

Main paper: “The effects of non-self-sustained oscillators on the entrainment ability of the suprachiasmatic nucleus”; Gu, Tang, Rohling & Yang; Nature Scientific Reports; 2016

- The SCN has two different types of neurons: two main types are light sensitive (VL) ~25% and light insensitive (DM) ~ 75%.
- Both VL and DM can be: non-self-sustaining, self-sustaining, dampened or arrhythmic. Self-sustaining neurons are the minority in the SCN
- Neurotransmitter proteins differ between types of neurons: VL uses VIP, DM uses AVP
- The VL region and the DM region are connected using GABA.
- Proportion of VL neurons does not affect free running period in total darkness, but affects the amount of entrainment possible for the system. Meaning that an SCN network with more VL has a higher ability to adjust to external light conditions for example.
- Location matters: if VL are located in the light sensitive sub region entrainment range decreases. If VL are located in the light insensitive region entrainment range increases.
- Coupling matters: non-self sustaining oscillators that are highly coupled can be well entrained and are particularly well synchronized.
- Model: use mean field coupling,

“Weakly Circadian Cells Improve Re-synchrony”; Webb, Taylor, Thoroughman, Doyle, Herzog; PLoS Comp Bio; 2012

- Cells in SCN differ in intrinsic characteristics, such as period, amplitude, gene expression, level of rhythmic ability and circadian free period.
- Individual characteristics of cells do not predict their ability or rate of resynchronization after exposure to toxin. They resynchronize at a system level (tissue) rate ???
- Dampened and short oscillators synchronize faster.
- Proximity to bifurcation point has implications on synchronization
- Small world topologies beneficial for synchronization
- Small changes in model parameters for single cells are causal of observable characteristics such as period and amplitude.
- Weak/low amplitude cells are better able to synchronize
- Weak cells become strong oscillators when coupled??
- Loss of synchronization is similar for all cells, regain is different and there are special patterns in how the cells regain synchrony
- Use multi-dimensional visualization techniques to understand (new way of) sensitivity analysis on parameter sets: heat map within a heat map.
- Phase heterogeneity in SCN cause by factors other than intrinsic cell properties

“Coupling governs entrainment range of circadian clocks”; Ute Abraham, Adrián E Granada, Pa'l O Westermark, Markus Heine, Achim Kramer, Hanspeter Herzel; Molecular Systems Biology 6; 2010

- The ratio between input strength and amplitude and rigidity of the system in terms of relaxation rate determine entrainment properties.
- Coupling of oscillators results in increased amplitude and rigidity.
- More weakly coupled networks are more easily entrained.
- Circadian systems are robust because they are resistant to noise when highly coupled.
- When cells are not highly coupled they can easily de-synchronize when the “master clock”

signals are removed.

- Used bifurcation diagrams, including toroidal oscillations and deterministic chaos to understand the robustness of the system.
- The strength of signals can impact the ability of a network to entrain. Oscillators can be characterized by amplitude, intrinsic period and stability with respect to amplitude perturbations captured by the Poincaré oscillator
- Oscillators with slower relaxation rates more easily entrained.
- Possible to predict response: signal strength/ amplitude predicts entrainment range when you control for intrinsic period and intrinsic relaxation rate.
- An increased coupling strength leads to a increase of the amplitude most pronounced for small values of the relaxation rate of the individual oscillators.
- Coupling makes the synchronized oscillatory state more rigid in two aspects: (i) resonance increases the amplitude and (ii) coupling leads to faster relaxation.

“Resynchronization dynamics reveal that the ventral entrains the dorsal suprachiasmatic nucleus”; Taylor, Wang, Granados-Fuentes, Herzog; J Bio Rhythms; 2017 (phase-amp)

- Cells in the DM stabilized their periods slower than those in the VM, and the VM is more coupled than the DM, thus the VM entrains the DM.
- Light profiles with long duration of light can cause the VM and DM to separate in phase.
- Using a clustering method blind to cell location, predicted VM-DM spatial organization
- Create a library: of different parameter sets for each of the cells in the network to have their own intrinsic periods and rate constants.
- DM and VM connections use nearest-neighbor topology, however the VM has additional long-range connections to the DM.
- Choose intrinsic period of VM oscillator from a Gaussian distribution centered at 25.1 h with a standard deviation of 1.3h.
- Choose intrinsic period of DM oscillator from a Gaussian distribution centered at 23.9 h with a standard deviation of 1.9 h
- Initial phase values chosen uniformly from 1-24
- VM cells tend to express intrinsically slower circadian periods than DM SCN cells.
- Steady state synchrony within the SCN was obtained when DM had a stable circadian period and a daily peak in PER2 a few hours before daily peak in the VM SCN
- Considered a particular topology to be realistic if the simulated VM and DM matched the behaviors of recordings of the VM and DM clusters
- Successful topology characteristics: VM had denser connections (random within-region connections in addition to the nearest neighbor) than the DM and stronger connections to the DM as compared to DM-to-VM connections
- DM-to-VM connections required 80–100% full strength for realistic results
- Topologies were not well calibrated for light input

“Spontaneous Synchronization of Coupled Circadian Oscillators”; Gonze, Bernard, Waltermann, Kramer, Herzog; BioPhysics J; 2005

- VIP induces *per1* and *per2* expression in a phase-dependent manner
- DM cells are not synchronized when they are disconnected from the rest of the SCN
- Used a three-state model similar to the Goodwin model
- Mean field coupling, is defined as the average concentration of the neurotransmitter.
- Coupling induces a damping in individual clocks, enabling efficient synchronization
- Quality of synchronization is computed by the order parameter, equation given in paper.
- When the coupling is small, the oscillators are not well synchronized and display quasiperiodic behavior
- Intermediate coupling strength both oscillators converge to a steady state.
- High coupling strength near a bifurcation, the system tends to a limit cycle corresponding to a synchronized state
- Synchronization is achieved by the oscillatory component of the mean field. Thus, the oscillating mean field drives all cells to fast synchronization
- Phase relationship between the oscillators is an intrinsic property of the oscillator network
- DM part is phase-advanced with respect to VL

“Toward a detailed computational model for the mammalian circadian clock”; Leloup, Goldbeter; PNAS; 2003 (LG16)

- Sustained circadian oscillations in continuous darkness have an anti-phase relationship between *Per/Cry/Rev- Erb* and *Bmal1* mRNAs.
- The phase of the oscillations can vary by several hours with small changes in parameter values.
- The network is characterized by negative feedback loops of auto-regulated gene, transcription, phosphorylation and dimerization and inhibition; 16 state model.
- Light can entrain circadian rhythms by inducing the expression of the *Per* gene.
- Assessment of quality model should allow entrainment of the oscillations by LD cycles
- Lack of robust entrainment caused by too low concentration of CRY protein Lack of entrainment can occur as a function of other control parameters as well.
- Since there are so many different feedback loops, mechanisms for producing sustained oscillations are not unique.

“Synchronization-Induced Rhythmicity of Circadian Oscillators in the Suprachiasmatic Nucleus”; Bernard, Didier Gonze, Cajavec, Herzel, Kramer; PLoS Comp Bio; 2007.

- This model combines intracellular and intercellular dynamics at the single-cell level.
- Amplitudes and phases of neurons are negatively correlated.
- Used a network of coupled but damped molecular circadian oscillators and three types of topologies: random sparse coupling, nearest-neighbor coupling, and SCN-like coupling combining nearest-neighbor and sparse coupling
- Coupling assumed to be accomplished by a neurotransmitter released upon PER/CRY complex activity.
- The strength of the coupling signal depends on the average concentrations of neurotransmitter released by all coupled cells at a particular phase.
- Autocrine neurotransmitter activation seems to be sufficient to sustain oscillations
- If the oscillators sense weak autocrine and paracrine signals their oscillations die out.
- Never encountered two coupled oscillators that are rhythmic but desynchronized. This indicates that for the model, rhythmicity is sufficient to induce synchronization.
- Uniform extracellular noise could contribute to synchronize the cells.
- Synchrony is necessary for rhythmicity of single oscillators
- For large numbers of SCN neurons, we found that synchrony is achieved even for very small connectivity values.
- Slow oscillators have a higher impact on the period than the faster ones. Does high amplitude imply slowness?
- After a 12-h phase-shift in the LD cycle, VL cells resumed their phase quickly (after 2 days), while DM cells took more than 10 days to resynchronize to the LD cycle.

“Global parameter search reveals design principles of the mammalian circadian clock”; Locke, Westermarck, Kramer and Herzel; BMC Sys Bio; 2008.

- Current models do not simulate the quick adjustment that is caused by a shift in LD cycles: takes 20 days in model and only 6 days in life.
- If the neurotransmitter has mostly damped, rather than self-sustained oscillators, it is possible to achieve fast phase resetting in simulation.
- Only a subsection of the actual SCN neurons express the VPAC2 receptor for the neurotransmitter VIP.
- The oscillators remain synchronized even when the individual parameters are rescaled to represent 5 fold larger fluctuations in period
- Damped single-cell oscillators could be advantageous for efficient synchronization
- Synchronized oscillations were possible for Hill coefficients varying from 0.7 – 9.8, this large range not seen in other models

Source 41: "A Molecular Model for Intercellular Synchronization in the Mammalian Circadian Clock"

- VIP is the key synchronizing agent.
- Constant light desynchronizes oscillators by maximizing VIP release.
- Only about 30% of SCN neurons show intrinsic rhythmicity in the absence of VIP signaling and these cells have a broad distribution of circadian periods
- Only about 40% of the cells produced sustained oscillations in the absence of VIP coupling.
- Perturbations that broadened the distribution of oscillator periods led to a monotonic decrease in synchrony.
- Arrhythmicity resulted from when Per and Cry were not coordinately driven in the system.
- The degree of synchronicity of a heterogeneous system depends on cell-specific features (e.g., mean and variability of parameters within the rhythm generating loop), as well as intercellular coupling strength.