Lecture 7

Modified Martiel & Goldbeter Model for Dicty Signalling

Variables (functions of x, y, t):

β = intracellular concentration of cAMP

γ = extracellular concentration of cAMP

ρ = fraction of receptors in active state

Equations

$$\frac{d\beta(x,y,t)}{dt} = s\Phi(\rho,\gamma) - \beta k_i - \beta k_t \quad [1]$$

Rate of change in intracellular [cAMP] = Production of cAMP − Intracellular hydrolysis − Secretion of cAMP

$$\frac{d\gamma(x,y,t)}{dt} = \frac{k_t}{h}\beta - k_e\gamma + D\nabla^2\gamma \quad [2]$$

Rate of change in extracellular [cAMP] = Secretion of cAMP − Extracellular hydrolysis + Diffusion of cAMP

$$\frac{d\rho(x,y,t)}{dt} = f_2(\gamma)(1-\rho) - f_1(\gamma)\rho \quad [3]$$

Rate of change in fraction of active receptor = Dephosphorylation of receptor − Phosphorylation of receptor

Positive Feedback Loop

- Extracellular cAMP increases (γ increases)
- ⇒ Rate of synthesis of intracellular cAMP increases (Φ increases)
- ⇒ Intracellular cAMP increases (β increases)
- ⇒ Rate of secretion of cAMP increases
- (⇒ Extracellular cAMP increases)

See Equations

Negative Feedback Loop

- Extracellular cAMP increases (γ increases)
- ⇒ cAMP receptors desensitize (f_1 increases, f_2 decreases, ρ decreases)
- ⇒ Rate of synthesis of intracellular cAMP decreases (Φ decreases)
- ⇒ Intracellular cAMP decreases (β decreases)
- ⇒ Rate of secretion of cAMP decreases
- ⇒ Extracellular cAMP decreases (γ decreases)

See Equations

Dynamics of Model

- Unperturbed ⇒ cAMP concentration reaches steady state
- Small perturbation in extracellular cAMP ⇒ returns to steady state
- Perturbation > threshold ⇒ large transient in cAMP, then return to steady state
- Or oscillation (depending on model parameters)

Circular & Spiral Waves Observed in:

- Slime mold aggregation
- Chemical systems (e.g., BZ reaction)
- Neural tissue
- Retina of the eye
- Heart muscle
- Intracellular calcium flows
- Mitochondrial activity in oocytes

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Cause of Concentric Circular Waves

- Excitability is not enough
- But at certain developmental stages, cells can operate as pacemakers
- When stimulated by cAMP, they begin emitting regular pulses of cAMP

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Spiral Waves

- Persistence & propagation of spiral waves explained analytically (Tyson & Murray, 1989)
- Rotate around a small core of of non-excitable cells
- Propagate at higher frequency than circular
- Therefore they dominate circular in collisions
- But how do the spirals form initially?

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Some Explanations of Spiral Formation

- "the origin of spiral waves remains obscure" (1997)
- Traveling wave meets obstacle and is broken
- Desynchronization of cells in their developmental path
- Random pulse behind advancing wave front

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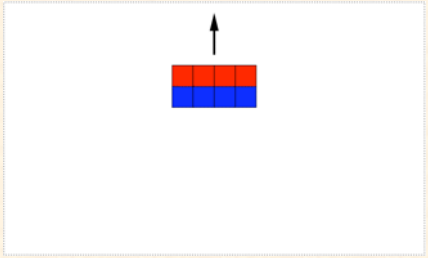
Step 0: Passing Wave Front



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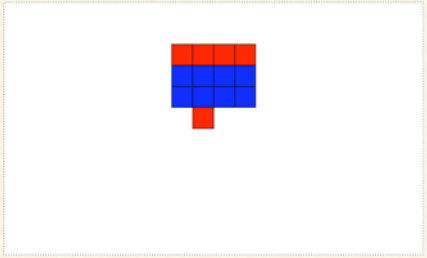
Step 1: Random Excitation



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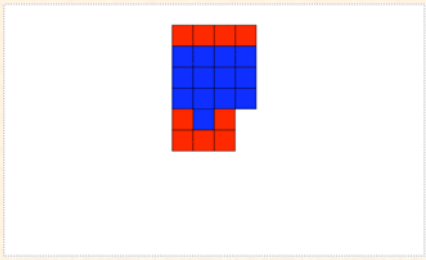
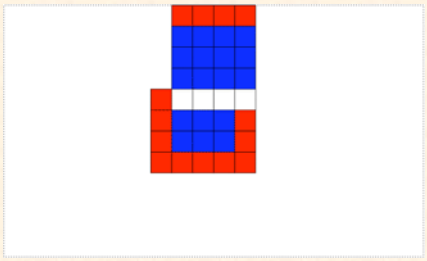
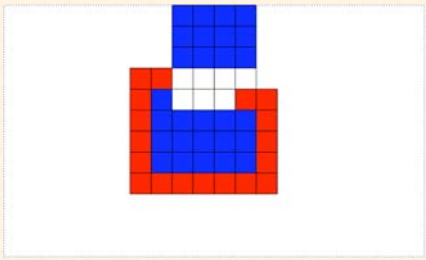
Step 2: Beginning of Spiral



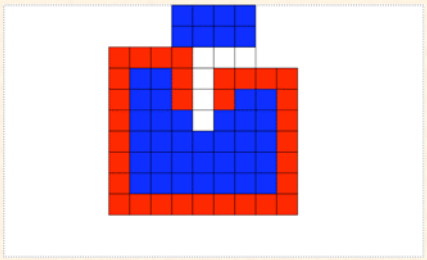
Step 3



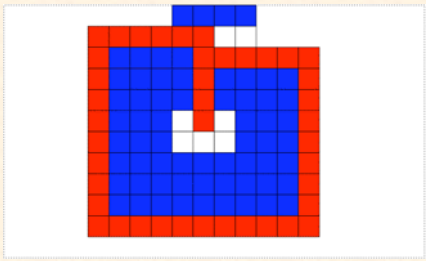
Step 4



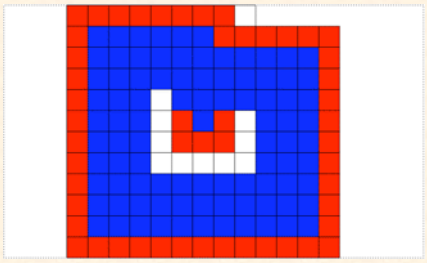
Step 5



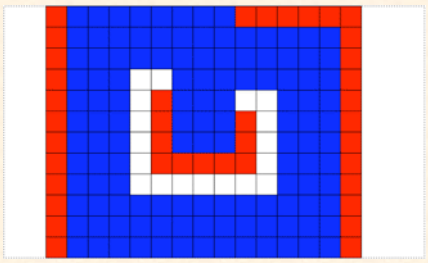
Step 6: Rejoining & Reinitiation



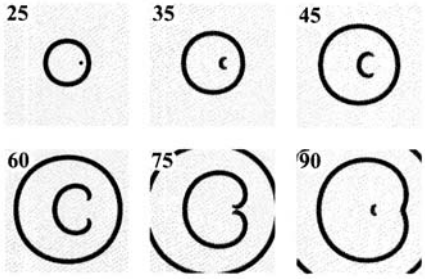
Step 7: Beginning of New Spiral



Step 8



Formation of Double Spiral



 from Pálsson & Cox (1996)

NetLogo Simulation Of Spiral Formation

- Amoebas are immobile at timescale of wave movement
- A fraction of patches are inert (grey)
- A fraction of patches has initial concentration of cAMP
- At each time step:
  - chemical diffuses
  - each patch responds to local concentration

Response of Patch

if patch is not refractory (brown) **then**
  if local chemical > threshold **then**
    set refractory period
    produce pulse of chemical (red)
else
  decrement refractory period
  degrade chemical in local area

Demonstration of NetLogo Simulation of Spiral Formation

Run SlimeSpiral.nlogo

Observations

- Excitable media can support circular and spiral waves
- Spiral formation can be triggered in a variety of ways
- All seem to involve inhomogeneities (broken symmetries):
  - in space
  - in time
  - in activity
- Amplification of random fluctuations
- Circles & spirals are to be expected

NetLogo Simulation of Streaming Aggregation

1. chemical diffuses
2. **if** cell is refractory (yellow)
3. **then** chemical degrades
4. **else** (it's excitable, colored white)
   1. **if** chemical > movement threshold **then**
      take step up chemical gradient
   2. **else if** chemical > relay threshold **then**
      produce more chemical (red)
      become refractory
   3. **else** wait

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Demonstration of NetLogo Simulation of Streaming

Run SlimeStream.nlogo

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Demonstration of NetLogo Simulation of Aggregation (Spiral & Streaming Phases)

Run SlimeAggregation.nlogo

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