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 work presents the first time, to the author's knowledge, where a comprehensive model population approach has been applied to the ischæmic environment.

The inclusion of variation in ischæmia modelling is of potentially key importance. It is already known through significant previous literature (see §?? for an actual literature review) that ischæmia provides an arrhythmogenic sustrate. 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 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,

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.*

it is implied that the results presented here will be ameliorated to a lesser degree by any cell-coupling.

A secondary goal of this section is to examine the effects of parameter variation within the ischæmic environment on the population. These two goals can be united under a single study, but for ease of analysis they will be treated separately initially, to make it simpler to tease out the causative agents in each cause. To this end, it can be considered that the primary goal examines the effect of variation in *cell parameters*, and the secondary goal investigates the effect of variation in *environment parameters*.

It should be noted that it would be relatively simple to combine the investigations by defining the accepted degree of variation in the environment parameters at each point during ischæmia, and then applying that degree of variation to a given population. However, it is known that the degree of variation within ischæmic parameters can be great, and thus the actual application of such a method could result in volumes of data that could overwhelm analysis to the point where underlying trends are disguised by the wealth of information—this thesis seeks to tease out the correlations and implications in the simplest form.

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 ??.

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.

1.2 Population Response to Ischæmia

The APs for the population are shown in Fig. 1.1, with histograms representing the APD_{90} values for the populations also shown. Data for the mean, 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 $(\text{d}V_m/\text{d}t)_{\text{max}}$ and APD_{90}).

1.2.1 APD_{90}

For both model populations, progression of ischæmia works to reduce populations variation in its early stages (until 4 min PO)—beyond this point, the response is population-dependent, as can be

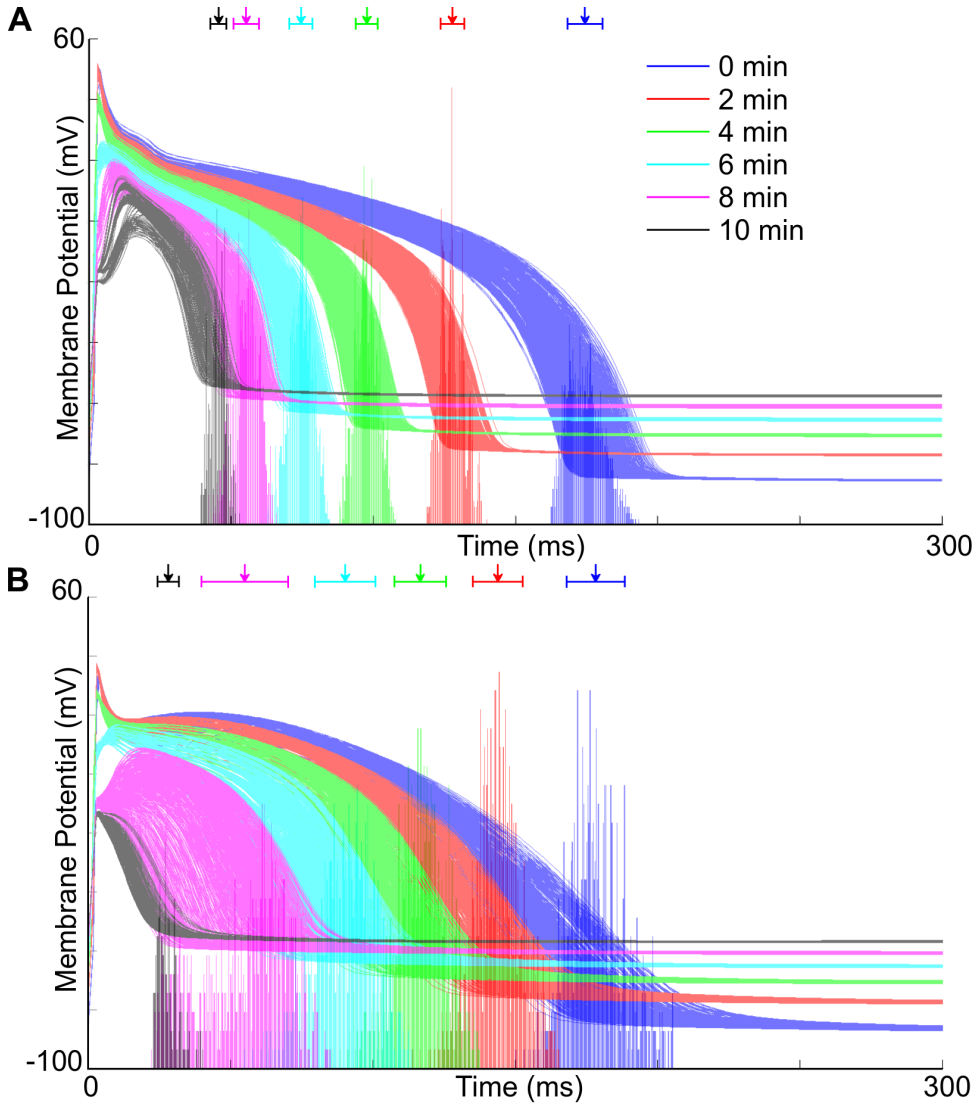

Figure 1.1: *Effect of different degrees of ischæmia on the Shannon (A) and Mahajan (B) model populations. The histograms respresent the APD_{90} values associated with the populations.*

			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.*

seen in Fig. 1.1 and Table 1.2.

1.2.2 ERP and PRR

1.2.3 Other Biomarkers

1.3 Effects within Ischæmic Parameter Space

1.4 Model Failure During Ischæmia

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.