A computational model of the circadian clock and its application to understanding renal disease

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The circadian clock allows an organism to schedule their internal physiology and behaviour to function at the appropriate time of day. The molecular components at the core of the clock and the interactions between them are highly conserved between all tissues and cells, but their phases and the downstream effects are generally tissue- or cell-specific. The renal circadian clock plays a pivotal role in regulating daily fluctuations in blood pressure through the modulation of sodium transport and extra-cellular fluid volume. Perturbations of this rhythm, particularly the nocturnal dip, confer increased risk for cardiovascular and renal disease. In order better understand the circadian biology of the kidney, we decided to construct a model of this system.

We first performed an exhaustive search of existing models and the primary literature that described the components of the mammalian circadian clock and the interactions between them. We then employed the modified Edinburgh Pathway Notation (mEPN) modelling language to build a graphical representation of the circadian clock using the principles of bipartite graphs to differentiate between pathway components (places) and processes (transitions). This then allowed us to run Petri net-based stochastic simulations of the system's dynamic activity. To parameterise the model, we used mRNA levels derived from transcriptomics data which describes the diurnal variation in gene expression in the kidney – the expression level of core clock genes in the kidney being used to define starting conditions (expression levels being used as a proxy for protein levels). The transcriptomics data was also used as a target readout of model activity and to achieve this various 'delay motifs' were added to modulate token flow.

The result of this work is a detailed network model of the core mammalian circadian clock, which summarises the current literature and understanding on how the circadian clock operates. It contains over 2013 nodes, 2100 edges and represents the interactions between 69 molecular species. The model has also been parameterised for computational modelling using known activity profiles of genes expressed in the kidney. In virtual knock out experiments, the model has been shown to reflect experimental data. It also identifies the points at which canonical clock genes may integrate with downstream processes regulating genes likely to affect blood pressure and other aspects of kidney function.