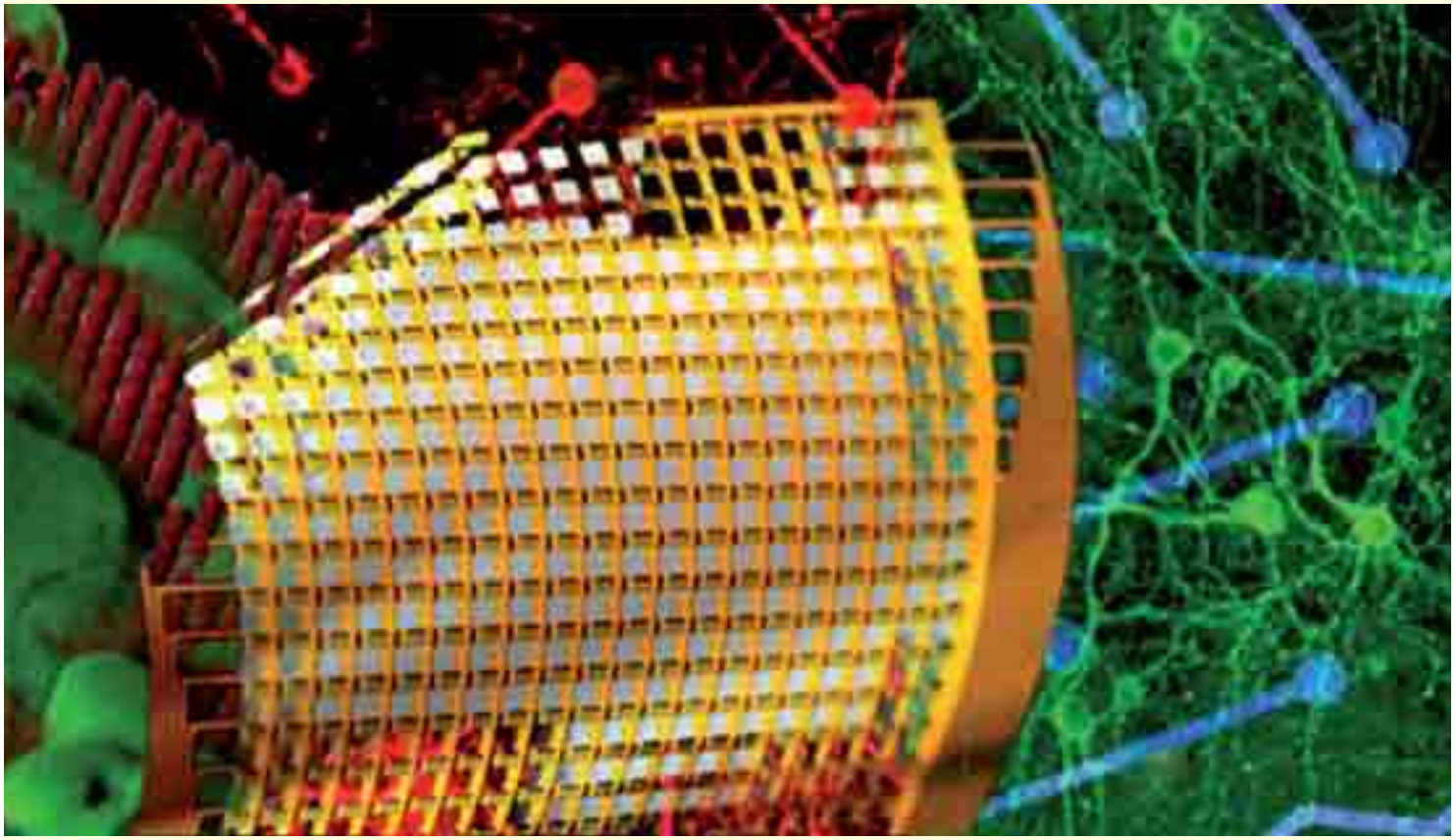
Proceedings

MEA Meeting 2012

July 10 - July 13, 2012, Reutlingen, Germany

8th International Meeting on Substrate-Integrated Microelectrode Arrays



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Modeling the dynamics of excitability and its temperature sensitivity

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1 Background/Aims

(Sub)cellular mechanisms underlying action potential (AP) generation in neurons grown on substrate arrays of microelectrodes (MEAs) were recently shown to display extremely rich dynamical properties [1]. Upon repeated electrical stimulation, antidromically evoked APs show instability, fluctuations, and intermittency, whose features are unexpected from conventional biophysical models.

A novel and more accurate quantitative description of excitability is then imperative, if neural dynamics and plasticity have to be captured *in silico* [2] for very large-scale neocortical simulations [3].

Here, we replicate the experiments of [1], and define a mathematical neuron model, introducing non-conventional state-dependent inactivation descriptions of sodium currents [4]. We qualitatively compare model and experiments under the same stimulation paradigm, and specifically use the model to predict the dependency of the stability and intermittency of evoked APs on temperature. We speculate that, by employing temperature as a global modulator of subcellular kinetics, access to complementary information on the excitability processes can be readily gained.

2 Methods

Rat cortical neurons were dissociated and plated, at 3000 cells/mm^2, over titanium nitride microelectrodes arrays (MEAs; 200 μm spacing, 30 μm electrode diameter) whose surface was previously treated by polyethylenimine (10 mg/ml) and laminin (0.02 mg/ml). Neurons were incubated at 37°C - 5% CO_2 [5] in culture medium (Neurobasal by 2% B-27, 10% serum, 1% L-glutamine, and 1% Penicillin-Streptomycin) that was changed 3 times a week.

Recordings were performed by a MCS1060BC amplifier at 25 kHz, in a low-humidity incubator with 5% CO_2 atmosphere, and at 35°C, 37°C, or 39°C. Thirty minutes before each recording session, synaptic receptors antagonists (i.e. 20 ⌠M AP-V, 10 ⌠M CNQX, 10 ⌠M SR-95531) were bath applied to block spontaneous activity. Changes of the incubating temperature were followed by an accommodation interval of at least 20 min, before data recording. Repetitive biphasic pulses (±0.8 V, 200 msec) were generated (STG1002) at 1-20 Hz, and delivered by one extracellular electrode, employed in monopolar configuration [6]. MC_Rack software was used for data acquisition. Offline high-pass filtering (400 Hz) and analysis were performed to extract the occurrence time of evoked APs.

A deterministic, single-compartment conductance-based mathematical model derived from the Connor-Stevens model [2] was developed and computer simulated in NEURON [7]. Briefly, the model includes a sodium current and delayed-rectifier and A-type potassium currents [4]. The sodium current was modified from the fast-inactivating description [2] to incorporate state-dependent inactivation as in [6] (Fig. 1A). The effect of temperature on the transition rates was accounted for by a multiplicative factor $Q_{10} = 3$ [2].

3 Results

- APs complex past-history dependence, first described in [1], is experimentally reproduced;
- APs latency and instability are highly temperature-sensitive, over a small range (±2°C);
- A novel biophysical model, based on state-dependent inactivation of sodium-currents (Fig. 1A), qualitatively captures the experimental data (Fig. 1D).
- The model predicts a latency decrease (~0.1-0.2 msec/°C) with increasing temperature, and an increase of the time-scales associated to APs generation instability (Fig.1B).
- Preliminary experiments reveal good agreement with both model predictions (Fig. 1C-D).

4 Conclusion/Summary

We replicated a recently proposed experimental paradigm, enabling to probe neuronal excitability over extended time-scales [1]. We formulated a novel mathematical model of AP generation to reproduce qualitatively the experimental data, with in mind its incorporation in large-scale simulations [3]. The same model allows us to make predictions on how temperature affects the dynamics of excitability. In fact, temperature has a global influence on the kinetics of a variety of sub-cellular phenomena, directly and indirectly related to excitability. Temperature might thus serve as a control signal, to extract

complementary information and to validate the model description. When model predictions were tested experimentally, a qualitatively good agreement was found, confirming non-trivial consequences on APs latency and APs generation instability. In conclusion, the recently disclosed dynamical complexity of single-cell excitability, and its accurate biophysical modeling, are of great impact for the study of emergence of activity-dependent correlations, long-lasting plasticities, information encoding and, ultimately, for behaviorally relevant time-scales.

References

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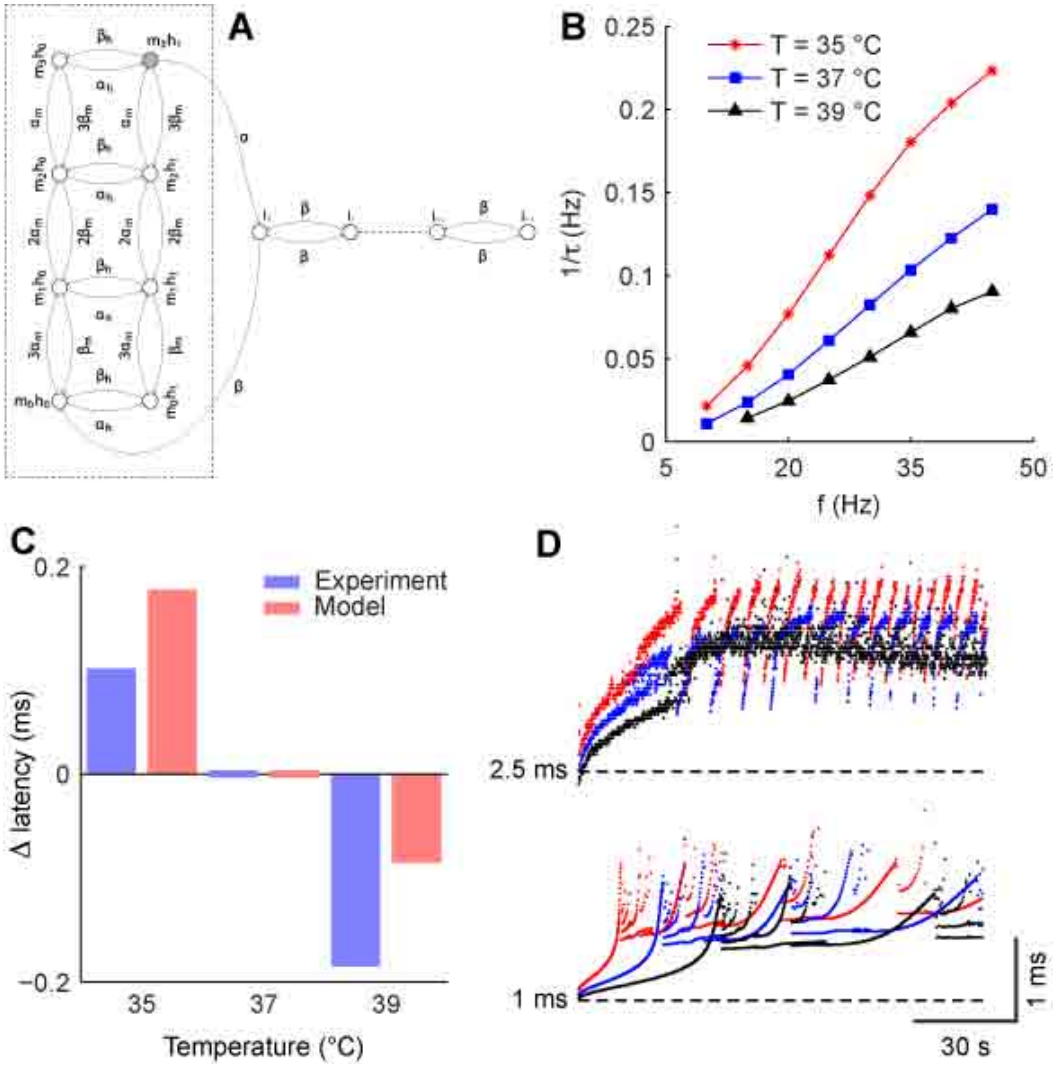

Figure 1: A standard sodium current model is altered as in [4], to include state-dependent inactivation in its kinetic description (**A**). When computer simulated, the model neuron replicates APs generation instability and intermittency, as well as a decrease in the time of intermittency onset for increasing stimulation frequencies (**B**). For a limited temperature range, the model predicts an overall speed-up of evoked APs (**C**), and a substantial increase in instability time-scales with increasing temperature (**D**). Preliminary experiments qualitatively confirm model predictions (**C**-**D**).