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## Stochastic resetting and hierarchical synchronization

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# The two-community noisy Kuramoto model as model for the Suprachiasmatic nucleus

This chapter has been submitted.

## Abstract

Recent mathematical results for the noisy Kuramoto model on a two-community network may explain some phenomena observed in the functioning of the suprachiasmatic nucleus (SCN). Specifically these findings might explain the types of transitions to a phase-split state of the SCN. The model requires only the community structure of the SCN to exhibit the phase-split state. This is in contrast to previous studies requiring time-delayed coupling or large variation in the coupling strengths and other variations in the model. Our model shows that a change in E/I balance of the SCN due to external protocols may result in the SCN entering an unstable state. With this altered E/I balance, the SCN would try to find a new stable state, which might in some circumstances be the split state. This shows that the two-community noisy Kuramoto model can help understand the mechanisms of the SCN and explain differences in behavior based on actual E/I balance.

## §6.1 Introduction

All life on earth is adapted to the external 24-h light-dark cycle, where mammals normally have one bout of activity each cycle, and one bout of sleep. However, when hamsters are placed in constant light conditions, this regular pattern of sleep and wakefulness is disturbed and splitting of the activity bout may occur. In this case, the single period of activity is dissociated into two components that ultimately settle in anti-phase, effectively producing sleep-wake cycles of approximately 12 h [106]. It has been shown that this behavioural phase splitting in hamsters and mice has its origin in the suprachiasmatic nucleus (SCN), which is the location of the master clock regulating the 24-h rhythms in physiology and behavior [37]. The SCN is a bilaterally paired nucleus, where splitting of the behavioral rhythm, caused by exposure to continuous light conditions, induces the left and right nucleus to activate in antiphase [37, 90].

Between species there are differences in phase splitting behavior. Hamsters show splitting when put in constant light conditions [106, 37]. In a mutant mouse strain, called CS mouse, rhythm splitting occurs in constant darkness [1]. Rats and mice can also show split behaviour when subjected to so called forced desynchrony protocols [21, 36, 22]. Rats were subjected to a 22-h light-dark cycle and mice to a chronic jet lag protocol. It was shown that in the forced desynchrony protocol, the dissociation arises between the ventral and the dorsal part of the SCN. Here, the ventral part follows the external light-dark cycle and the dorsal part has a period close to the endogenous free-running period of the animal. It is unknown whether these different types of splitting, let's call them left-right splitting and ventral-dorsal splitting, have different underlying mechanisms, or not.

It is known that the interaction within the ventral part is mainly based on the neurotransmitter vasoactive intestinal polypeptide (VIP), which is excitatory. In the dorsal SCN the interaction is mainly done through arginine vasopressin (AVP), which is also excitatory in nature. The communication between the ventral and dorsal part of the SCN is done through  $\gamma$ -butyric acid (GABA), which can be inhibitory, but in the SCN also excitatory [26, 51, 99]. For the left-right distinction, there is less known about the communication mechanisms, let alone if these are excitatory or inhibitory [94].

Recently a variety of models have been proposed in order to explain why the phase-split state of the SCN occurs. These models have typically tried to modify the standard two-oscillator-models for the SCN by including time-delays in the coupling [65], assuming large variation in the coupling strengths [117] or taking the intra-community coupling to be negative [98]. The model proposed by Oda et al [98] models each community of the SCN as a single oscillator and connects these using coupled Pittendrigh-Pavlidis equations. They consider coupled identical oscillators as well as non-identical oscillators, making a distinction between morning and evening oscillators. Indic and coworkers [65] consider a model most similar to the one we will consider. They include the possibility of a delay in the interaction between oscillators and observe that the network structure is essential to realize the phase-split state. Their work includes analysis of the stability of the phase-split state. The paper by

Schroder [117] uses a model proposed by Leloup, Gonze and Goldbeter [77, 54] and applies this to two groups of 100 oscillators. The results are based on numerical simulations and show that the split state can arise without a change in the structure or strength of the interactions between oscillators, but by a change in the circadian properties of individual oscillators. None of the models have addressed the question of the different transitions observed en-route to the phase-split state.

In this paper we interpret recent findings on the phase diagram of the noisy Kuramoto model on a two-community network [93] in the context of the phase-split SCN, where the left and right SCN, or the ventral and dorsal part of the SCN, dissociate into two anti-phasic neuronal communities, instead of using a two-oscillator model. Here the community structure of the network plays the central role in making the phase split state possible and enriches the model significantly in comparison to the original one-community version. This is a surprising finding in itself as the modification to consider the model on a two-community network seems almost trivial a priori. Not only does this model exhibit the phase-split state, but it also exhibits a bifurcation point in the phase-diagram which determines the existence of a non-symmetrically synchronized state which might explain the different transitions to the phase split state observed in experiments. We investigate stability properties of the various states by using simulations of the system and find that the system might have to pass through the non-symmetrically synchronized solution when it is above the bifurcation point.

## §6.2 Model

In order to model the SCN we modify the noisy Kuramoto model by placing it on a two-community network structure. Each community consists of  $N$  oscillators which correspond to neurons in the SCN. Oscillators in the same community interact with a strength  $K$  and oscillators in different communities interact with strength  $L$ . We will take  $K$  to be positive (attractive) and will allow  $L$  to be both positive and negative (attractive or repulsive). We will also simplify the system by taking all oscillators to have the same natural frequency, namely, zero. This seems unrealistic but since any constant frequency can be rotated out by changing the frame of reference for the system, any constant average natural frequency can be chosen.

We will denote the phase of the oscillators (which can be between 0 and  $2\pi$ ) in the first community by  $\theta_{1,i}$  with  $i = 1, \dots, N$  and the phase of the oscillators in the second community by  $\theta_{2,j}$  with  $j = 1, \dots, N$ . Note that in the current model both communities contain the same number of oscillatory neurons  $N$ . Each angle represents a state of the neuron. The equations governing their evolution are then

$$\frac{d\theta_{1,i}(t)}{dt} = \frac{K}{2N} \sum_{k=1}^N \sin(\theta_{1,k} - \theta_{1,i}(t)) + \frac{L}{2N} \sum_{l=1}^N \sin(\theta_{2,l}(t) - \theta_{1,i}(t)) + \xi_{1,i} \quad (6.2.1)$$

and

$$\frac{d\theta_{2,j}(t)}{dt} = \frac{K}{2N} \sum_{l=1}^N \sin(\theta_{2,l} - \theta_{2,j}(t)) + \frac{L}{2N} \sum_{k=1}^N \sin(\theta_{1,k}(t) - \theta_{2,j}(t)) + \xi_{2,j}. \quad (6.2.2)$$

Here  $\xi_{1,i}$  and  $\xi_{2,j}$  are white noise terms. These can be understood as the effect of the thermal environment that the SCN is in (i.e. external noise) or as time-dependent variations in the natural frequencies of individual oscillators. As in the standard Kuramoto model we define order parameters to measure the amount of synchronization and the average phase in each community:

$$r_{1,N}(t)e^{i\psi_{1,N}(t)} = \frac{1}{N} \sum_{i=1}^N e^{i\theta_{1,i}} \quad (6.2.3)$$

$$r_{2,N}(t)e^{i\psi_{2,N}(t)} = \frac{1}{N} \sum_{j=1}^N e^{i\theta_{2,j}}. \quad (6.2.4)$$

The synchronization levels  $r_{1,N}(t)$  and  $r_{2,N}(t)$  can take values between 0 and 1 with 0 meaning that the relevant community is completely unsynchronized and 1 being completely synchronized. The average phases  $\psi_{1,N}(t)$  and  $\psi_{2,N}(t)$  can take values between 0 and  $2\pi$ . When taking the limit of the number of oscillators going to infinity, we see that the system can be described by a probability distribution in each community, namely,  $p_1(t; \theta)$  and  $p_2(t; \theta)$  giving the probability of finding an oscillator with a given phase at a given time in community one and two respectively. These distributions depend on all of the order parameters.

Note in this respect that in the circadian field, the synchronization term is often treated differently. Where mathematical phase indicates the state of one oscillator at a specified timepoint, in the circadian field the time of a certain state is taken for each oscillator. So, synchronization in the mathematical sense indicates a synchronization in oscillator state, while in the circadian sense it indicates a synchronization of the oscillators in time. Thus, we define the circadian synchronization here as time-synchronization.

In the long-time limit the distributions reach a steady-state (a state in which the order parameters are stationary) which can be described analytically (see [93]). Which values the order parameters  $r_1, r_2, \psi_1$  and  $\psi_2$  can take in the steady-state distributions is determined by a system of self-consistency equations:

$$r_1 = \int_0^{2\pi} \cos(\psi_1 - \theta) p_1(\theta) d\theta, \quad (6.2.5)$$

$$r_2 = \int_0^{2\pi} \cos(\psi_2 - \theta) p_2(\theta) d\theta, \quad (6.2.6)$$

$$0 = \int_0^{2\pi} \sin(\psi_1 - \theta) p_1(\theta) d\theta, \quad (6.2.7)$$

$$0 = \int_0^{2\pi} \sin(\psi_2 - \theta) p_2(\theta) d\theta. \quad (6.2.8)$$

Due to the invariance of the system under rotations, one of the average phases can be set to zero, i.e.,  $\psi_1 = 0$ . This ensures that (6.2.7) is satisfied. In [93] it is proved that the only values  $\psi_2$ , which now also represents the phase difference ( $\psi = \psi_2 - \psi_1$ ) between the two communities, can take are 0 and  $\pi$ . Simultaneously solving (6.2.5)

and (6.2.6) for  $r_1, r_2$ , while fixing  $\psi_1 = \psi_2 = 0$  or  $\psi_1 = 0$  and  $\psi_2 = \pi$ , gives a stationary point for the dynamics of the system. Consider first the case where the average phases are aligned so that their phase difference is 0, i.e.,  $\psi_1 = \psi_2 = 0$ . The system only assumes synchronized solutions when the critical condition is met, which is  $K + L > 2$ . When this is the case the system can always be in the symmetrically synchronized state where  $r_1 = r_2 = r > 0$  (which is stable) or in the unsynchronized state  $r_1 = r_2 = 0$ . Here  $r$  is the synchronization in the mean-field Kuramoto model with interaction strength  $K + L$ . The system however also displays a bifurcation point. Consider fixing  $L < 0$ . Then we can plot the possible solutions for  $r_1$  and  $r_2$  as a function of  $K$  as in Fig. 6.1. We see that at  $K = 4$  the symmetrically synchronized state appears. At around  $K = 5$ , however, non-symmetric solutions appear, where  $r_1 \neq r_2$ . Since both communities are the same in our analysis, both can be in either the yellow or the purple solution. The other community is then forced to take on the opposite solution. (i.e. the system can be in the states  $r_1 = \text{yellow}, r_2 = \text{purple}$ ;  $r_2 = \text{yellow}, r_1 = \text{purple}$  or  $r_1 = r_2 = \text{blue}$ .)

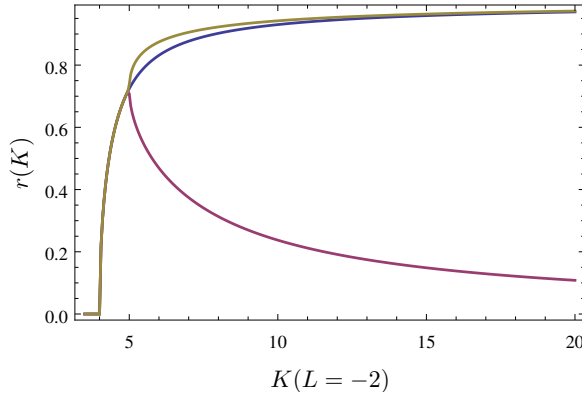


Figure 6.1: Solutions of the self-consistency equations (6.2.5) and (6.2.6) for different values of  $K$  while  $L = -2$  and the phase difference is 0. Symmetric solution (blue) non-symmetric solutions (yellow and purple).

The point at which the non-symmetric solution bifurcate from the symmetric solutions gives a line in the phase diagram. In Fig. 6.2 we plot the phase diagram given that the average phases are aligned, i.e.,  $\psi = 0$  and given that the phases are anti-aligned, i.e.,  $\psi = \pi$ . In this figure we see the red area in which the oscillators in both communities are completely unsynchronized. If the circadian system is in the green area, the system can either be in a state where both communities are synchronized in the same phase, or both communities are completely unsynchronized. In the blue area, the same holds true, but there is also another possible state, namely the non-symmetrically synchronized state, where one community is more synchronized than the other ( $r_1 \neq r_2$ ).

Note that, depending on external conditions, the circadian system can move through this phase diagram since the interaction strength parameters might change due to extreme external conditions. Due to the conjecture in [93] about the possible phase differences in the steady-state we assume that these are the only two phase



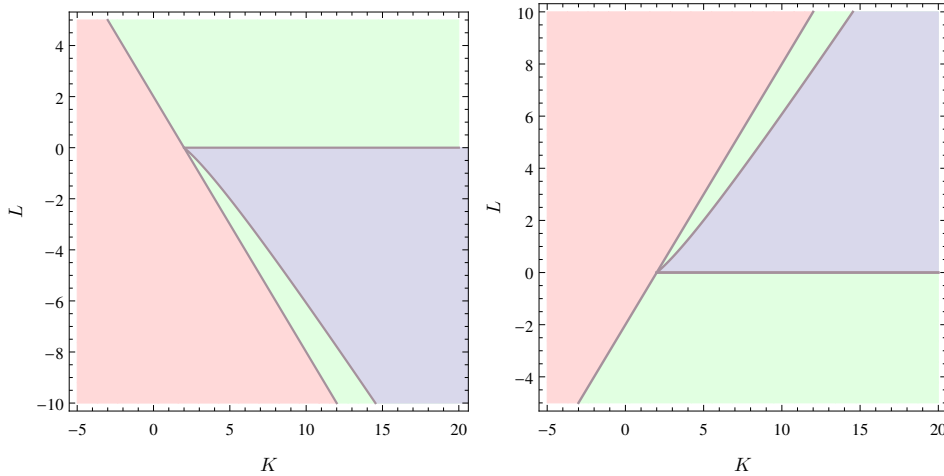


Figure 6.2: Phase diagram when the average phases are aligned (left) and when they are anti-aligned (right). In the light red region we have only unsynchronized solutions. In the light green region we have two solutions: the unsynchronized solution and the symmetrically synchronized solution and in the light blue region we have three solutions: the unsynchronized, the symmetrically synchronized and an non-symmetrically synchronized solution.

diagrams for the steady-state.

The analysis done in [93] and summarized here concerns the stationary points of the system of equations (6.2.5)–(6.2.8) for the order parameters, where each solution corresponds to a pair of stationary distribution profiles,  $p_1(\theta)$  and  $p_2(\theta)$ . It does not give information about the stability of these stationary points. Stability is a delicate issue to treat mathematically and is an open problem. The link between the symmetric solution and the solution of the mean-field Kuramoto model suggests that this solution is stable while the unsynchronized solution ( $r_1 = r_2 = 0$ ) should be unstable above the critical condition. In the next section we will present the results of simulations of the system and interpret them in the context of these stability questions.

### §6.3 Simulations

We can simulate the system to investigate the stability properties of the various solutions. We summarize the observed stability properties in Table 6.1. What is meant by metastable here is that the system can, if prepared correctly, stay in this state for a long time but will eventually move to a stable stationary state (it does not refer to the mathematical definition of metastability). Intuitively this table makes sense. If the interaction between communities is positive we can, roughly speaking, say that the two communities attract one another. If the system is in a state where the average phases are anti-aligned, with both communities sufficiently synchronized, it can stay there for a while but would ultimately prefer to be in a state with the phases being aligned. This is because the mean-field Kuramoto model corresponding to the aligned state has interaction strength parameter  $K+L$  which is greater than the

one corresponding to the anti-aligned state,  $K - L$ . (In the mean-field model greater interaction strength implies a larger synchronization level.) Example are given in Fig. 6.1.

Table 6.1: **Stability of possible solutions when  $K + L > 2$ . Here  $\psi = \psi_2 - \psi_1$ .**

Sol.	unsync	sync $L < 0$	sync $L > 0$	non sym
$\psi = 0$	unstable	metastable	stable	unstable
$\psi = \pi$	unstable	stable	metastable	unstable

The simulations are of 10000 oscillators per community. In the first simulations (Fig. 6.1A) we initialize the two communities to have approximately the same synchronization level (upper frame) and with the average phases of the two communities aligned (lower frame). We take  $L = -2$  and  $K = 5$ . In this situation we expect the aligned state to be metastable since oscillators in different communities repel one another. In the simulation we see that the system indeed stays in the aligned state for some time before moving to the anti-aligned state. The synchronization level in each community increases during this transition. In Fig. 6.1B a similar example is shown for  $L = 2$ . Here the metastable state is the anti-aligned state (see table 6.1).

In the second simulation (Fig. 6.1C) we again initialize the average phases to be aligned but this time one community is more synchronized than the other (upper frame). We take  $L = -2$  and  $K = 7$ . Again the system would like to be in the phase split state but this time the transition occurs by one community having to move to a much lower level of synchrony before the average phases can move apart and assume the higher level of synchrony of the phase-split state. Fig. 6.1D shows a similar situation for  $L = 2$ . Here the metastable state is the anti-aligned state (see table 6.1).

## §6.4 Discussion

The metastable anti-aligned state discussed in the previous section might be the state observed in hamsters displaying two periods of activity in a single 24-hour cycle [106].

The underlying cause of splitting, both left-right splitting as well as ventral-dorsal splitting, seems to be that a two-community structure must be present in the SCN. As these communities interact with each other, in normal circumstances they remain synchronized. However, in particular conditions, these two communities can arrive in the metastable anti-aligned state. This state is, as described, metastable, so after some time it will return to the stable synchronized state. However, it appears that keeping animals in a forced desynchronization protocol, this metastable state can be maintained, even though the SCN is inclined to return to the stable synchronized state.

Apparently, according to Fig. 6.2, the circadian system of animals is normally either in the green or blue area of the state space, which means that the coupling strengths within and between the communities added together are always larger than 2. In different conditions, the parameters  $K$  and  $L$ , which signify the strengths in the communication within one community and between both communities, can change.

It has been shown, for example, that in long photoperiods there is more excitatory GABAergic coupling than there is in short photoperiods [51, 99]. So, the strengths of these coupling parameters can shift the circadian system through this phase diagram, enabling other possible states to arise, such as the split state, or even a desynchronized state.

Studying the dynamics of the system between the various states mathematically is difficult. Simulations of the system give an impression for what might be typical behavior and they might be relevant for understanding the unpredictable response of the SCN to the different transitions to and from the phase-split state when animals are exposed to constant light or forced desynchronization protocols. Changes in external conditions may affect the ability to synchronize by changing interaction strength  $L$  for example. If  $L$  decreases and the system is usually in the situation where  $L > 0$  and  $\psi = 0$ , then after the shift the system could be in the negative  $L$  region. If this is the case it would either be in the blue region where the non-symmetrically synchronized solutions exist or in the green region where they do not. From the stability property table 6.1 we see that the symmetrically synchronized state is then no longer stable. The system would then want to move to a new stable state for the new balance between  $K$  and  $L$ . It finds this new stable state in the phase split state, which corresponds to a point in the phase diagram on the right of Fig. 6.2. If it was shifted in the first phase diagram to a point in the blue region the system might be forced through the non-symmetrically synchronized state before being able to move to the symmetrically synchronized anti-aligned state while it might be able to move directly to this state when it is shifted into the green region (Fig. 6.1). We assume here that the parameters  $K$  and  $L$  are changed by the extreme conditions on a time scale much shorter than the time scale on which the system responds to this change.

To better study the trajectories that the system may take, jet lag studies may be employed to collect data on single cells and review the dynamics between the ventral and dorsal communities. In jet lag experiments, a dissociation between the ventral and dorsal SCN is also observed. When a phase shift is applied to the SCN, Albus et al [4] have shown that the ventral SCN shifts immediately with the new light-dark cycle, while the dorsal SCN lags behind. The dissociation observed between both communities is dissolved after 6 days [111]. Using the jet lag protocol the dynamics of both communities could be studied in subsequent days.

## §6.5 Conclusion

The novelty of this paper is pointing out the existence of the bifurcation point in the two-community noisy Kuramoto model and noting that this might be the reason for seeing different transitions to the phase-split state of the SCN. To prove this is mathematically challenging since that would require studying the dynamics between different states of the two-community noisy Kuramoto model. There is also no experimental work measuring the activity of individual neurons in the phase-split state or during the transition into it to which one could compare the simulations done here. The conclusion of this paper is then that the two-community noisy Kuramoto model has more to offer in terms of explaining the behavior of the SCN.

The table predicts that the stable state of the system is the anti-aligned state when  $L < 0$ . This would mean in the case of the ventral-dorsal communities that when GABA is mainly inhibitory, the system would prefer a split state over the aligned state. However, experimental research clearly shows that this is not the case: in normal circumstances the ventral and dorsal communities are aligned. This may be due to the fact that we used the simplest model possible, where both communities are the same, having the same number of neurons and where the interaction strengths within both communities is also the same as well as the interaction parameters between both communities. A more realistic model would have a different number of neurons for each community, an  $N_1$  and  $N_2$  [111]. Also the communication strengths of VIP in the ventral SCN and AVP in the dorsal SCN would not be the same ( $K_1$  and  $K_2$ ) and the communication between both communities would not be symmetrical ( $L_1$  AND  $L_2$ ) [4]. Finally, the natural variation in the frequencies of the neurons firing could be included by adding a term  $\omega_{1,i}$  drawn from a distribution  $\mu_1(\omega)$  in equation (6.2.1) and a term  $\omega_{2,j}$  drawn from a distribution  $\mu_2(\omega)$  in equation (6.2.2). These changes make the mathematical analysis significantly more difficult. In order to decide which mathematical generalizations are worthwhile pursuing, more experimental information is needed regarding the relative numbers of  $N_1$  versus  $N_2$ ,  $K_1$  versus  $K_2$ , and  $L_1$  versus  $L_2$  as well as the distribution of natural frequencies in the two communities. What is clear is that, although the mechanism remains unchallenged, the actual stability diagrams would change, possibly finding stable solutions for an aligned state even when the GABAergic communication  $L$  is inhibitory.

This does not invalidate the current model though, as the main message we want to bring forward is that a change in external circumstances brings about a change in the E/I balance of the system, in that the coupling between and within the communities may change due to the external conditions. This change in E/I balance may move the system into an unstable or metastable state, and the system will search through its state space for a stable state based on the changed E/I balance.

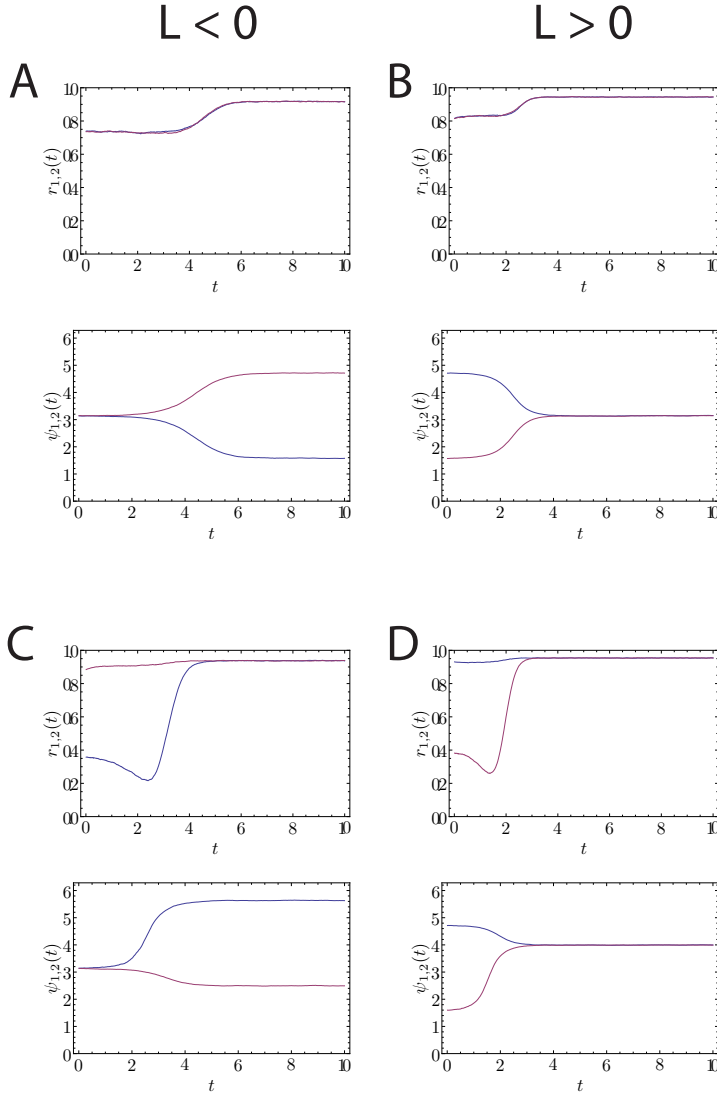


Figure 6.1: Simulation of 10000 oscillators per community with  $K = 5$  and  $L = -2$  (A and C) or  $L = 2$  (B and D). The time step is set at  $dt = 0.01$ . The top images show the synchronization levels ( $r_1$  and  $r_2$ ), the bottom the average phases ( $\psi_1$  and  $\psi_2$ ). (A) and (B) show the case where  $r_1$  and  $r_2$  are the same, whereas (C) and (D) show the case where they differ at first but both approach 1 when the stable state is reached.

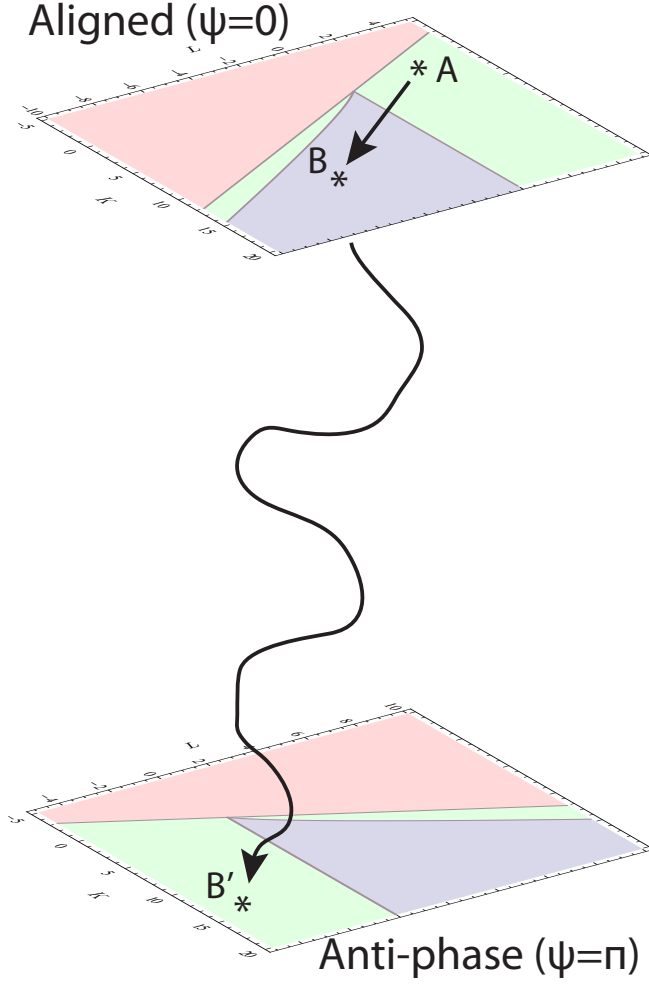


Figure 6.1: Mechanism of the SCN changing states. A disturbance in the external conditions changes the E/I balance of the system, causing the system to go from stable state A to a unstable state B. The system will then be forced to find a new stable state corresponding to the new E/I balance, which could be found in the stable state B', which lies in the plane where both communities are in anti-phase.

