Modeling the entrainment of liver clock by feeding/fasting cycles

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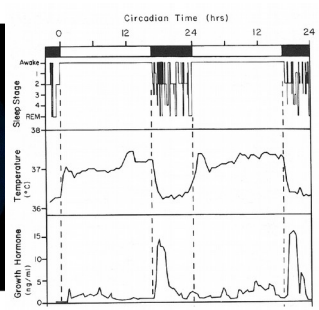
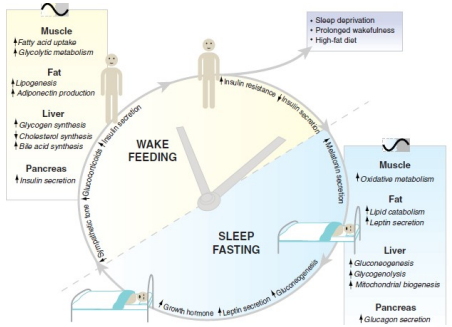
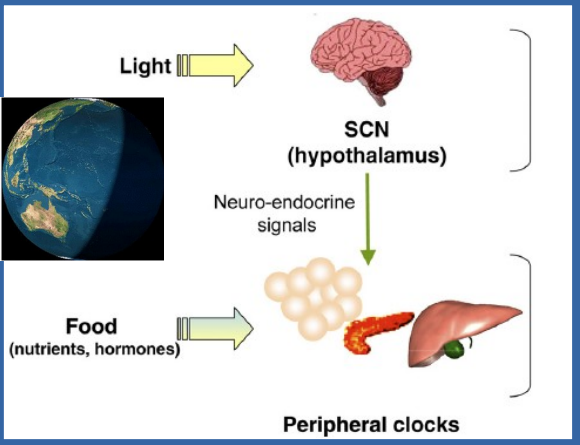
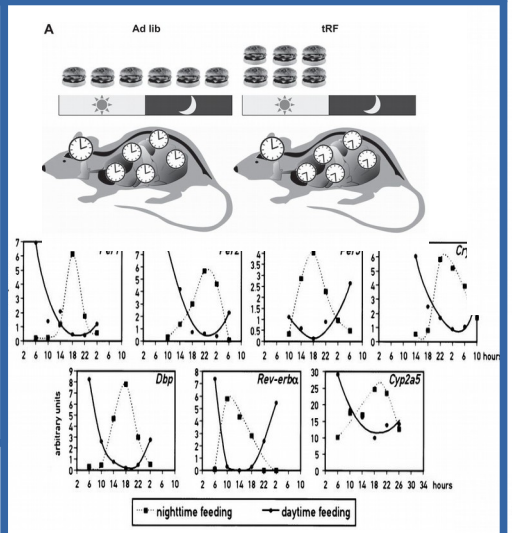






Food is the primary zeitgeber for liver clock

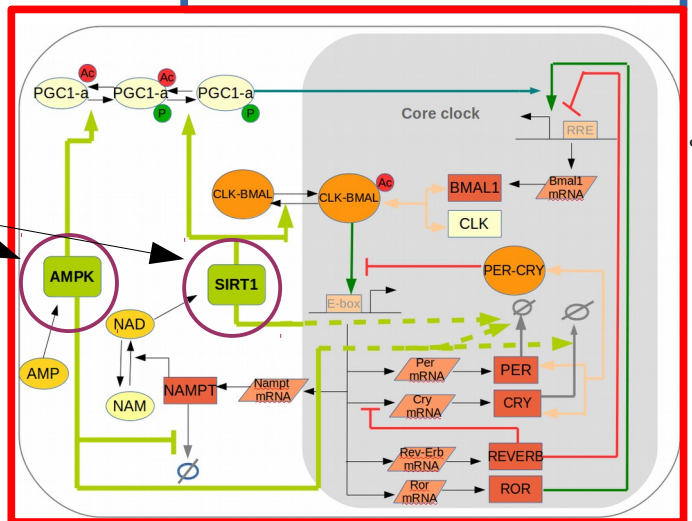


Damiola Genes Dev 2000

Metab. gauges:
AMP/ATP,
NAD+/NADH

Sensors: AMPK (AMP), SIRT1 (NAD+)

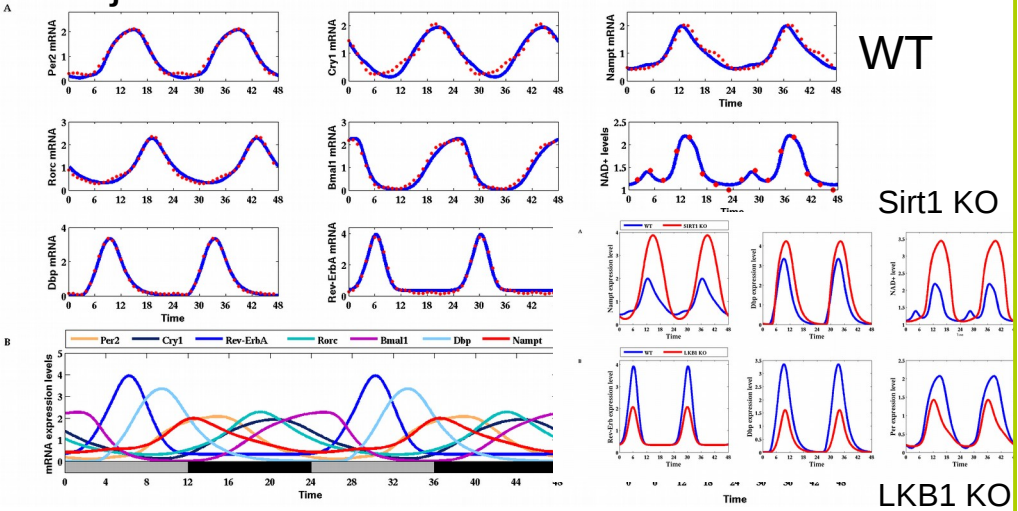
Clock network incorporating the sensors SIRT1 and AMPK ----->



Build a mathematical model of clock network...

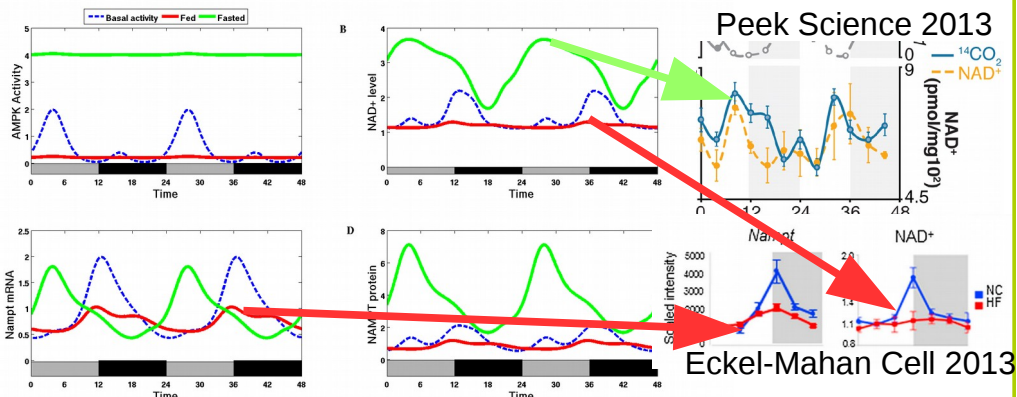
$$\frac{\left(basal\_mper\cdot\left(1+fold\_per\cdot\left(\frac{[CB]}{thr\_percb\cdot(1+c\_srt\cdot[Sirt1])}\right)^{hill\_percb}\right)\right)}{\left(1+\left(1+\left(\frac{[PC]}{thr\_perpc}\right)^{hill\_perpc}\right)\left(\frac{[CB]}{thr\_percb\cdot(1+c\_srt\cdot[Sirt1])}\right)^{hill\_percb}\right)}$$

Adjustment of the mathematical model



Clock gene data: Hughes et al. Plos Genet. 2012 (Hogenesch gr.), NAD+ data: Hatori et al. Cell Metab 2012 (Panda group).

Simulate various diets by different AMPK profiles



Our minimal mathematical model reproduces the **loss of amplitude in clock gene expression and NAD+ levels under high-fat diet** as well as phase shift under fasting

Can we design a pharmacological approach to rescue clock profiles? => see poster