**$Ca^{2+}$ homeostasis—remember the balance**

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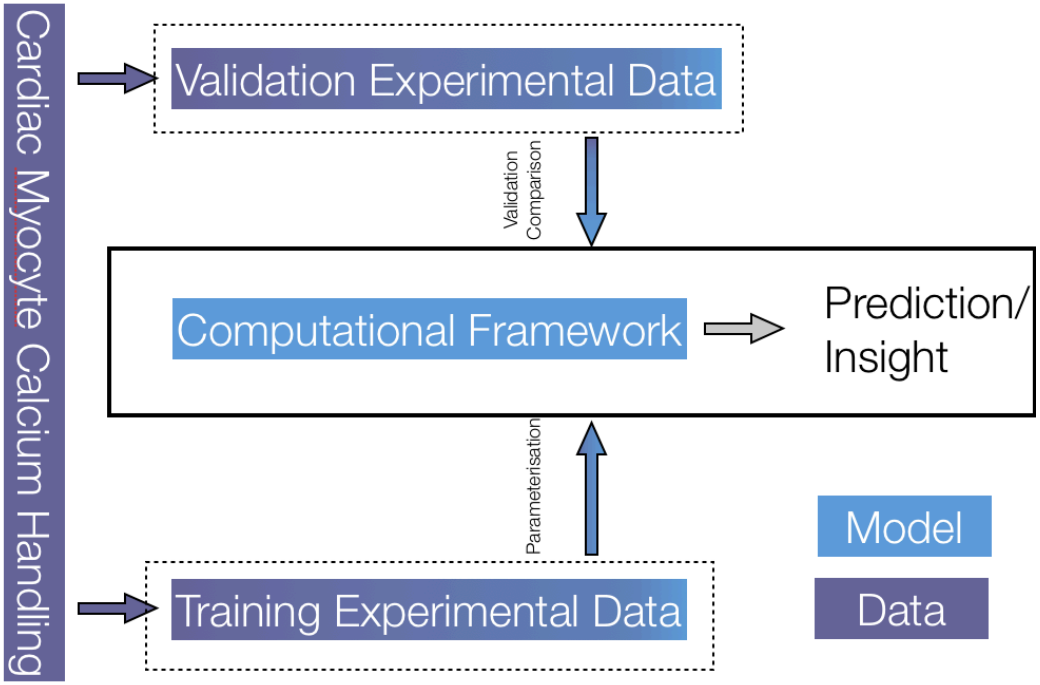
Beat to beat calcium homeostasis is a fundamental and essential regulatory property of the cardiac myocyte. However, there are multiple control points in this regulatory pathway which has, in turn, motivated analysis of calcium homeostasis using mathematical models to understand measurement differences across species, experimental perturbations, changes in genetic background and disease etiology. A range of different modelling frameworks have been developed for this purpose from stochastic to deterministic and spatially distributed to zero dimensional representations (See [1] for review).

Within the experimental community there is close to universal acknowledgement of the importance of collecting consistent data sets (species, temperature experimental conditions) to enable analysis. However, in comparison, relatively little attention has been paid in the model development process to both this issue and the related topic of uniquely defining the relationship between model parameters and experimental data. This situation has lead to models being developed which integrate data from a wide range of species and temperatures [2]. Furthermore within even modestly complex model frameworks, it is often difficult to determine if the data used to fit an emergent model response is in fact sufficient to uniquely constrain important parameter values. At the core of this issue is the need for the cellular modelling communities to acknowledge that the process of converting a measurement to a parameter or comparing a model result to measured data is also a model itself: wither this be a linear fit or a more complex parameter estimation process (see schematic below).



While these issues remain to be fully addressed within the modelling community computational frameworks have provided insights into many of the detailed mechanisms underpinning compensated and decompensated changes in calcium homeostasis associated with both ageing and heart failure. Specifically, in both these cases, the loss of SERCA has been shown to be efficiently compensated by increased NXC and L-type calcium to maintain SR calcium load and diastolic and systolic calcium levels below and above pathological levels respectively [3]. However, despite its initial effectiveness this compensatory mechanism is ultimately metabolically inefficient potentially leading to acidosis and sodium overload in the cell [4]. Finally, the importance of calcium homeostasis for regulating ec coupling and organ pump function has stimulated development of multi-scale whole heart models. In these frameworks the effect of cellular level changes has been translated to modifications in whole organ pump function. Most recently this approach has shown tissue level length and velocity dependent coupling to cellular calcium handing as a significant regulator of whole organ cardiac mechanics [5.6].


1. 2011 Fink M., Niederer S.A., Cherry E.M., Fenton F.H., Koivumäki J.T. Seemann G. Thul R. Zhang H. Sachse F.B., Beard D., Crampin E.J. Smith N.P. Cardiac cell modelling: Observations from the heart of the cardiac physiome project, Prog. Bio. Phys. Mol. Bio. 104 1-3 2-21
2. 2009 Niederer S. A., Fink M., Noble D., Smith N.P., A Meta Analysis of the Physiome Paradigm with application to cardiac electrophysiology, Experimental Physiology 94(5):486-95
3. 2011 Li L, Louch W.E, Niederer S.A., Andersson, K.B., Sejersted, O.M., Smith N.P. Calcium Dynamics in the VentricularMyocytes of SERCA2 KO Mice: A Modelling Study, Biophysical Journal, 100(2), 322-331
4. 2012 Li L.,Louch W.E., Niederer S.A., Aronsen J.M., Christensen G., Sejersted O.M., Smith N.P. Sodium Accumulation in SERCA KO Induced Heart Failure, Biophysical Journal (accepted)
5. 2011 Niederer S.A., Plank G., Chinchapatnam P., Ginks M., Lamata P., Rhode K.S., Rinaldi C.A., Razavi R., Smith N.P. Length-Dependent Tension in the Failing Heart and the Efficacy of Cardiac Resynchronisation Therapy, Cardiovascular Reserach (in press)
6. 2012 Land S., Niederer S.A., Aronsen J.M., Espe E.K.S, Zhang L., Louch W.E., Sjaastad I.,Sejersted O.M., Smith N.P.An analysis of deformation dependent electromechanical coupling in the mouse heart, J. Physiol (accepted)