A Mathematical Model of the Electrical and Mechanical Activity of the Uterine Cell

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Introduction

Premature or malfunctions of uterus muscle contraction is the major cause of pre-term birth, which is associated with a higher risk of mortality and morbidity for the foetus. However, the mechanisms underlying the genesis of electrical and mechanical dynamics of the mammalian uterus are not well understood. Multi-scale physical models of mammalian uterus with biophysical, histological and anatomically details provide a powerful platform for studying the electrical and mechanical dynamics of uterine systems. The aim of the study was to develop a mathematical model to simulate the electrical action potentials, intracellular Ca^{2+} handling and mechanical force development for murine uterine cells.

Methods and Results

A new model of the murine uterine cell was constructed based on extant experimental data on the kinetics of ionic channels and the intracellular Ca^{2+} handling. Model equations and parameters for each individual ion channel were derived from and validated against to experimental data (1). Myometrial electrical activity was then coupled to the corresponding cellular mechanical contractions. A bifurcation analysis algorithm XPPAUT (2) was then used to identify the parameter range that gives rise to automaticity of the model.

Figure 1 shows the simulated spiked action potential (AP; top panel) and the corresponding intracellular Ca^{2+} transient ($[Ca^{2+}]_i$; middle panel) in response to an external stimulus (I_{st}; bottom panel) with an amplitude -0.5 pA/pF and a duration of 2 s. Such a spiked AP and a stepped increased of $[Ca^{2+}]_i$ during the time course of spiked APs are matching to experimental data.

Figure 2 shows the simulated APs, intracellular $[Ca^{2+}]_i$, fraction stress and cellular force development in response to a single stimulus (Figure 2A) and a series of stimuli (Figure 2B). An increase in the fraction of stress was observed from 60% at a single stimulus to 80% at a series of stimuli. This is due to an increased $[Ca^{2+}]_i$ in response to a series of stimuli.

Further bifurcation analysis demonstrated that varying the maximal channel conductance of I_{CaL}, I_{Cl}, I_{K2} and I_{Na} resulted in a cascade of bifurcation processes that lead the model to transient from a quiescent cell with a stable steady state to pacemaking cell with auto-rhythmic oscillating states. As an example, Figure 3 shows results of bifurcation analysis with changes of g_{CaL}. In this case, Hopf bifurcation occurs near the turning points of a continuous steady state, marking the region leading to auto-rhythmic bursting activity of the uterine cell model.

Conclusions and Discussion

We have constructed a novel biophysically detailed mathematical model for the electrical and mechanical activities of the single murine uterine cell. The model was based on experimental data and

validated by its ability to reproduce the electrical AP and mechanical force development of the cell, which match to experimental data. Using bifurcation analysis, we have identified the mechanisms underlying the genesis of auto-rhythmic action potentials. The results help to explain the genesis of regular, forceful contractions experienced during parturition.

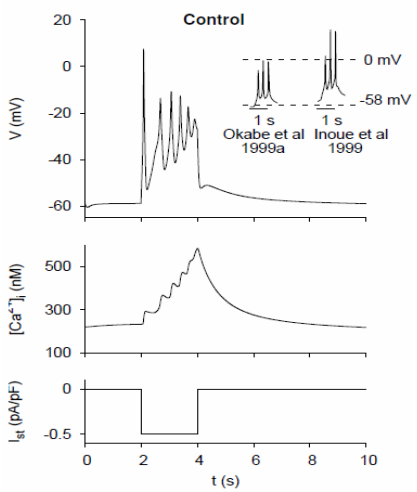

Figure 1. Simulated AP, $[Ca]_i^{2+}$ and the stimulus current in control condition.

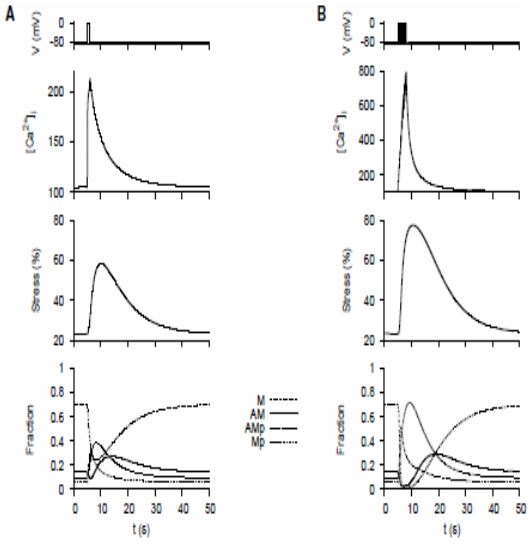

Figure 2. Mechanical stress development with (A) a single pulse from -80 to 0 mV for 200 ms reaching 60% of fraction stress produced by cell and (B) a series of ten 100 ms pulses from -80 to 0 mV at 3Hz reaching 80% of fraction stress. The increase being due to the higher concentration of $[Ca]_i^{2+}$ resulting in increased tension within the cell.

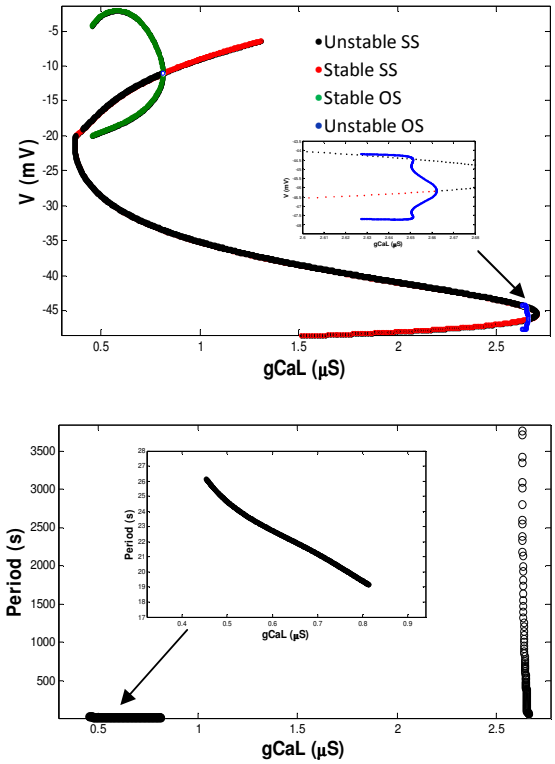

Figure 3. Bifurcation analysis and frequency profiles of I_{CaL}. The turning point around 2.75 µS has a nearby unstable oscillating state. The oscillating state near 0.75 µS is stable.

References.

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