D.
Excitable Media

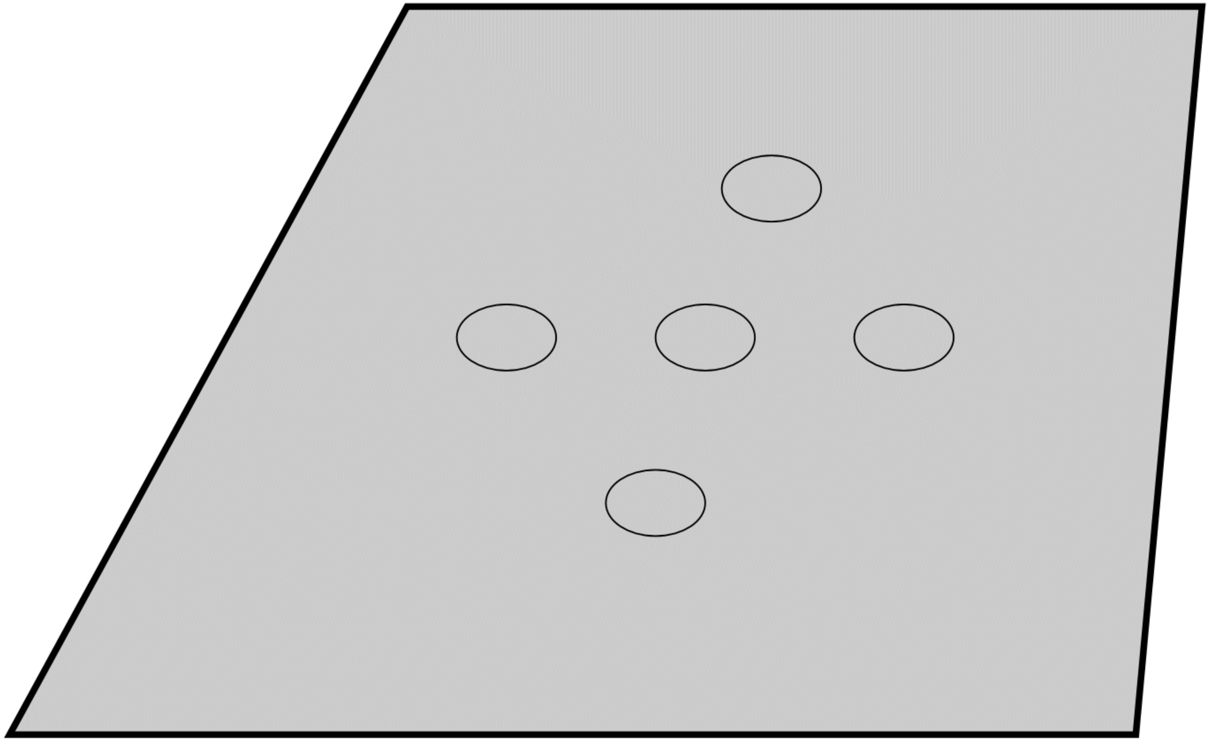
Examples of Excitable Media

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

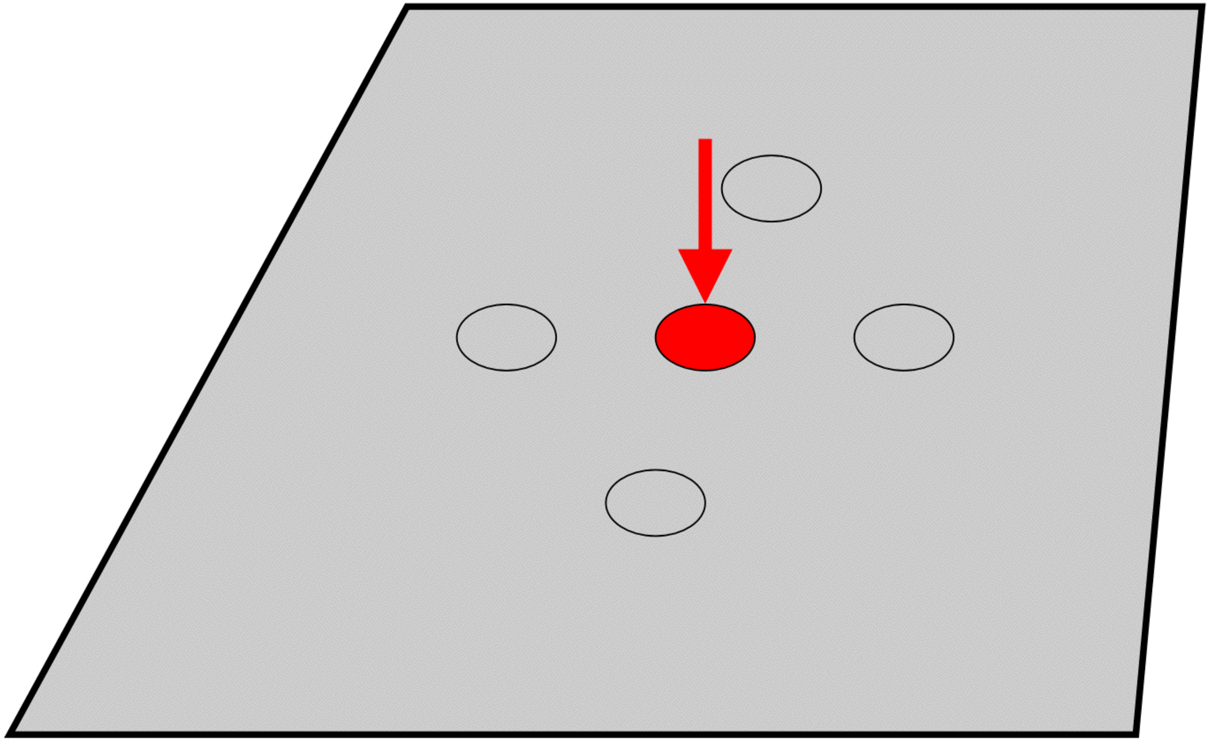
Characteristics of Excitable Media

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

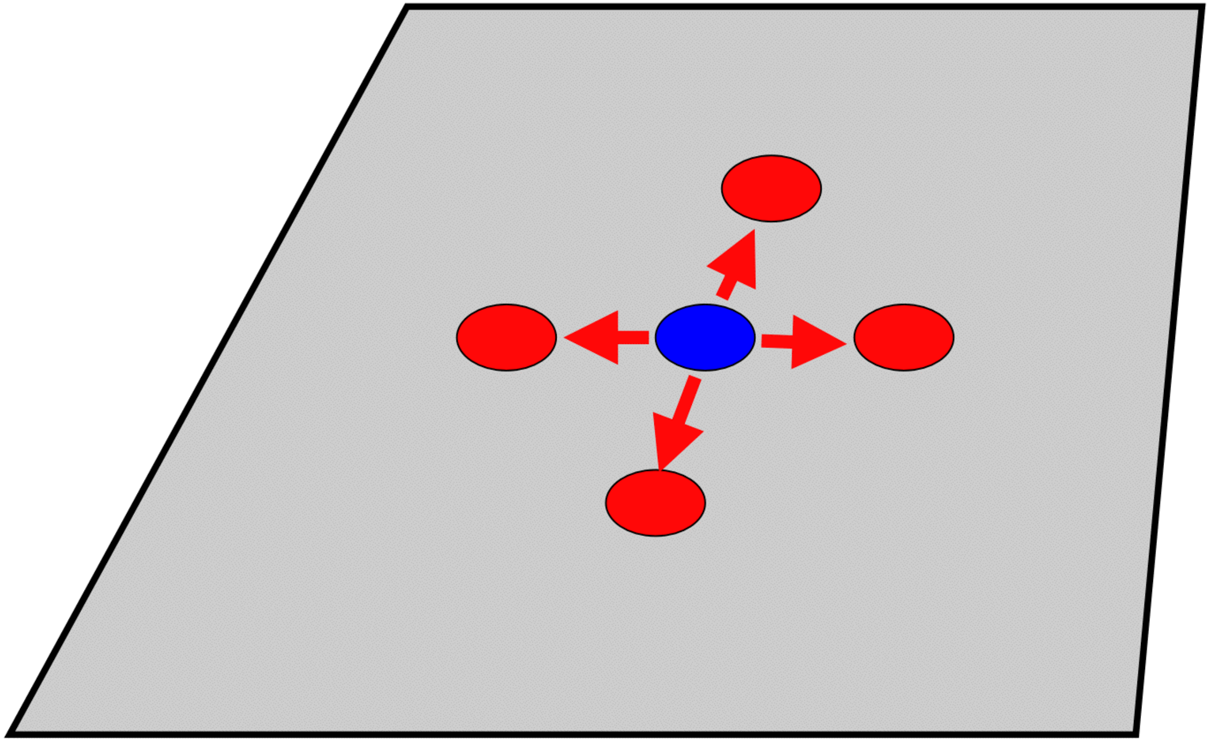
Behavior of Excitable Media



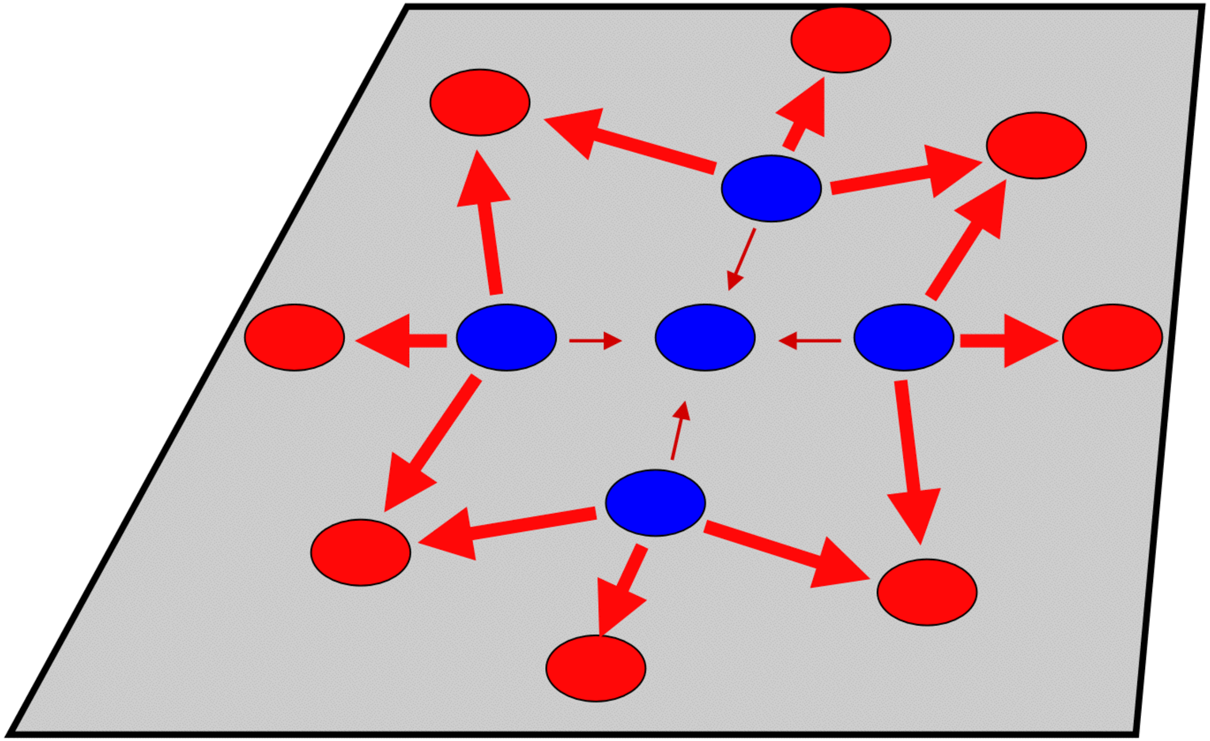
Stimulation



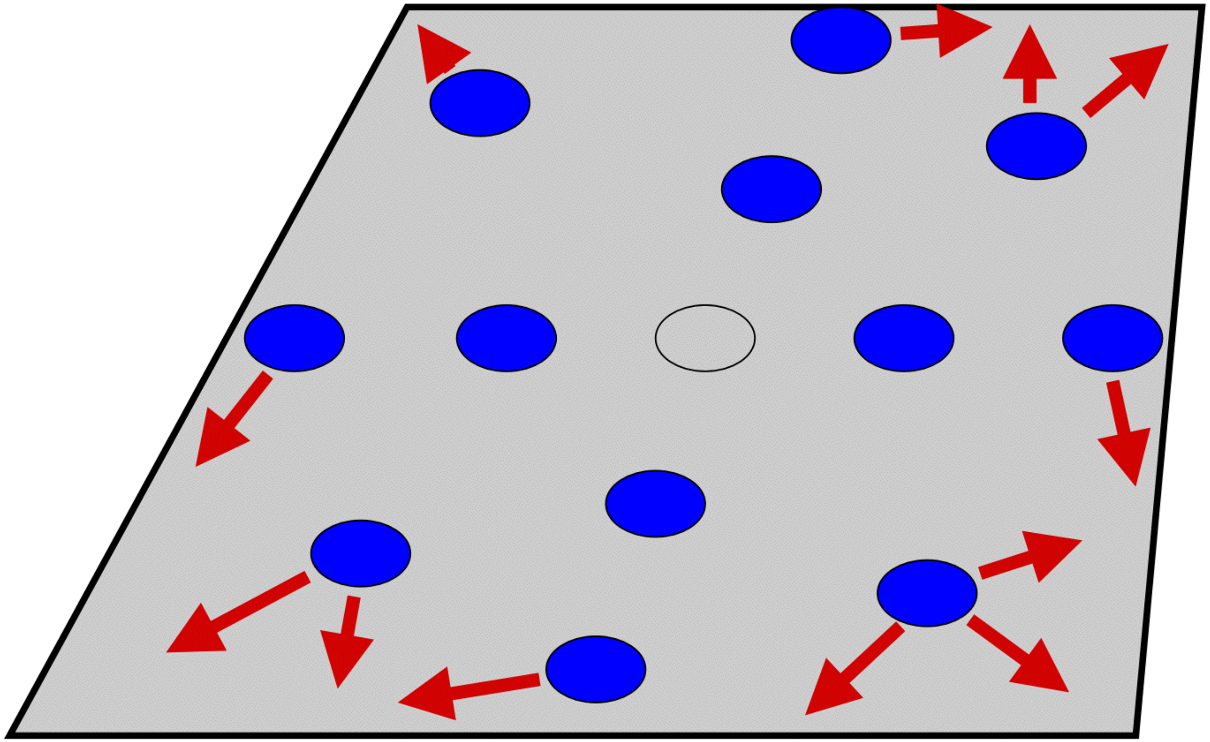
Relay (Spreading Excitation)



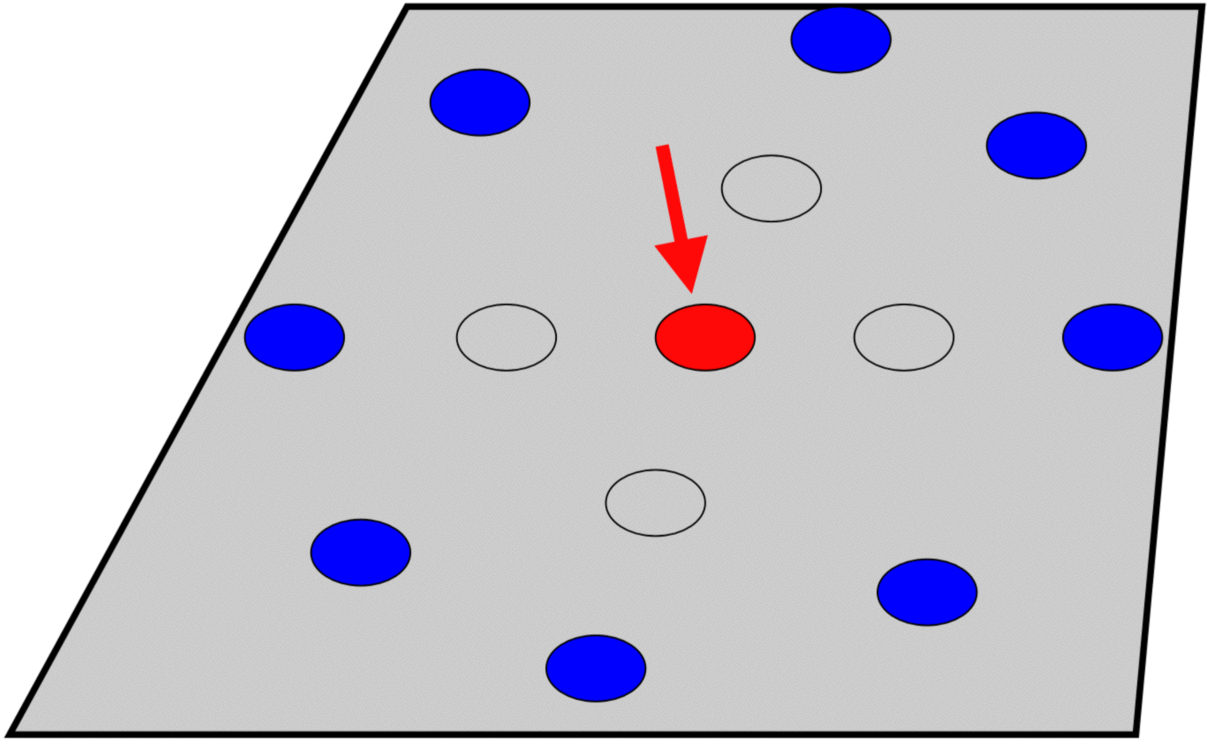
Continued Spreading



Recovery



Restimulation



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

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

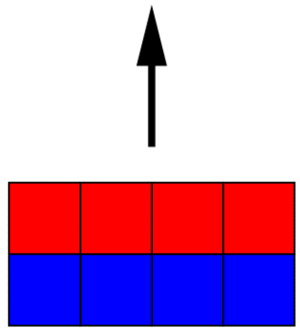
Spiral Waves

- 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?

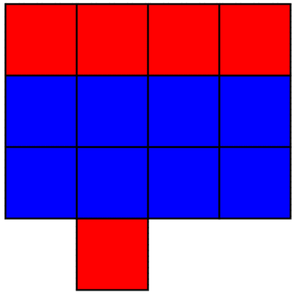
Some Explanations of Spiral Formation

- "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

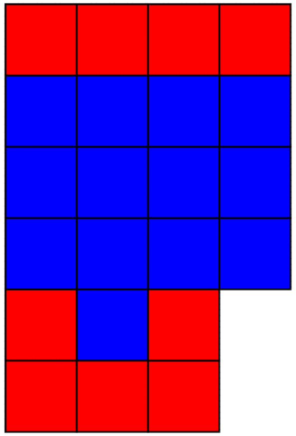
Step 0: Passing Wave Front



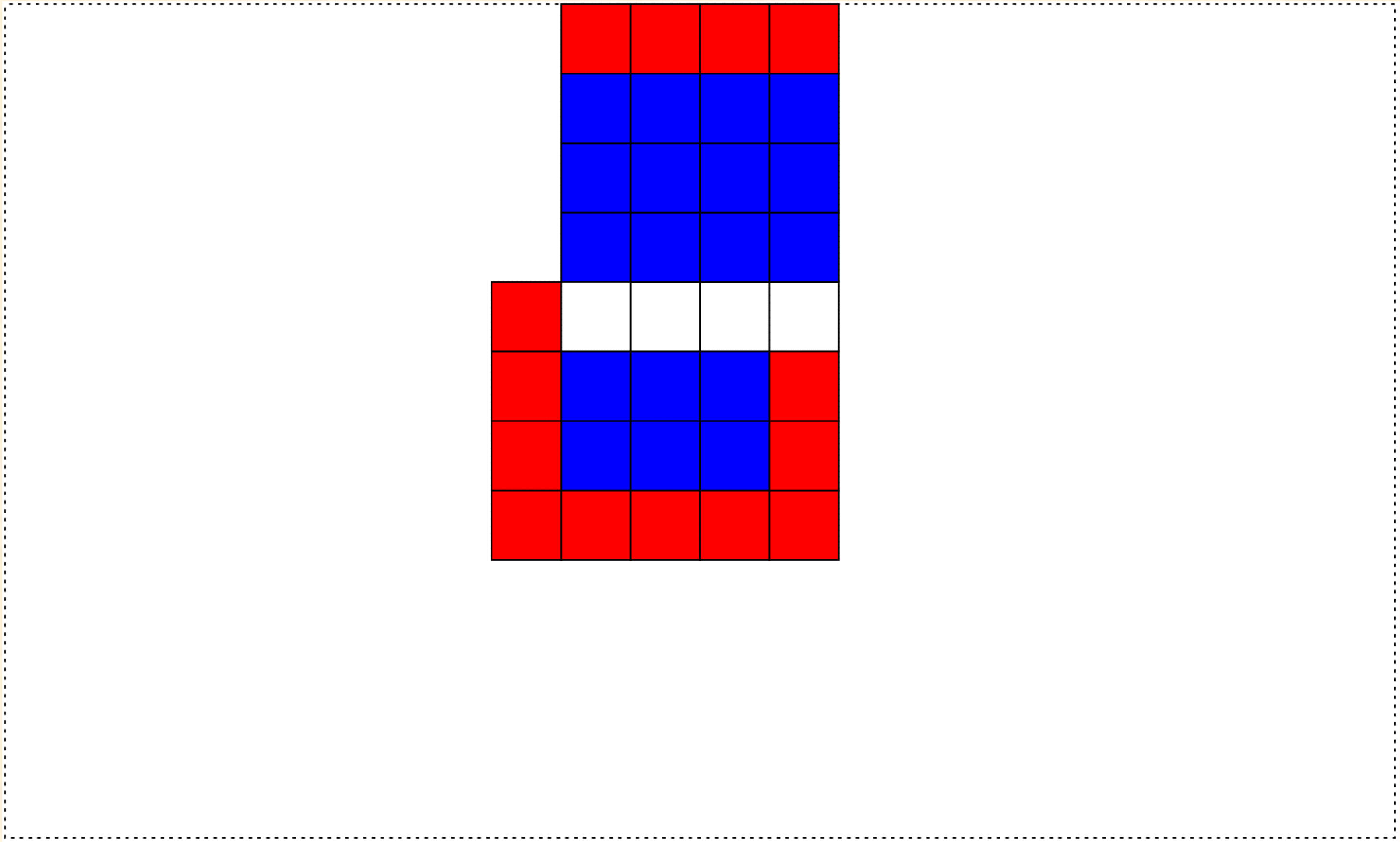
Step 1: Random Excitation



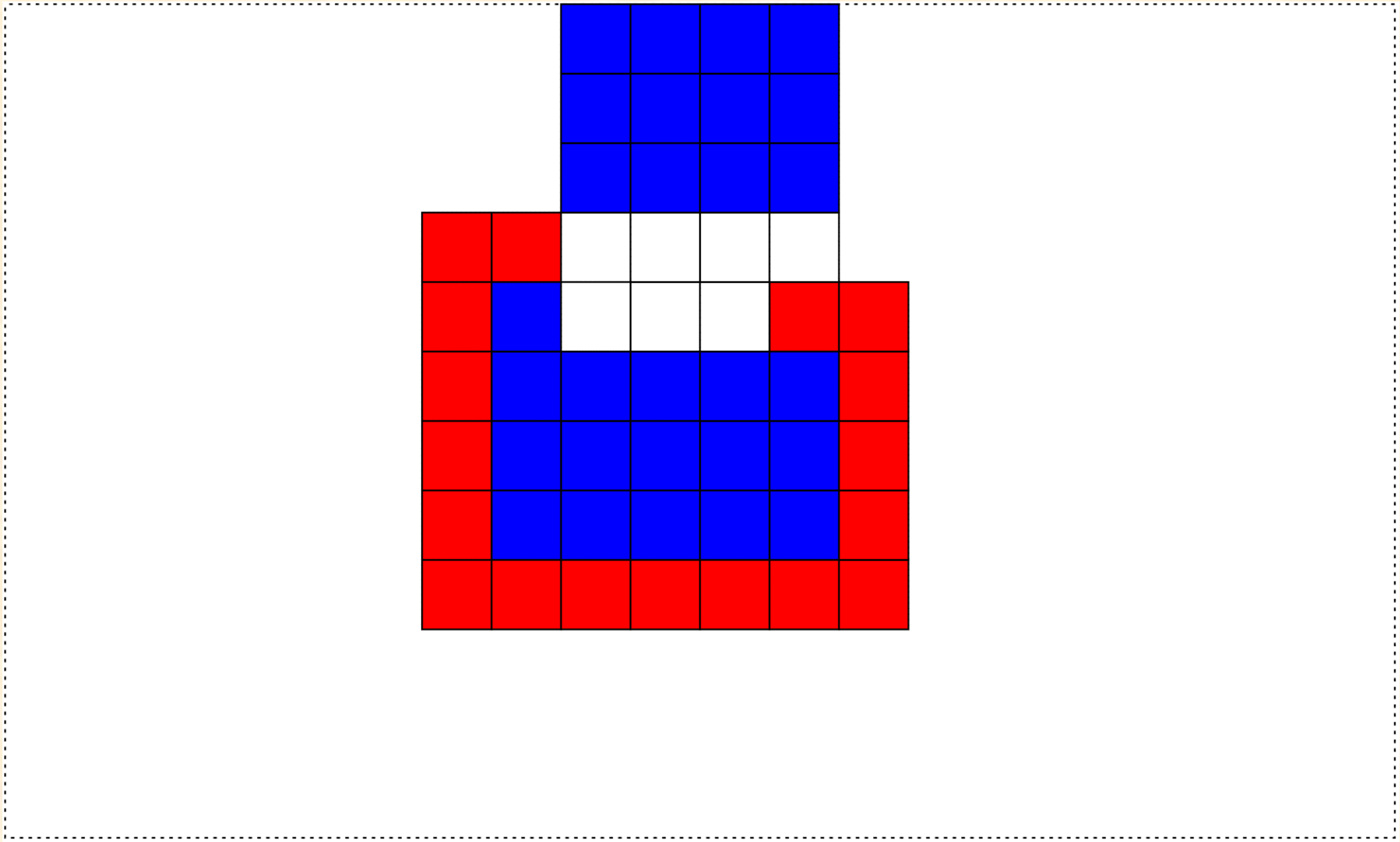
Step 2: Beginning of Spiral



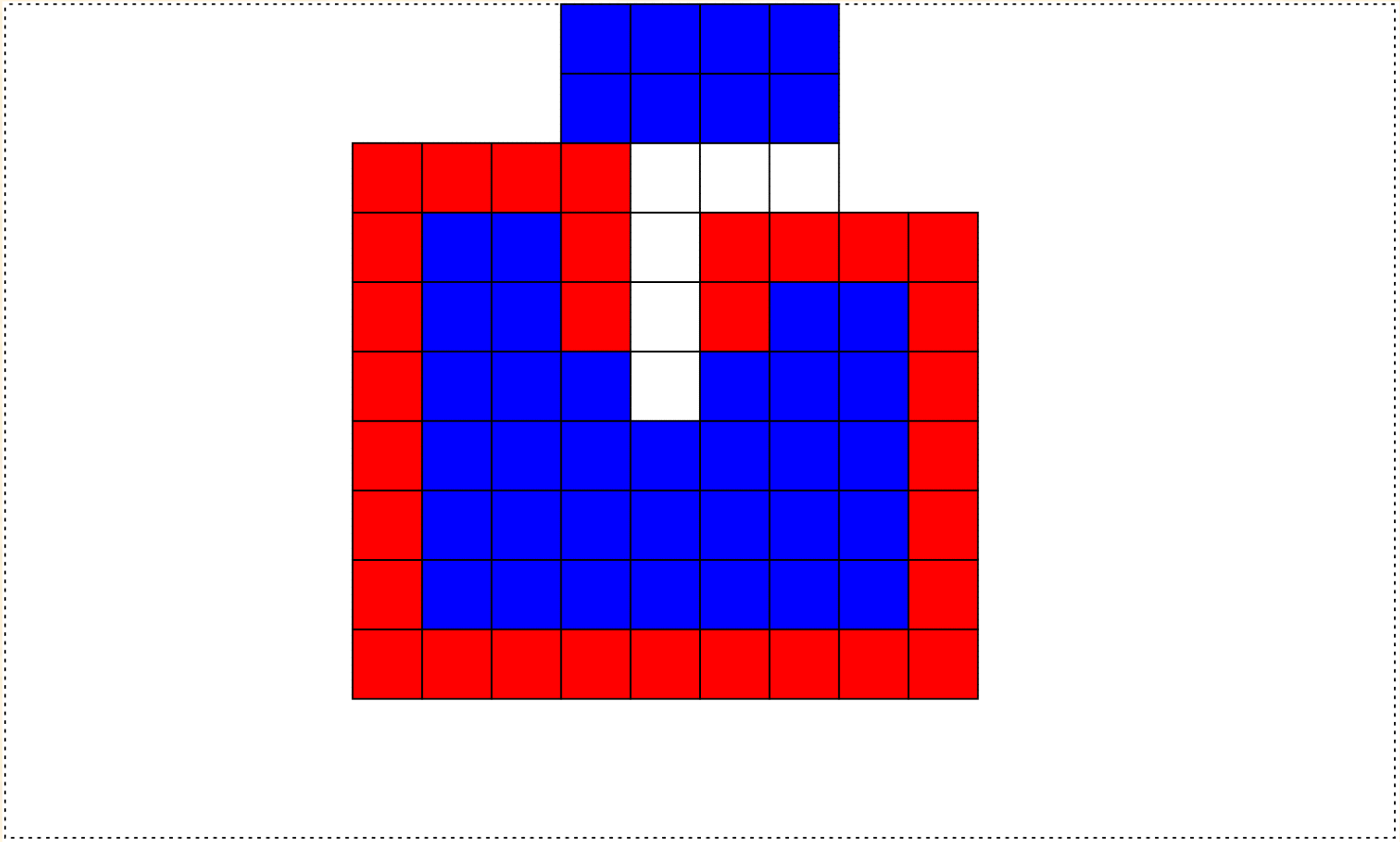
Step 3



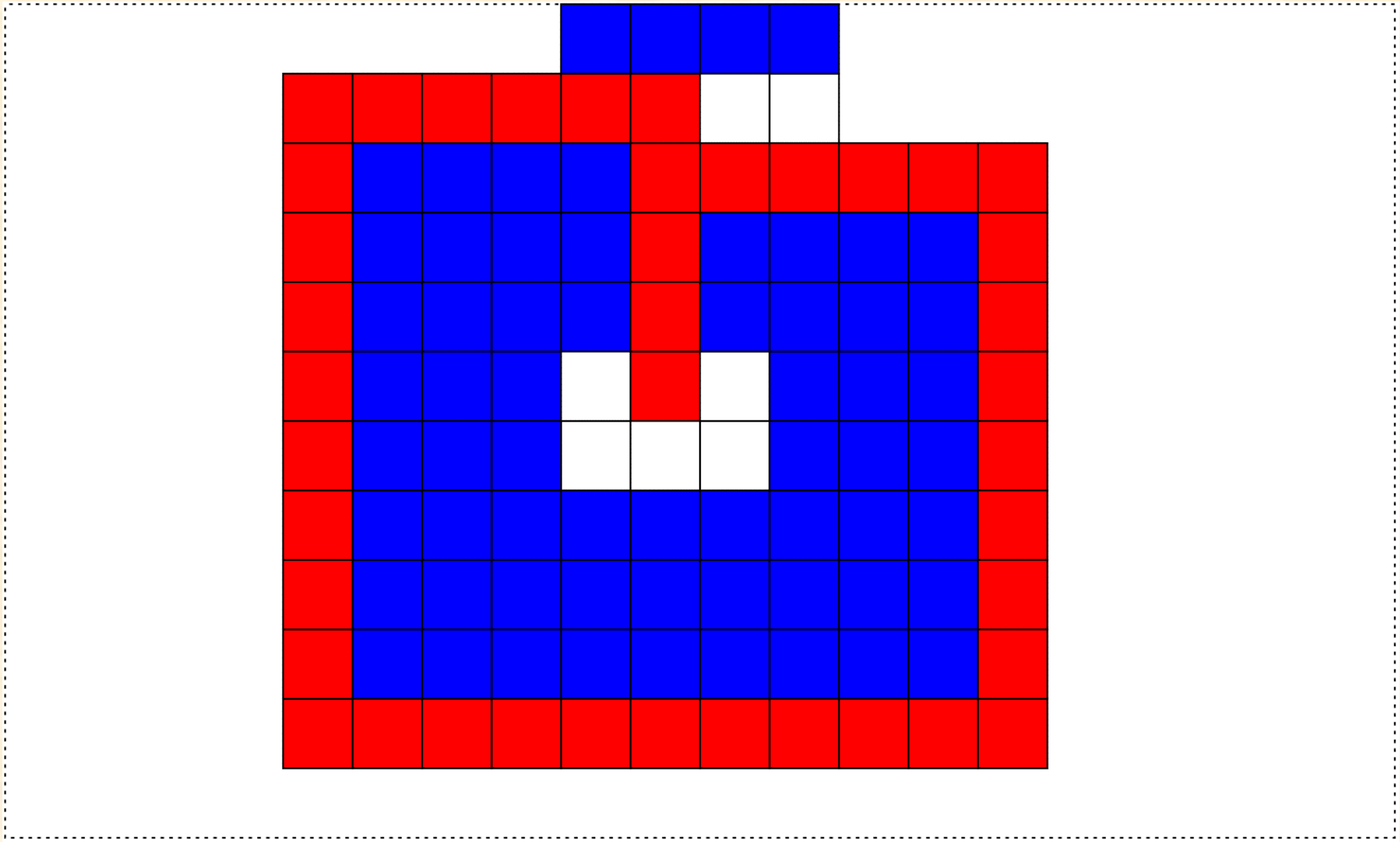
Step 4



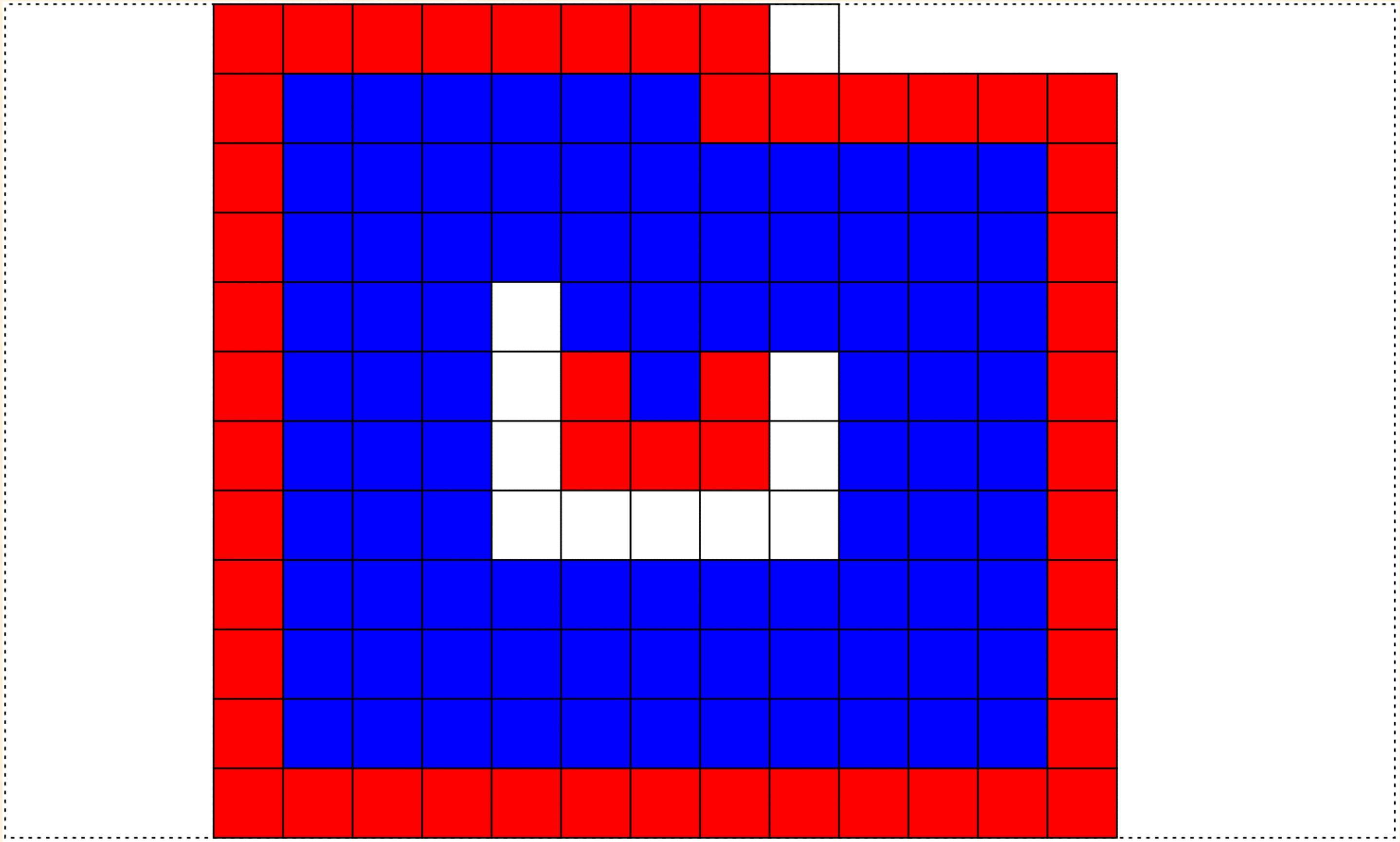
Step 5



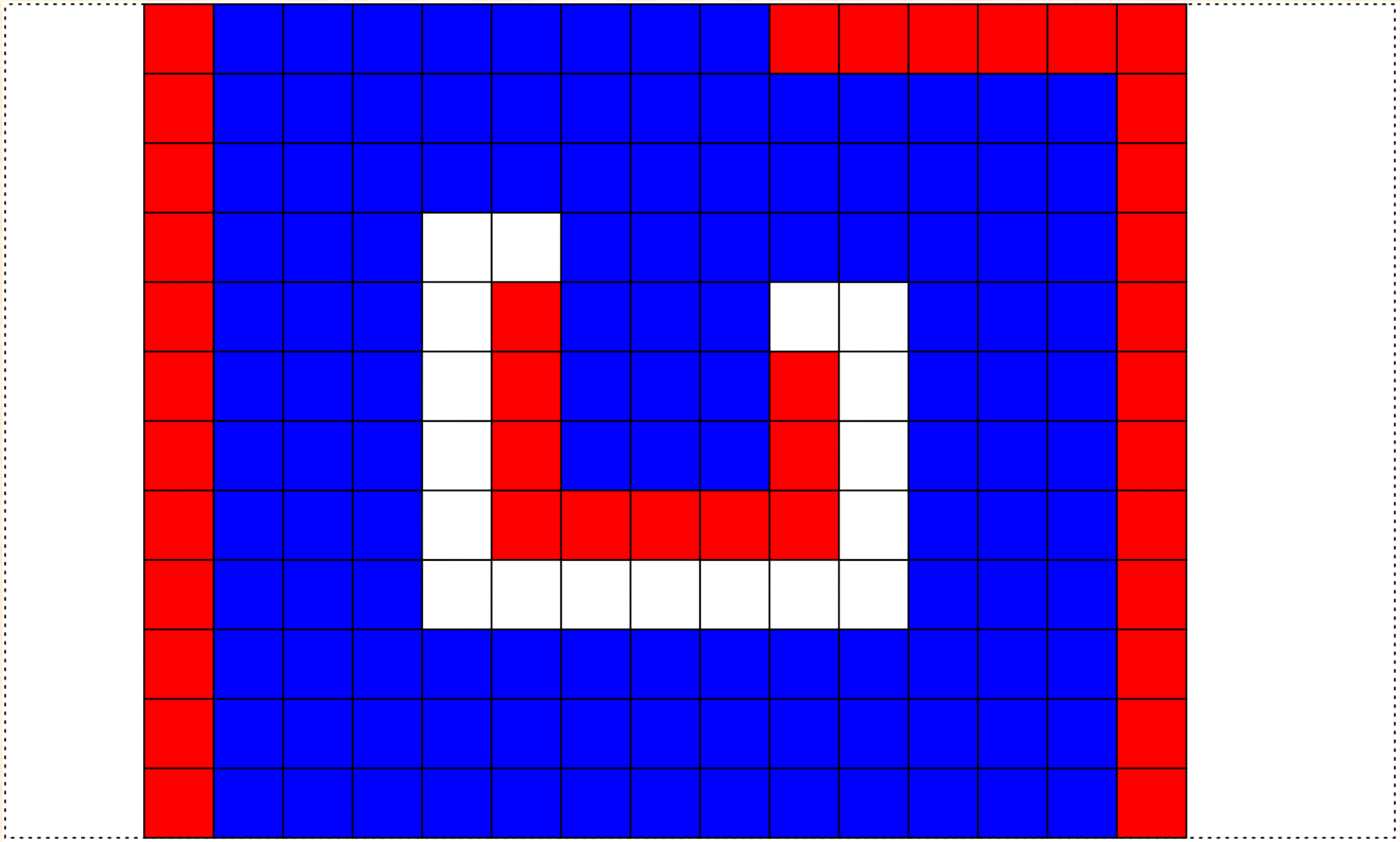
Step 6: Rejoining & Reinitiation



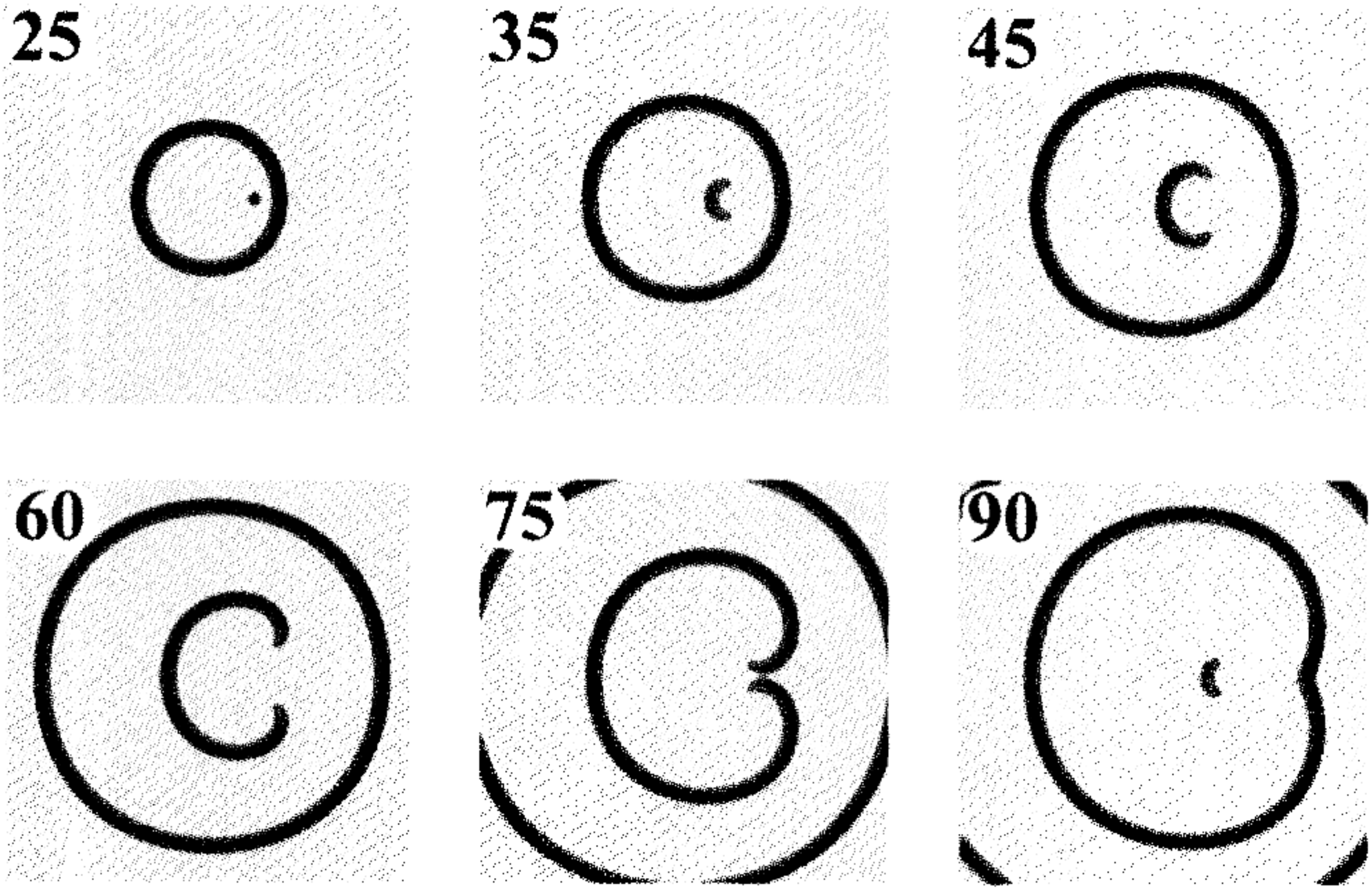
Step 7: Beginning of New Spiral



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

Demonstration of NetLogo Simulation of Spiral Formation (a closer look)

Run SlimeSpiralBig.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

Demonstration of NetLogo Simulation of Streaming

Run SlimeStream.nlogo

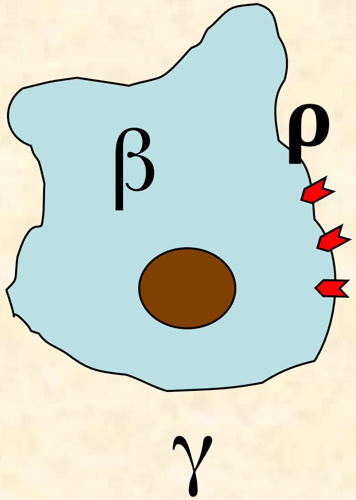
Modified Martiel & Goldbeter Model for Dicty Signalling

Variables (functions of x, y, t):

β = intracellular concentration of cAMP

γ = extracellular concentration of cAMP

$\boldsymbol{\rho}$ = fraction of receptors in active state



Equations

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

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

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

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

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

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)
- $\Rightarrow$ cAMP receptors desensitize
  (f_1 increases, f_2 decreases, ρ decreases)
- $\Rightarrow$ Rate of synthesis of intracellular cAMP decreases
  (Φ decreases)
- $\Rightarrow$ Intracellular cAMP decreases
  (β decreases)
- $\Rightarrow$ Rate of secretion of cAMP decreases
- $\Rightarrow$ 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, and then return to steady state
  – *or* oscillation (depending on model parameters)

Typical Equations for Excitable Medium (ignoring diffusion)

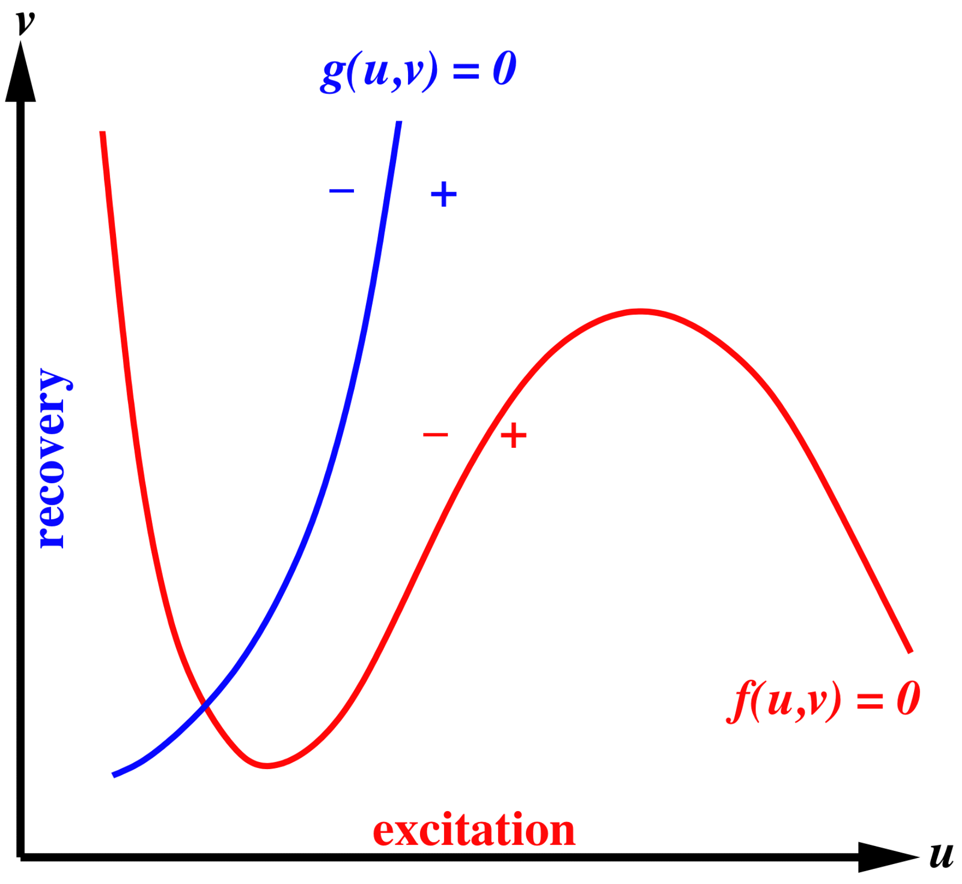
- Excitation variable:

$$\dot{u} = f(u,v)$$

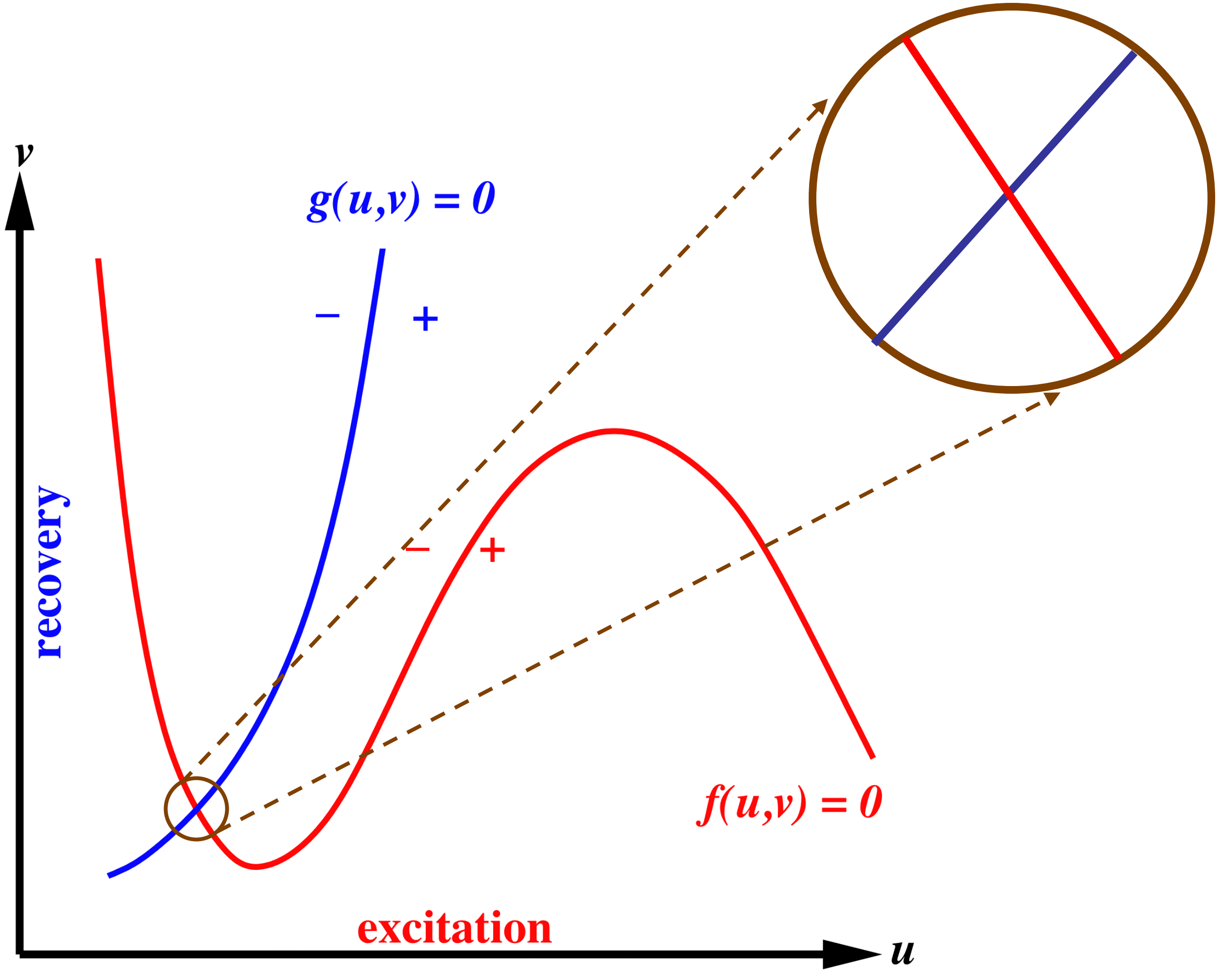
- Recovery variable:

$$\dot{v} = g(u,v)$$

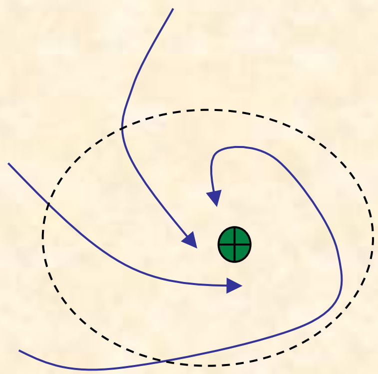
Nullclines



Local Linearization

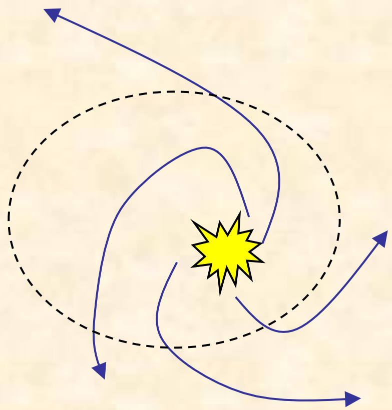


Fixed Points & Eigenvalues



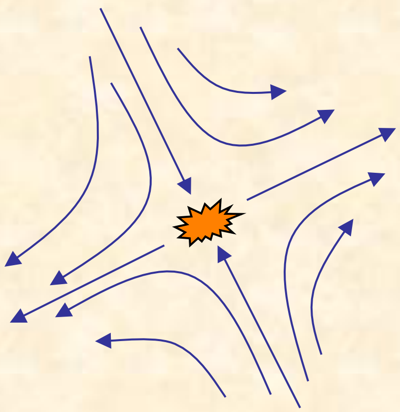
stable fixed point

real parts of eigenvalues are negative



unstable fixed point

real parts of eigenvalues are positive



saddle point

one positive real & one negative real eigenvalue

Neural Impulse Propagation

$$C\frac{dv}{dt} = I - g_{Na}m^3h(V - V_{Na}) - g_Kn^4(V - V_K) - g_L(V - V_L)$$

$$\frac{dm}{dt} = a_m(V)(1-m) - b_m(V)m$$

$$\frac{dh}{dt} = a_h(V)(1-h) - b_h(V)h$$

$$\frac{dn}{dt} = a_n(V)(1-n) - b_n(V)n$$

$$a_m(V) = .1(V+40)/(1-\exp(-(V+40)/10))$$

$$b_m(V) = 4\exp(-(V+65)/18)$$

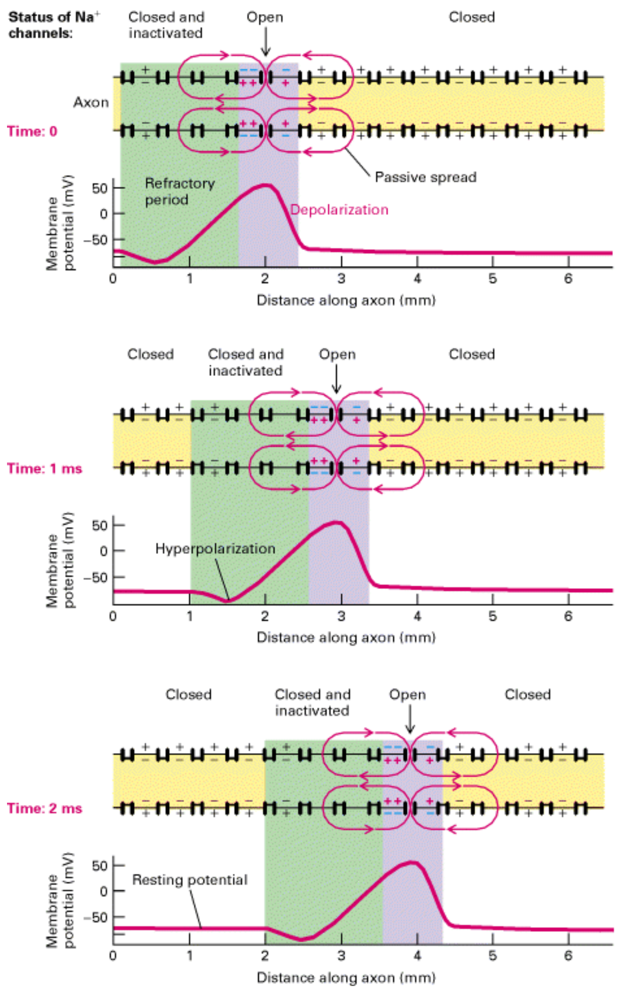
$$a_h(V) = .07\exp(-(V+65)/20)$$

$$b_h(V) = 1/(1+\exp(-(V+35)/10))$$

$$a_n(V) = .01(V+55)/(1-\exp(-(V+55)/10))$$

$$b_n(V) = .125\exp(-(V+65)/80)$$

- Hodgkin-Huxley equations



FitzHugh-Nagumo Model

- A simplified model of action potential generation in neurons
- The neuronal membrane is an excitable medium
- *B* is the input bias:

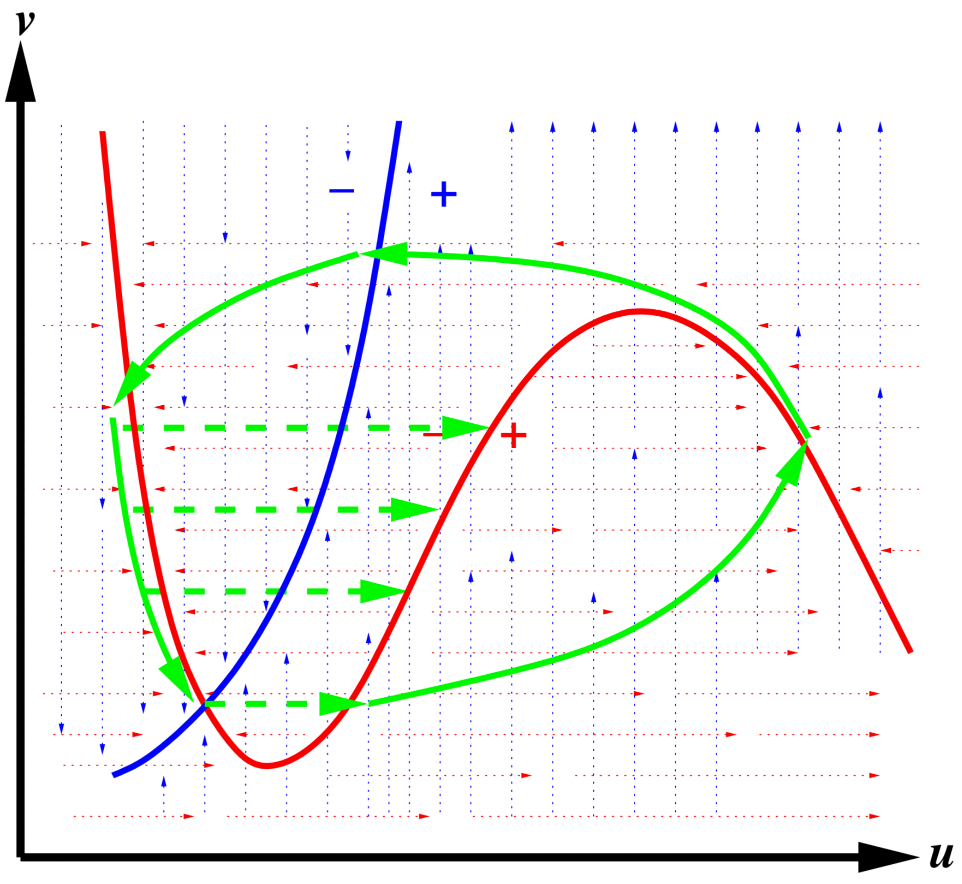
$$\dot{u} = u - \frac{u^3}{3} - v + B$$

$$\dot{v} = \varepsilon(b_0 + b_1 u - v)$$

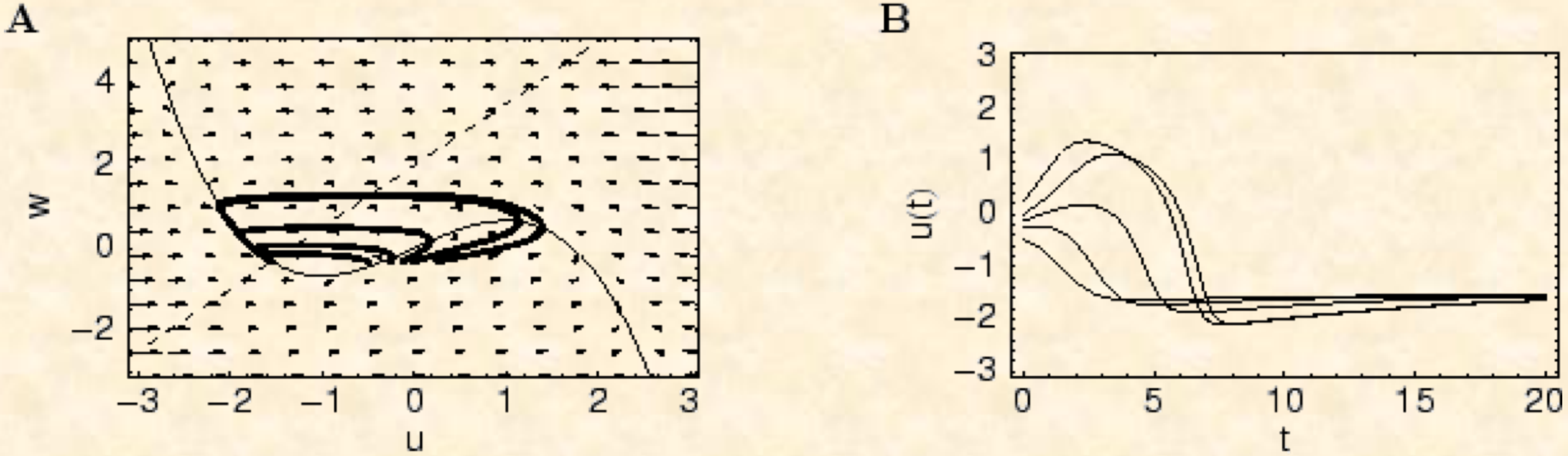
NetLogo Simulation of Excitable Medium in 2D Phase Space

(EM-Phase-Plane.nlogo)

Elevated Thresholds During Recovery



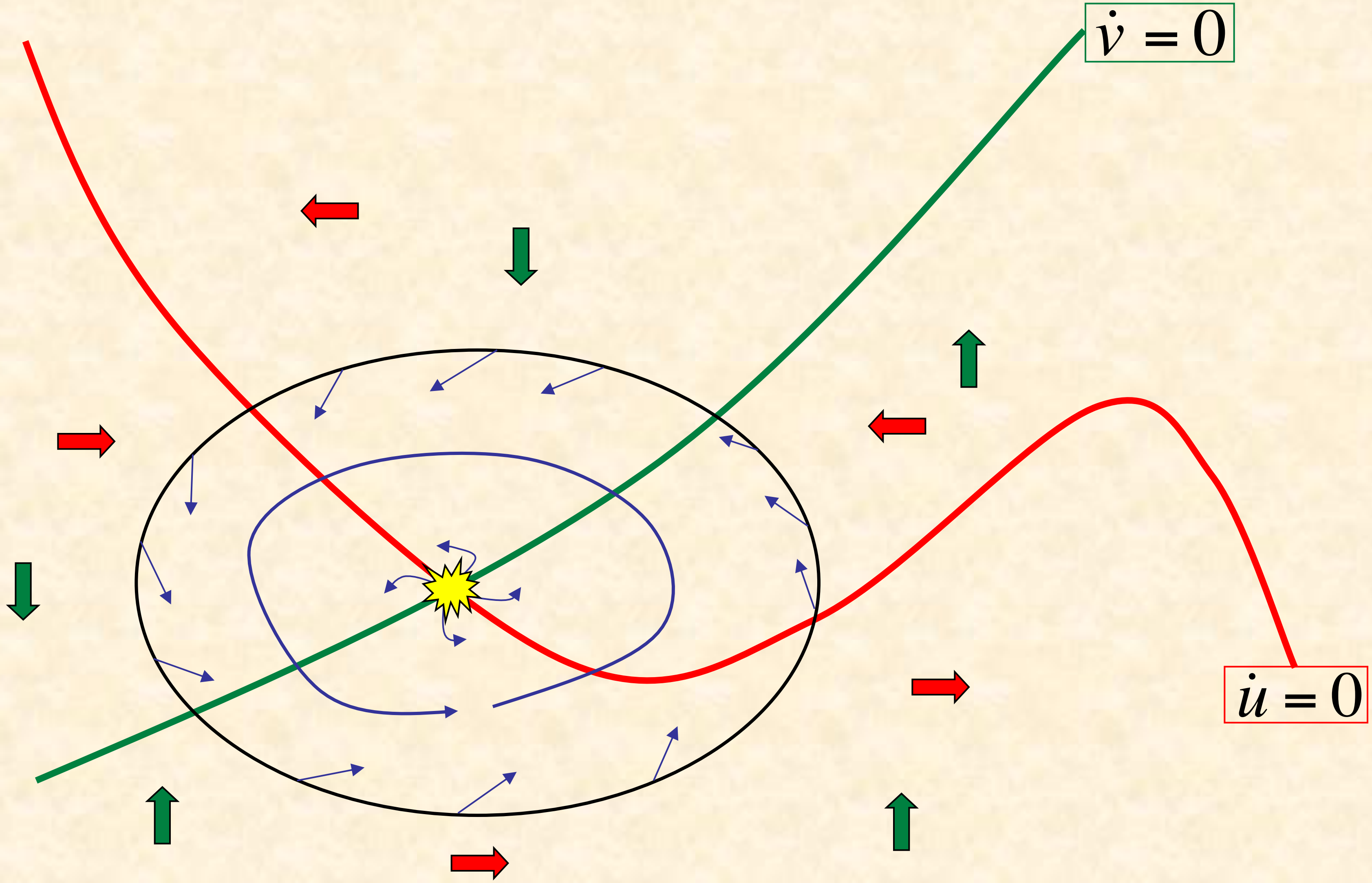
Type II Model



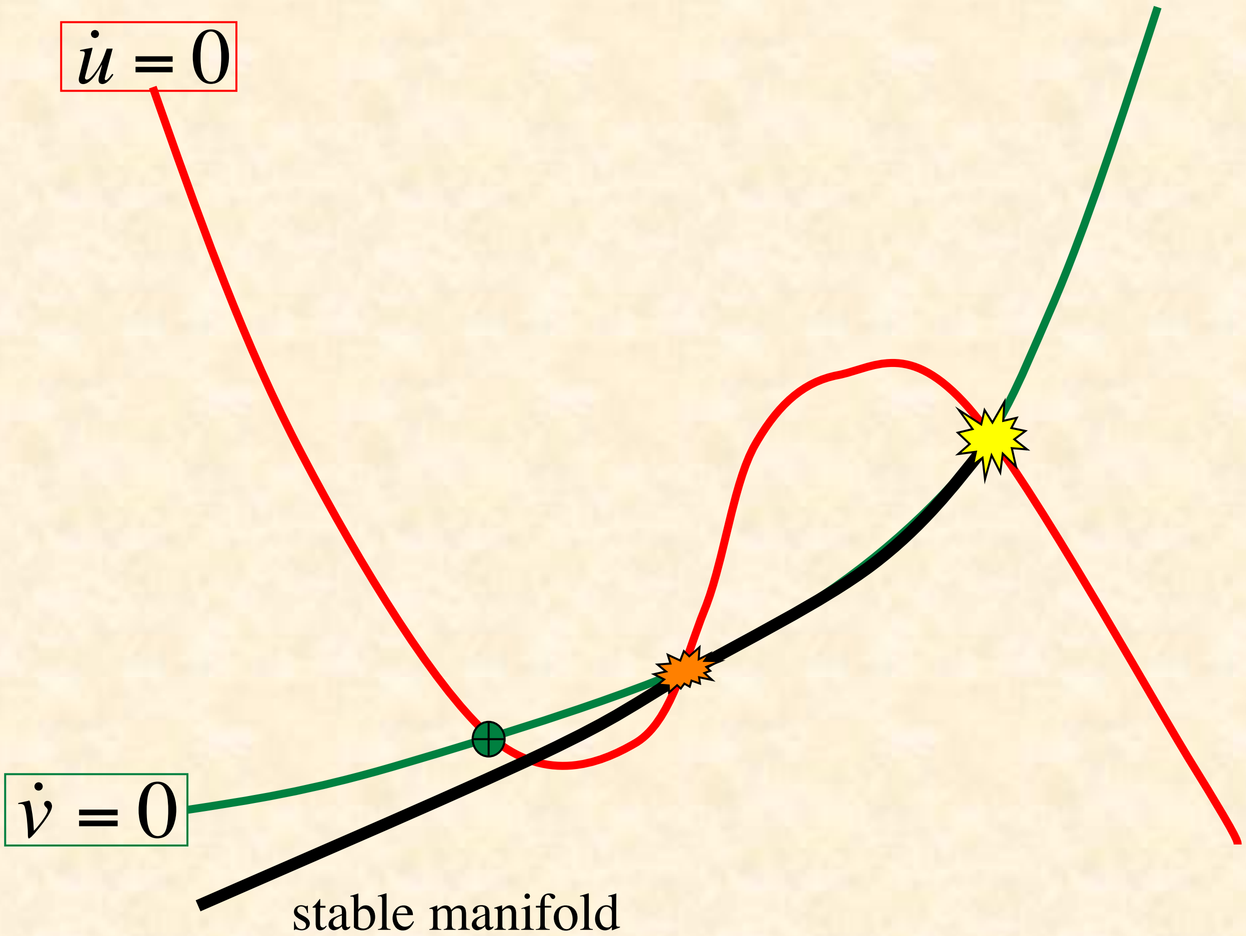
- Soft threshold with critical regime
- Bias can destabilize fixed point

fig. < Gerstner & Kistler

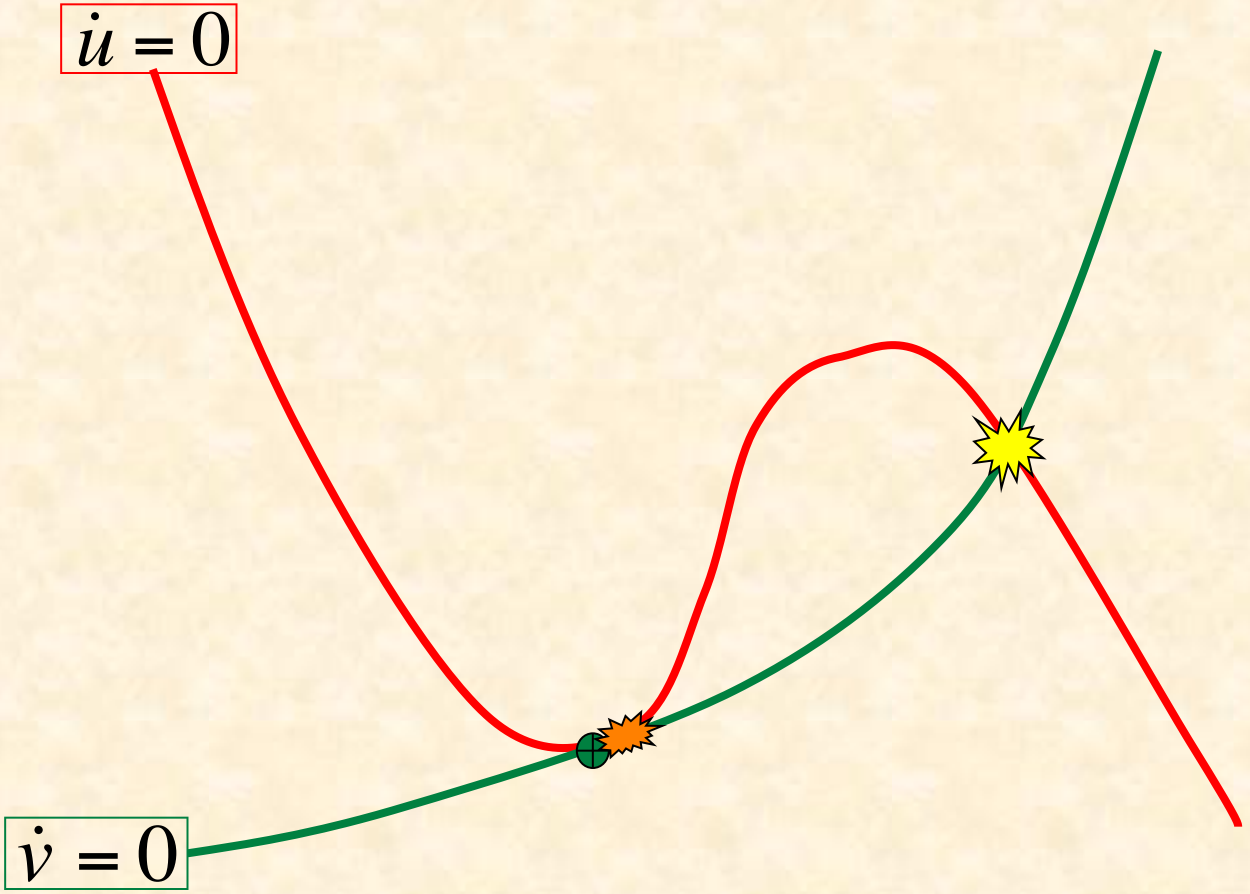
Poincaré-Bendixson Theorem



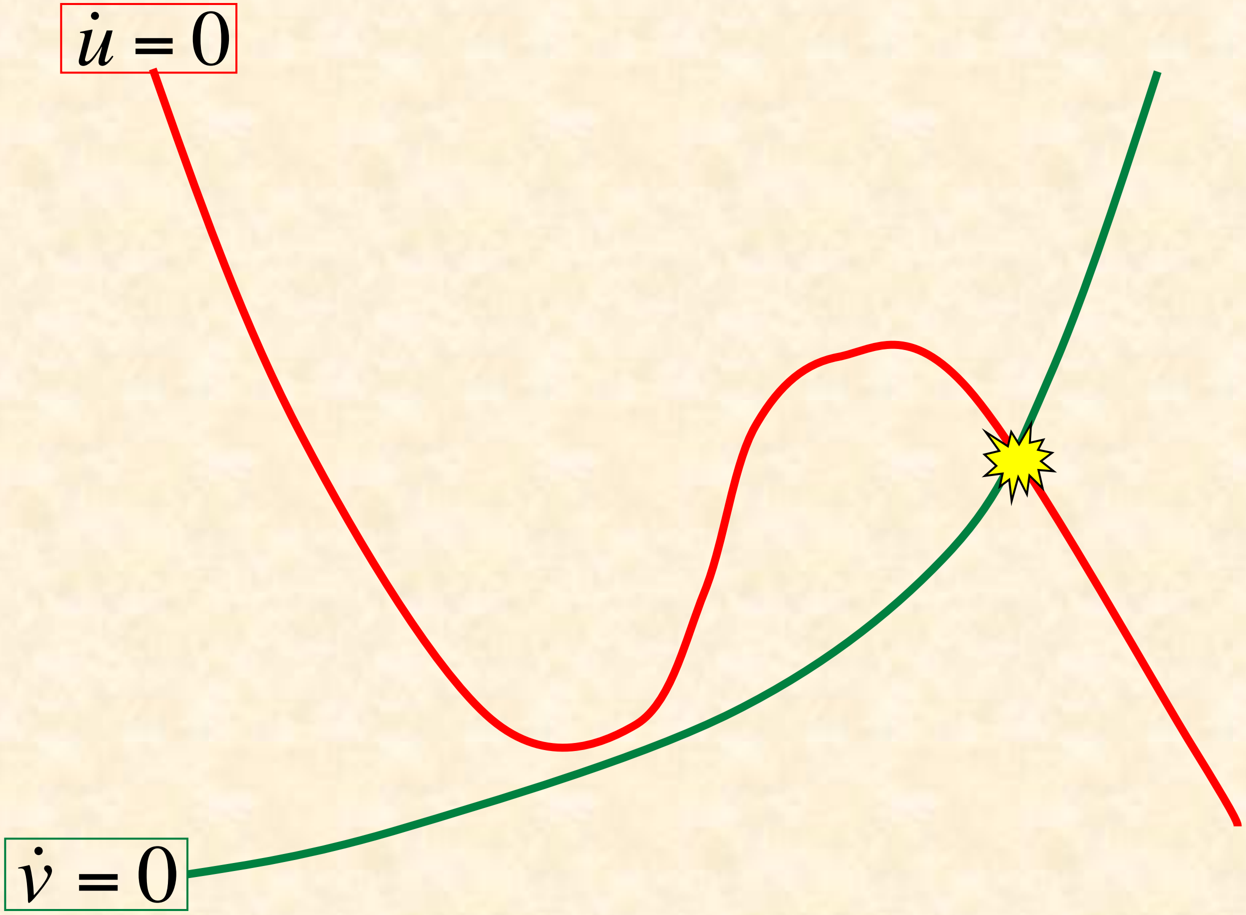
Type I Model



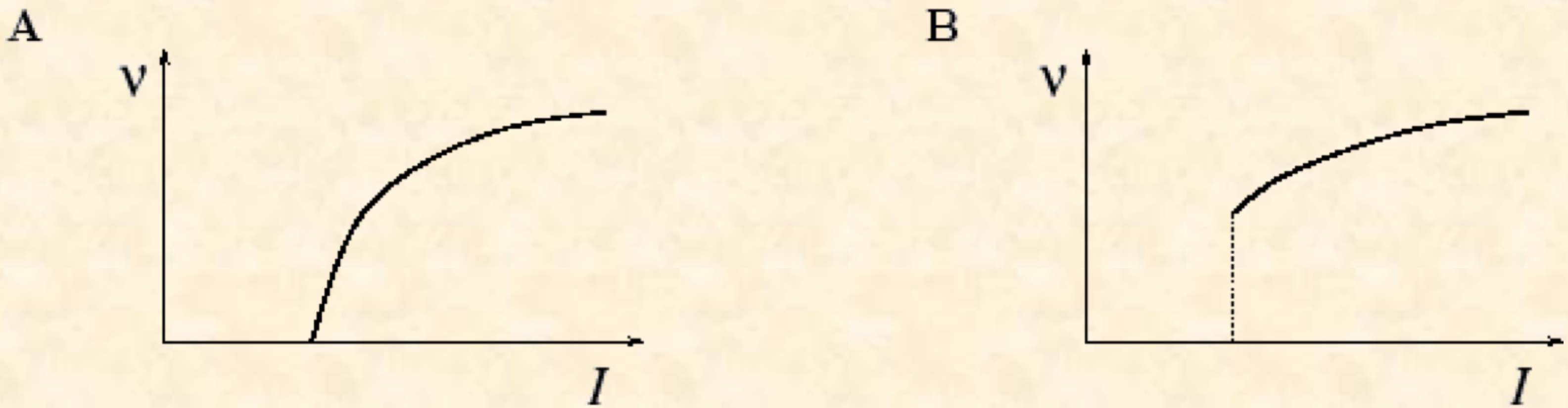
Type I Model (Elevated Bias)



Type I Model (Elevated Bias 2)



Type I vs. Type II



- Continuous vs. threshold behavior of frequency
- Slow-spiking vs. fast-spiking neurons

fig. < Gerstner & Kistler

II.E

Additional Bibliography

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2. Gerhardt, M., Schuster, H., & Tyson, J. J. "A Cellular Automaton Model of Excitable Media Including Curvature and Dispersion," *Science* **247** (1990): 1563-6.
3. Tyson, J. J., & Keener, J. P. "Singular Perturbation Theory of Traveling Waves in Excitable Media (A Review)," *Physica D* **32** (1988): 327-61.
4. Camazine, S., Deneubourg, J.-L., Franks, N. R., Sneyd, J., Theraulaz, G.,& Bonabeau, E. *Self-Organization in Biological Systems*. Princeton, 2001.
5. Pálsson, E., & Cox, E. C. "Origin and Evolution of Circular Waves and Spiral in *Dictyostelium discoideum* Territories," *Proc. Natl. Acad. Sci. USA*: **93** (1996): 1151-5.
6. Solé, R., & Goodwin, B. *Signs of Life: How Complexity Pervades Biology*. Basic Books, 2000.