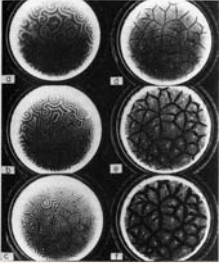


## Lecture 6

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### Emergent Patterns During Aggregation



- a-c. As aggregate, wave lengths shorten
- d. Population divides into disjoint domains
- e-f. Domains contract into "fingers" (streaming stage)

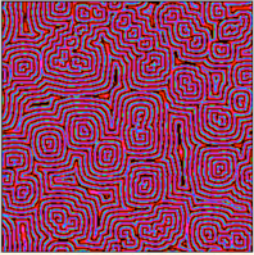
9/10/07 2 fig. from Solé & Goodwin

### Belousov-Zhabotinski Reaction



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### Hodgepodge Machine



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### Demonstration of Hodgepodge Machine

[Run NetLogo B-Z Reaction Simulator](#)  
 or  
[Run Hodgepodge simulator at CBN Online Experimentation Center](#)  
<mitpress.mit.edu/books/FLAOH/cbnhtml/java.html>

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### Universal Properties

- What leads to these expanding rings and spirals in very different systems?
- Under what conditions do these structures form?
- What causes the rotation?
- These are all examples of *excitable media*

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## Reading

Read Flake, ch. 16

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## Excitable Media

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### Examples of Excitable Media

- Slime mold amoebas
- Cardiac tissue (& other muscle tissue)
- Cortical tissue
- Certain chemical systems (e.g., BZ reaction)
- Hodgepodge machine

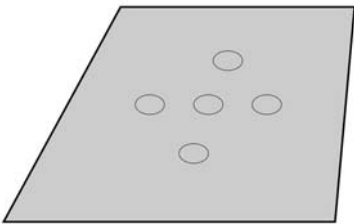
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### Characteristics of Excitable Media

- Local spread of excitation
  - for signal propagation
- Refractory period
  - for unidirectional propagation
- Decay of signal
  - avoid saturation of medium

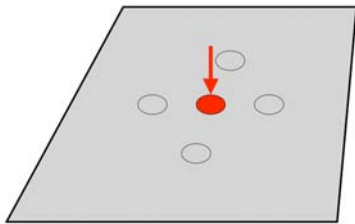
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### Behavior of Excitable Media

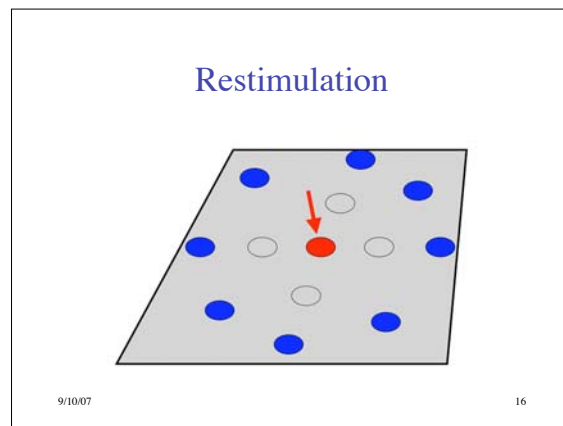
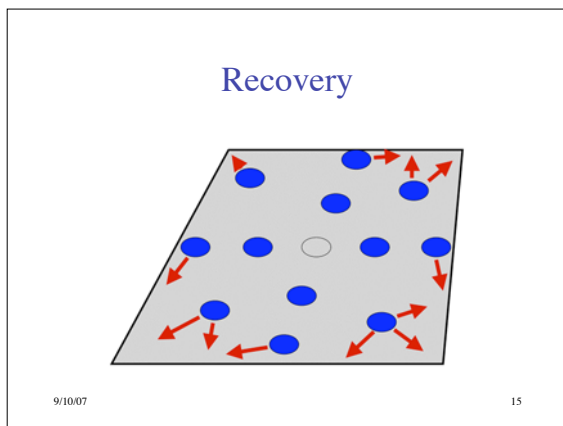
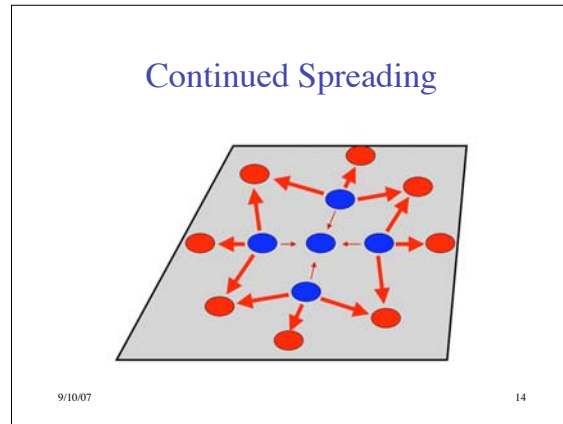
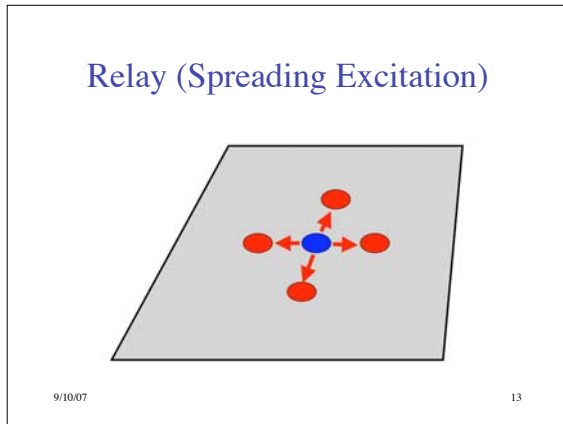


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### Stimulation



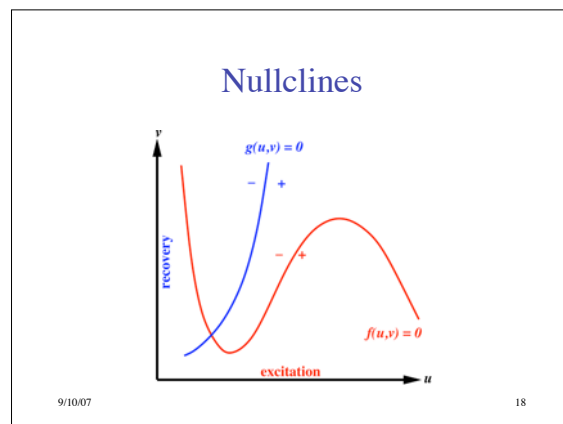
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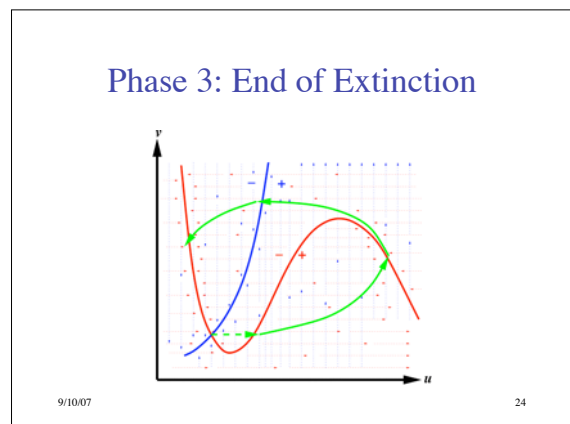
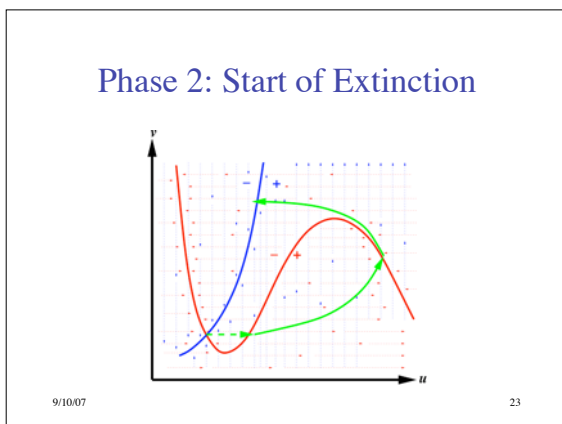
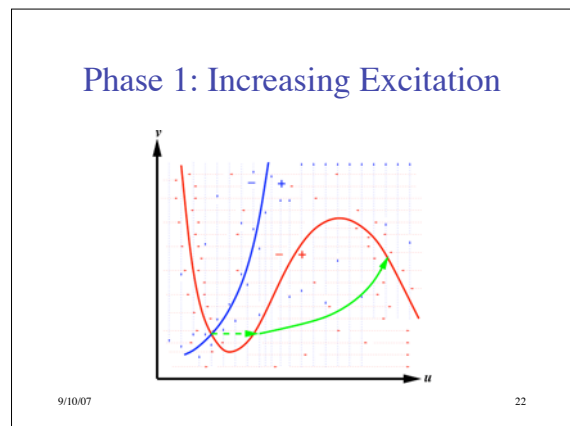
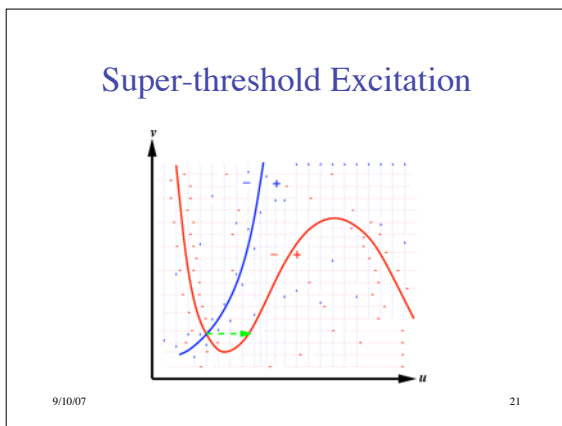
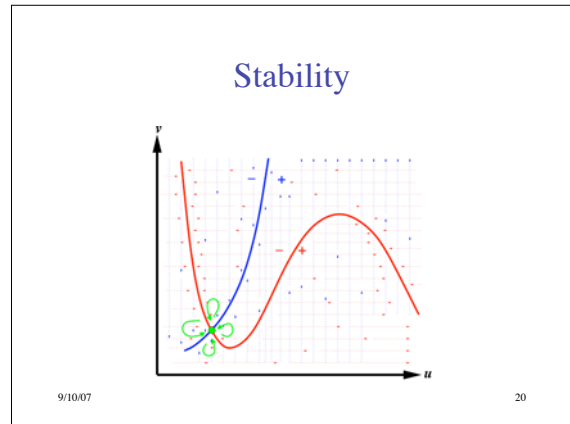
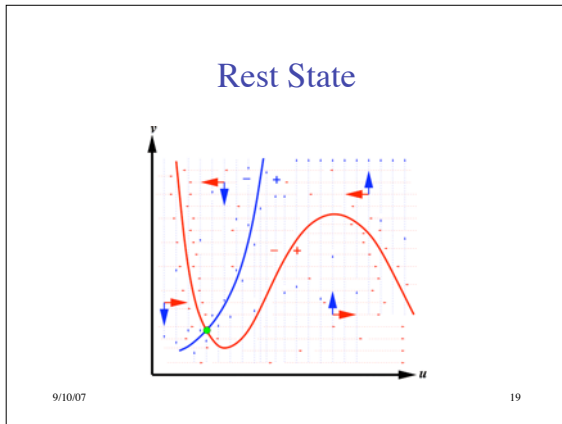


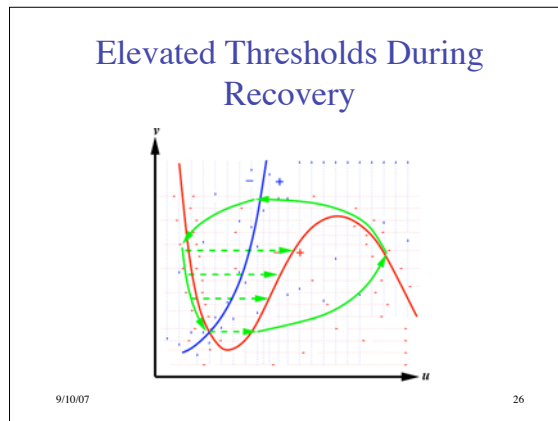
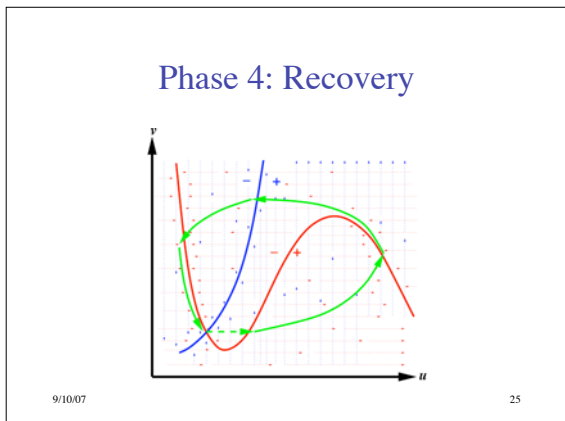
### Typical Equations for Excitable Medium (ignoring diffusion)

- Excitation variable:
 
$$\dot{u} = f(u, v)$$
- Recovery variable:
 
$$\dot{v} = g(u, v)$$

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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

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

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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[See Equations](#)

### 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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[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)

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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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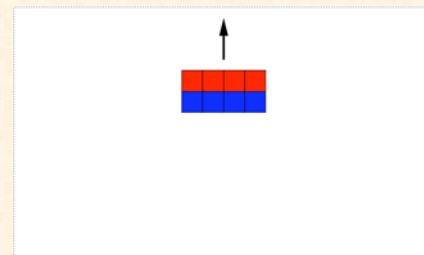
### Some Explanations of Spiral Formation

- “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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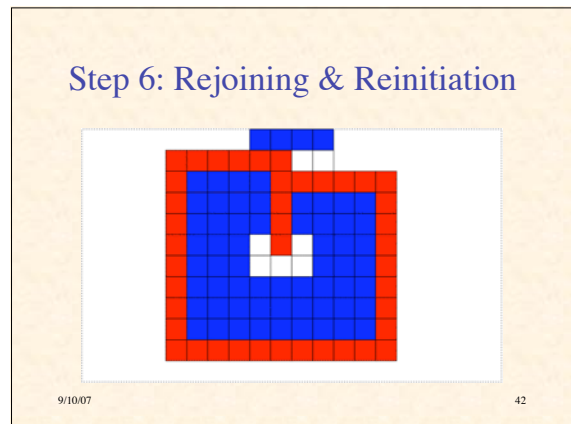
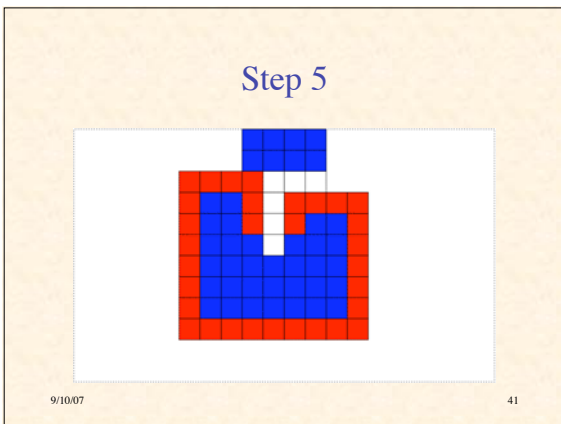
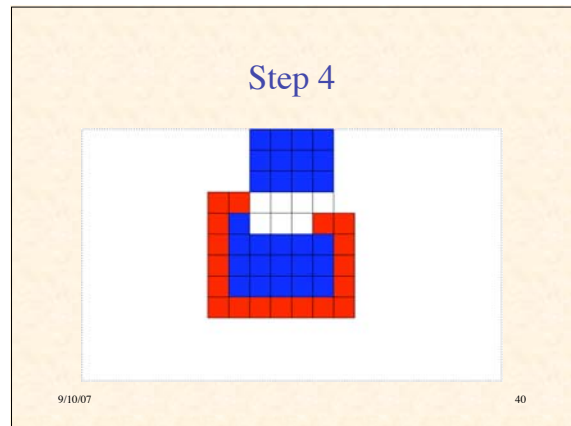
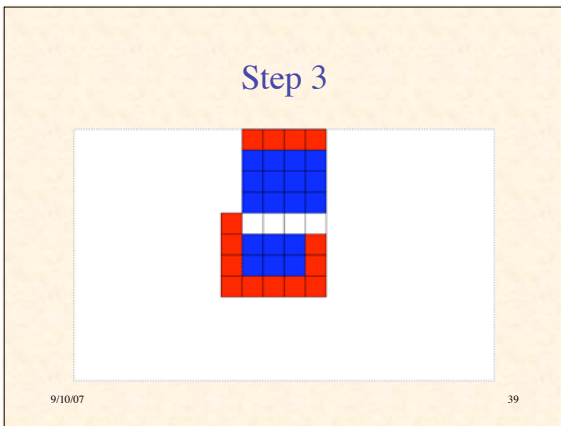
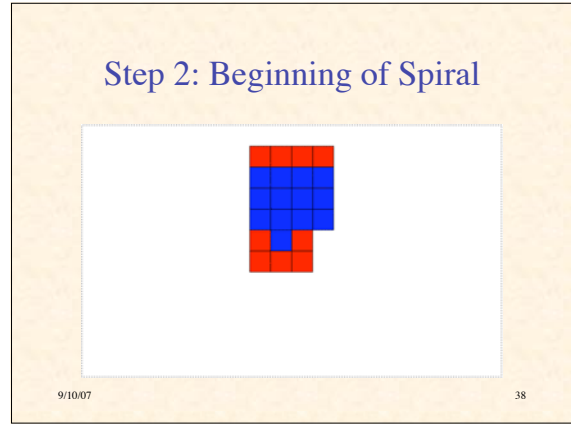
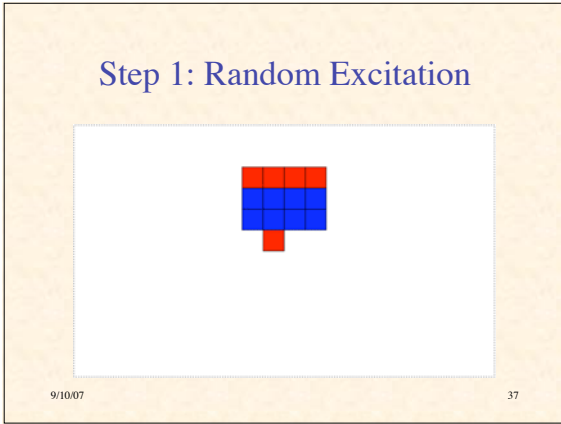
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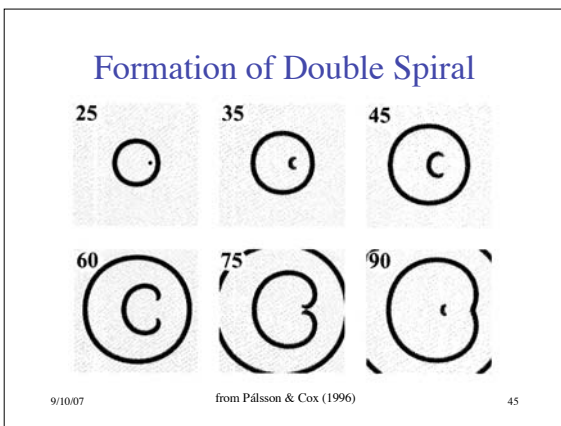
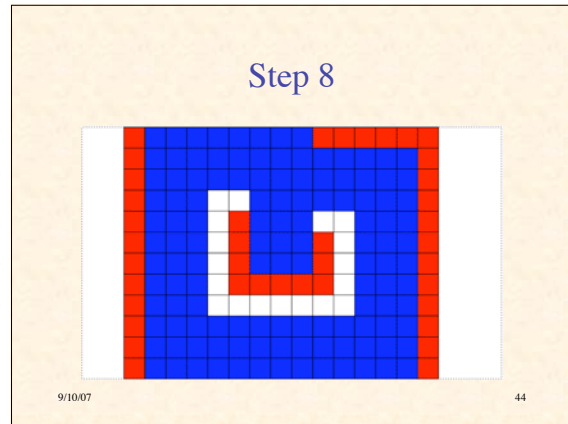
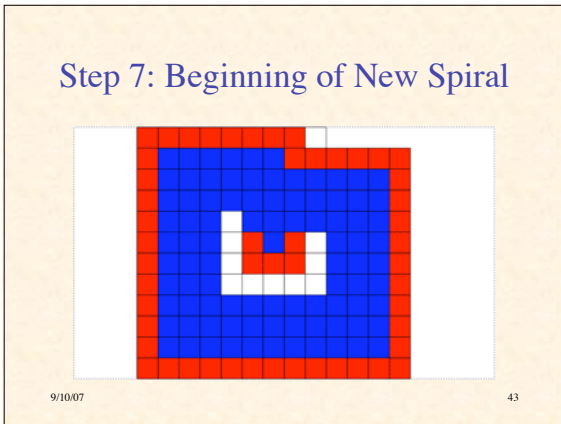
### Step 0: Passing Wave Front



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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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