

# A Mathematical Model of the Liver Circadian Clock Linking Feeding and Fasting Cycles to Clock Function

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To maintain energy homeostasis despite variable energy supply and consumption along the diurnal cycle, the liver relies on a circadian clock synchronized to food timing. Perturbed feeding and fasting cycles have been associated with clock disruption and metabolic diseases; however, the mechanisms are unclear. To address this question, we have constructed a mathematical model of the mammalian circadian clock, incorporating the metabolic sensors SIRT1 and AMPK [1]. The clock response to various temporal patterns of AMPK activation was simulated numerically, mimicking the effects of a normal diet, fasting, and a high-fat diet. The model reproduces the dampened clock gene expression and NAD<sup>+</sup> rhythms reported for mice on a high-fat diet and predicts that this effect may be pharmacologically rescued by timed REV-ERB agonist administration. Our model thus identifies altered AMPK signaling as a mechanism leading to clock disruption and its associated metabolic effects and suggests a pharmacological approach to resetting the clock in obesity.

## R ef erences

1. A. Woller, H. Duez, B. Staels, and M. Lefranc, A Mathematical Model of the Liver Circadian Clock Linking Feeding and Fasting Cycles to Clock Function, *Cell Reports* **17**, 1087-1097 (2016).