Mathematical modelling of energy demand and supply in the cardiac myocyte

By Kenneth Tran

Supervised by
Associate Professor Edmund J. Crampin
Associate Professor Denis S. Loiselle
Professor Nicolas P. Smith

A thesis submitted in partial fulfilment of the requirements for the degree of
Doctor of Philosophy in Bioengineering
The University of Auckland, 2010.

Auckland Bioengineering Institute

3rd September 2010

Abstract

The mechanisms that regulate the control of energy demand and energy supply in the heart muscle are crucial for maintaining normal cardiac function, yet they are not very well understood. Although a number of mechanisms have been proffered by which mitochondrial supply of ATP can change to match varying workload in the myocardium, identifying the underlying regulatory pathways remains controversial.

In this study, we have developed mathematical models of the sarcoplasmic endoplasmic reticulum Ca^{2+} ATPase (SERCA) pump and the acto-myosin cross-bridge cycle which, along with the Na^+/K^+ pump, are the key energy-consuming processes in the cardiomyocyte. These models encapsulate both thermodynamic considerations and metabolite sensitivity into a cycle-based framework. The parameters of these models are constrained by experimental data which characterise their physiological behaviour. These models are then placed within the context of a whole-cell electrophysiological framework, alongside a model of mitochondrial energy supply, to investigate the mechanisms that regulate energy control and to shed light on two experimental observations which, for many decades, have evaded a mechanistic explanation: the apparent linearity of the $VO_2 - PVA$ (pressure-volume area) relationship and the metabolic stability hypothesis, wherein demand-supply homeostasis is maintained despite negligible variation in metabolite concentrations at varying workloads.

The predictions from our model simulations indicate that, under constant metabolite concentrations, the ATP-FTI (force-time integral) relationship is linear, while the ATP-

FLA (force-length-area, cellular equivalent of $VO_2 - PVA$) relationship is linear only at low work rates. The linearity of the ATP-FTI relationship is found to arise from kinetic properties of the cross-bridge model. This property is not retained in the ATP-FLA relationship and is lost when metabolite concentrations are allowed to vary, as during normal variation with changing workload. This suggests that FTI and FLA are not equivalent, and that the $VO_2 - PVA$ relationship may only be approximately linear.

Finally, we show that metabolite concentrations change significantly with increasing workload if Pi feedback onto mitochondrial oxidative phosphorylation is removed from the model, suggesting that Pi-regulation alone is sufficient to maintain metabolic homeostasis in the absence of other regulatory mechanisms.

Acknowledgements

I would like to acknowledge the tremendous support of my supervisors: Associate Professors Edmund Crampin and Denis Loiselle and Professor Nic Smith. I would like to thank Edmund for his guidance, his patience and his generous open door policy. Your encouragement and enthusiasm for the project was a constant source of inspiration for me. I would like to thank Denis for his diligient and meticulous reading of my work and for being the counter-weight to such a heavy modelling-based project. Your input has been invaluable and your, at times, cryptic comments have been simultaneously confusing and amusing. I would also like to thank Nic for initially getting me invovled in this project. I have thoroughly enjoyed my last five years working with you all.

The Auckland Bioengineering Institute has provided a very supportive and enjoyable environment and I would like to acknowledge the people who have, in one way or another, helped me along the way. In particular, I have thoroughly enjoyed the many discussions and distractions with my fellow colleagues in the systems biology group: Dan, Jonna, Joe, Ivo, Ollie and Yikan. I also want to thank Professor Daniel Beard and Dr Fan Wu from the Medical College of Wisconsin for their collaboration on the modelling of the mitochondria.

This thesis would not have been possible without the generous sources of financial support from the Tertiary Education Commission (TEC), the Royal Society of New Zealand and the National Institute of Health (NIH).

Finally, I would like to acknowledge the support from my family, particularly my parents, for the sacrifices they have made in coming to New Zealand and the hard work they have put it in in order for me and my brother to have the opportunities that we currently have. So it is to them that I dedicate this thesis. To my brother Henry, your attempts at critiquing my work were admirable. Thank you for being more than just a little brother to me.

And last, but not least, to my wonderful wife, for being so understanding and supportive, and for putting up with me these past few years. I love you very much.

Contents

List of Figures

List of Tables

Acronyms and Abbreviations

Cellular compartments

i	Intracellular/cytosolic compartment
e	Extracellular medium
sr	Sarcoplamisc reticulum
im	Intermembrane space of the mitochondria
x	Mitochondrial matrix

Abbreviations

α**KG**	$\alpha-$ketoglutarate
ADP	Adenosine diphosphate
AM1	Fractional occupancy within state XB_{PostR}, where no MgADP is bound
AM2	Fractional occupancy within state XB_{PostR}, where MgADP is bound
ANT	Adenosine nucleoside translocase
ATP	Adenosine triphosphate
CaRU	Ca^{2+} release unit
CICR	Ca^{2+}-induced-Ca^{2+}-release
CoA	Co-enzyme A

EC	Excitation-contraction
FAD	Flavin adenine dinucleotide
$FADH_2$	Reduced form of FAD
FLA	Force-length area
FTI	Force-time integral
GTP	Guanosine triphosphate
JSR	Junctional sarcoplasmic reticulum
LCC	L-type Ca^{2+} channel
MgADP	Magnesium-bound adenosine diphosphate
MgATP	Magnesium-bound adensosine triphosphate
MVO_2	Rate of myocardial oxygen consumption
N_{XB}	Fractional occupancy of the non-permissive state, where no Ca^{2+} is bound
NAD^+	Nicotinamide adenine dinucleotide
NADH	Reduced form of **NAD^+**
NSR	Network sarcoplasmic reticulum
OAA	Oxaloacetate
P_{XB}	Fractional occupancy of the permissive state, where Ca^{2+} is bound
P-MRS	Phosphate magnetic resonance spectroscopy
Pi	Inorganic phosphate
P_i	Proportion of complexes in state i
PCr	Phosphocreatine
PVA	Pressure-volume area
P_{XB}	Fractional occupancy of the permissive cross-bridge state
RyR	Ryanodine channel receptors
SERCA	Sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase
SL	Sarcomere length
SR	Sarcoplasmic reticulum
TCA	Tricarboxylic cycle
VO_2	Rate of oxygen consumption

$\mathbf{XB_{PostR}}$	Fractional occupancy of the bound cross-bridge state, post rotation
$\mathbf{XB_{PreR}}$	Fractional occupancy of the bound cross-bridge state, pre rotation