Cellular Oscillatory Synchronization and Aggregation with the Cellular Potts Model

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Background

Synchronization in biology found at
- Organismal Scale (synchronized fireflies' bioluminescence)
- Cellular Scale (*Dictyostelium discoideum*, myxobacteria)

Cells have oscillatory molecular clocks. The time, or phase, of these clocks can synchronize, which influences the aggregation and pattern formation of the cells. Rippling patterns and body formation result from behavior.

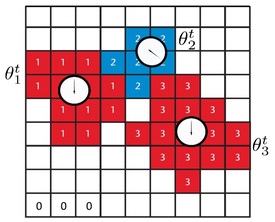
Myxobacteria fruiting body aggregates and ripples[4]

Current Models

- **Cellular Potts Model[1] (CPM)**
  - A cellular automata model that simulates cells governed by the Hamiltonian energy function and predetermined constraints.
  - Cell movement via spin flips is attempted at all lattice sites of every cell with some successes per time step. Spin flips tend to occur with some probability when lattice site movements or cell growth minimizes a cell's energy.
- **Swarmalators Model[2]**
  - A one-dimensional point model of cell oscillatory synchronization using the Hamiltonian and motivated by the Kuramoto model.

Objectives

- Develop an abstract CPM two-dimensional model combining CPM[1] structure and Swarmalators Model[2] oscillatory processes to understand clock synchronization of cells with spatial significance.
- Determine the influence of spatial attraction[2] (***J***) and phase coupling strength[2] (***K***) parameters on phase synchronization.



Example CPM where color represents cell clock phase

Methods

Model Assumptions

- Cell behavior is based on in vitro experiments, control parameter values are from Zhang et al.[3]
- All cells are of the same type.
- Population remains constant with zero growth or change.
- Each cell has a working internal clock (oscillator) that influences its adhesion to other cells based on clock phase.
- Oscillatory and synchronization processes are inspired by the Kuramoto model.

Governing Equation (for cell $s = 1, \dots N$)

- Clock phase

$$\theta_s^{t+\Delta t} = \theta_s^t + \omega \Delta t \cdot (1 + K \cdot \frac{1}{\#\text{ neighbors of } s} \sum_{\text{neighbor } u \text{ of } s} \sin(\theta_u - \theta_s)) \quad (1)$$

- Hamiltonian energy function

$$\mathcal{H} = \sum_{\text{neighboring sites } \mathbf{i},\mathbf{j}} (1 - \delta_{\sigma(\mathbf{i}),\sigma(\mathbf{j})}) f(\sigma(\mathbf{i}),\sigma(\mathbf{j})) + \lambda \sum_{\text{cell } s} (\text{Area}(s) - A_{\text{target}})^2$$

- Cell-cell adhesion energy

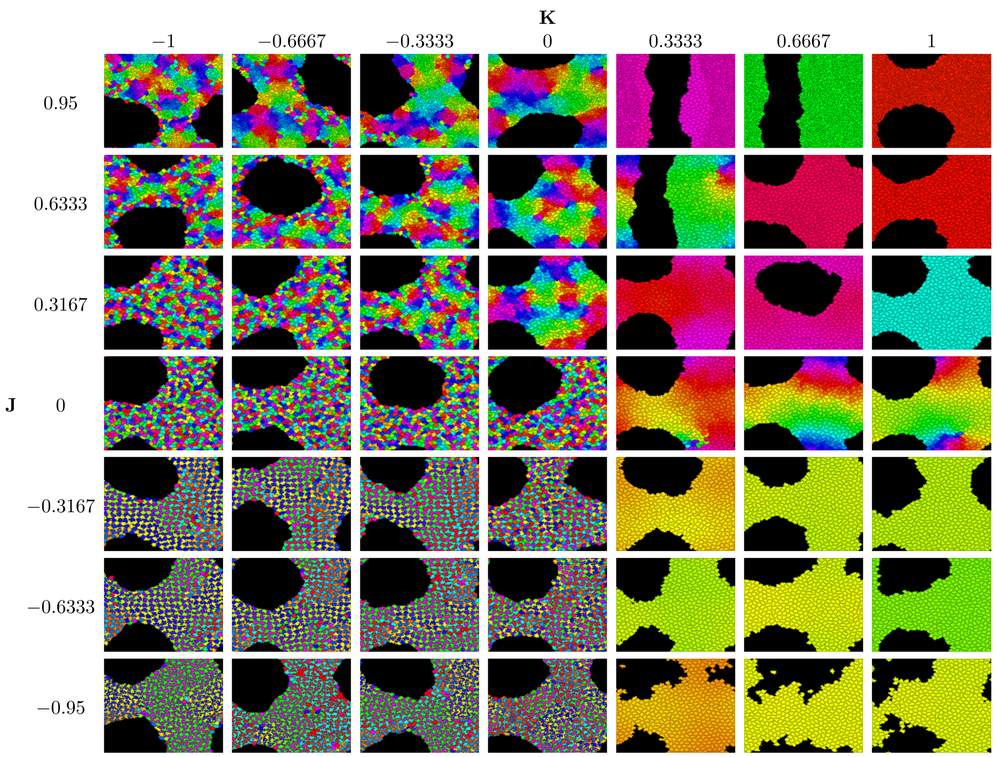
$$f(\sigma_1,\sigma_2) = \begin{cases} J_0(1 - J\cos(\theta_{\sigma_1} - \theta_{\sigma_2})) & \text{if } \sigma_1 \neq 0 \text{ and } \sigma_2 \neq 0 \\ J_0 & \text{if } \sigma_1 = 0 \text{ or } \sigma_2 = 0 \end{cases} \quad (2)$$

Model Mechanics

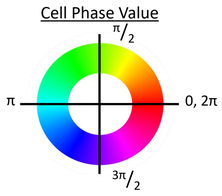
- CompuCell3D software
- Implementation and manipulation of (1) and (2) in general CPM with its Hamiltonian
- ***J*** and ***K*** parameter variability analysis

Results

Phase Diagram



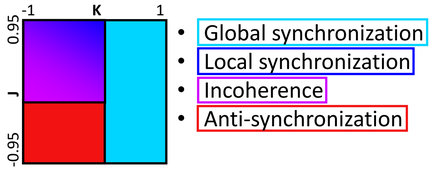
The four distinct phase states exhibited by different *J*, *K* combinations: global synchronization (*K>0*), local synchronization (*K≈-J → J>>0,K≤ 0*), incoherence (*J≥0,K<0 → K≈-J*), and anti-synchronization (*J<0,K≤0*). Color represents each cell's phase. Simulations were for *N* = 445 cells for 250,000 Monte Carlo Steps (MCS), each with the same initial conditions.



Parameters of Interest

K>0:	neighbors seek to *synchronize*
K<0:	neighbors *anti-synchronize*
J>0:	like attracts like
J<0:	opposites attract

Simplified Phase Diagram



Order Parameters

Different phase states are quantitatively distinguished through order parameters, which are zero in one state and non-zero in another state.

Kuramoto Order Parameter calculates the degree to which all cells' phases are synchronized globally and locally. Therefore, *r=1* is complete synchronization and *r=0* is complete incoherence or anti-synchronization.

Kuramoto global r value:

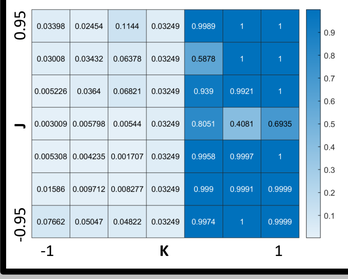
$$r_{\text{global}} = \left| \frac{1}{\#\text{ total cells}} \sum_{j=1}^{\#\text{ total cells}} e^{i\theta_j} \right|$$

Kuramoto local r value:

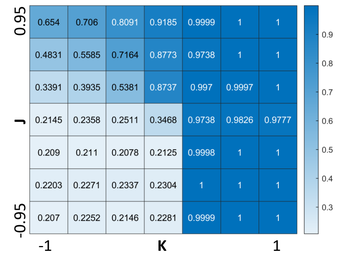
$$r_{\text{local}} = \left| \frac{1}{\#\text{ neighbors of } j} \sum_{j=1}^{\#\text{ neighbors of } j} e^{i\theta_j} \right|$$

Chessboard Order Parameter calculates the total cells' lattice sites that neighbor other lattice sites that are within 6.25% of complete opposite phase.

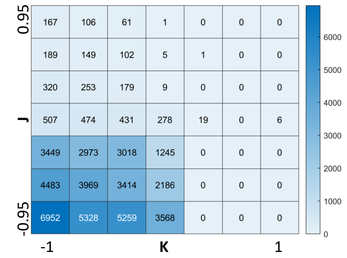
Global synchronization for *K>0*



Local synchronization for *K>0* and *J>0, K≤0*



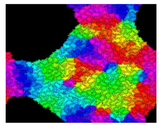
Anti-synchronization for *J<0, K≤0*



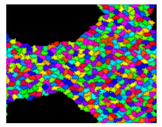
Long-term Phase States

Global Synchronization
Regardless of which phase (color), all cells are in the same phase.

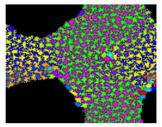
Local Synchronization
Neighborhoods of cells have synched clocks.



Incoherence
Cells cluster randomly without organized spatial or phase attraction.

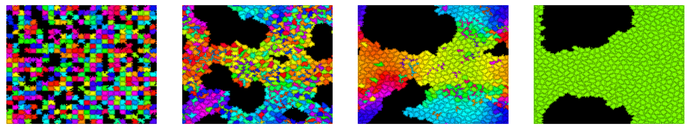


Anti-Synchronization
Cells prefer neighbors in opposite phase, creating a chessboard pattern.



Example Sequence of Synchronization

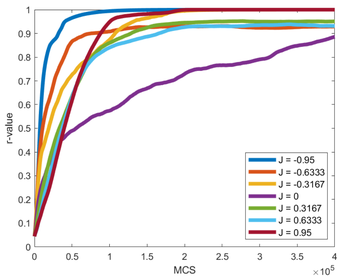
- A single model run with *J*=-0.6333, *K*=1
- Sequence shows cells aggregating and reaching global synchronization over time (MCS)



0 MCS | 4000 MCS | 25000 MCS | 250000 MCS

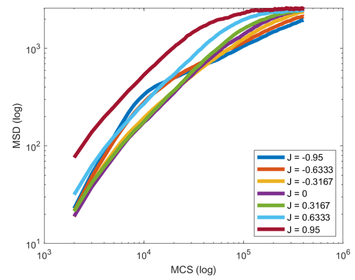
Cell Behavior over Time

Kuramoto Global Synchronization r vs MCS (K=1)



Rate of synchronization is fastest for extreme *J<0.*

Mean Square Displacement vs MCS (K=1)



Cells move most but synchronize slowly for *J>0.*

Conclusions

- Parameters *J* and *K* greatly influence clock synchronization and phase states of the cells.
  - Parameter *K* plays larger role in cells' prioritization of synchronizing.
- Synchronization occurs fastest when opposites attract.
  - When cells prefer neighbors in opposite phase (*J<0*), they do not need to move far (least MSD per MCS) to synchronize when they prioritize neighborly synchronization *(K>0)*.

Future Steps and Applications

- Implementation of cell characteristics (polarity, chemotaxis, etc.)
- Analysis of cell pattern formation with different confluences
- Study of rippling behavior and fruiting body development rate for different *J*,*K* value combinations

References

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