

# Activity Index from Continuous Telemetry in a Mouse Model of Voluntary Wheel Exercise Training

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## Abstract

*Mouse models are now widely used for studying gene function and facilitating drug discovery and development within the pharmaceutical industry. The availability of murine biomedical signals brings new challenges in terms of obtaining recordings, signal processing and analysis. Heart rate variability (HRV) is predictive of prognosis in cardiovascular disease states, especially heart failure, and also provides a measure of autonomic function. Reliable estimation of HRV metrics are of interest to those carrying out biomedical research with mouse models. A voluntary murine wheel running model is employed to test how HRV is mediated by the autonomic nervous system. Telemeters are used to measure the blood pressure waveform at 500 Hz in freely moving mice, providing a time series of cardiac interbeat intervals. An activity index is derived from the heart rate signal and compared with an independent measure of three activity states: (i) rest; (ii) activity; and (iii) exercise.*

## 1. Introduction

Exercise is generally associated with better health conditions and regular physical exercise in humans is known to reduce cardiovascular risk [1] and can have beneficial effects for individuals suffering from cancer [2] and depression [3]. Genetically modified mouse models are increasingly used to investigate the molecular mechanisms underlying complex disease states. Whilst mouse models have the potential to provide insight into these mechanisms, quantitative evaluation of the hemodynamic responses to acute and chronic exercise in mice remains limited in spite of the fact that they can undertake vast amounts of voluntary wheel running.

By continuously monitoring the electrical activity of the heart for 24 hours or more, electrocardiogram (ECG) recordings obtained from ambulatory devices, such as Holter monitors, have proved useful for facilitating medical diagnosis of cardiac disorders. Different levels of physical activity can, however, confound measurements of heart rate variability (HRV) and the analysis of cardiac

arrhythmias. An activity index provides a means of reducing the intra-subject variability that may arise due to physical activity when performing cardiac studies. A previous study focused on ECG-based indices of physical activity for human subjects and demonstrated that while mean heart rate is dependent on the level of activity, this variable is inadequate in isolation [4]. It was concluded that physical activity was best quantified by including two additional variables derived from the instantaneous heart rate, total power and a measure of stationarity. The power provides a measure of peak-detection errors that may arise due to omitted, superfluous and misidentified peaks; occurrence of these errors is likely to be greater when the subject is active.

In this paper we investigate the cardiac interbeat intervals and blood pressure recordings from a population (n=9) of mice during voluntary exercise training. The level of physical activity was categorised by three distinct states: (i) rest; (ii) a telemetry-based measure of cage activity; and (iii) voluntary wheel running exercise (measured using an optically activated wheel odometer).

## 2. Methods

All animals were 10- to 11-week-old C57BL/6 strain littermates from an inbred colony. Mice were provided with standard chow and water *ad libitum* and housed singly at 24°C in individually ventilated cages (IVC, Techniplast Italy). All mice were exposed to a regular 12:12-hour light-dark cycle. Studies were performed in accordance with both the UK Home Office Animals (Scientific Procedures) Act of 1986 and the guidelines for the care and use of experimental animals of the National Institutes of Health.

The mice were provided with an angled rotating running track (Lillico, Surry, UK), circumference 37.8 cm, mounted on a greased steel axle [5]. Wheel running was monitored using either an optical or a magnetic switch attached to a novel computerised exercise monitoring system (Micro 1401 (CED, Cambridge, UK)), and analyzed by computer with Spike 2 software (CED).

The Data Sciences International (DSI) Physiotel® telemetry system facilitates the continuous monitoring of animals while they move freely within their cages. PAC10

murine blood pressure telemeters were implanted in the left carotid artery of subject animals with the body of the telemeter placed in a left subcutaneous pocket equidistant from the fore and hind paw. Following ten days of post operative recovery, telemetered mice were placed in cages fitted with optically monitored running wheels. DSI telemetry was used to measure the blood pressure waveform at 500 Hz in freely moving mice over 24 hour periods. The running activity was merged with the blood pressure signal from the telemetry system allowing precise correlation of blood pressure with activity.

We calculated the sequence of cardiac beat arrival times by detecting peaks in the blood pressure signal; these are denoted by  $t_n$  where  $n$  is the beat number. An instantaneous heart rate signal, expressed in units of beats per minute was derived using  $H = 60/(t_n - t_{n-1})$ . The mean and standard deviation of the heart rate sequence were computed for each day during the exercise training. The standard deviation represents the HRV and is simply the square root of the total power in the heart rate signal. Although the power is capable of detecting changes in the autonomic system, it is also affected by the accuracy of the peak detections. Both of these effects contribute to its use as a feature for classifying physical activity.

### 3. Results

In this section we provide the results for the exercise training parameters, the dependence on the state of physical activity and finally our ability to use the biomedical signals as the basis of an activity index.

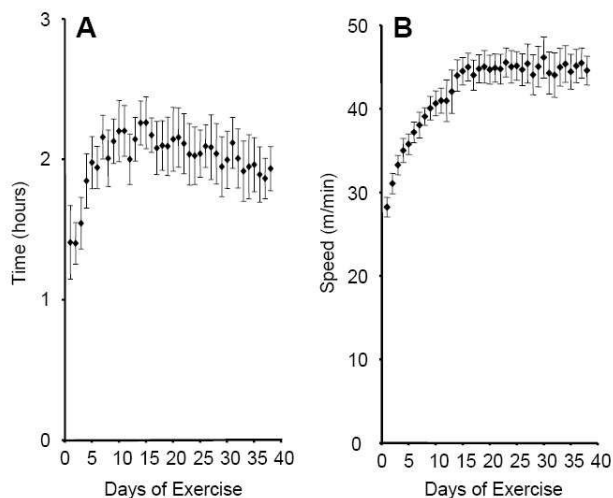


Figure 1: Time spent running (A) and average speed (B) during exercise training.

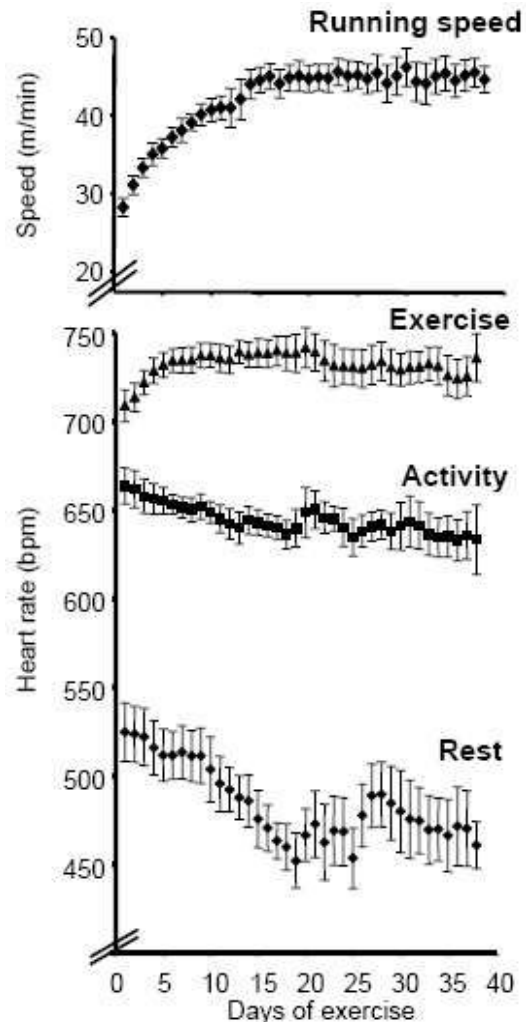


Figure 2: Changes in heart rate during exercise training.

#### 3.1 Voluntary exercise training

Mouse running performance was measured each day using an optical or magnetic switch activated by wheel rotation. This provided the total distance, time spent running and therefore the average speed for each day. The mice spontaneously ran large distances with the total time spent running increasing during the first few days, reaching a plateau after seven days and a peak at day 14 (Fig. 1a). The average running speed was much less variable from day to day and increased logarithmically during training from an initial speed of 28 m/min to a plateau of 45 m/min after 14 days (Fig. 1b). Mice were found to prefer running at a single modal speed or *cruising* speed that was higher than the average speed.

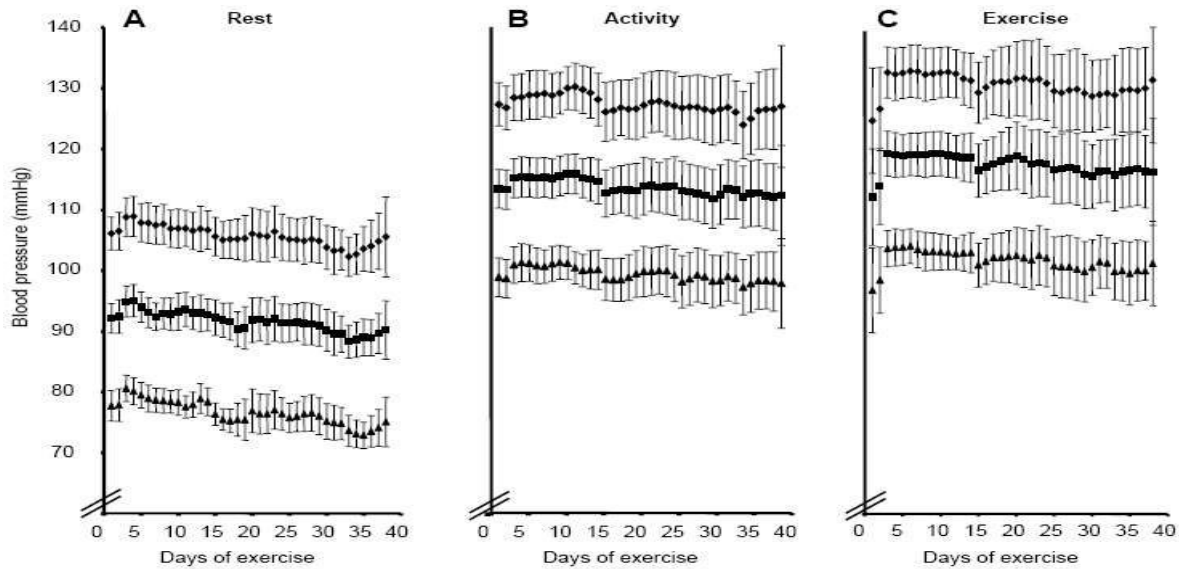


Figure 3: Changes in systolic  $\diamond$ , mean  $\blacksquare$ , diastolic  $\blacktriangle$  blood pressure during rest (A), activity (B) and exercise (C).

### 3.2 Physical activity states

Three distinct states were defined as rest, cage activity and wheel running exercise. By separating the recordings based on these states we calculated the heart rates corresponding to each state during the exercise training period. As the running speed increased the heart rate during exercise was found to increase steeply over the first five days, increase gradually over the following 15 days and finally decrease slowly in the remaining days. Heart rate during activity decreased gradually during the exercise training. During the resting state, the heart rate decreased dramatically over the first 19 days (Fig. 2).

The blood pressure values (systolic, mean and diastolic) all decreased with exercise training during each of the states (Fig. 3). As both heart rate and systolic blood pressure contain information about the different states, we constructed two-dimensional graphs showing the joint distributions of these two variables throughout the exercise training for all three states and for all combined states (Fig. 4). There is a considerable amount of overlap between the exercise and activity state, especially in the systolic blood pressure.

### 3.3 Classification of activity states

Both changes in the power spectrum and delay reconstructions of the interbeat intervals were investigated but were not found to offer any discriminatory power above that of the mean and total power of the heart rate signal. By investigating these two variables after an initial training period, we found that this two-dimensional feature space was capable of separating all three states (Fig. 5).

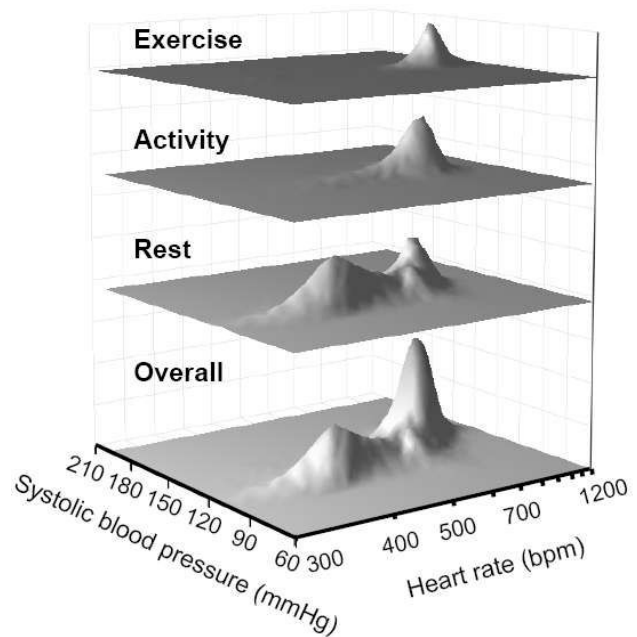


Figure 4: Joint distribution of systolic blood pressure and heart rate for overall, rest, activity and exercise.

### 3.4 Activity index

As the mean heart rate and HRV were sufficient for separating these three states, we defined an activity index based on the clusters in the two-dimensional feature space shown in Fig. 5. A nearest-neighbour classification

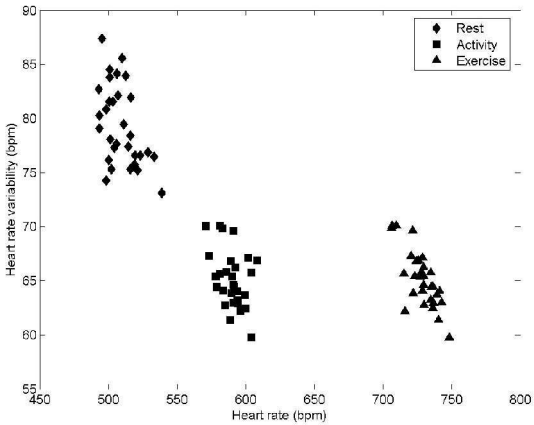


Figure 5: Heart rate variability (standard deviation) versus mean heart rate for different days after reaching a plateau in the exercise training.

technique based on the Euclidean distance from the means of the clusters was employed. In order to process continuous signals, we defined a sampling period and a time window for estimation. An activity index was computed every 50 interbeat intervals. For this sampling rate, a window of 100 intervals was found to give the best classification performance. An example of the quality of the activity index is presented for a segment of data in Fig. 6, showing that the estimated activity index closely resembles that given by the spike 2 and DSI telemetry monitoring of activity state.

#### 4. Discussion and conclusions

The controlled environment under which the voluntary exercise training data was collected provides a unique dataset from which to investigate the effects of physical activity on the cardiovascular system. Exercise training provided significant decreases in both heart rate and blood pressure. From a classification point of view, while blood pressure was useful for detecting the rest state it showed little variation between activity and exercise. Although the mean heart rate reflects the change between activity and exercise, we found that combining the mean of the heart rate time series and the HRV metric facilitated detection of transitions between rest and activity. We demonstrated how both the mean heart rate and HRV provide an accurate activity index.

#### Acknowledgements

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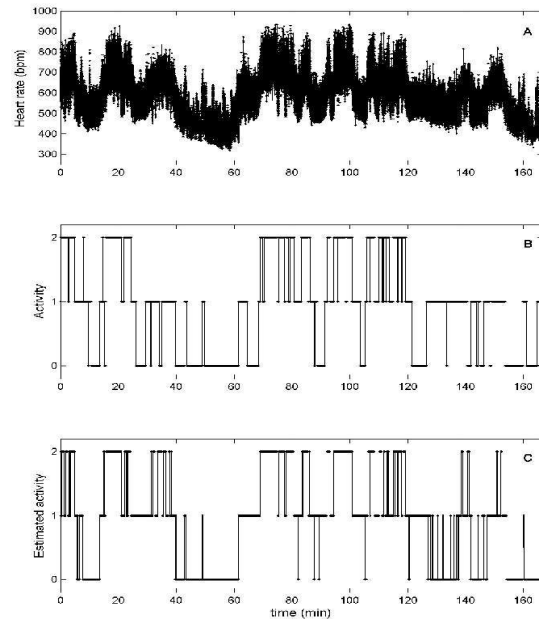


Figure 6: Heart rate (A), actual mouse activity (B) and estimated activity (C). Activity states: 0 = rest; 1 = cage activity; and 2 = wheel running exercise.

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