Conditions for partial and full synchronization of indirectly coupled molecular oscillators

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In this thesis, I study the coupling of a collection of oscillators, focusing both on abstract models and molecular systems, called repressilators, interacting indirectly through enzymatic saturation. In the past two decades, advances in synthetic biology have provided researchers with the ability to implement complex dynamic systems both in-vivo and in-vitro. Among those dynamical systems, particular focus has been given to oscillators, both for their complex behaviors and their biological relevance.

First, I focused on an extended Kuramoto model, which can be studied from an analytical point of view. Specifically, it can be applied to model brain wave patterns. In this model, the brain waves called alpha waves are dominant in the calm state, but when external stimuli are added, the high frequency beta and gamma waves become dominant. The model consists of a time evolution equation of the time-varying amplitude and the phase of the two oscillators trying to synchronize with each other. By plotting the time series data, it can be confirmed that the frequency of the oscillator increases when there are external stimuli, and returns to the original frequency after enough time has passed without any external stimulus. In order to calculate the frequency, the observed phase was obtained. The observed phase is calculated from the band-pass filtered time series data and Hilbert transformed time series data. The band-pass filter is a tool that cuts off frequency components in a signal except for a specific band. The long time average of the time variation of the observed phase is the averaged frequency. I changed the center frequency of the filter and the width of the frequency band and plotted the phase diagram. In the absence of external stimuli, small frequencies were dominant and, in the presence of external stimuli, large frequencies were dominant. In addition, the frequencies that can be detected differ greatly depending on the central frequency and frequency band of the filter, so it is difficult to set the appropriate central frequency and frequency band of the filter for each system.

However, other oscillatory systems, such as molecular oscillators, are more favorable to the use of external stimuli, as a way to perform computation. Nevertheless, coupling in those systems is seldom studied, but could improve the expressivity of behaviors. Next, I studied the coupling of a collection of molecular oscillators, called repressilators, interacting indirectly through enzymatic saturation. A repressilator system is made from a cycle of three negative feedbacks. The autocorrelation function was used for calculating the period. The coupling was computed in function of two model parameters: the Michaelis-Menten constant for enzymatic saturation and the transcription rate. The behavior map of the coupled oscillators showed regions of asynchronized, partially synchronized, or completely synchronized systems. When the amplitude of the repressilators are similar, the repressilators are always at least partially synchronized. When the impact of competitive enzymatic saturation is low, the overall synchronization of the system tends to decrease. When the differences of transcription rate are very large, the periods and amplitudes of the oscillators are too different to allow for synchronization. Interestingly, I could observe an island of asynchronous behavior is surrounded by synchronized behaviors, which shows the non-linearity of the behaviors. In order to further analyze the system, time-series data was plotted. One of the repressilators seems to reach a different mode, with a period nearly doubled in the previously mentioned island. The change is continuous in the autocorrelation function, but leads to an abrupt change in the overall synchronization of the system. Finally, a spectral analysis of the system was performed and it highlighted the natural frequency of each oscillator and the additional frequency due to the impact of enzymes.

Indirect coupling, in molecular robotics, is usually seen as having a negative impact on the system as those are more non-linear and thus harder to control. However, the results show that, in this case, it provides a complex behavior space allowing us to sharply transition between different coupling modes. By setting the system near the transition area, we may force a system in and out of synchronization over temporal or spatial patterns. Potential applications range from developing controllers for molecular robots, where each oscillator affects a different type of robot, and designing active materials, locking in areas where multiple oscillators peak at the same time.