Ionic Mechanisms of Propagation in Cardiac Tissue: Roles of the Sodium and L-type Calcium Currents During Reduced Excitability and Decreased Gap Junction Coupling
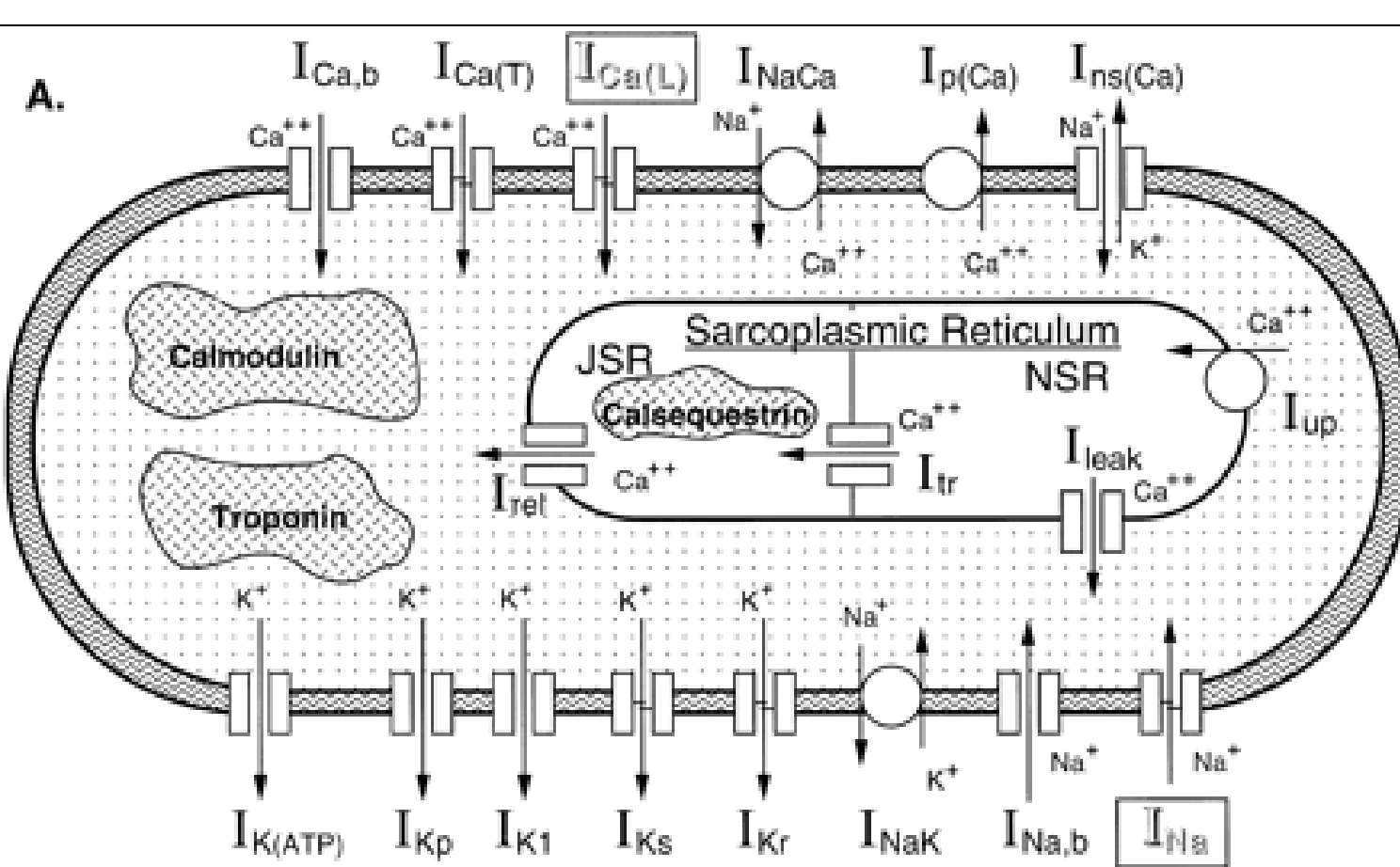
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Abstract: In cardiac tissue, reduced membrane excitability and reduced gap junction coupling both slow conduction velocity of the action potential. However, the ionic mechanisms of slow conduction for the two conditions are very different. We explored, using a multicellular theoretical fiber, the ionic mechanisms and functional role of the fast sodium current, I_{Na}, and the L-type calcium current, $I_{Ca(L)}$, during conduction slowing for the two fiber conditions. A safety factor for conduction (SF) was formulated and computed for each condition. Under normal conditions and conditions of reduced excitability, $I_{Ca(L)}$ had a minimal effect on SF and on conduction. However, $I_{Ca(L)}$ played a major role in sustaining conduction when intercellular coupling was reduced. This phenomenon demonstrates that structural, nonmembrane factors can cause a switch of intrinsic membrane processes that support conduction.

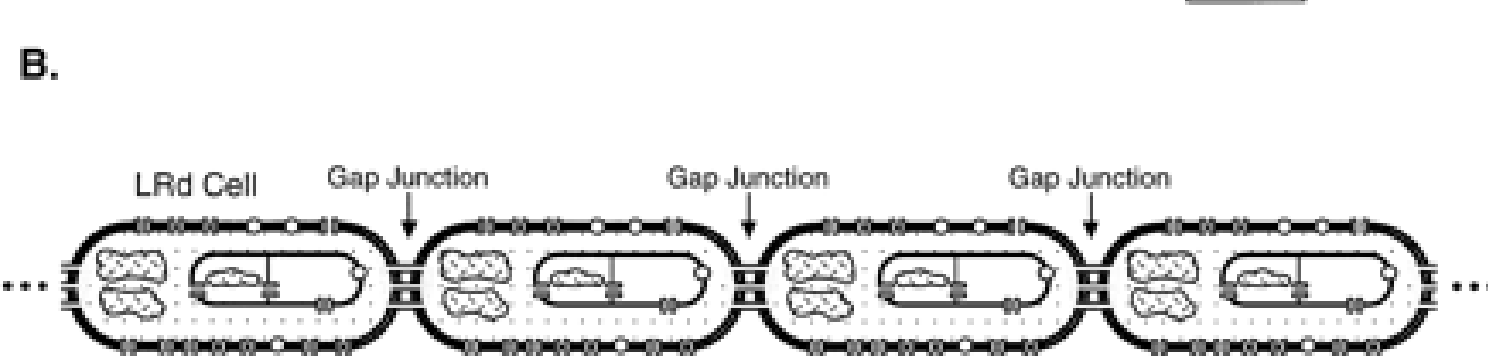$$SF = \frac{\int_A I_C \cdot dt + \int_A I_{out} \cdot dt}{\int_A I_{in} \cdot dt} A \mid Q_m > 0$$

Conduction succeeds for SF>1; Fails for SF<1

Safety Factor for Conduction (SF)

• Reduced excitability lowers SF (I_C is the capacitive current of the cell, I_{out} is the axial current between the cell and its downstream neighbor and I_{in} is the axial current that enters the cell from its upstream neighbor).

• Long intercellular propagation delays associated with highly reduced gap junction coupling suggest a role for $I_{Ca(L)}$ in supporting conduction.
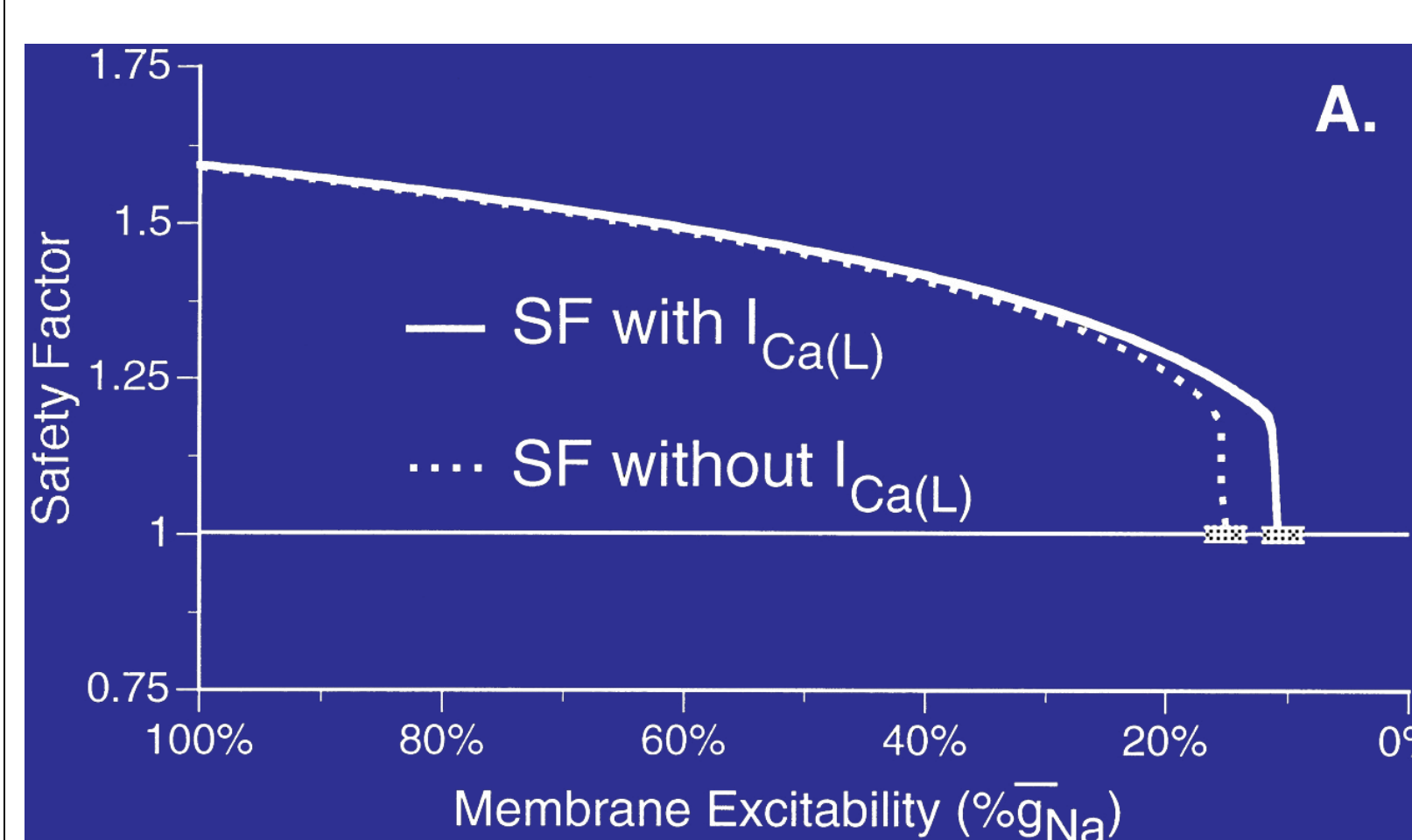

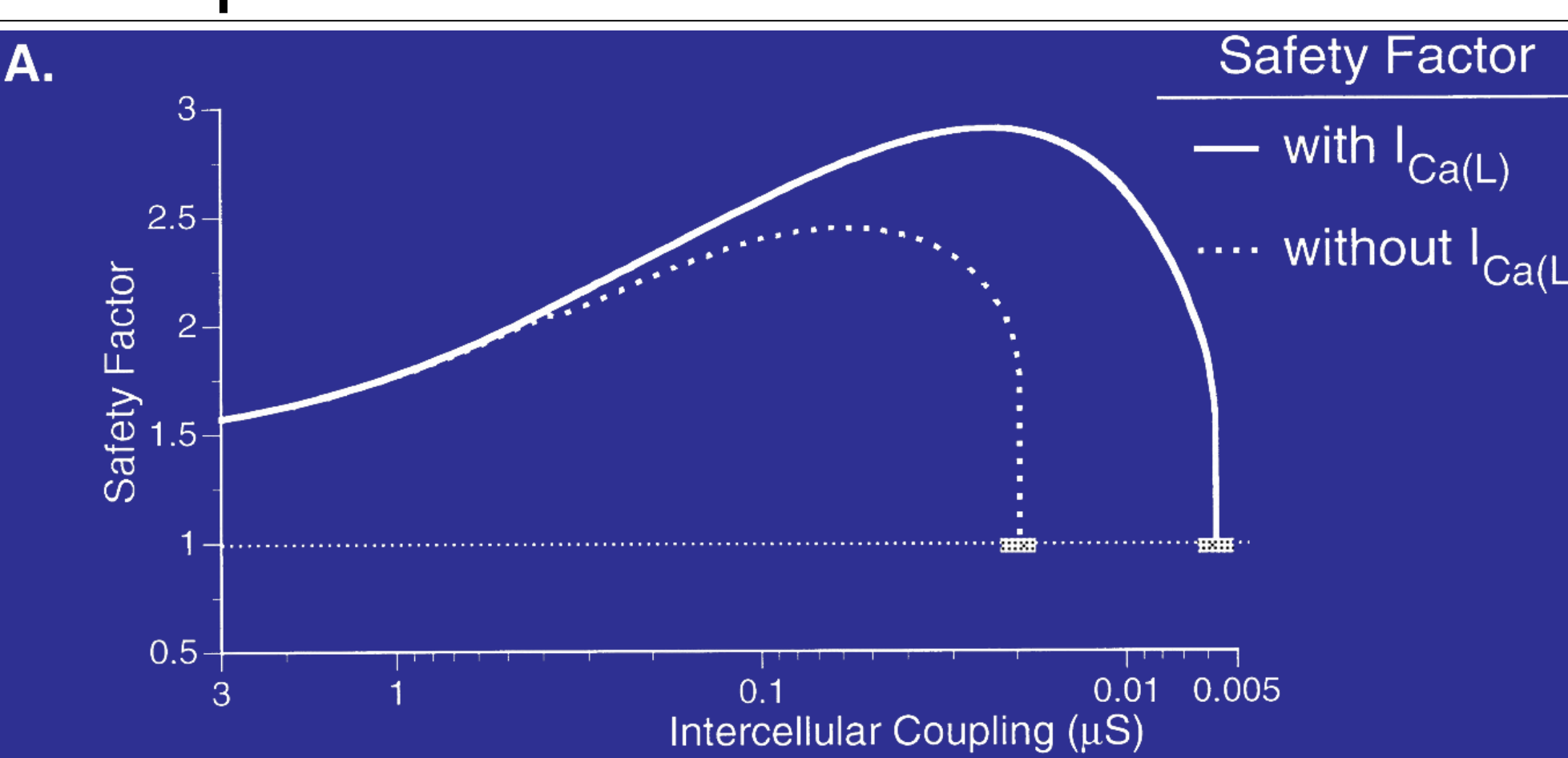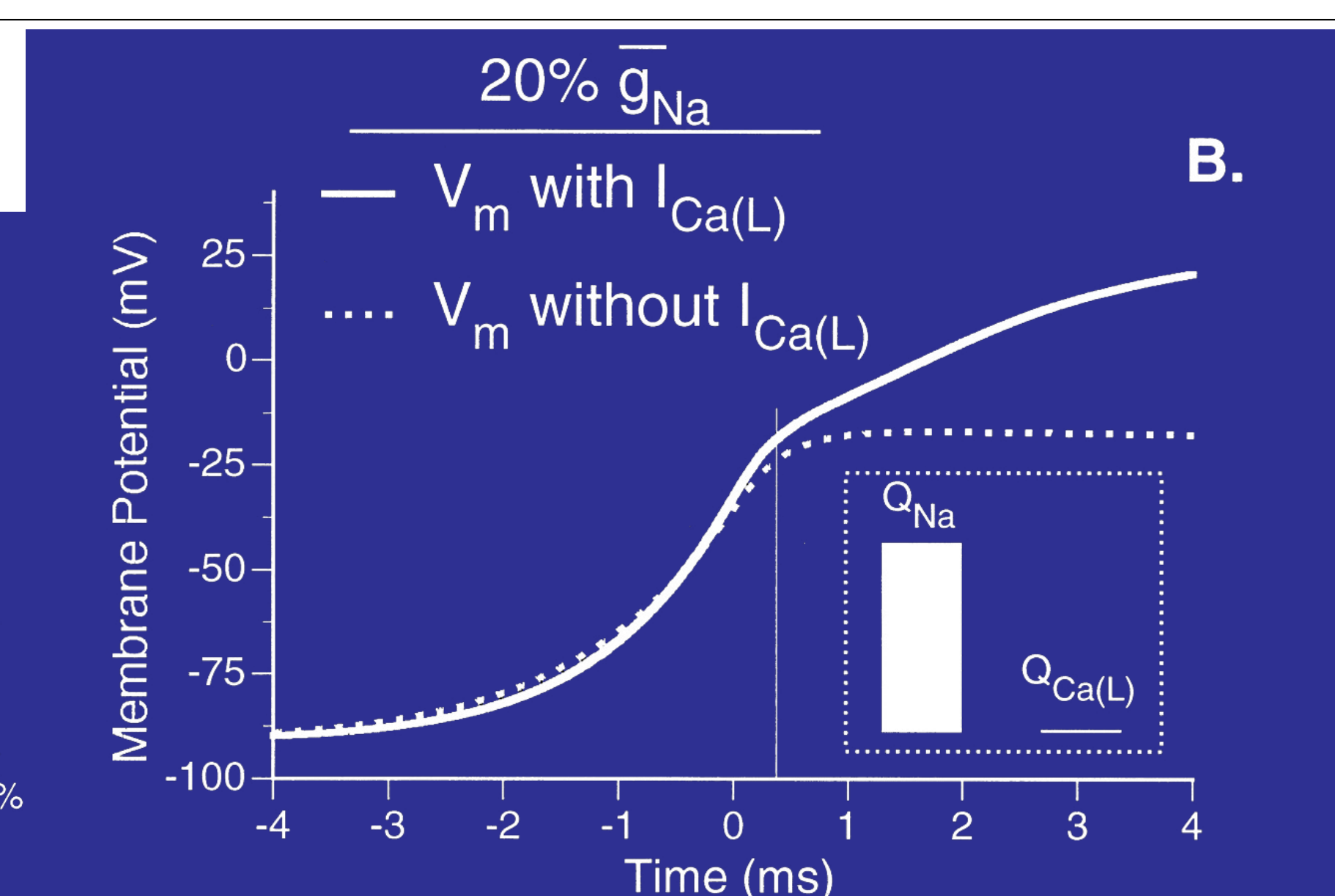The theoretical fiber (**B**), is composed of serially arranged Luo-Rudy ventricular cell models (**A**) interconnected by resistive gap junctions. Temporal transmembrane current fluxes are related to spatial current flow by a finite difference approximation of the cable equation.

Reduced Excitability

• SF for a fiber without $I_{Ca(L)}$ drops faster as excitability is reduced than for a fiber with $I_{Ca(L)}$ (**A**).

• Even when excitability is reduced to 20% (**B**), charge contributed by I_{Na} to support conduction is much larger than charge contributed by $I_{Ca(L)}$ (**B** inset bar graph).

Reduced Intercellular Coupling

• SF shows biphasic behavior (increase then decrease) as a function of intercellular coupling (**A**).

• $I_{Ca(L)}$ supports conduction that otherwise fails (SF<1) over more than threefold decrease in intercellular coupling (**A**).

• When decreased coupling causes long propagation delays (**B**), $I_{Ca(L)}$, which is the main depolarizing current during the action potential plateau, becomes extremely important (**B** inset).

• For highly reduced coupling (**C**), I_{Na} is necessary to bring the membrane into the activation range of $I_{Ca(L)}$, but the major source of depolarizing charge (**C** inset) and the most significant current to sustain propagation is $I_{Ca(L)}$.
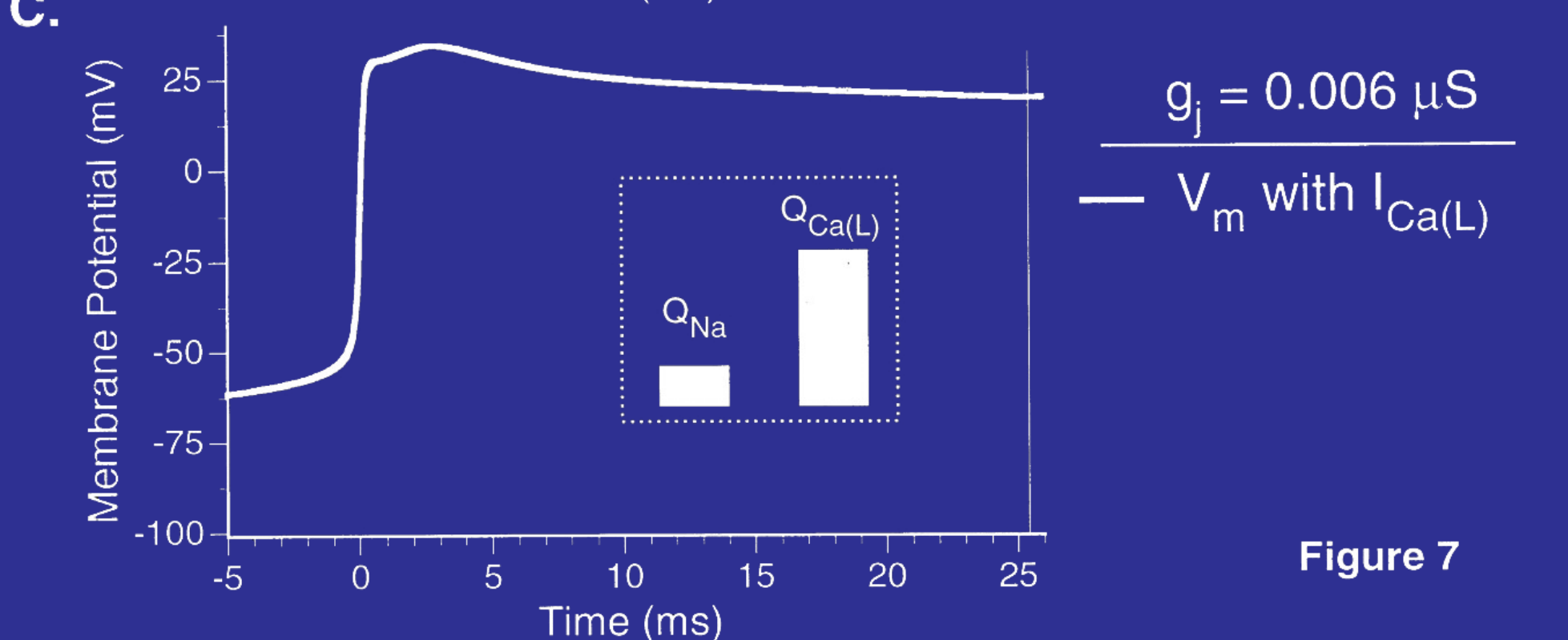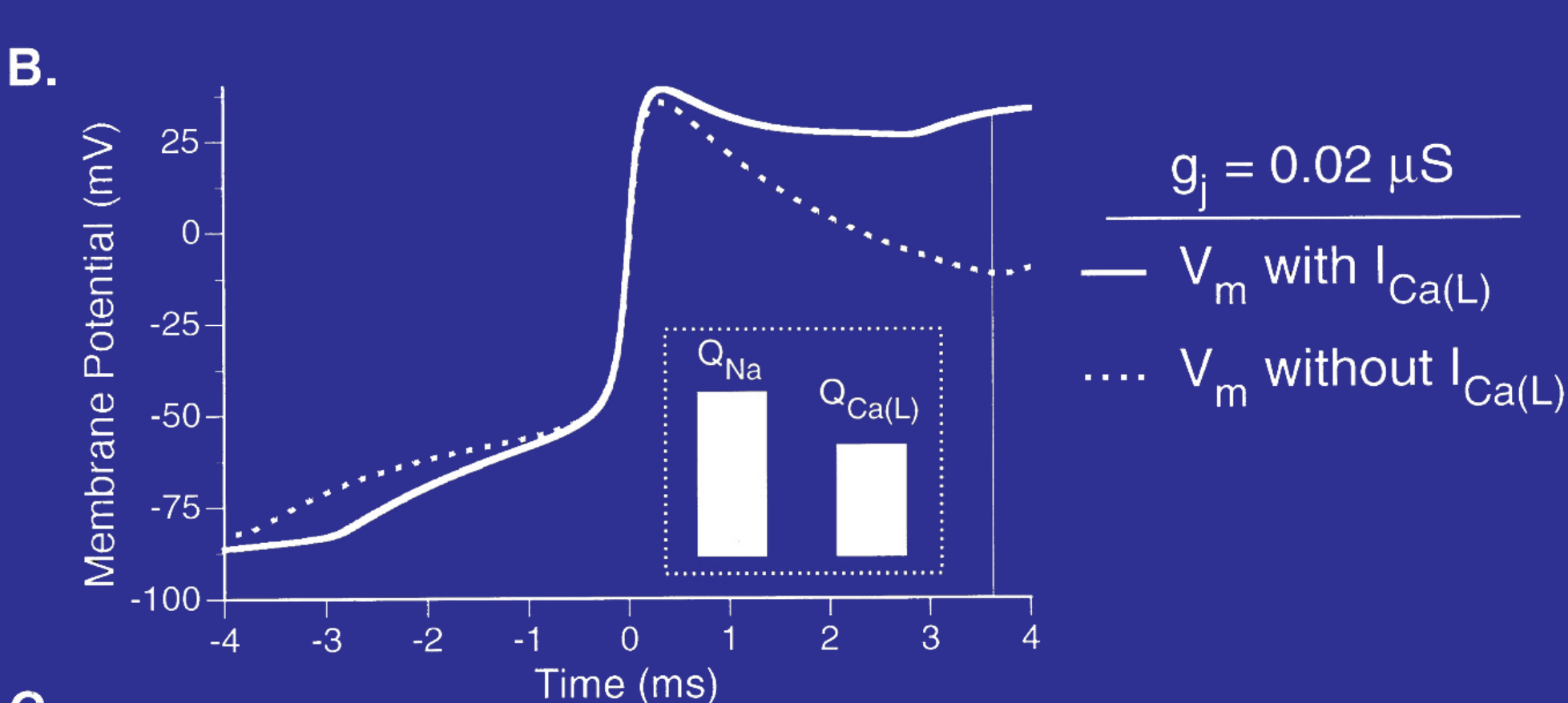
Conclusions

• A fiber with depressed membrane excitability still relies on I_{Na} for action potential conduction.

• Slow conduction due to gap junction decoupling is robust (high SF).

• Reduced gap junction coupling changes the dynamics of membrane currents during the action potential and switches the membrane to an $I_{Ca(L)}$-dependent mode of operation.

• Targets for intervention (drug treatment, genetic modification) should be very different in treating propagation-related arrhythmias (reentry) associated with reduced excitability or intercellular coupling.