D.
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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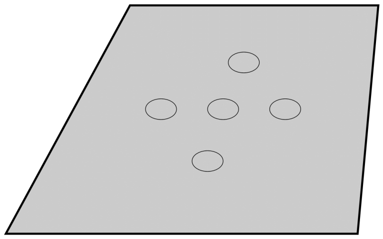
Behavior of Excitable Media



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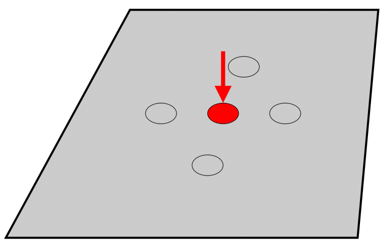
Stimulation



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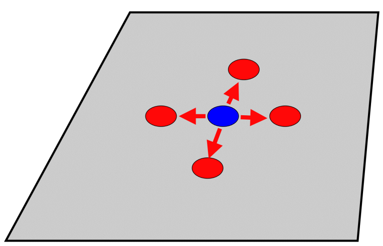
Relay (Spreading Excitation)



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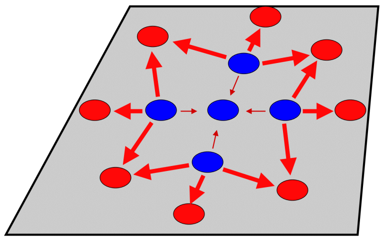
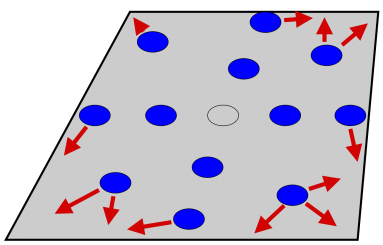
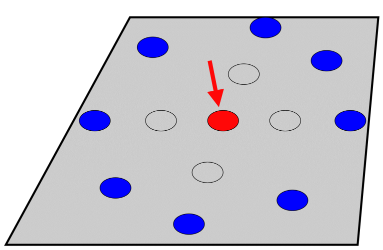
Continued Spreading



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

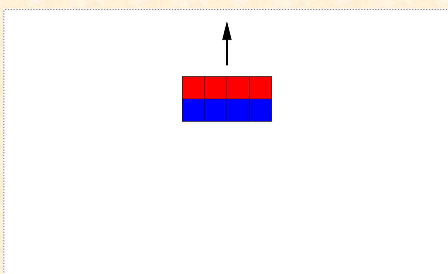
Spiral Waves

- 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?

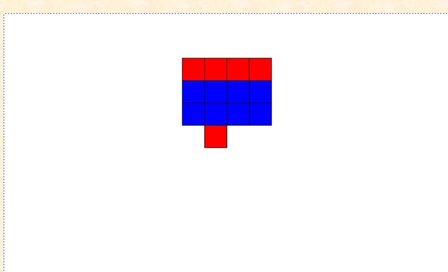
Some Explanations of Spiral Formation

- "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

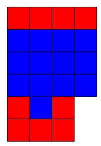
Step 0: Passing Wave Front



Step 1: Random Excitation



Step 2: Beginning of Spiral



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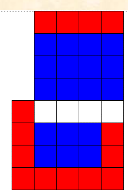
Step 3



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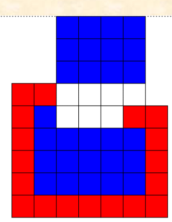
Step 4



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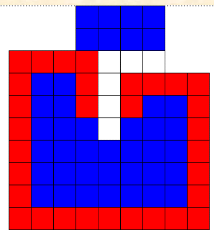
Step 5



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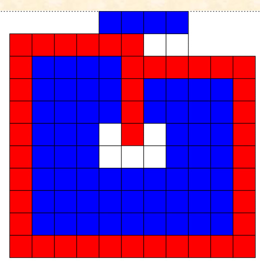
Step 6: Rejoining & Reinitiation



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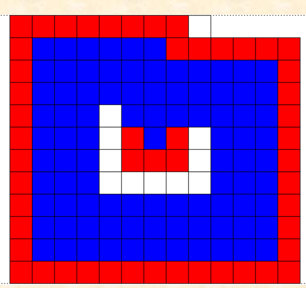
Step 7: Beginning of New Spiral



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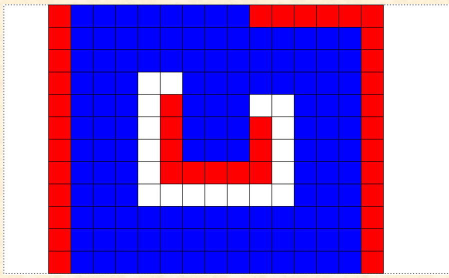
Step 8



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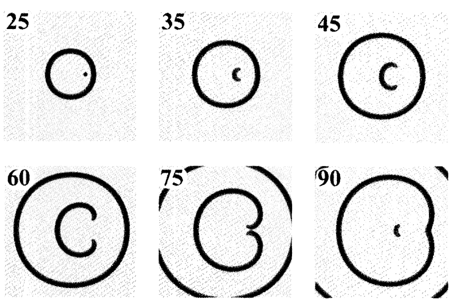
Formation of Double Spiral



from Pálsson & Cox (1996)

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

Run SlimeSpiralBig.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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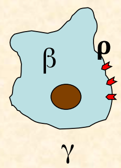
Modified Martiel & Goldbeter Model for Dicty Signalling

Variables (functions of x, y, t):



β = intracellular concentration of cAMP

γ = extracellular concentration of cAMP

ρ = fraction of receptors in active state

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Equations

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

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

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

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

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

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

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Positive Feedback Loop

- Extracellular cAMP increases
  (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)

2/8/17 See Equations 33

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)

2/8/17 See Equations 34

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, and then return to steady state
  - *or* oscillation (depending on model parameters)

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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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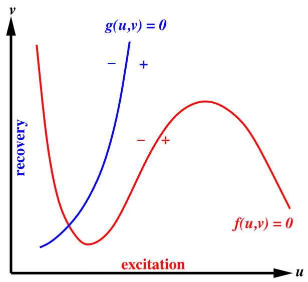
Nullclines



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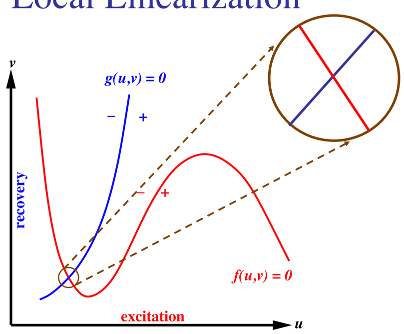
Local Linearization



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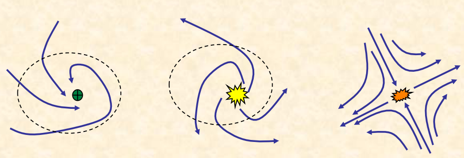
Fixed Points & Eigenvalues



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

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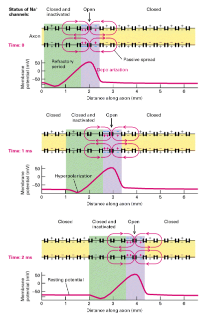
Neural Impulse Propagation

$$
\begin{aligned}
C\frac{dv}{dt} &= I - g_{Na}m^3h(V - V_{Na}) - g_K n^4(V - V_K) - g_L(V - V_L) \\
\frac{dm}{dt} &= a_m(V)(1-m) - b_m(V)m \\
\frac{dh}{dt} &= a_h(V)(1-h) - b_h(V)h \\
\frac{dn}{dt} &= a_n(V)(1-n) - b_n(V)n \\
a_m(V) &= .1(V+40)/(1-\exp(-(V+40)/10)) \\
b_m(V) &= 4\exp(-(V+65)/18) \\
a_h(V) &= .07\exp(-(V+65)/20) \\
b_h(V) &= 1/(1+\exp(-(V+35)/10)) \\
a_n(V) &= .01(V+55)/(1-\exp(-(V+55)/10)) \\
b_n(V) &= .125\exp(-(V+65)/80)
\end{aligned}
$$



☞ Hodgkin-Huxley equations

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FitzHugh-Nagumo Model

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

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

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

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NetLogo Simulation of Excitable Medium in 2D Phase Space

(EM-Phase-Plane.nlogo)

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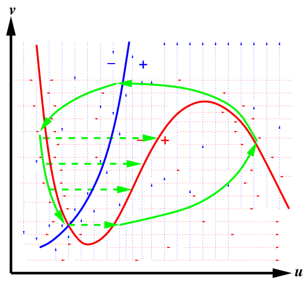
Elevated Thresholds During Recovery



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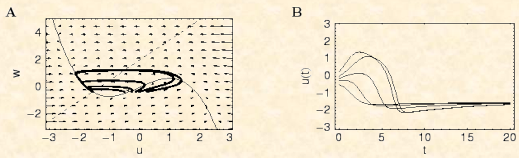
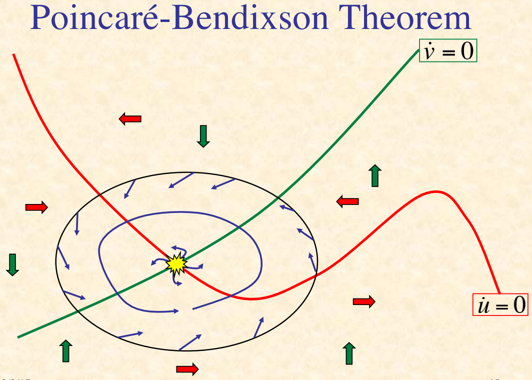
Type II Model



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

2/8/17 fig. < Gerstner & Kistler 44

Poincaré-Bendixson Theorem



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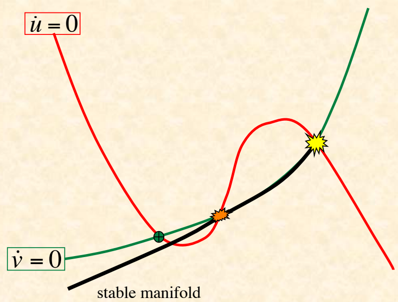
Type I Model



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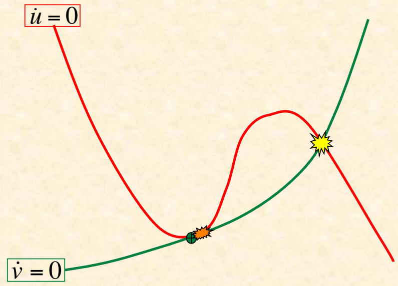
Type I Model (Elevated Bias)



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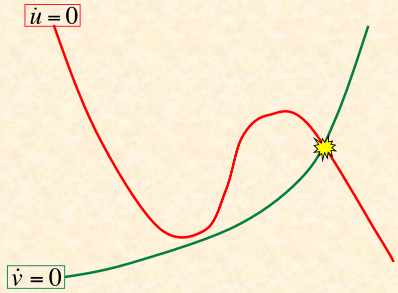
Type I Model (Elevated Bias 2)



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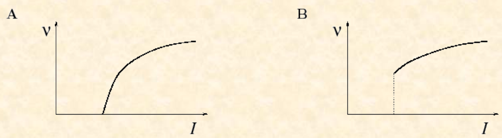
Type I vs. Type II



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

fig. < Gerstner & Kistler

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Additional Bibliography

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3. Tyson, J. J., & Keener, J. P. "Singular Perturbation Theory of Traveling Waves in Excitable Media (A Review)," *Physica D* **32** (1988): 327-61.
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6. Solé, R., & Goodwin, B. *Signs of Life: How Complexity Pervades Biology*. Basic Books, 2000.

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