NC3Rs Maths Study Group - Applying mathematics to 3Rs problems

Modelling heart rate changes in the mouse as a system of delayed, weakly coupled oscillators

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Background to the problem

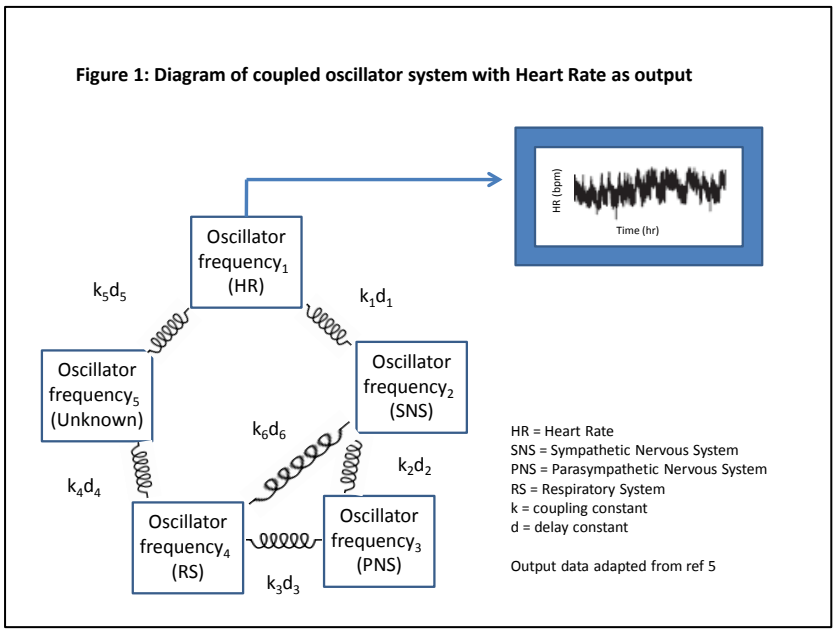
The measurement of cardiovascular variables such as heart rate (HR) and blood pressure (BP) in conscious experimental animals is complicated by the complexity of the signals involved. In anaesthetised (or over short time periods in conscious) animals the BP can be simply described as a sinusoidal wave with peak and trough defined as systolic and diastolic BP, respectively, whilst the HR is the reciprocal of the beat to beat interval. However, the influence of other oscillating systems such as the respiratory cycle, neuronal (sympathetic and parasympathetic) and endocrine hormone outflow on the cardiovascular system alters the HR and BP signals such that they become considerably more complex. Conventional methods tend to under-analyse this complexity.

Details of the problem

The effect of the interaction between complex, coupled oscillators on the cardiovascular system *in vivo* is the generation of a chaotic HR signal, where periods of apparent rhythmicity are punctuated by asynchronous behaviour; it is this heart rate variability (HRV) which seems to characterise the 'normal' state. Indeed, in pathophysiological states such as septicaemia and congestive heart failure, a reduction in HRV is associated with poor outcome. Some authors[1] have described the reduced HRV in septic shock (which occurs in mice and humans) as 'oscillator uncoupling' although there is also evidence that forcing the system to synchrony (e.g. through mechanical ventilation setting the respiratory rhythm[2]) may have the same effect; in this case it would be the equivalent of 'oscillator coupling'. An interesting outcome of this weakly-coupled oscillator model is that the 'normal' condition for HRV seems to reside somewhere between complete synchrony and chaos, possibly because in a conscious animal each of the oscillators in the system receives an occasional increase in power.

Experiments that determine long-term changes in BP and HR in mice are usually conducted by implanting a blood pressure transducer/transmitter that allows data to be collected remotely from a conscious, freely moving animal. These systems are capable of collecting large amounts of potentially continuous data over long time periods, but these data series are often irregular, strongly non-stationary, and noisy. Conventionally, the data are summarised by averaging, time-binning and filtering (to remove obvious artefacts) and are often presented as discontinuous blocks where, for example, an average BP or HR estimate over a 10 minute time window is used to represent the output for each hour of recording. This approach has the disadvantage that a) much of the data is collected but never analysed and b) more subtle interpretations such as the determination of HRV are often ignored. Nevertheless, in experiments where HRV is analysed in mice it is clear that there is oscillator coupling between respiratory cycles and HR, that there is an autonomic sympathetic and parasympathetic component to the control of HR, and that in mouse models of septic shock, reduced HRV precedes the onset of temperature and BP changes[3,4,5]. In all three respects, clinical studies of HRV in normal human subjects parallel the mouse data, with evidence of synchronisation with respiration (referred to as respiratory sinus arrhythmia[6,7]), modulation by the sympathetic and parasympathetic nervous system[8] and a tendency to reduced HRV in response to endotoxaemia[1]. The latter response has been proposed as an early clinical marker in sepsis[9,10,11], post-stroke infections[12] and multiple organ dysfunction syndrome[13].

Available data for informing possible mathematical models



This problem proposes that we move beyond simple descriptors of the variable nature of HR, such as HRV, towards modelling the complexity of HR changes by reference to a series of delayed, weakly coupled oscillators[14]. The system can be simply described by Figure 1. This model has been applied to neural oscillations and may provide the basis for modelling other biological systems. In the case of the mouse cardiovascular system, some of the oscillators can be described; the heart has an intrinsic (uncoupled) frequency of around 8Hz, but oscillates between ~ 10Hz and ~7Hz under the influence of the autonomic nervous system, which has oscillator frequencies of ~0.1 Hz and 1Hz for sympathetic and parasympathetic modulation, respectively. Respiratory oscillations in the conscious mouse occur in the 2-6Hz frequency range[3,4]. There may be other oscillators that influence the system in this species too; the glucocorticoid dexamethasone has been shown to increase HRV, for example[5], suggesting a role for steroid hormones in modifying the system either as oscillators or by changing the coupling between the existing oscillators. We can provide raw BP data (from which HR and other oscillator frequencies can be derived) collected over long time periods at a 1 kHz time base, from both anaesthetised and conscious mice. In the case of anaesthetised mice, the respiratory oscillator frequency is fixed, but the effect of anaesthetic on other oscillators is unknown.

Questions you would like to see answered

1. Can the HR signal be described as the output from a series of weakly coupled oscillators?
2. If so, what is the minimum number of oscillators required to model the data?
3. Do the modelled oscillator frequencies match the literature values?
4. Do the coupling and delay constant estimates seem empirically reasonable?
5. What further experiments would be required to refine the model?
6. Does the model predict that reduced HRV in sepsis is the result of ‘synchrony’ or ‘uncoupling’ of the oscillators?

The potential impact on animal use

We will use gold standard refined techniques such as radiotelemetry in order to minimise pain and distress in the animals. The potential impacts on animal use are three-fold.

Firstly, as this project aims to improve methods for analysing and interpreting large data sets, it would enable re-analysis of existing electronic datasets which will likely unveil novel biological data without requiring any further animal experimentation. Secondly, knowledge of respiratory patterns is important in numerous diseases, including septic shock where respiratory changes are indicative pathophysiological alterations in acid-base balance. At present, respiratory rate is monitored by whole body plethysmography, independently of blood pressure/heart rate. However, we believe it will be possible to accurately calculate respiratory patterns through detailed analysis of heart rate/blood

pressure waveforms, thereby circumventing the need to perform plethysmography in independent cohorts of animals. This would result in a reduction in animal use, compared to current practice, in all preclinical studies where cardiovascular parameters are monitored. Thirdly this method may allow refinement of current animal models of sepsis by aligning the endpoints towards those used in the clinic (reduced HRV, oscillator uncoupling) which are likely to occur at earlier stages providing a predictive tool for assessing the onset of septic shock, and away from more commonly used severe endpoints such as organ failure and survival.

References

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