An inactivation switch enables rhythms in a Neurospora clock model

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An autonomous endogenous time-keeping 1 is ubiquitous across many living organisms known as circadian clock when it has a period of about 24 hours. Interestingly, the fundamental design principle with a network of interconnected negative and positive feedback loops is conserved through evolution, although the molecular components differ. Filamentous fungus Neurospora crassa is a well established chrono-genetics model organism to investigate the underlying mechanisms. The core negative feedback loop of the clock of Neurospora is composed of the transcription activator White Collar Complex (WCC) (heterodimer of WC1 and WC2) and the inhibitory element called FFC complex which is made of FRQ (Frequency protein), FRH (Frequency interacting RNA Helicase) and CK1a (Casein kinase 1a). While exploring their temporal dynamics we investigate how limit cycle oscillations arise and how molecular switches support self-sustained rhythms. We develop a mathematical model of 10 variables with 26 parameters to understand the interactions and feedback among WC1 and FFC elements in nuclear and cytoplasmic compartments. We performed control and bifurcation analysis to show that our novel model produces robust oscillations with a wild-type period of 22.5 hrs. Our model reveals a switch between WC1 induced transcription and FFC assisted inactivation of WC1. Using the new model we also study possible mechanisms of glucose compensation. A fairly simple model with just 3 nonlinearities helps to elucidate clock dynamics revealing a mechanism of rhythms production. The model can further be utilized to study entrainment and temperature compensation.

Keywords: Circadian clock, Mathematical modelling, Molecular switch, Fungi (Neurospora crassa), Glucose compensation