

Choice of parameter set for use with a mathematical model of mechanical force generation in the heart

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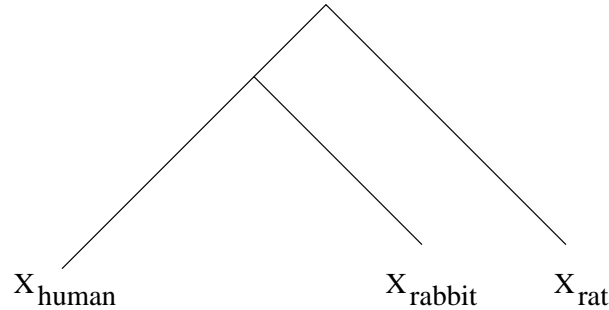
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The contraction of cardiac tissue that is seen when the heart beats is the consequence of a complex series of biophysical processes. First, electrical activity of the heart is initiated by self-exciting pacemaker cells. This electrical activity propagates through cardiac tissue with the help of both conduction and several biochemical reactions. Finally, a further series of biophysical processes results in the generation of force in cardiac cells which causes these cells to contract. For a recent review of modelling whole heart function see, for example, Hunter *et al.* [1].

The propagation of electrical activity through the heart has been studied extensively by many groups over the last 40 years, resulting in a very large collection of mathematical models. Less well understood is the series of biophysical processes that generate force in cardiac cells, although a mathematical model has recently been published by Niederer *et al.* [2]. This model consists of several ordinary differential equations coupled to a collection of algebraic equations. These equations contain a large number of parameters which must be known before the equations may be solved. However, there are several problems when determining these parameters. First, a complete set of parameters is not available for any one species of animal, and these parameters are known to vary between species. A second problem is that the parameters depend critically on physiological conditions such as temperature—see Appendix A in Niederer *et al.* [2]. As a result published values of these parameters may vary by more than an order of magnitude. Hence, as acknowledged by the authors, it is impossible to find a complete set of parameters taken from the same species of animal, measured under the same physiological conditions, and consistent with all experimental studies. The aim of this project is to investigate whether there is a systematic method for determining these parameters from published values.

The problem of parameterisation of heart models has great similarity with the phylogenetic analysis of quantitative characters that has been studied for decades in evolutionary biology, but in the last few decades this field have been in the shadow of phylogenetic analysis based on molecular sequences. In the present problem, we want to make statements about the parameters of the human Heart. The full model needs k parameters, the parameters of the models— $X(t)$ —is evolving according to a Brownian motion, i.e. $X(t_1) - X(t_2) \sim N(0, (t_1 - t_2)\Sigma)$, where Σ is a covariance matrix. Two additional factors complicate the problem: (i) Each observation is subject to error, which again could be modelled by adding a k -dimensional normally distributed variable Y to each observed heart; and (ii) the physiological parameters have not been determined under identical conditions, but under varying pH, temperature etc. This adds a regression problem to the basic modelling.

The present setting is the natural for the use of parameters from multiple species. In an ideal situation many extremely interesting questions can be addressed: How has the parameters evolved? With which rates? Are their evolution correlated? What was the ancestral values of



different parameters? Such questions can realistically be answered with sequence data, but it is doubtful that there is sufficient power in the data to address such questions, there the data (each parameter) is of much smaller quantity. But with the increasing importance of such models, it could well be that such evolutionary analysis will one day be of relevance. Nevertheless, being the natural formulation is plenty of motivation for pursuing such an analysis.

Work Plan

1. Analyze the present data set with existing program packages. A list of these can be found at <http://evolution.genetics.washington.edu/phylip/software.html>. The data set can be found at ???
2. Analyze the existing data set, by models and programs tailored to the present data set.
3. Simulation analysis relating to the value of obtaining multiple values of the same parameters from different species and how should model species should be chosen to give optimal information on parameter values.

References

- [1] P.J. Hunter, A.J. Pullan & B.H. Smaill. Modelling total heart function. Annual Review of Biomedical Engineering, vol. 5, pp. 147-177, 2003
- [2] S.A. Niederer, P.J. Hunter & N.P. Smith. A quantitative analysis of cardiac myocyte relaxation: a simulation study. Biophysical Journal, published ahead of print as doi:10.1529/biophysj.105.069534.
- [3] J. Felsenstein. Inferring Phylogenies, Chapters 23 and 24. Sinauer.