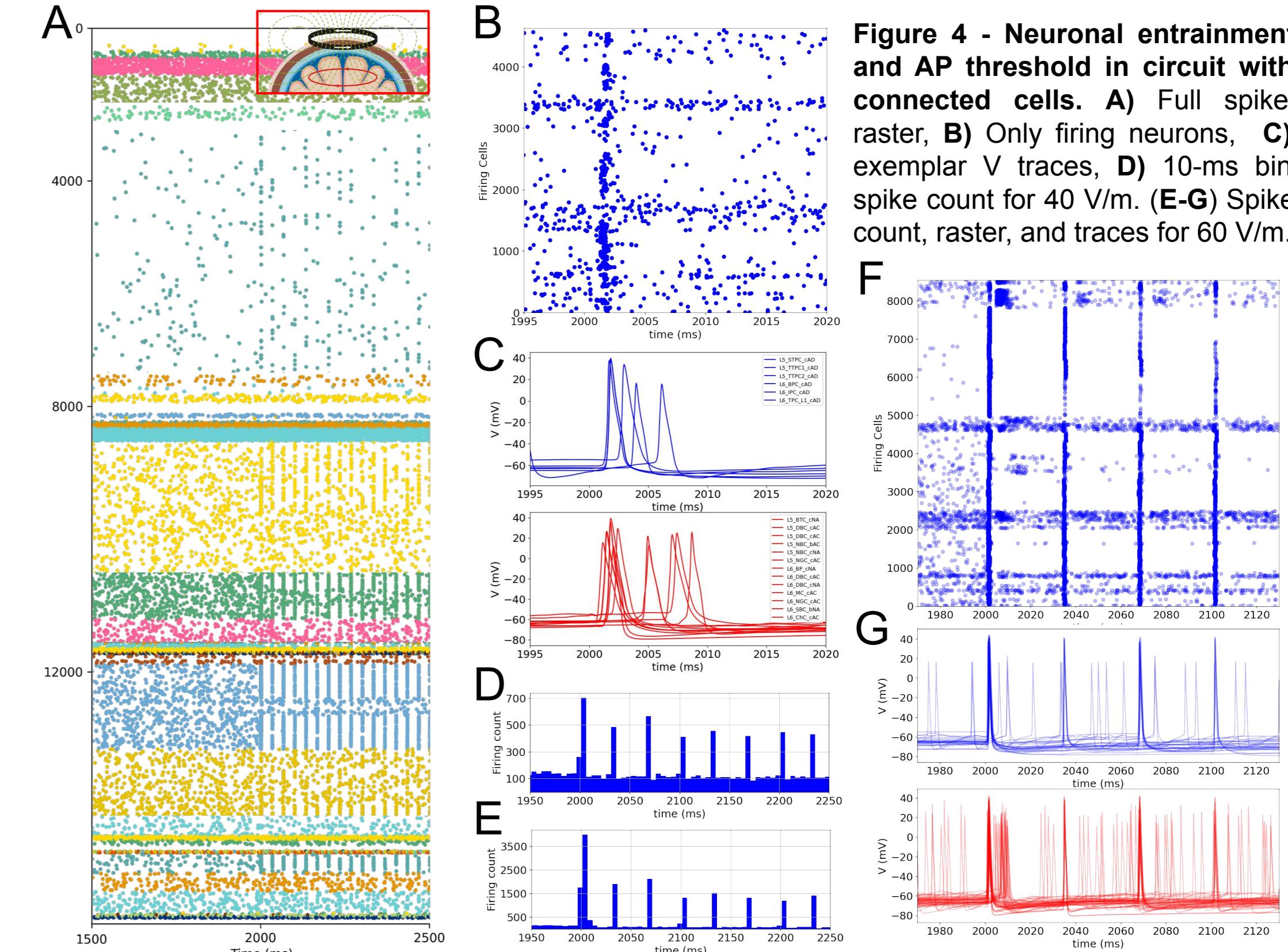
**Figure 2 - Human cell distribution based on electron microscopy reconstruction (h01)<sup>5</sup>.** (A) Example of a reconstructed neuron with axons projections. (B) Cell distribution over the cortical layers (inset rotated positions). (C) Distribution of 15,567 neurons from h01. (D-E) Number of cells for excitatory and L1-3 inhibitory populations in our network.

## AP threshold and cell variability

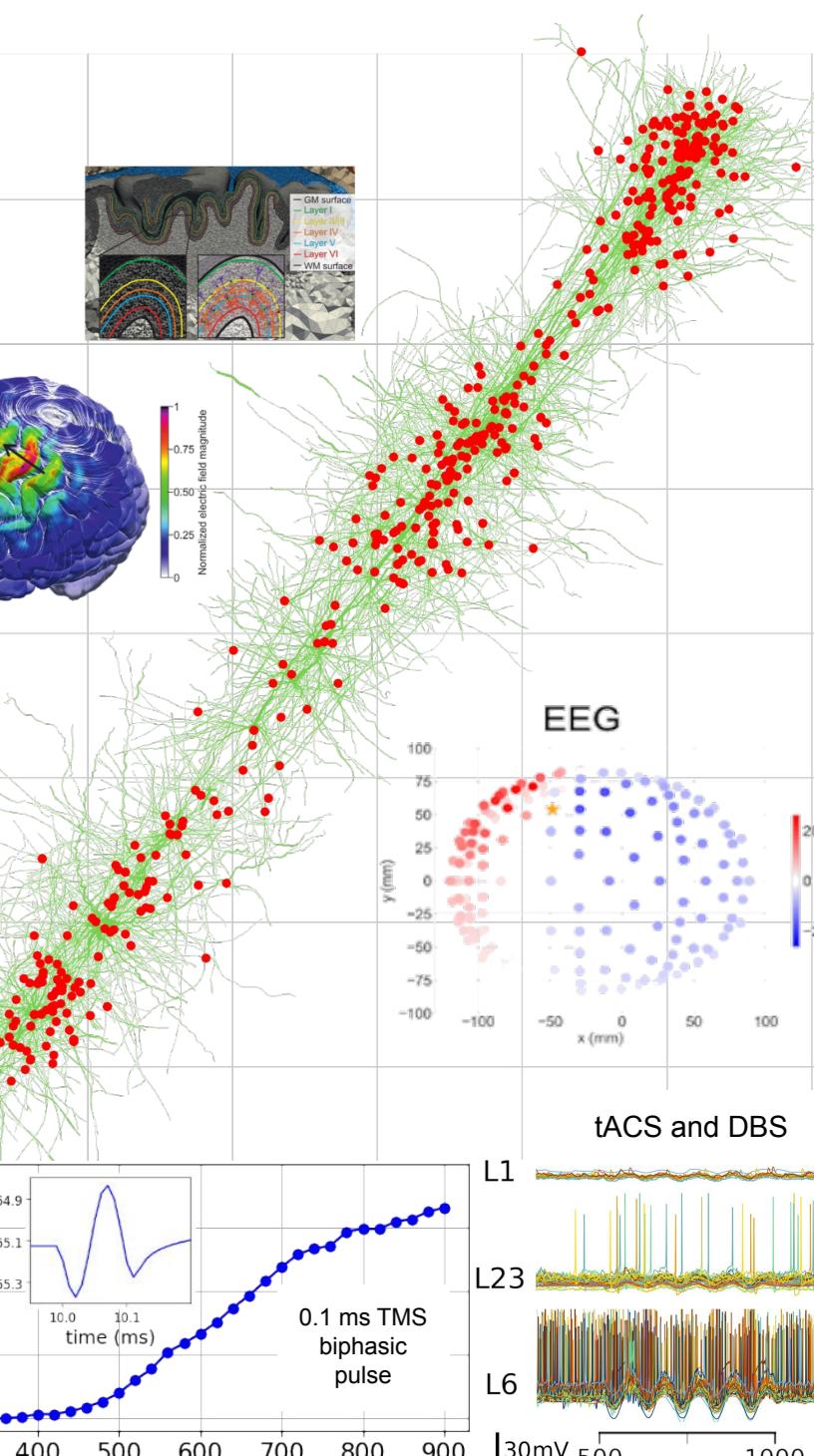
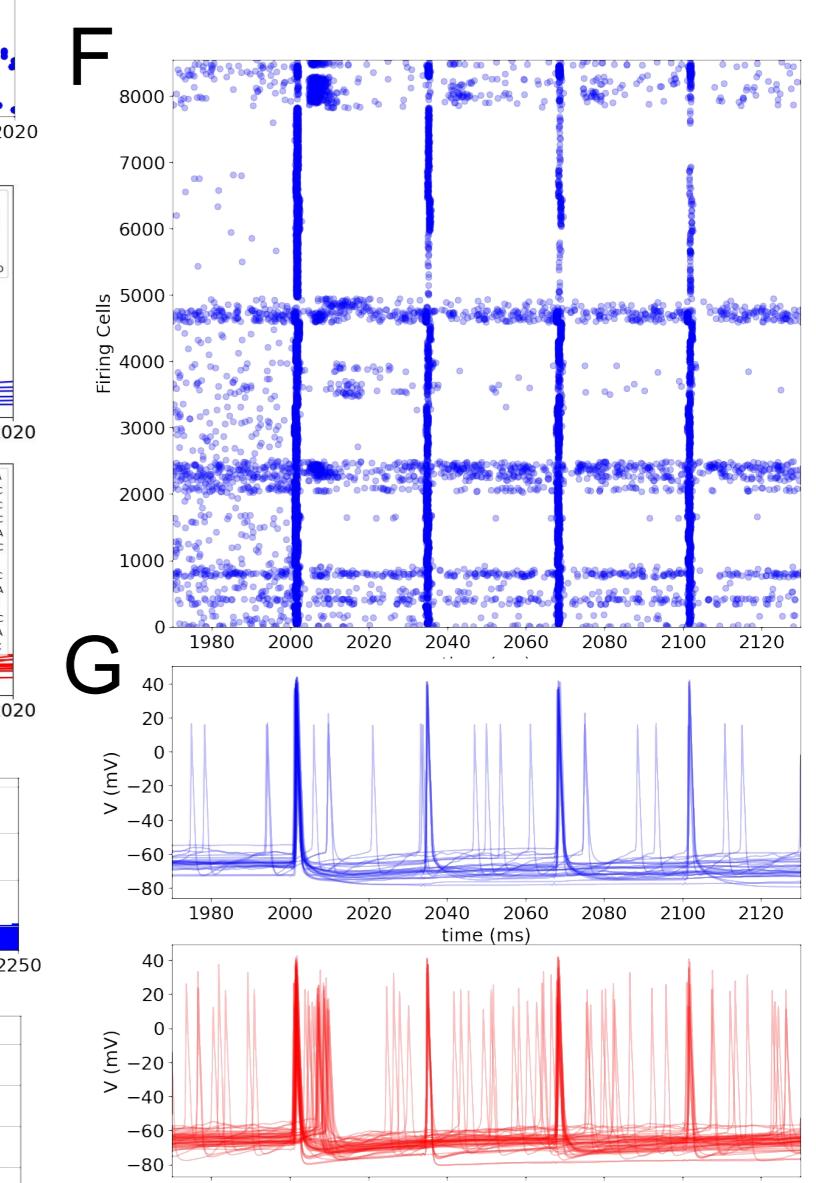


**Figure 3 - TMS simulation for isolated neurons.** (A) All traces for 20 V/m. (B) only one spike for 40 V/m. (C) Raster plot for 60 V/m. (D) Number of cells affected for each E-field intensity. (E) Raster plot for 200 V/m. All TMS E-field intensities are given for a 1ms biphasic pulse.

## rTMS in human cortical model with *in vivo*-like activity



**Figure 4 - Neuronal entrainment and AP threshold in circuit with connected cells.** A) Full spike raster, B) Only firing neurons, C) exemplar V traces, D) 10-ms bin spike count for 40 V/m. (E-G) Spike count, raster, and traces for 60 V/m.



## Conclusions and Perspectives

- We build the first detailed network model of human cortex with realistic soma, dendrites, and axons physiology and morphology.
- In response to 1 ms duration biphasic TMS pulses, the cells exhibited AP threshold diversity as observed in patients<sup>6,7</sup>.
- Neural network firing activity plays a fundamental role in altering the TMS AP threshold. Robust neuronal entrainment to TMS occurred in active networks for 40 V/m and 60 V/m (Fig 4), whereas minimal response is observed in isolated neurons (Fig 3) for these E-fields.
- Our approach can be adapted to study Transcranial Alternating Current Stimulation (tACS) and Deep Brain Stimulation (DBS)
- Next steps:
  - Human cortical reconstruction (h01): correct cells with severed morphology and add new synapses
  - Cell physiology and whole brain: TVB, BICAN, SimNIBS, ...
  - Validate against human TMS-EEG clinical data
  - Simulate electrophysiological biomarkers: Alzheimer, epilepsy, depression, and schizophrenia
  - Optimization of TMS parameters for personalized therapies via simulation

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