


## Lecture 7

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## Modified Martiel & Goldbeter Model for Dicty Signalling

Variables (functions of  $x, y, t$ ):

- $\beta$  = intracellular concentration of cAMP
- $\gamma$  = extracellular concentration of cAMP
- $\rho$  = fraction of receptors in active state



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## 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

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

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

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## Positive Feedback Loop

- Extracellular cAMP increases ( $\gamma$  increases)
- $\Rightarrow$  Rate of synthesis of intracellular cAMP increases ( $\Phi$  increases)
- $\Rightarrow$  Intracellular cAMP increases ( $\beta$  increases)
- $\Rightarrow$  Rate of secretion of cAMP increases
- ( $\Rightarrow$  Extracellular cAMP increases)

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## Negative Feedback Loop

- Extracellular cAMP increases ( $\gamma$  increases)
- $\Rightarrow$  cAMP receptors desensitize ( $f_1$  increases,  $f_2$  decreases,  $\rho$  decreases)
- $\Rightarrow$  Rate of synthesis of intracellular cAMP decreases ( $\Phi$  decreases)
- $\Rightarrow$  Intracellular cAMP decreases ( $\beta$  decreases)
- $\Rightarrow$  Rate of secretion of cAMP decreases
- $\Rightarrow$  Extracellular cAMP decreases ( $\gamma$  decreases)

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## Dynamics of Model

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

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### 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 non-excitable cells
- Propagate at higher frequency than circular
- Therefore they dominate circular in collisions
- But how do the spirals form initially?

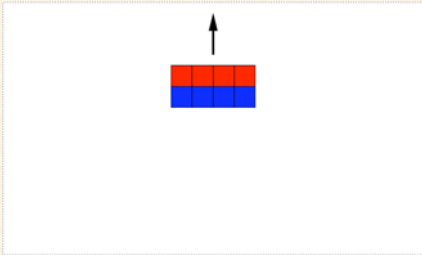
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### Some Explanations of Spiral Formation

- “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

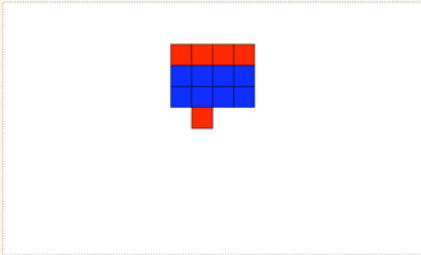
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### Step 0: Passing Wave Front

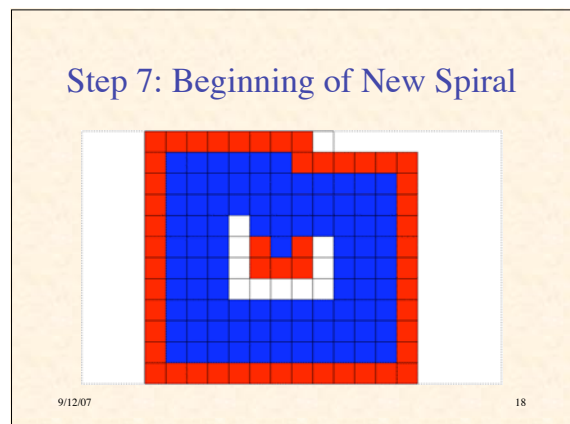
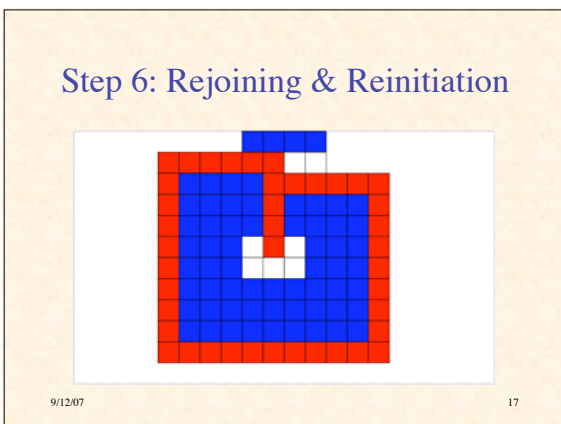
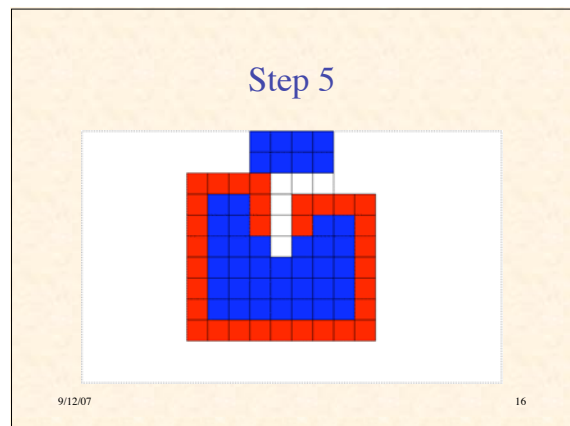
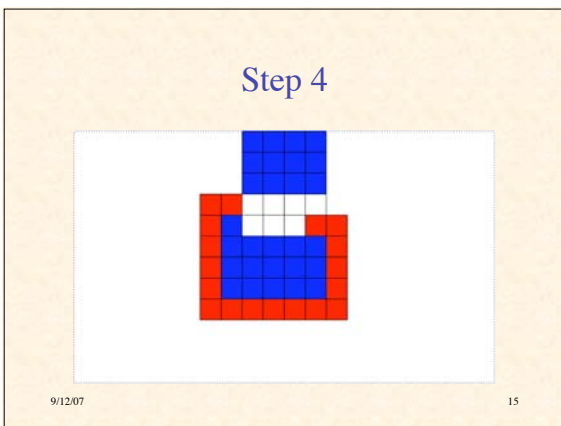
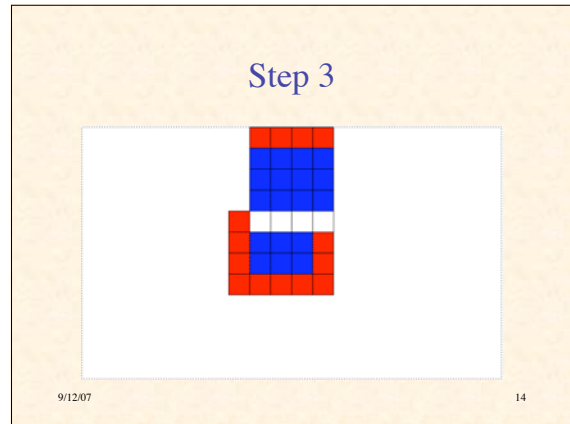
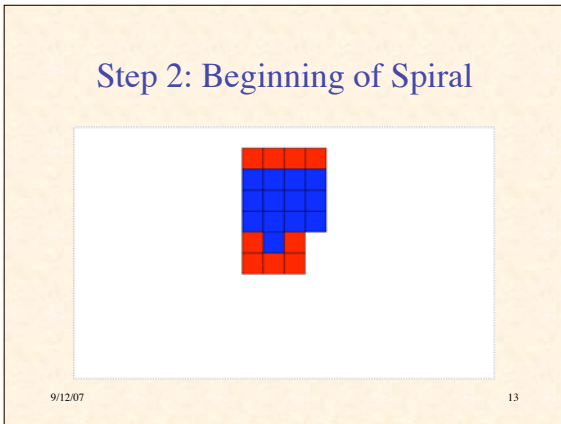


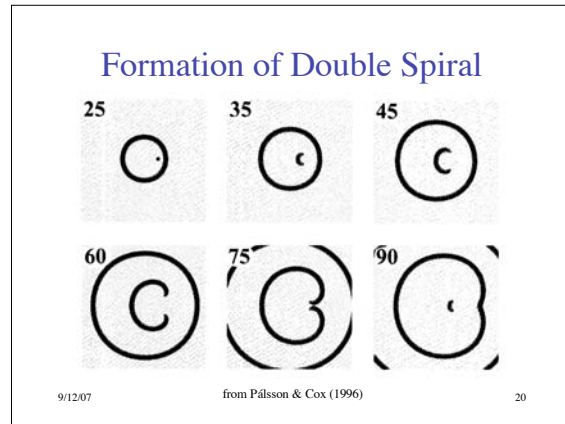
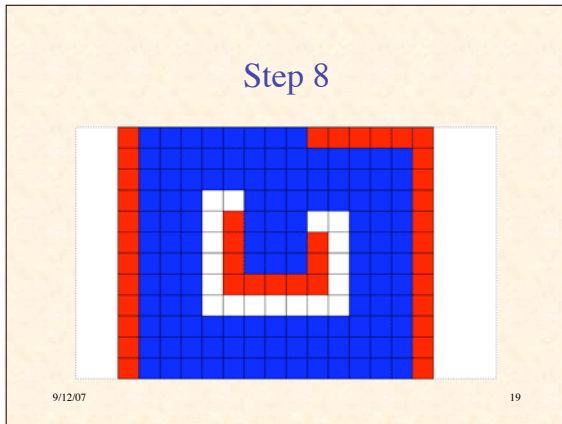
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### Step 1: Random Excitation



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### 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

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### 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
    
```

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### Demonstration of NetLogo Simulation of Spiral Formation

[Run SlimeSpiral.nlogo](#)

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### 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

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### 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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