BMC Bioinformatics

BioMed Central

Oral presentation

Open Access

Biological clocks in theory and experiments

Andrew J Millar*[1,2]

Address: [1]School of Biological Sciences, University of Edinburgh, Edinburgh, UK. and [2]Interdisciplinary Programme for Cellular Regulation, University of Warwick, Coventry, UK.

Email: Andrew J Millar* - Andrew.Millar@ed.ac.uk

* Corresponding author

from BioSysBio: Bioinformatics and Systems Biology Conference
Edinburgh, UK, 14–15 July 2005

Published: 21 September 2005

BMC Bioinformatics 2005, **6**(Suppl 3):S2

Eukaryotes and some prokaryotes have adapted to the 24 h day/night cycle by evolving circadian clocks. The circadian clock now controls 24-hour rhythms in very many aspects of metabolism, physiology and behaviour. Day-length (photoperiod) measurement depends on the circadian clock, so the 24 h clock mechanism also governs seasonal rhythms, such as reproduction. In the model plant species, *Arabidopsis thaliana*, the clock controls the expression of about 10% of genes, and this proportion is similar in other eukaryotes. Fundamental properties of the clock are shared across taxonomic groups, such as phase resetting by light signals and temperature compensation of the circadian period.

All the known clock mechanisms include a gene circuit with negative feedback, involving 24 h rhythms in the levels of positive- and negatively-acting transcriptional regulators. Molecular genetics has identified 5–15 genes that are involved in constructing these regulatory loops in cyanobacteria, Drosophila, Neurospora, Arabidopsis and mouse, though other components almost certainly remain to be discovered. The protein sequences of the clock components are largely distinct to each taxonomic group but some features of the regulatory circuits are shared among groups, suggesting that the circuit architecture may be important for clock function. Circadian regulation is ubiquitous, pervasive and has complex properties, yet the number of components in the clock is relatively small, making this an excellent prototype for reverse engineering of a genetic sub-network.

My experimental group has identified new components of the plant circadian clock, using the bioluminescent reporter gene luciferase (*LUC*) to reveal gene expression rhythms with high spatial and temporal resolution. As the details revealed by molecular genetics do not necessarily lead to greater understanding of a regulatory circuit, we have also developed differential equation models for the plant clock and photoperiod sensor, together with our collaborators in IPCR. The models incorporate molecular components in a realistic manner, so numerical simulations using the models are now directing the design and evaluation of molecular experiments. We have developed an experimentalist-friendly interface for the models, to allow other groups to use these methods (free online at http://www.amillar.org/Downloads.html). David Rand and colleagues have established a novel analytical method to assess the contribution of each component of the model (RNA or protein) at each phase of the cycle. This work indicates a general explanation for the evolution of multi-loop structures, to allow flexible regulation, providing one of the design principles that may underlie the architecture of the circadian clock gene circuits. Funded by BBSRC, EPSRC and DTI. More information can be found at http://www.amillar.org.

References

1. Young MW, Kay SA: **Time zones: A comparative genetics of circadian clocks.** *Nat Rev Genet* 2001, **2:**702-715.
2. Goldbeter A: **Computational approaches to cellular rhythms.** *Nature* 2002, **420:**238-245.
3. Rand DA, Shulgin BV, Salazar D, Millar AJ: **Design principles underlying circadian clocks.** *J Roy Soc Interface* 2005, **1:**119-130.
4. Locke JCW, Millar AJ, Turner MS: **Modelling genetic networks with noisy and varied experimental data: the circadian clock in *Arabidopsis thaliana*.** *J Theor Biol* 2005, **234:**383-393.
5. Locke JCW, *et al.*: **Extension of a genetic network model by iterative experimentation and mathematical analysis.** *Mol Syst Biol* 2005. doi:10.1038/msb4100018