1 Ischæmic Variation

Quotation (Source)

This chapter presents insights into the ischæmic parameter space. A brief introduction is given to the work, and the justification behind the methodology used here. The changes of the parameter space defined in the previous chapter are discussed, followed by an analysis of the effects of the ischæmic parameter space itself. The possible consequences of model failure are discussed.

1.1 Variation Within Ischæmia

As has previously been commented upon, computational modelling of variation is promising new insights into the causes and consequences of variation. Coupled to this progress in computational modelling are the benefits when investigating ischæmia: due to the rapidly changing nature of the ischæmic milieu, comprehensive experimental validation of hypotheses is difficult. Computational modelling allows a rapid, flexible manner with which to test hypotheses regarding ischæmia. This is especially useful for assessing the import of factors that are difficult to constrain and control experimentally.

This work presents the first time, to the author's knowledge, where a comprehensive model population approach has been applied to the ischæmic environment. Furthermore, the parameter space methodology is applied to the ischæmic environment itself. This provides two important possible benefits. First of all, in the same way that the previous chapter postulated variation in the model itself as being partly responsible for natural variation, it is reasonable to extend this same postulate of variability, and thus the methodology used, to the environment itself. Secondly, it can be remembered that ischæmia rarely exists in isolation, and that there is commonly a 'border zone' that exists between the central ischæmic zone and the surrounding healthy tissue. As was commented upon in §??, the changes in environmental conditions associated with ischæmia do not vary in a spatially uniform manner—Fig.?? in that section (originally from Tice et al. (2007)) demonstrates that it can be expected that hyperkalæmic conditions can exist while other environmental changes associated with

Time (min PO)	0	2	4	6	8	10
$[K^+]_o$ (mM)	5.40	7.72	10.04	12.36	14.68	17.00
$f_{\text{K-ATP}}$ (%)	0.00	0.16	0.32	0.48	0.64	0.80
f_{inhib} (%)	0	5	10	15	20	25
f_{Na} (%)	0	6	12	18	24	30

Table 1.1: *Table showing what parameters are used in simulation to approximate a given time post-occlusion.* $f_{\text{K-ATP}}$ *represents the degree of activation of* $I_{\text{K-ATP}}$*,* f_{inhib} *represents the degree of inhibition applied to* I_{Na} *and* $I_{\text{Ca,L}}$*, and* f_{Na} *represents the percentage increase/decrease in* $[Na^+]_i$ *and* I_{NaK}*, respectively.*

ischæmia are not present. Performing a parameter space search allows us to examine this spatial variation.

The inclusion of variation in ischæmia modelling is of potentially key importance. It is already known through significant previous literature (see §?? for a review) that ischæmia provides an arrhythmogenic substrate. It has also been demonstrated that arrhythmogenesis is favoured in heterogeneic substrate—indeed, Tice et al. (2007) demonstrated that the heterogeneity introduced by changes from the central ischæmic zone, to the border zone, to normal tissue, can provide the substrate for arrhythmias.

It is based on these observations that the primary hypothesis being tested here is: does the application of ischæmic conditions lead to an increase in heterogeneity within the population that could, in tissue, be arrhythmogenic? To put it another way, one could ask whether the benign variation that is being modelled by the population then transitions to malign variation under ischæmic conditons. It should be remembered that the results presented in this work cannot be said to imply arrhythmogenesis, which is a super-cellular behaviour. However, there is a silver lining to the simulation of ischæmia—since it has been noted that ischæmia reduces the extent of cell-coupling, it is implied that the results presented here will be ameliorated to a lesser degree by any cell-coupling.

The work presented in this chapter will also examine the importance of studying population responses, and the aspects of these responses that would not be observed using single model simulations.

In this chapter, it must be remembered that the term 'x minutes post-occlusion (PO)' is used as shorthand, and it is wise to consider the data presented with such a label in terms of the underlying conditions instead; the corresponding values are given in Table 1.1.

As a further matter of nomenclature in this chaper, two different measures of variation are used in this chapter: the variance and the range (defined as the difference between the maximum and the minimum values found amongst the population for a given set of environmental conditions. When both measures demonstrate the same trend, the term variation shall be used directly. It must also be considered that it is not always sufficient to use simply these measures, but sometimes to examine the data directly—such measures will be used in the following analysis.

1.2 Population Response to Ischæmia

The APs for the population at various discrete points during ischæmia are shown in Fig. 1.1, with histograms representing the APD_{90} values for the populations also shown. Associated data for the mean,

			Time PO (min)					
			0	2	4	6	8	10
Shannon	APD_{90}	Mean	174.1	127.4	97.4	74.2	55.0	45.3
		Std	6.23	4.17	3.89	4.14	4.44	2.82
		Range	30.9	20.9	19.7	21.8	23.5	13.5
	ERP	Mean	175.9	132.7	107.5	93.2	94.8	182.9
		Std	6.20	4.21	3.85	3.77	2.87	31.47
		Range	30.7	21.3	19.5	19.9	15.5	324.0
	PRR	Mean	1.8	5.3	10.1	19.0	39.8	137.6
		Std	0.09	0.19	0.23	0.49	1.96	31.94
		Range	0.4	1.1	1.1	2.1	8.2	319.9
Mahajan	APD_{90}	Mean	177.9	143.6	116.3	90.0	54.7	27.8
		Std	10.20	8.77	9.04	10.64	15.25	3.75
		Range	55.0	51.4	54.0	58.4	62.5	17.4
	ERP	Mean	174.2	148.7	128.0	112.0	100.8	600.0
		Std	9.32	8.82	9.43	11.44	18.31	0.00
		Range	50.2	51.4	56.2	63.3	77.5	0.0
	PRR	Mean	−3.7	5.1	11.7	22.0	46.1	572.2
		Std	1.98	0.32	0.48	0.91	3.17	3.75
		Range	7.9	2.0	2.3	5.0	15.5	17.4

Table 1.2: *Effect of different degrees of ischæmic severity on the population level response for common biomarkers for the Mahajan and Shannon frameworks, according to mean, standard deviation (Std) and range.*

standard deviation and range responses for common biomarkers for both populations are shown in Table 1.2.

Both populations show a qualitative and quantitative (based on mean population response) agreement with expected AP response (increase in V_{rest}, decrease in $(\mathrm{d}V_m/\mathrm{d}t)_{\max}$ and APD_{90}). However, the AP morphology of the two populations, while initially similar, shows different population-level responses to ischæmia. The Shannon population demonstrates secondary depolarisation as iscæmia progresses, *i.e.* beyond 4 min PO, $V_{\max}$ is not reached during the initial upstroke, but rather during secondary depolaristion during Phase 2 of the AP. It should be noted that this increased prominence of the dome in the AP is not due to an increase in the dome itself, but rather the decline of the initial upstroke occurs at a far greater rate. The Mahajan population initially shows the same process—the dome phase of the AP is less affected by the progression of ischæmia, and 6 min PO $V_{\max}$ occurs during Phase 2. However, at 8 min PO some models in the Mahajan population exhibit a phenomenon that shall be termed 'dome collapse', *i.e.* the dome exhibited during Phase 2 is no longer sustained; this shall be explored in further detail in §1.2.1. It can be noted that the Mahajan population tends to demonstrate a greater sensitivity to ischæmic conditions—this shall be expanded upon with regards the effect of biomarker response.

1.2.1 APD_{90}

For both model populations, progression of ischæmia works to reduce population variation in its early stages (until 4 min PO)—beyond this point, the response is population-dependent (Fig. 1.1 and Table 1.2).

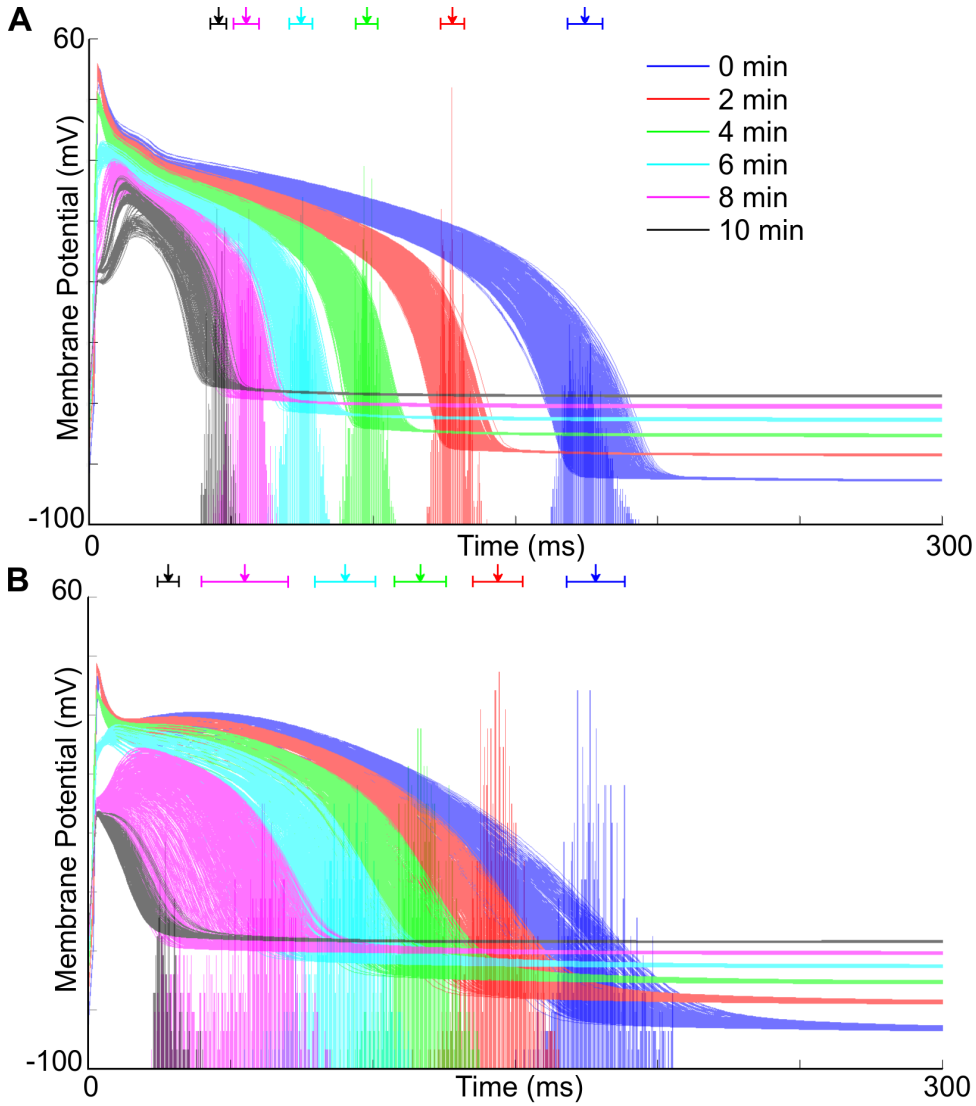

Figure 1.1: *Effect of different degrees of ischæmia on the Shannon (A) and Mahajan (B) model populations. The histograms respresent the APD_{90} values associated with the populations.*

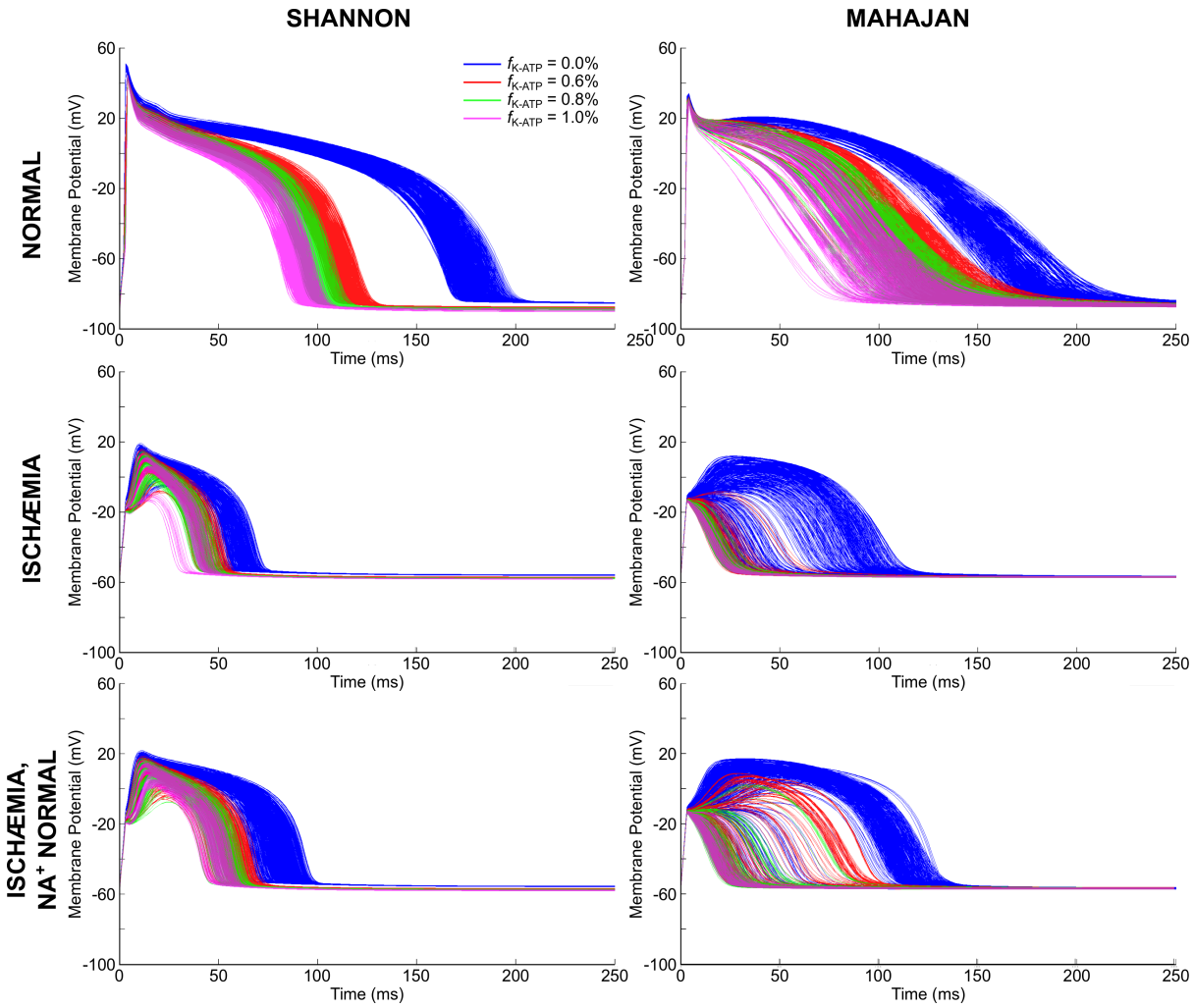

Figure 1.2: *Effect of $f_{\text{K-ATP}}$ variation on Shannon (left) and Mahajan (right) model populations given normal conditions (top, $[K^+]_o$= 5.4 mM, f_{inhib} = 0%, f_{Na} = 0%), ischæmic conditions (middle, $[K^+]_o$= 17.0 mM, f_{inhib} = 25%, f_{Na} = 30%), and ischæmic conditions where changes in the Na^+ system of the cell are not modelled (bottom, $[K^+]_o$= 17.0 mM, f_{inhib} = 25%, f_{Na} = 0%).*

The Shannon population variation never exceeds the variation evident under 'normal' conditions.

1.2.2 ERP and PRR

1.2.3 Other Biomarkers

1.3 Model Failure During Ischæmia

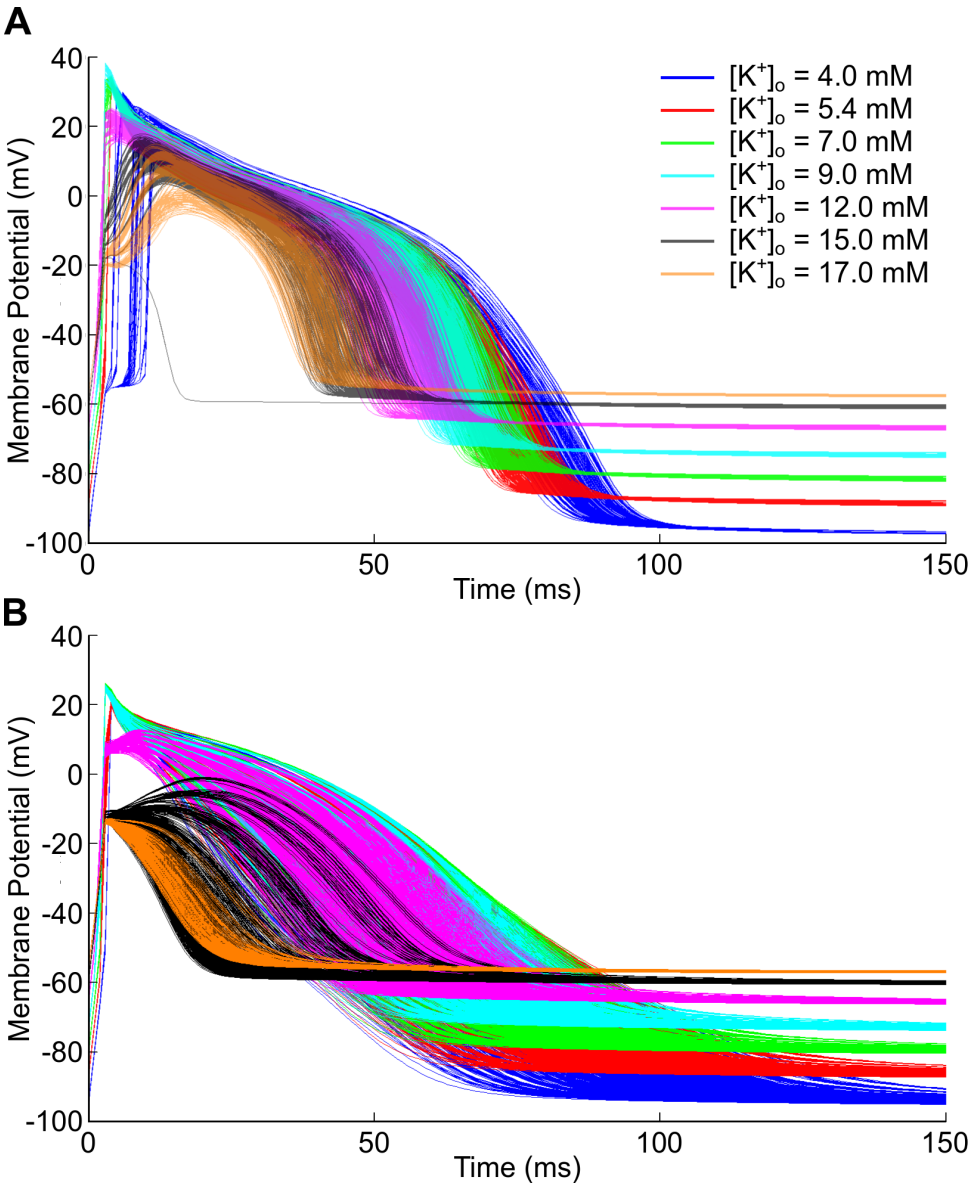

Figure 1.3: *Effect of different degrees of ischæmia on the Shannon (A) and Mahajan (B) model populations. The histograms respresent the APD_{90} values associated with the populations.*

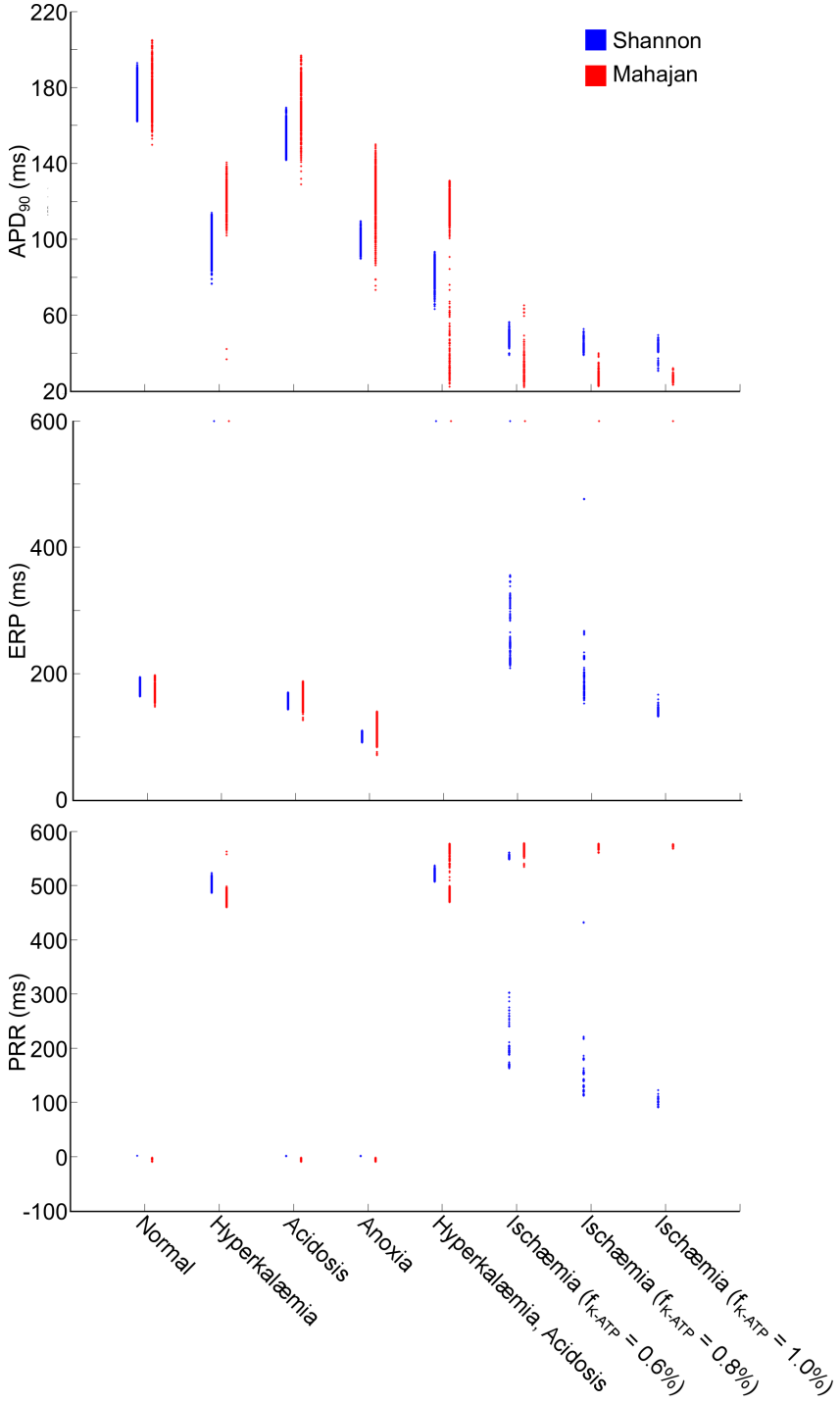

Figure 1.4: *Distribution of values within the population for non-failing models for APD_{90}, ERP and PRR, under specified conditions: normal ($[K^+]_o$= 5.4 mM, f_{inhib} = 0%, $f_{\text{K-ATP}}$ = 0.0%, f_{Na} = 0%), hyperkalæmia ($[K^+]_o$= 17.0 mM, f_{inhib} = 0%, $f_{\text{K-ATP}}$ = 0.0%, f_{Na} = 0%), acidosis ($[K^+]_o$= 5.4 mM, f_{inhib} = 25%, $f_{\text{K-ATP}}$ = 0.0%, f_{Na} = 0%), anoxia ($[K^+]_o$= 5.4 mM, f_{inhib} = 0%, $f_{\text{K-ATP}}$ = 0.8%, f_{Na} = 0%), hyperkalæmia and acidosis ($[K^+]_o$= 17 mM, f_{inhib} = 25%, $f_{\text{K-ATP}}$ = 0.0%, f_{Na} = 0%), and ischæmia with varying degrees of $f_{\text{K-ATP}}$ activation ($[K^+]_o$= 5.4 mM, f_{inhib} = 0%, $f_{\text{K-ATP}}$ = {0.6%, 0.8%, 1.0%}, f_{Na} = 0%).*

$[K^+]_o$ (mM)	$f_{K\text{-}ATP}$	f_{inhib}	f_{Na}	Shannon		Mahajan	
				Failure	ERP≥CL	Failure	ERP≥CL
5.4	0.00	0	0	0	0	0	0
7.72	0.16	5	6	0	0	0	0
10.04	0.32	10	12	0	0	0	0
12.36	0.48	15	18	0	0	0	0
14.68	0.64	20	24	0	0	0	0
17.0	0.80	25	30	605 (44.7%)	0	613 (78.7%)	166 (100%)
17.0	0.60	25	30	414 (30.6%)	471 (50.2%)	578 (78.7%)	201 (100%)
17.0	1.00	25	30	847 (62.6%)	0	720 (78.7%)	59 (100%)
17.0	0.00	0	0	3 (0.0%)	1349 (100%)	0	779 (100%)
5.4	0.80	0	0	0	0	0	0
5.4	0.00	25	0	0	0	0	0
5.4	0.00	0	30	0	0	0	0
5.4	0.80	25	30	0	1349 (100%)	0	779 (100%)
17.0	0.00	25	30	72 (5.3%)	1280 (100%)	183 (23.5%)	596 (100%)
17.0	0.80	0	30	150 (11.1%)	192 (16.0%)	432 (55.5%)	347 (100%)
17.0	0.80	25	0	411 (30.4%)	82 (8.7%)	584 (75.0%)	193 (99.0%)

Table 1.3: *Effect of different conditions associated with ischæmia on the number of models within the populations that fail, and of those that do not fail, those which exhibit ERP≥CL. The first group represent those conditions simulating linear progression from normal to ischæmic conditions; the second group represent ischæmic conditions with decreased/increased $I_{K\text{-}ATP}$ activation; the third group represent each individual change in ischæmia applied individually; the fourth group represent ischæmia when one condition remains 'normal'.*

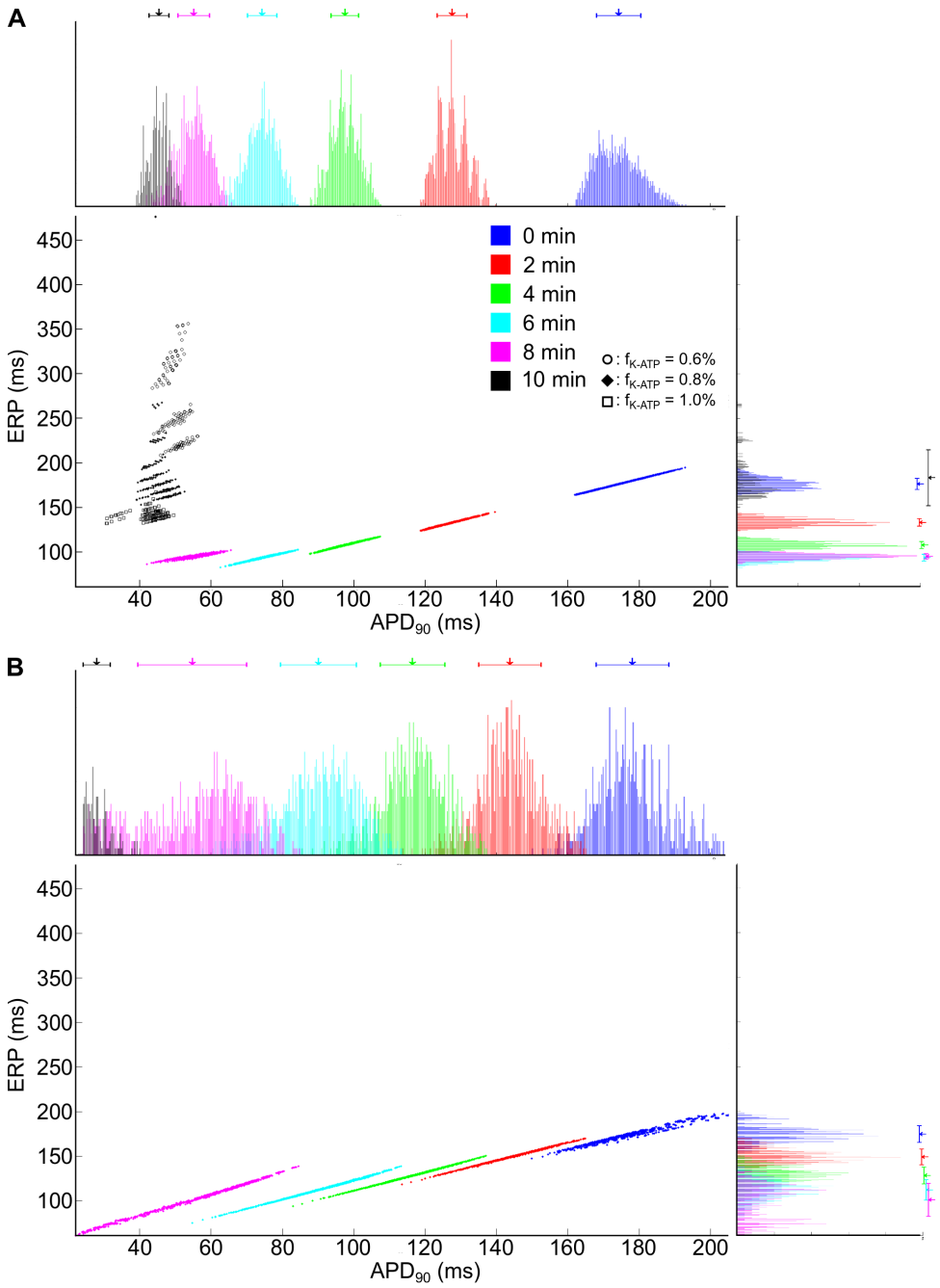

Figure 1.5: *Relation between APD_{90} and ERP at various points during ischæmia for the Shannon (A) and Mahajan (B) populations. For 10 min PO, the APD_{90}/ERP relation is also shown for increased/decreased $f_{K\text{-}ATP}$ at 10 min PO. Histograms using the same scales as the main plot are given: APD_{90} above the main plot, ERP to the right.*

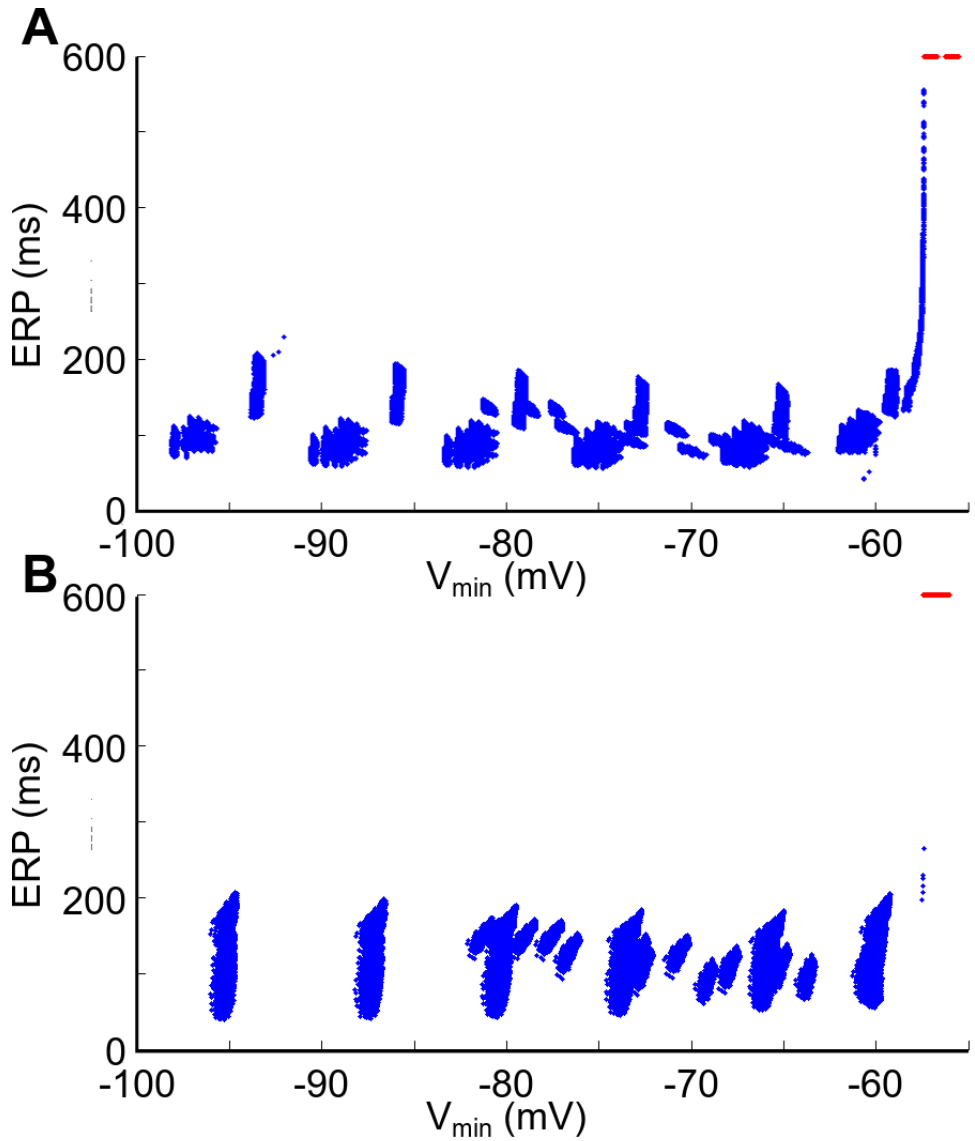

Figure 1.6: *Relation between V_{rest} and ERP across Shannon (A) and Mahajan (B) populations for all simulated conditions. Those models with ERP≥CL are highlighted in red.*

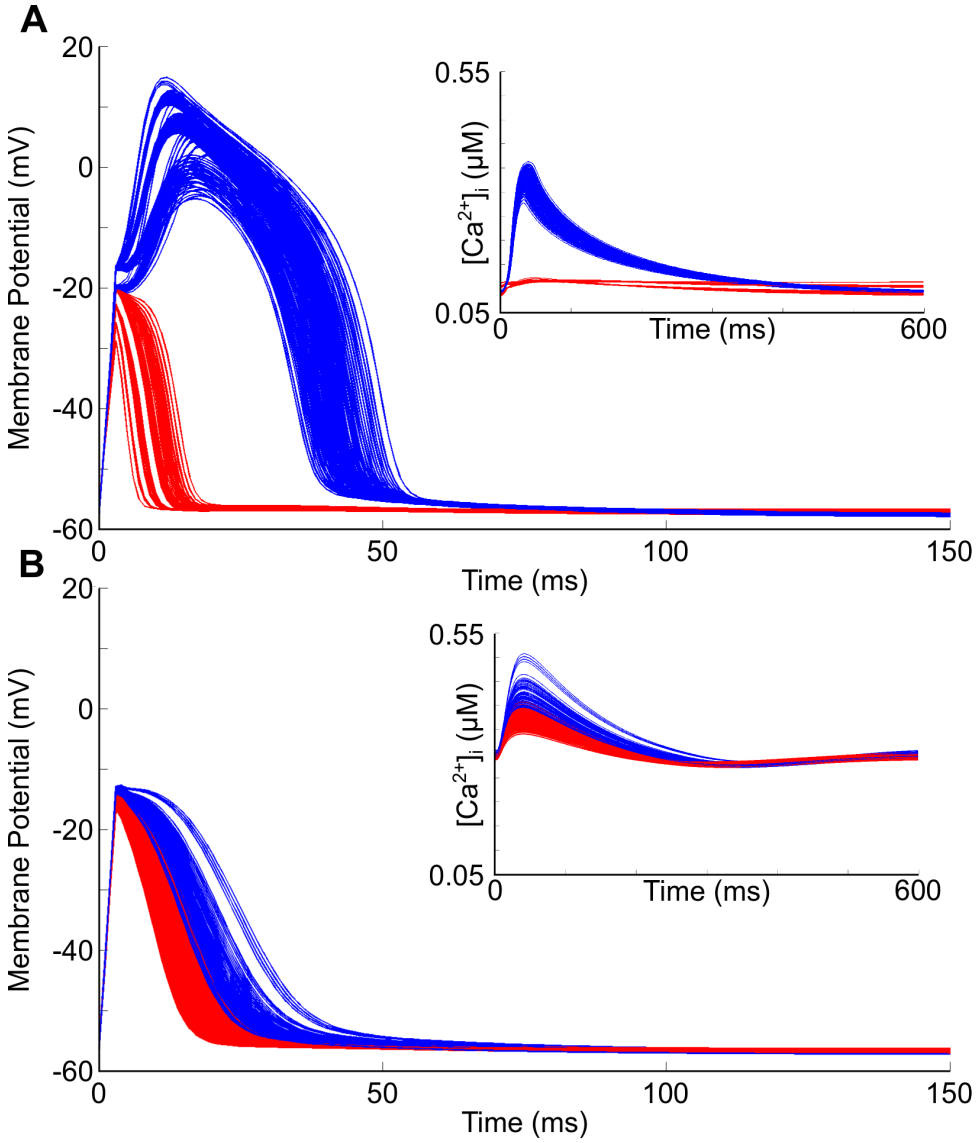

Figure 1.7: *Illustration of failing and non-failing APs at 10 min PO for the Shannon (A) and Mahajan (B) populations; APs classed as non-failing are shown in blue, those classed as failing are shown in red.* Inset: *Data for* $[Ca^{2+}]_i$.

Bibliography

Tice, B. M., Rodríguez, B., Eason, J. C., and Trayanova, N. A. (2007). Mechanistic investigation into the arrhythmogenic role of transmural heterogeneities in regional ischaemia phase 1A. *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology*, 9 Suppl 6:vi46–58.