D.
Excitable Media

2013/2/8 1

Examples of Excitable Media

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

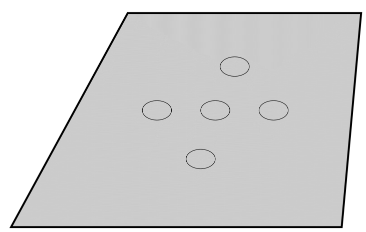
2013/2/8 2

Characteristics of Excitable Media

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

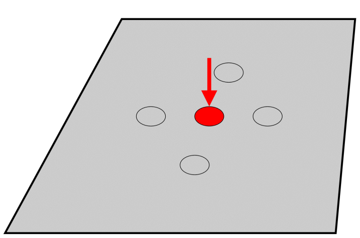
2013/2/8 3

Behavior of Excitable Media



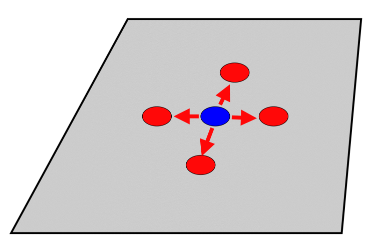
2013/2/8 4

Stimulation



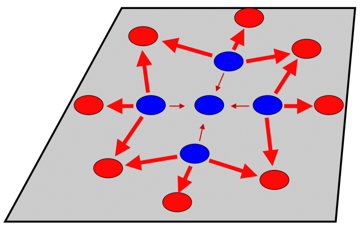
2013/2/8 5

Relay (Spreading Excitation)



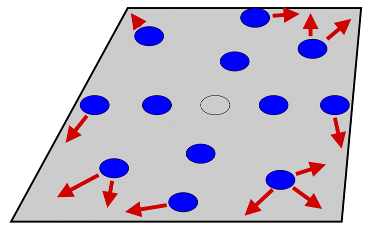
2013/2/8 6

Continued Spreading



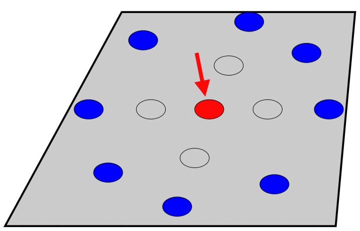
2013/2/8 7

Recovery



2013/2/8 8

Restimulation



2013/2/8 9

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

2013/2/8 10

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

2013/2/8 11

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?

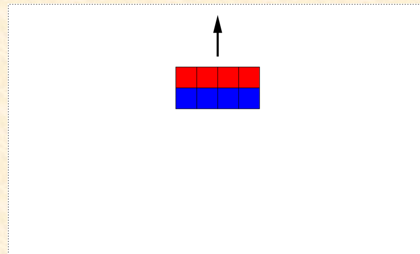
2013/2/8 12

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

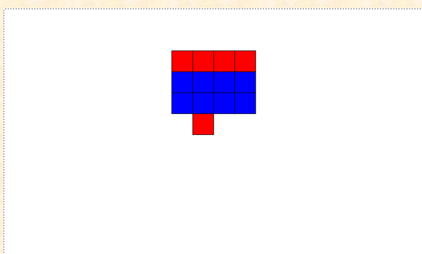
2013/2/8 13

Step 0: Passing Wave Front



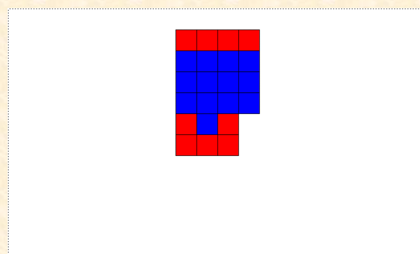
2013/2/8 14

Step 1: Random Excitation



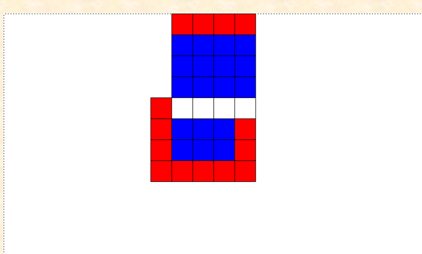
2013/2/8 15

Step 2: Beginning of Spiral



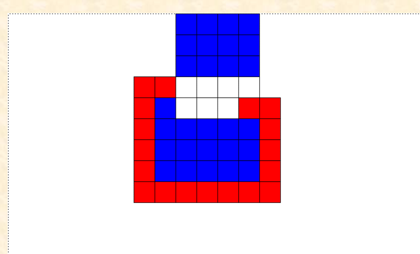
2013/2/8 16

Step 3



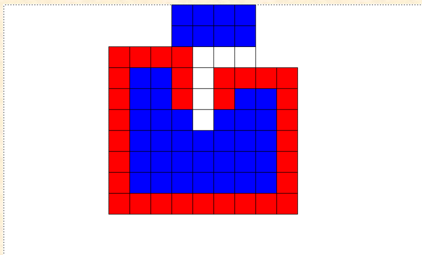
2013/2/8 17

Step 4



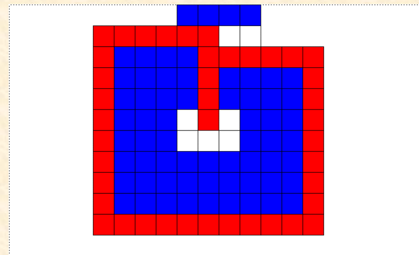
2013/2/8 18

Step 5



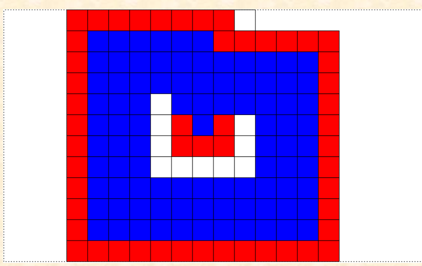
2013/2/8 19

Step 6: Rejoining & Reinitiation



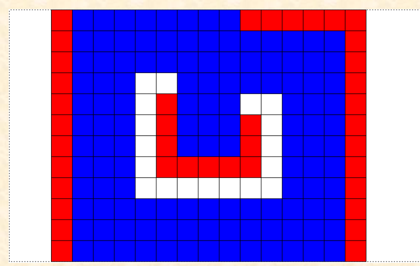
2013/2/8 20

Step 7: Beginning of New Spiral



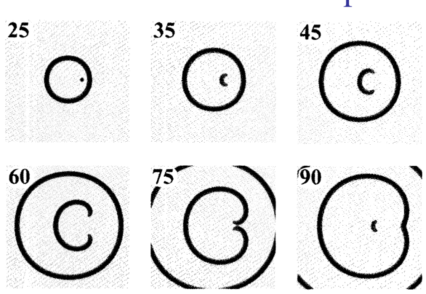
2013/2/8 21

Step 8



2013/2/8 22

Formation of Double Spiral



from Pálsson & Cox (1996)

2013/2/8 23

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

2013/2/8 24

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

2013/2/8 25

Demonstration of NetLogo Simulation of Spiral Formation

Run SlimeSpiral.nlogo

2013/2/8 26

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

Run SlimeSpiralBig.nlogo

2013/2/8 27

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

2013/2/8 28

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

2013/2/8 29

Demonstration of NetLogo Simulation of Streaming

Run SlimeStream.nlogo

2013/2/8 30

Typical Equations for Excitable Medium (ignoring diffusion)

- Excitation variable:

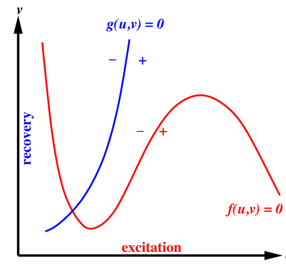
$$\dot{u} = f(u,v)$$

- Recovery variable:

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

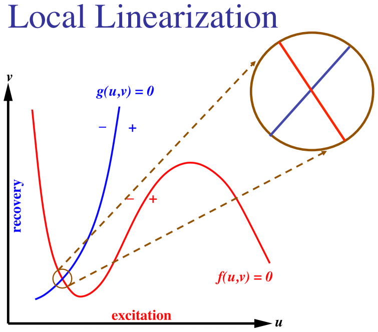
2013/2/8 31

Nullclines



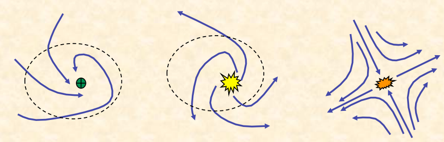
2013/2/8 32

Local Linearization



2013/2/8 33

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

2013/2/8 34

FitzHugh-Nagumo Model

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

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

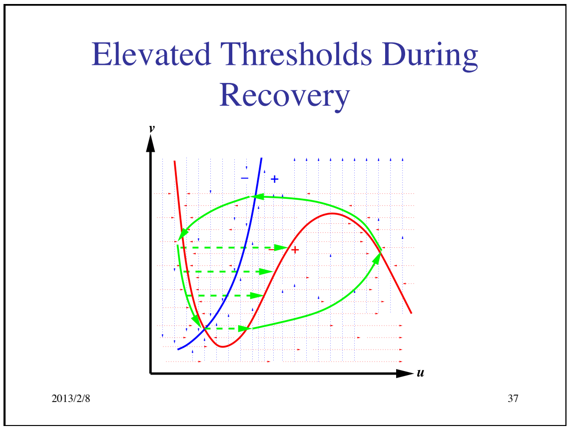
$$\dot{v} = \varepsilon(b_0 + b_1 u - v)$$

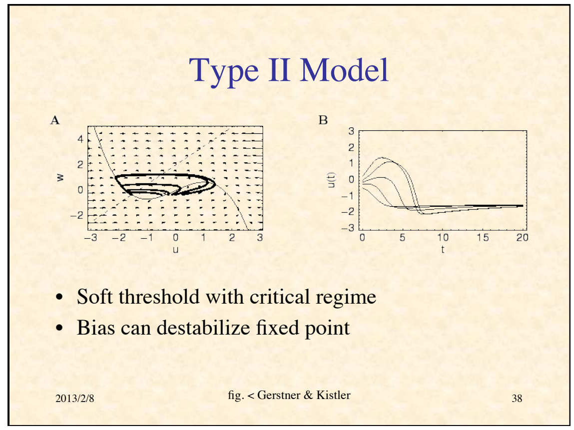
2013/2/8 35

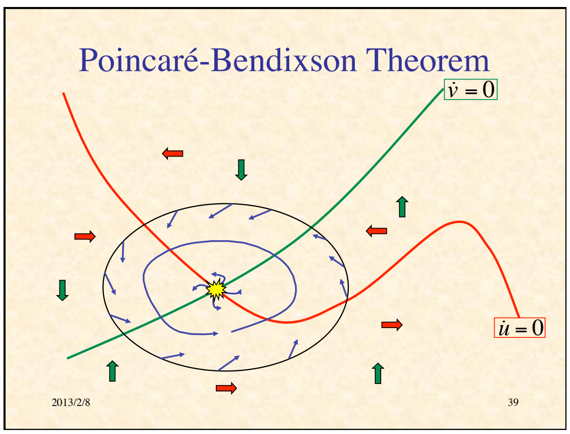
NetLogo Simulation of Excitable Medium in 2D Phase Space

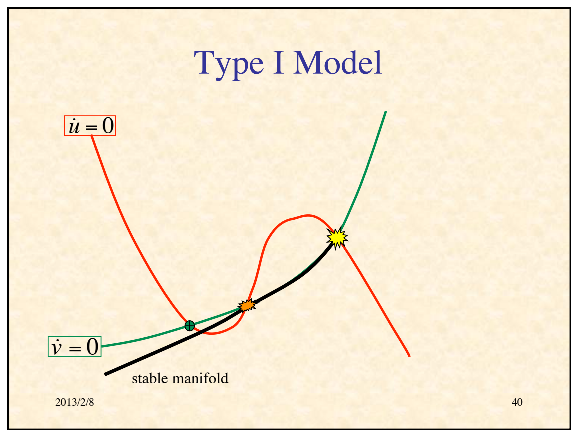
(EM-Phase-Plane.nlogo)

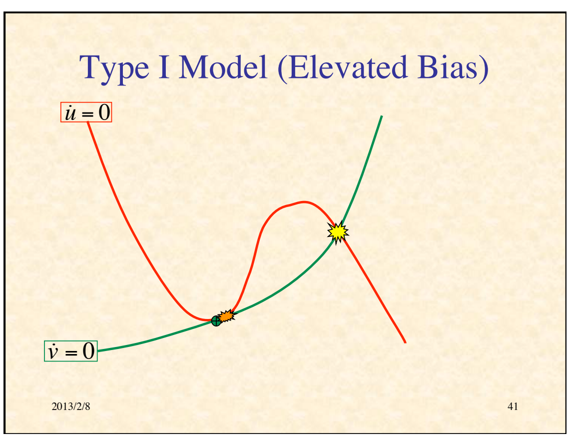
2013/2/8 36

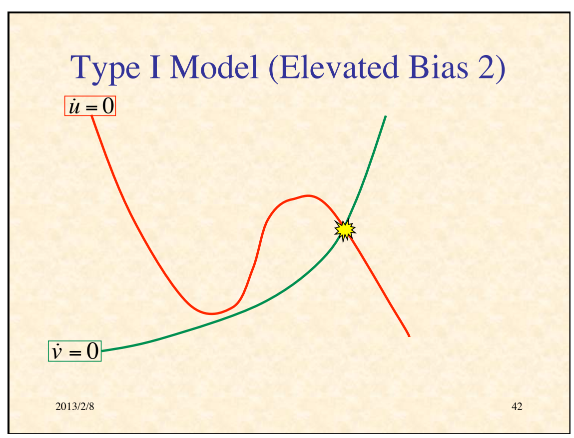

Elevated Thresholds During Recovery
v
u
2013/2/8
37


Type II Model
A
B
• Soft threshold with critical regime
• Bias can destabilize fixed point
2013/2/8
fig. < Gerstner & Kistler
38

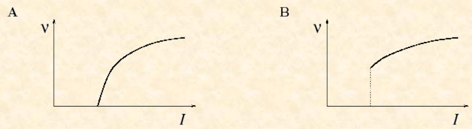

Poincaré-Bendixson Theorem
$\dot{v} = 0$
$\dot{u} = 0$
2013/2/8
39


Type I Model
$\dot{u} = 0$
$\dot{v} = 0$
stable manifold
2013/2/8
40


Type I Model (Elevated Bias)
$\dot{u} = 0$
$\dot{v} = 0$
2013/2/8
41


Type I Model (Elevated Bias 2)
$\dot{u} = 0$
$\dot{v} = 0$
2013/2/8
42

Type I vs. Type II



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

fig. < Gerstner & Kistler

2013/2/8 II.E 43

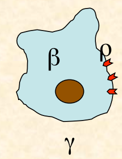
Modified Martiel & Goldbeter Model for Dicty Signalling

Variables (functions of x, y, t):

β = intracellular concentration of cAMP

γ = extracellular concentration of cAMP

ρ = fraction of receptors in active state



2013/2/8 44

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

2013/2/8 45

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)

2013/2/8 See Equations 46

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)

2013/2/8 See Equations 47

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)

2013/2/8 48

Additional Bibliography

1. Kessin, R. H. *Dictyostelium: Evolution, Cell Biology, and the Development of Multicellularity*. Cambridge, 2001.
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.