Generation of Sex-Specific Atrial Cell Model Populations by Optimal Biomarker Combination

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Mathematical cellular models allow to personalize therapeutic strategies, but current cellular models do not include sex-specific relevant differences at cellular level. Fitting atrial electrophysiological models using multiple biomarkers may become infeasible when strict physiological constraints are imposed. In this work, we identify optimal combinations of biomarkers that enable the generation of subpopulations of sex-specific ionic models including inter-patient variability.

A population of 15,000 0-D ionic models was generated by varying key conductances (g_{Na}, g_{K1}, g_{CaL}, g_{to}; Panel A), and action potential biomarkers ($APD_{\{20,50,90\}}$, APA, RMP, V_{max}; Panel B) were computed at steady state. Subpopulations were selected by enforcing sex-specific biomarker ranges, and a rarity-based filtering was applied to discard non-representative sex-specific subpopulations. The resulting combinations were evaluated based on their ability to reproduce ionic conductance differences reported in the literature.

The optimal combination (V_{max} and APD_{20}; Panel C-D) enabled the generation of distinct male and female populations and reproduced relevant electrophysiological trends. These results demonstrate that selecting biomarker combinations is a viable alternative for identifying ionic models that capture sex-related variability.