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MATHEMATICAL MODELLING OF THE CIRCADIAN CORE-CLOCK CAN BE USED TO CHARACTERISE THE TEMPORAL PROFILE OF HUMAN CELLS AND TO SIMULATE THE IMPACT OF CIRCADIAN DYSREGULATIONS.

Abstract

Circadian clocks generate daily endogenous rhythms in organisms across all phyla, facilitating the adaption of physiological and behavioural processes to the solar day-night-cycle. Malfunctions of the circadian system have been associated with various pathological phenotypes ranging from sleep disorders to cancer. The mammalian circadian network is represented by a distinct set of 14 core-clock genes and proteins that form two interconnected transcriptional/translational feedback loops. Together, these loops generate tissue-specific circadian rhythms that are detectable in over 40% of all protein-coding genes. Despite remarkable developments in the circadian field, a detailed mechanistic insight into the clock machinery and the subsequent propagation of rhythmic signals is still lacking. To further dissect the underlying dynamics of clock and clock-controlled genes and their role in cell fate decision, our group developed a semi-quantitative gene regulatory network model for the mammalian core clock using ordinary differential equations (ODE) that has recently been extended to include elements of the cell cycle network and allows for the interpretation and prediction of the dynamics of the clock system. However, the model parametrisation process is often complicated due to the paucity of available experimentally measured quantitative information. For this reason, logical modelling approaches that describe the qualitative temporal behaviour of a biological system using discrete two-state logic are extremely valuable. To date, none of the existent logical models of the circadian clock take the interconnected feedback loops of the mammalian circadian system into account. In parallel to our ODE model, we developed a Boolean model of the mammalian core-clock that can be extended to more clock-controlled genes and allows for a broader overview of the impact of punctual perturbations on the circadian system. We will present simulations for both models and discuss its utility in analysing and simulating circadian rhythms in human cells, as well as in predicting the impact of circadian dysregulation in terms of the cell division cycle and other biological processes.