SUPPLEMENTARY MATERIAL

A PREPRINT

Figure S1 - Correlation between API and FPD-based biomarkers

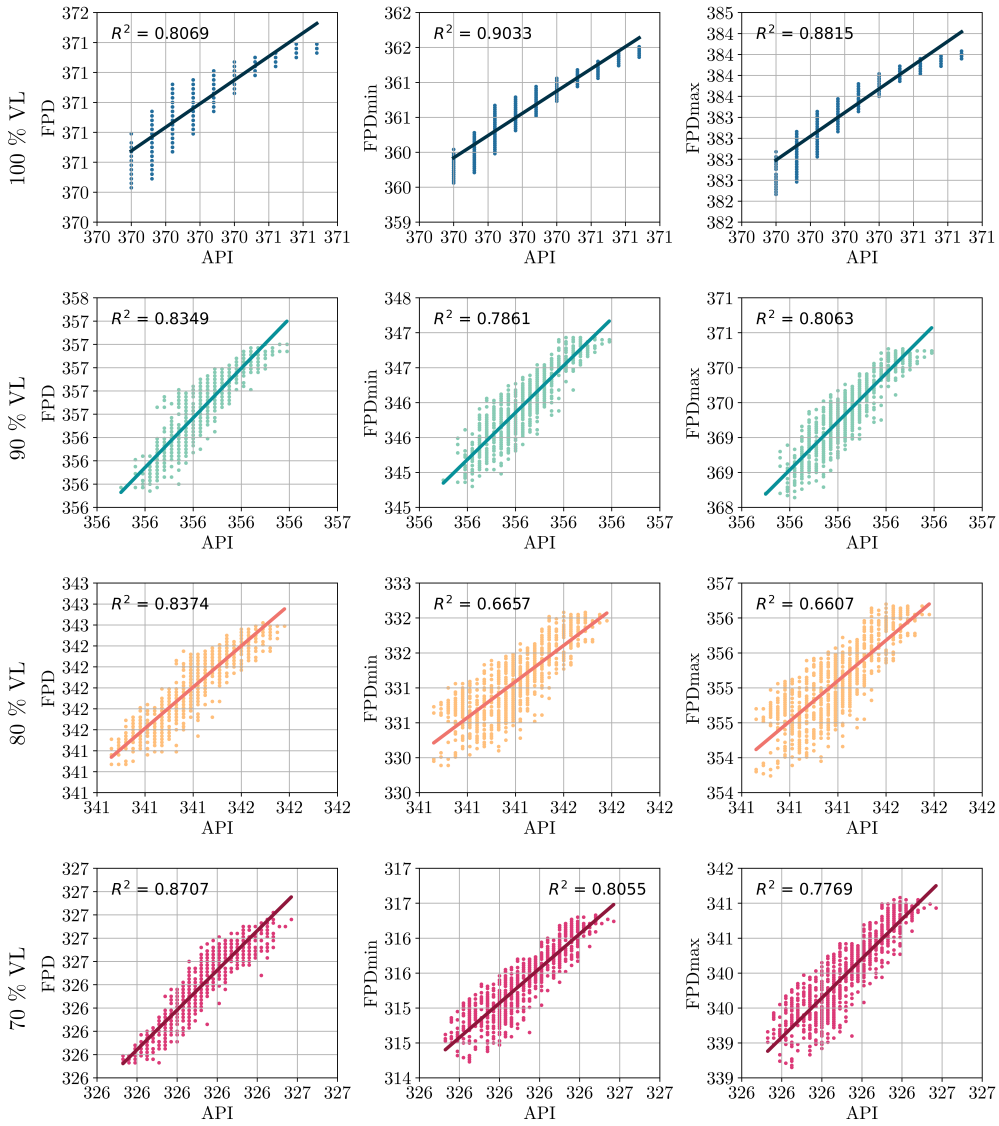

Figure S1: Correlation between API and FPD-based biomarkers (FPD, $\mathrm{FPD_m}$, $\mathrm{FPD_M}$) for decreasing percentages of VL cells (100%–70%). Each panel shows scatter plots with linear regression and R^2. Data points exhibit vertical clustering, reflecting the reduced variability of API compared to FPD-based measures.

When considering API as the reference intracellular biomarker, the correlation patterns differ from those observed with APD and $\mathrm{APD_{90}}$. In particular, scatter plots show a clear vertical clustering of data points, indicating that multiple FPD values correspond to similar API values.

This behavior is primarily related to the definition of API, which does not rely on temporal derivatives but instead captures a more global property of the AP. As a result, API exhibits reduced variability and is less sensitive to local changes in repolarization dynamics. In contrast, FPD-based biomarkers depend on derivative-based definitions and retain a higher degree of variability.

The mismatch in sensitivity between API and FPD leads to a many-to-one mapping, where variations in FPD are not reflected by corresponding changes in API. This results in vertically aligned point distributions and limits the strength of the correlation, particularly in heterogeneous conditions.

Overall, this highlights that API, while numerically robust, may not capture the full variability of repolarization features reflected in extracellular biomarkers.

Figure S2 - Correlation between FPD and AP-based biomarkers

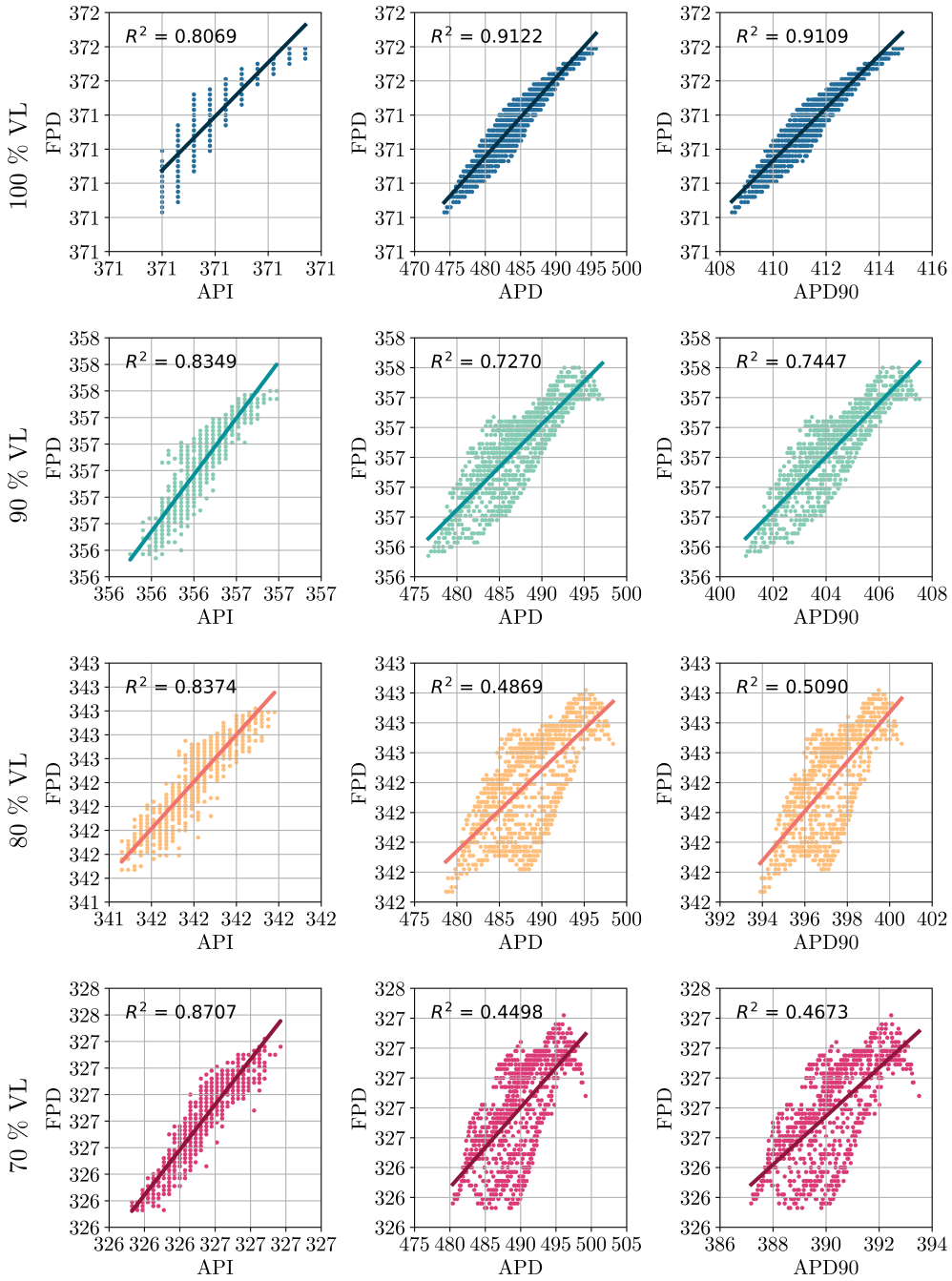

Figure S2: Correlation between FPD and intracellular biomarkers (API, APD, APD_{90}) for decreasing percentages of VL cells (100%–70%). Each panel shows scatter plots with linear regression and R^2. A vertical clustering of points is observed, indicating reduced accuracy in FPD estimation.

The correlation analysis based on FPD exhibits a clear deviation from the trends observed for intracellular and extracellular biomarkers. In particular, scatter plots reveal a pronounced vertical clustering of data points, indicating that FPD assumes a limited set of discrete values while the corresponding intracellular biomarkers (APD, APD_{90}, and API) vary more continuously.

This effect is primarily of numerical origin. By definition, FPD relies on the identification of activation and repolarization times from extrema of the first temporal derivative of the FP. Such derivative-based markers are inherently sensitive to temporal discretization and numerical noise. As a result, small variations in the signal may not translate into changes in the detected extrema, leading to a quantization of the extracted timings.

This discretization-induced clustering reduces the effective variability of FPD and introduces a bias in the correlation analysis, particularly for APD and APD_{90}. Consequently, the observed loss of correlation with increasing heterogeneity is not solely attributable to physiological effects, but also reflects limitations in the numerical extraction of derivative-based biomarkers.

Figure S3 - 4-AP effect on tissue dynamics

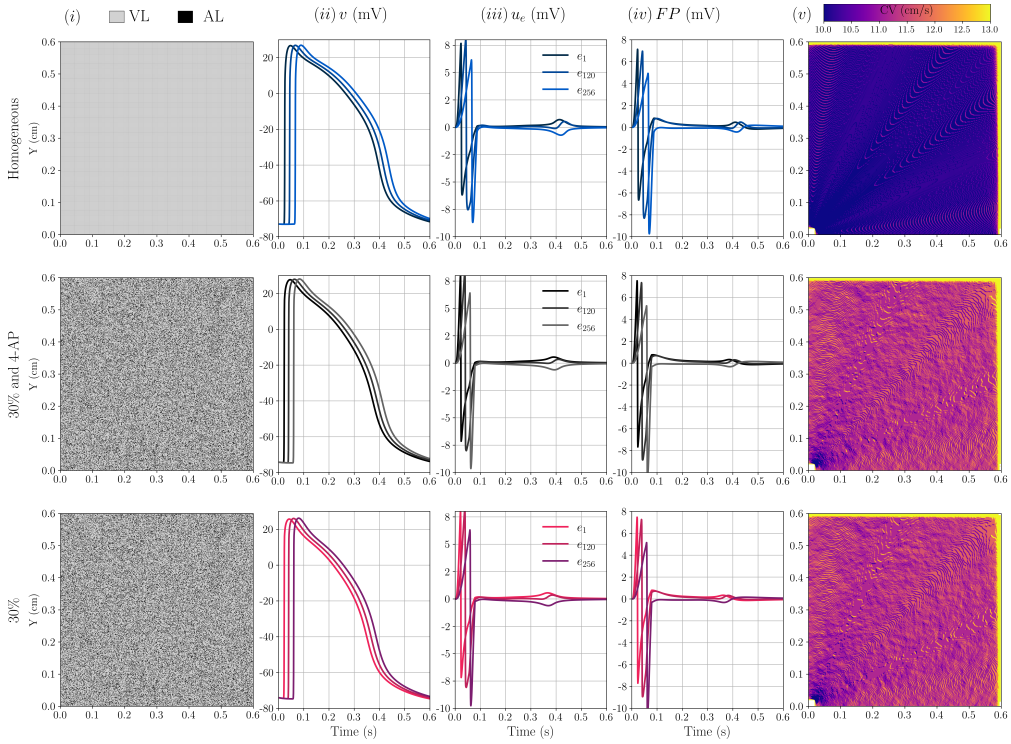

Figure S3: Effect of 4-AP on heterogeneous tissues. The layout of the figure is the same as in Fig. **??**. The three rows correspond to homogeneous VL tissues and tissues with 30% AL cells randomly distributed within VL tissue, without (top) and with (bottom) 4-AP treatment. Columns report the spatial phenotype distribution, intracellular APs recorded at three locations along the main diagonal, extracellular potentials (u_e) at the same positions, FPs recorded by three electrodes aligned along the diagonal, and the corresponding pointwise CV maps. The comparison highlights the electrophysiological changes induced by retinoic acid in heterogeneous tissues.

At the intracellular level, the comparison between the second and third rows shows a clear prolongation of the repolarization phase in AL regions after 4-AP exposure. This effect is consistent with the expected atrial-selective action of the drug and is mainly reflected in the morphology and duration of the AP traces, whereas activation timing and propagation organization remain largely preserved. In agreement with the CV maps, no appreciable changes in conduction velocity or in the global activation pattern are observed across the domain.