Brain Control

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It's not just for Mad Scientists!!
BAD BRAINS

Outline / Inspiration

Parkinson's Disease

- **model**: population of neural oscillators
- **goal**: desynchronize neural activity
- **reduction**: based on isochrons
- **two control methods**: chaotic desync, optimal phase resetting

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Parkinson's Disease

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Cardiac Arrhythmias

- **model**: excitable cells
- **alternans goal**: stabilize unstable periodic orbit
- **reduction**: based on isostables
- **fibrillation goal**: eliminate spirals

Outline / Inspiration from Snowbird

- DS01 - Peter Tass talk

- Complex Phase Resetting Techniques for Desynchronization

- DS05 - meeting with Eric Shea-Brown during break

- collaboration: Optimal Inputs for Phase Models of Spiking Neurons, 2006

- DS05 - Danny Forger talk

- Stochastic Stimulation of the Mammalian Circadian Clock

- DS07 - co-organized MS "Mathematics of PD", w/ Jon Rubin

- also co-organized related MS's in DS11, DS13

- DS11 - Tay Netoff talk

- Using PRC's to Understand How Antiepileptic Drugs and Deep Brain Stimulation Prevent Seizures

- DSXX - talks by Bard Ermentrout, Steve Schiff,…

- DS13 – meeting with Flavio Fenton and Elizabeth Cherry during break

Parkinson's disease

- affects 1,000,000 people in the US
- estimated cost: $25 billion/year
- symptoms
  - tremors
  - postural instability
  - bradykinesia – slowness of movement
  - rigidity

- one hypothesis
  associated with pathological synchronization of neural activity in motor control region
- treatment
  - drugs
  - Deep Brain Stimulation

Deep Brain Stimulation

Video:
Andrew Johnson (Auckland, New Zealand)
diagnosed with early onset PD at age 35

blog: http://youngandshaky.com

video: http://www.youtube.com/watch?v=uBh2LxTW0s0

Deep Brain Stimulation

http://www.youtube.com/watch?v=uBh2LxTW0s0

Control Objective:

- find electrical stimulus which leads to desynchronization of neural activity using minimal power

DESYNC

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Isochrons

$$\frac{d\mathbf{x}}{dt} = \mathbf{F}(\mathbf{x}), \qquad \mathbf{x} \in \mathbb{R}^n, \qquad (n \geq 2)$$

stable hyperbolic periodic orbit $\mathbf{x}^\gamma(t)$**, period** T

isochron:

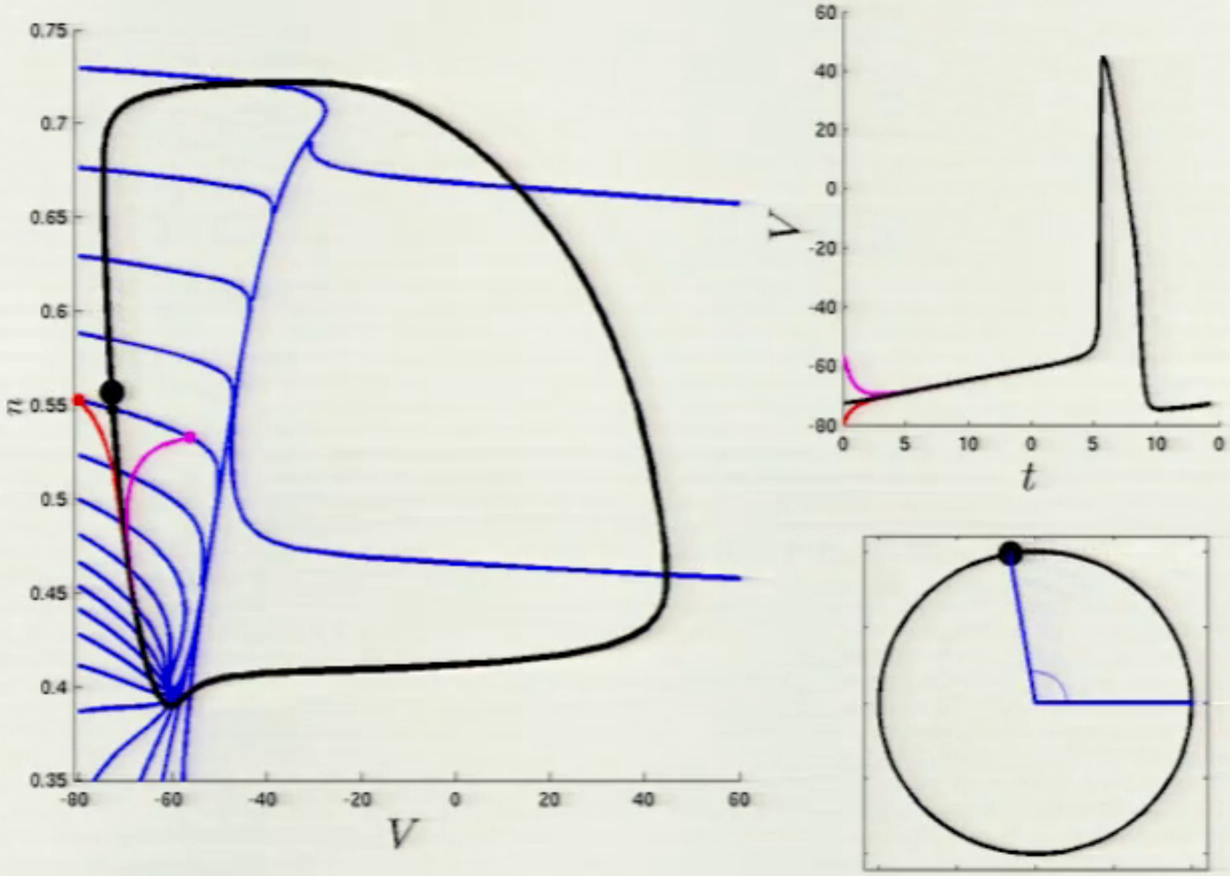
- a set of initial conditions that share the same asymptotic convergence to a periodic orbit

- a level set of phase variable $\theta(\mathbf{x})$

on and off periodic orbit:

$$\boxed{\frac{d\theta}{dt} = \frac{2\pi}{T} \equiv \omega}$$

Initial Conditions on Same Isochron



Computation of Isochrons – Some New Methods

- **Continuation of a two point boundary value problem (2D)**
  - Osinga, M - *SIADS* 2010

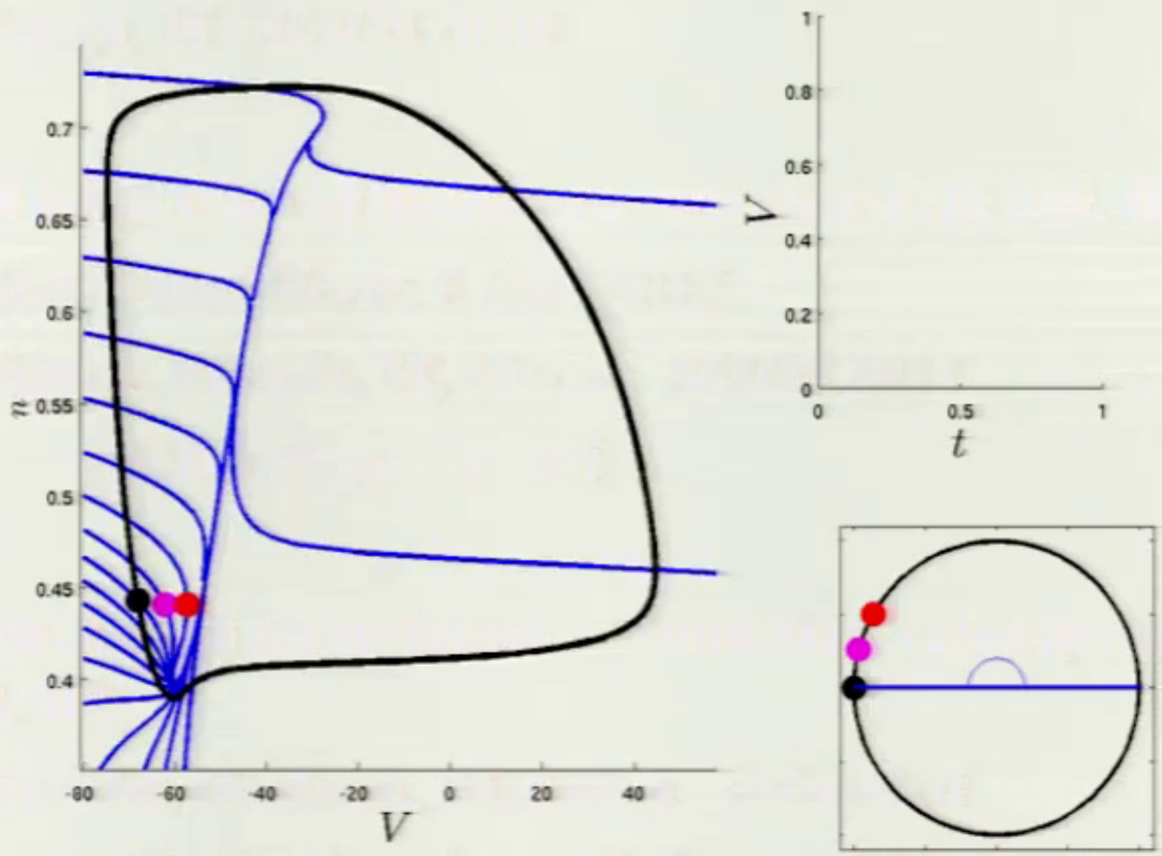
- **Spectral properties of Koopman operator (2D, 3D, 4D,…)**
  - Mauroy and Mezic, *Chaos* 2012
  - Mauroy, Rhoads, M, Mezic – *SIADS* 2014

    (3D bursting neurons)

- **Hamilton-Jacobi formulation of boundary value problem (2D, 3D, 4D,...)**
  - Detrixhe, Doubeck, M, Gibou – submitted

    (3D mixed mode oscillations, 4D Hodgkin-Huxley model)

Initial Conditions on Different Isochrons



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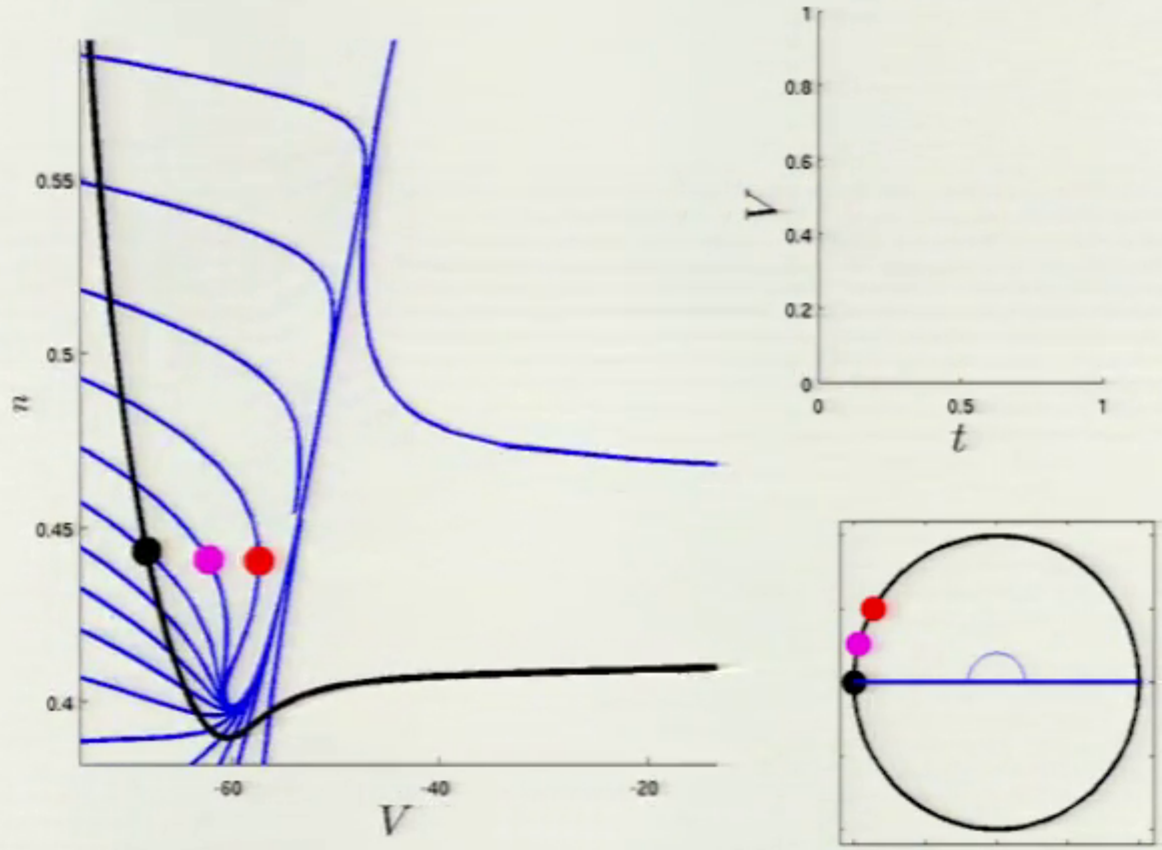

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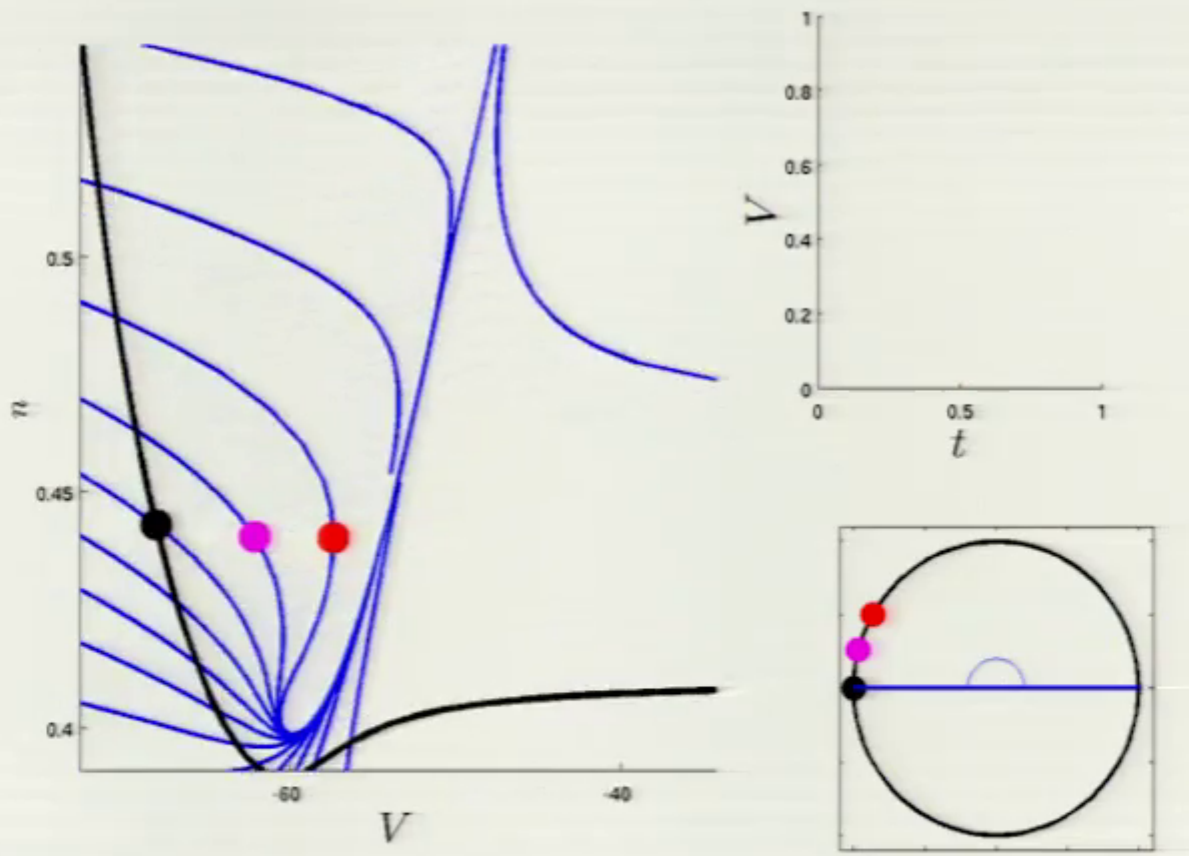

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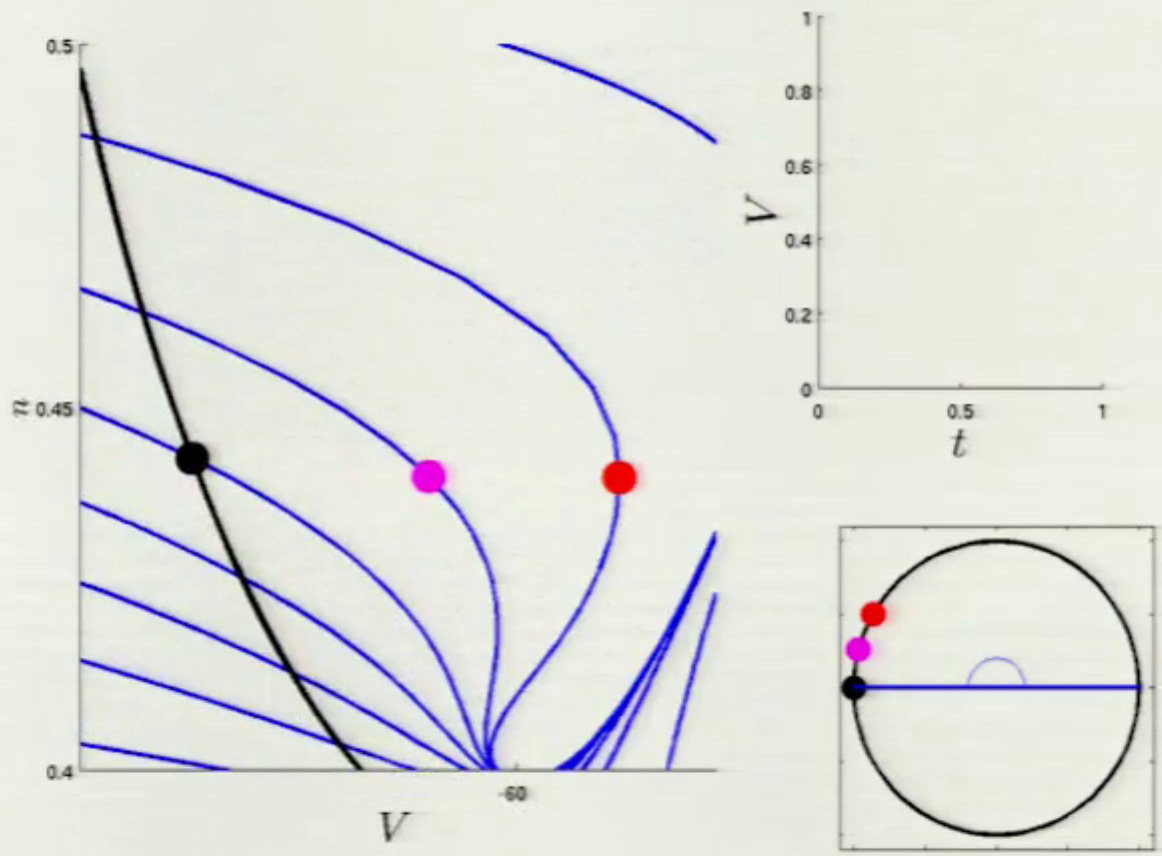

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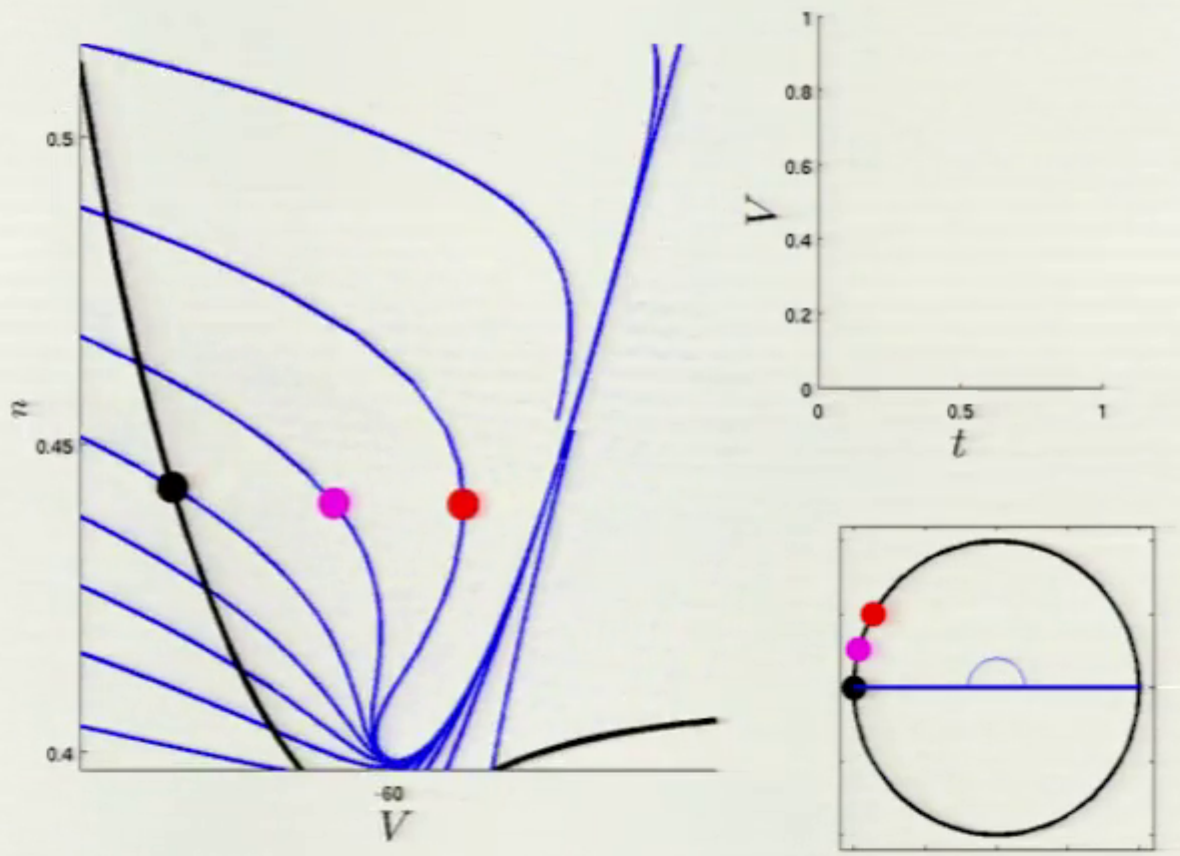

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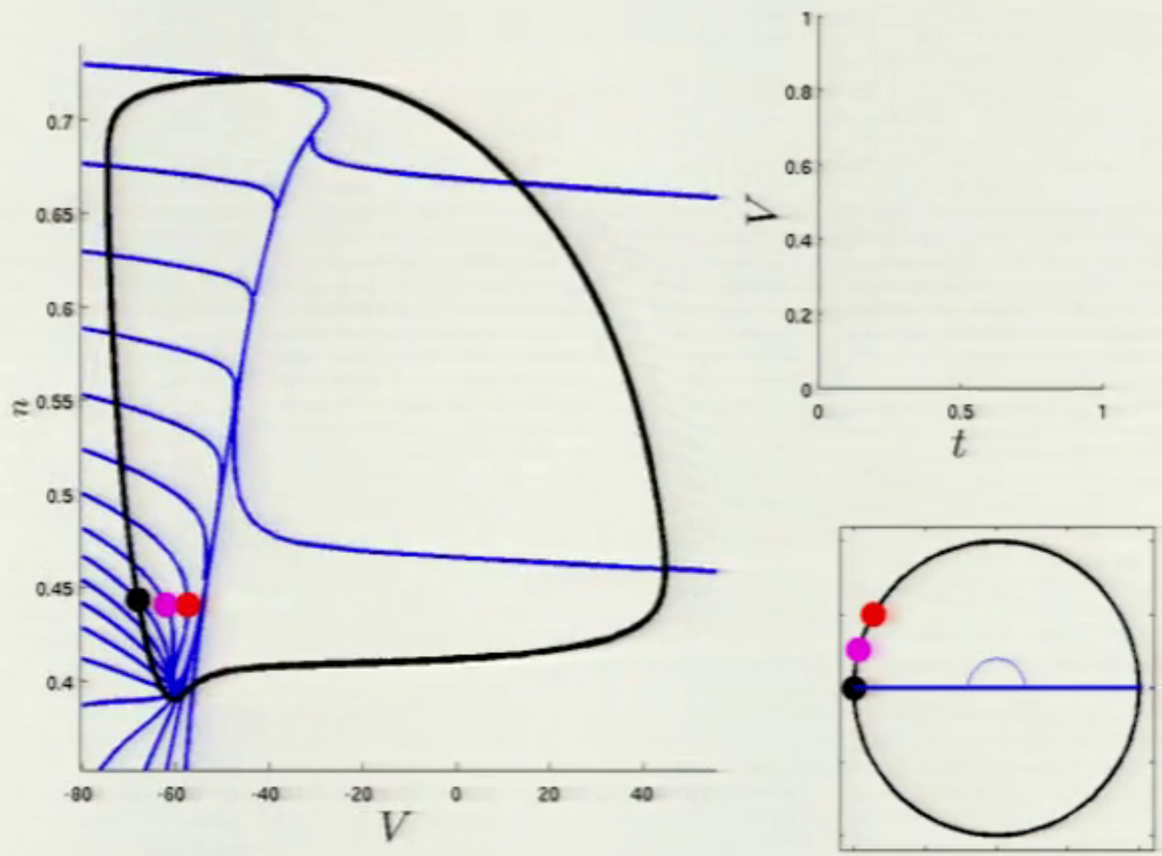

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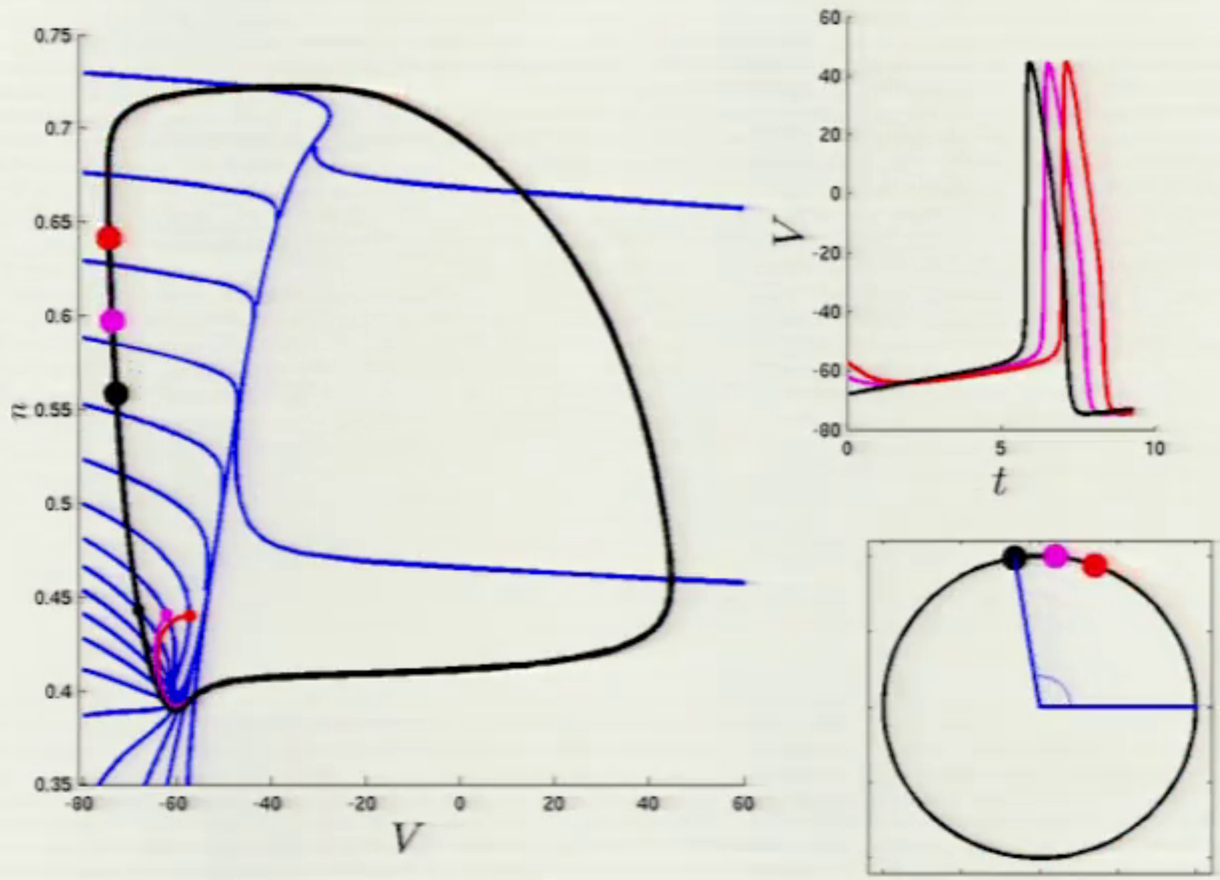

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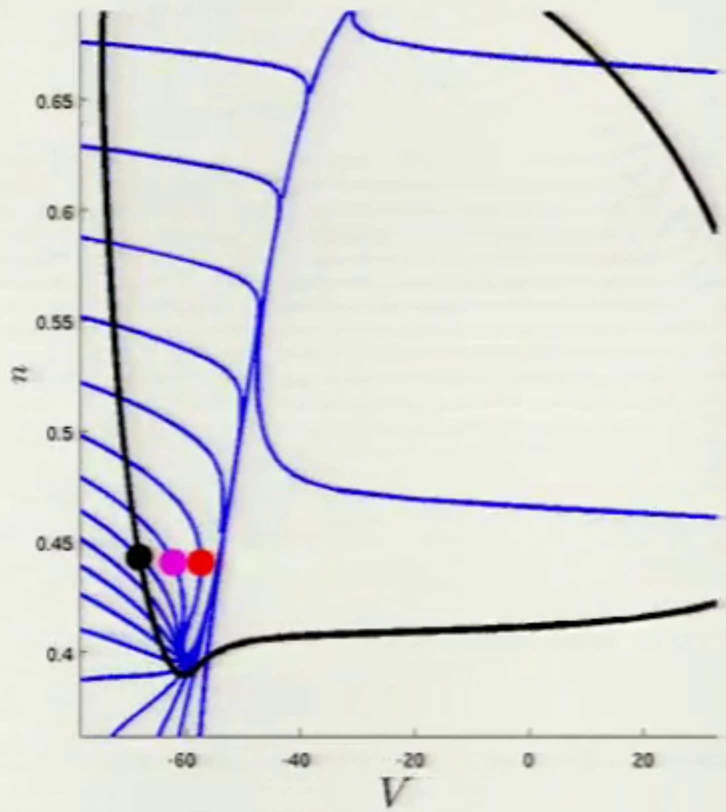

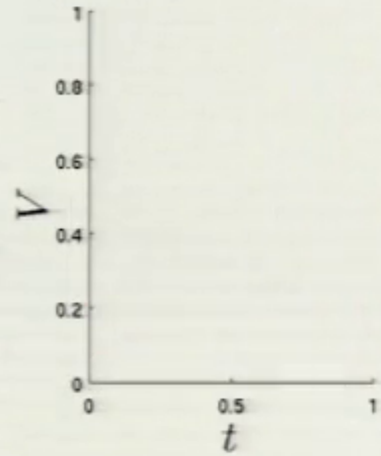

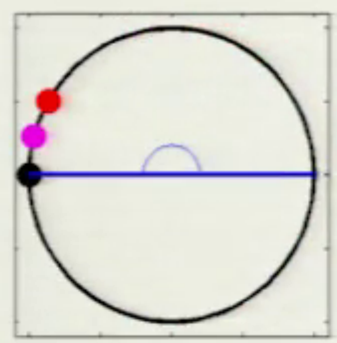

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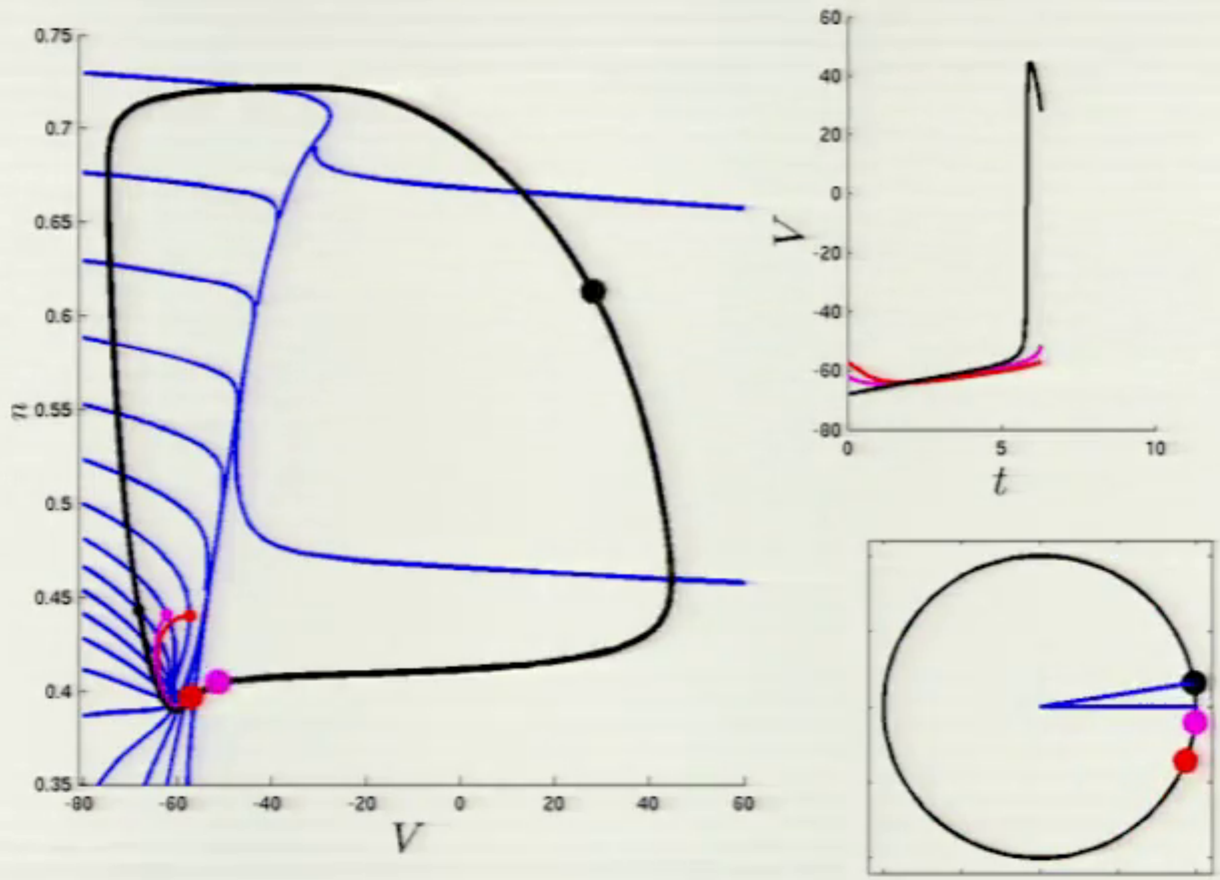

Optimal Chaotic Desync

Phase model:

$$\frac{d\theta_i}{dt} = \omega + Z(\theta_i)u(t), \quad i = 1, 2,$$

where $Z(\theta)$ **is phase response curve,** $u(t)$ **is input current.**

Let $\phi \equiv |\theta_2 - \theta_1|$**:**

$$\frac{d\phi}{dt} = Z'(\theta)u(t)\phi + \mathcal{O}(\phi^2),$$

$$\Rightarrow \qquad \phi(t) \sim e^{\Lambda(t)t}, \qquad \Lambda(\tau) = \frac{\log(\phi(\tau))}{\tau} = \frac{\int_a^{a+\tau} Z'(\theta(s))u(s)ds}{\tau}.$$

Here $\Lambda(\tau)$ **is the Lyapunov exponent for time** τ**.**

Wilson, M - *SIADS* 2014

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Optimal Chaotic Desync

Use calculus of variations to minimize (with $\beta > 0$)

$$C[u(t)] = \int_0^{t_1} \left\{ u(t)^2 - \beta Z'(\theta)u(t) + \lambda \left(\frac{d\theta}{dt} - \omega - Z(\theta)u(t) \right) \right\} dt$$

This gives the two point boundary value problem

$$\dot{\theta} = Z(\theta)[\beta Z'(\theta) + \lambda Z(\theta)]/2 + \omega$$

$$\dot{\lambda} = -[\beta Z'(\theta) + \lambda Z(\theta)][\beta Z''(\theta) + \lambda Z'(\theta)]/2$$

$$\theta(0) = 0, \qquad \theta(t_1) = \omega t_1$$

$$\boxed{u(t) = [\beta Z'(\theta) + \lambda Z(\theta)]/2}$$

If average voltage exceeds threshold, apply this $u(t)$

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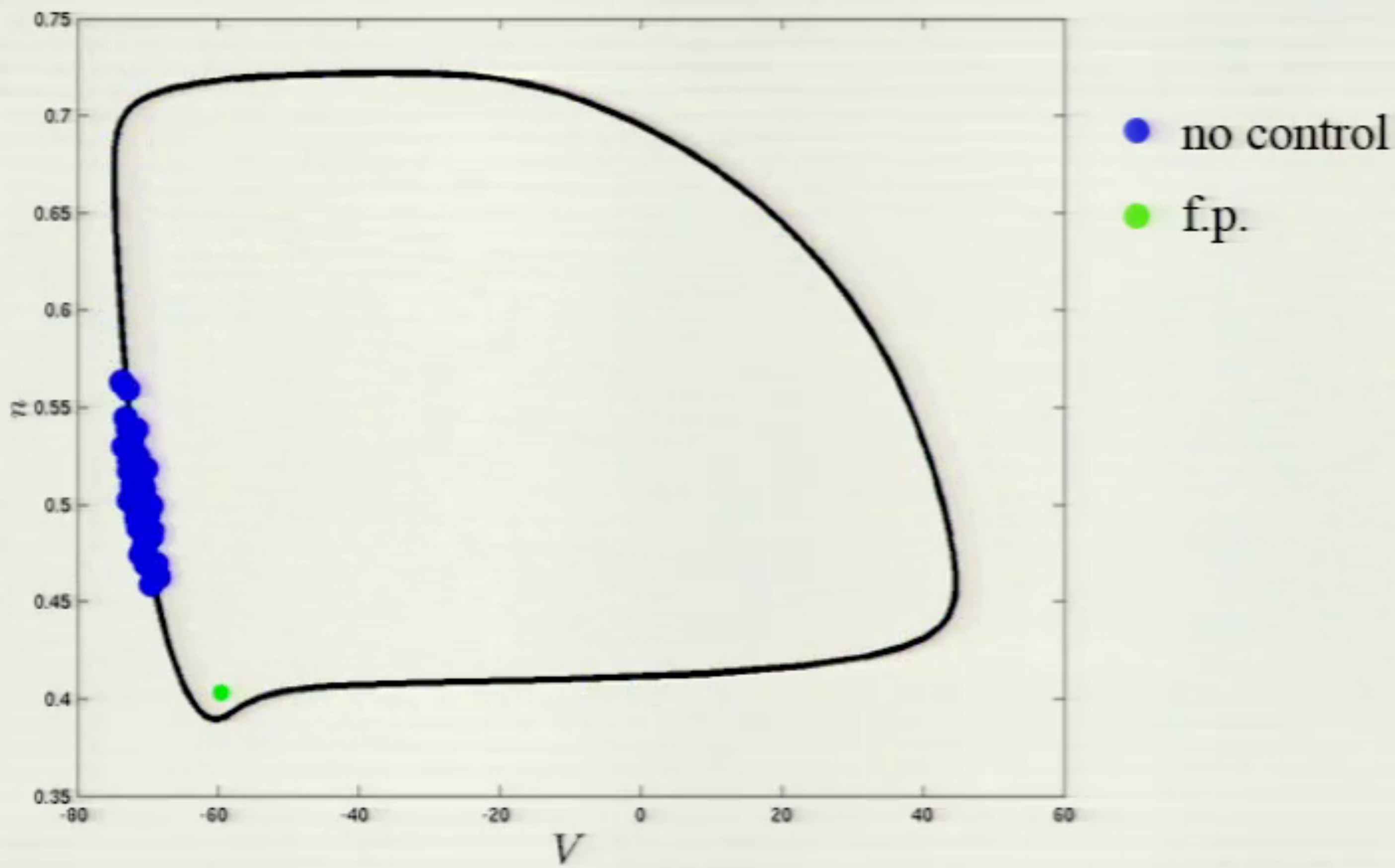
Coupled, Noisy Neurons – No Control



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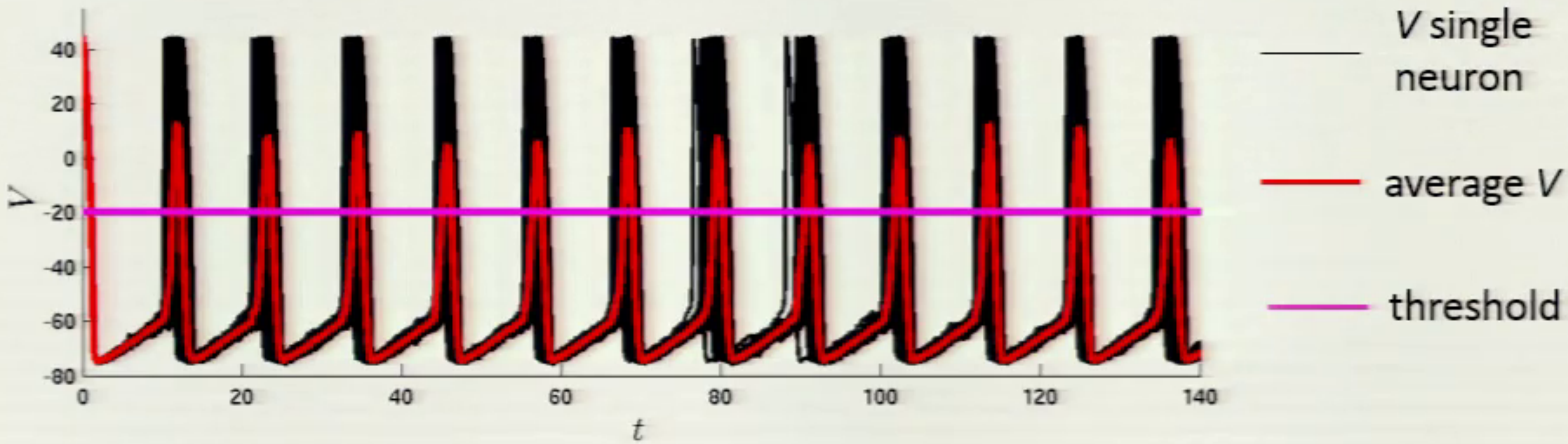
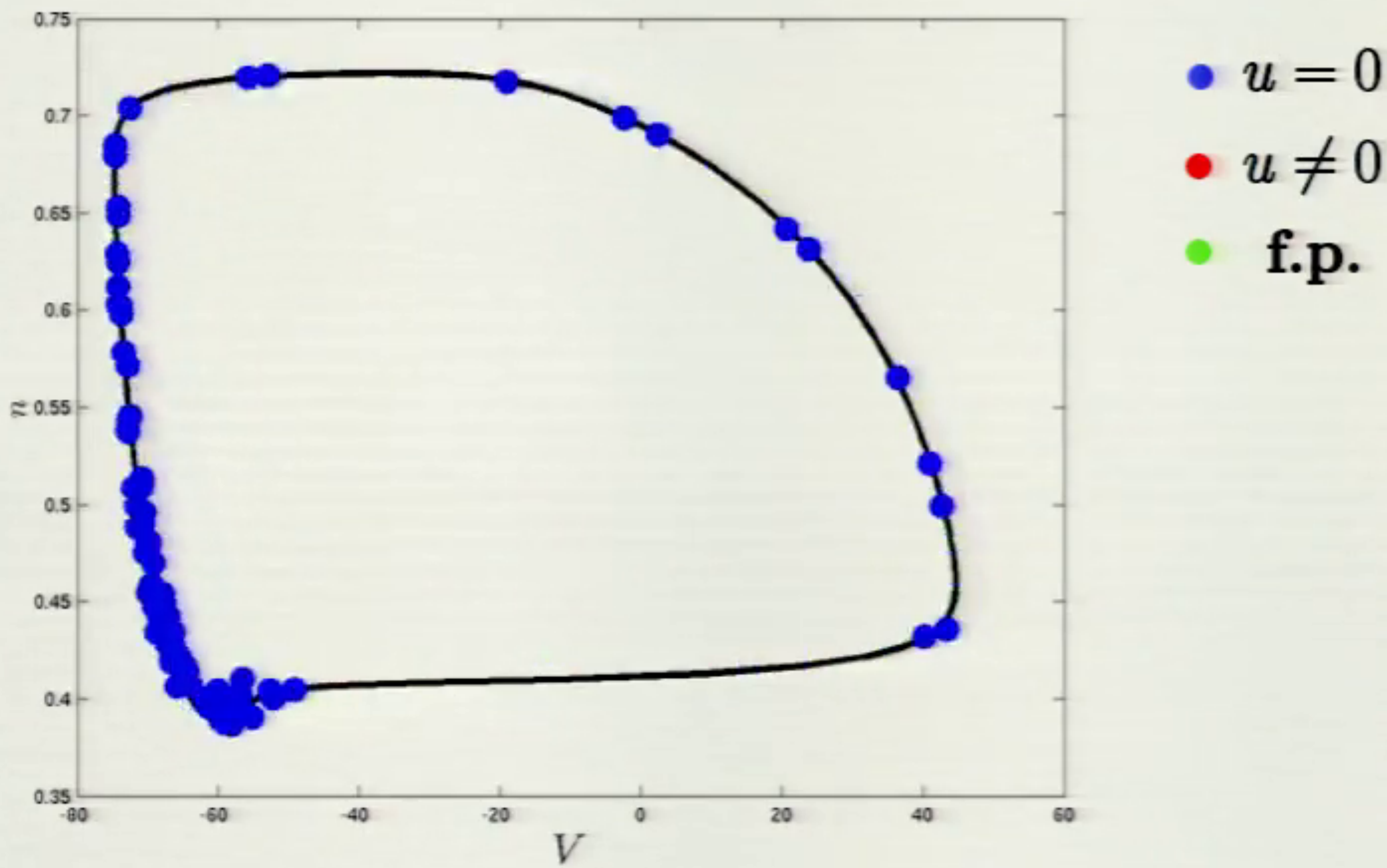


Coupled, Noisy Neurons – Chaotic Desync



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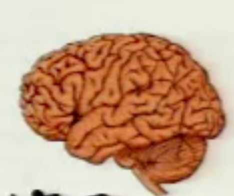

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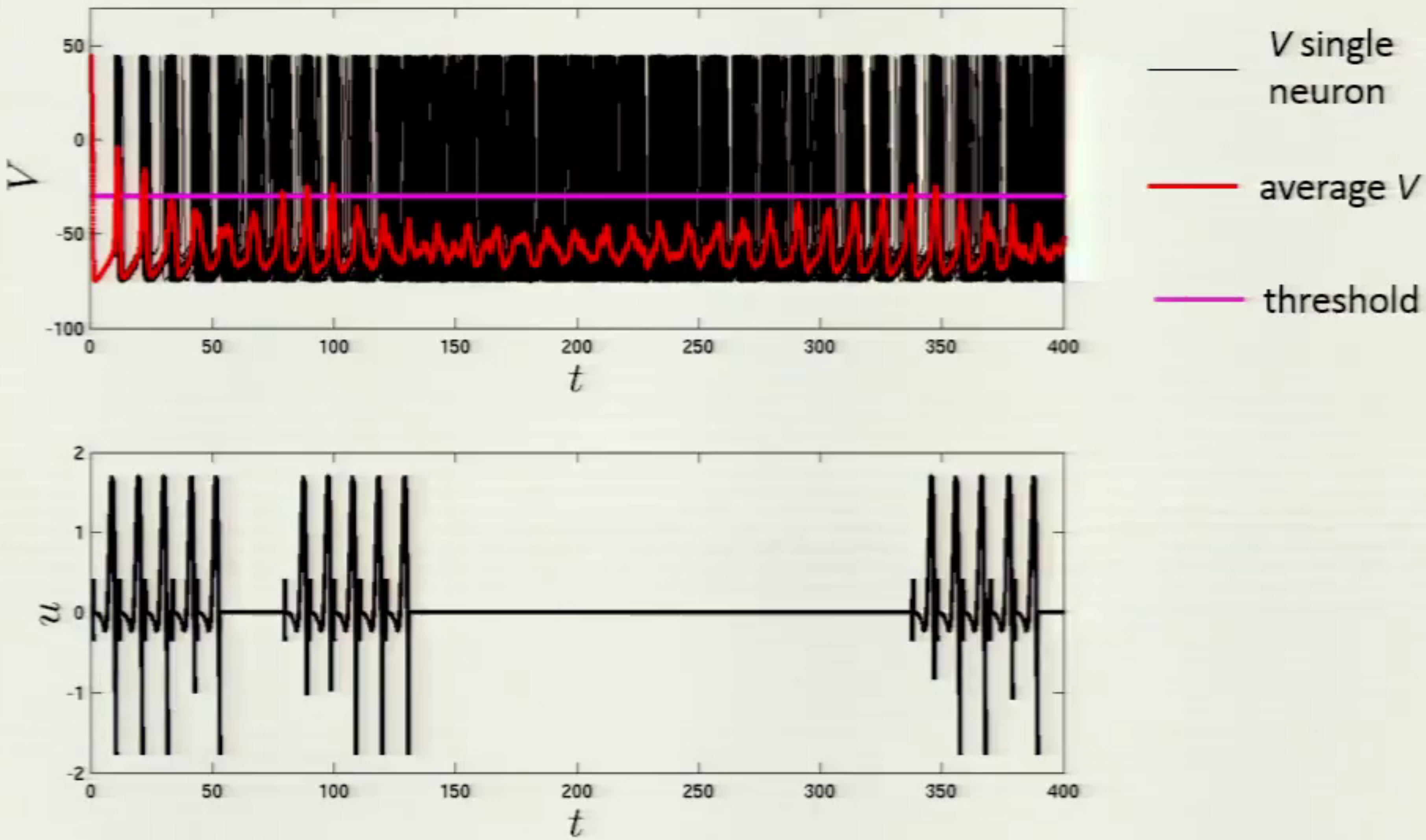

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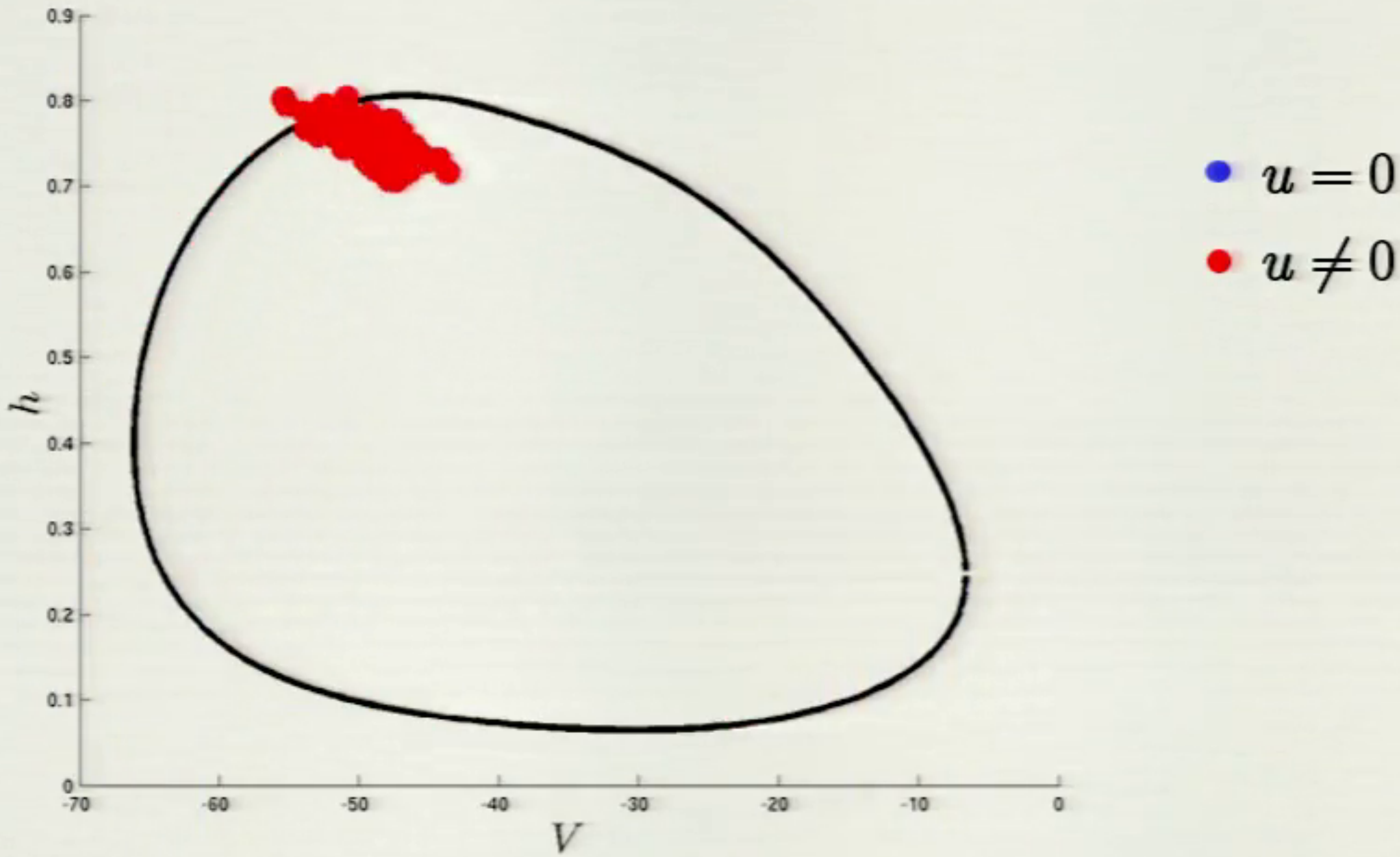
Chaotic Desync of Thalamic Neurons



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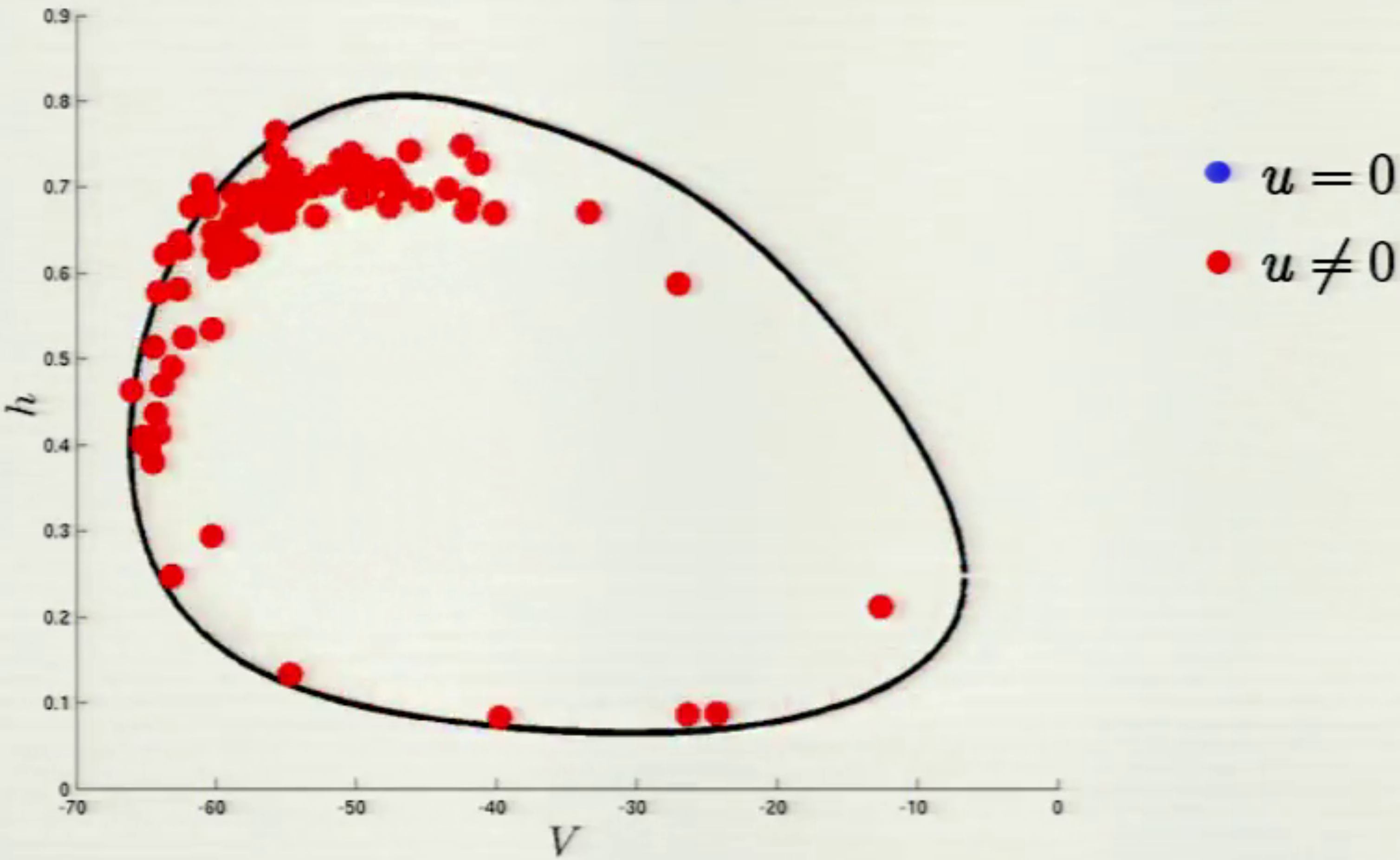

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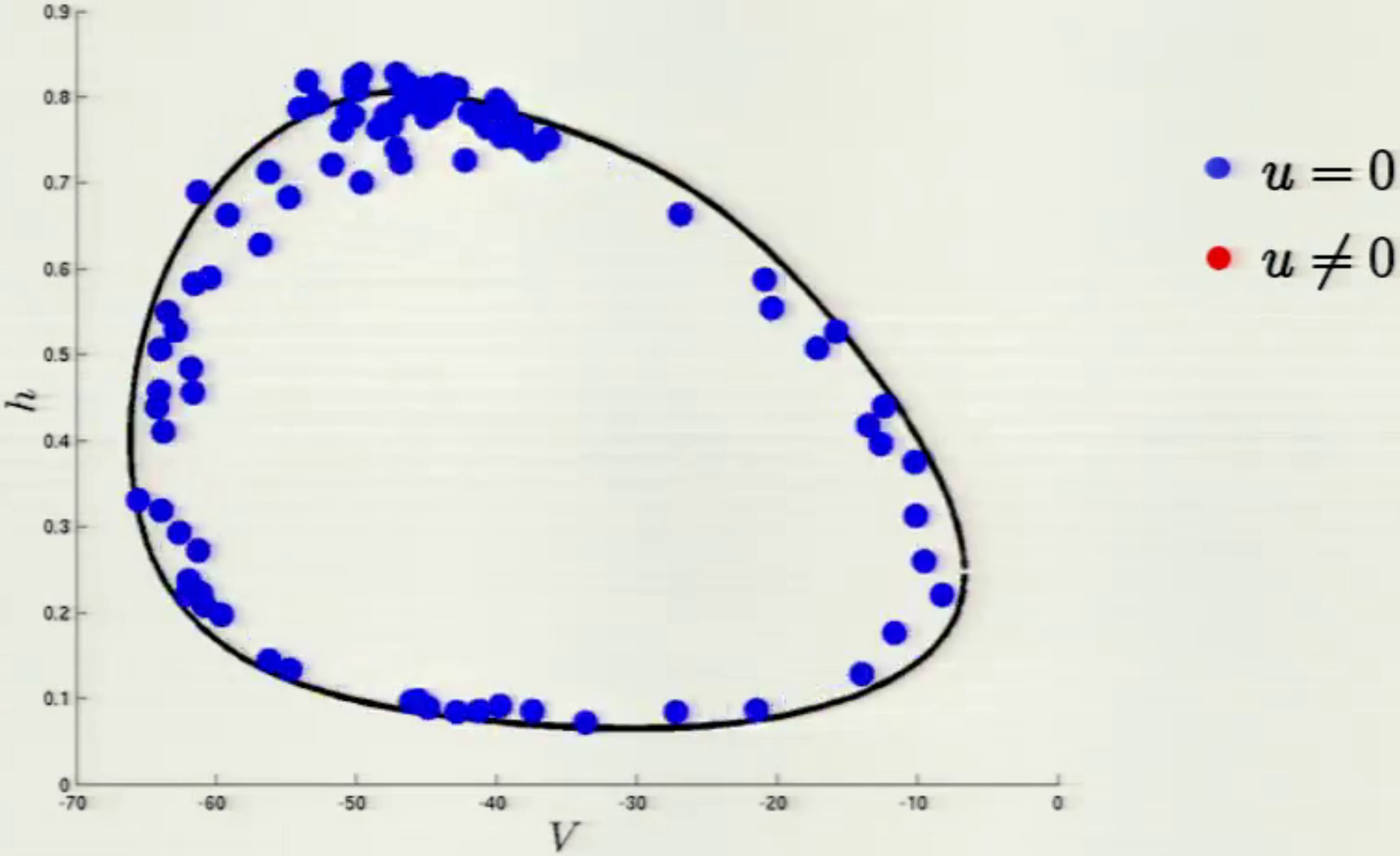

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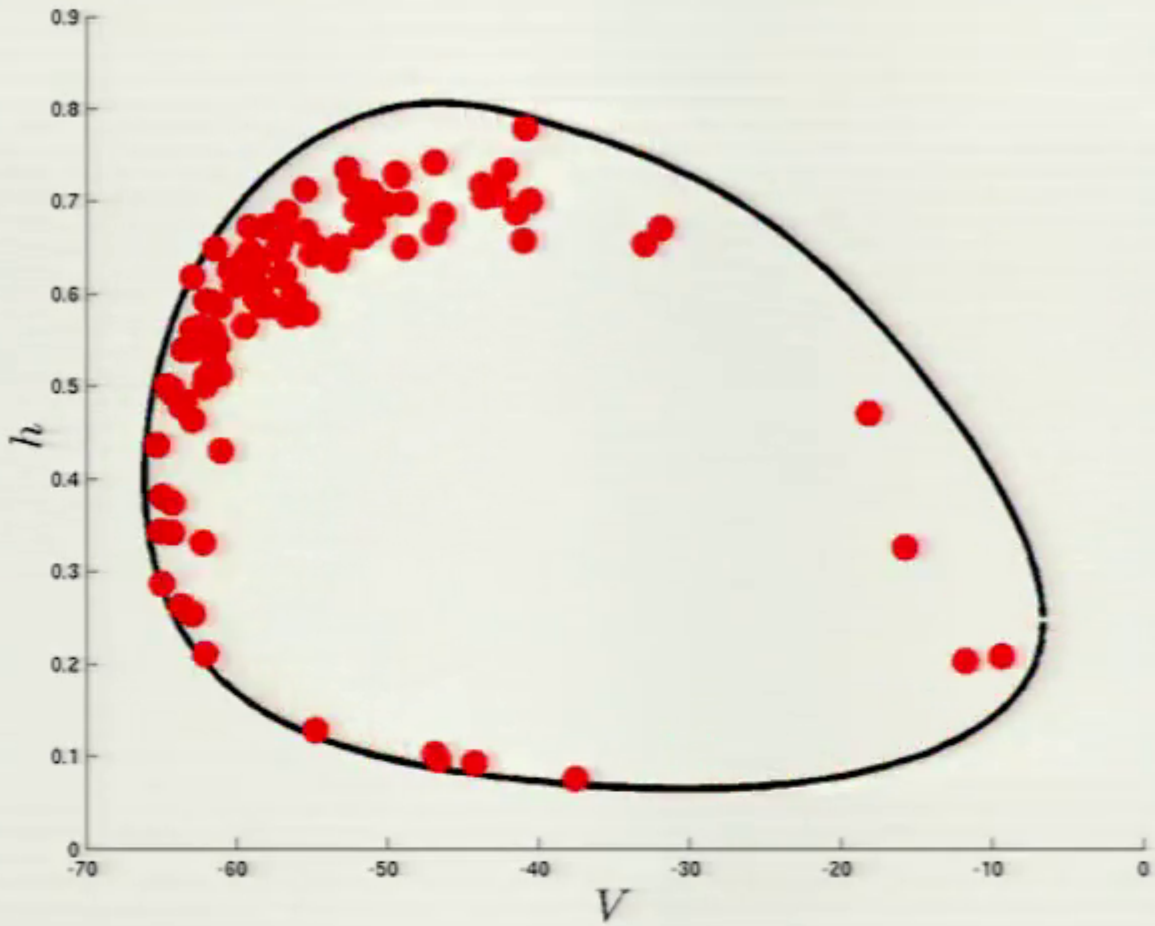

$u = 0$

$u \neq 0$

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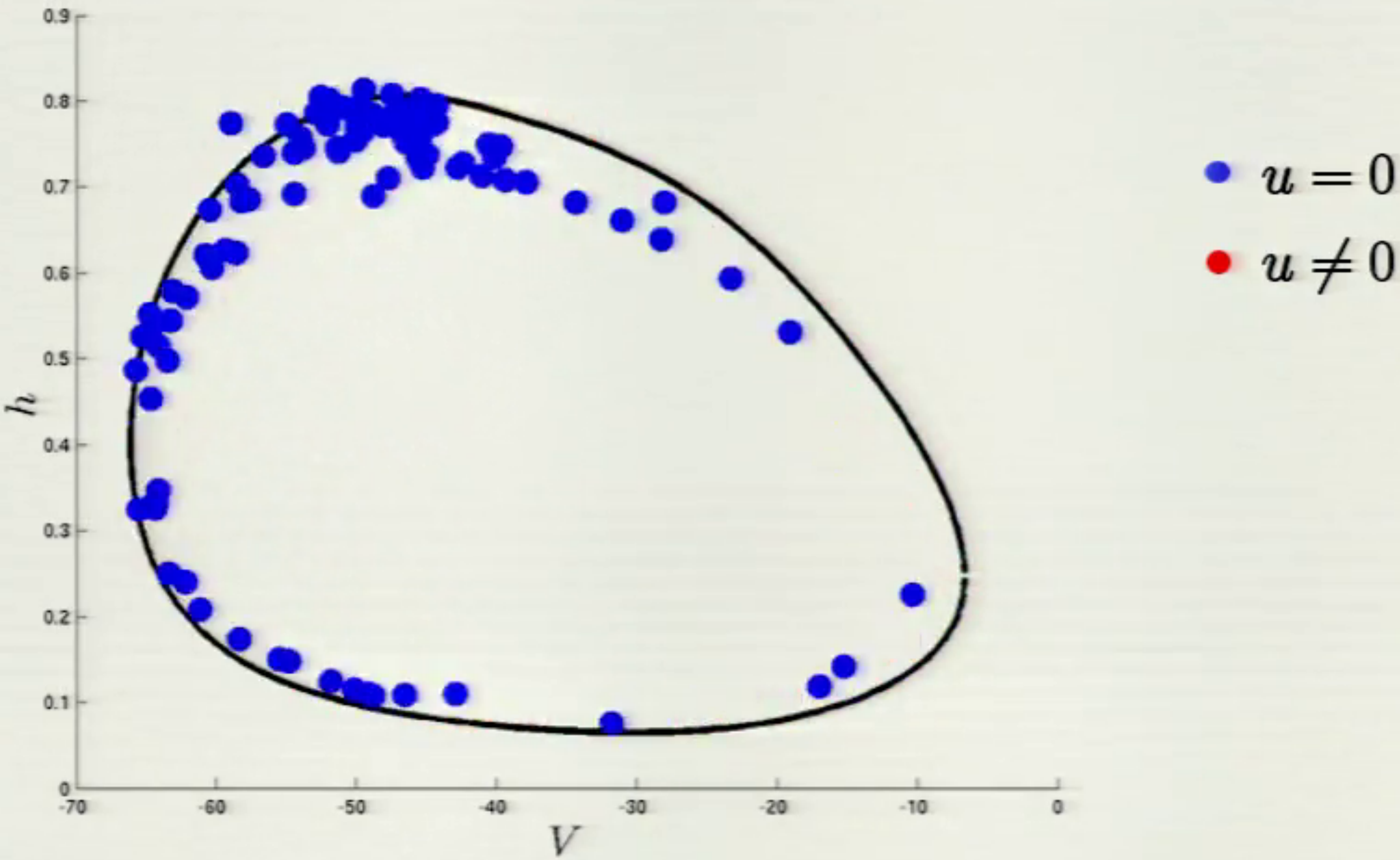

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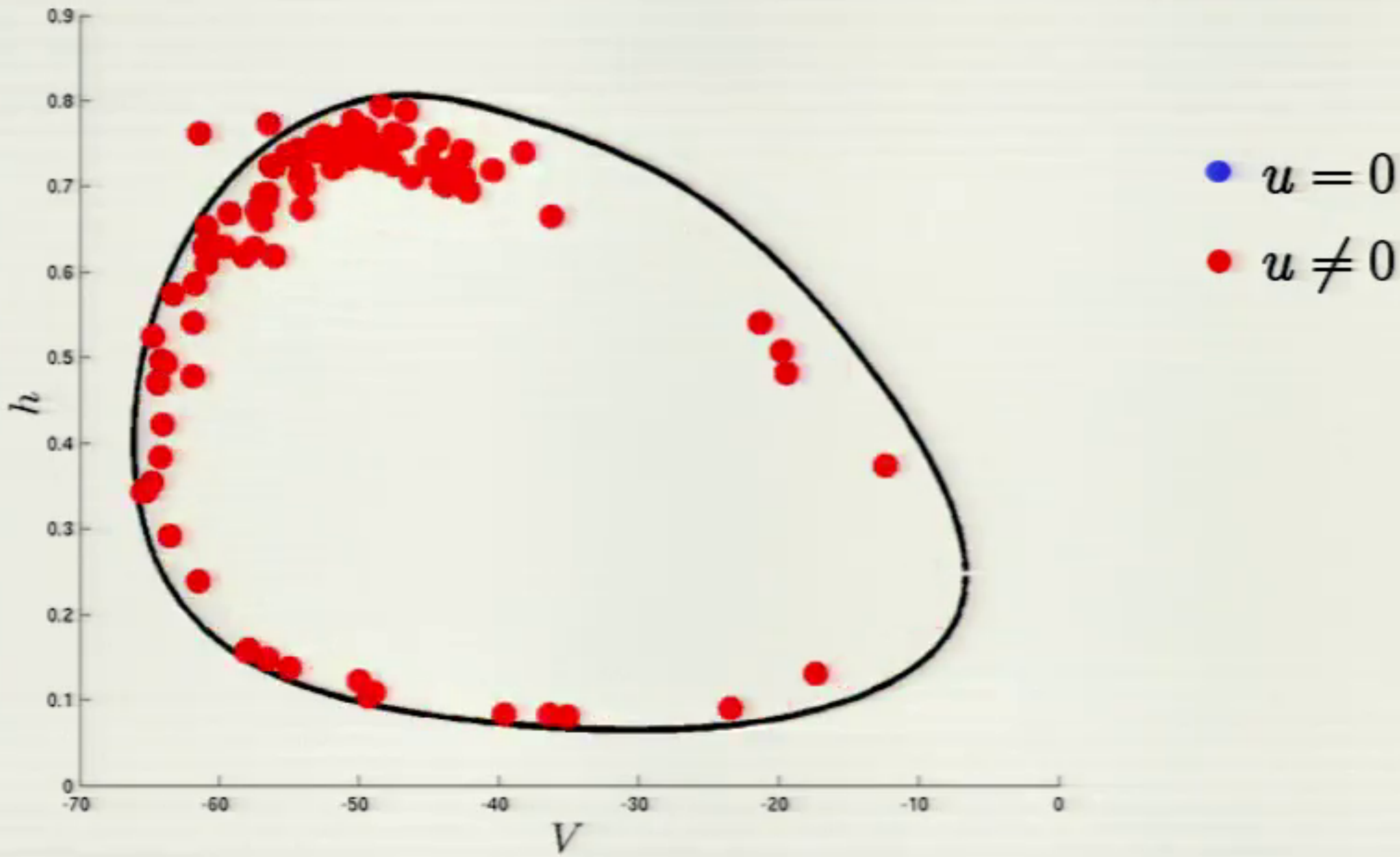

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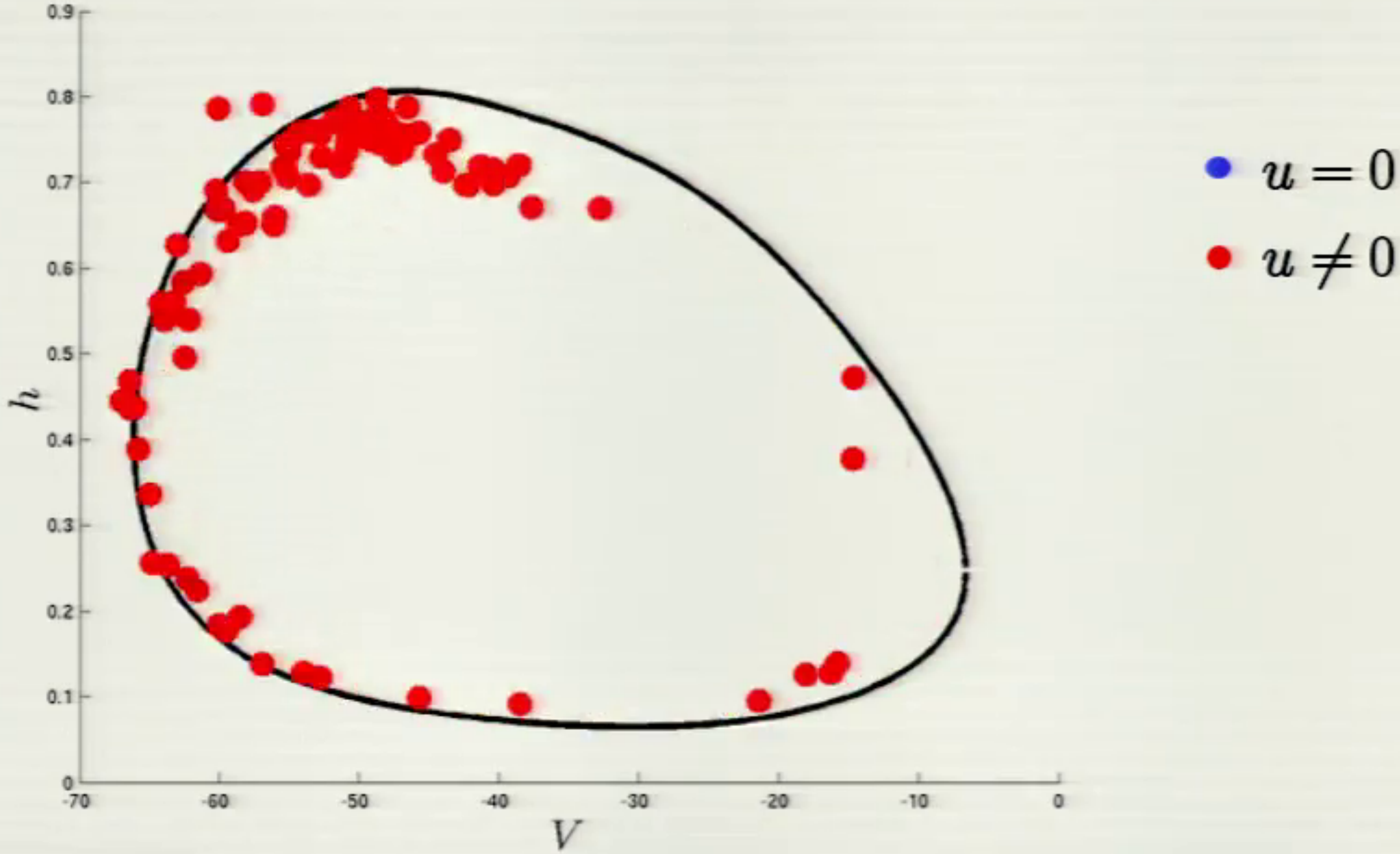

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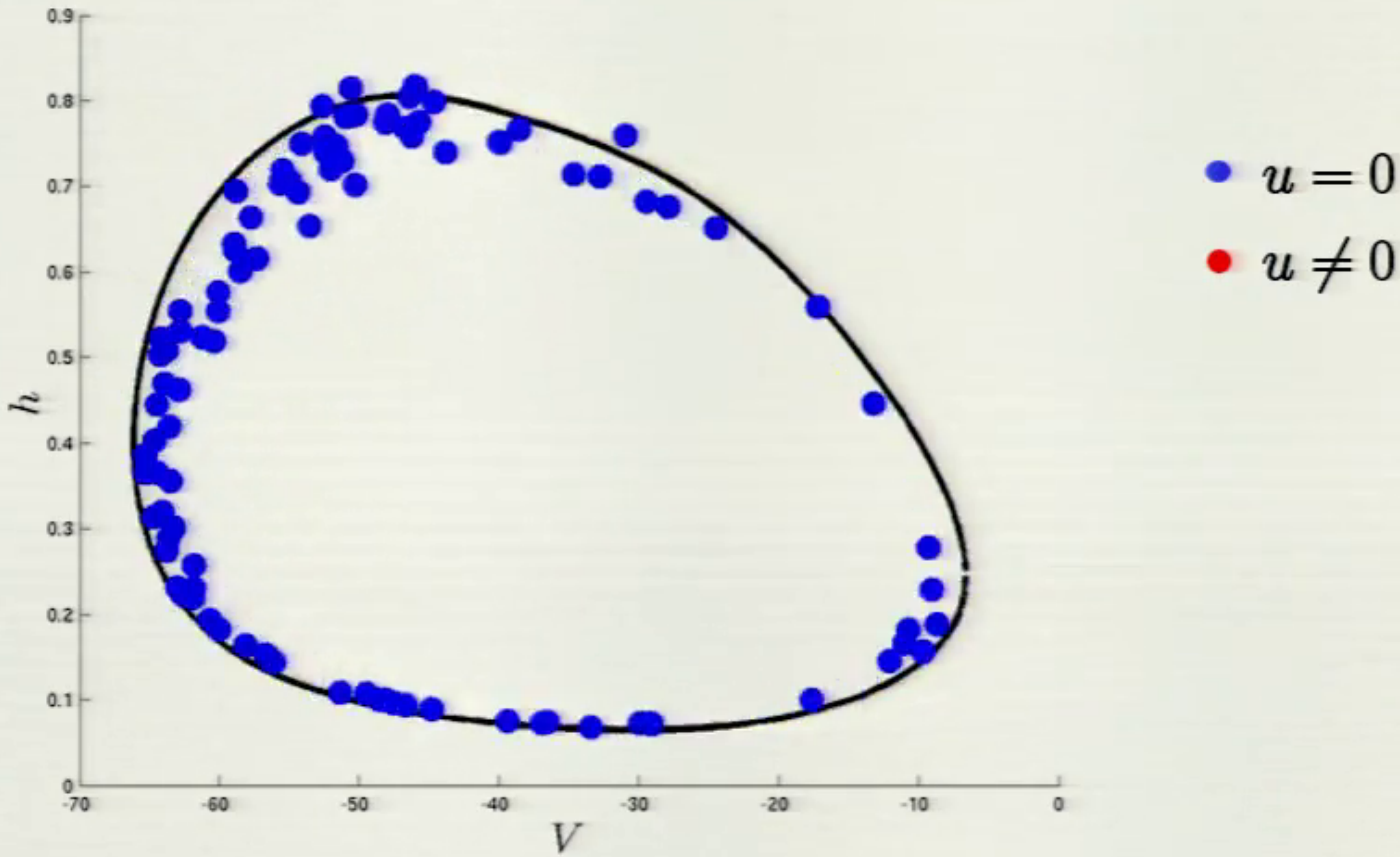

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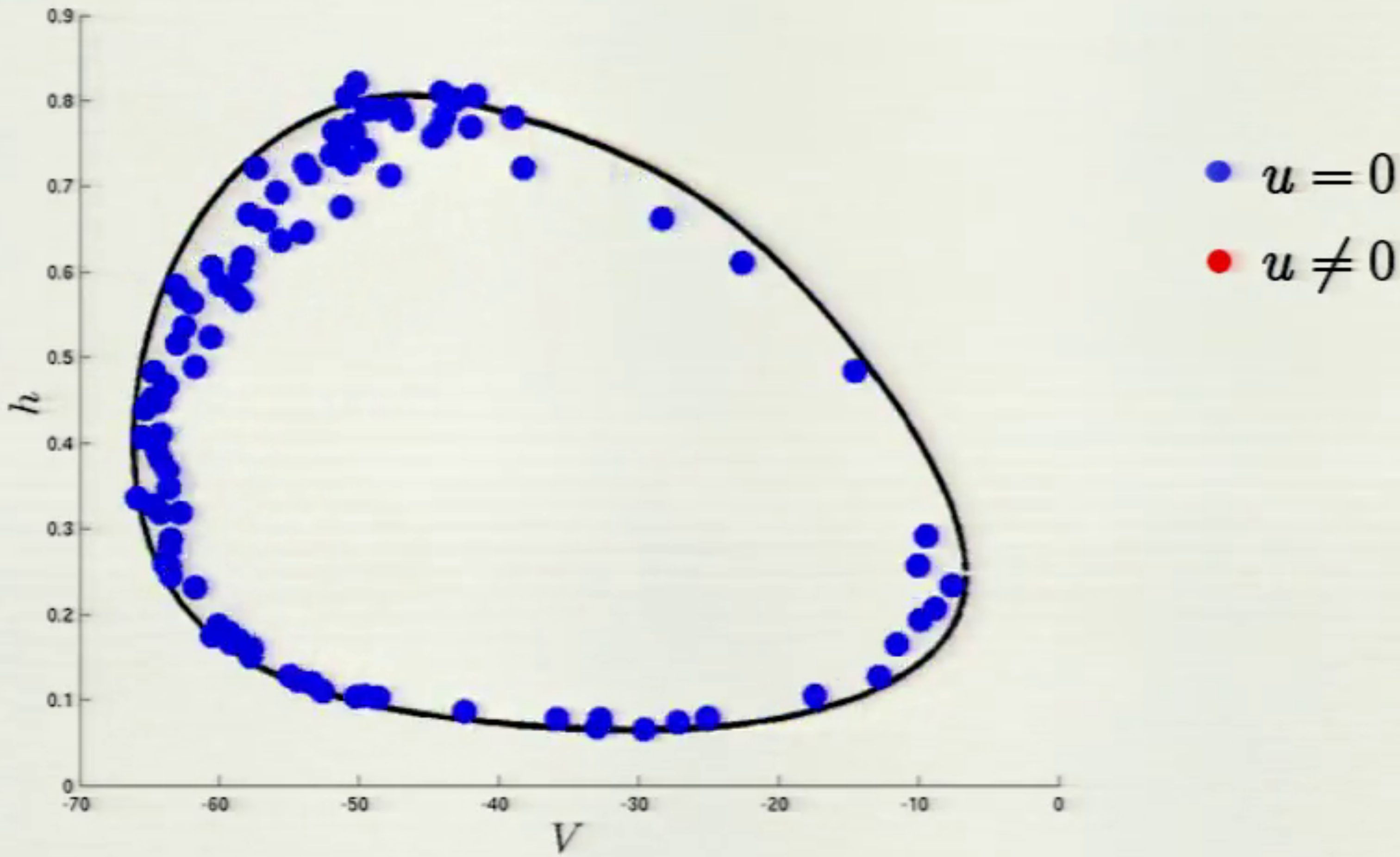

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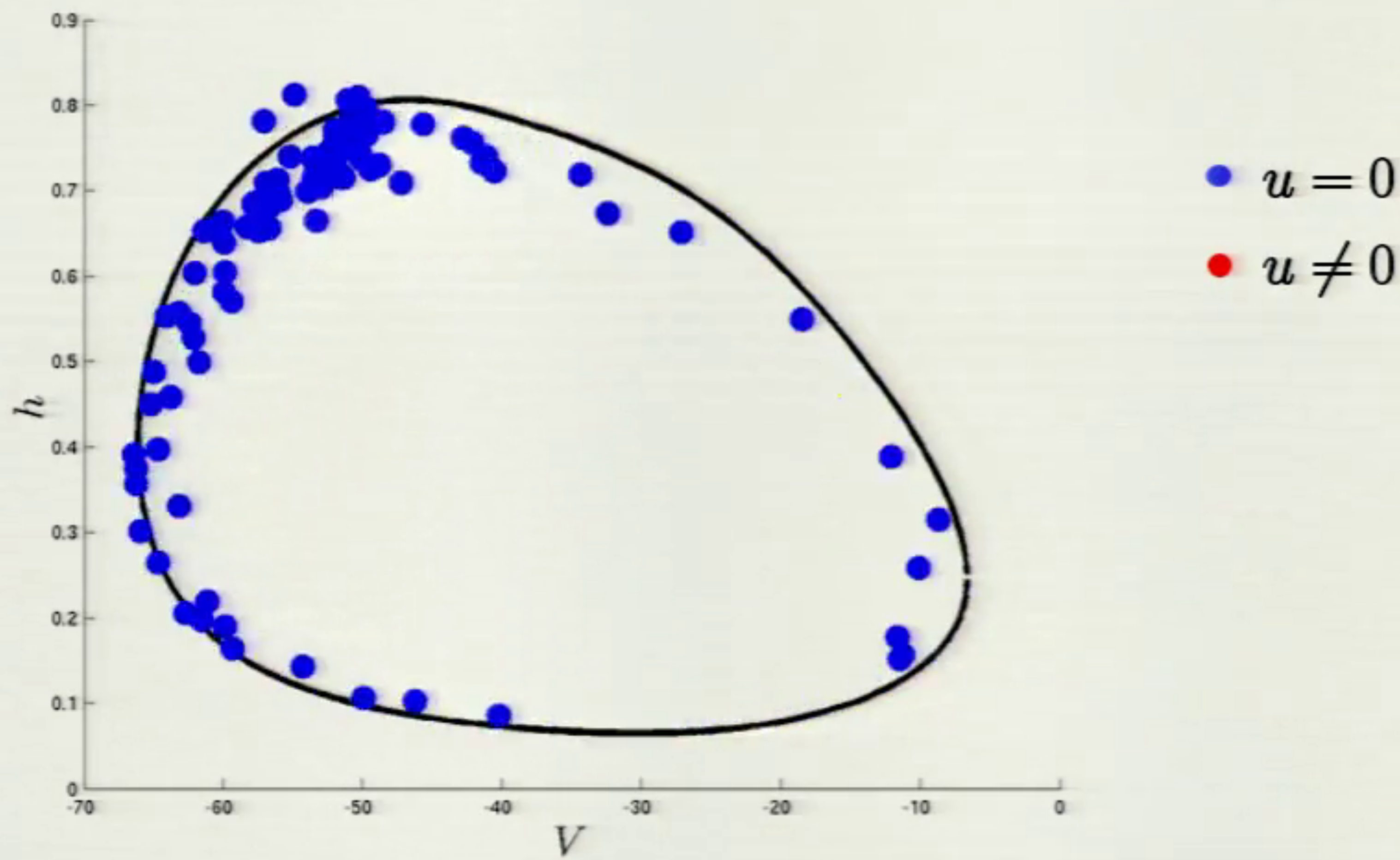

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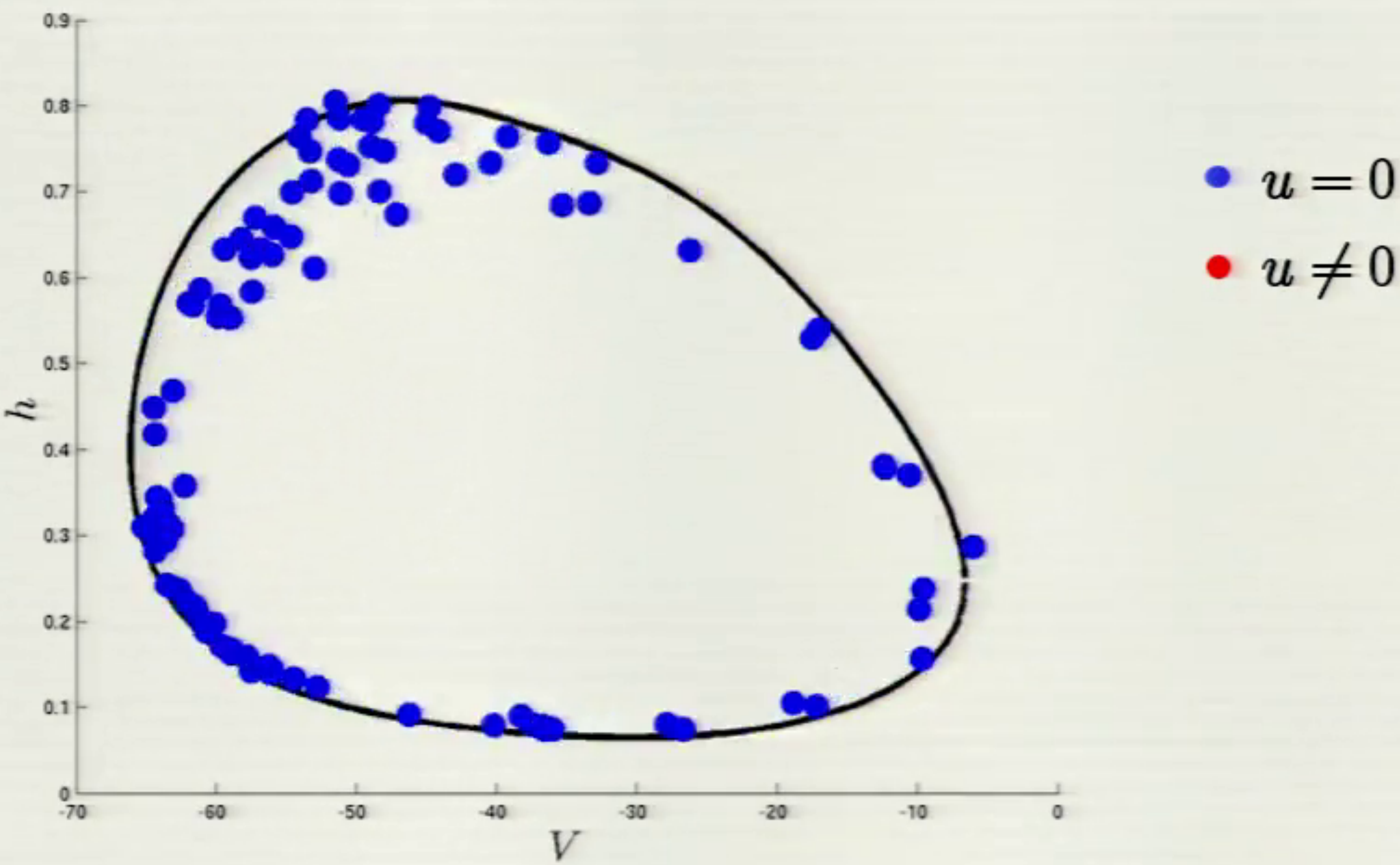

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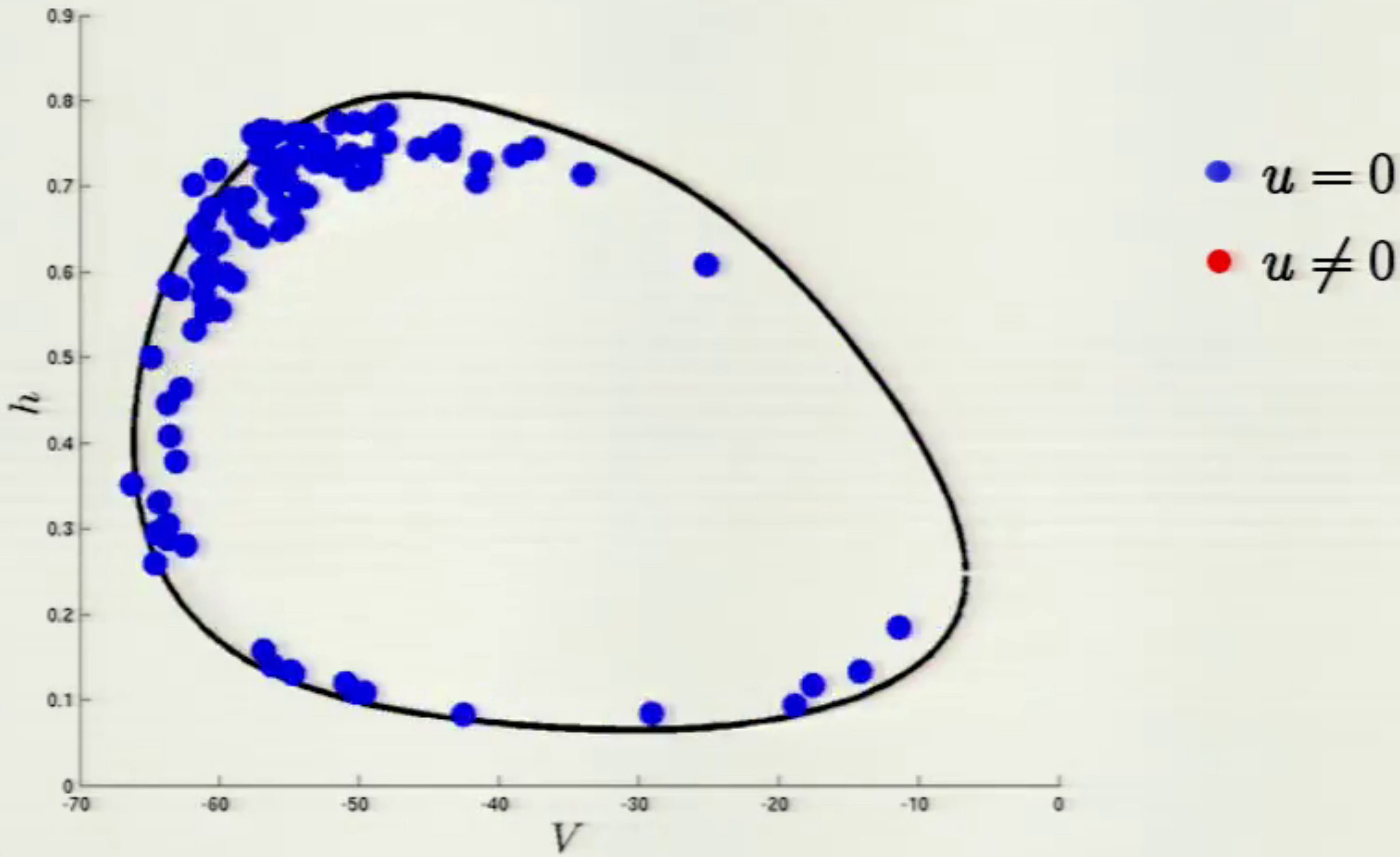

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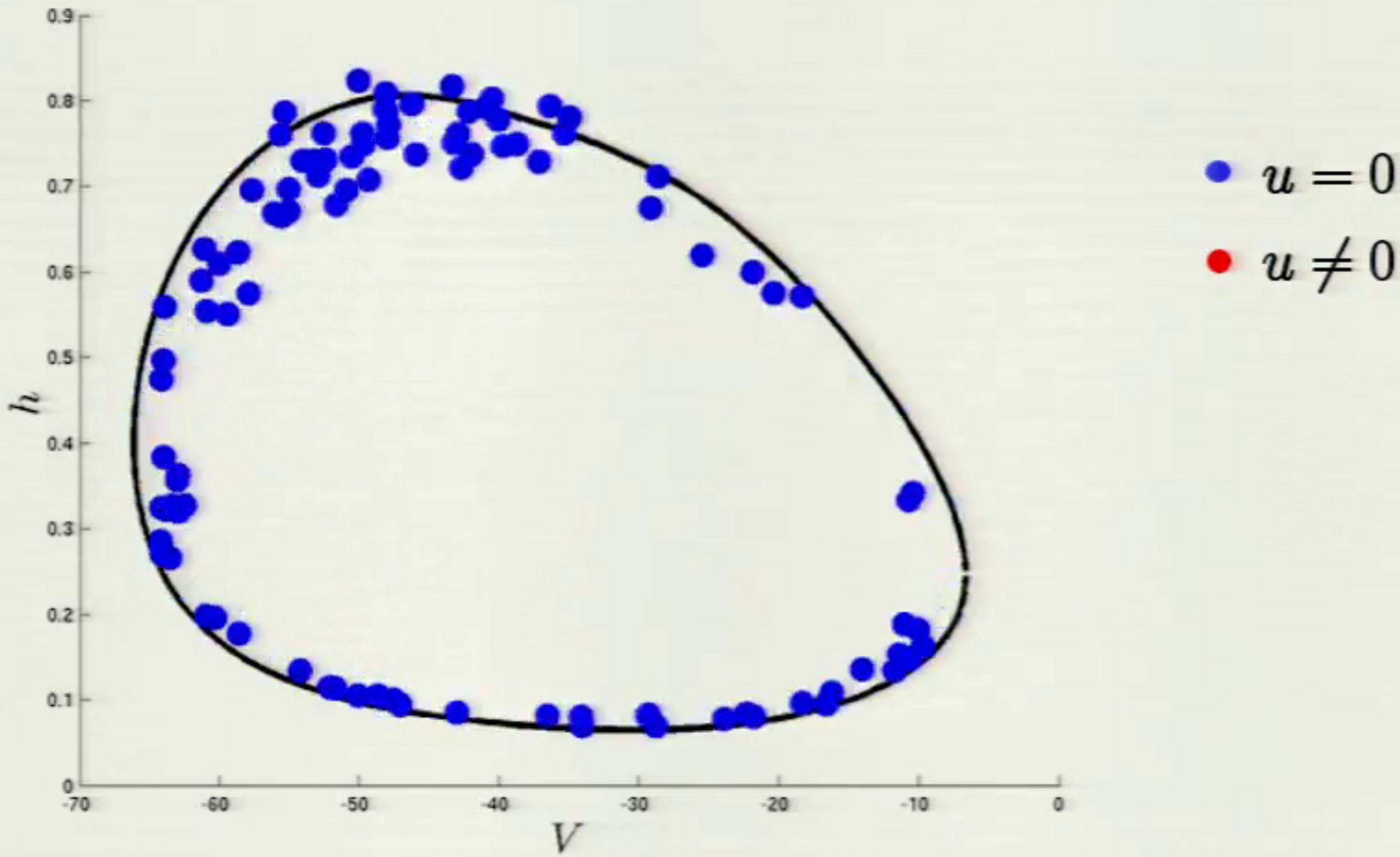

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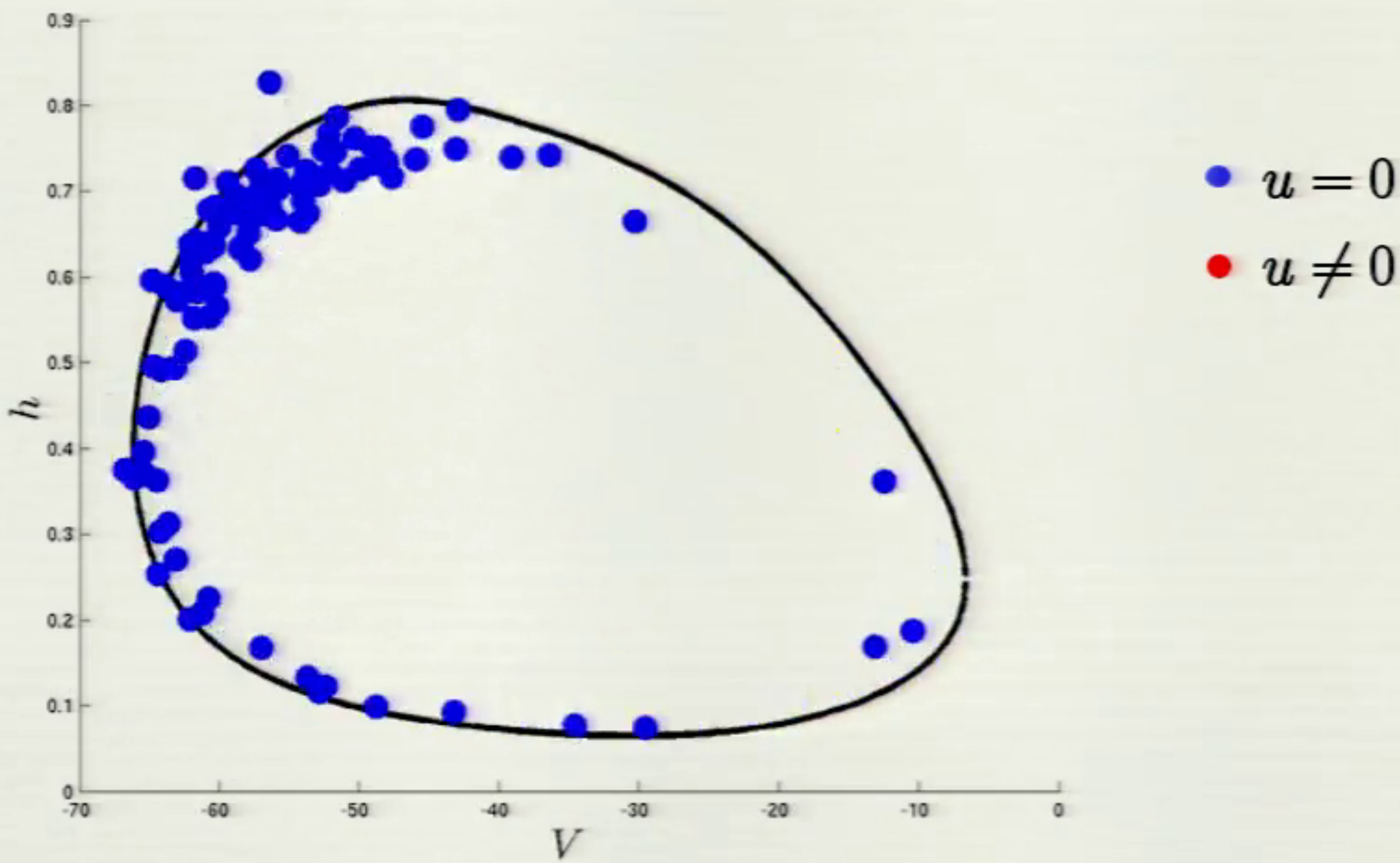

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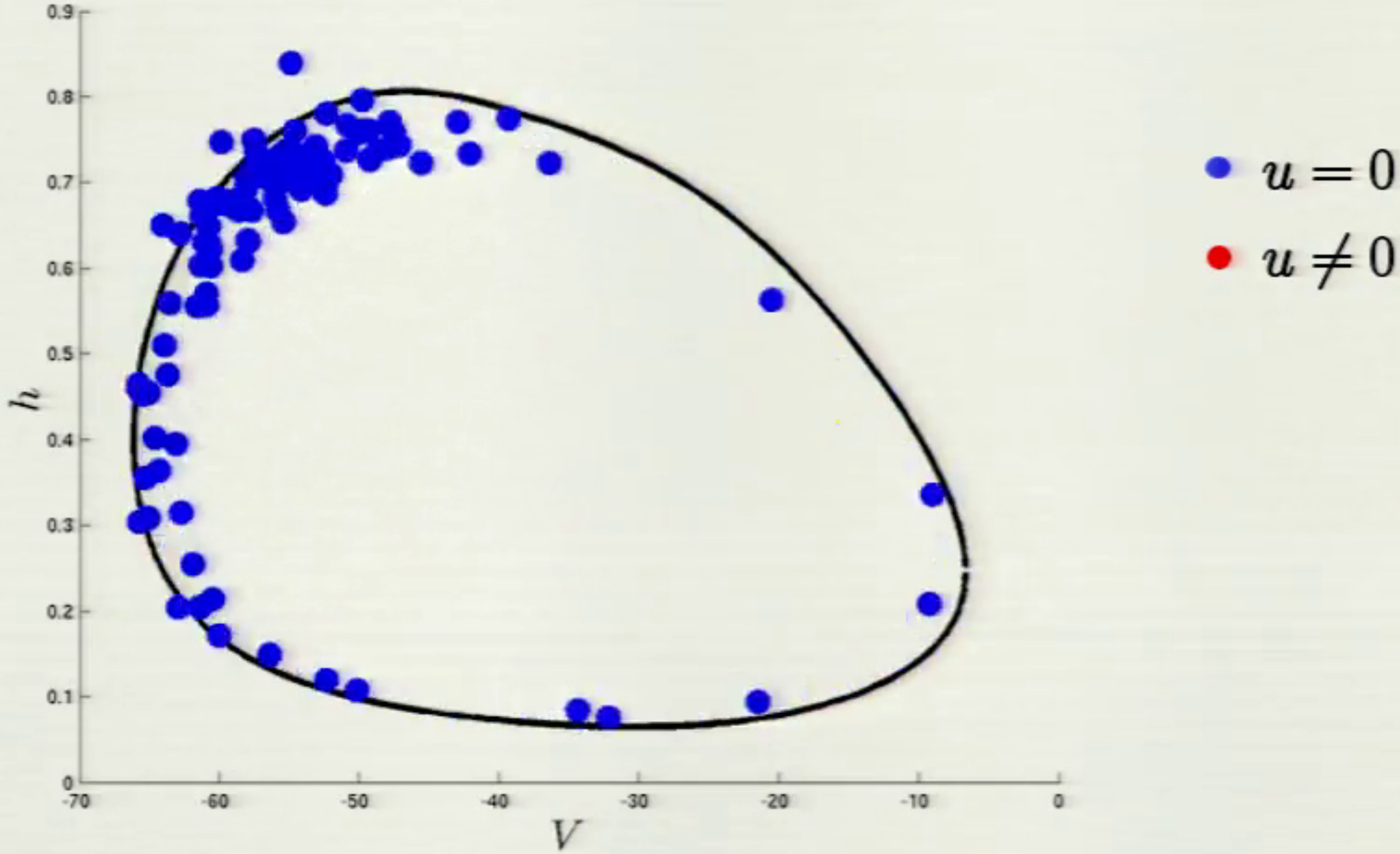

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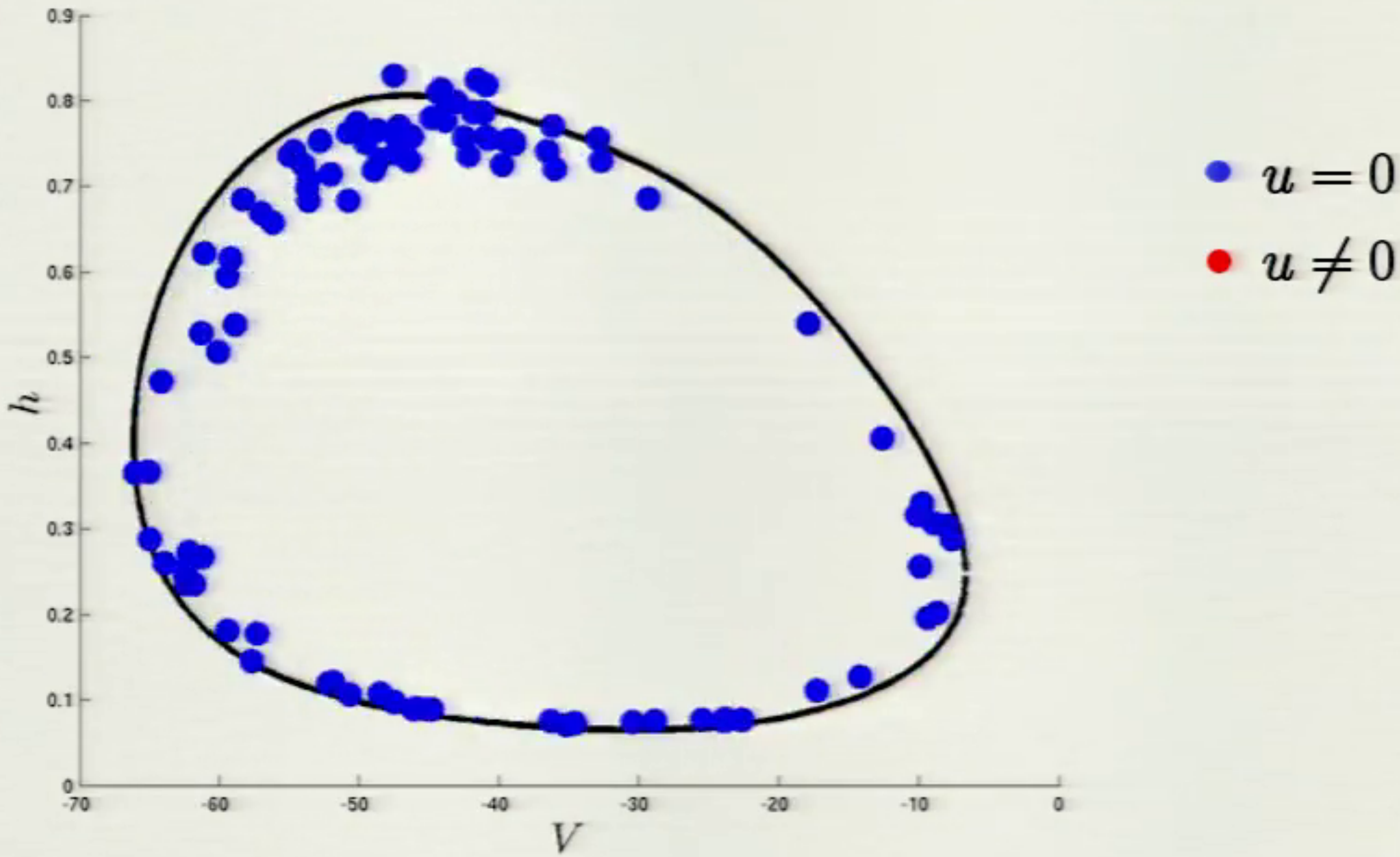

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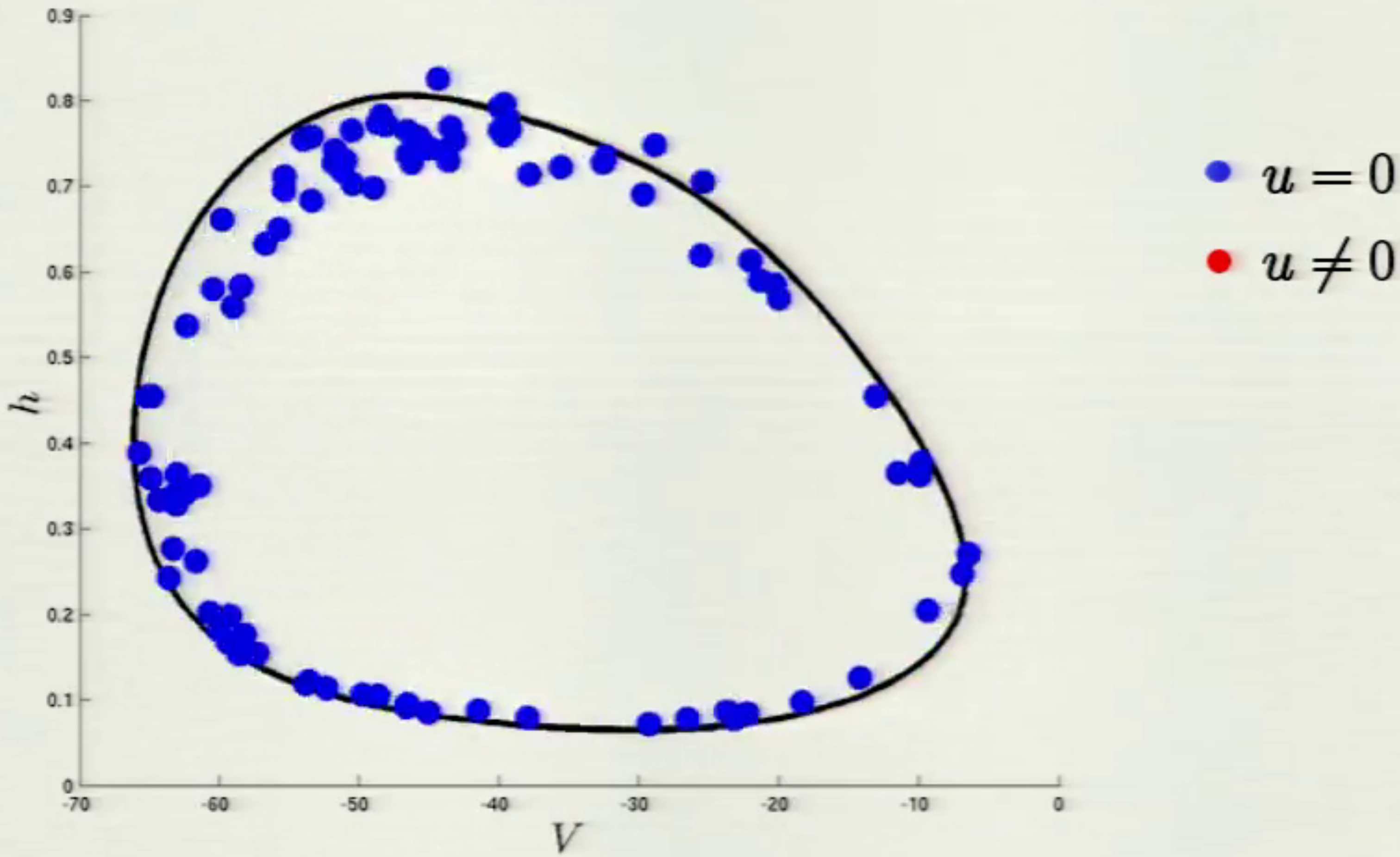

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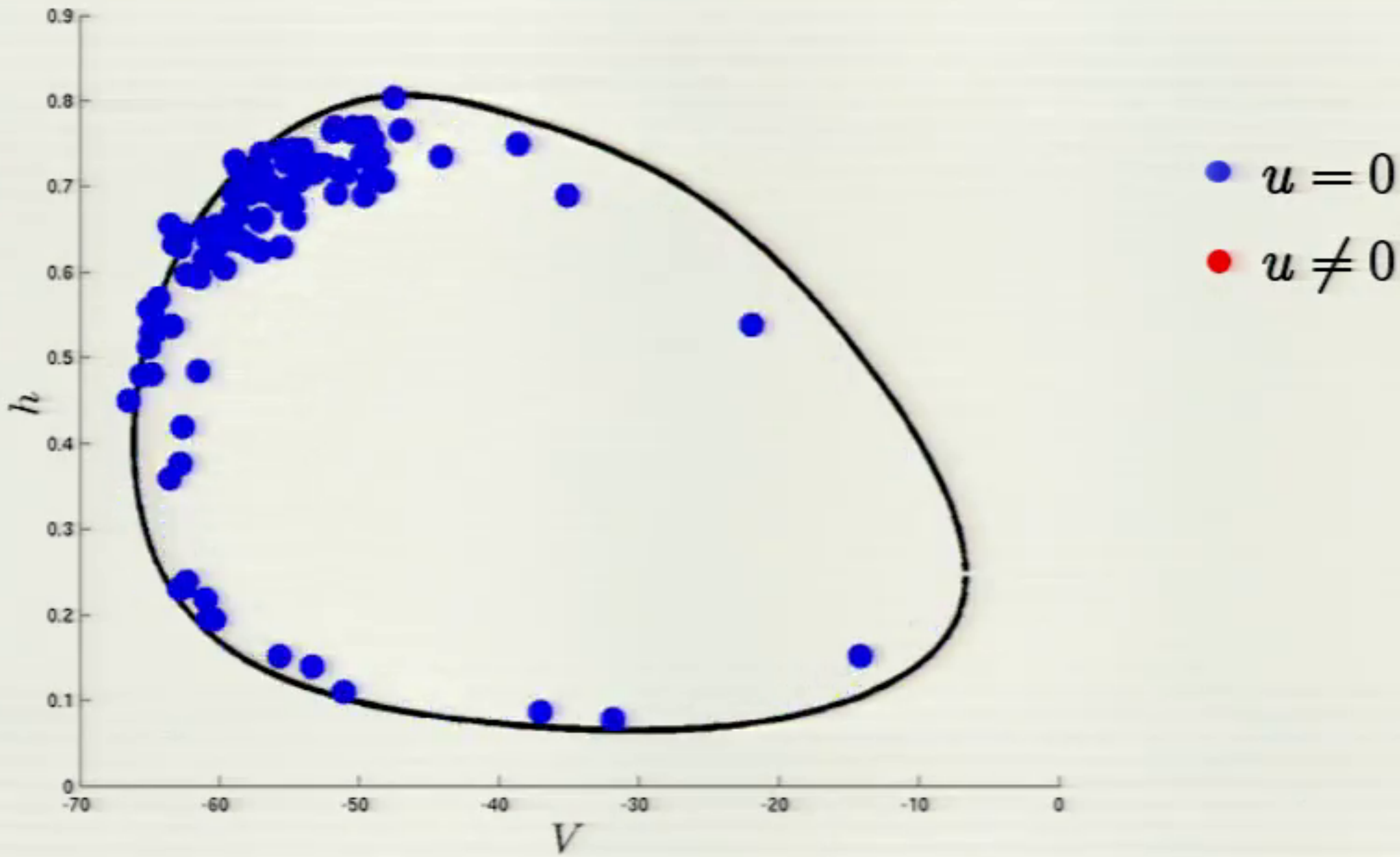

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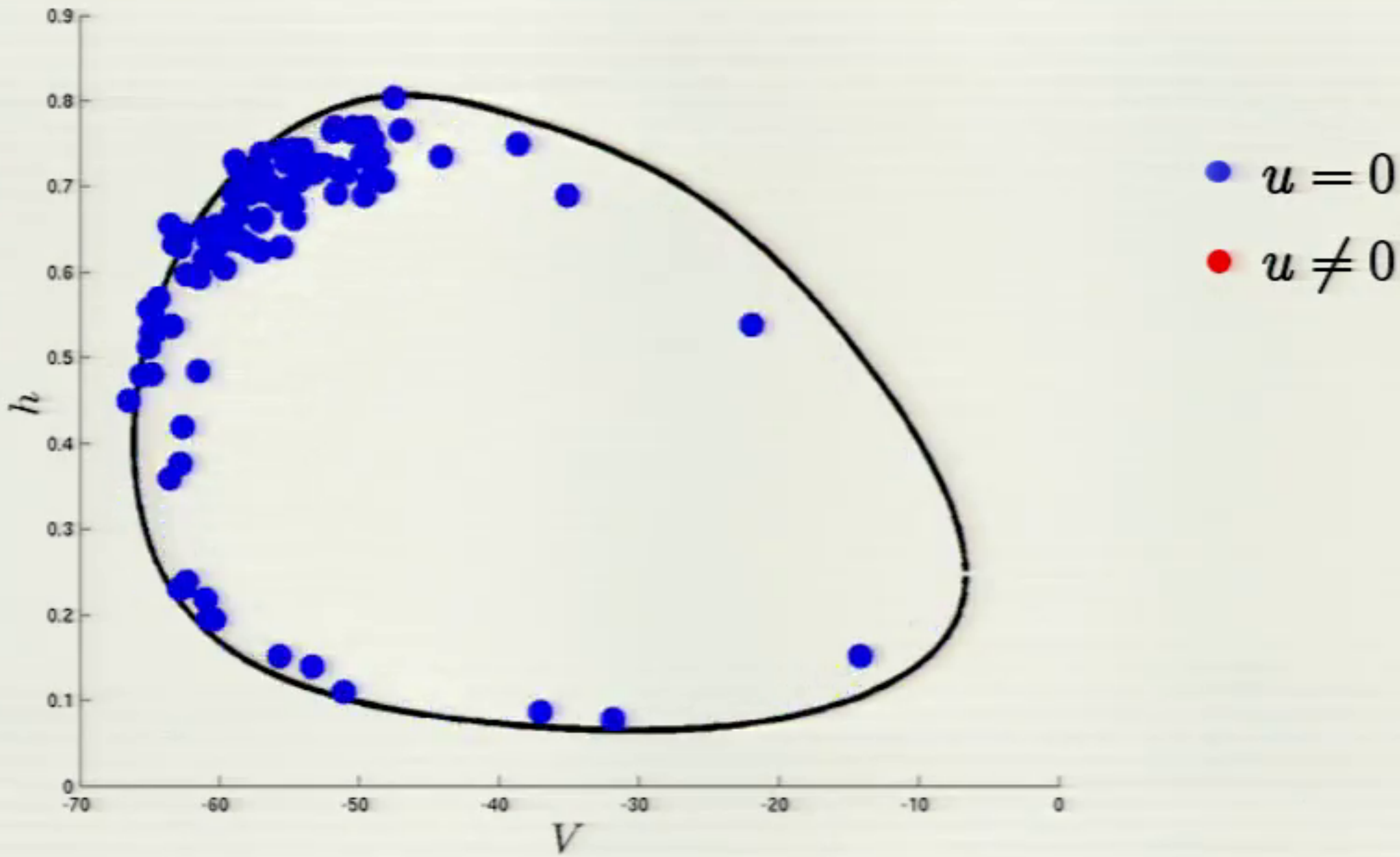

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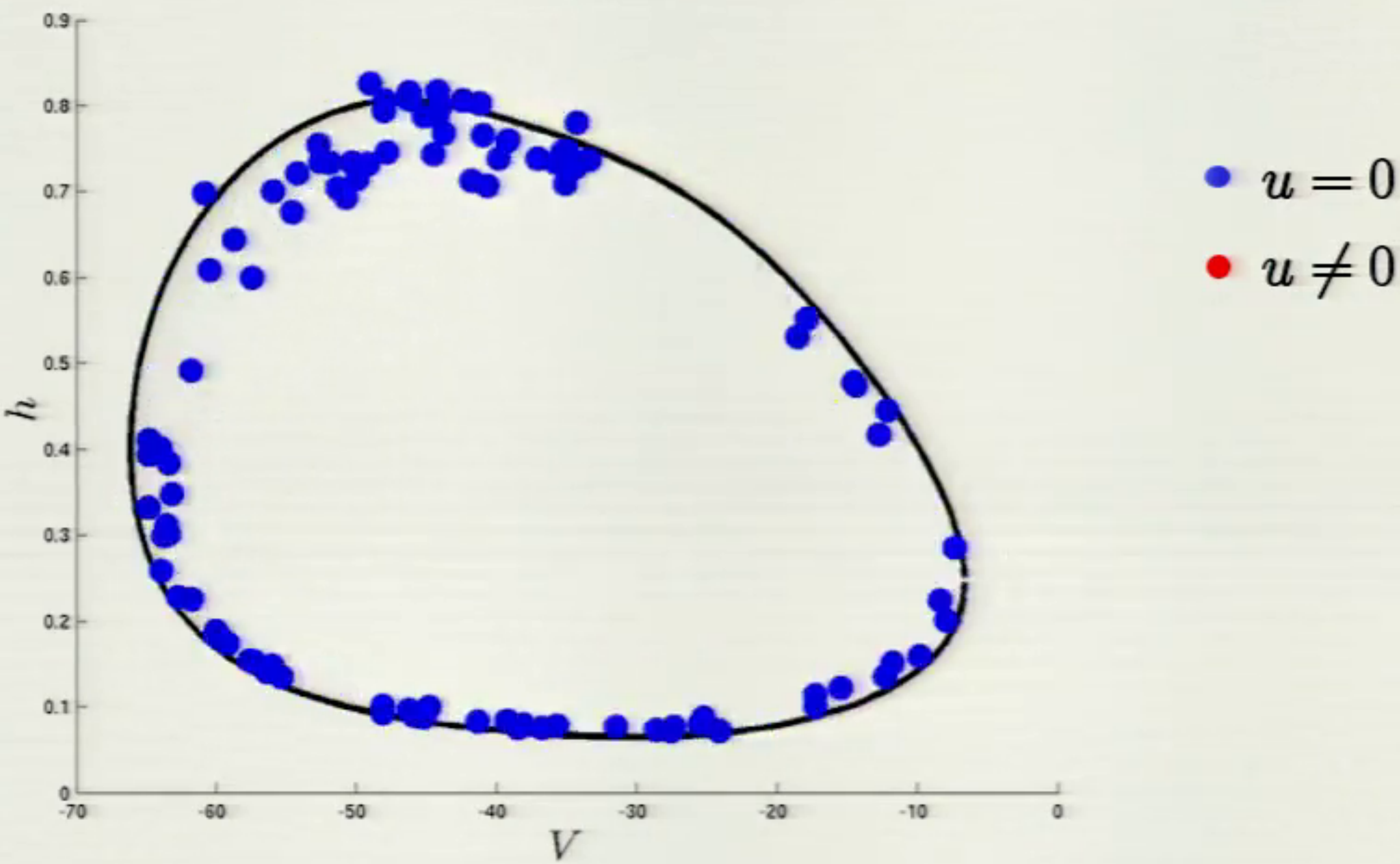

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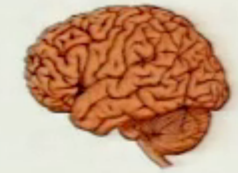

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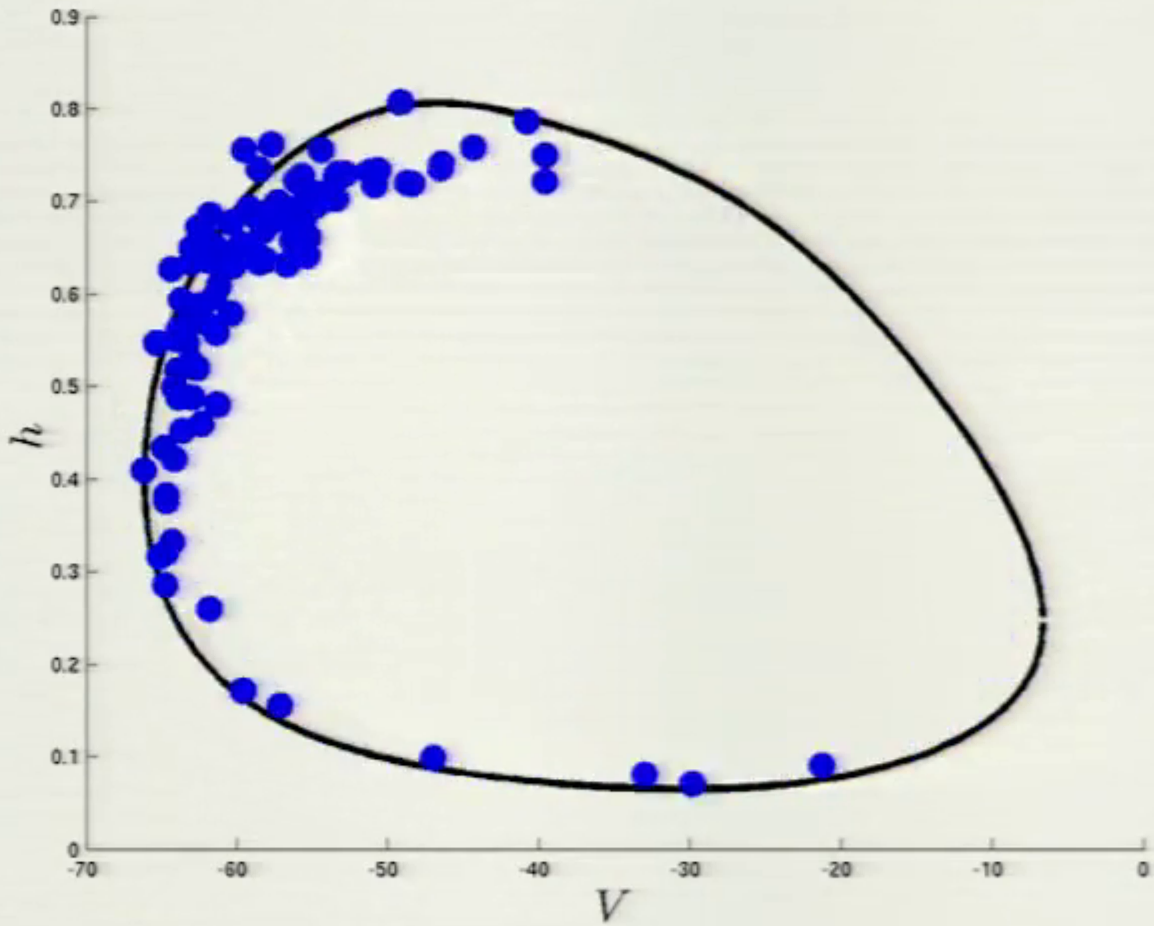

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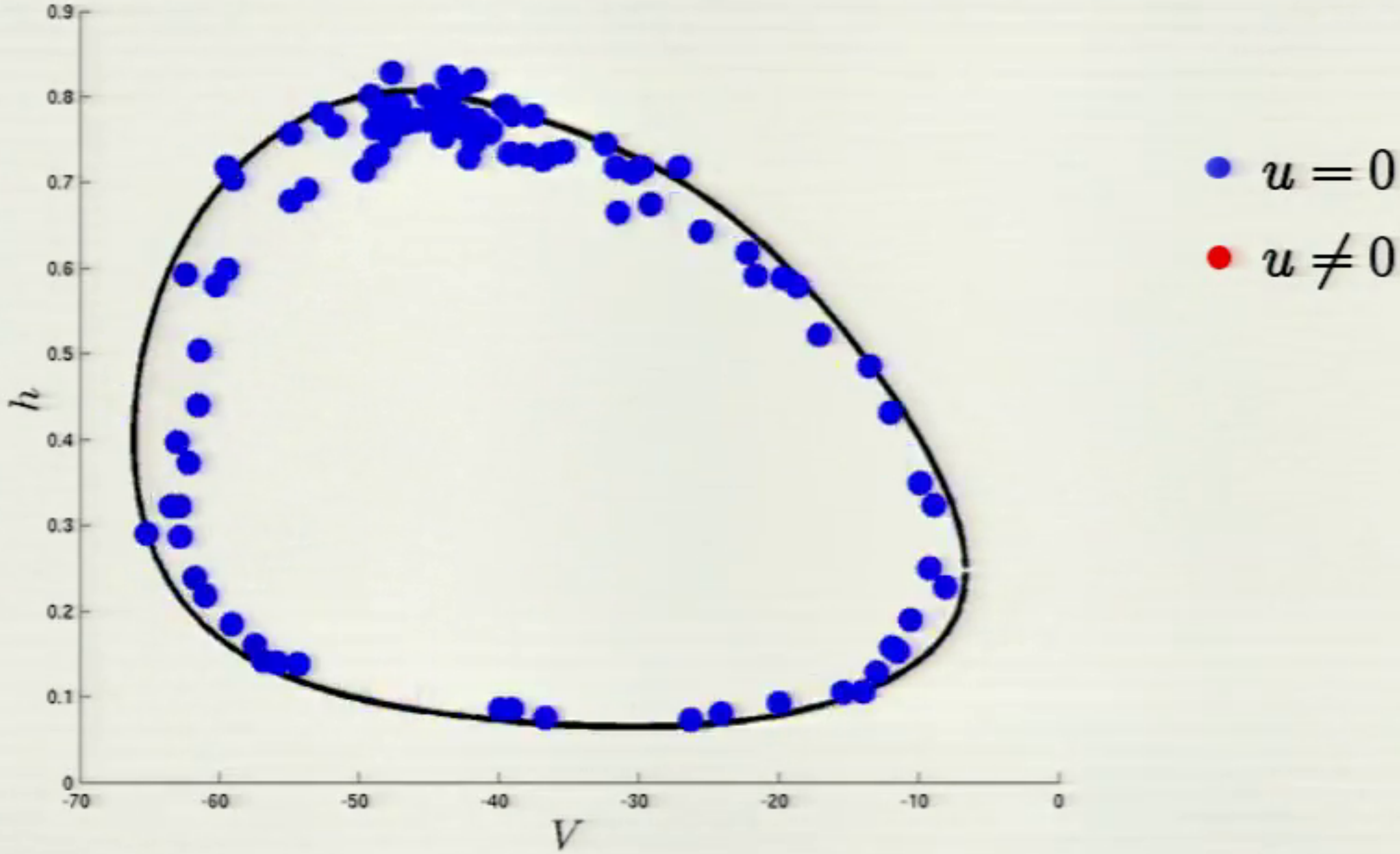

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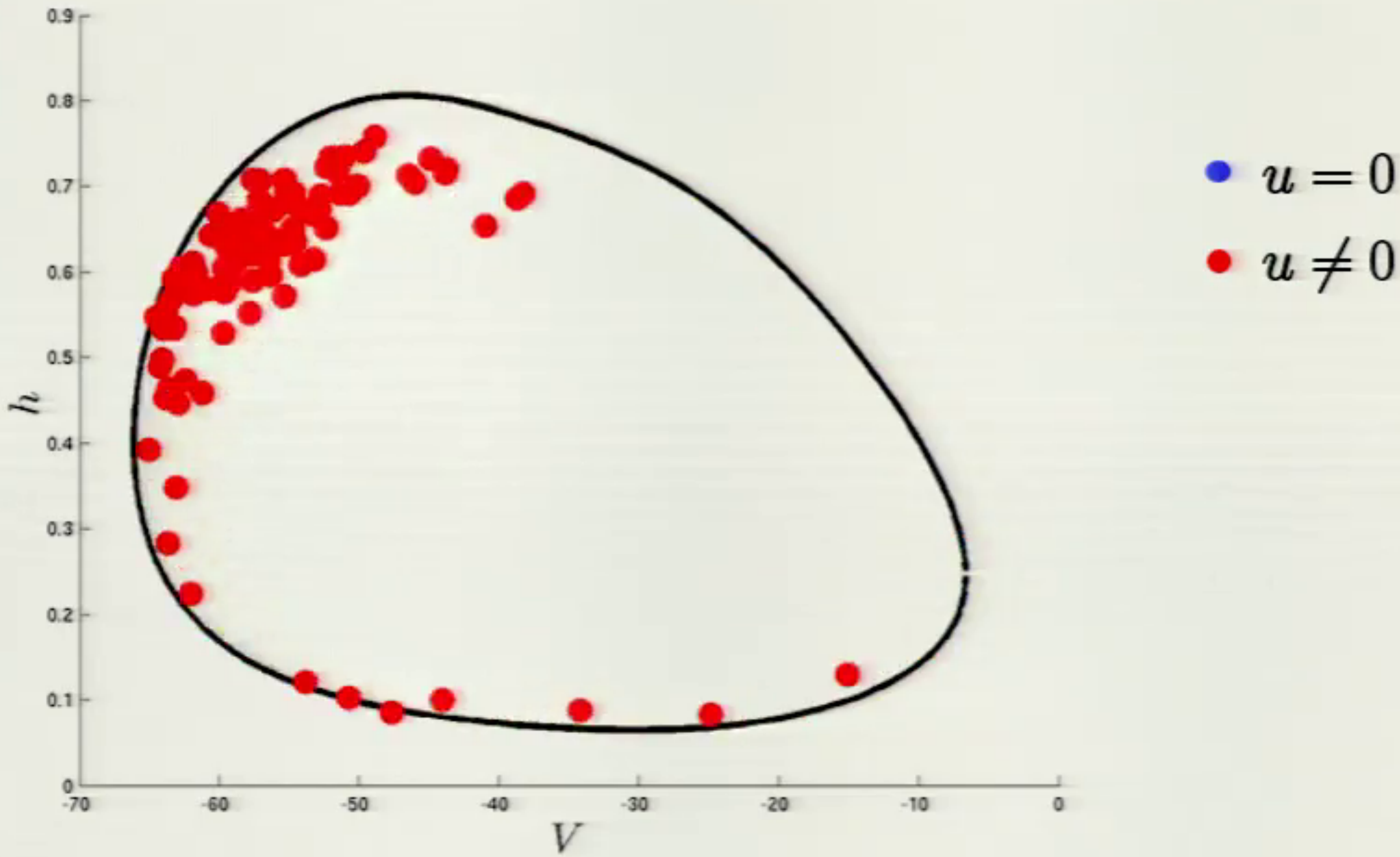

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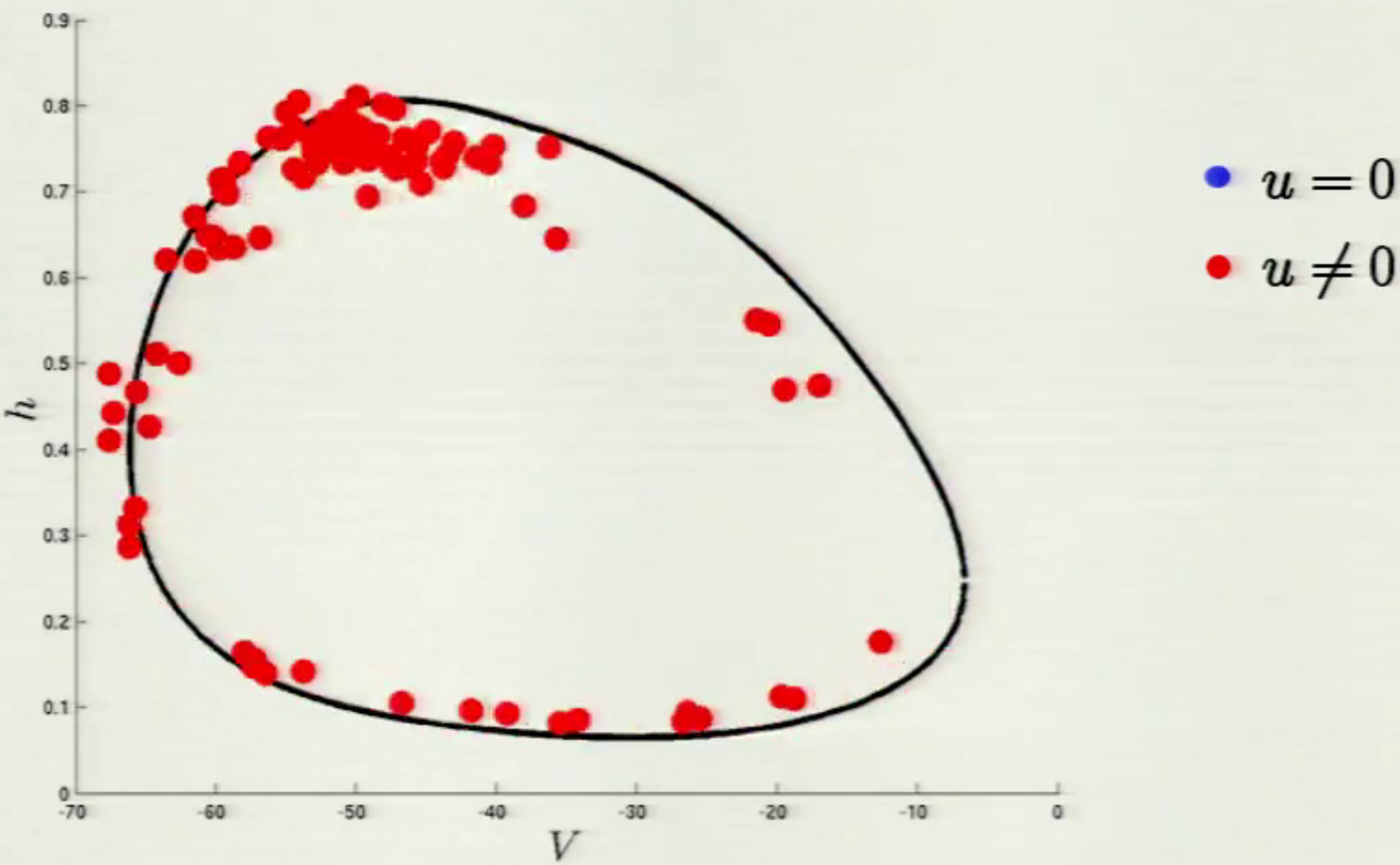

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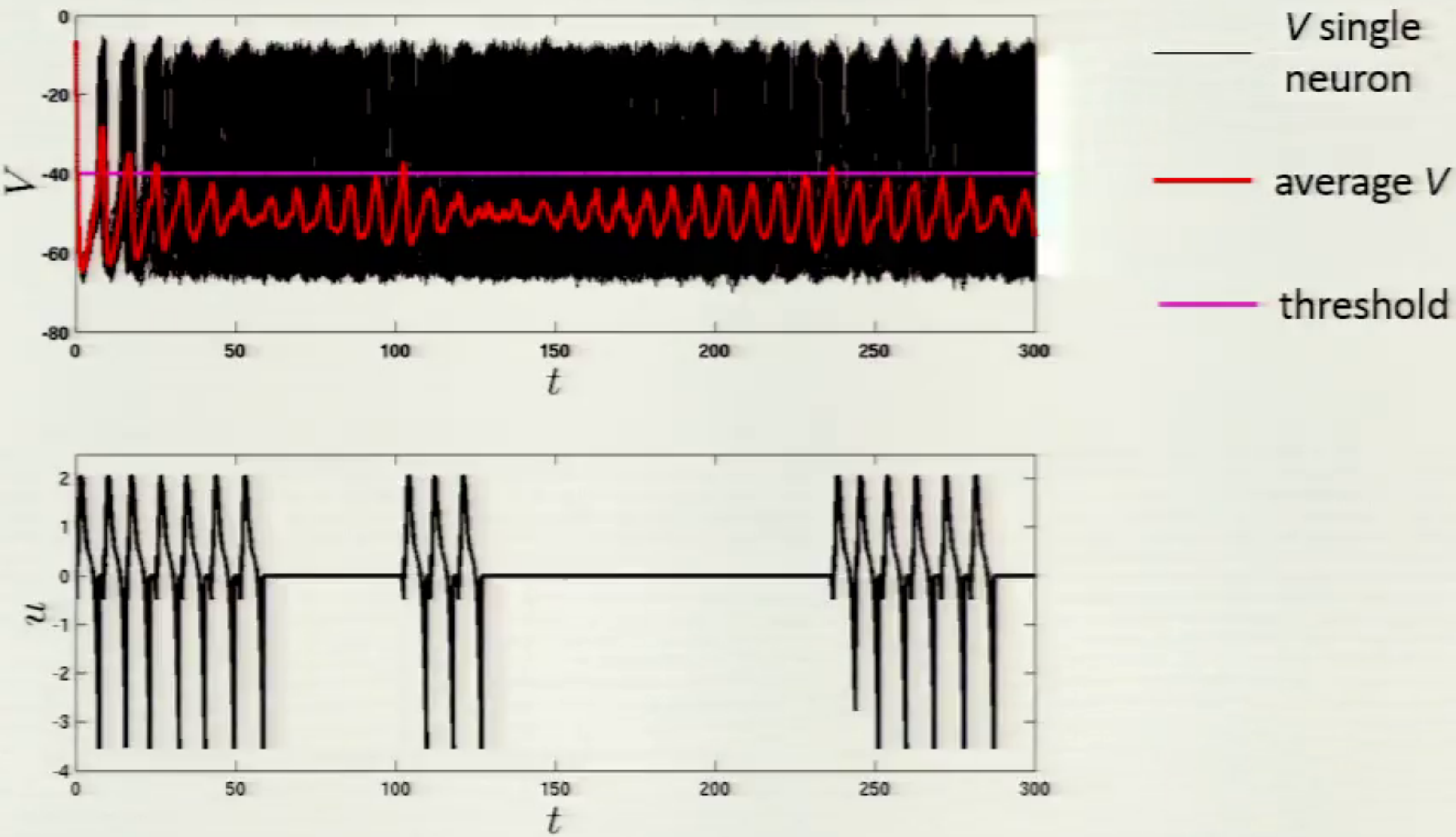

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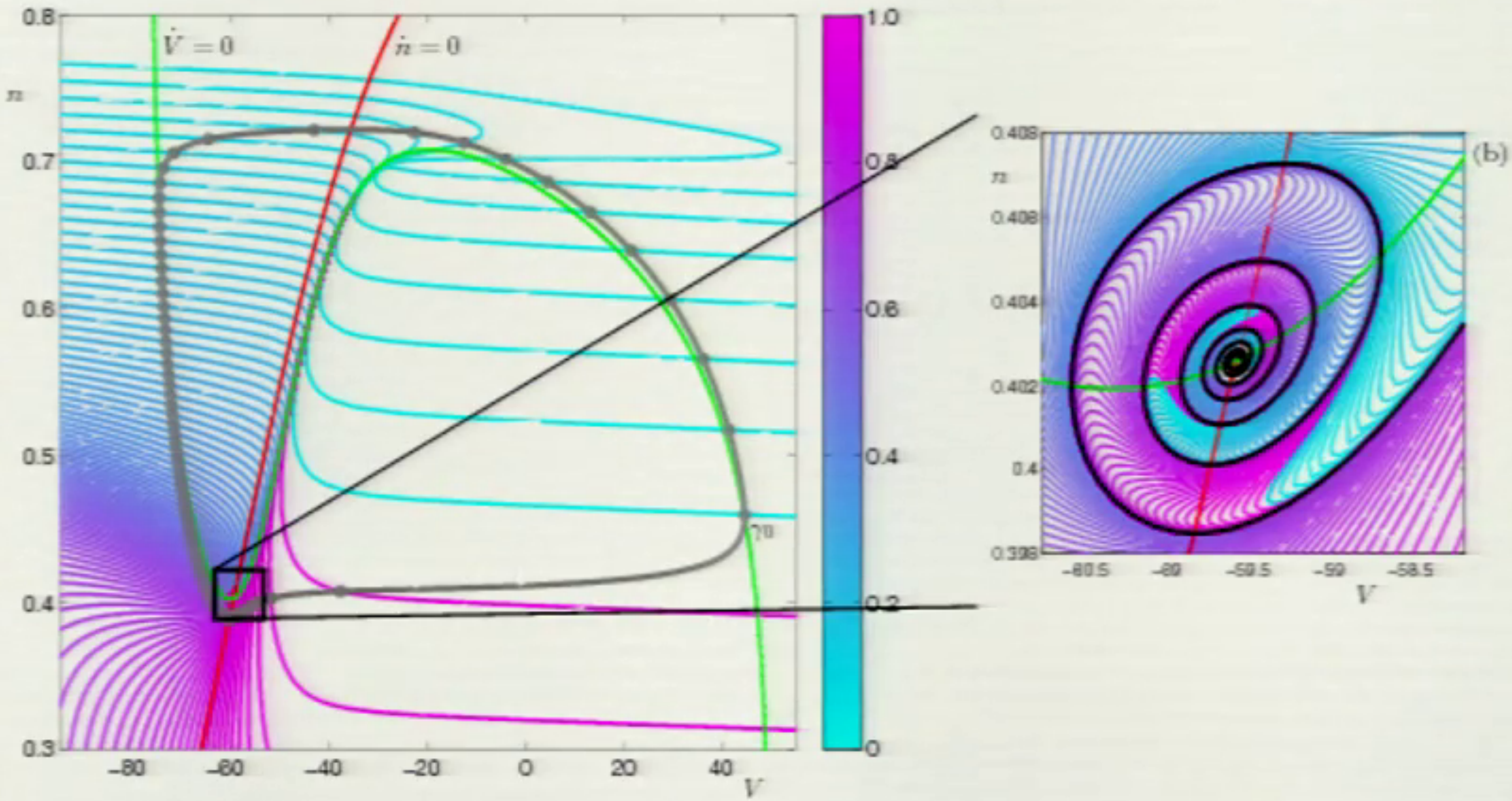
Isochrons Near the Phaseless Set



Osinga, M - *SIADS* 2010

Optimal Phase Resetting

$$\frac{d\mathbf{x}}{dt} = \mathbf{F}(\mathbf{x}) + (u(t), 0, 0, \cdots)^T, \qquad |u(t)| \le u_{max}$$

cost function to be minimized:

$$J(\mathbf{x}, u(t)) = \int_0^{T_{end}} u^2 dt + \gamma q(\mathbf{x}(T_{end}))$$

q **is end-point cost**

Hamilton-Jacobi-Bellman equation:

$$\frac{\partial V}{\partial t} + \min_{|u| \le u_{max}} [u^2 + \nabla V(\mathbf{x}, t)(\mathbf{F}(\mathbf{x}) + (u(t), 0, 0, \cdots)^T)] = 0$$

$$u^*(t) = \arg \min_{|u| \le u_{max}} [u^2 + \nabla V(\mathbf{x}^*, t)(\mathbf{F}(\mathbf{x}^*) + (u(t), 0, 0, \cdots)^T)]$$

where $\mathbf{x}^*(t)$ **is optimal trajectory**

Nabi, Mirzadeh, Gibou, M - *JCNS* 2013

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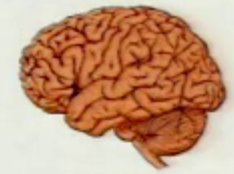
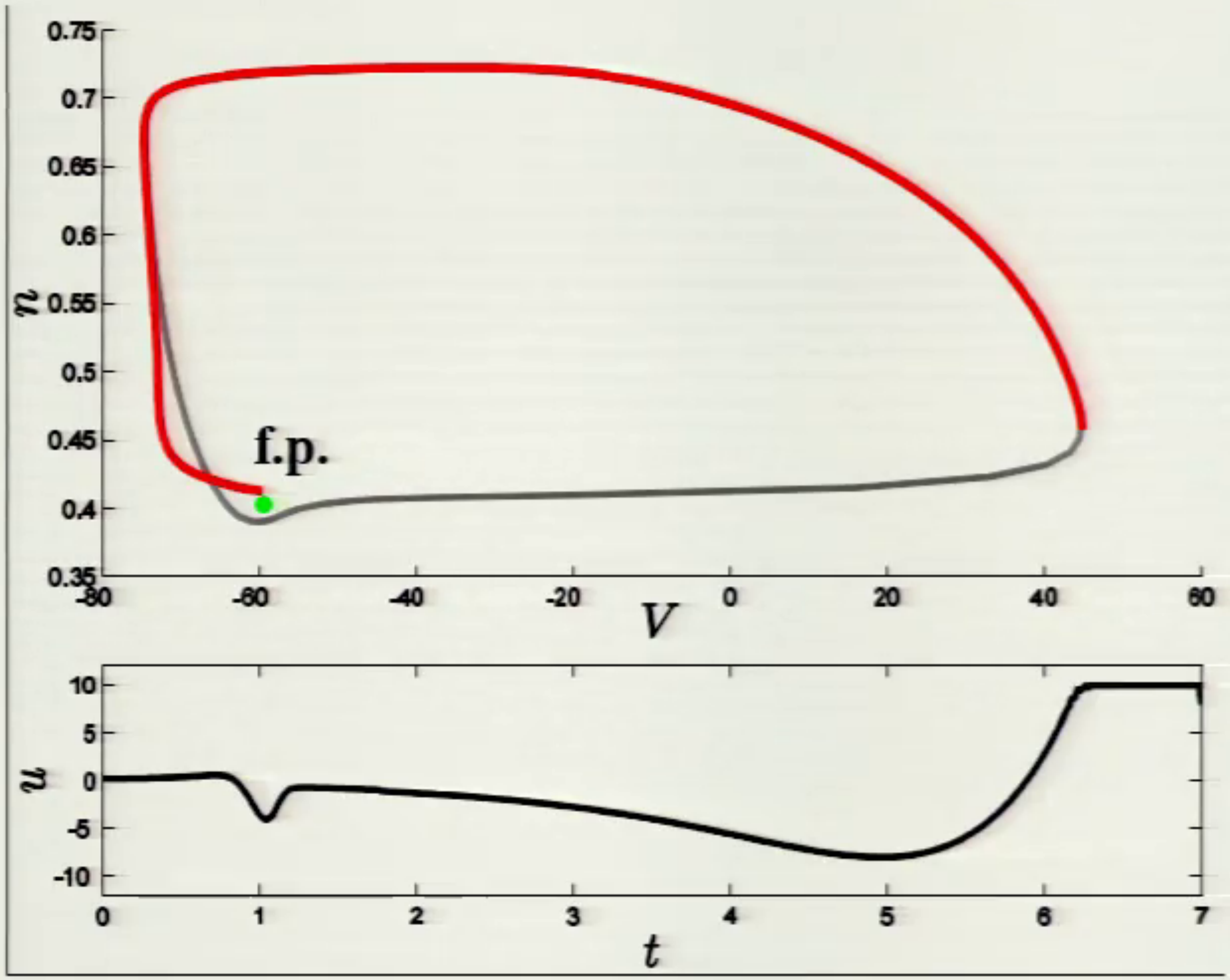


Optimal Phase Resetting



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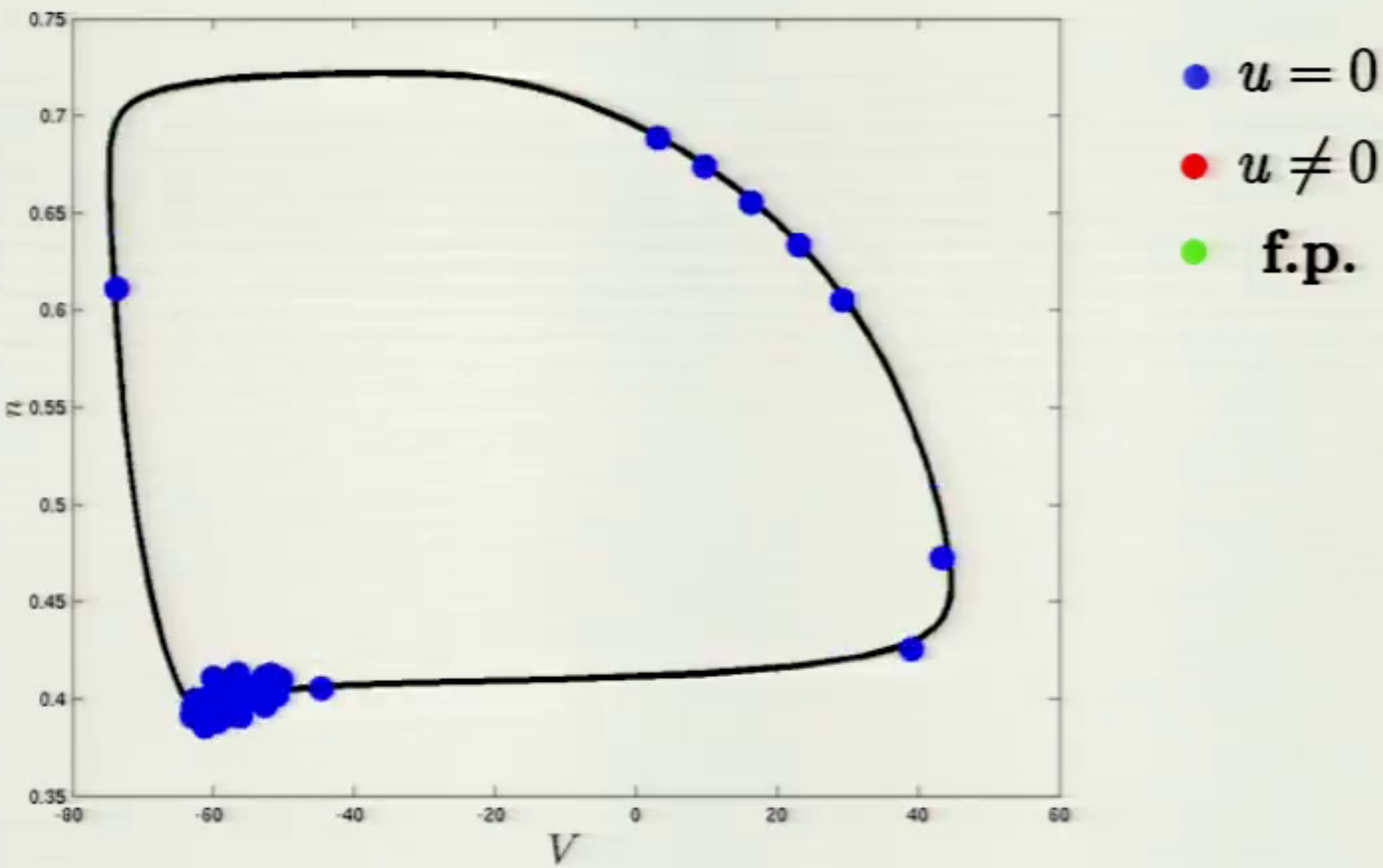
Coupled, Noisy Neurons – Phase Resetting



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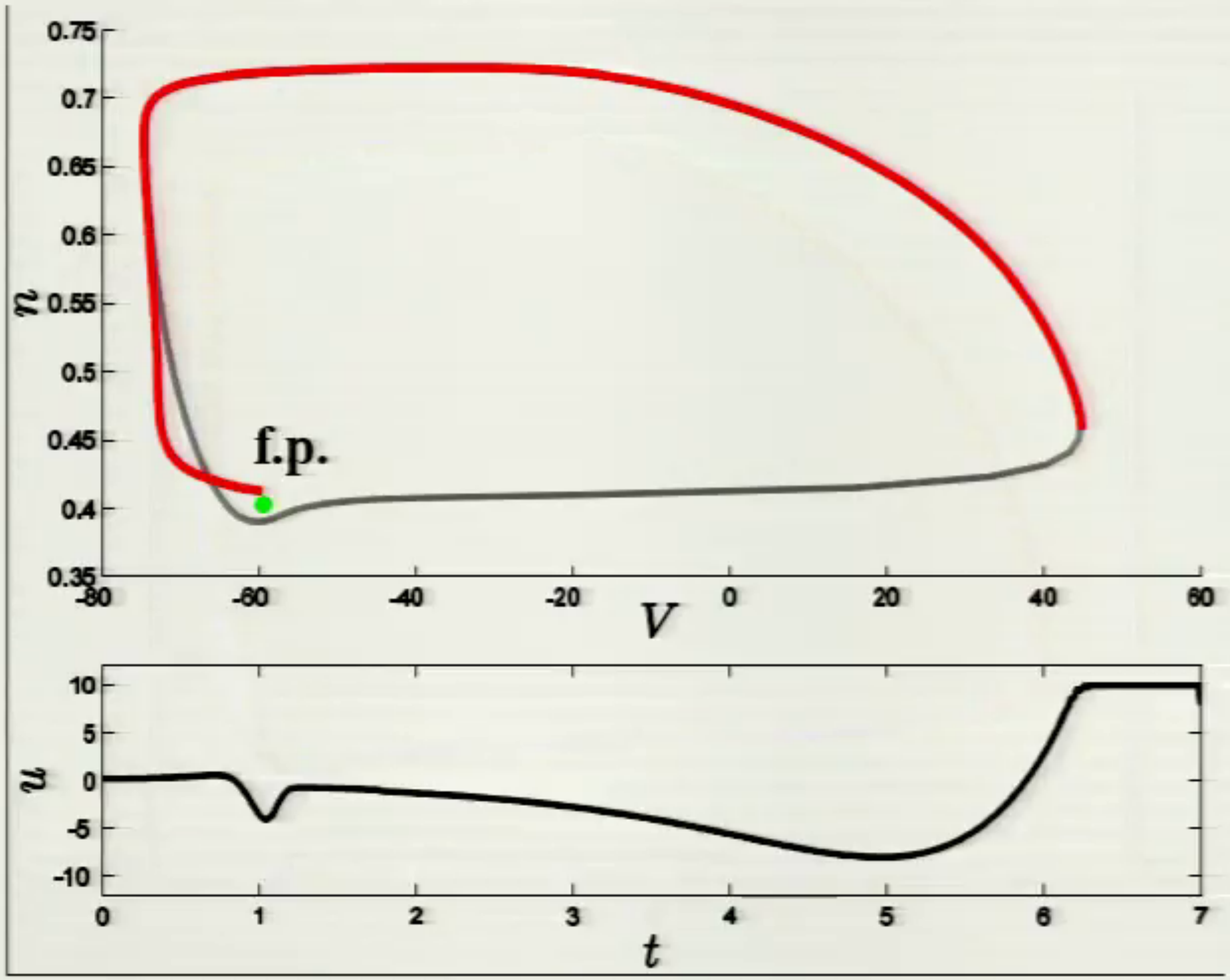
Optimal Phase Resetting



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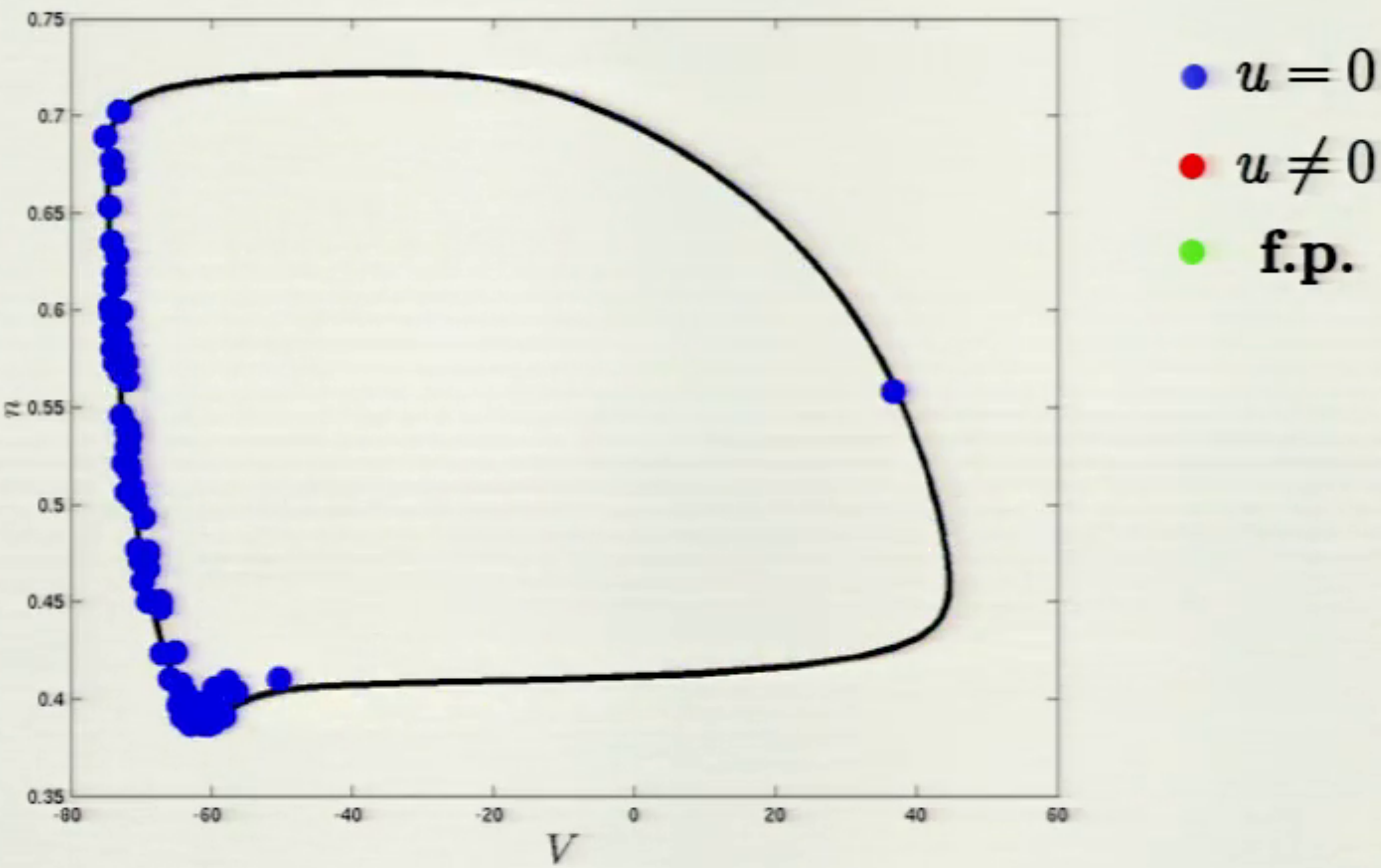
Coupled, Noisy Neurons – Phase Resetting



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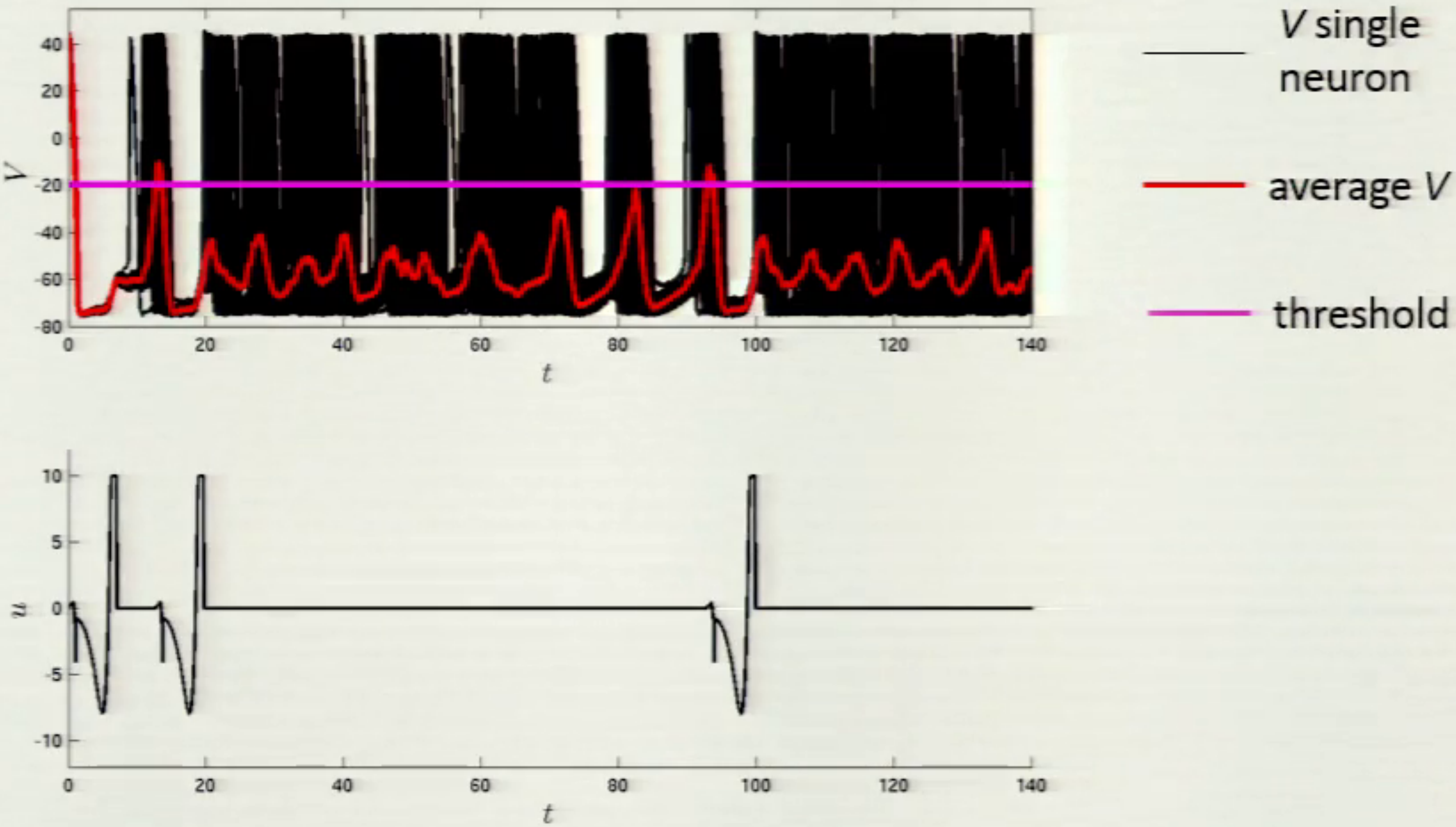

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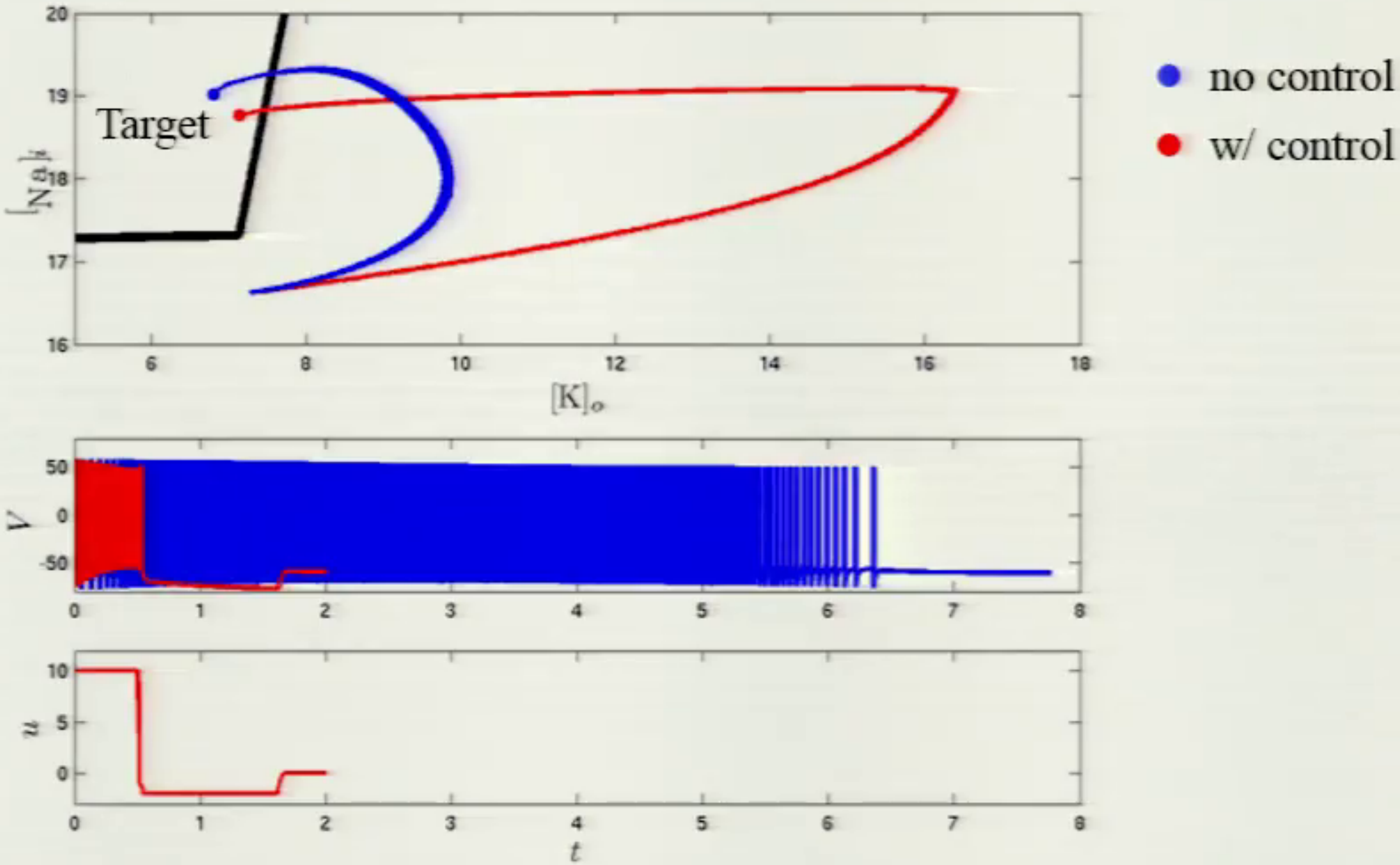
Control of Seizure-like Bursting



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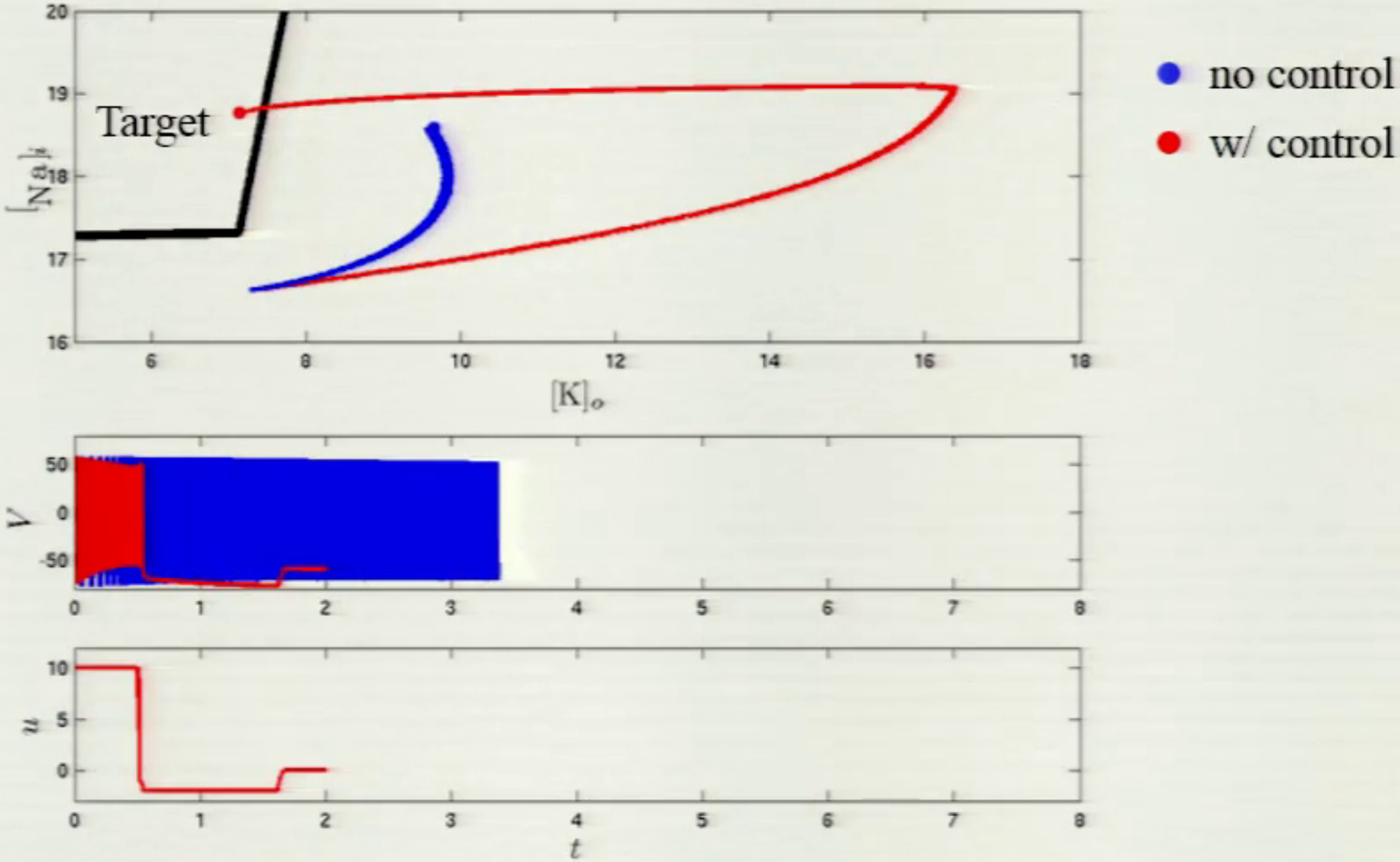

Wilson, M - *JCNS* 2014

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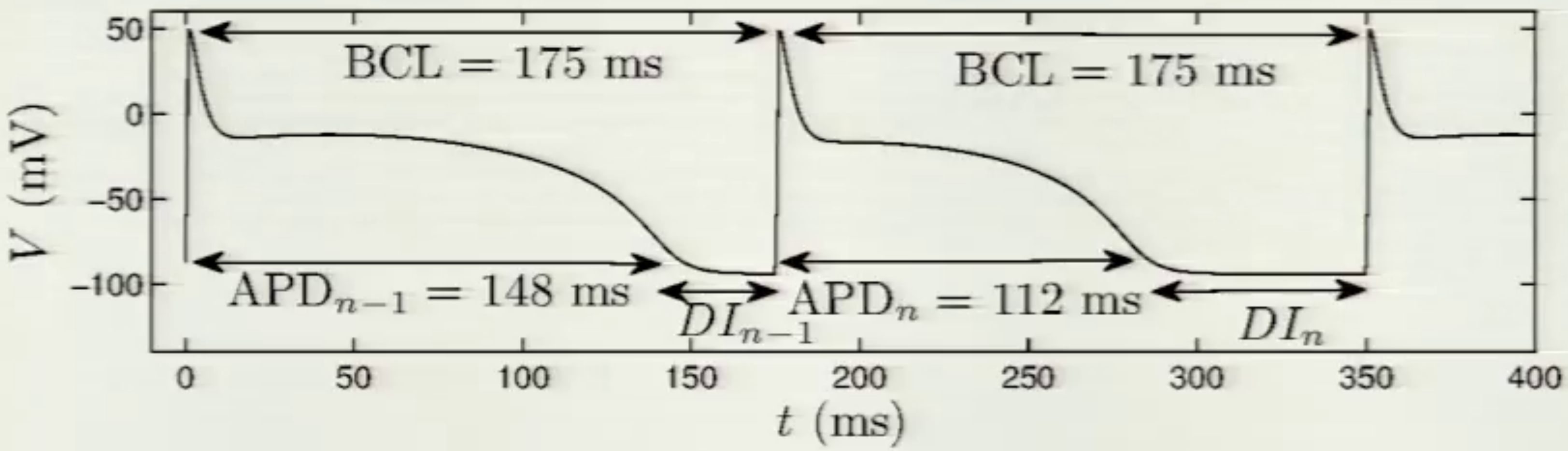

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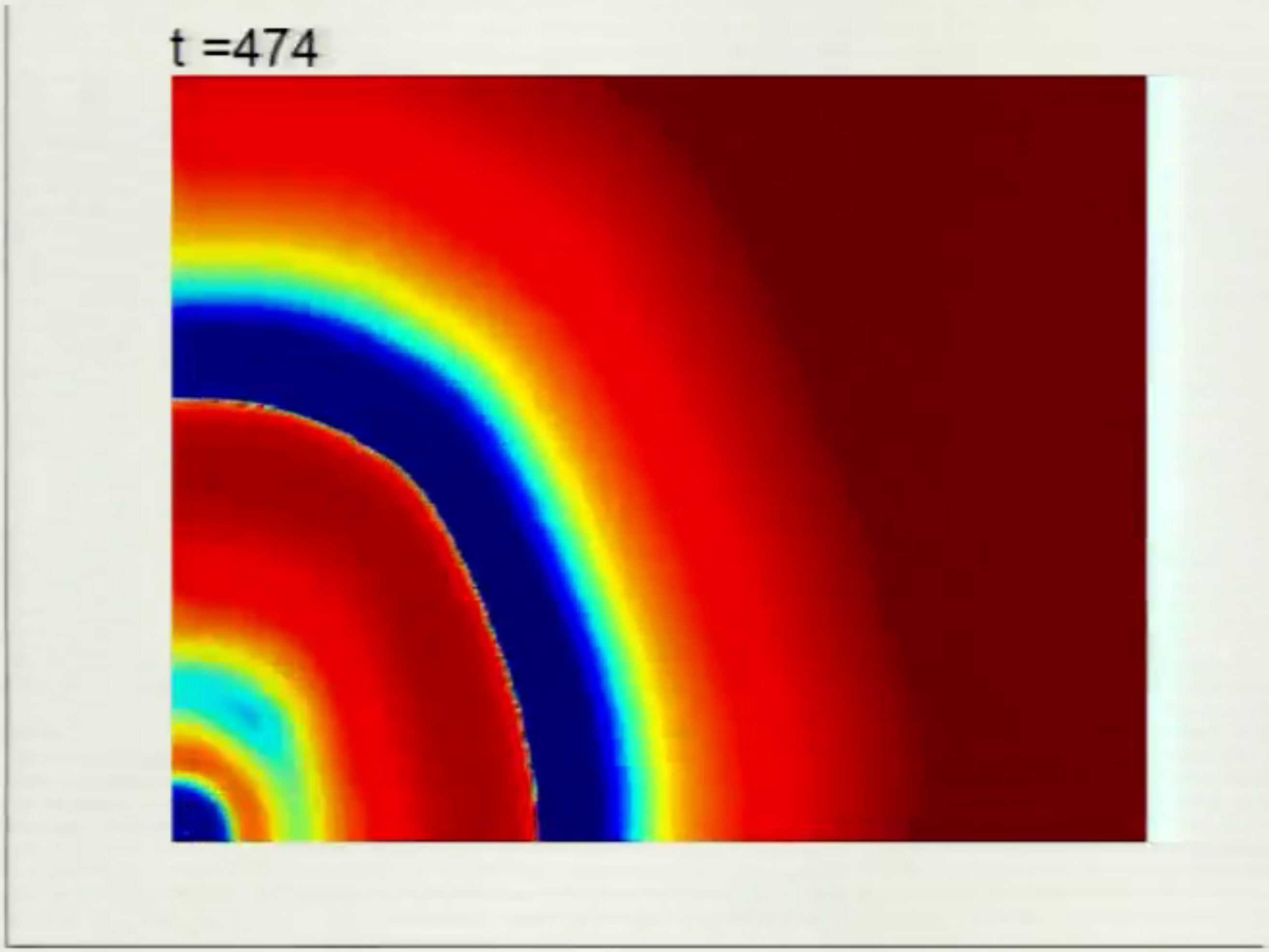
Alternans: Possible Precursor to Fibrillation



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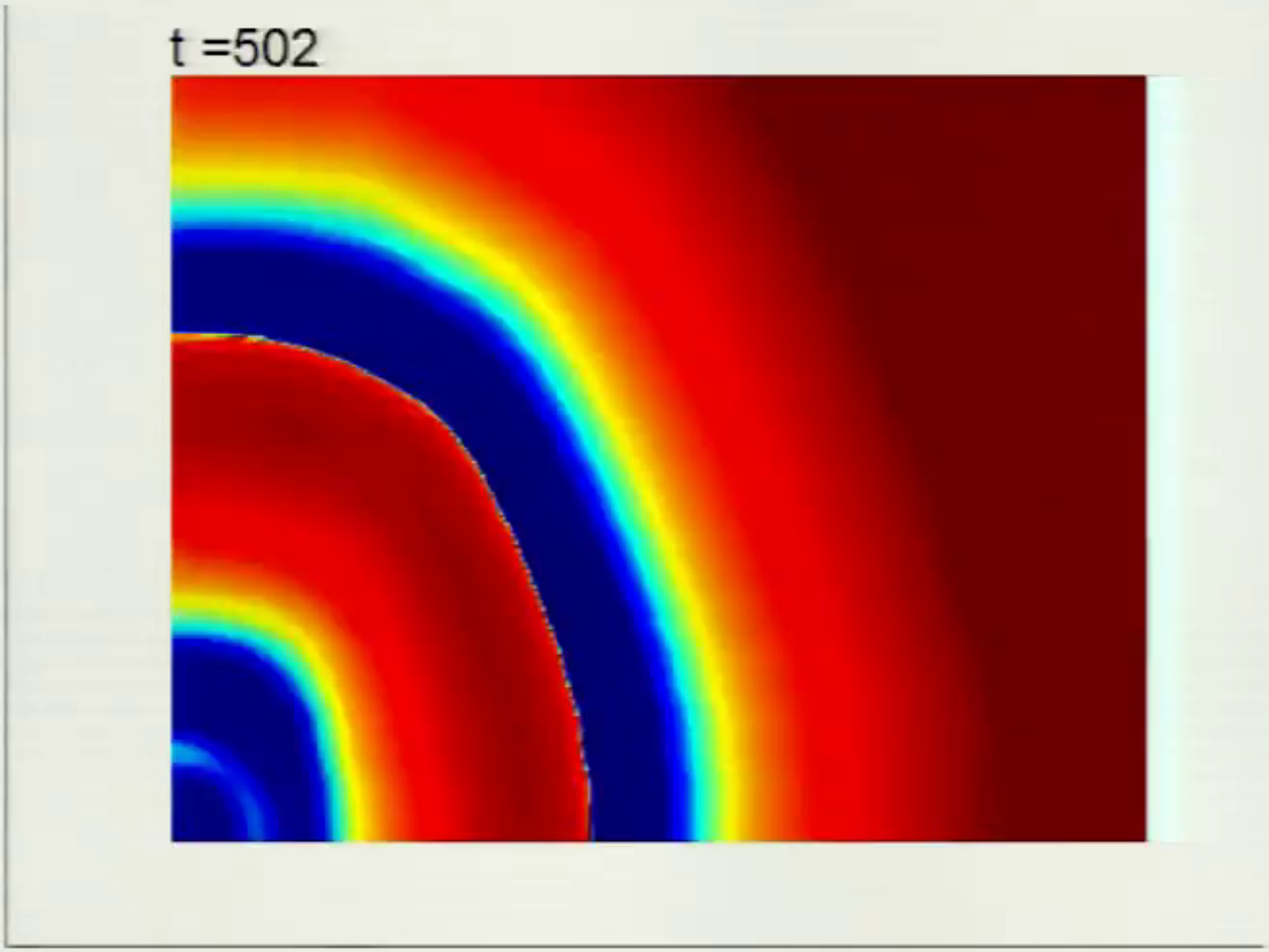

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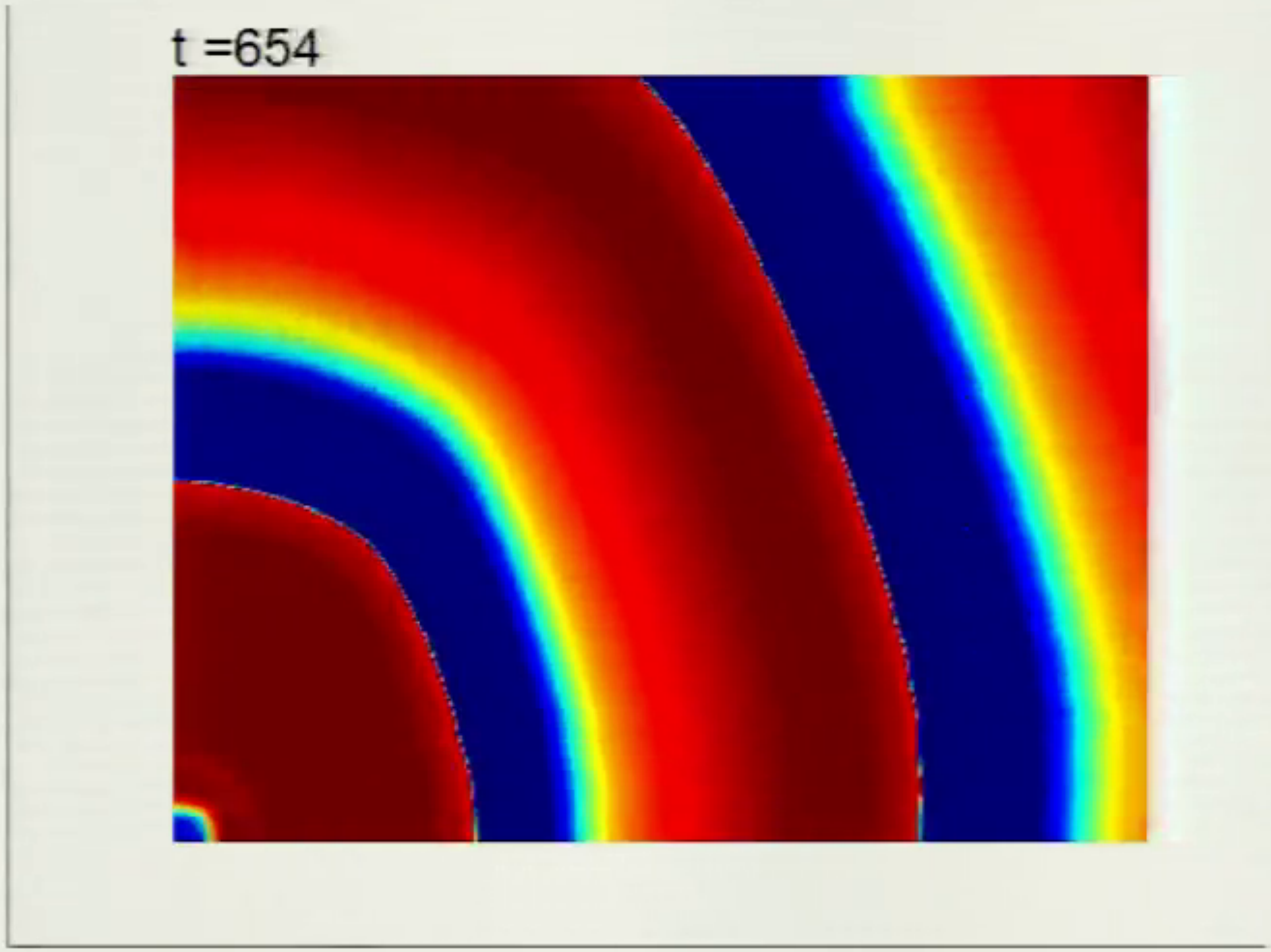

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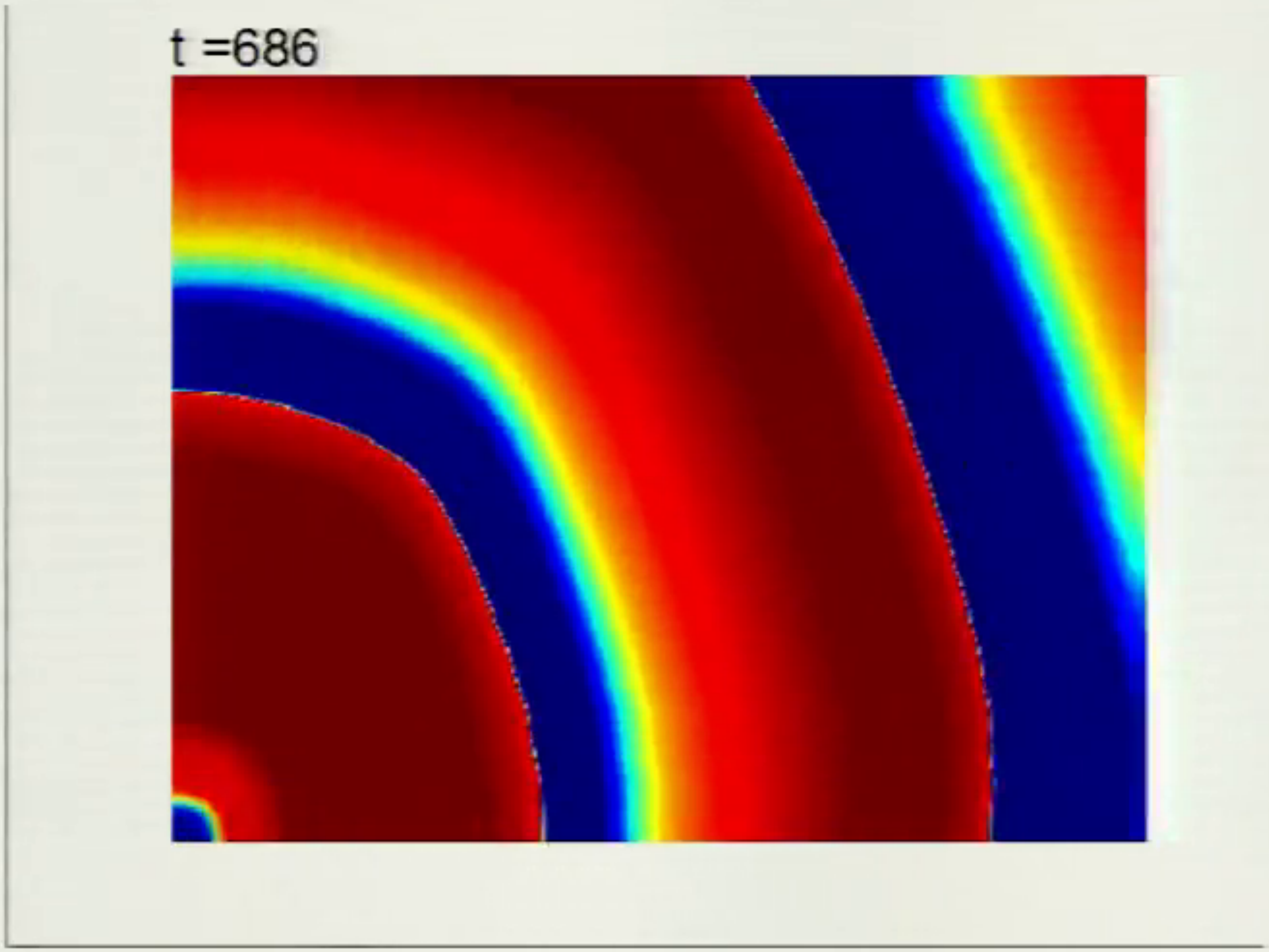

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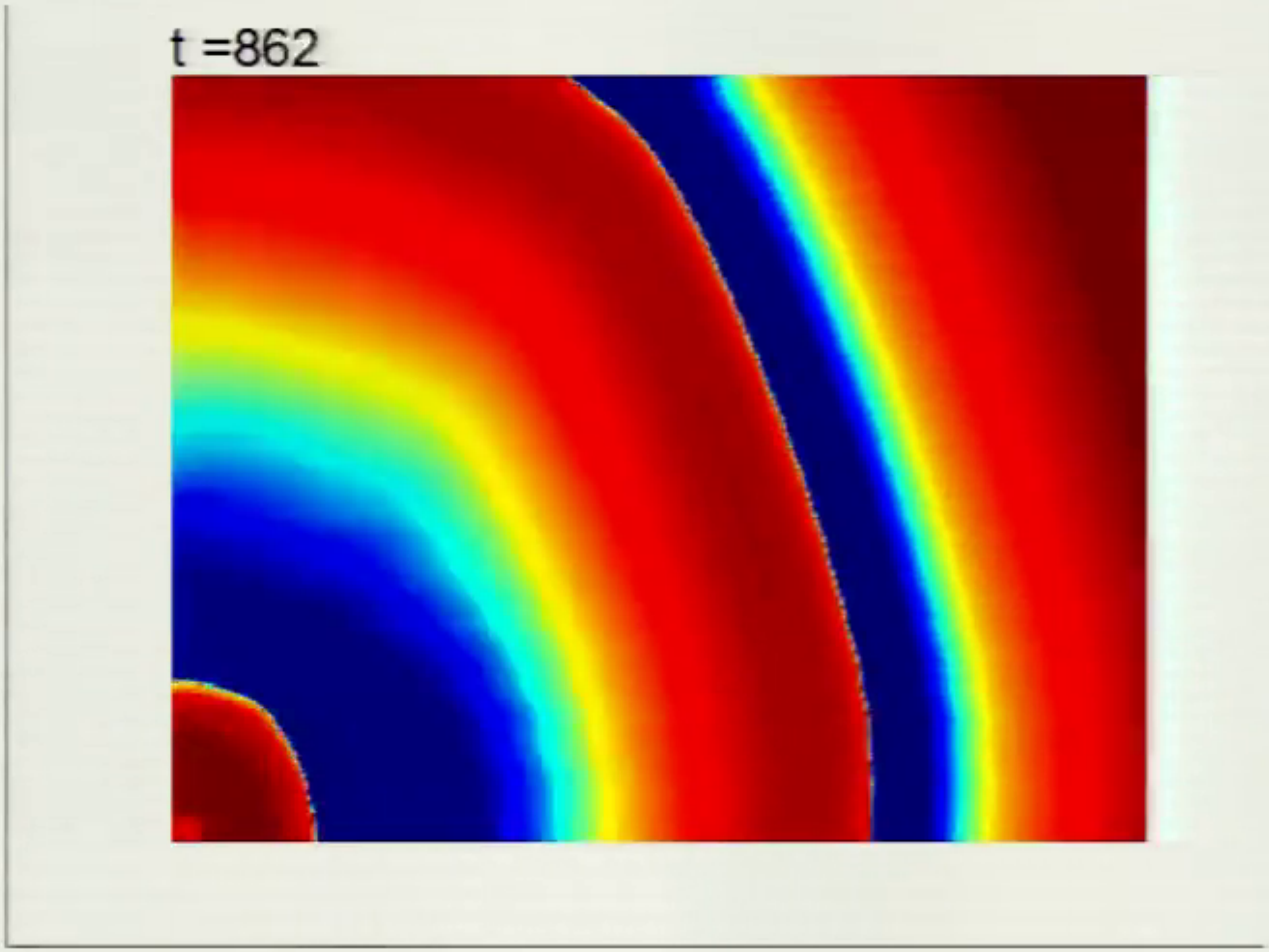

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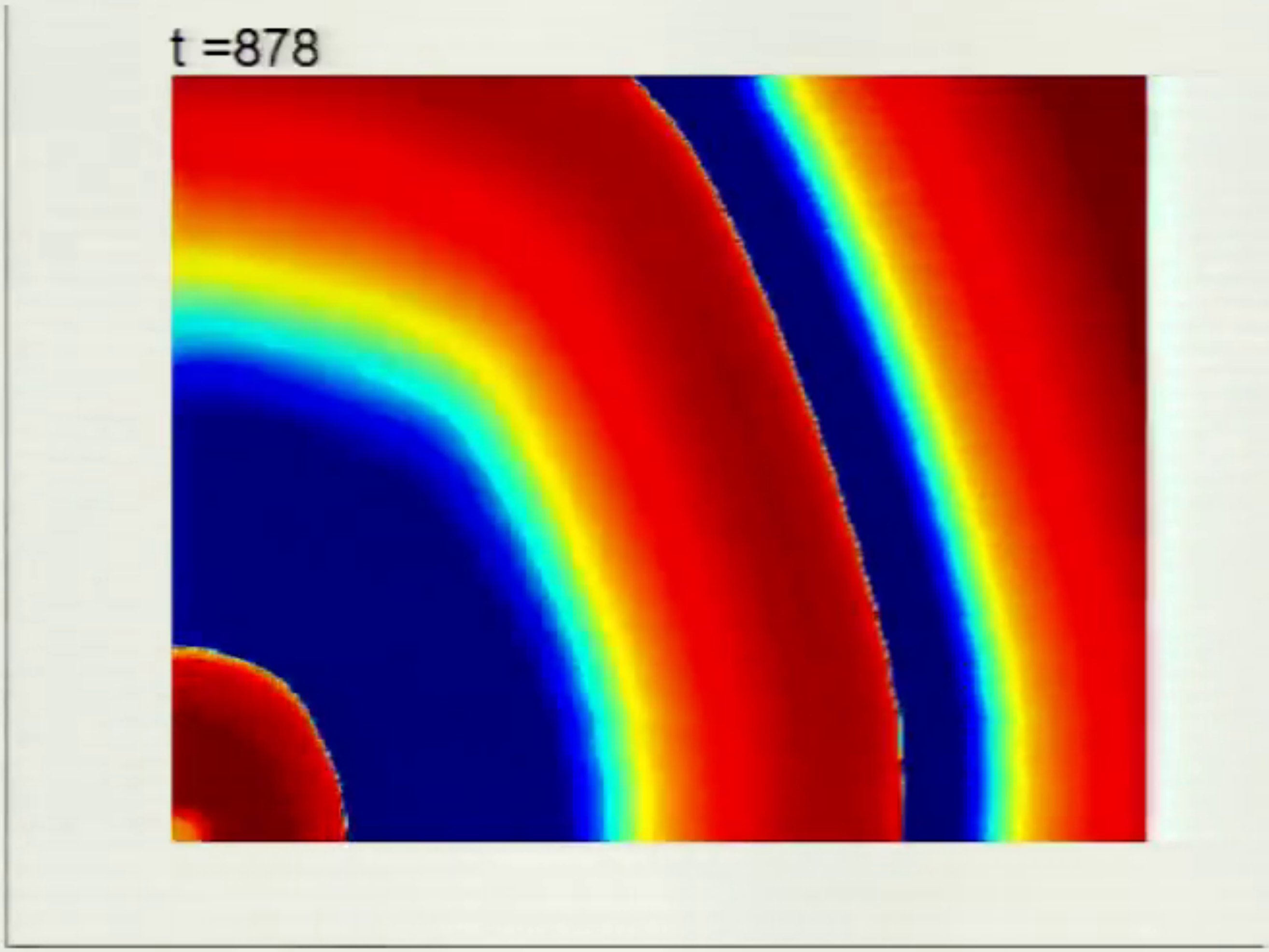

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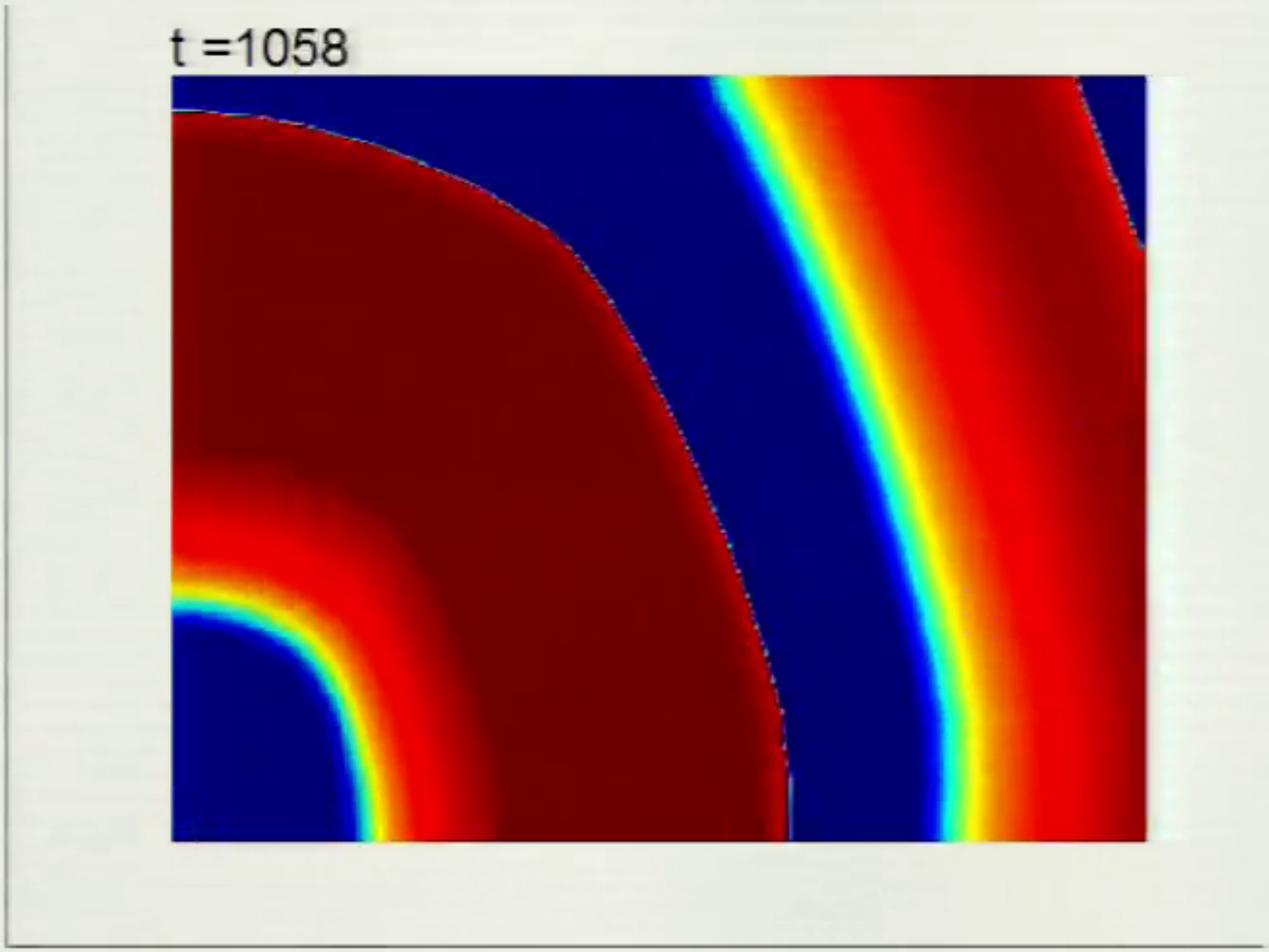

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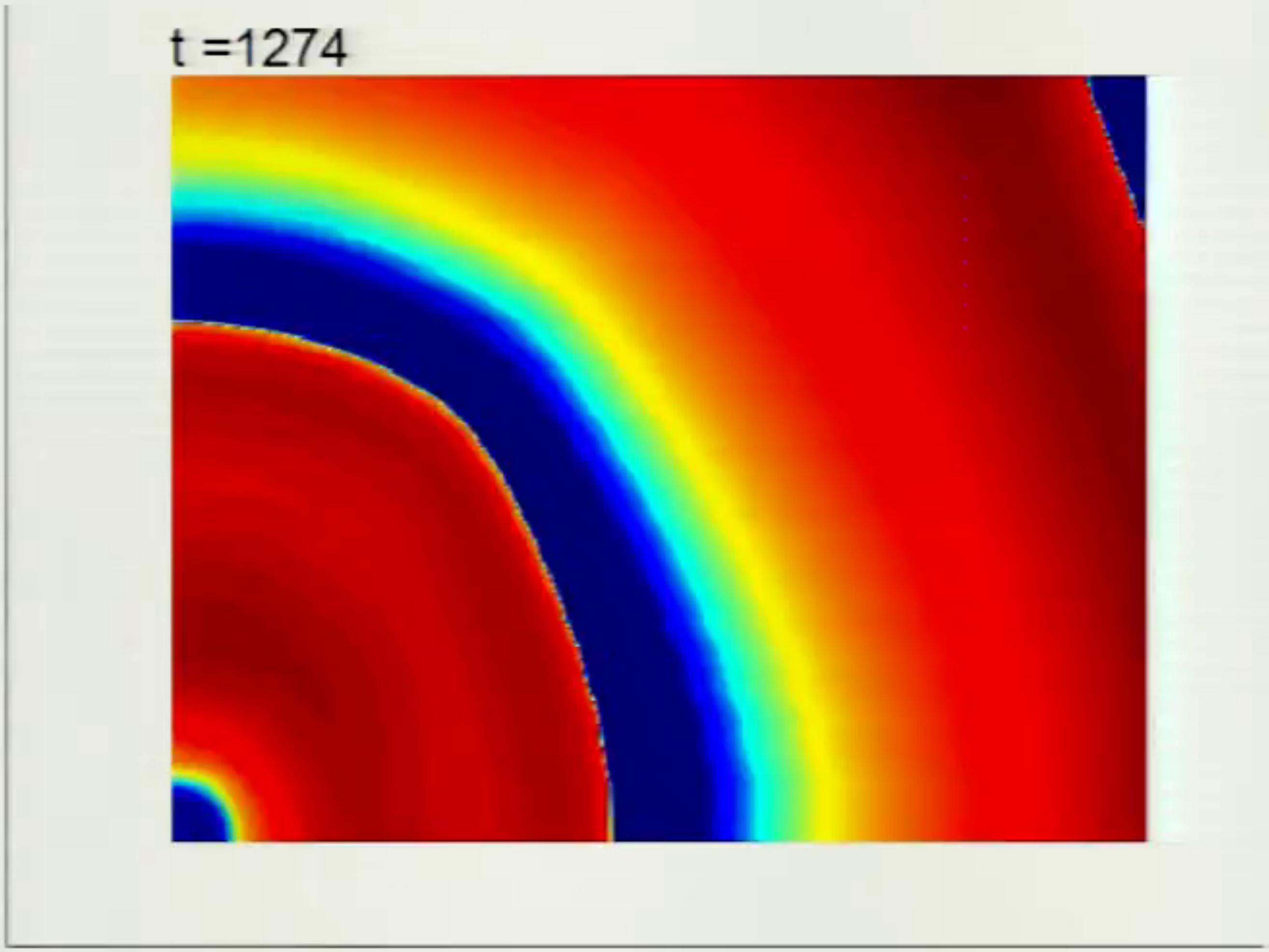

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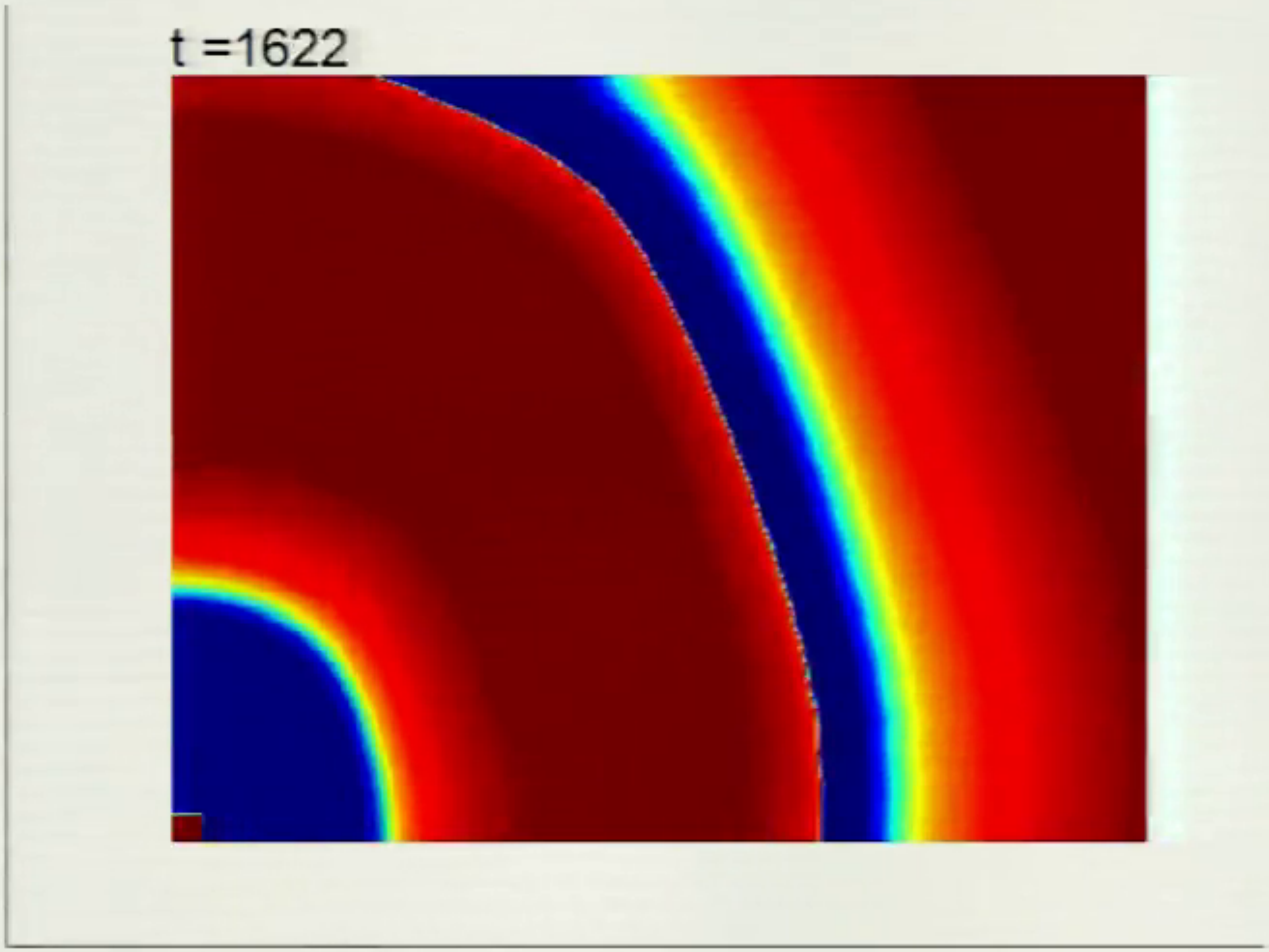

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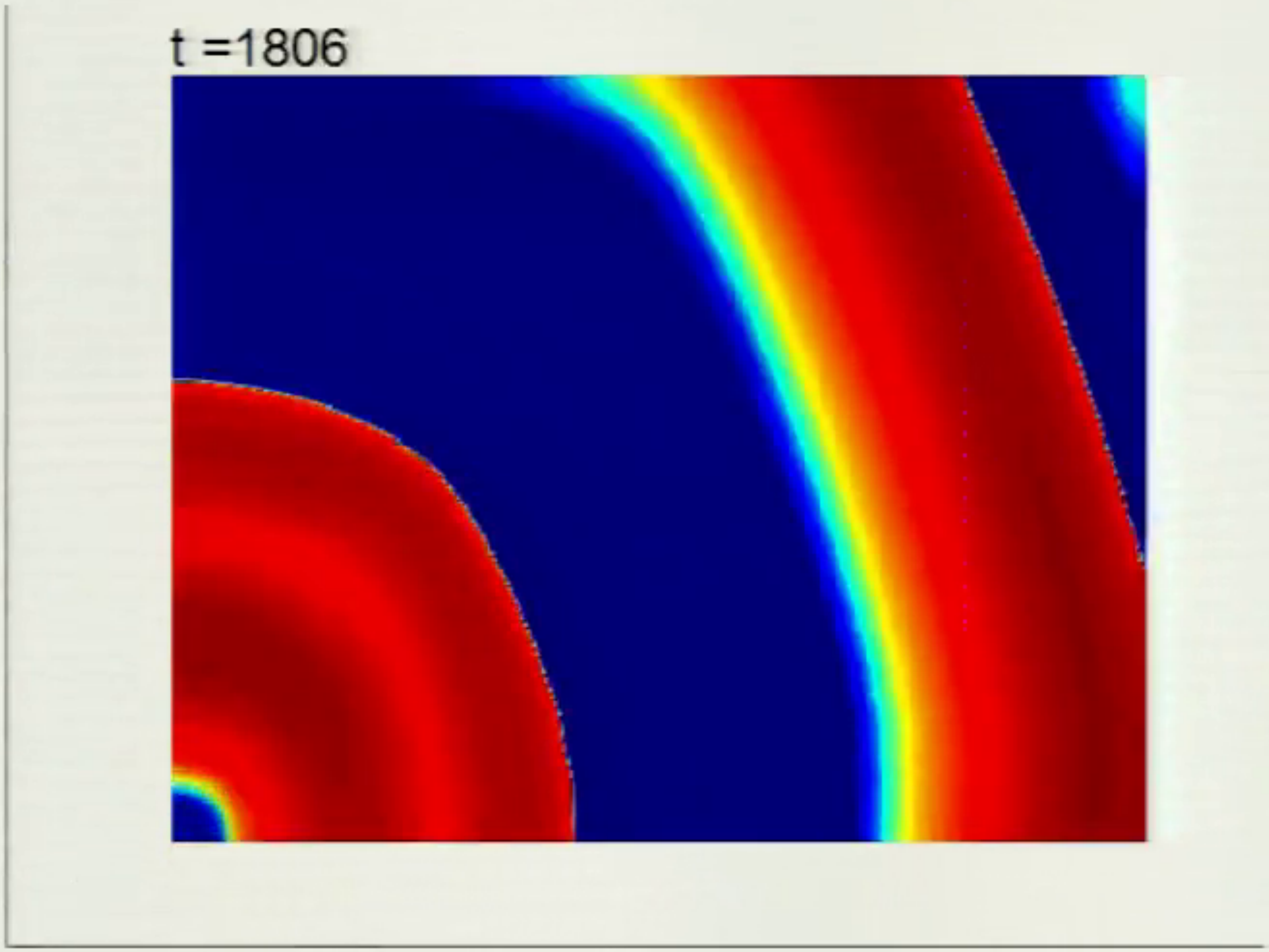

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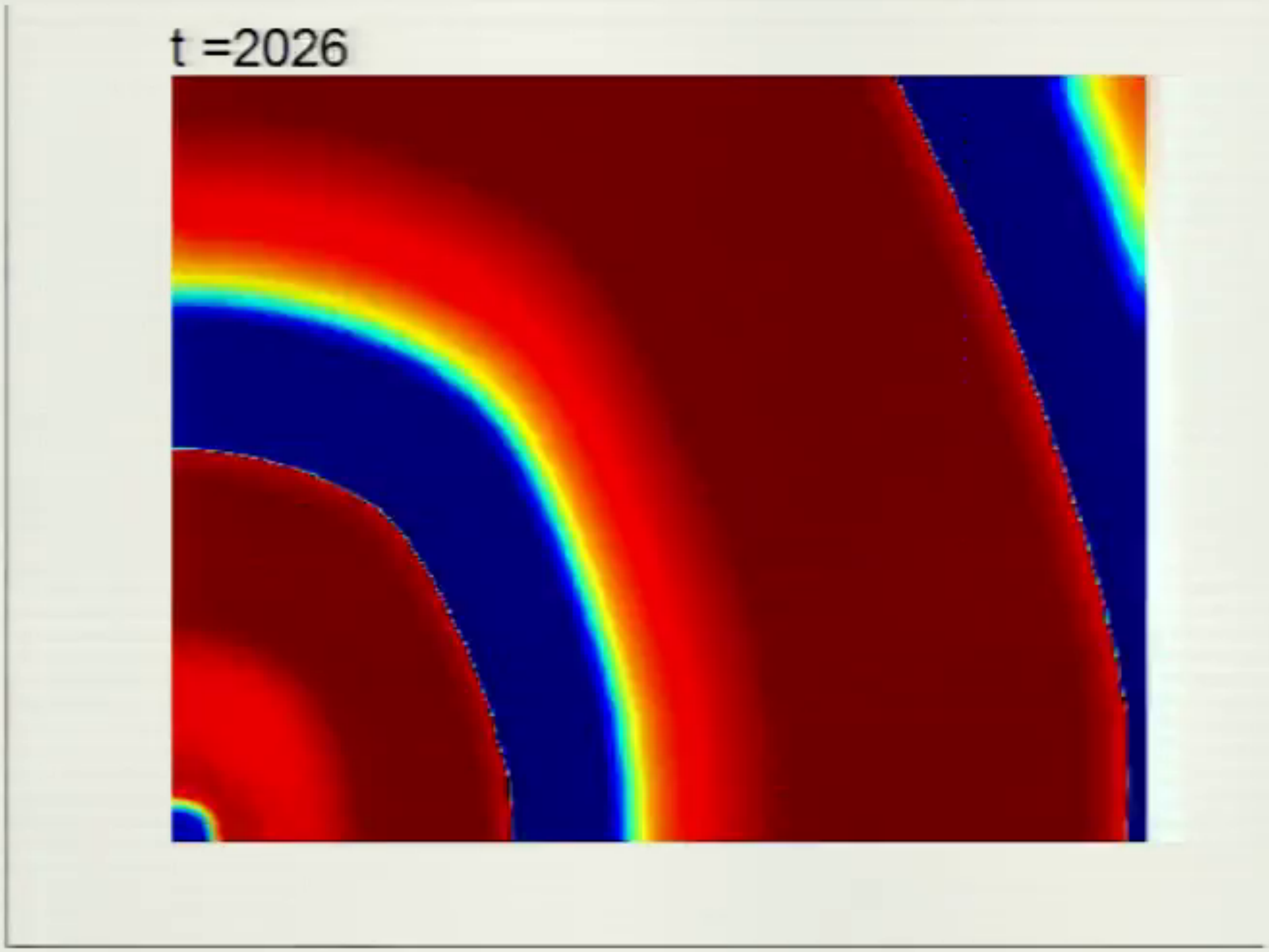

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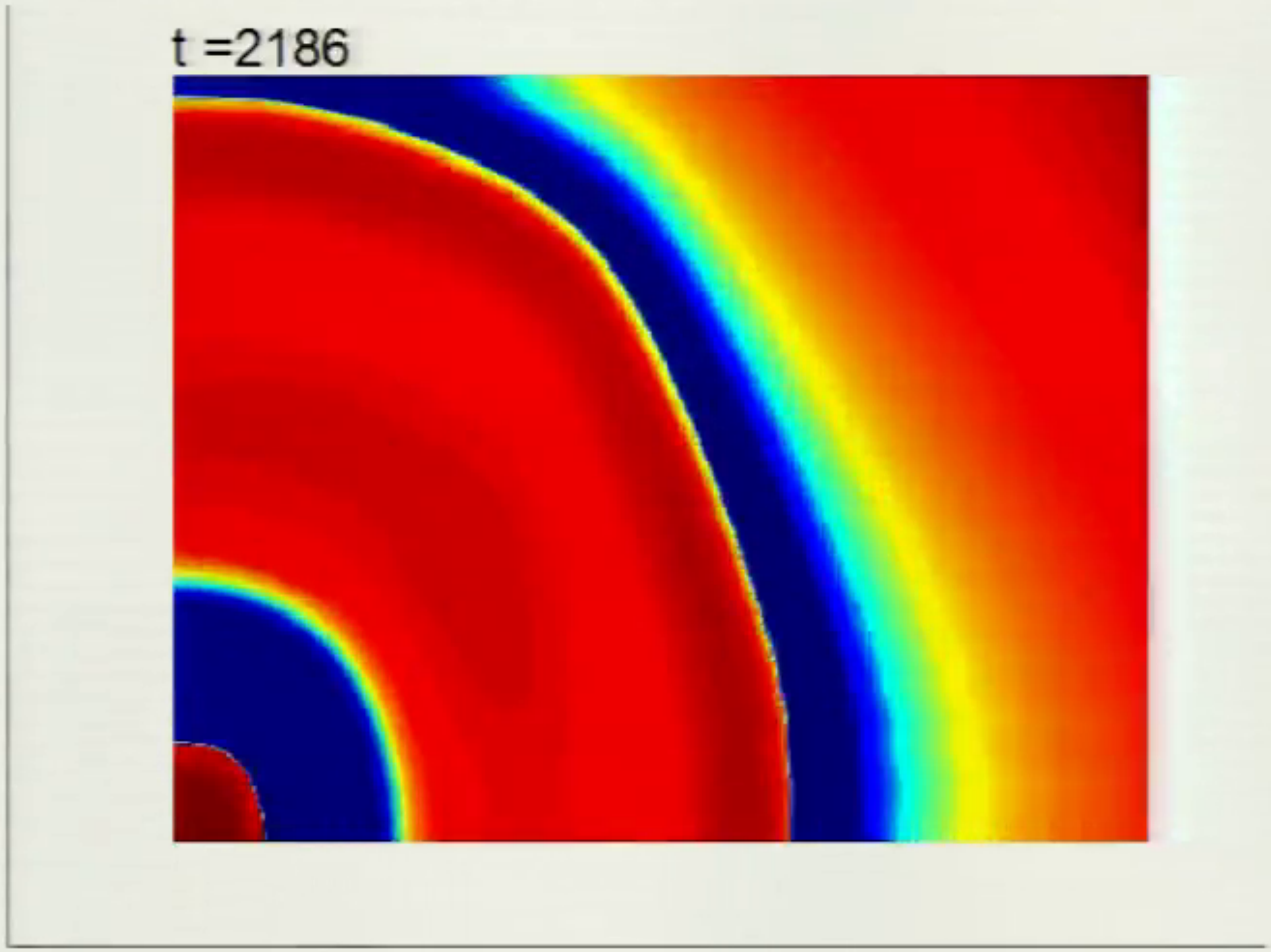

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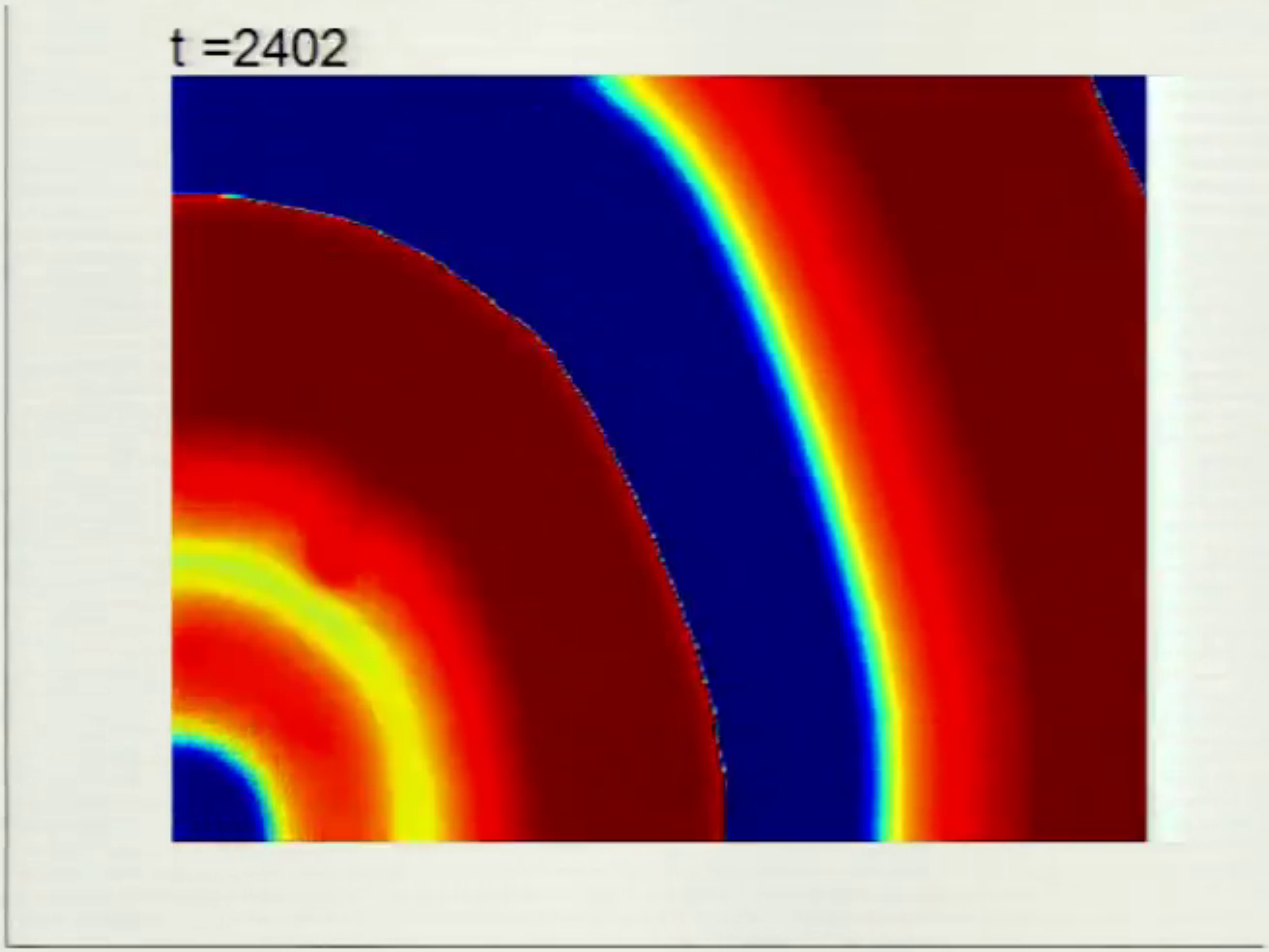

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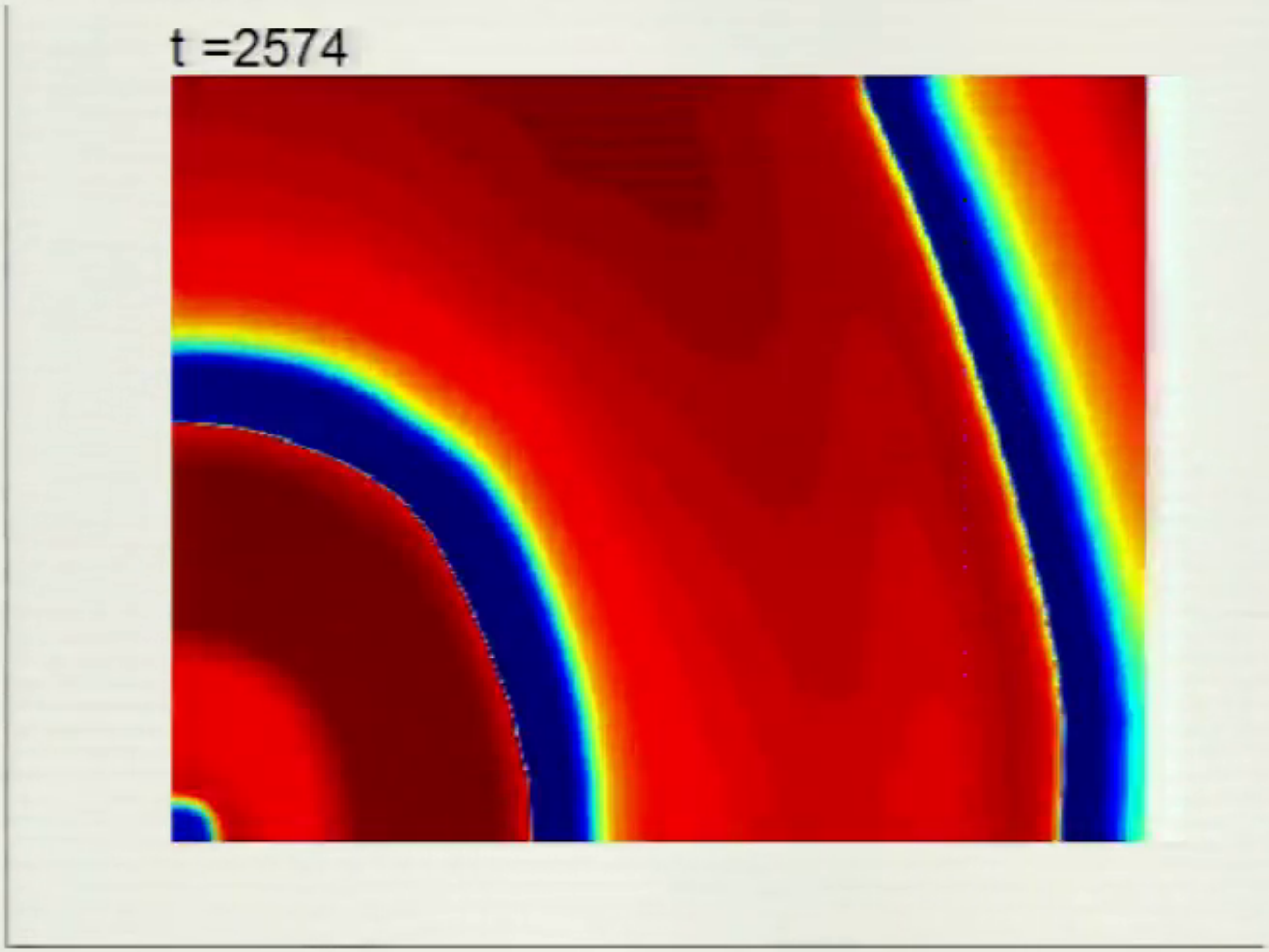

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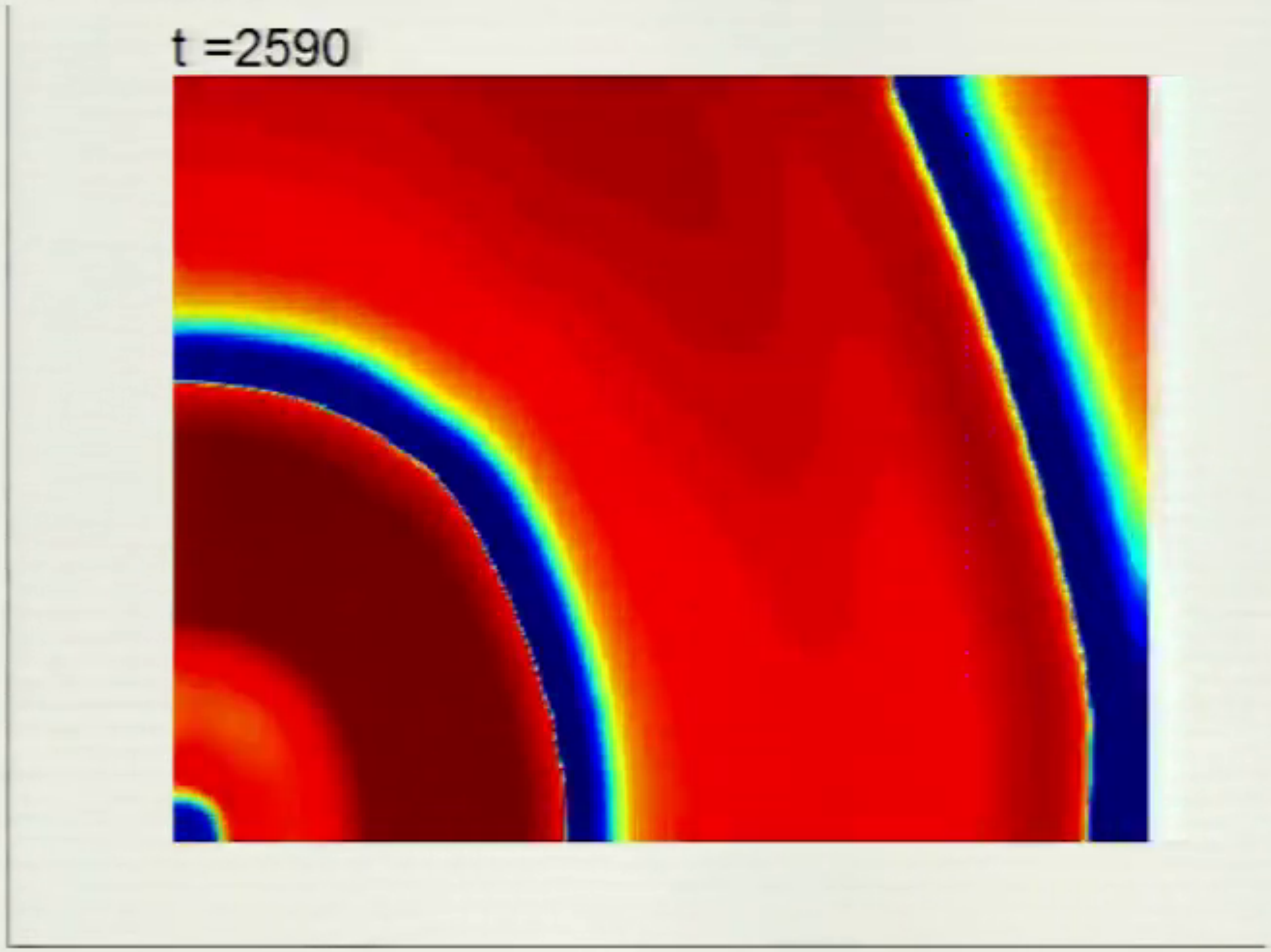

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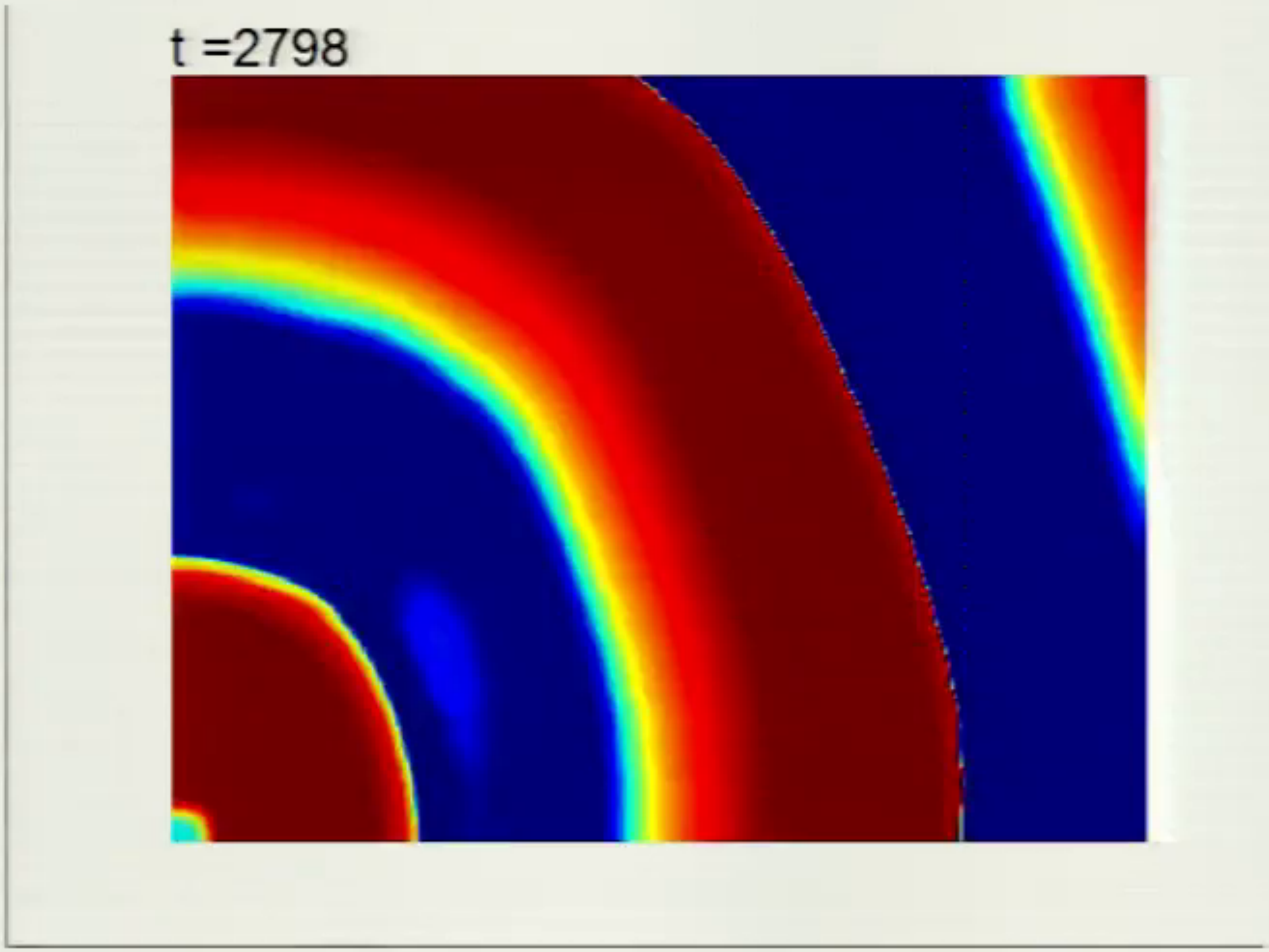

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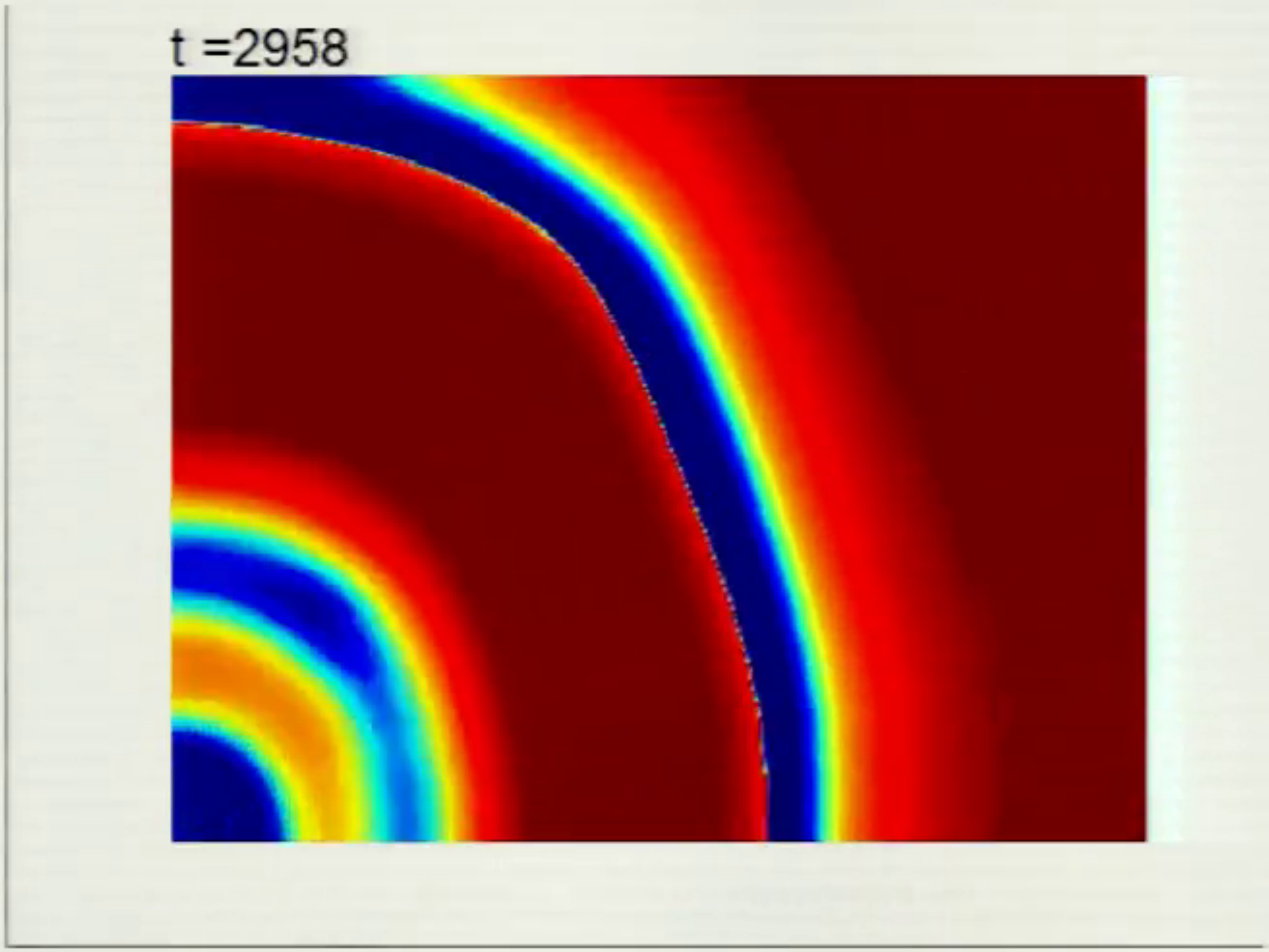

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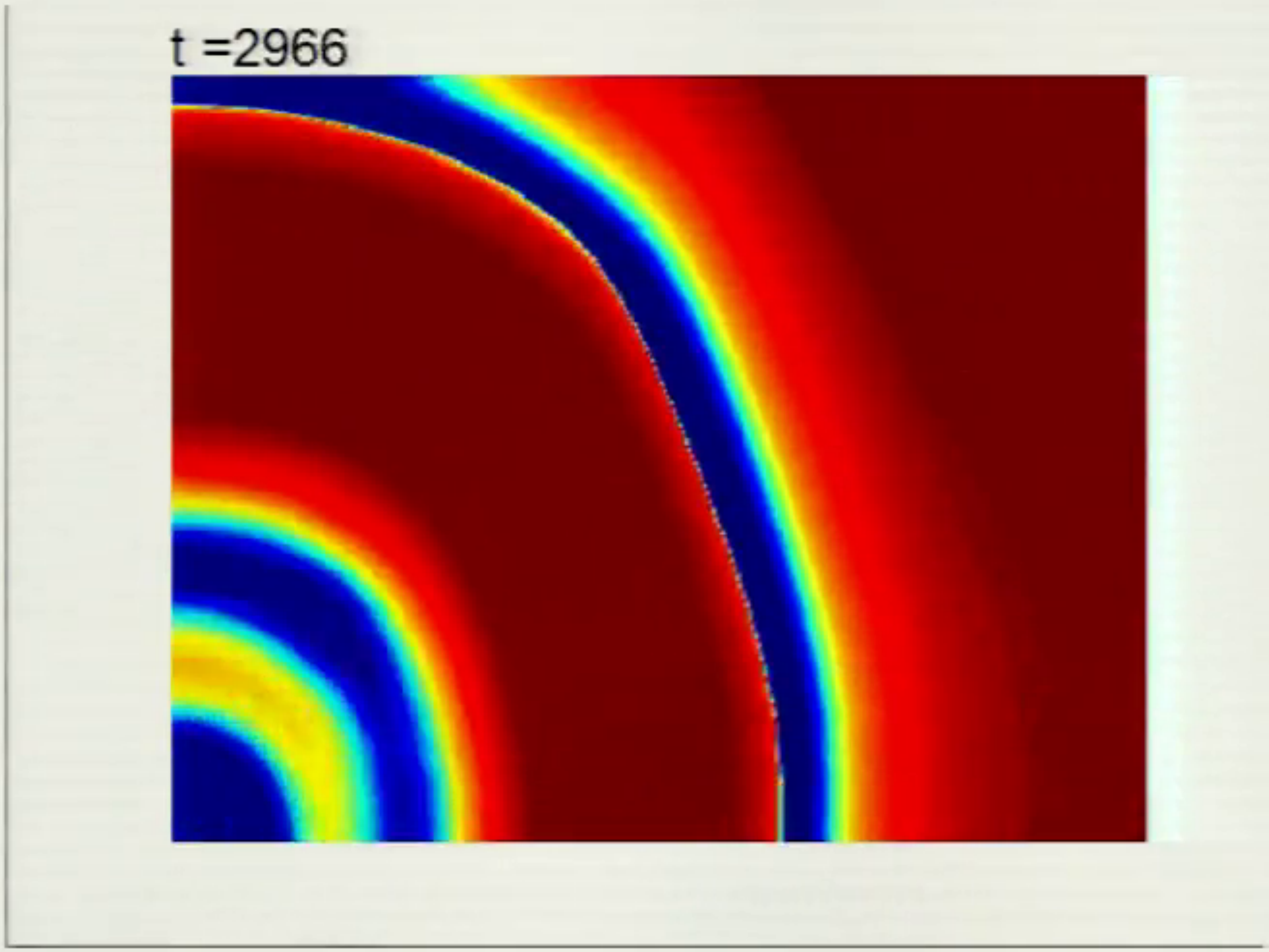

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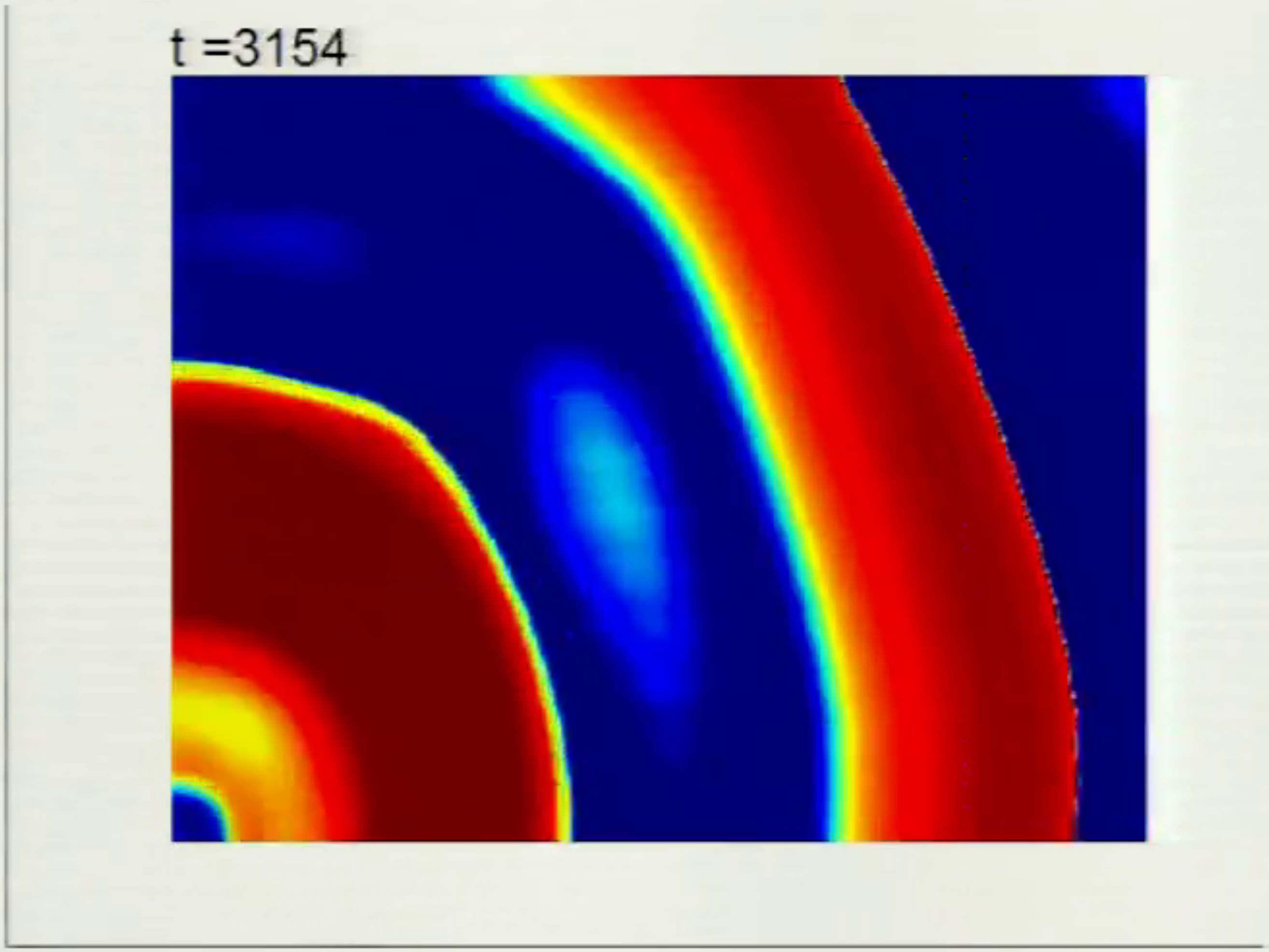

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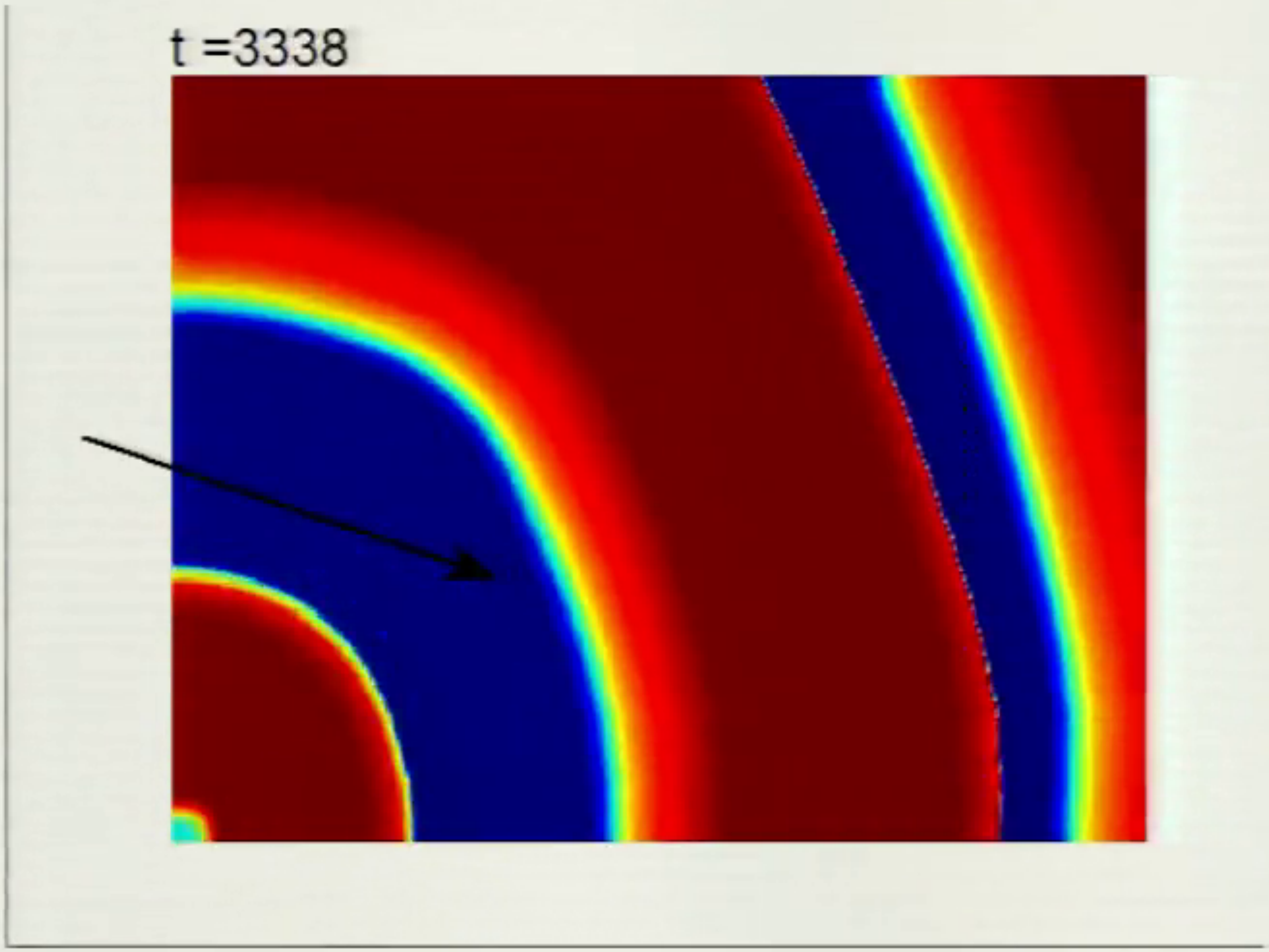

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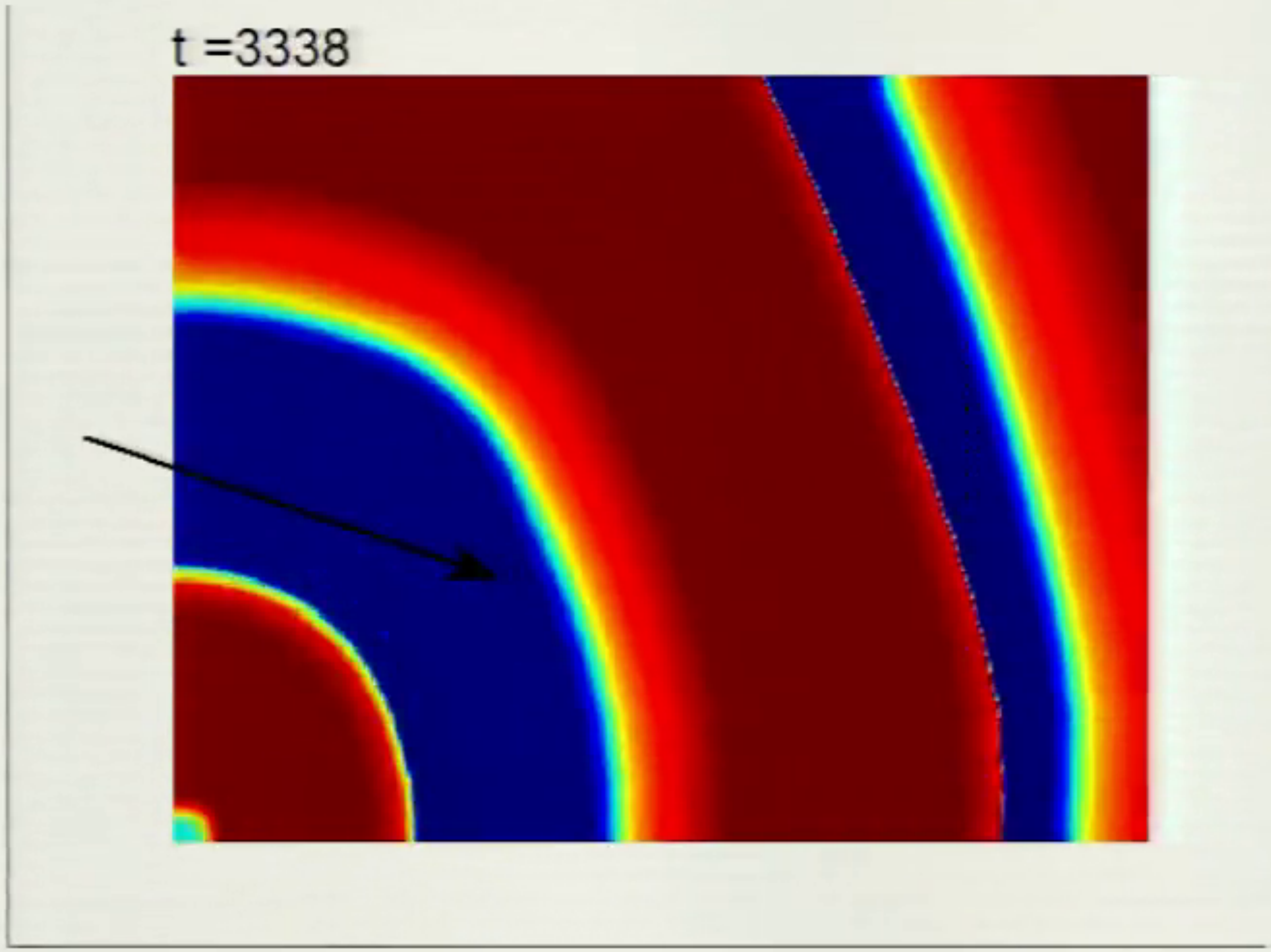

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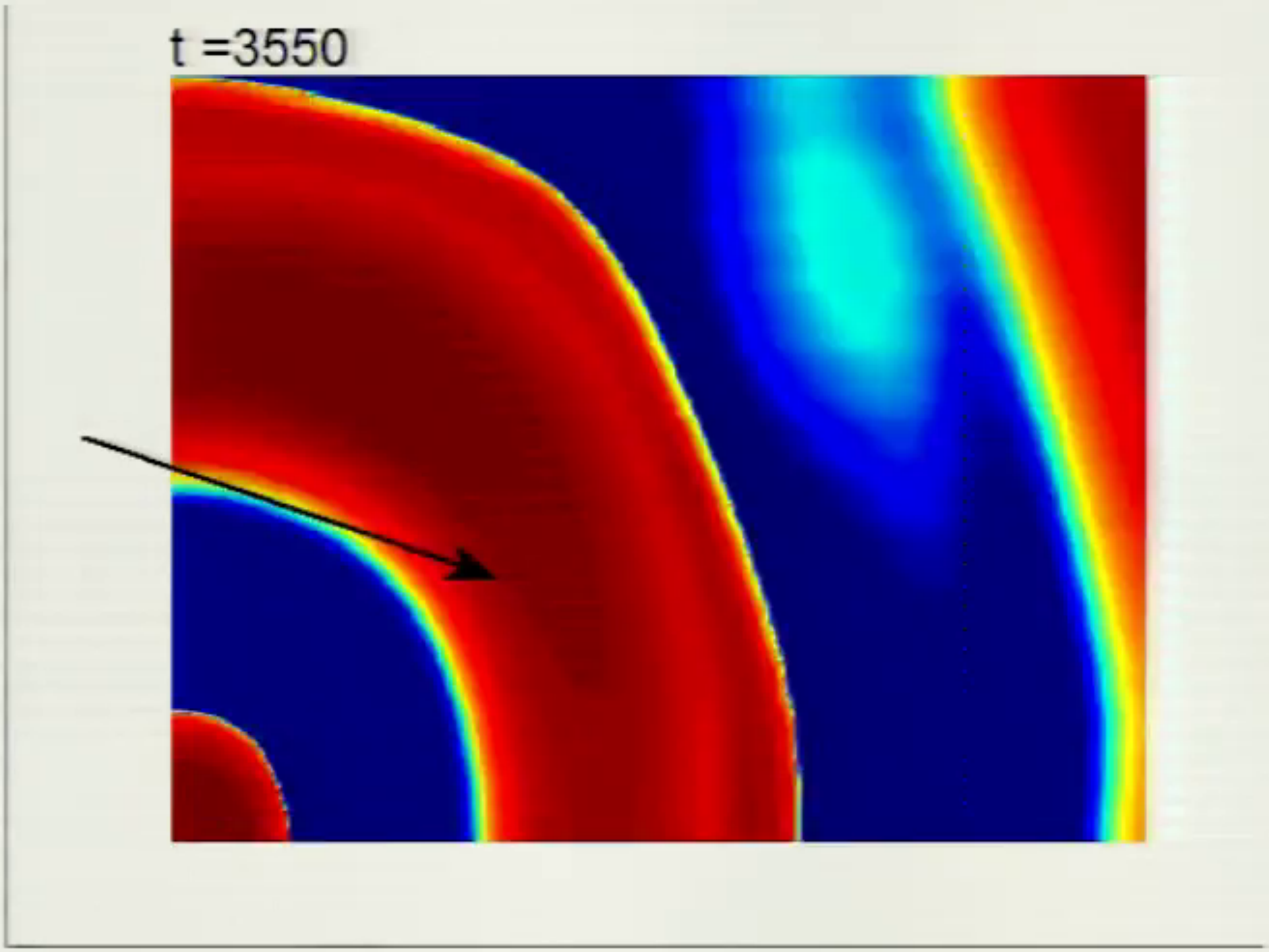

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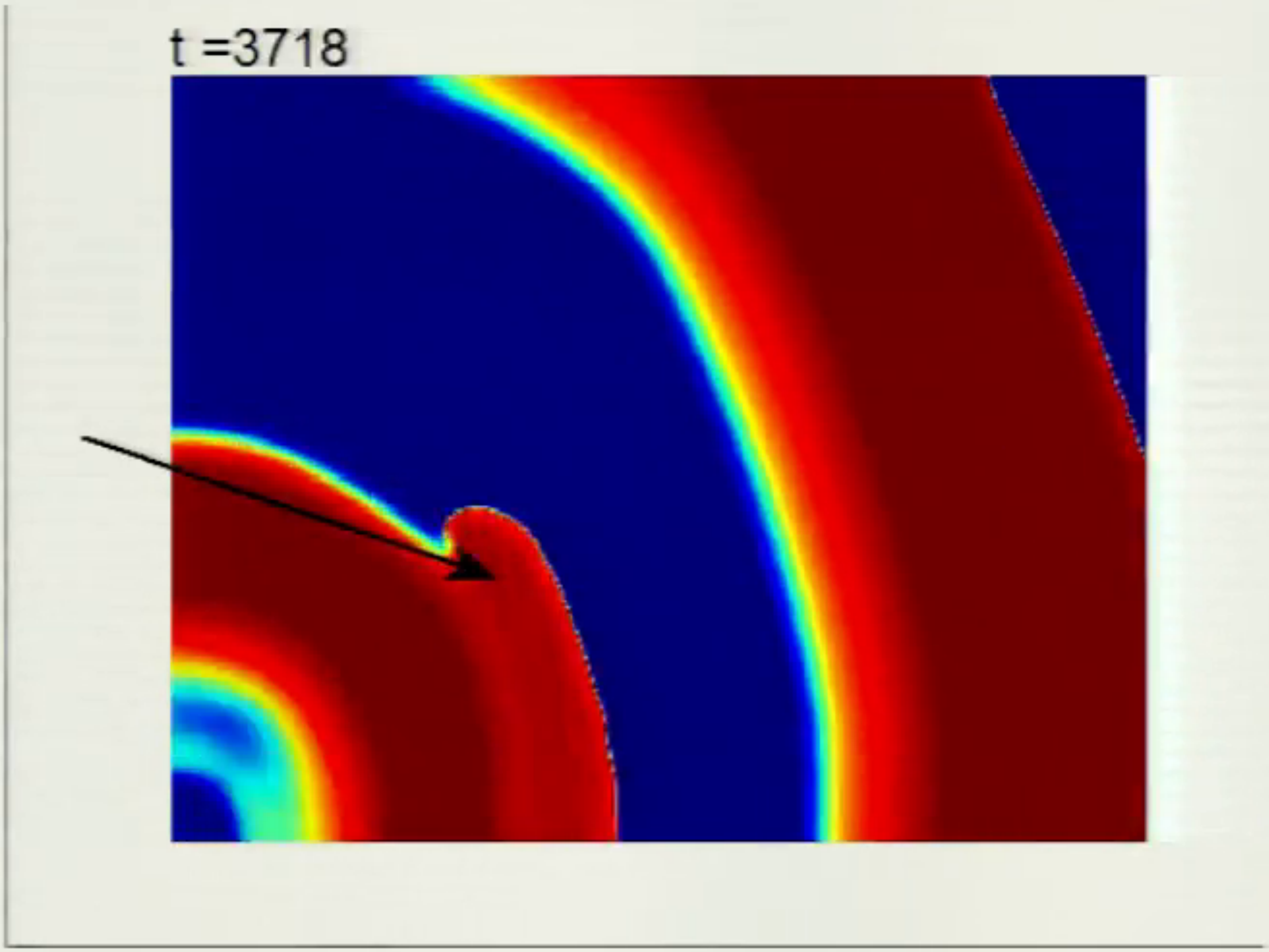

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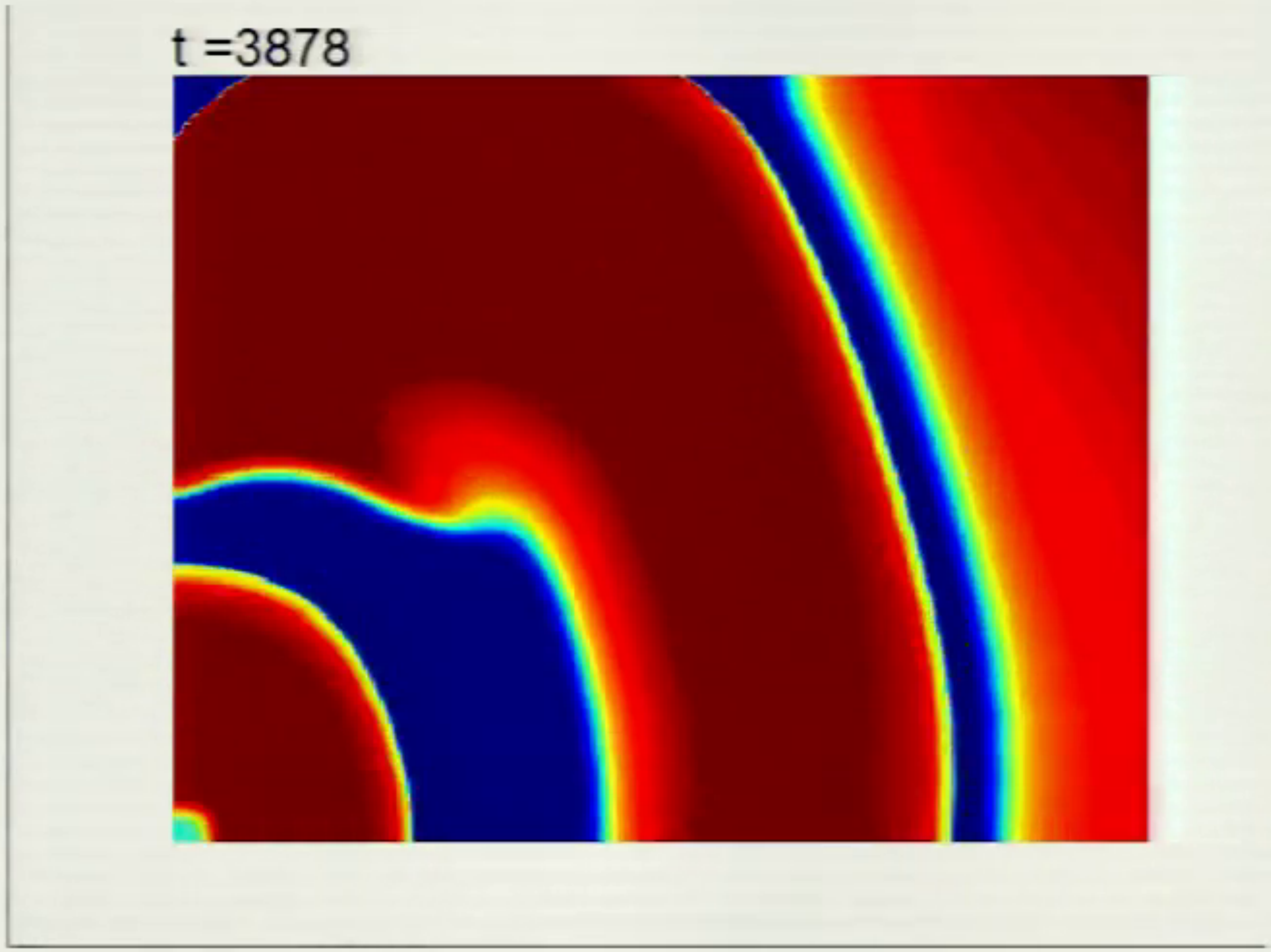

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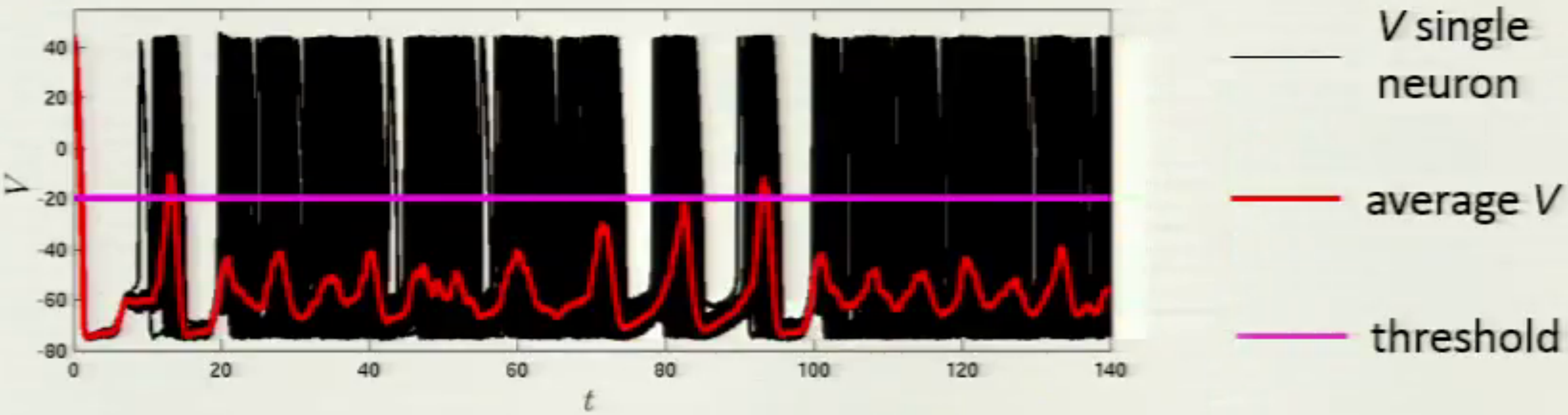

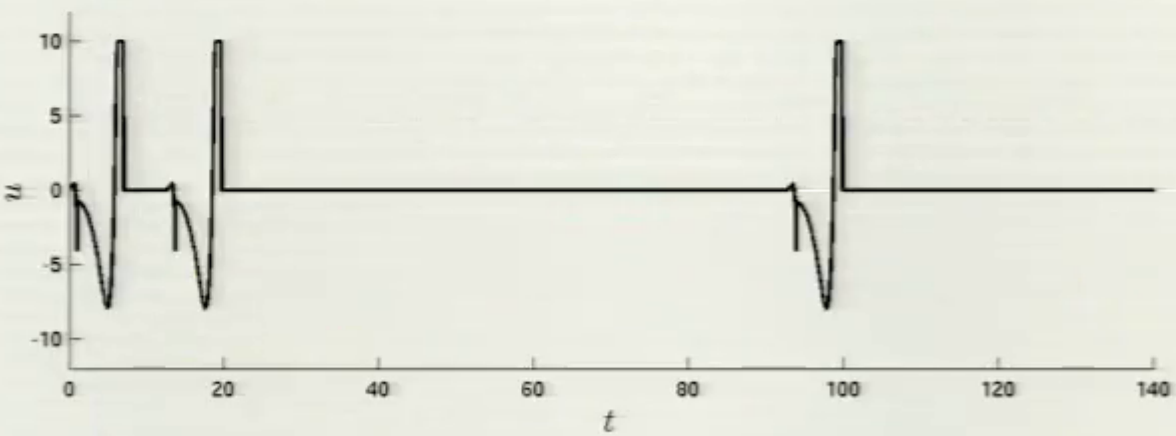

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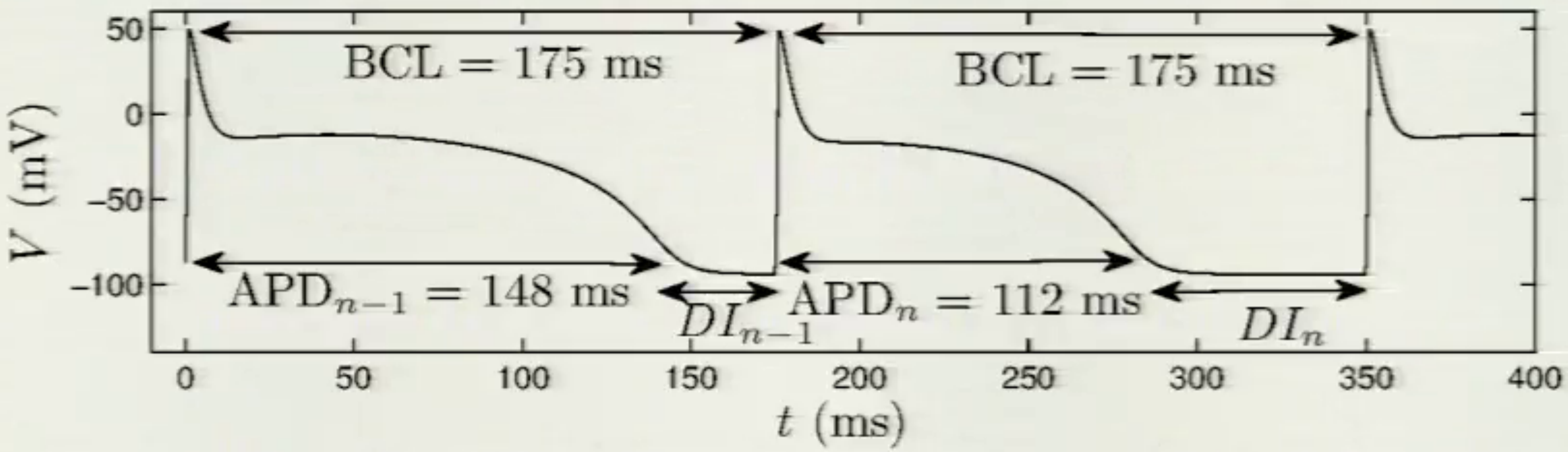

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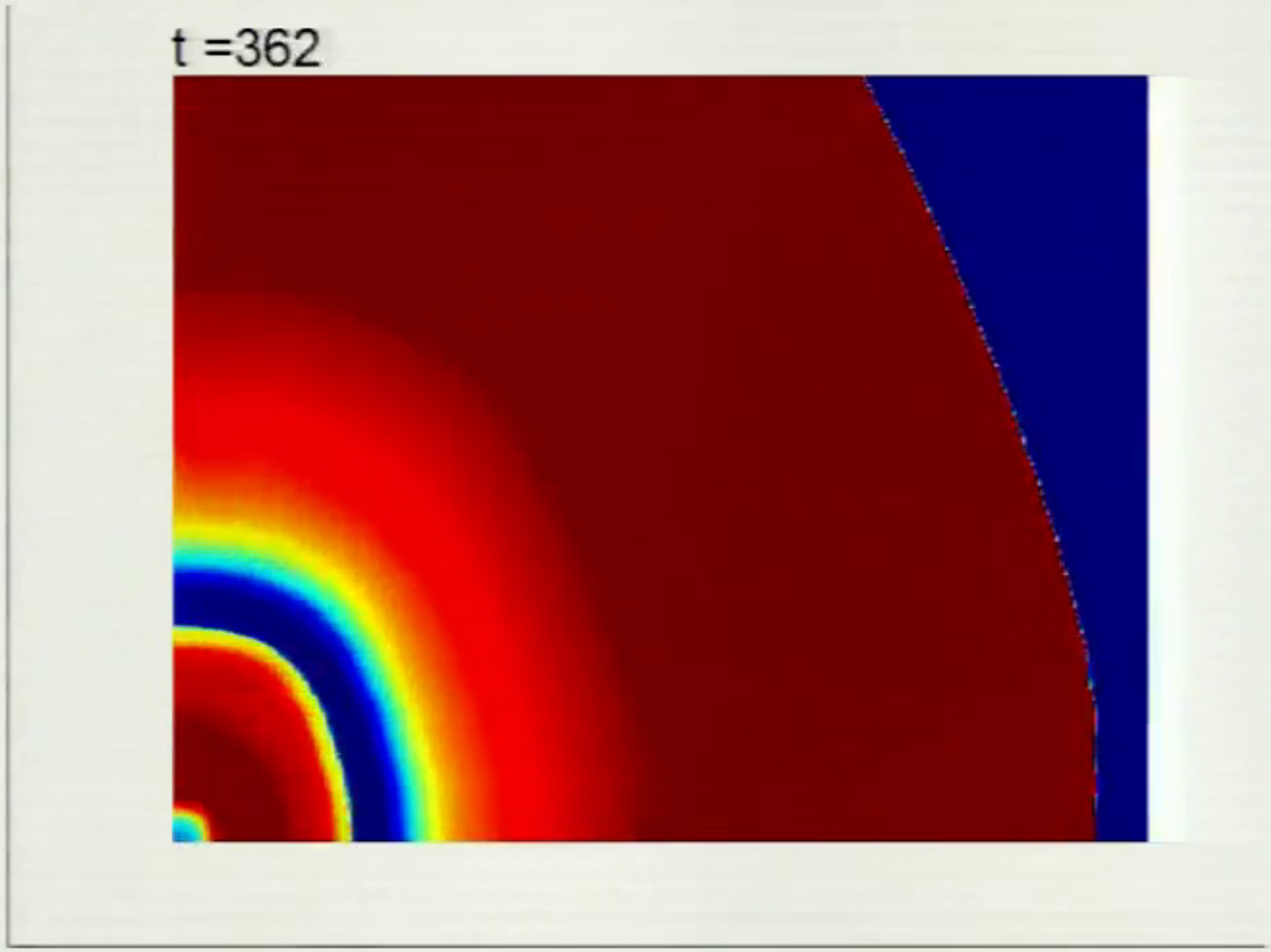

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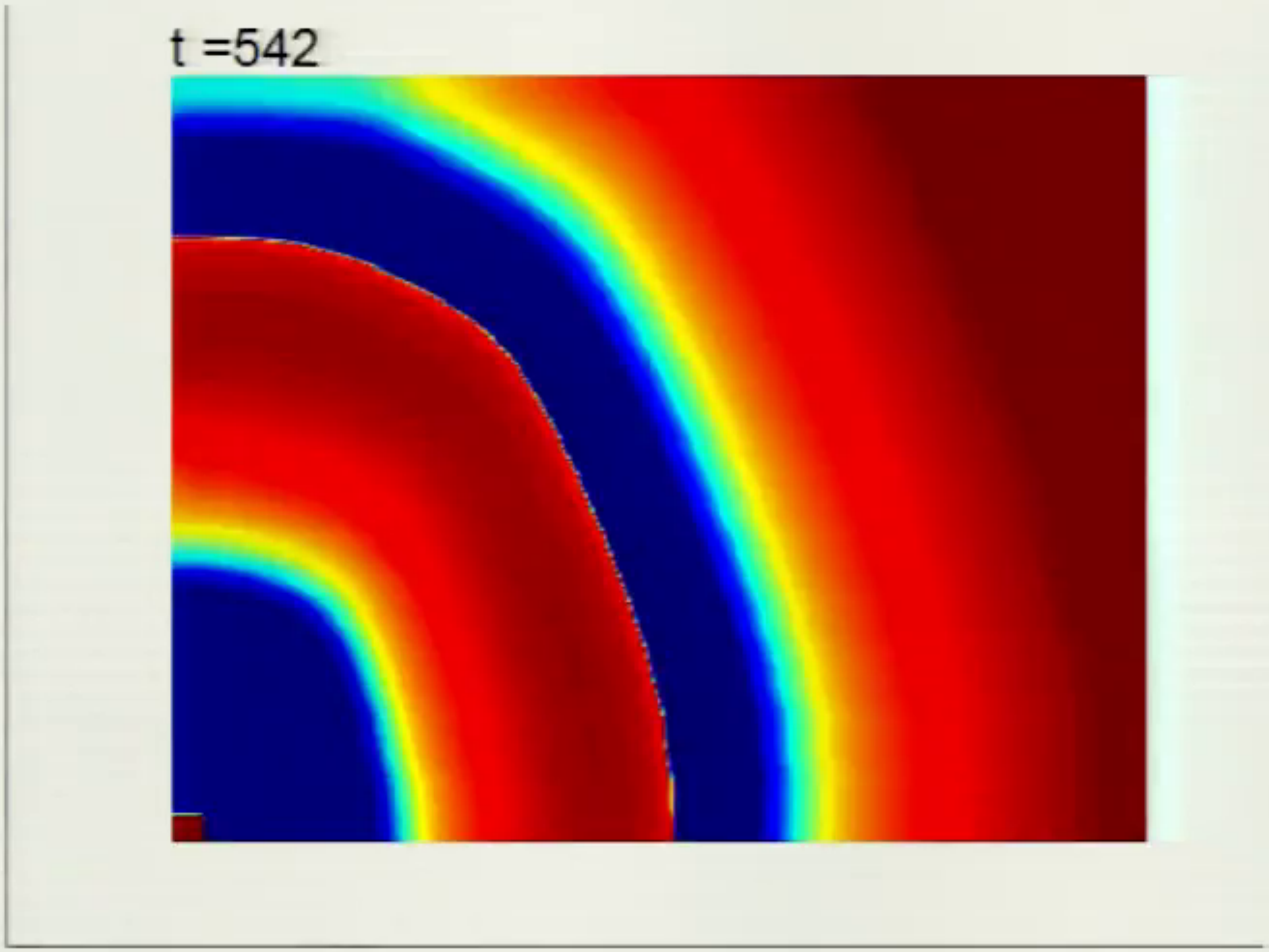

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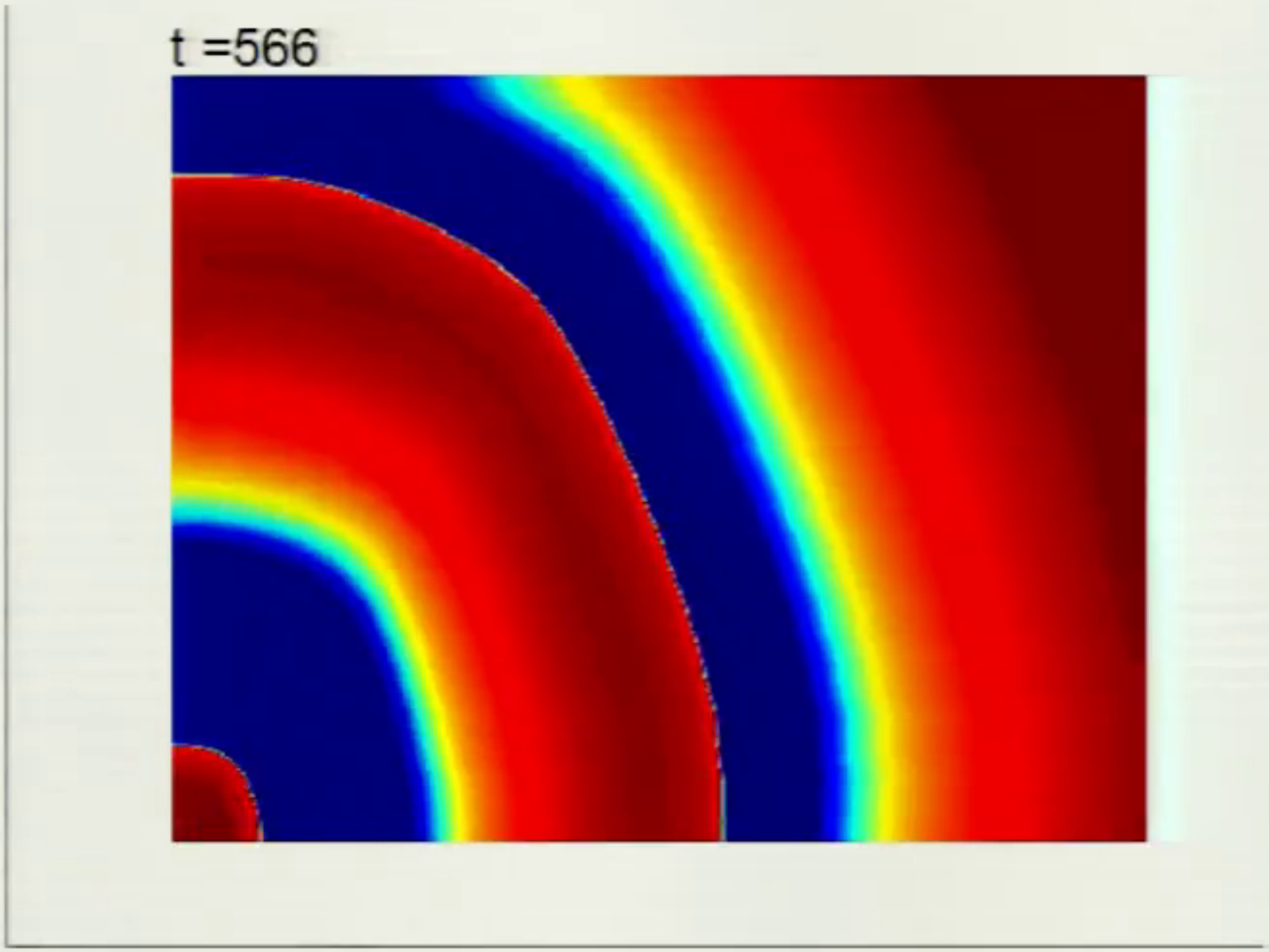

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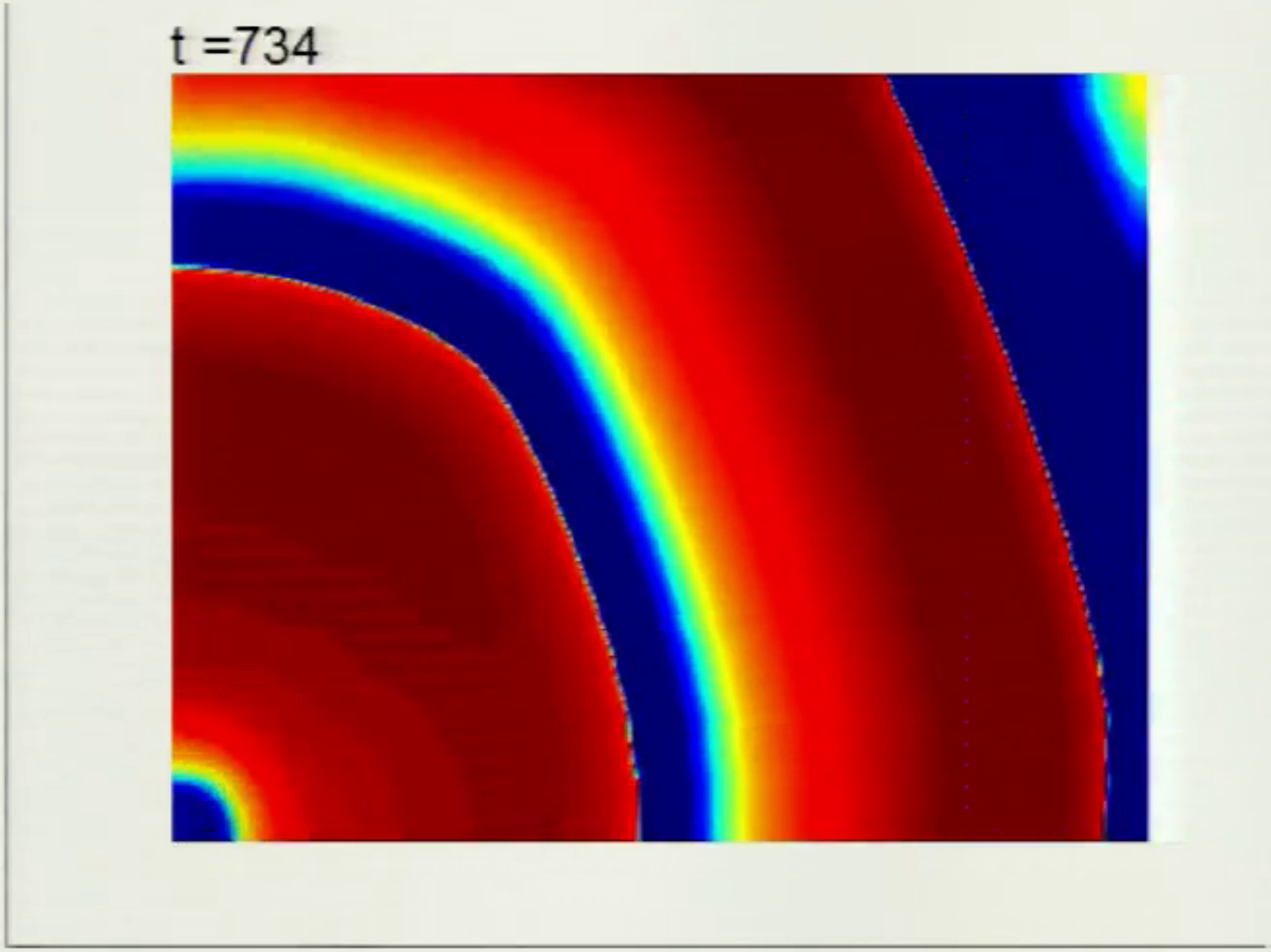

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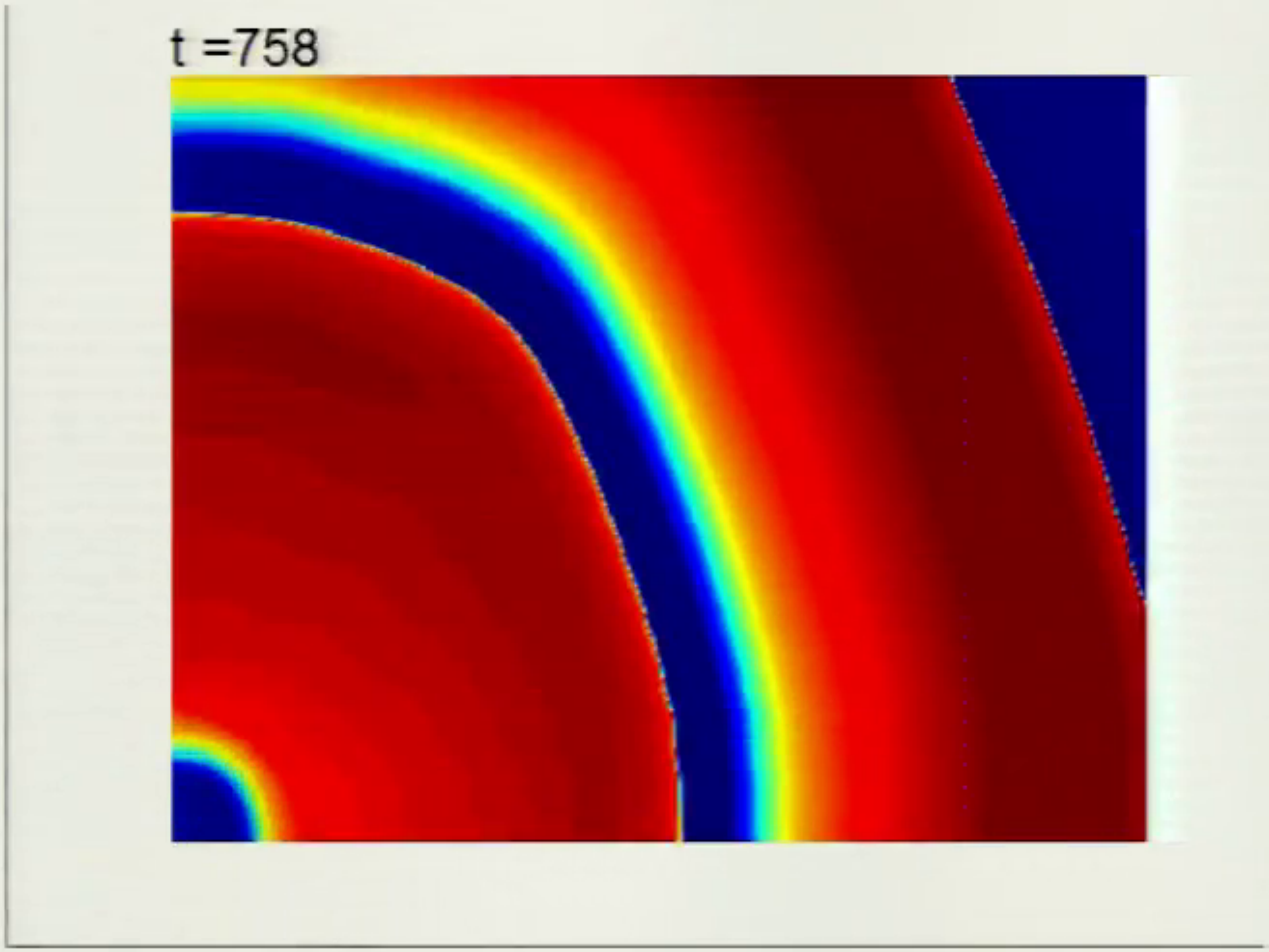

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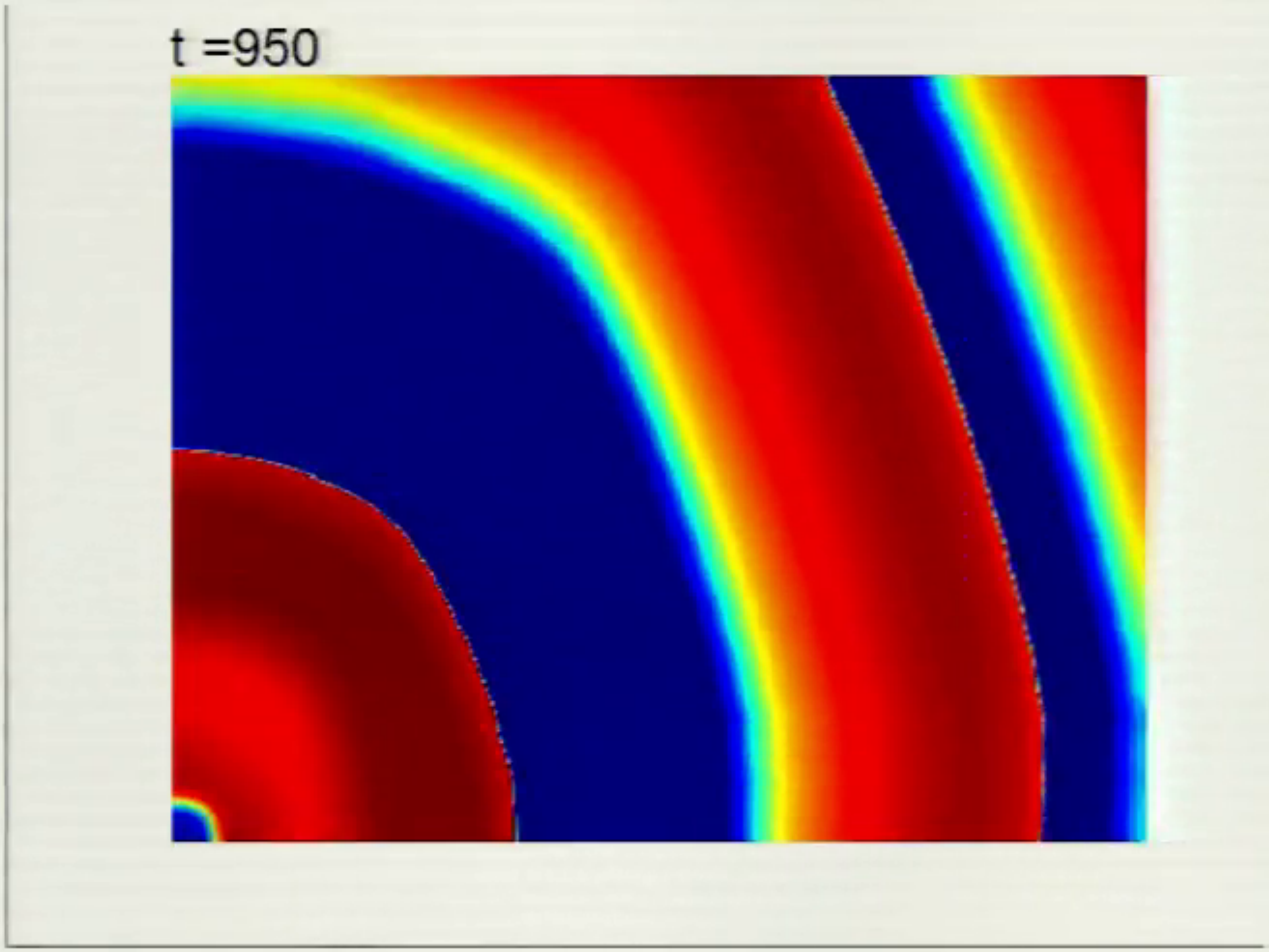

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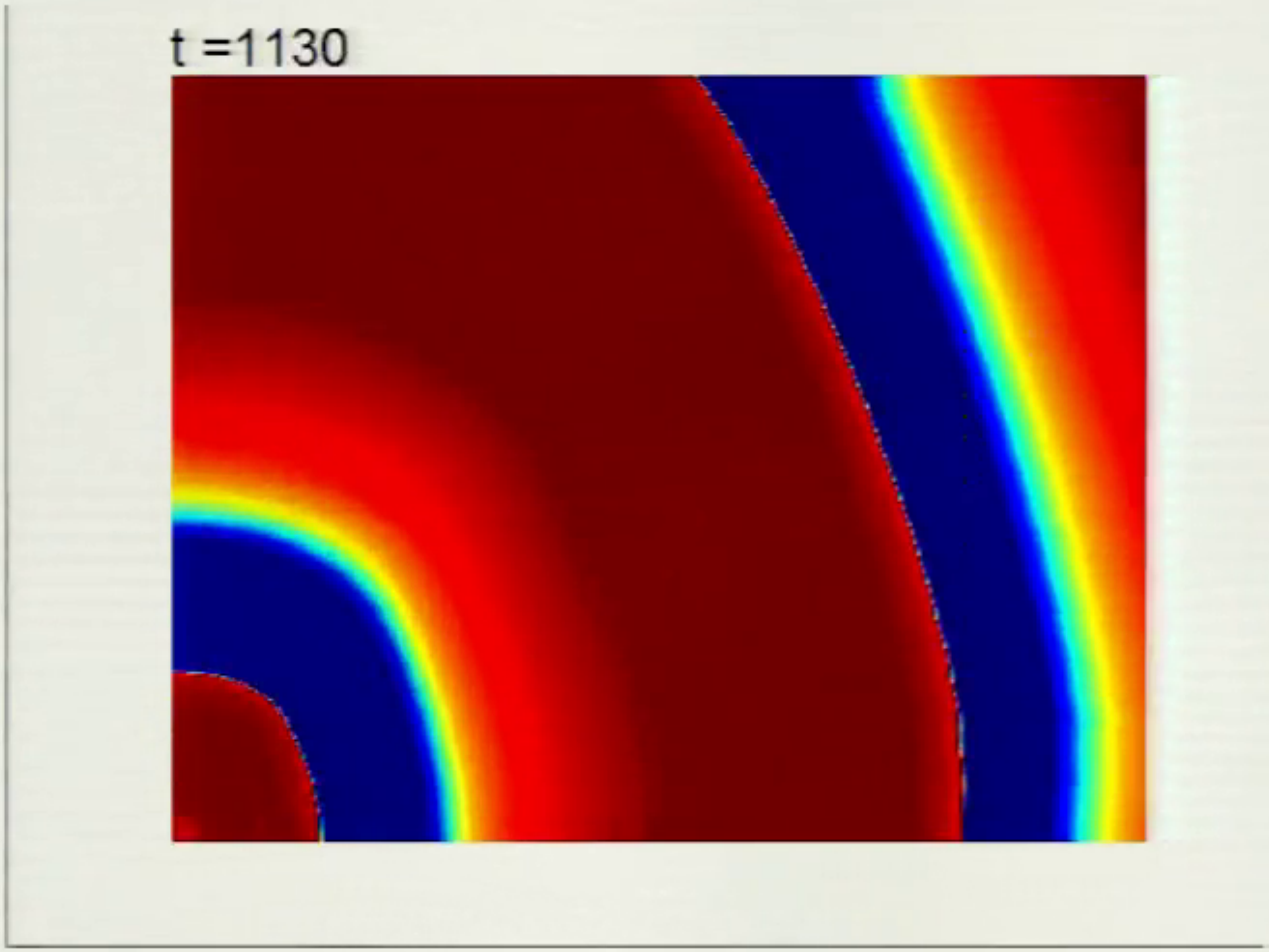

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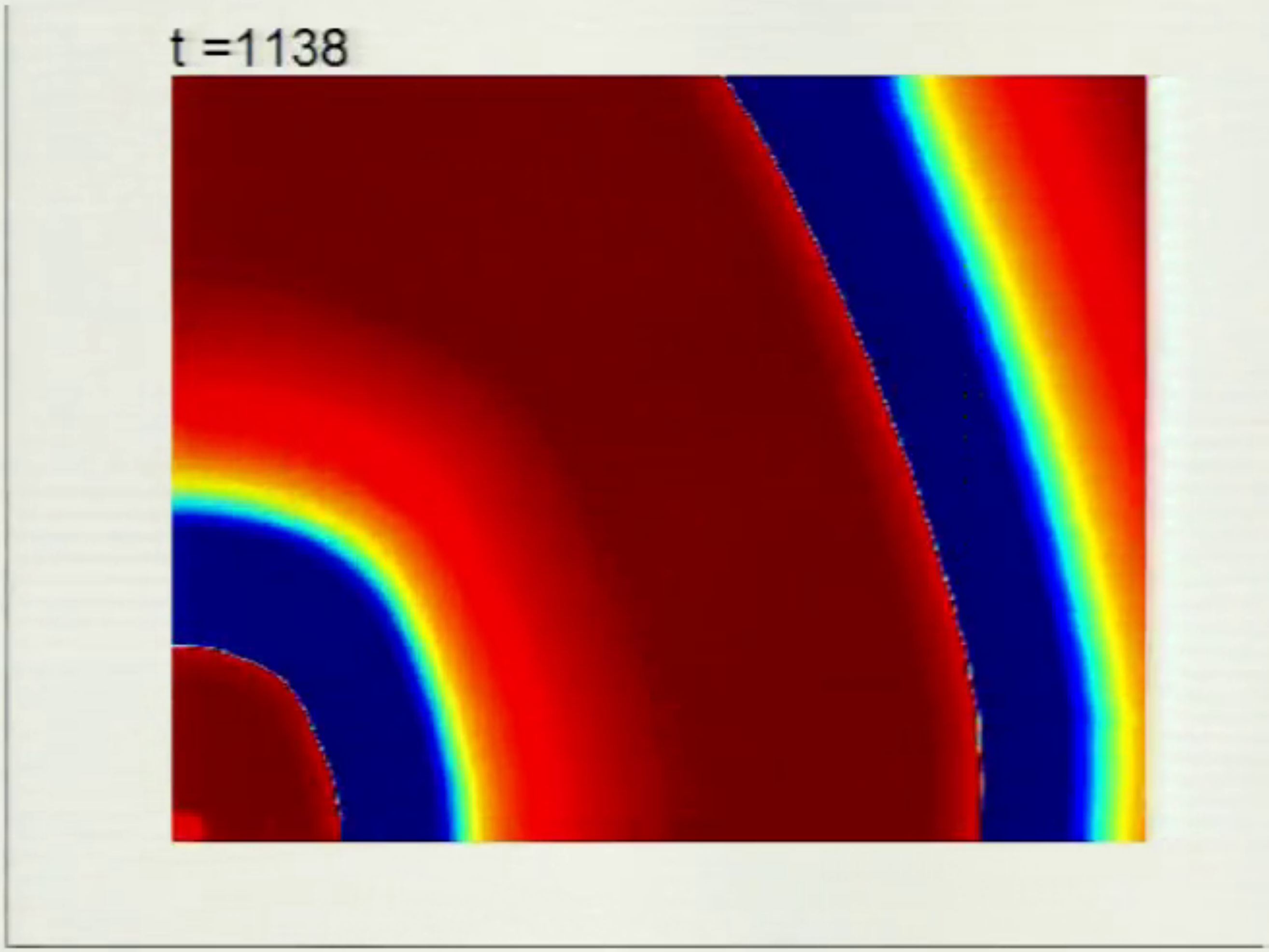

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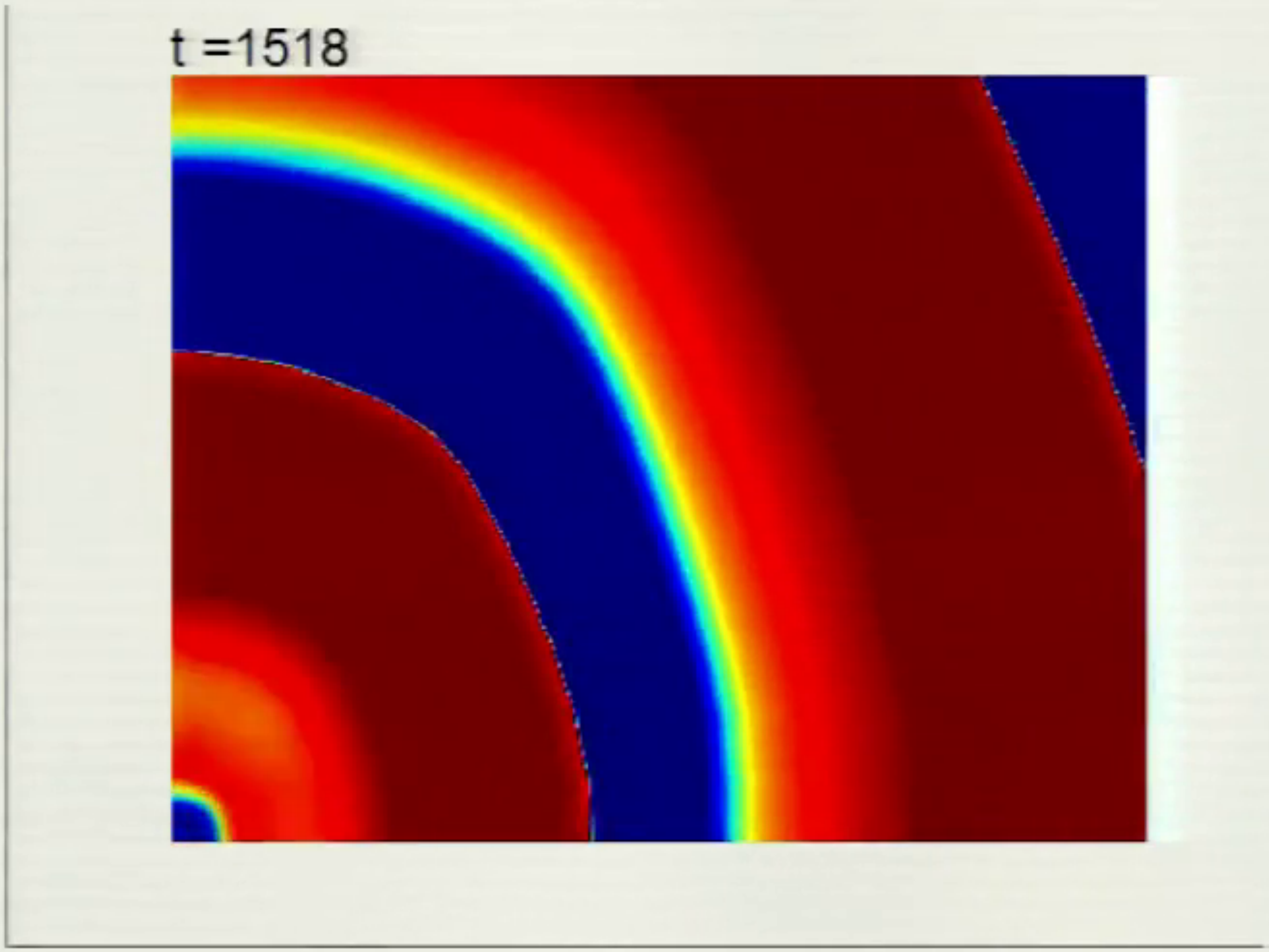

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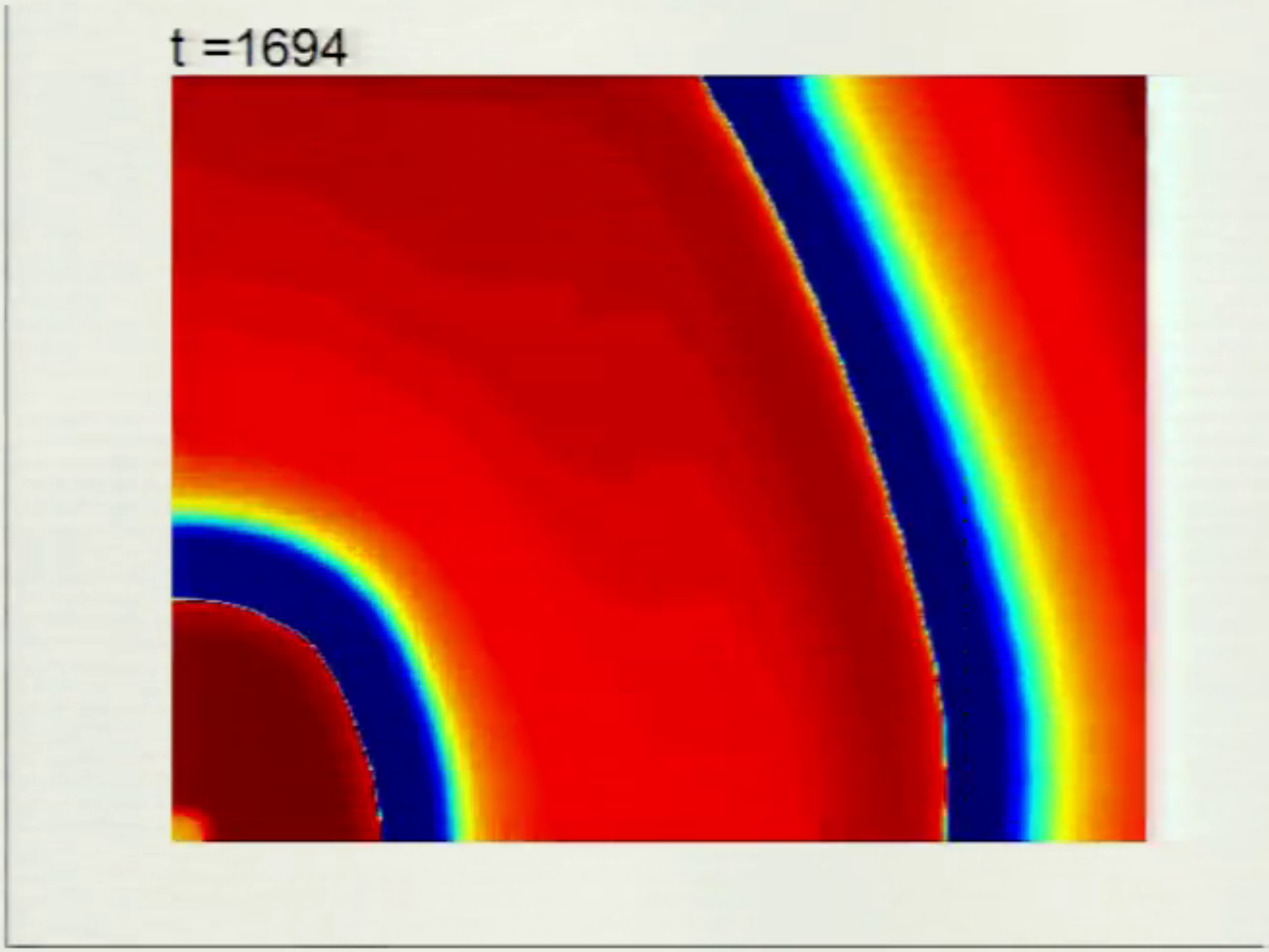

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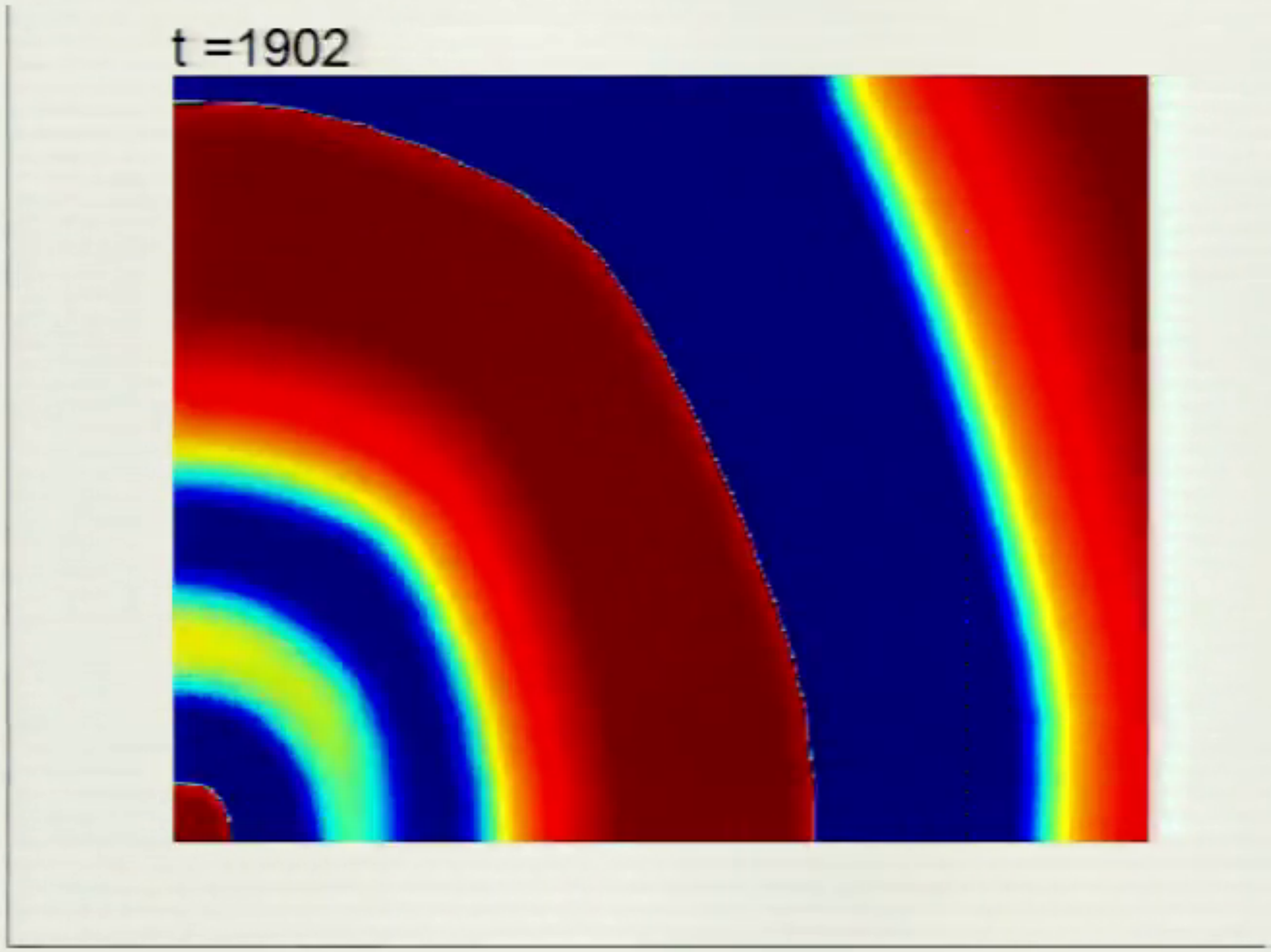

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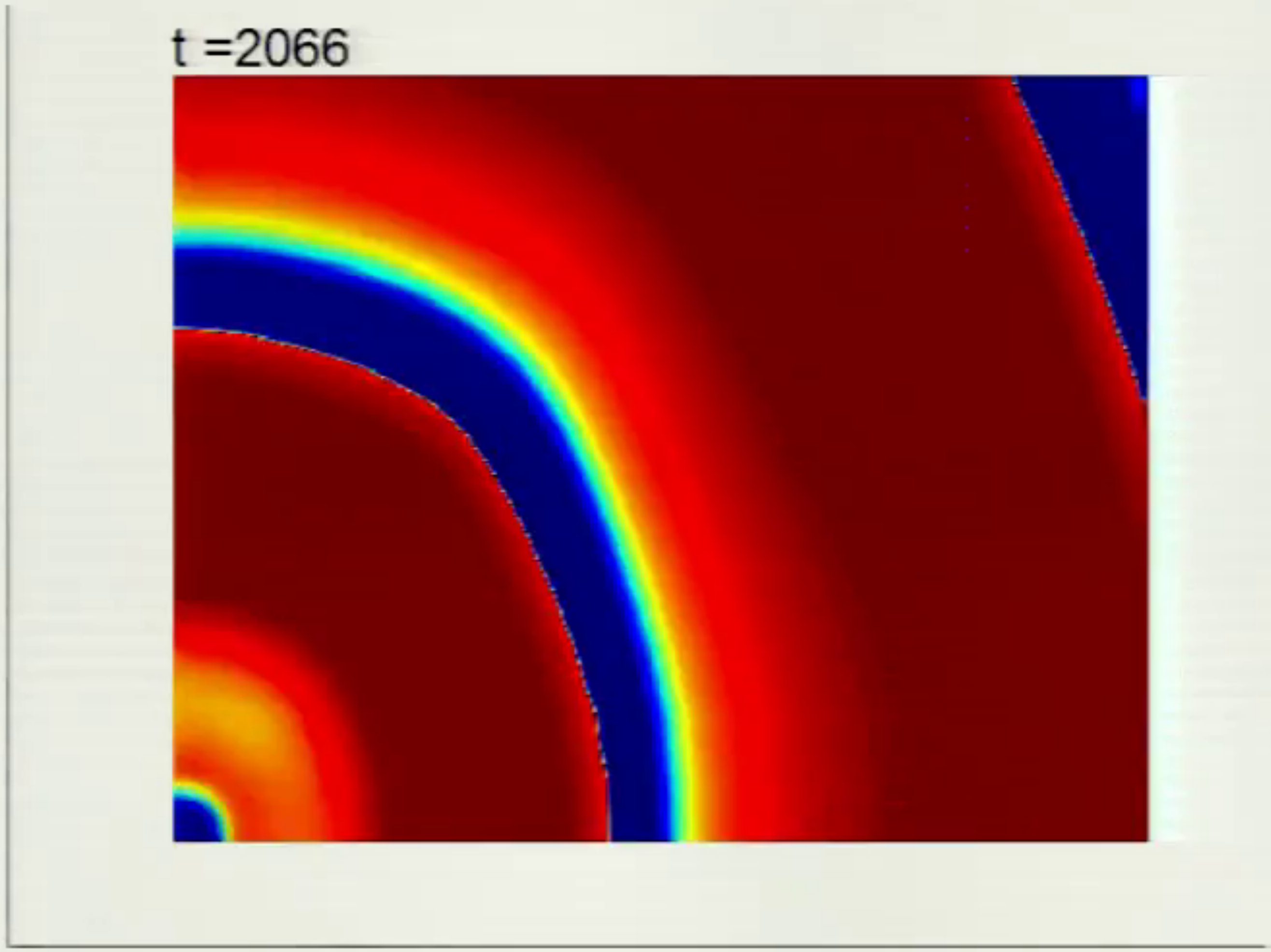

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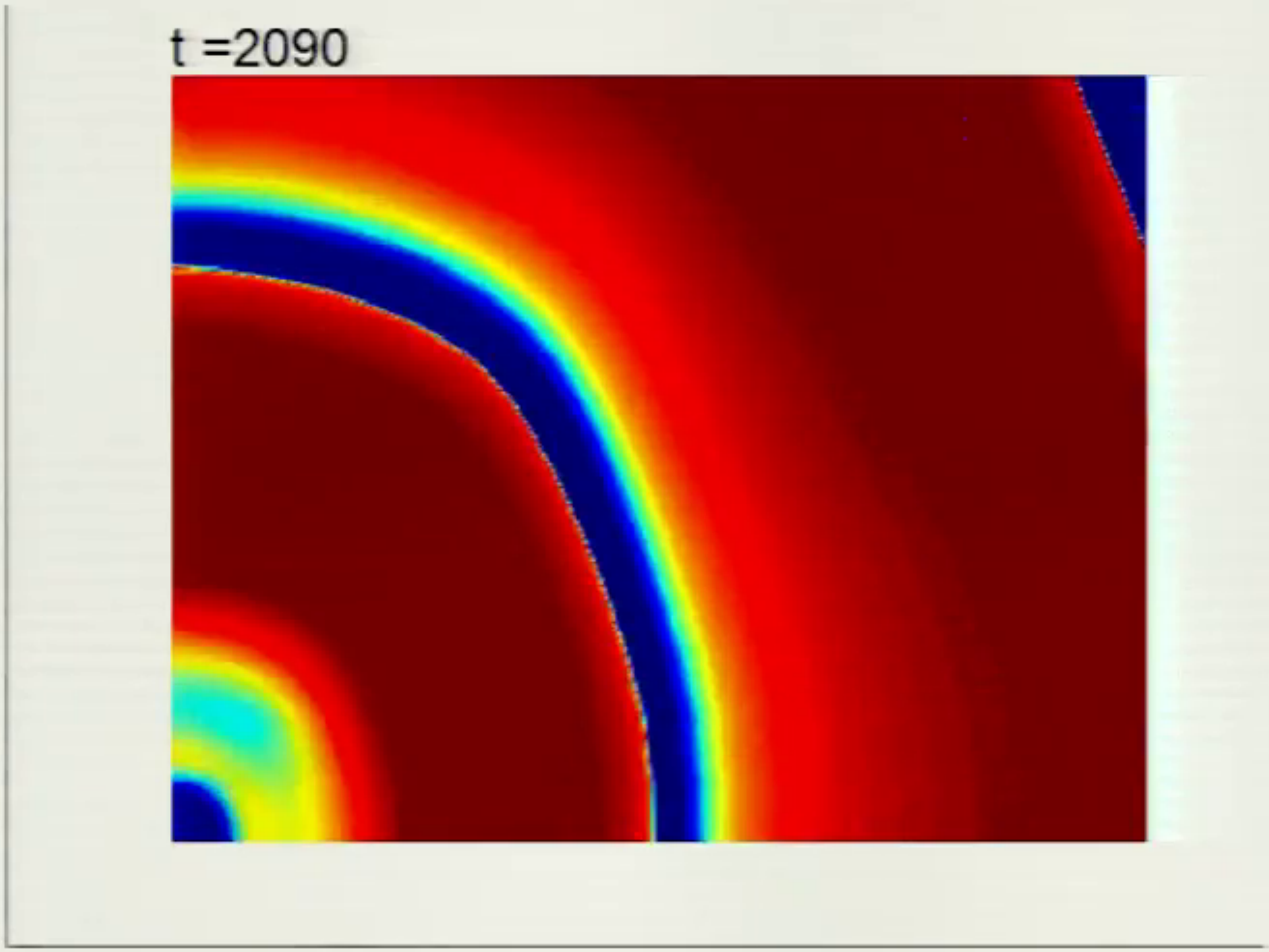

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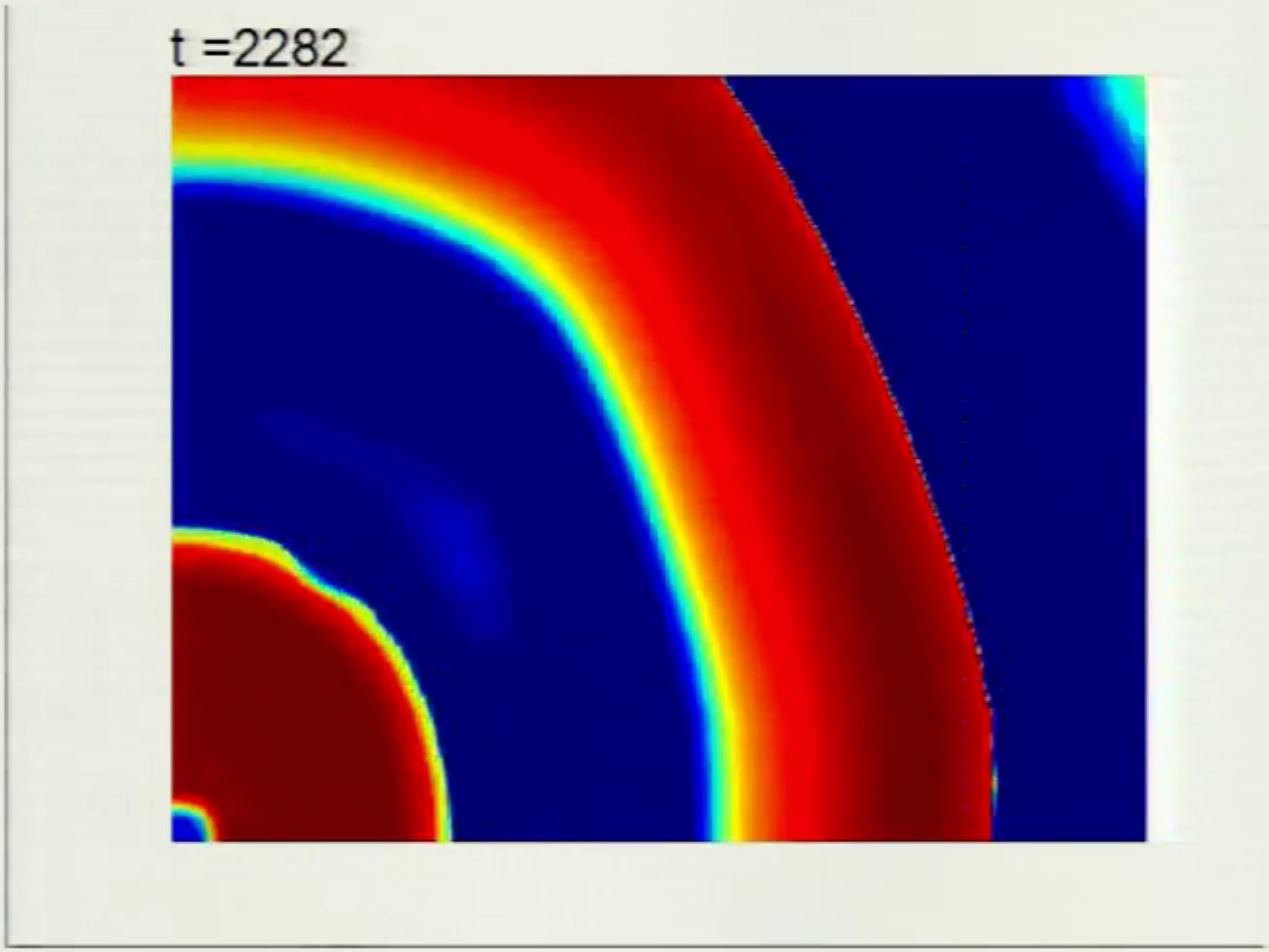

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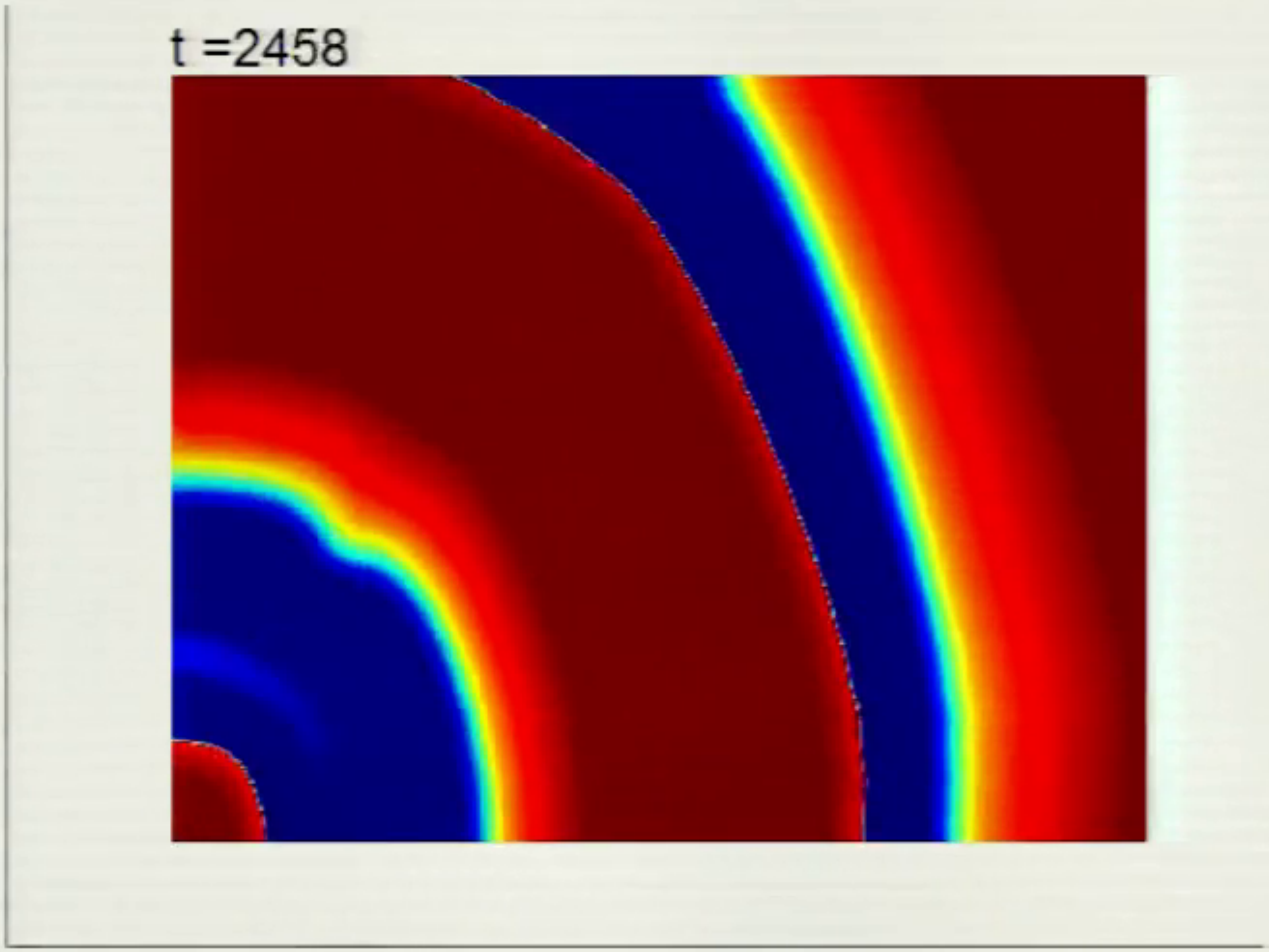

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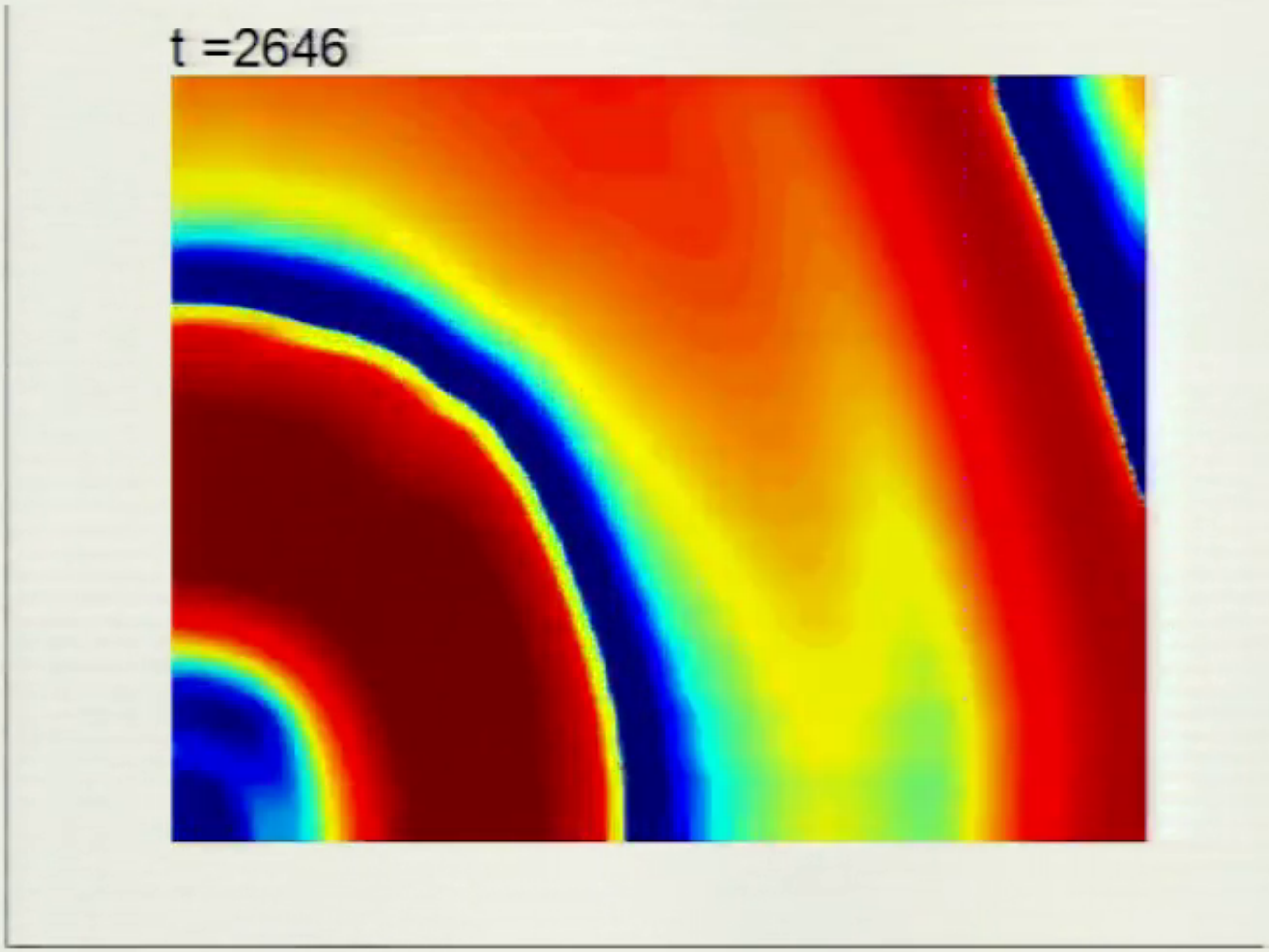

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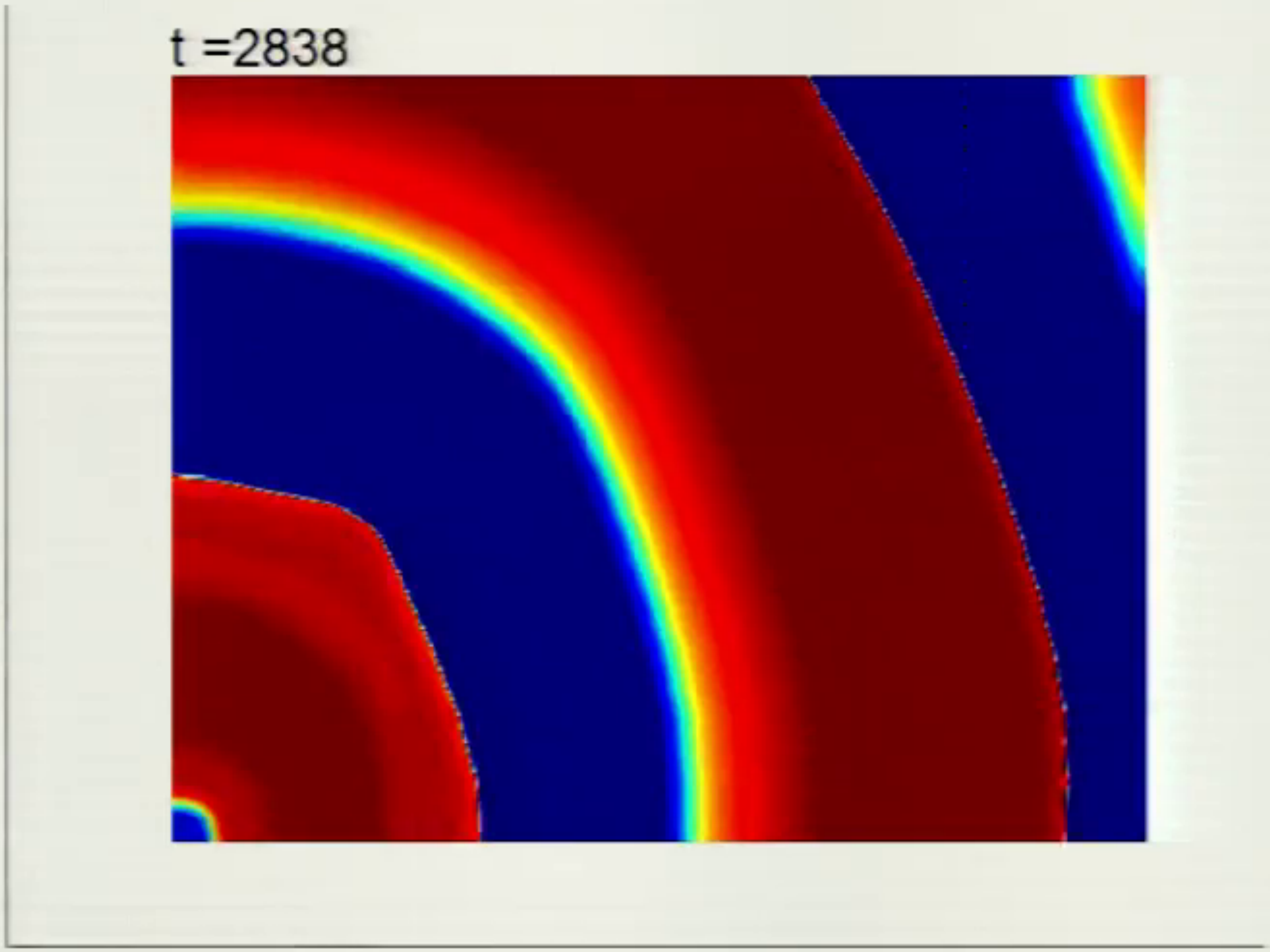

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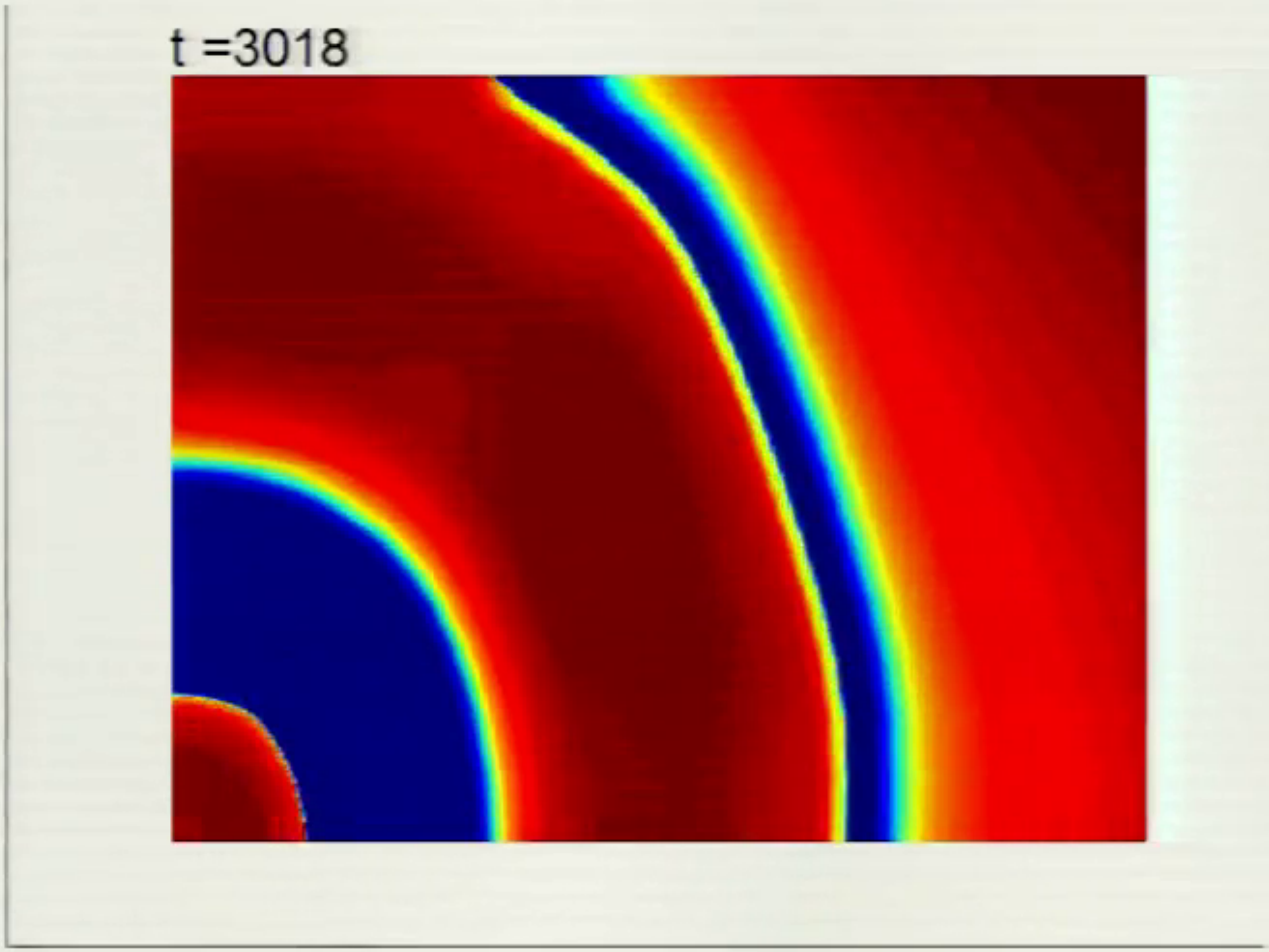

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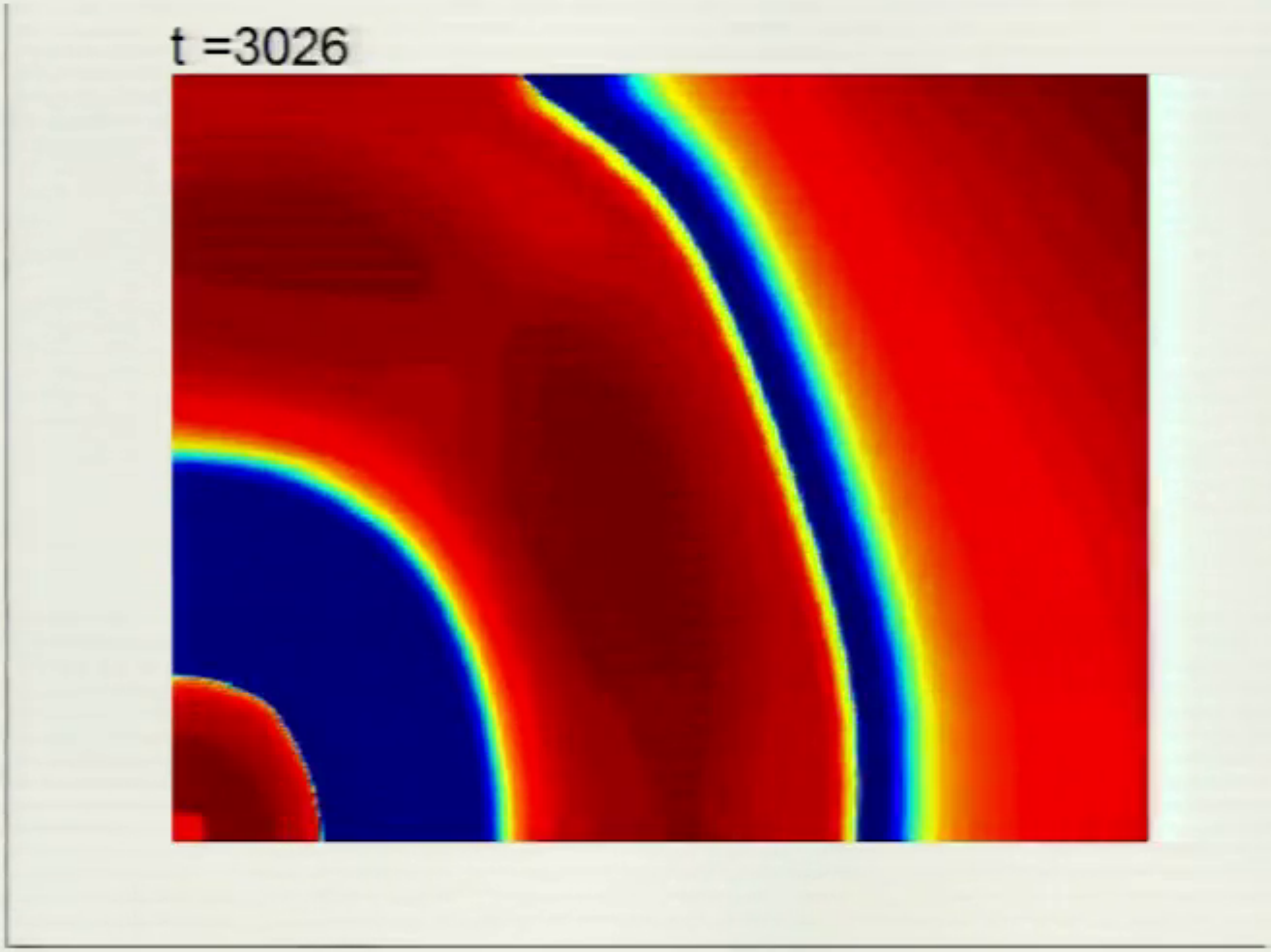

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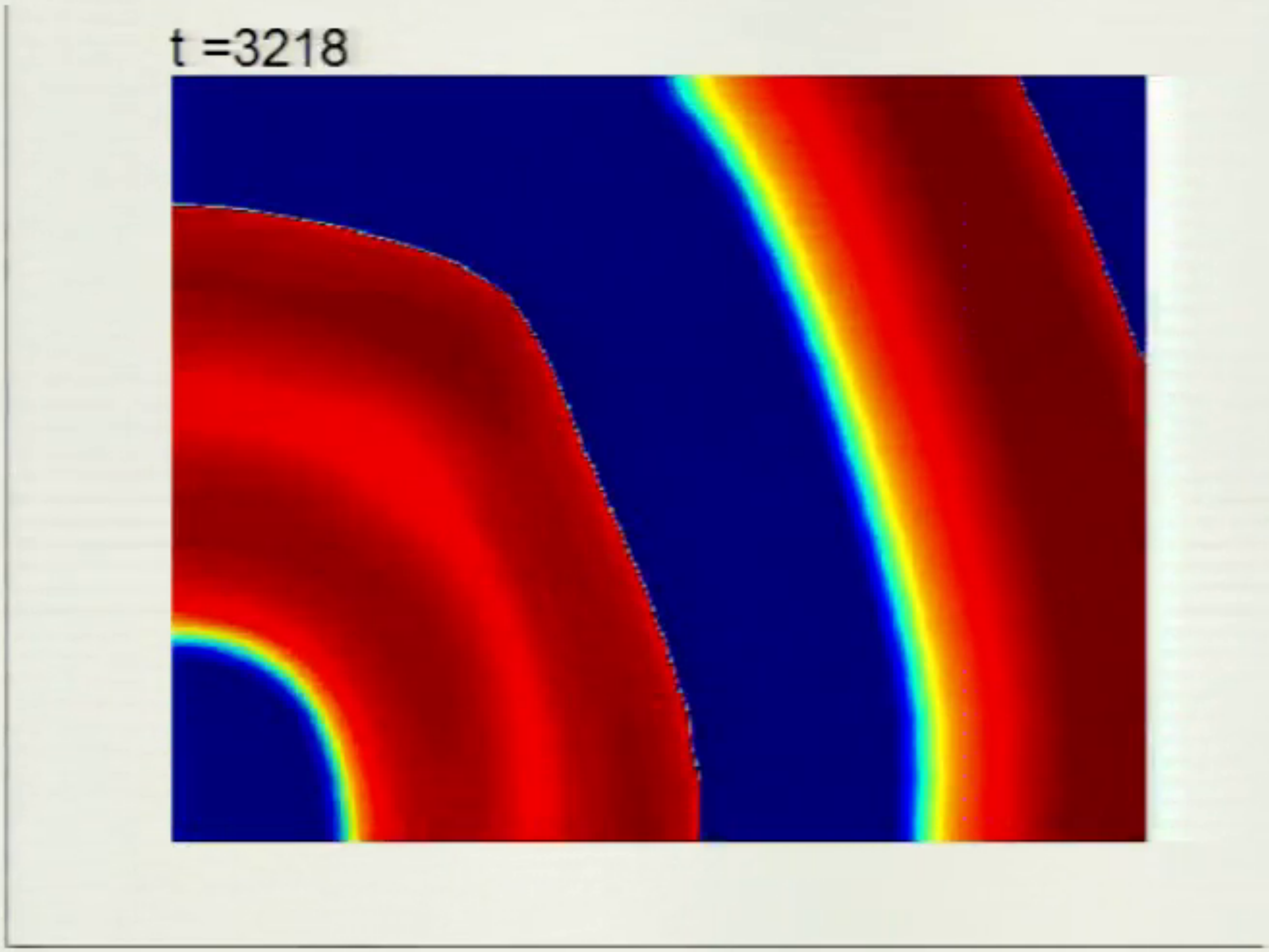

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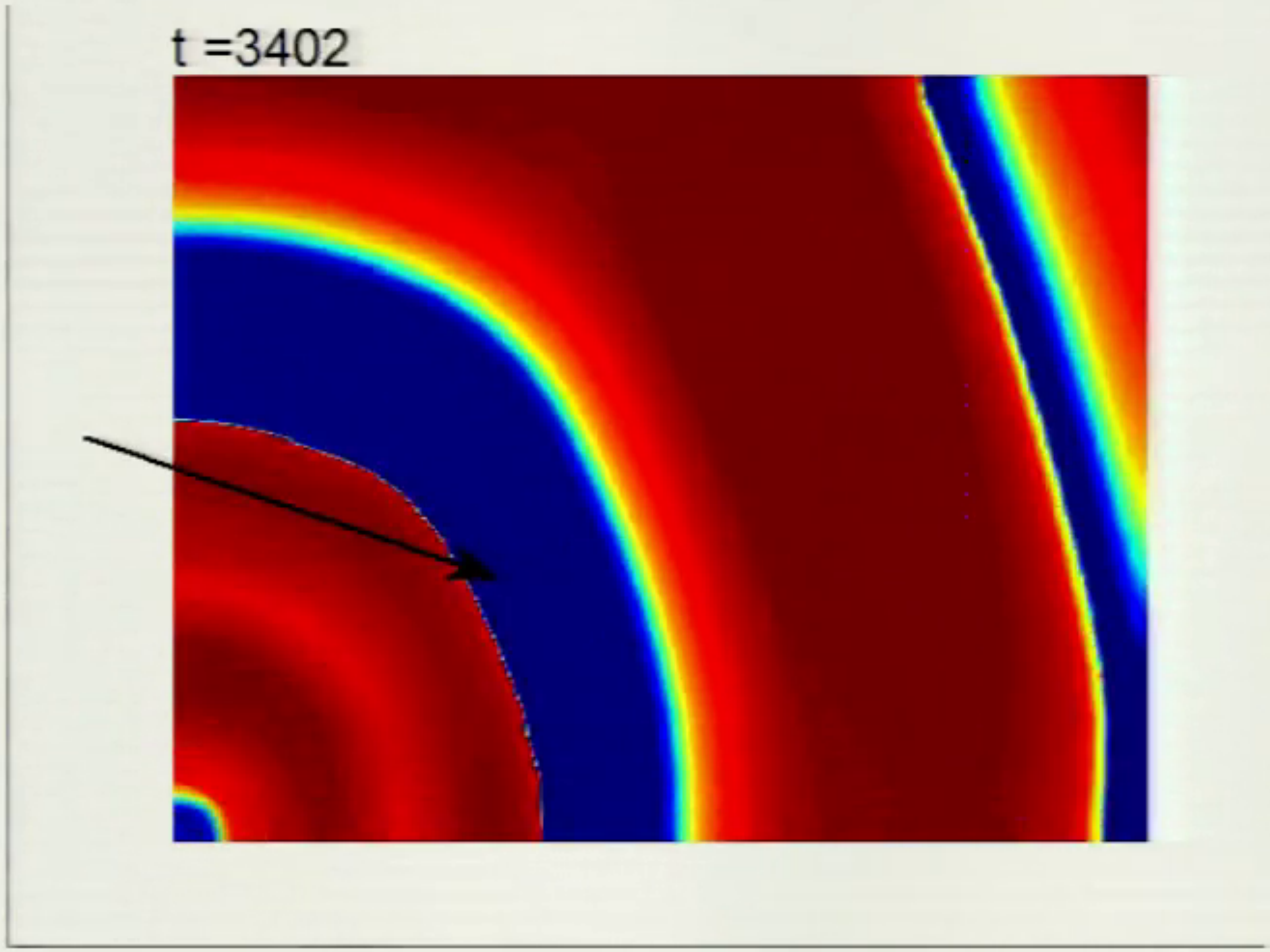

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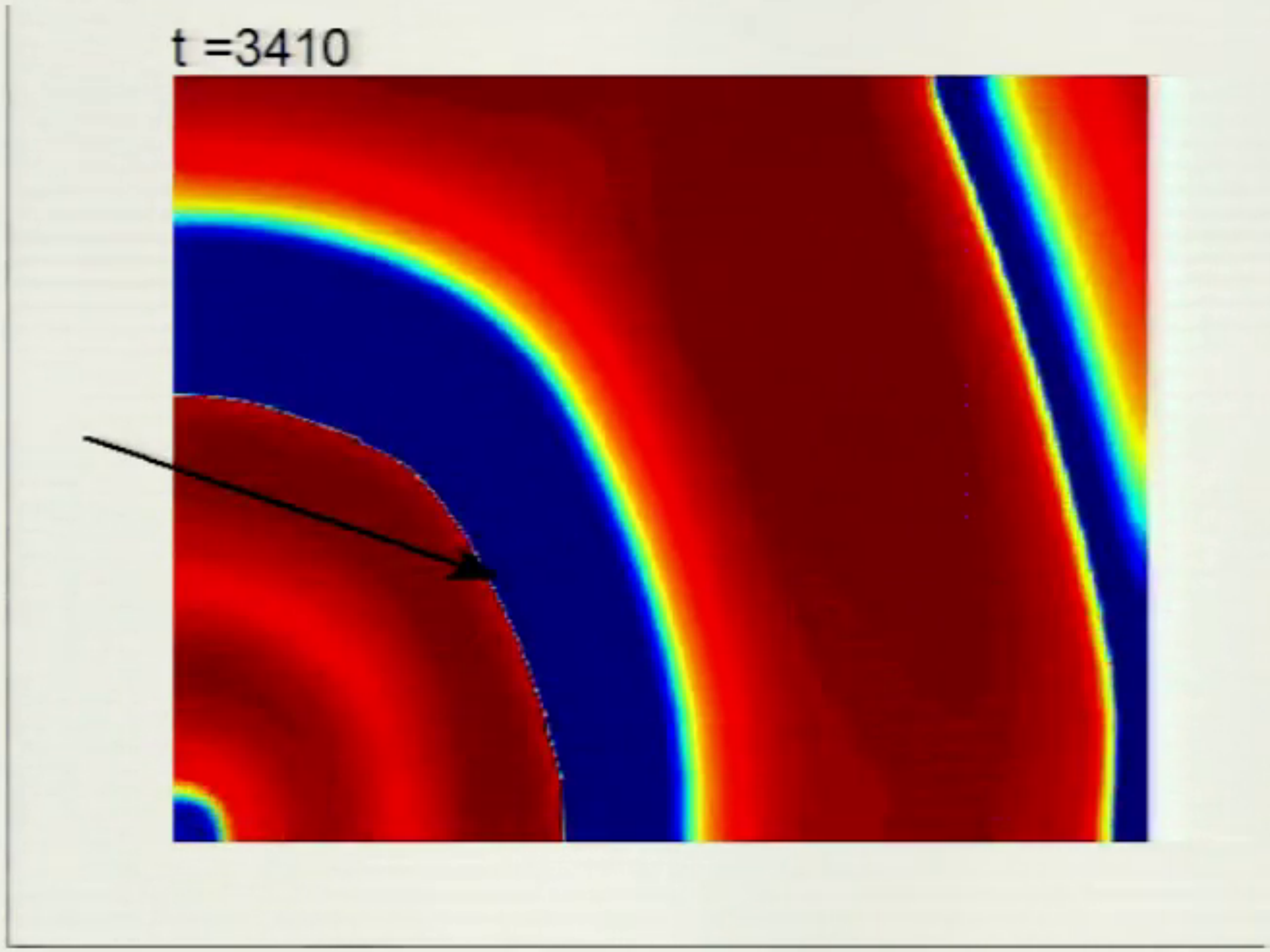

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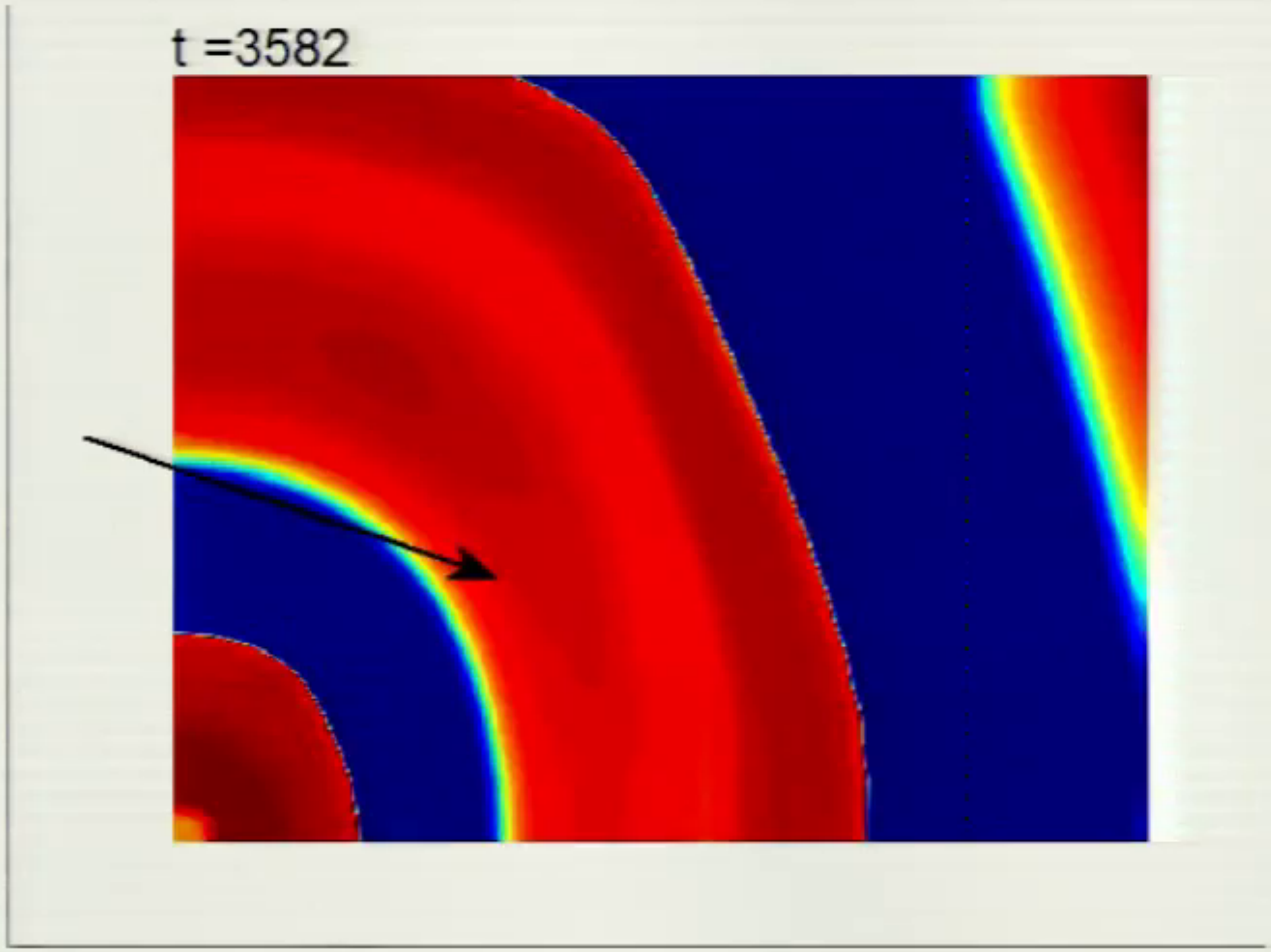

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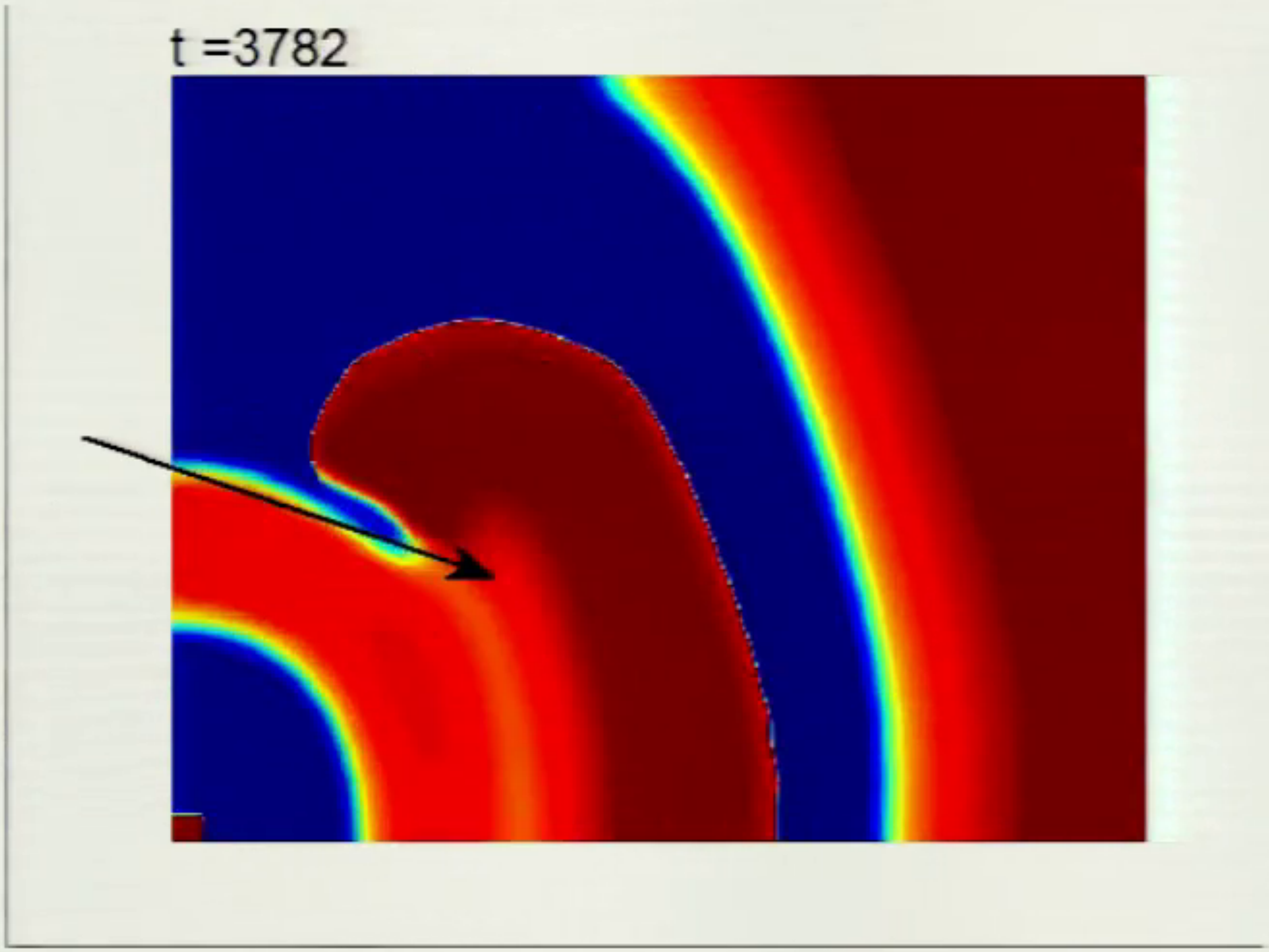

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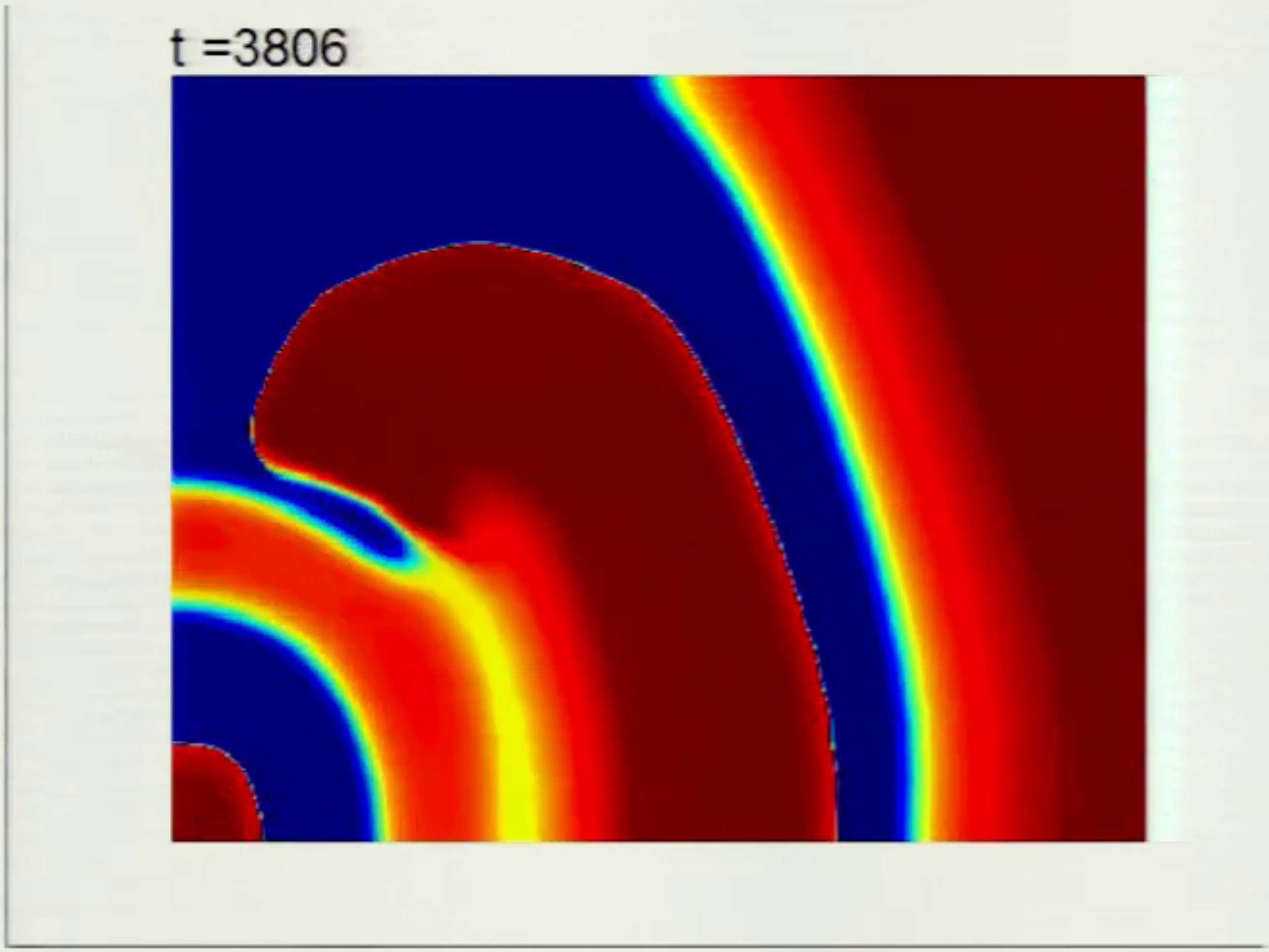

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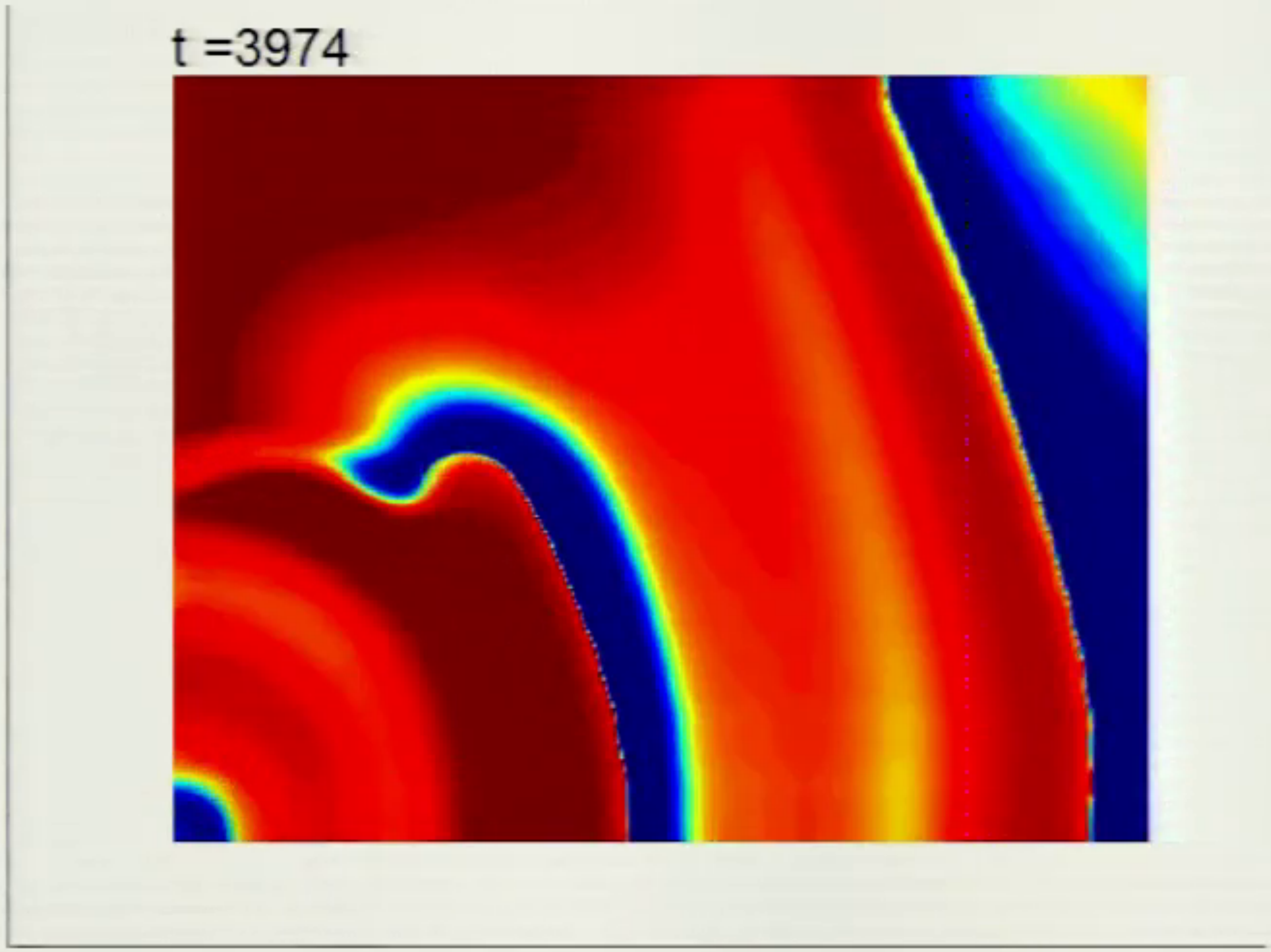

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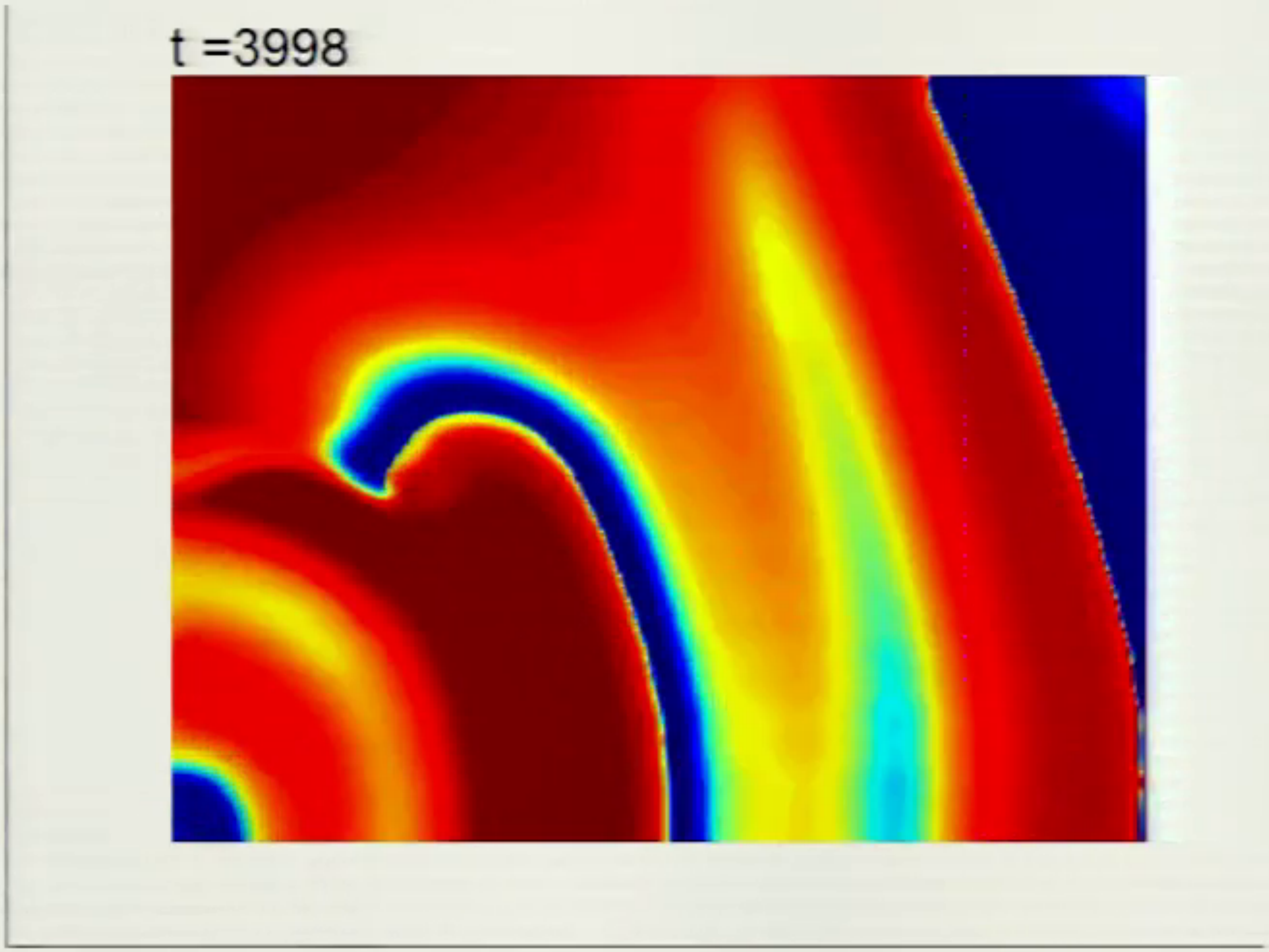

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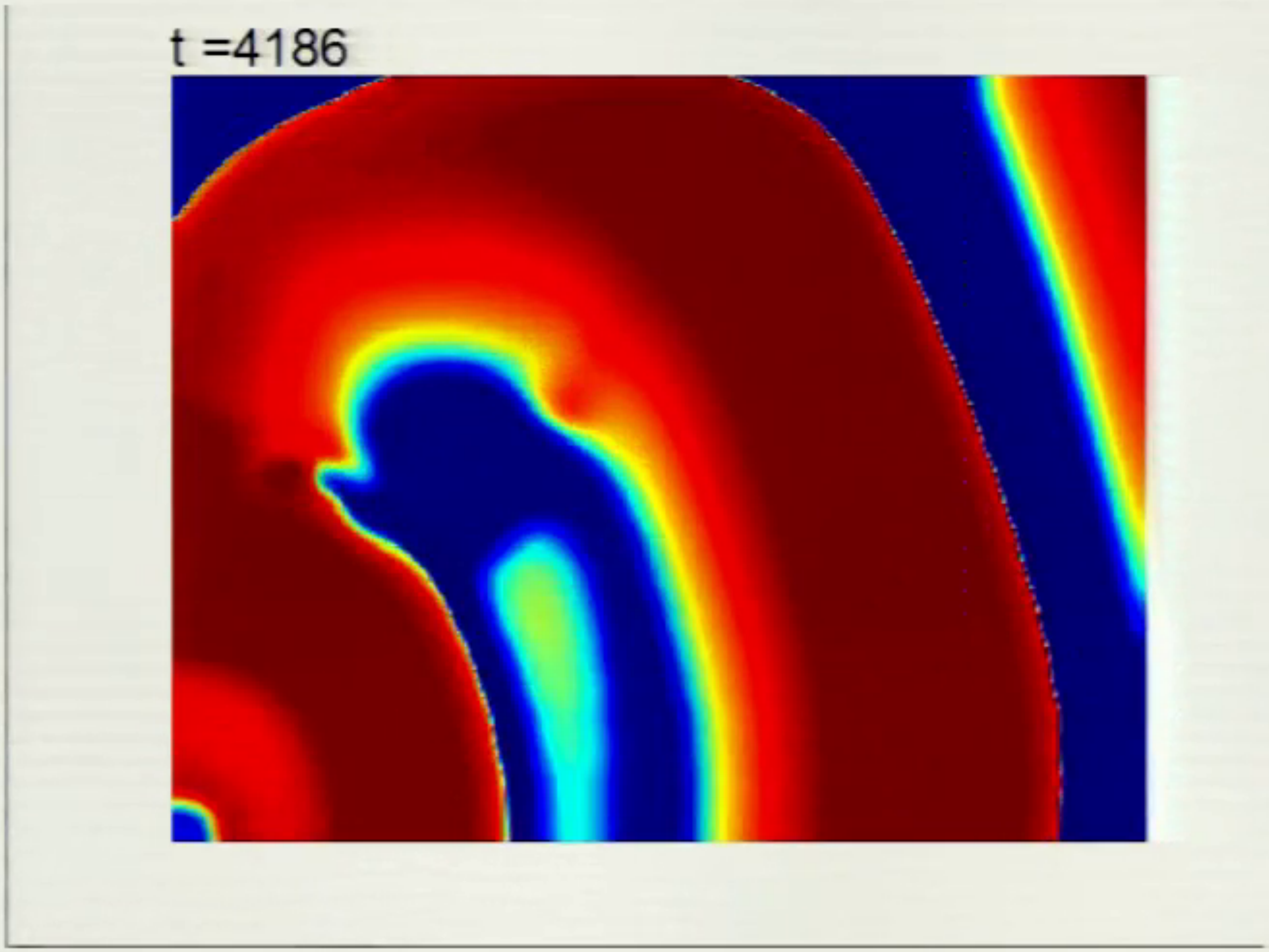

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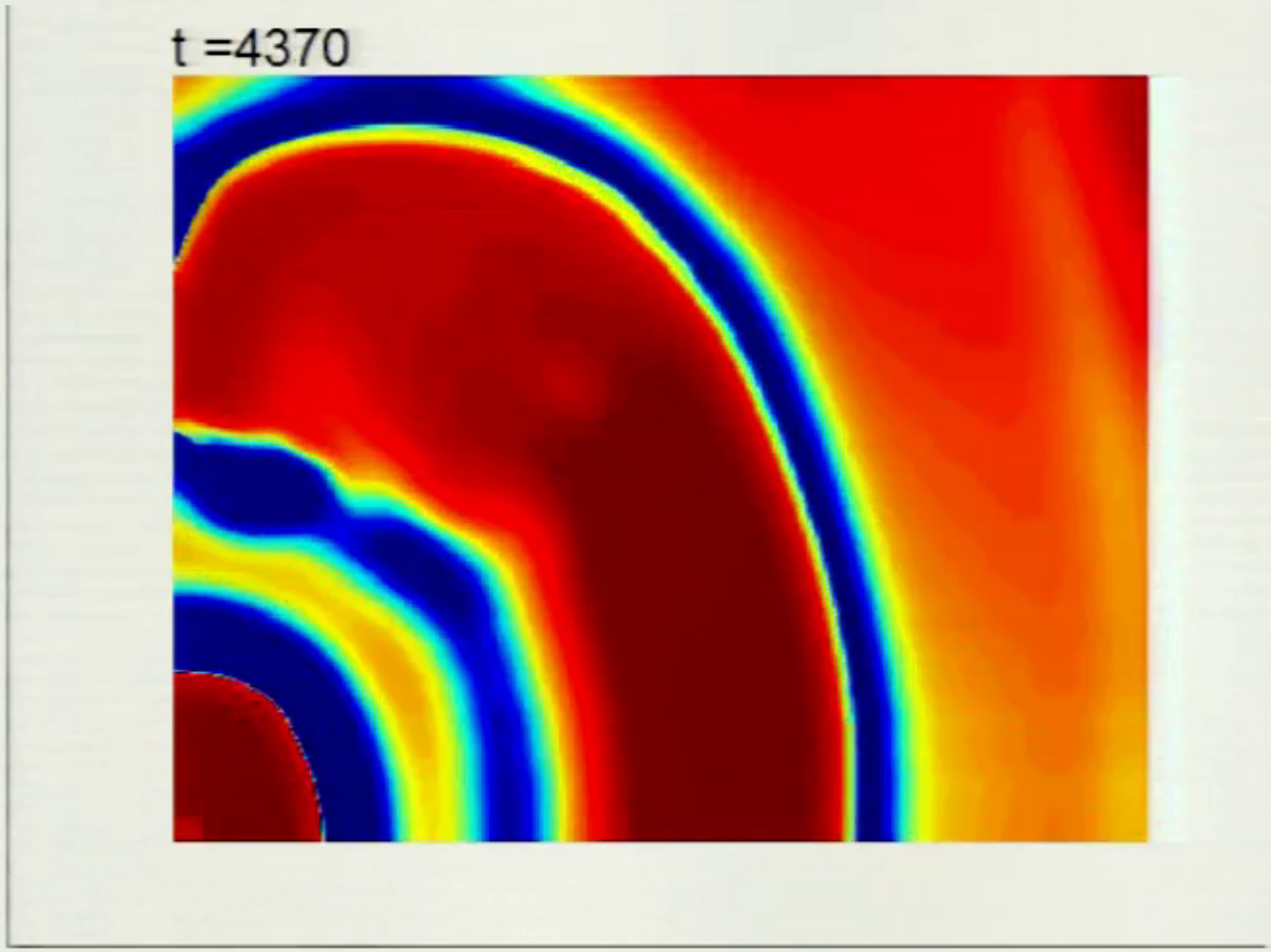

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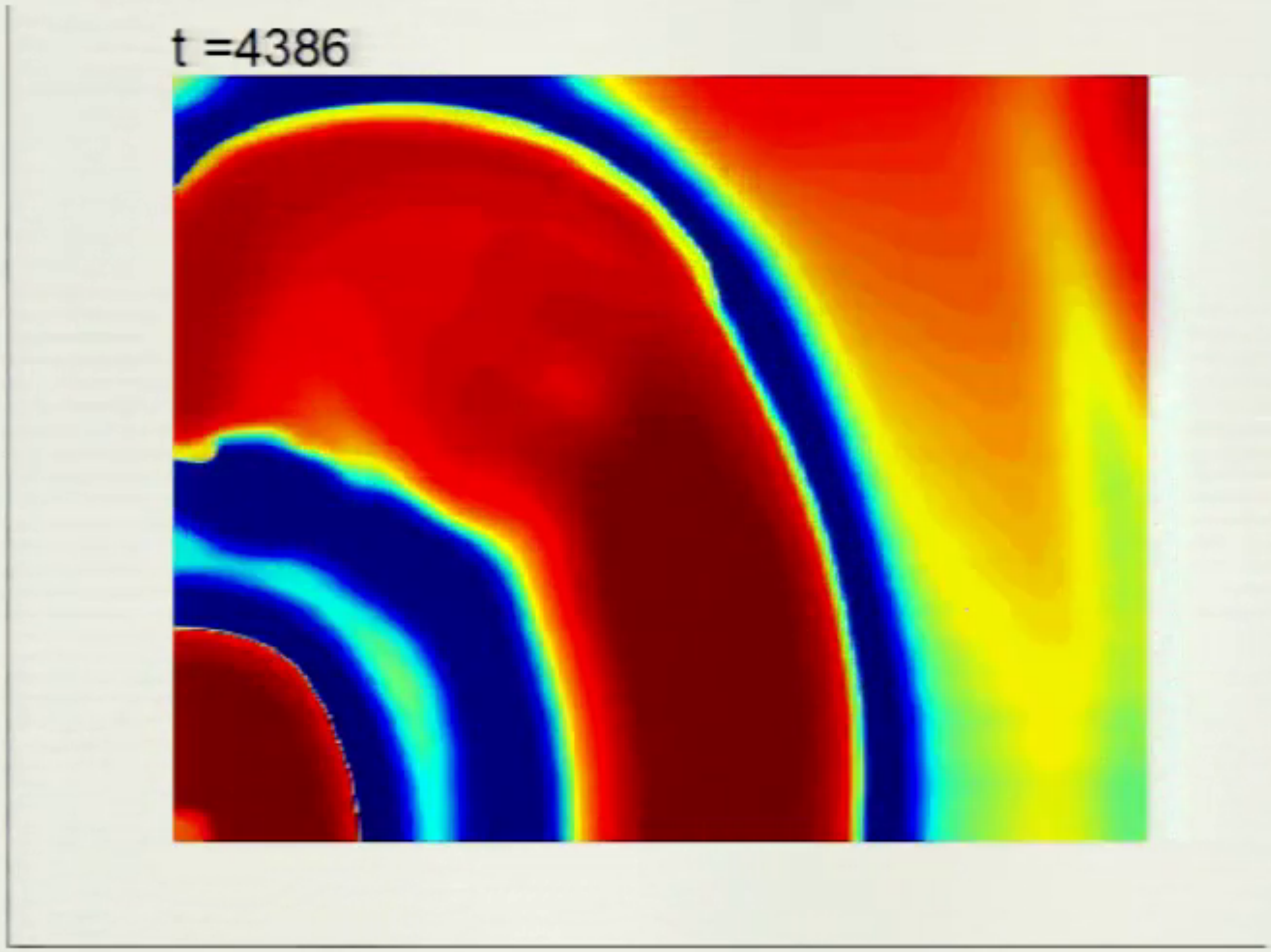

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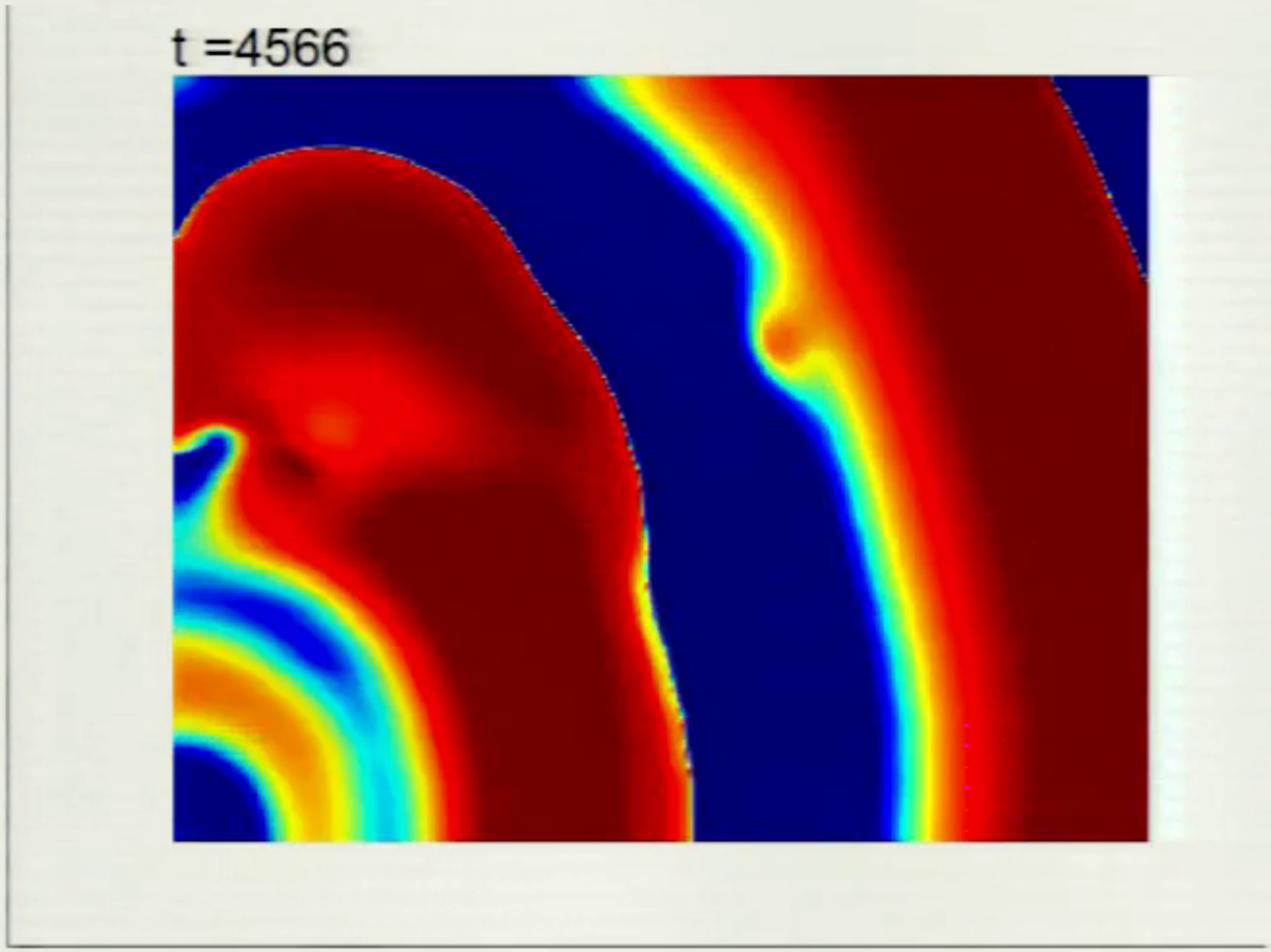

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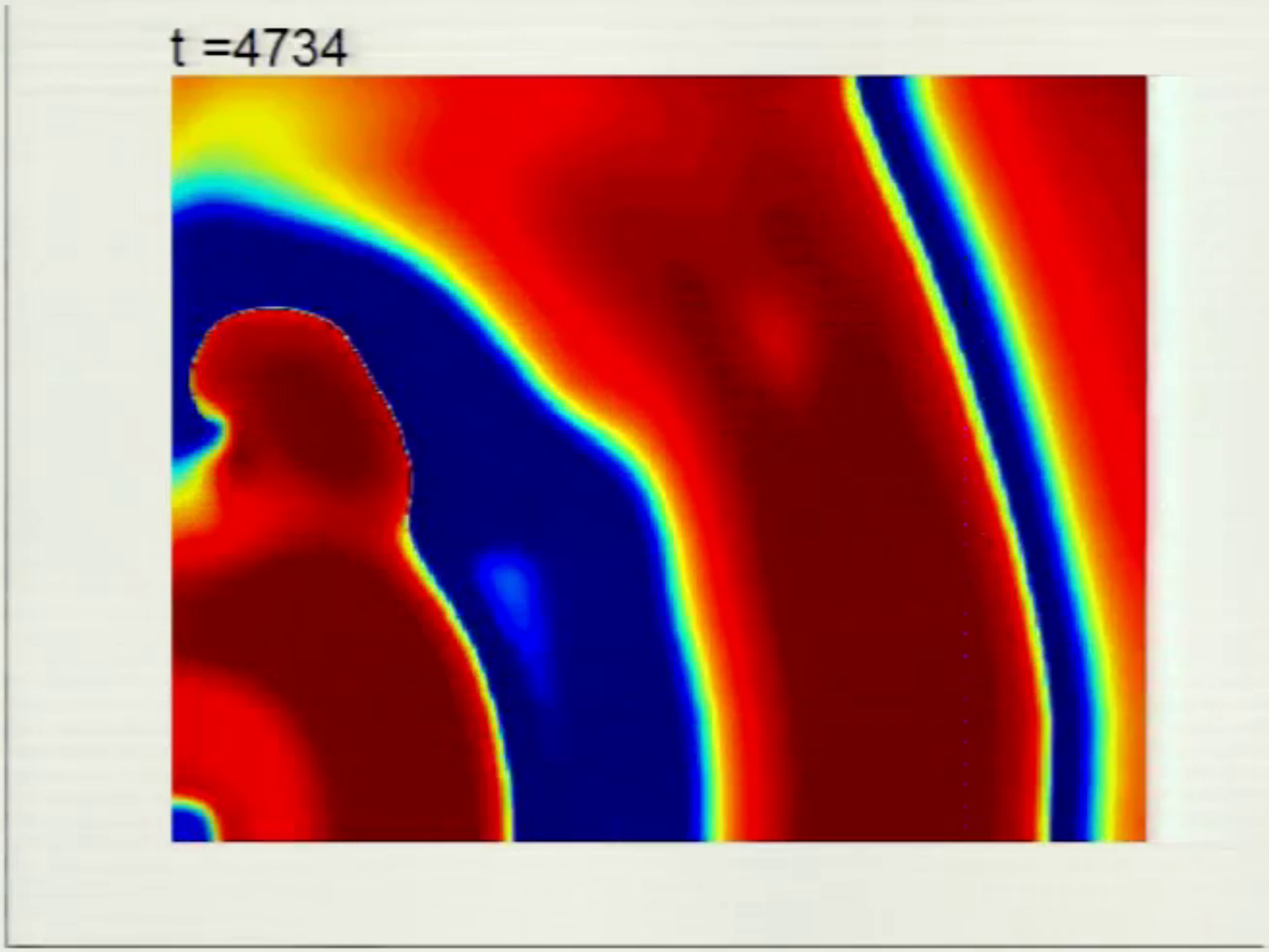

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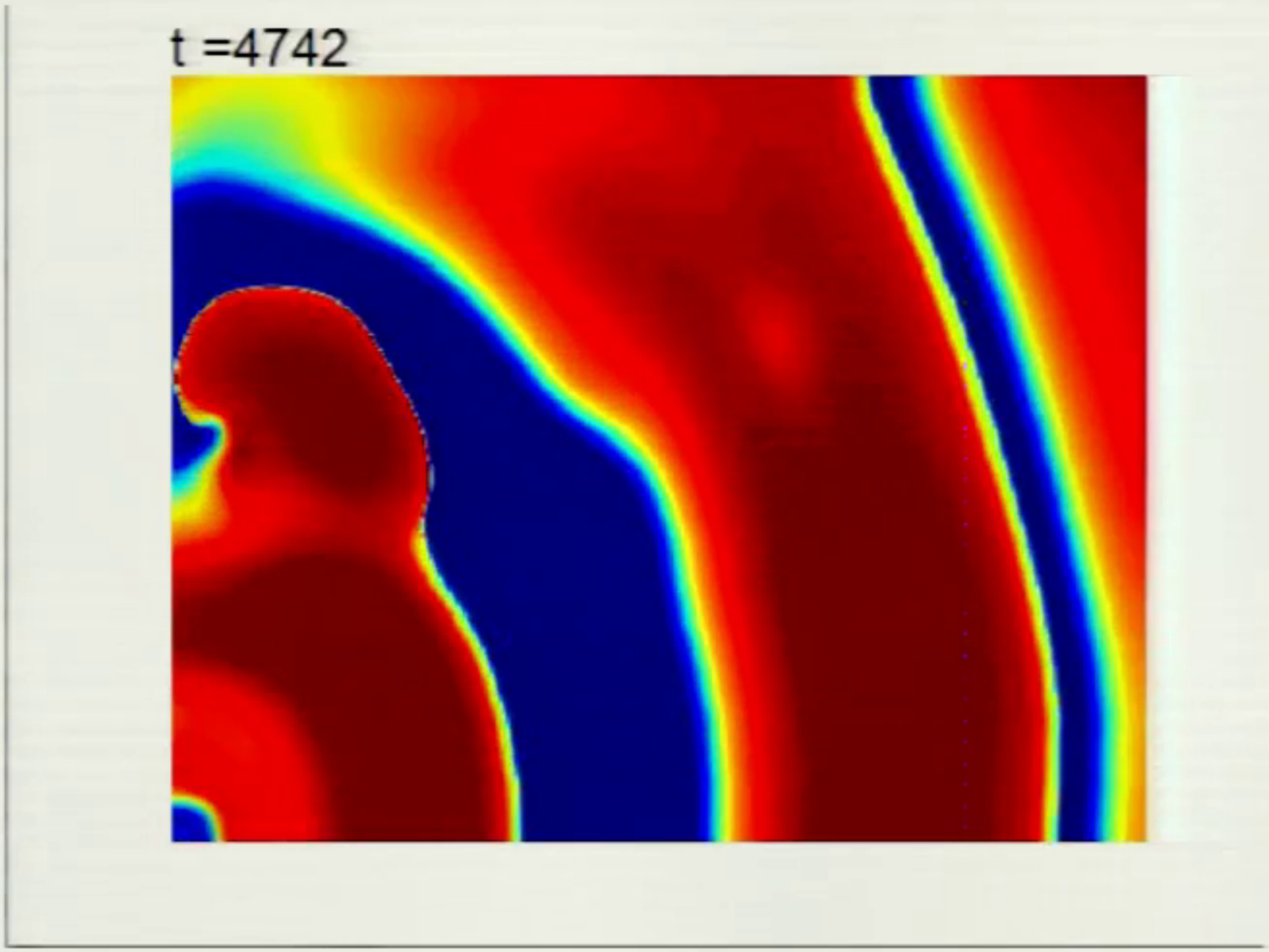

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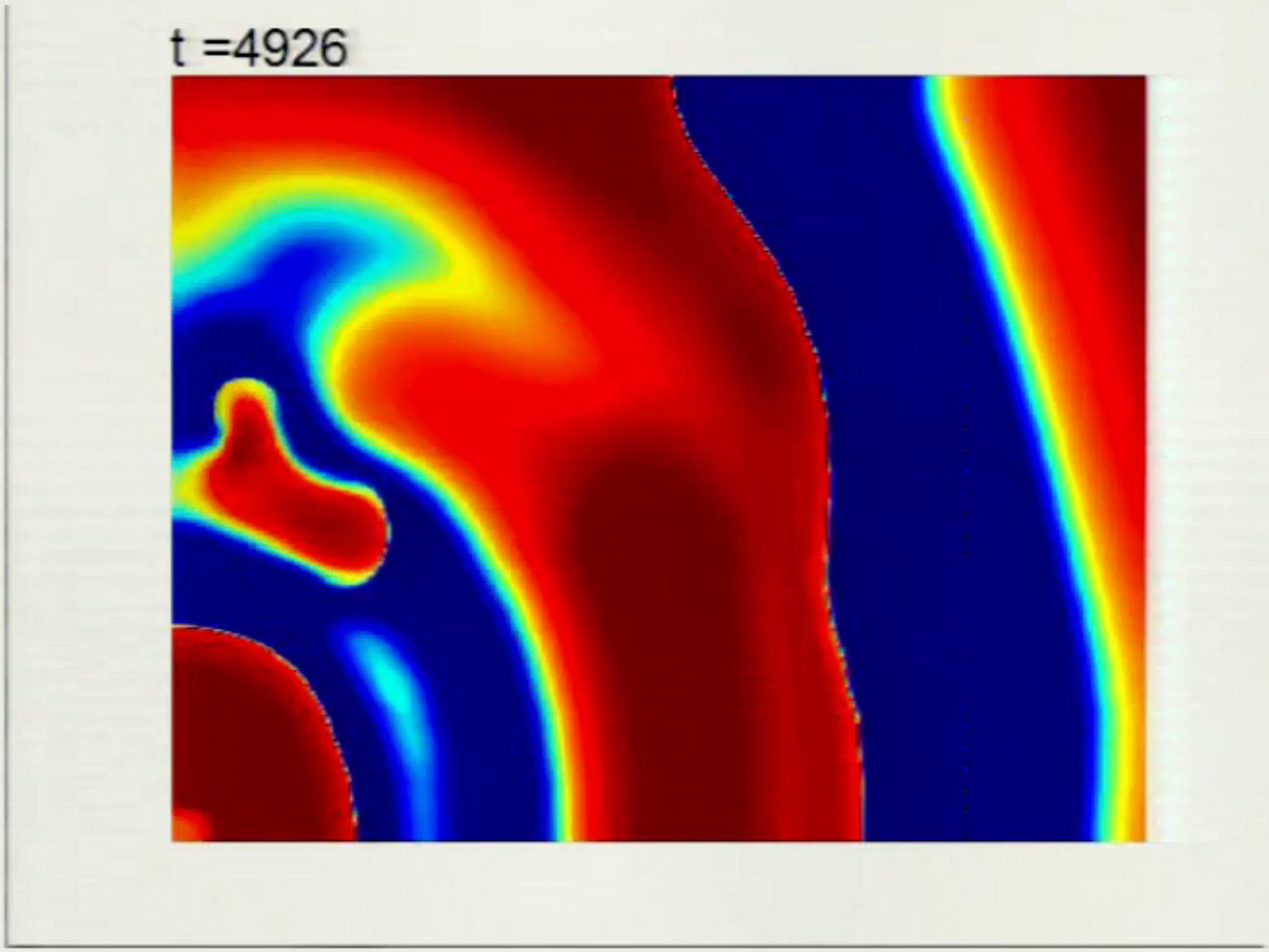

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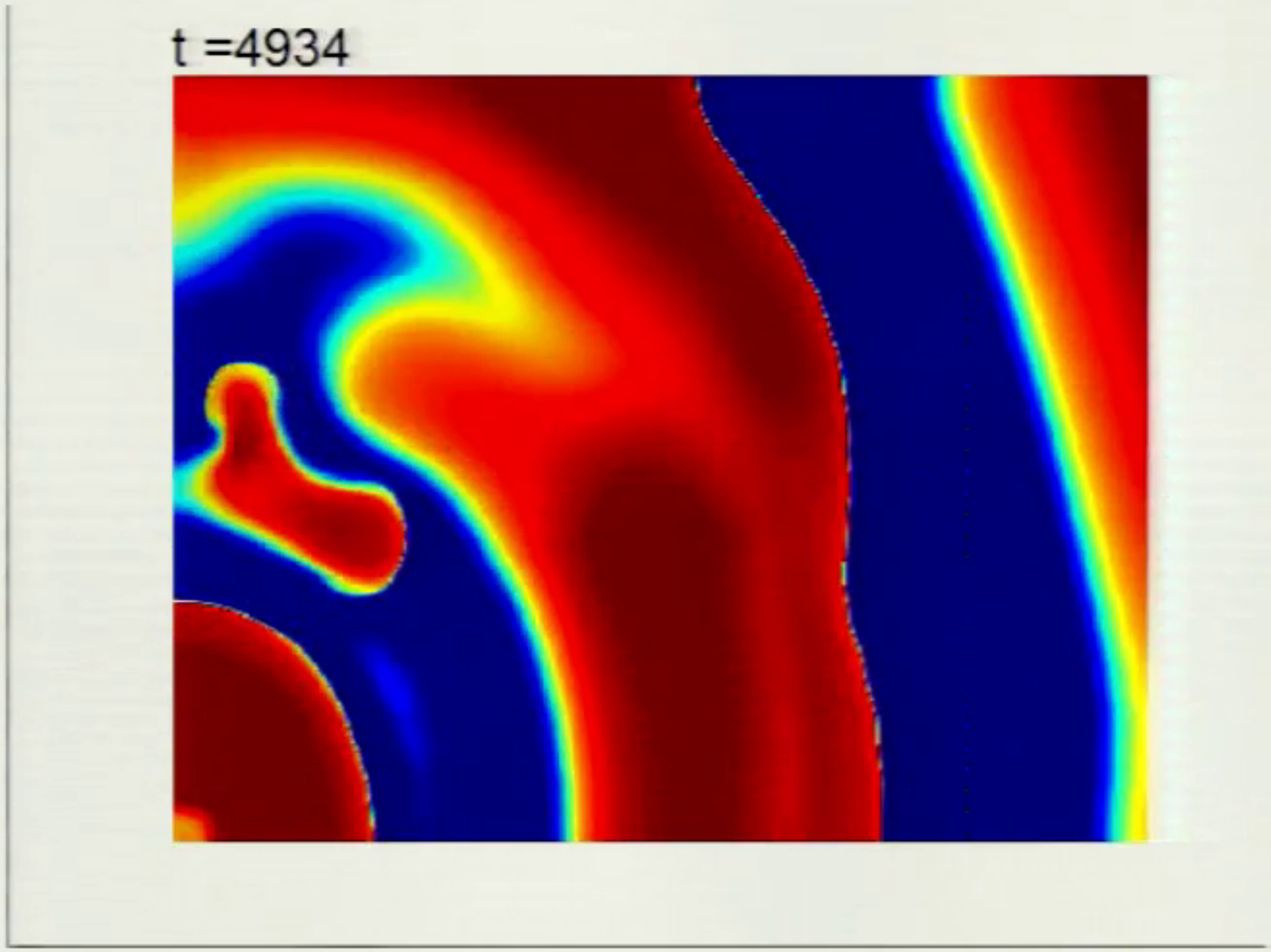

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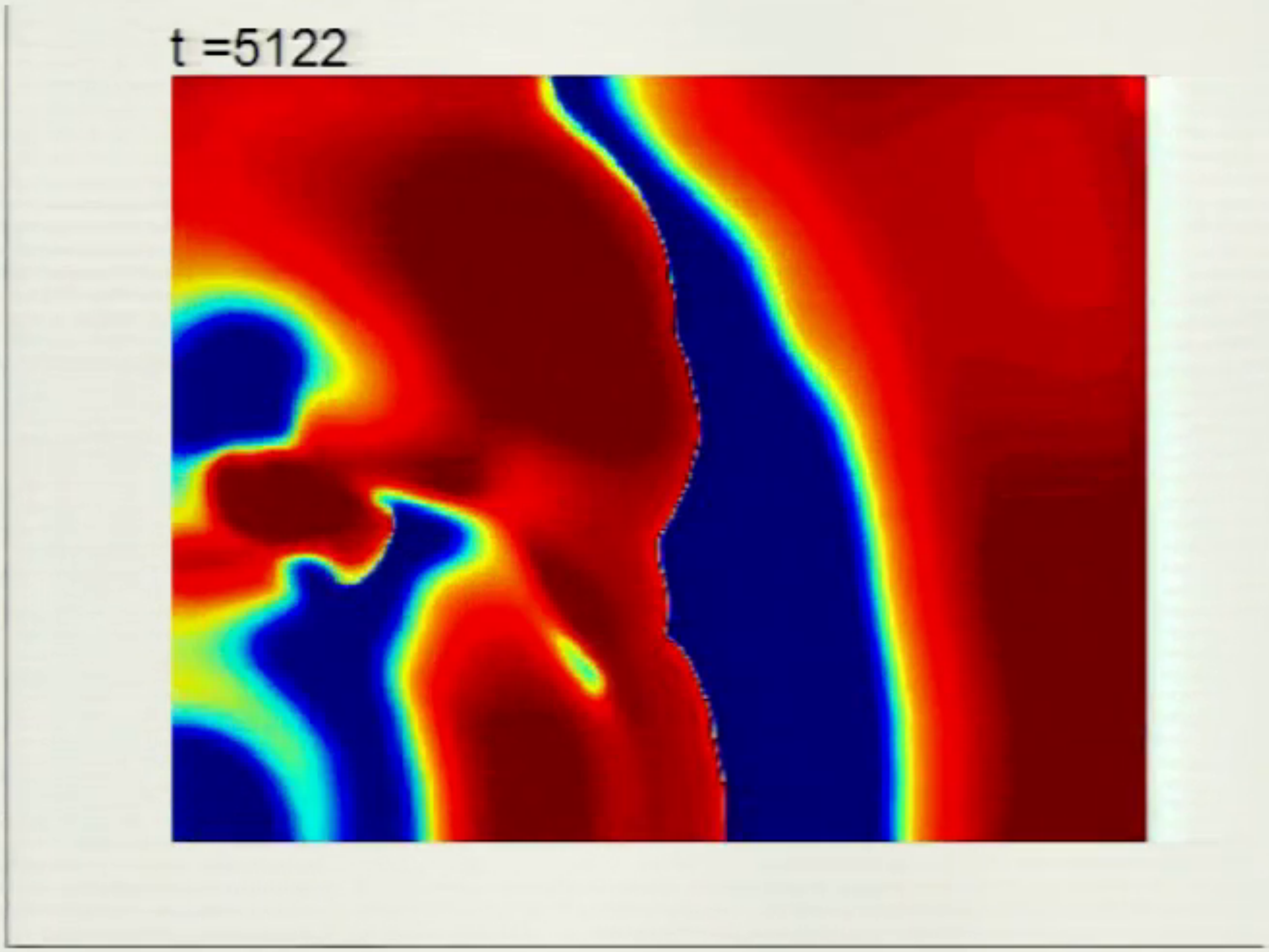

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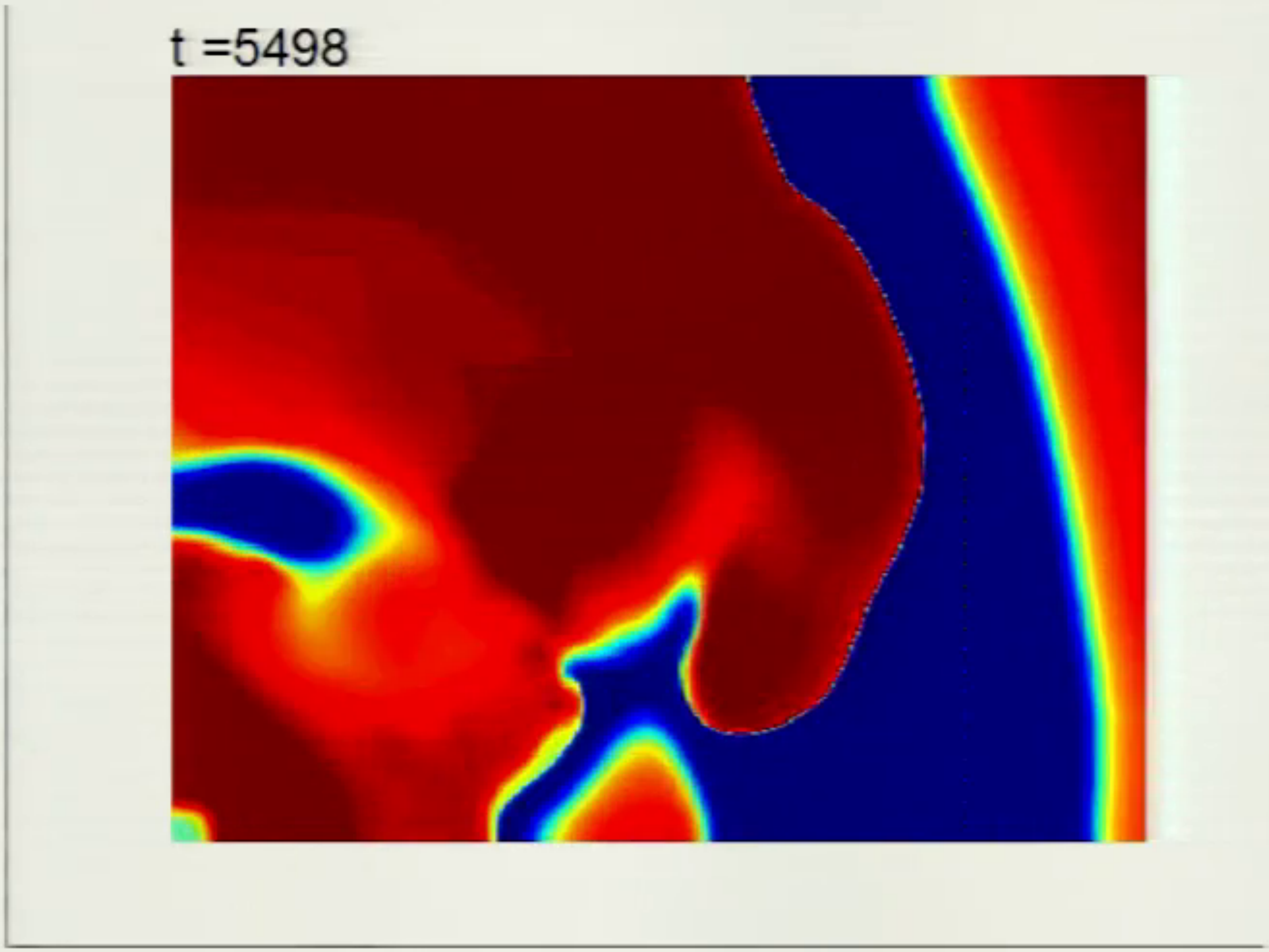

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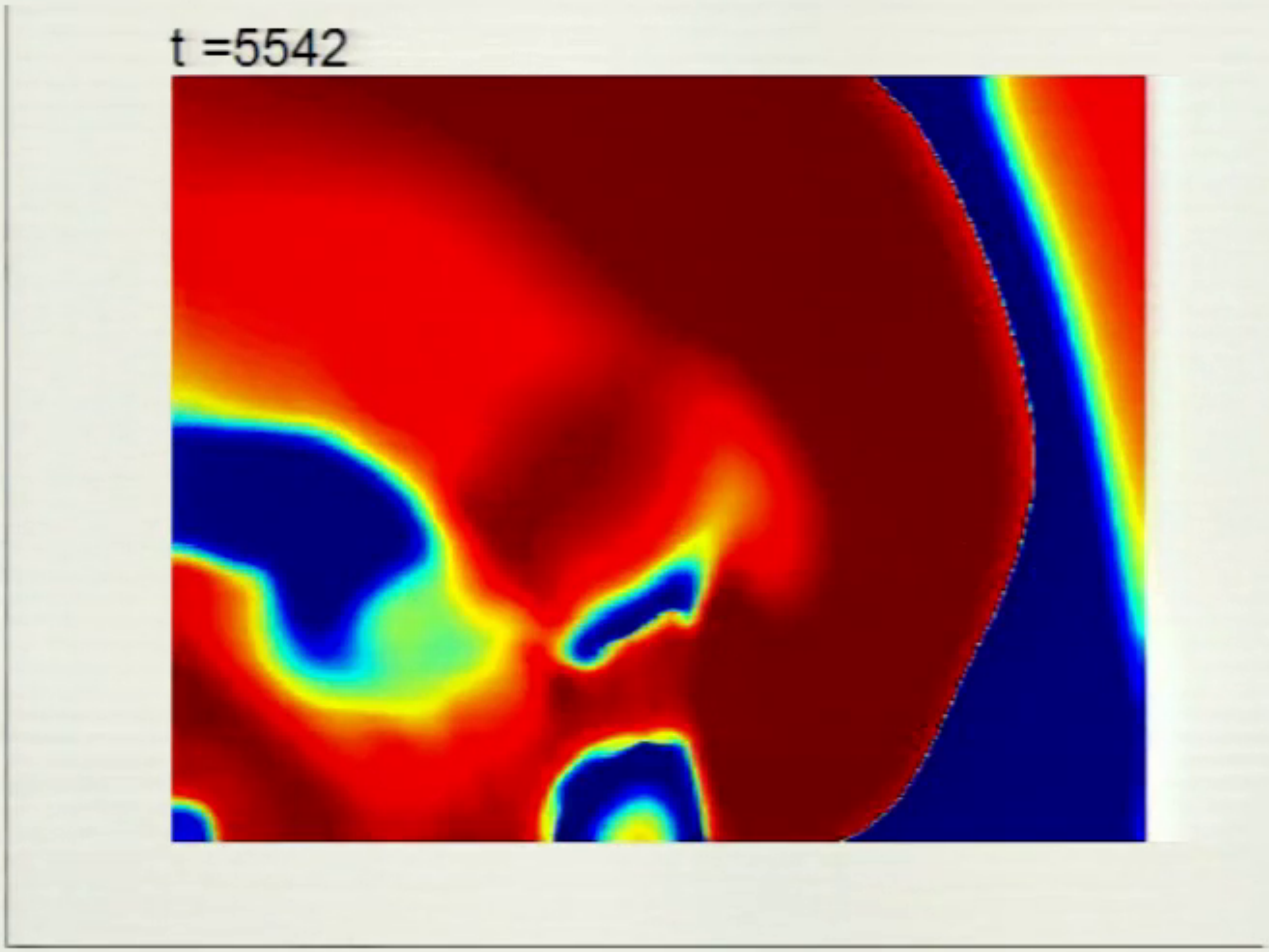


Alternans Control Objective:

- find electrical stimulus which stabilizes period-1 action potentials using minimal power

Wilson, M – *SIAM Review* 2015

Isostables

$$\frac{d\mathbf{x}}{dt} = \mathbf{F}(\mathbf{x}), \qquad \mathbf{x} \in \mathbb{R}^n$$

stable fixed point $\mathbf{x}^*$

isostable:

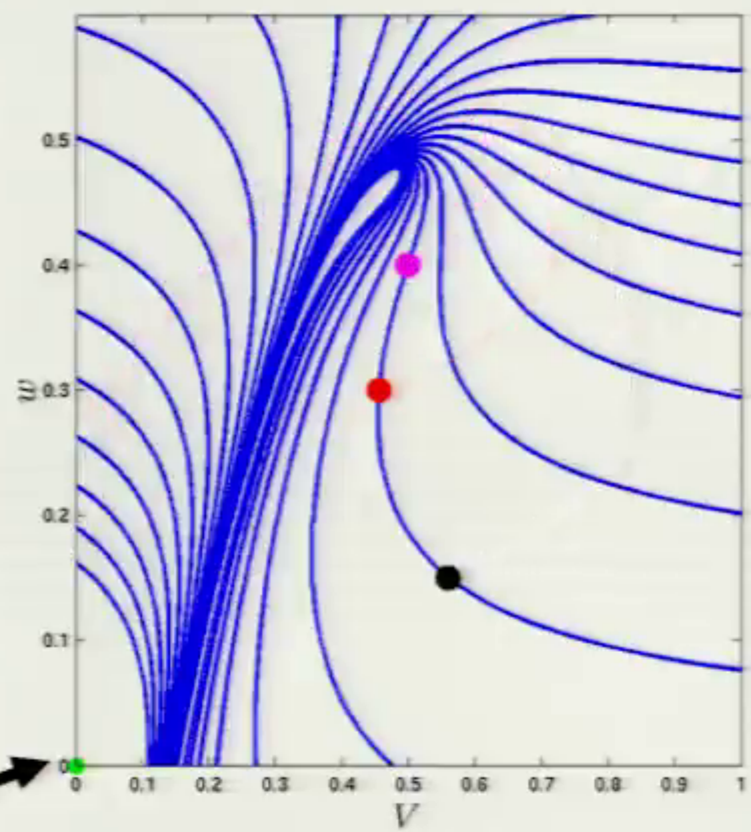
- a set of initial conditions that share the same asymptotic convergence to a fixed point

- a level set of phase-like variable $\psi(\mathbf{x})$

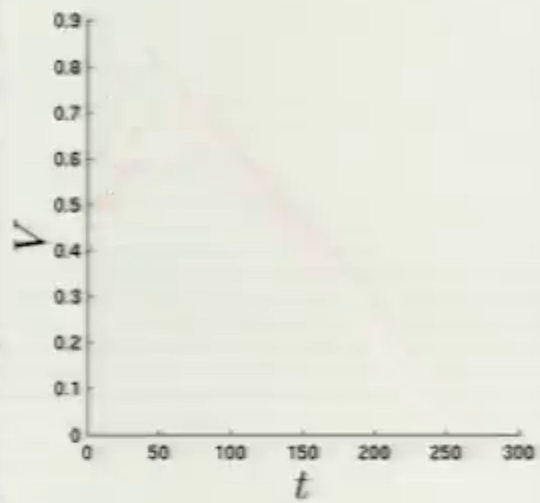
$$\boxed{\frac{d\psi}{dt} = \kappa}$$

Mauroy, Mezic, M – *Physica D* 2013
Wilson, M – *SIAM Review* 2015

Initial Conditions Same Isostable (Real Evalues)

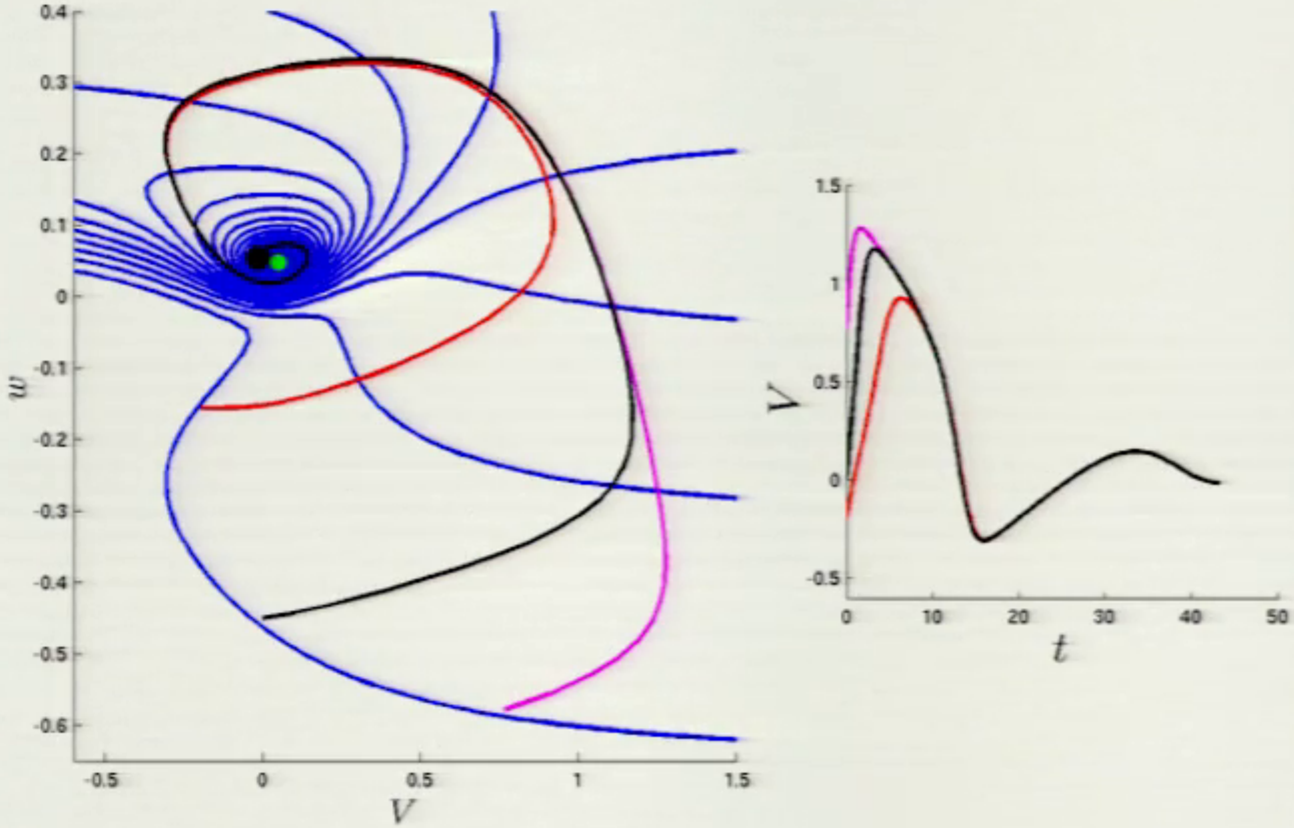


f.p.



Mauroy, Mezic, M – *Physica D* 2013

Initial Conditions Same Isostable (Complex Evalues)

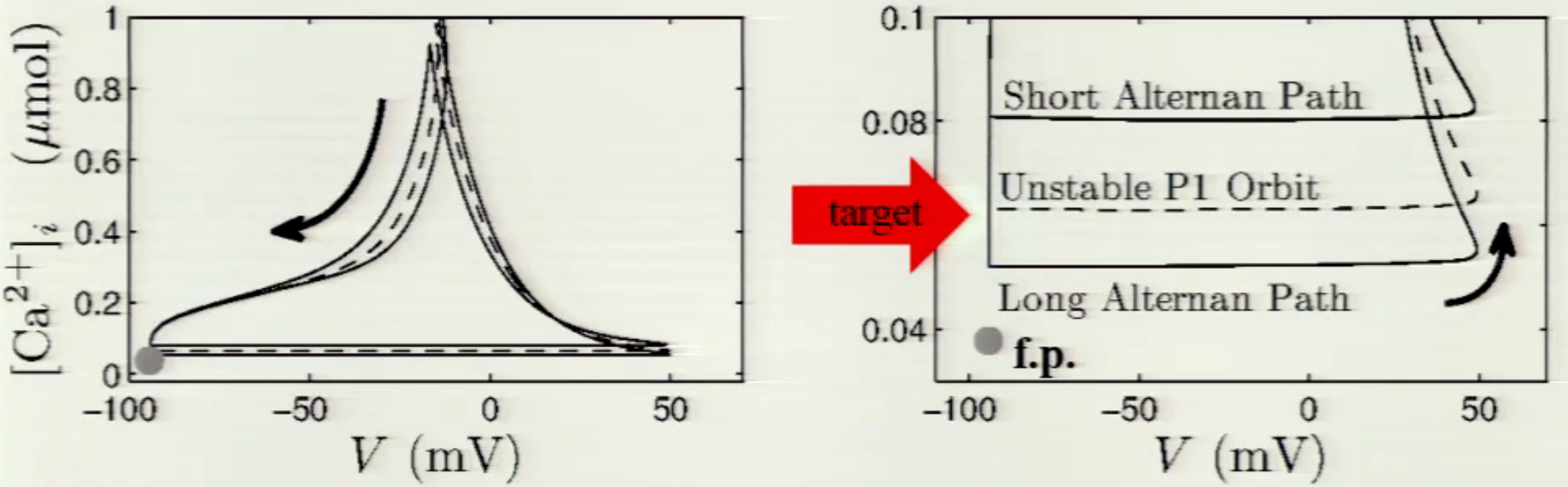


Mauroy, Mezic, M – *Physica D* 2013

Control based on Isostable Reduction

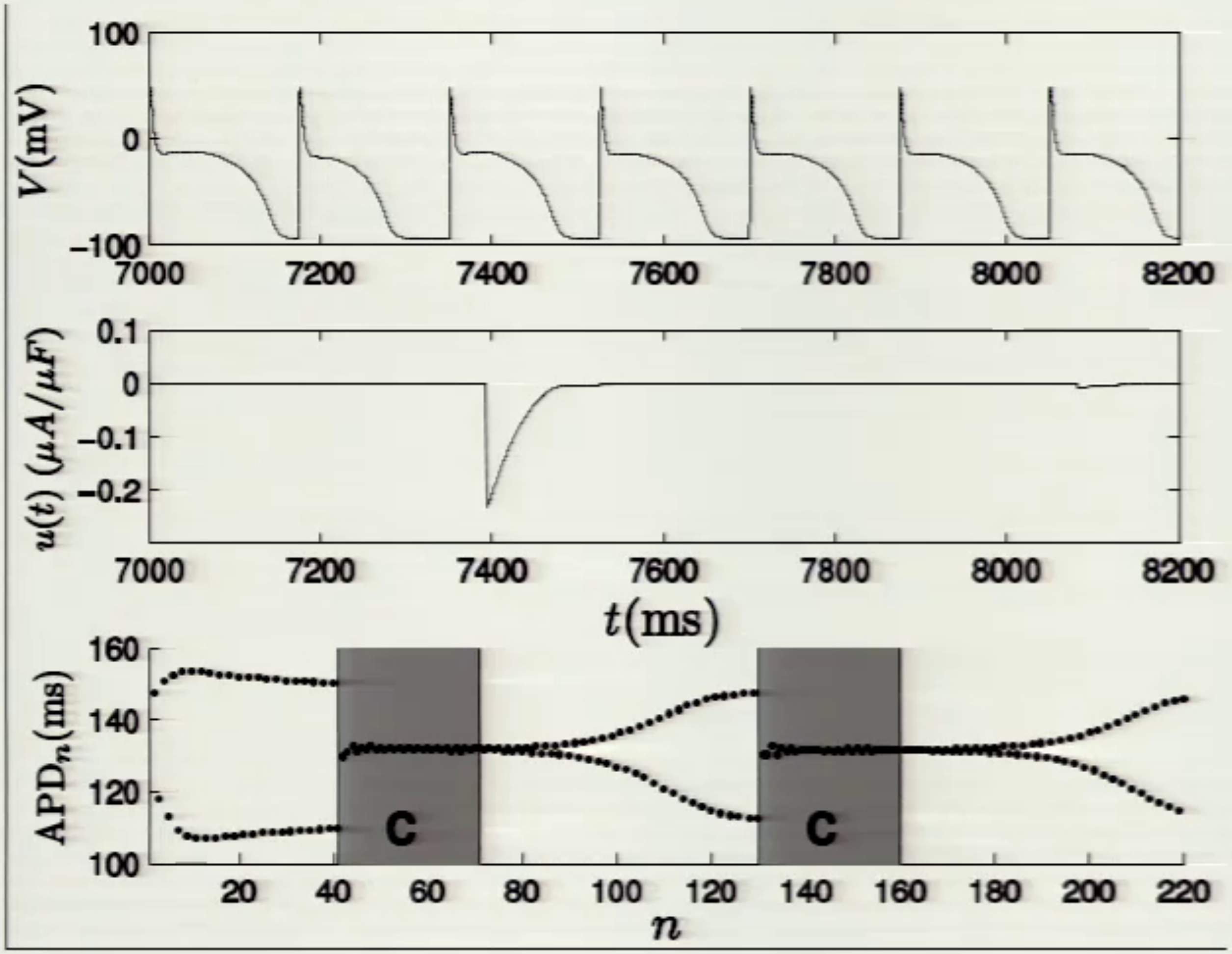
$$\frac{d\psi}{dt} = \kappa + I(\psi)u(t)$$

$u(t)$ **is input current,** $I(\psi)$ **is** ***isostable response curve***



Wilson, M – *SIAM Review* 2015

Control based on Isostable Reduction



Wilson, M – *SIAM Review* 2015

Control based on Isostable Reduction of PDEs

Consider a ring of connected cardiac tissue:

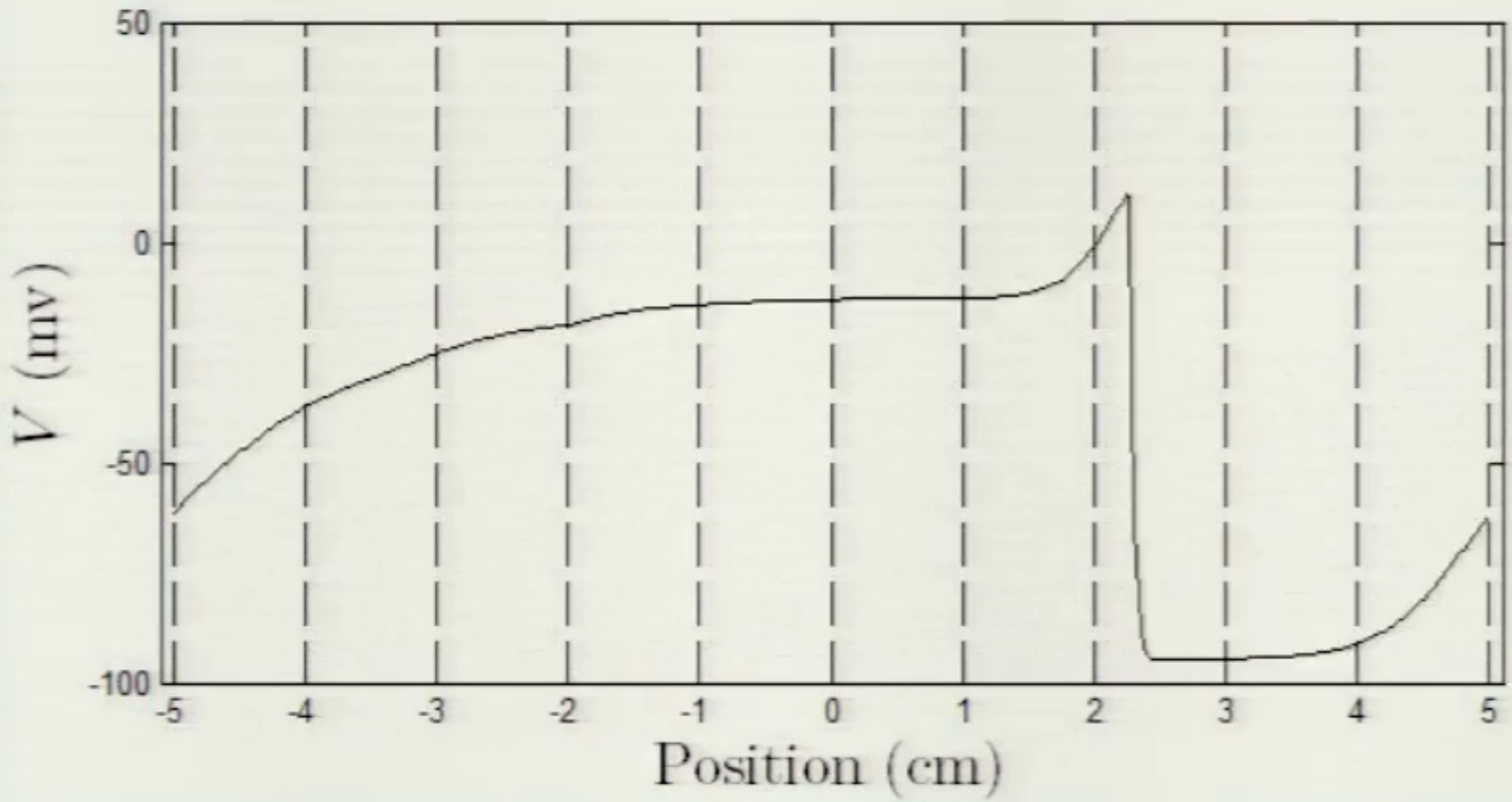
$$C_m \frac{\partial V(r,t)}{\partial t} = D \frac{\partial^2}{\partial r^2} V(r,t) + (-I_{ion} + I_{stim}(r,t)).$$

After isostable reduction:

$$\dot{\psi} = \kappa + \langle \mathcal{I}(r,\psi), I_{stim}(r,\psi) \rangle.$$

Wilson, M – submitted

Control based on Isostable Reduction of PDEs



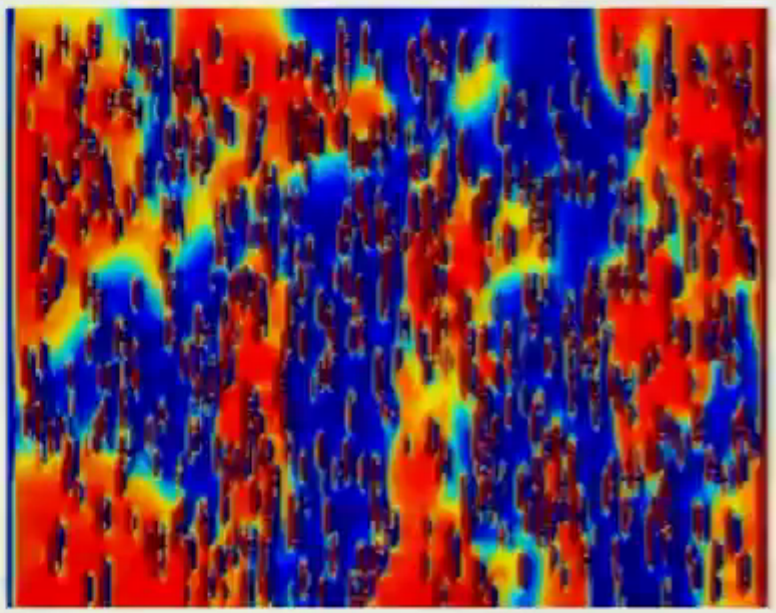
Wilson, M – submitted

Fibrillation Control Objective:

- find electrical stimulus which eliminates recurrent spiral waves by synchronizing the cell activity

Wilson, M – submitted

Unsuccessful "Defibrillation": single pulse



Wilson, M – submitted

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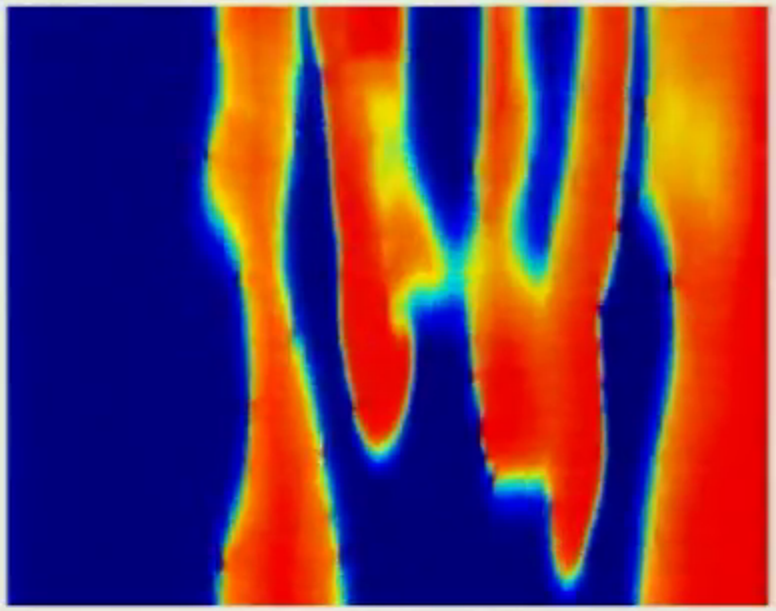
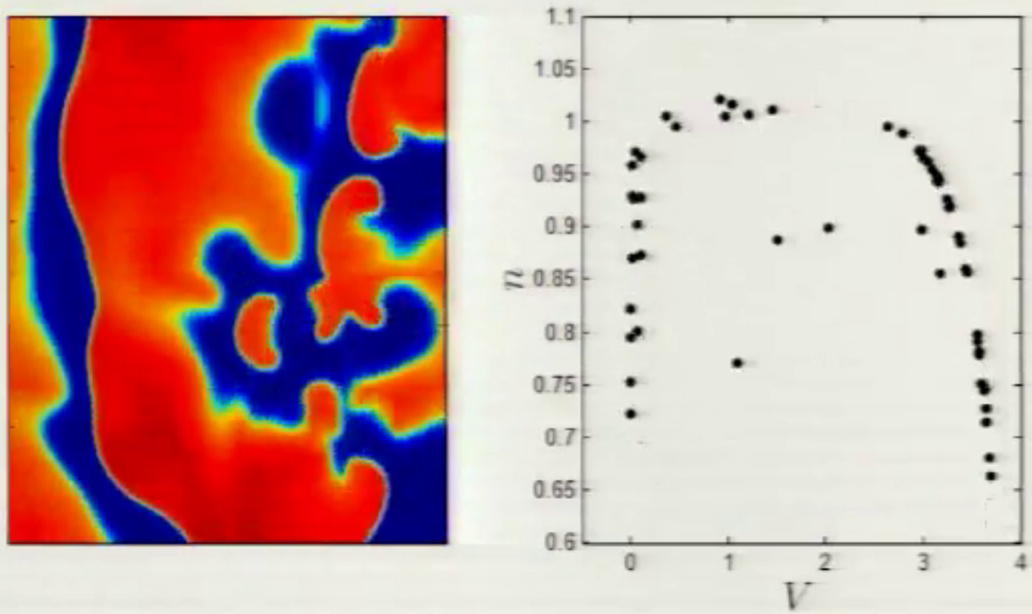


Wilson, M – submitted

Cell Dynamics Follow Transient Attractor:

can reduce dimensionality



Wilson, M – submitted

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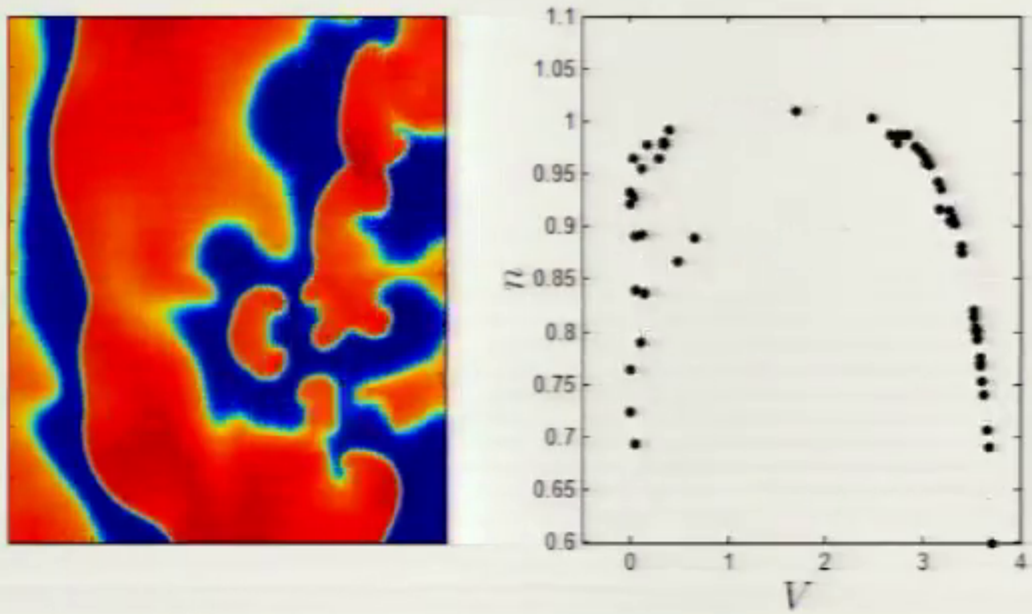

Wilson, M – submitted

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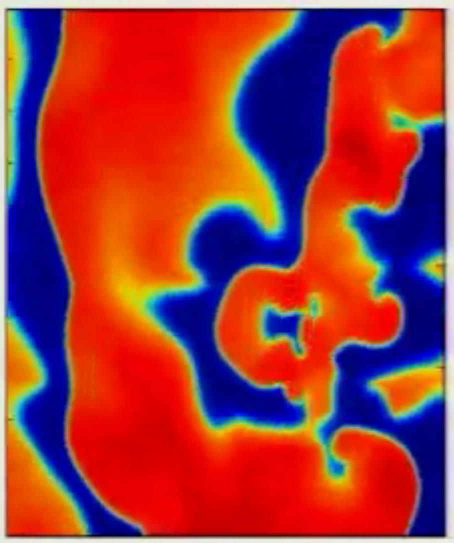

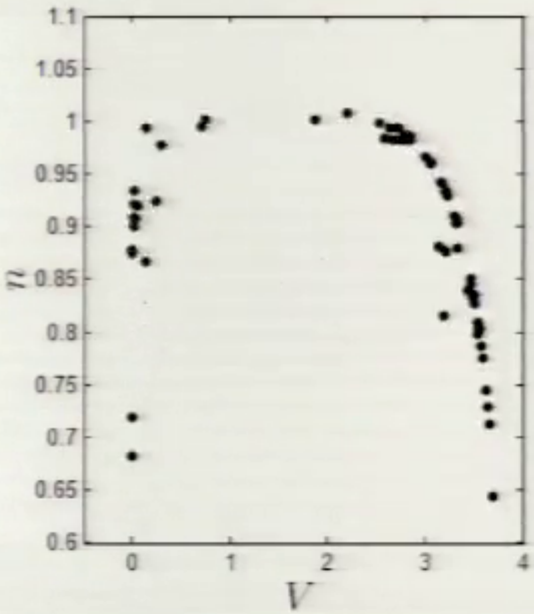

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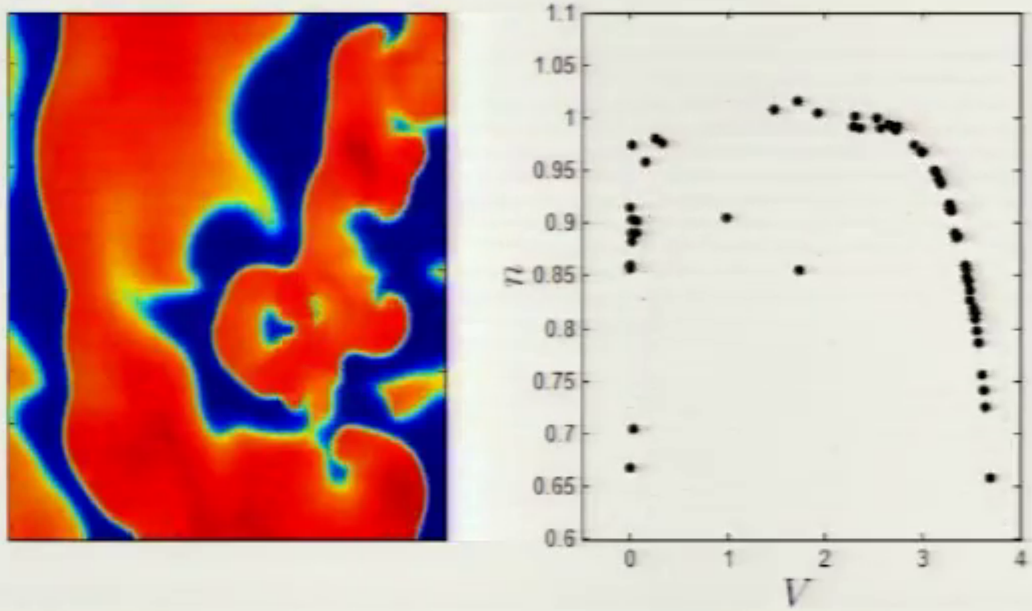

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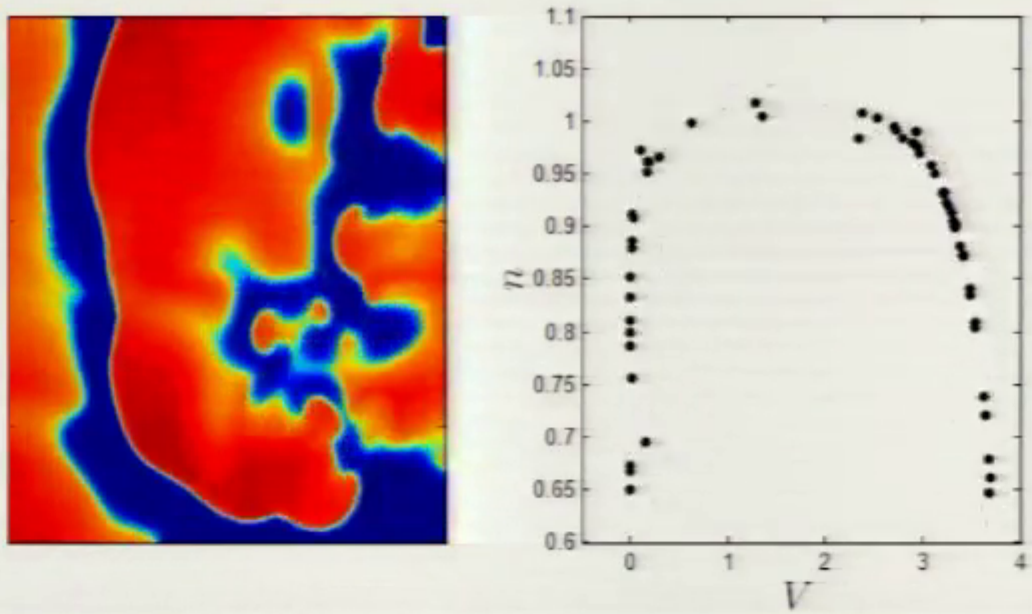

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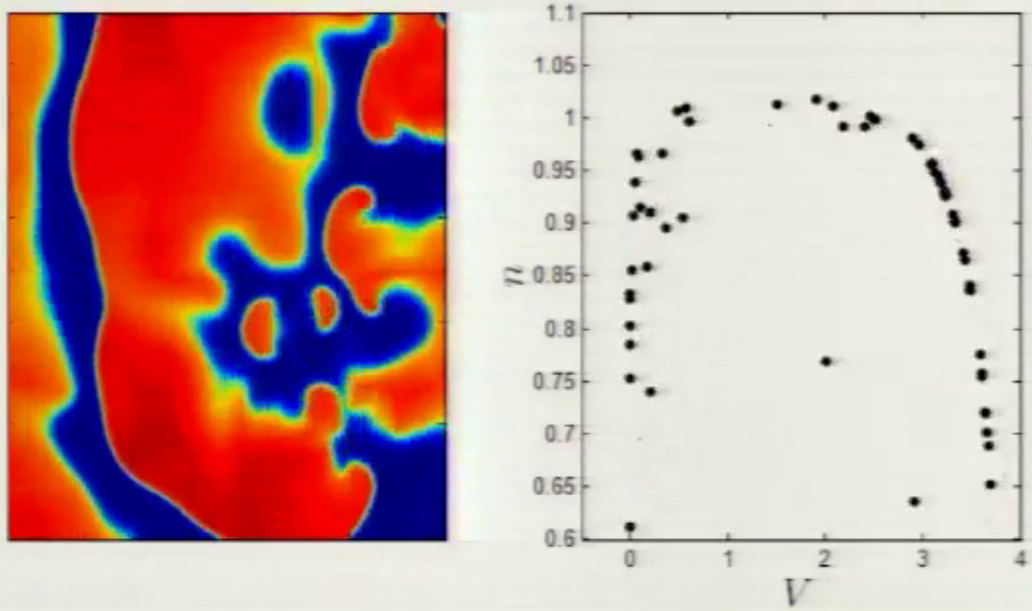

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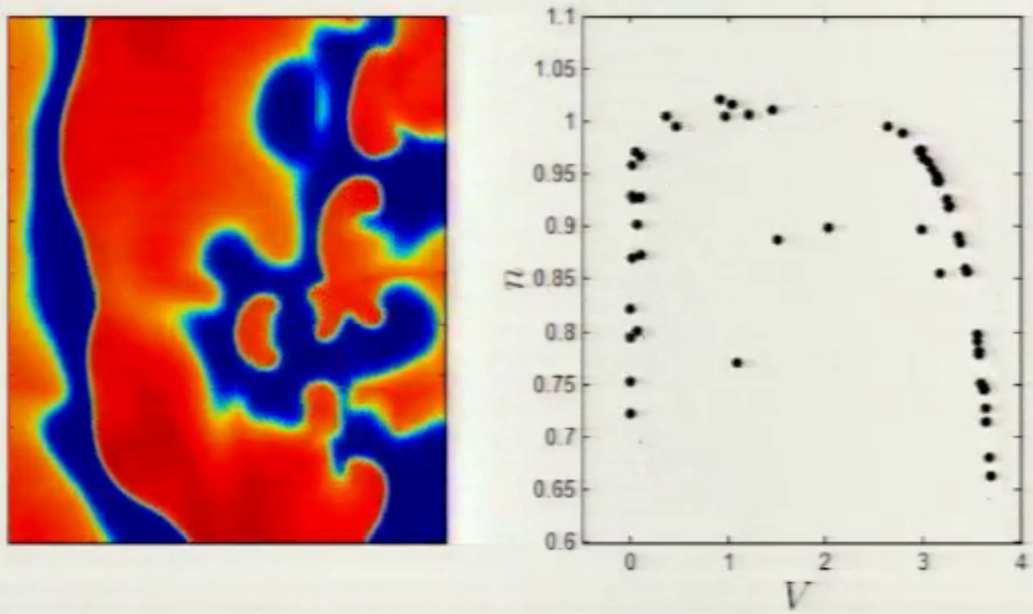

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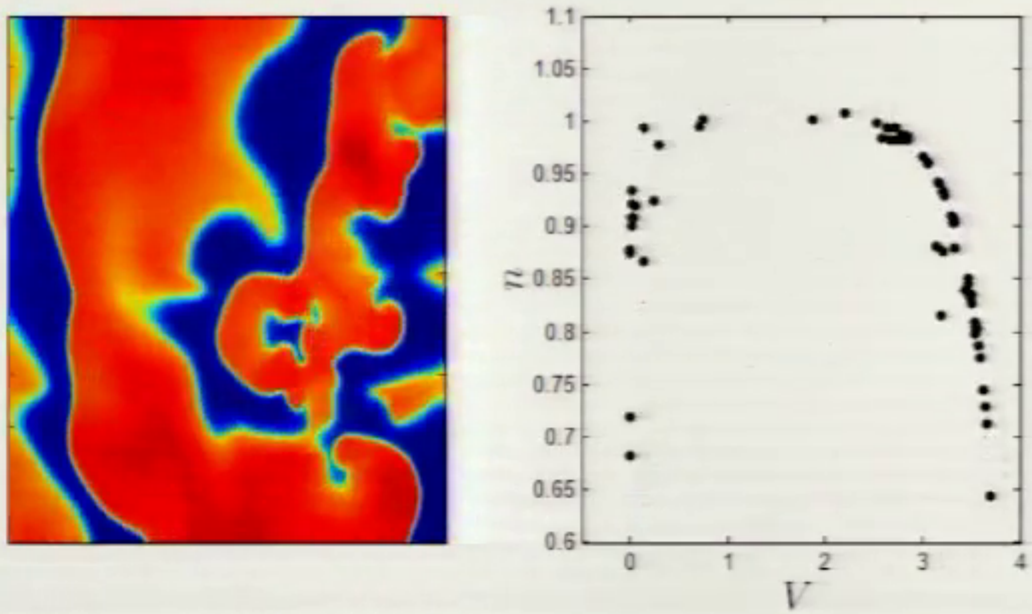

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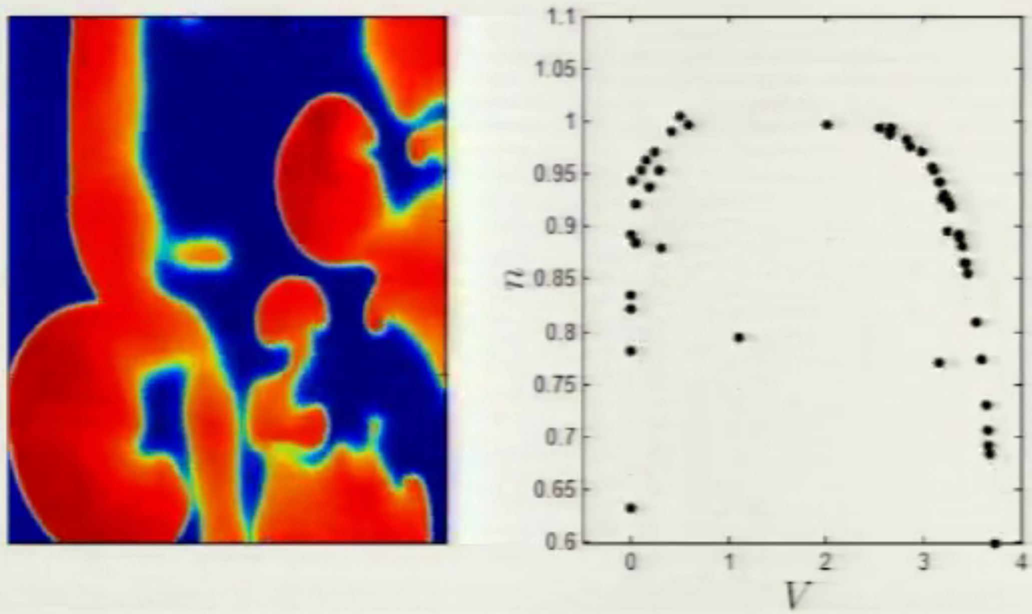
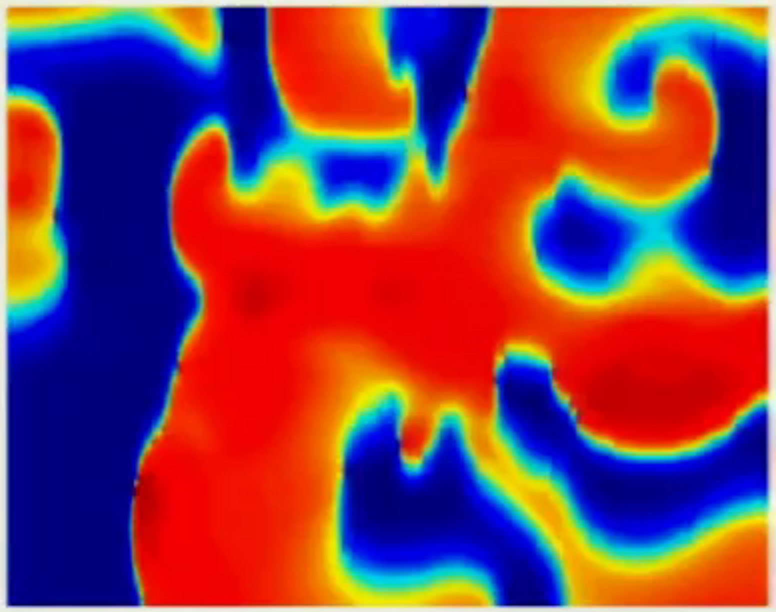


Wilson, M – submitted

Successful "Defibrillation":

pulse timing found using dynamic programming which optimizes synchronization of cell activity



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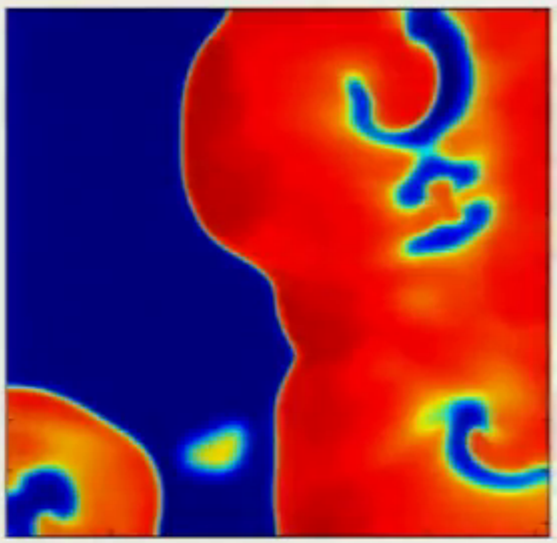

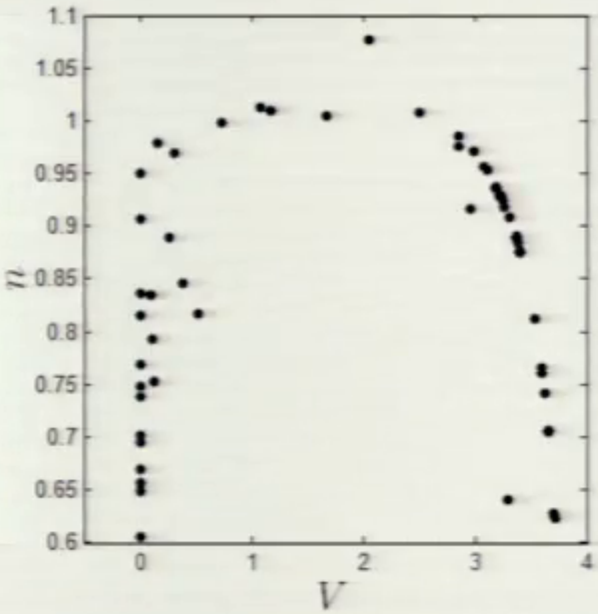

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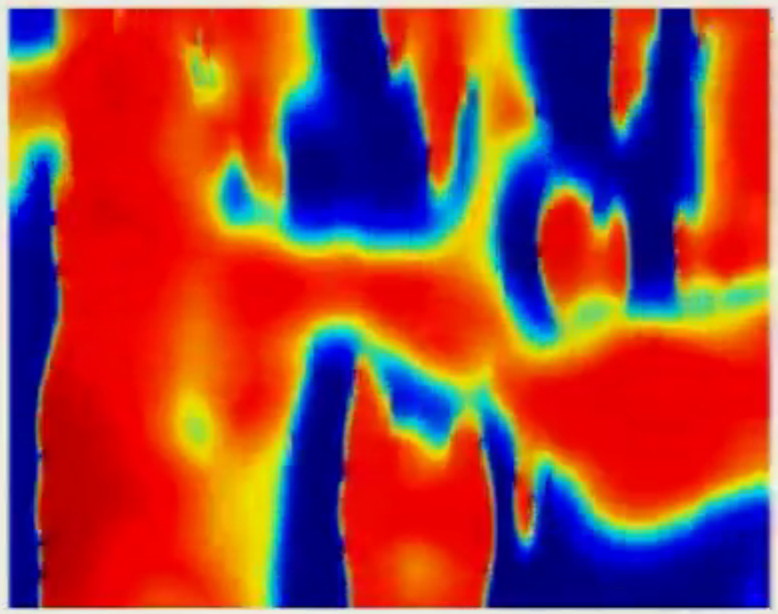

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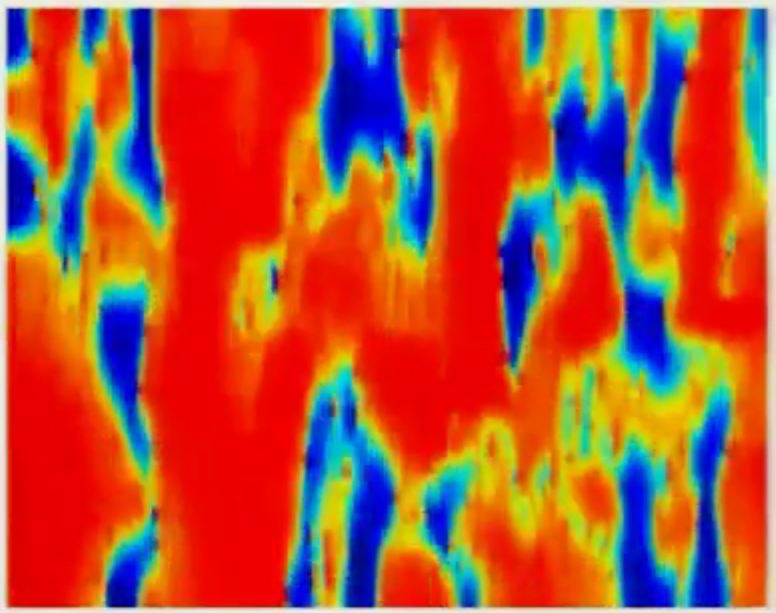

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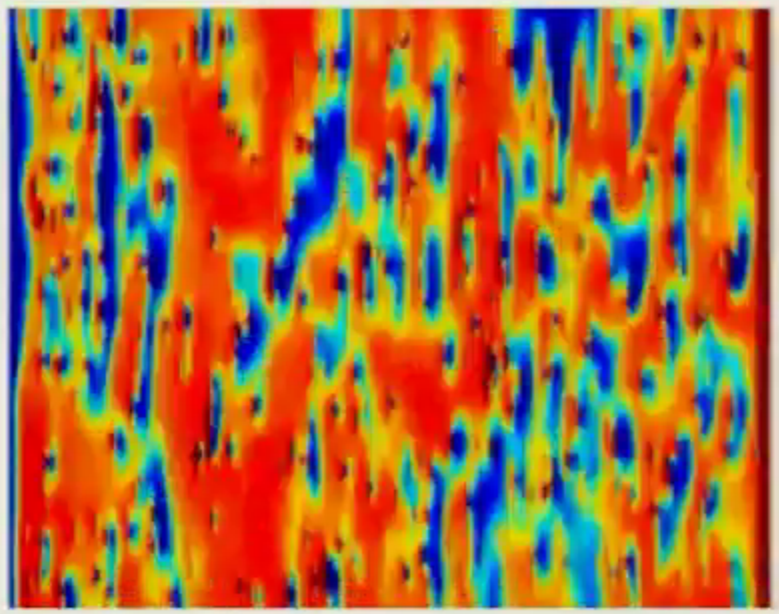

Wilson, M – submitted

Successful "Defibrillation":

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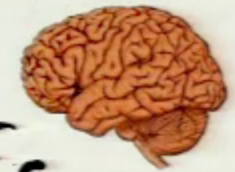
Wilson, M – submitted

Desync from Isostable Reduction of PDEs



Phase density evolves according to

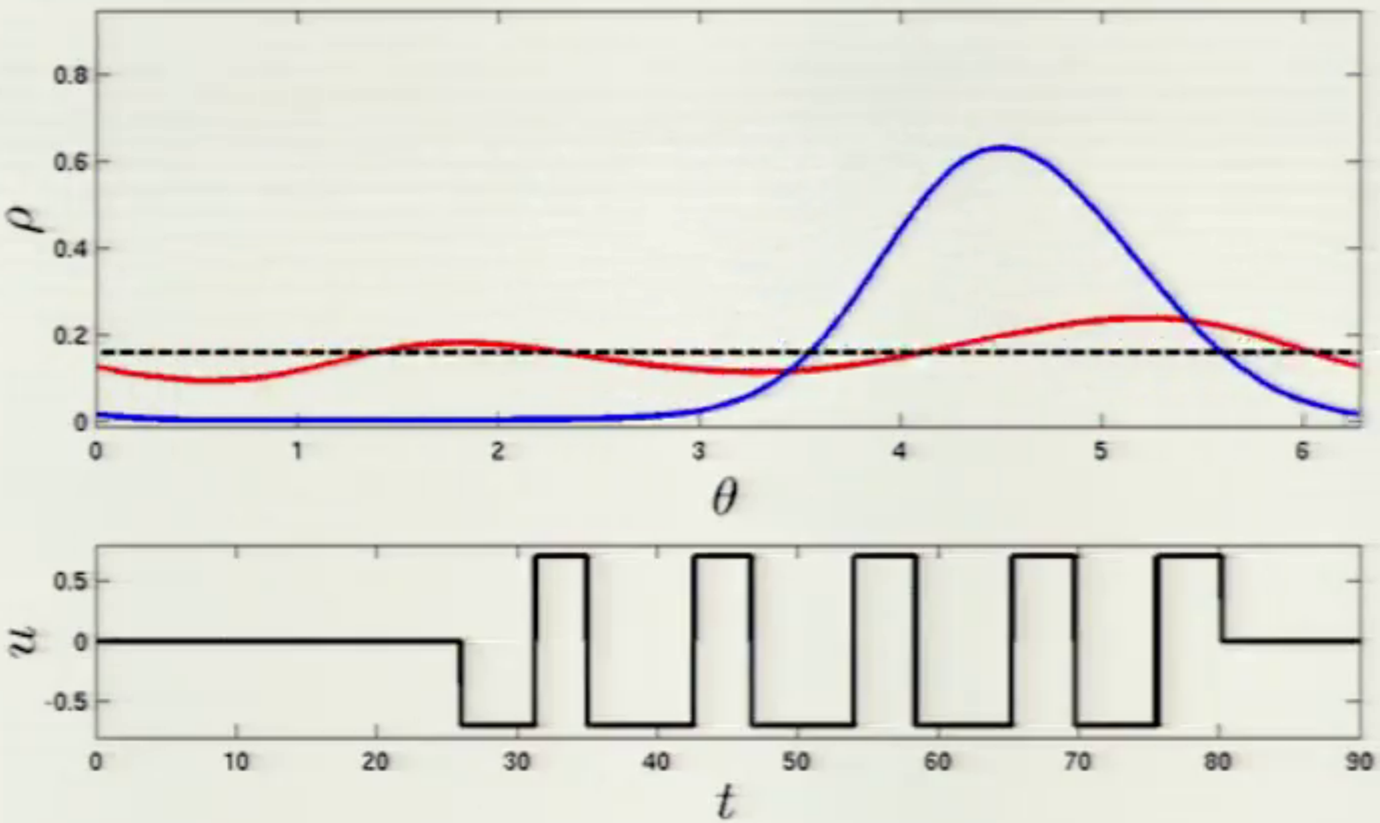
$$\frac{\partial \rho(\theta,t)}{\partial t} = -\omega \frac{\partial \rho}{\partial \theta} + \frac{B^2}{2}\frac{\partial^2 \rho}{\partial \theta^2} + \text{input} + \text{coupling}.$$

After isostable reduction:

$$\dot{\psi} = \kappa + \langle \mathcal{I}, \text{input} + \text{coupling} \rangle.$$

Wilson, M – submitted

Desync from Isostable Reduction of PDEs



Wilson, M – submitted

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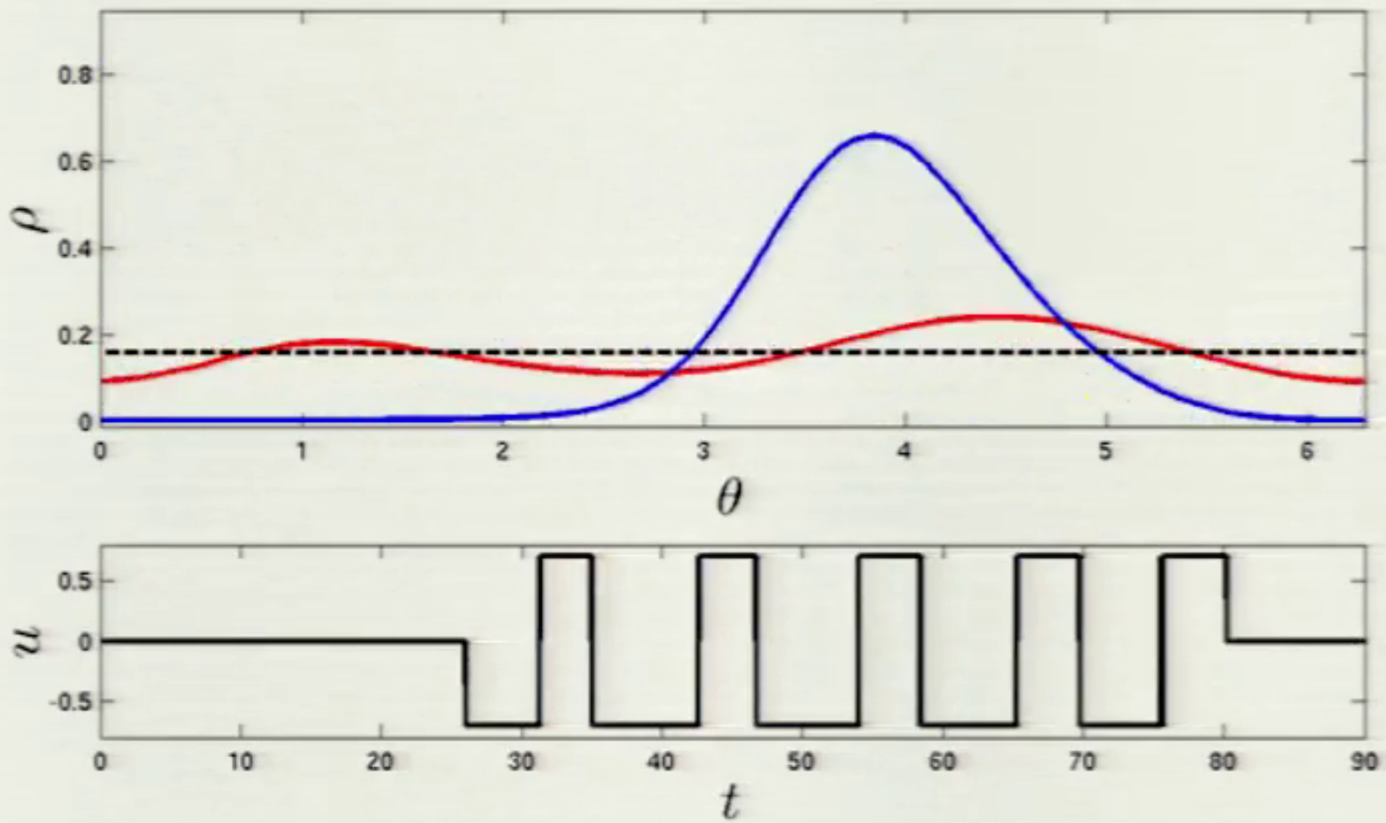

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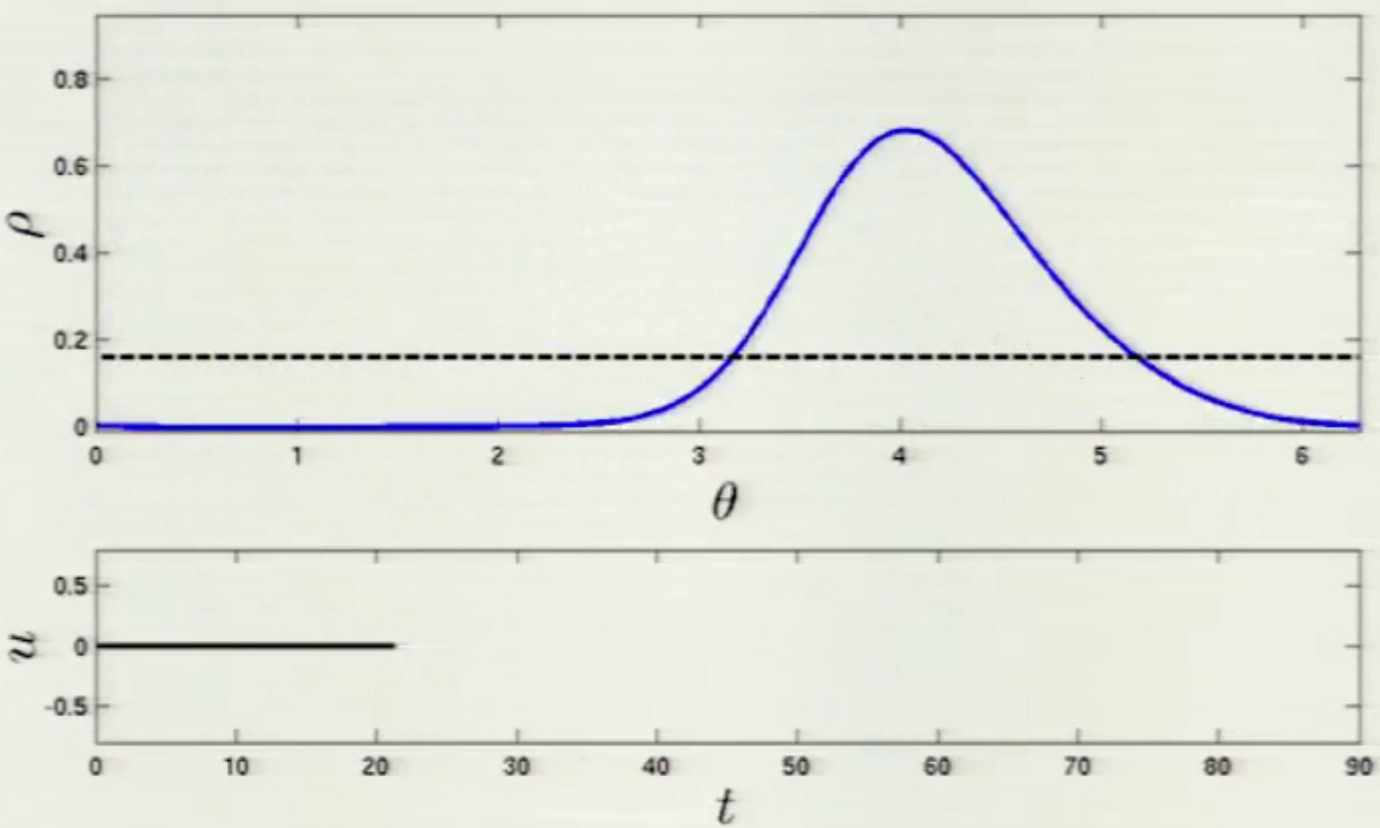


Wilson, M – submitted

Other Related Research

- Chaotic desync for extracellular stimulation

- Wilson, M - *JCNS* 2014

- Time optimal phase resetting

- Danzl, Hespanha, M – *Bio Cyb* 2009

- Dynamic programming control of neural populations

- Nabi, M - *J Neural Engr* 2011

- Control with time-delayed signals

- Orosz, M, Murray - *Bio Cyb* 2010

- Control of circadian oscillators

- Wilson, M - *Biophys J* 2014

- Experimental control of neurons

- Wilson, Holt, Netoff, M – *Front Neuro* 2015
- Nabi, Stigen, M, Netoff - *J Neural Engr* 2013
- Stigen, Danzl, M, Netoff - *J Neurophys* 2011

- Experimental control of chemical oscillators

- w/ Ken Showalter's group, Tay Netoff's group

Collaborators on the Presented Work

UCSB

- **Dan Wilson**
- Miles Detrixhe
- Frederic Gibou
- Igor Mezic

Former UCSB

- Ali Nabi
- Mohammad Mirzadeh
- Marion Doubeck
- Blane Rhoads
- Alexandre Mauroy (now at U Liege)

Auckland

- Hinke Osinga

Other Recent Collaborators on Related Work

Former and Current UCSB

- Per Danzl
- Tim Matchen
- Joao Hespanha
- Gabor Orosz (now U Mich)
- Gerd Schmidt (visitor from Stuttgart)

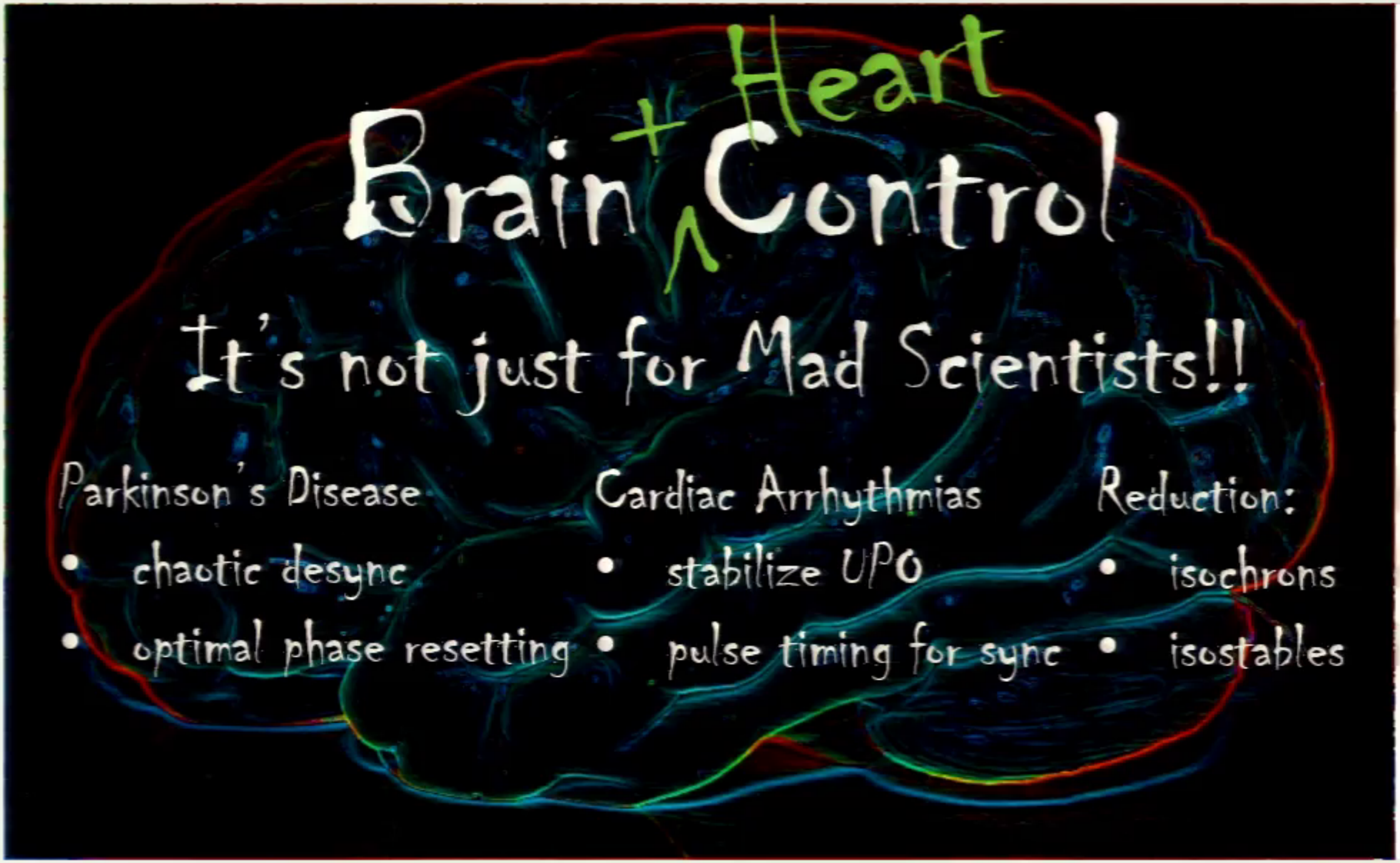
U Minn

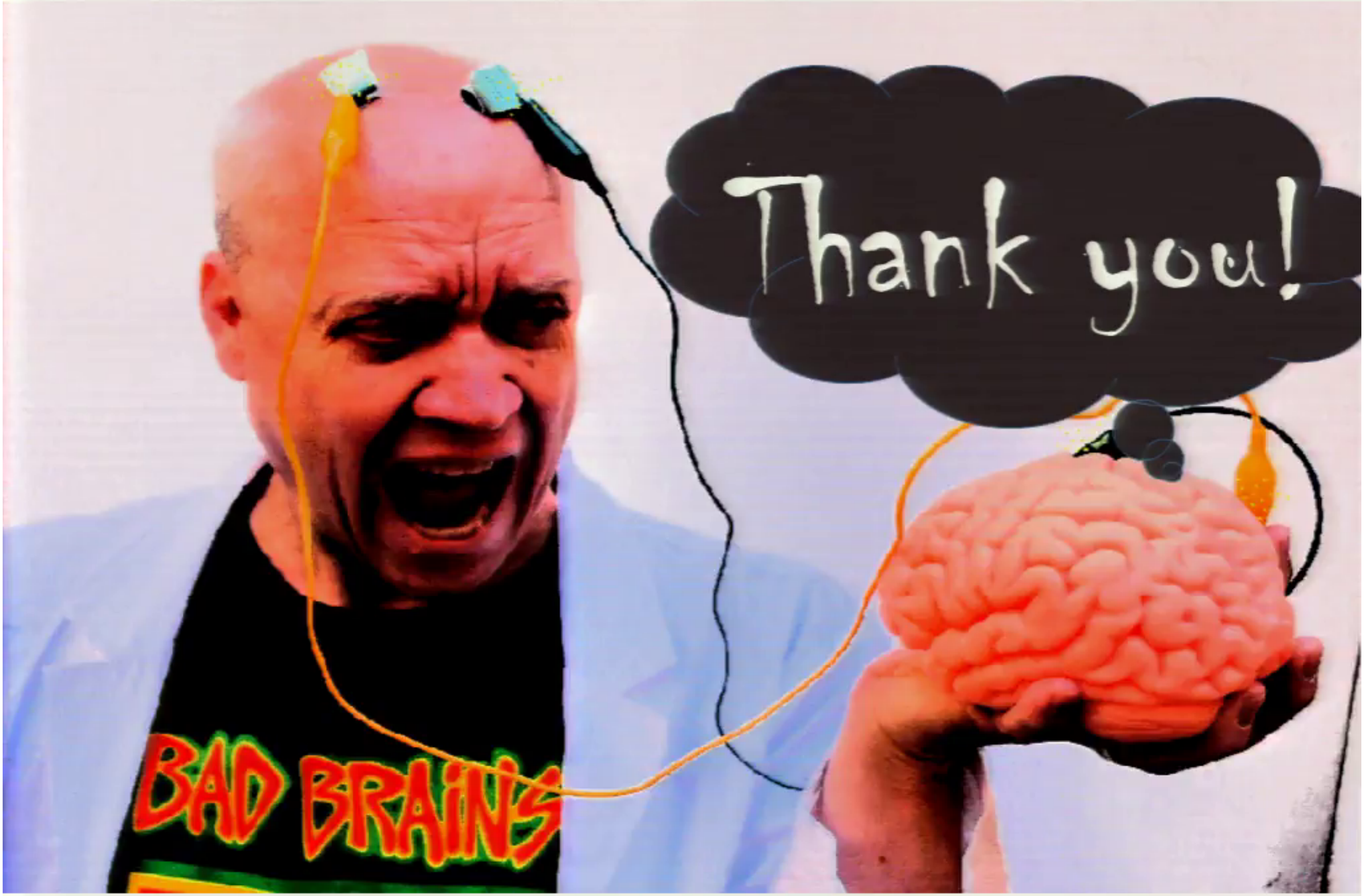
- Abbey Holt
- Tyler Stigen
- Tay Netoff

WVU

- Ken Showalter
- Mark Tinsley

Thanks to the
NSF for funding!


Brain + Heart Control
It's not just for Mad Scientists!!
Parkinson's Disease
• chaotic desync
• optimal phase resetting
Cardiac Arrhythmias
• stabilize UPO
• pulse timing for sync
Reduction:
• isochrons
• isostables


Thank you!
BAD BRAINS