Simple Models in a Complex World

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What in the world do I do?

That's a tough question.

What in the world do I do?

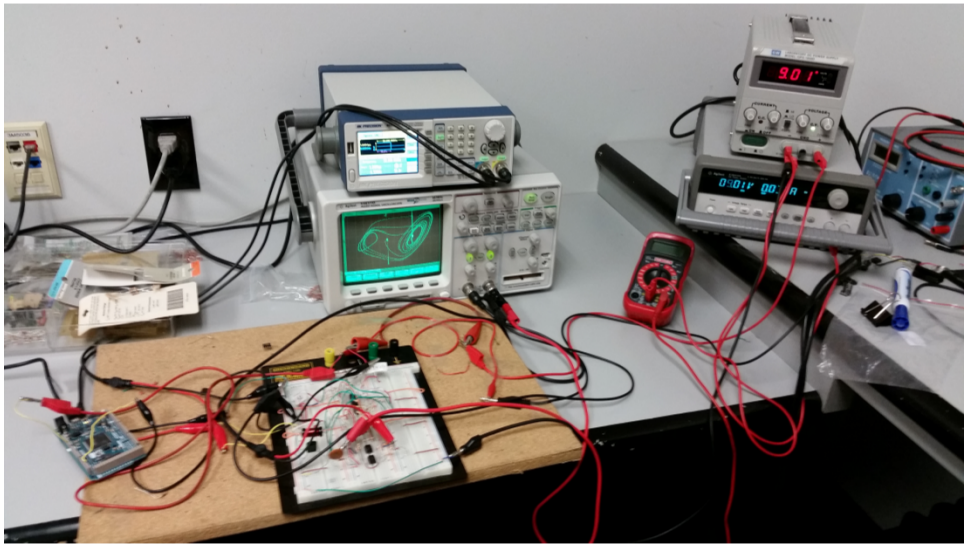
Mechanistically modeling problems arising from real world phenomena, often using the tools of dynamical systems and bifurcation theory, with an inclination for reduced ("simple") models and a slight affinity for theory.

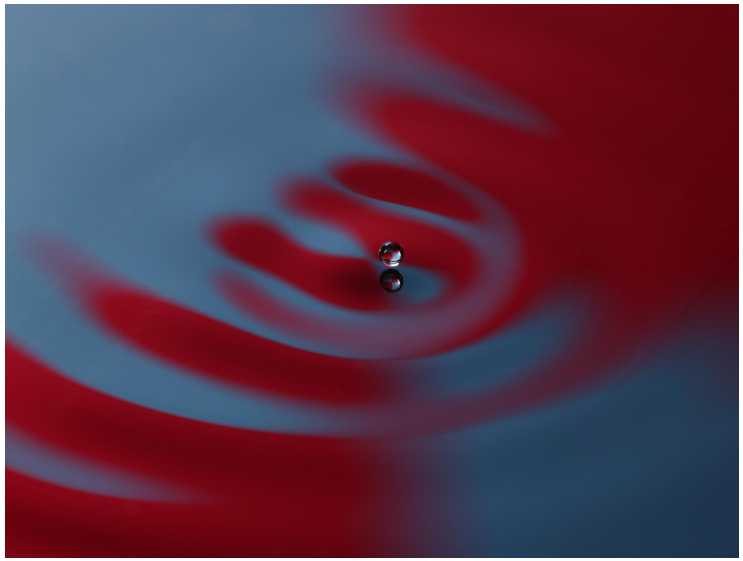
Why reduced modeling?

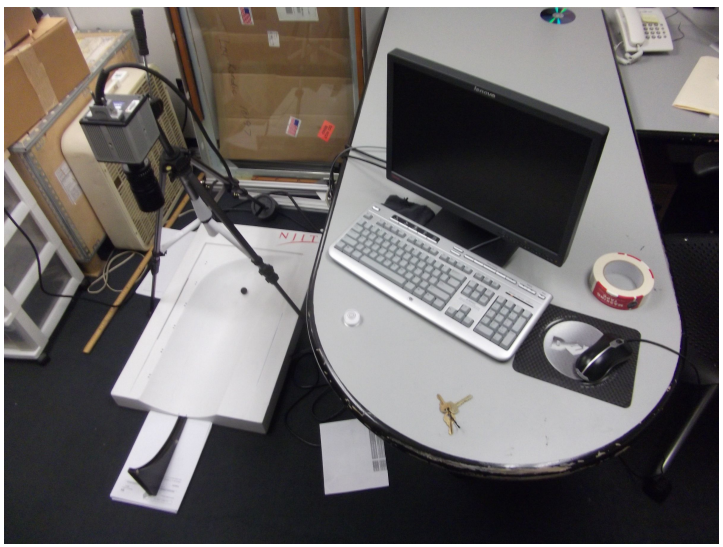
Everything should be made as simple as possible, but not simpler.

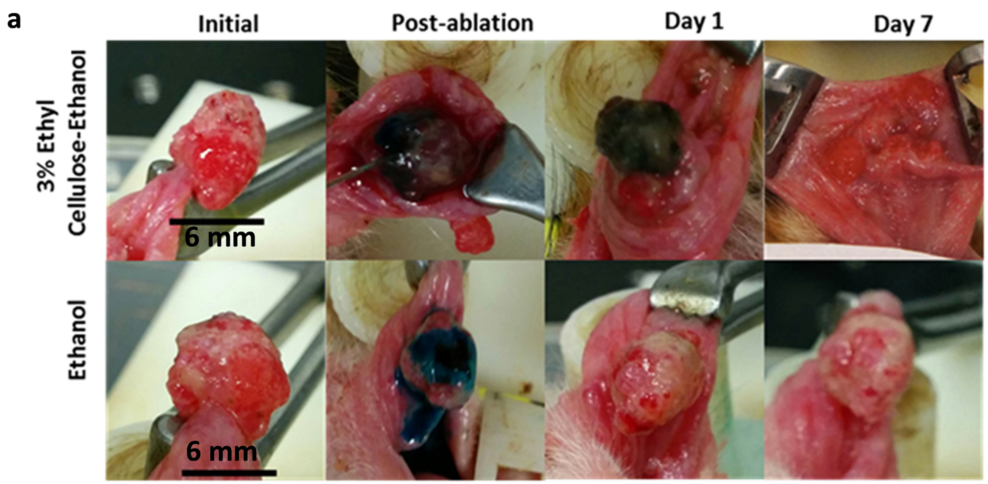
Albert Einstein

Stuff I'll be talking about today

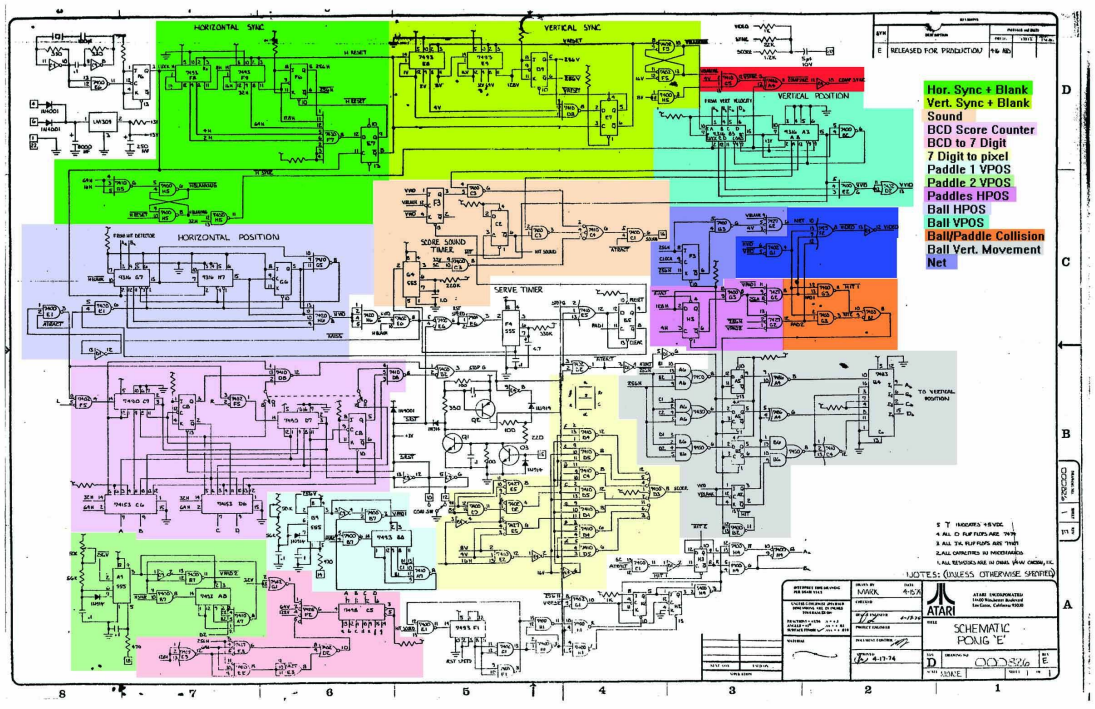


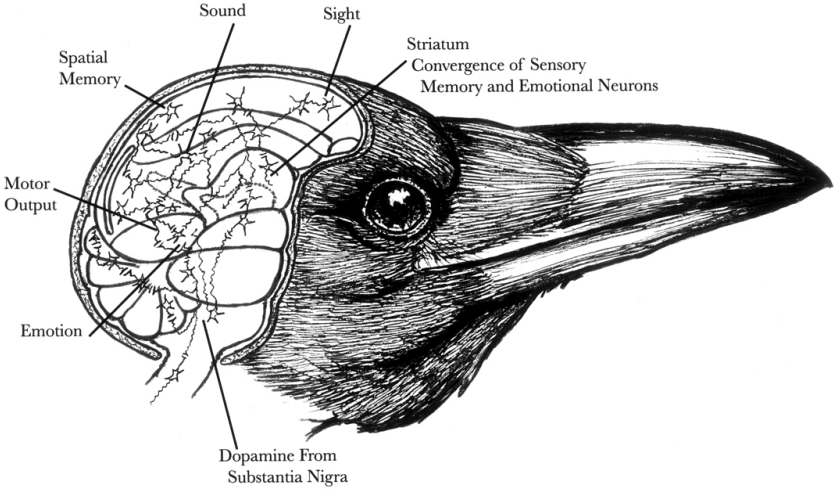


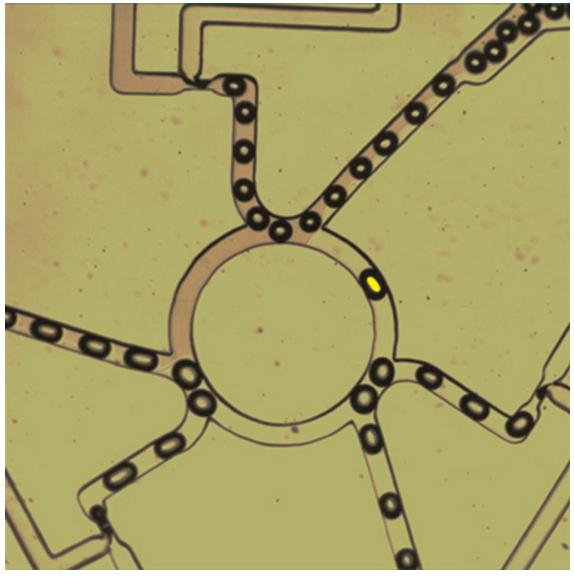




Logical Circuits

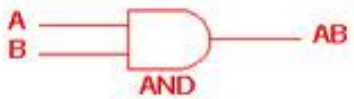






History: Logic Gates

AND



x	y	$F(x,y) := x \wedge y$
0	0	0
0	1	0
1	0	0
1	1	1

NOT

x	$F(x,y) := \neg x$
0	1
1	0

OR

x	y	$F(x,y) := x \vee y$
0	0	0
0	1	1
1	0	1
1	1	1

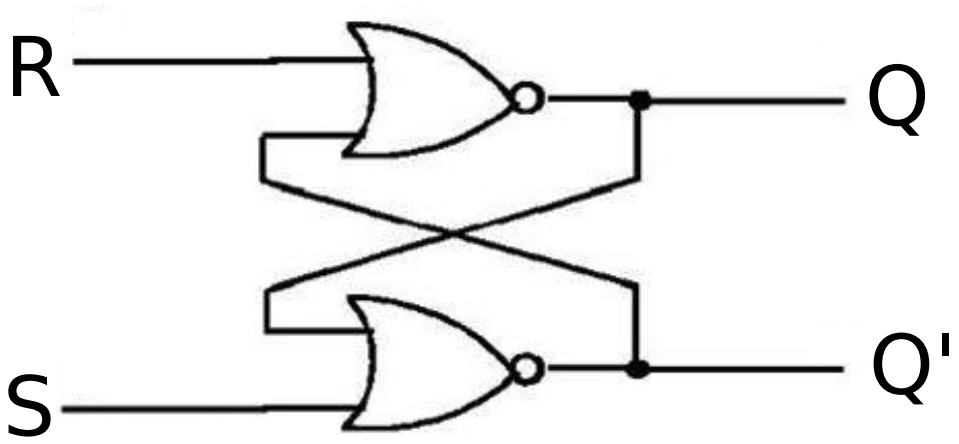
NAND

x	y	$F(x,y) := \neg(x \wedge y)$
0	0	1
0	1	1
1	0	1
1	1	0

NOR

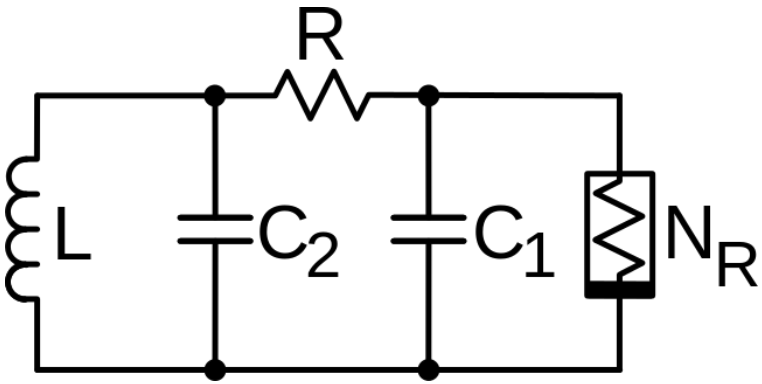
x	y	$F(x,y) := \neg(x \vee y)$
0	0	1
0	1	0
1	0	0
1	1	0

History: RS flip-flop



Inputs		Outputs	
R	S	Q	Q'
0	1	1	0
1	0	0	1
0	0	keep	keep
1	1	undefined	undefined

History: Chaotic Circuits



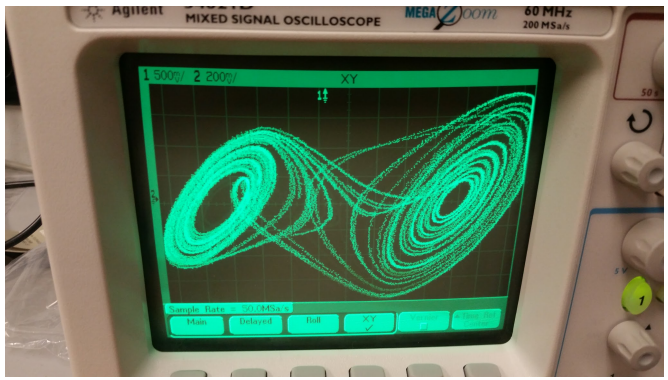


Figure: Source: [Chua 1983(Patent)]

$$
\begin{aligned}
C_1 \frac{dV_{C_1}}{dt} &= G(V_{C_2} - V_{C_1}) - g(V_{C_1}) \\
C_2 \frac{dV_{C_2}}{dt} &= G(V_{C_1} - V_{C_2}) + \chi_L \\
L \frac{d\chi_L}{dt} &= -V_{C_2}
\end{aligned}
\tag{1}
$$

Chaotic NOR gate/RS flip-flop

- Some SPICE sims, but no experiments and no models (till now).
- System is too complex for traditional ODE models.

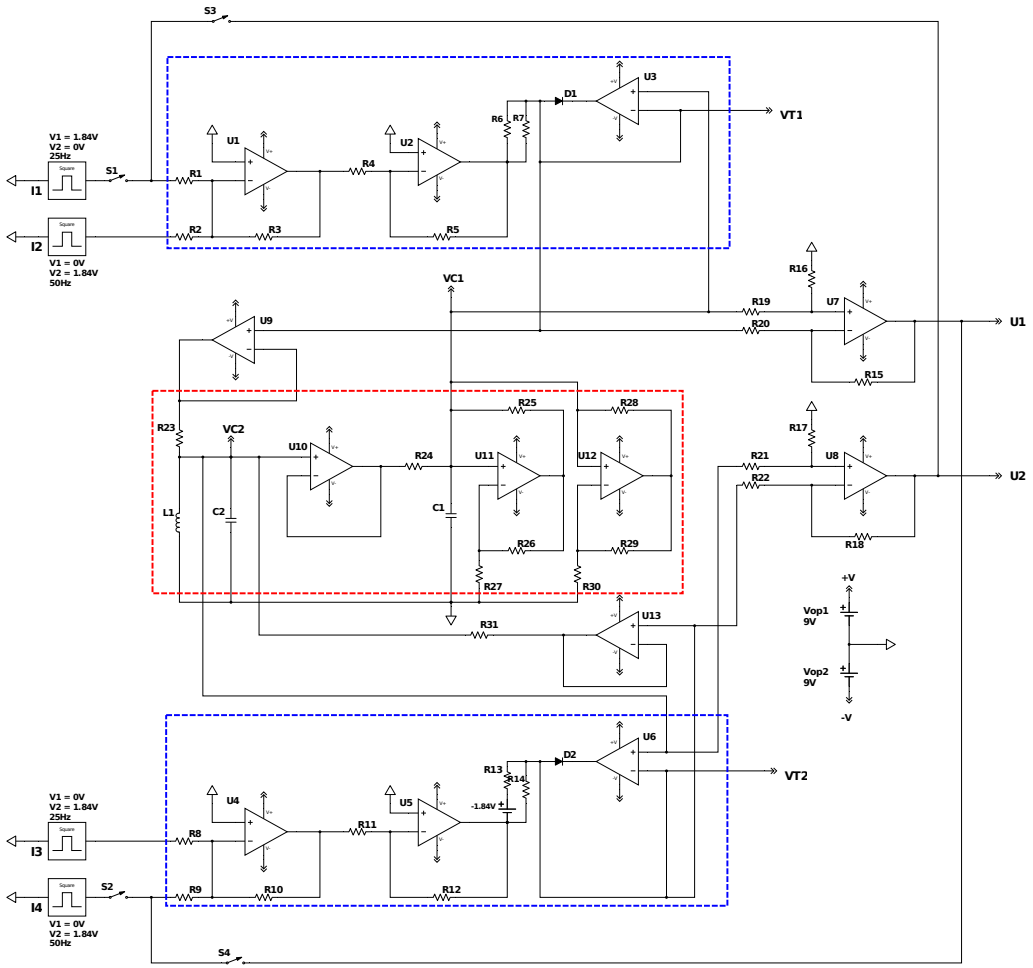
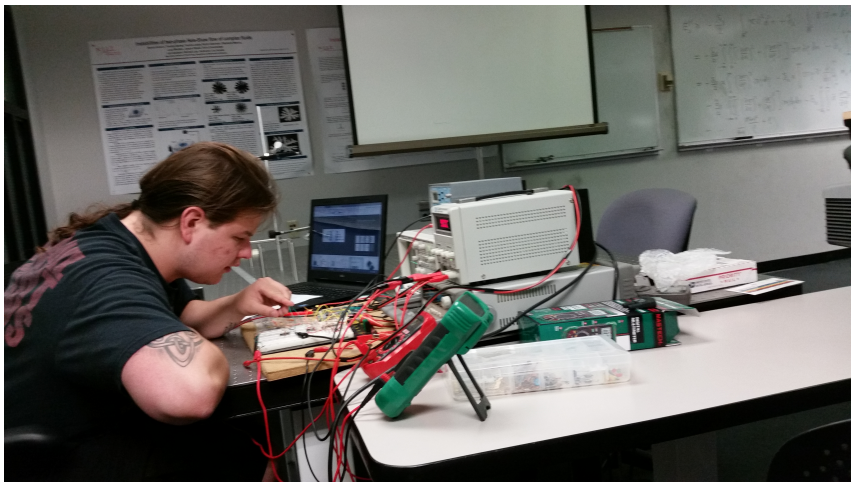
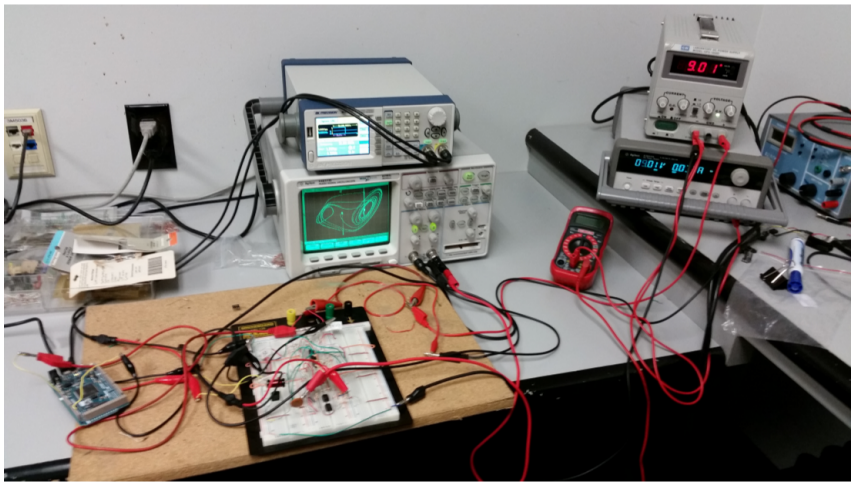


Figure: Source: [Rahman, Jordan, Blackmore. *Proc. Roy. Soc. A* (2018)]

Experimentation

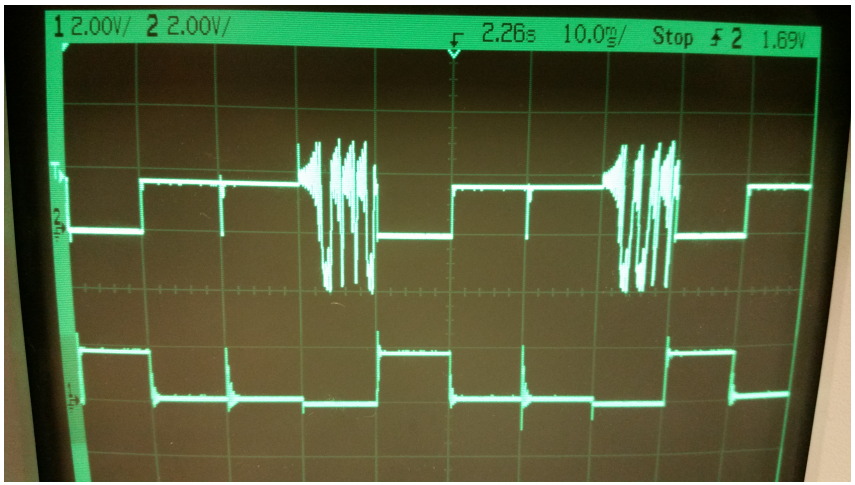


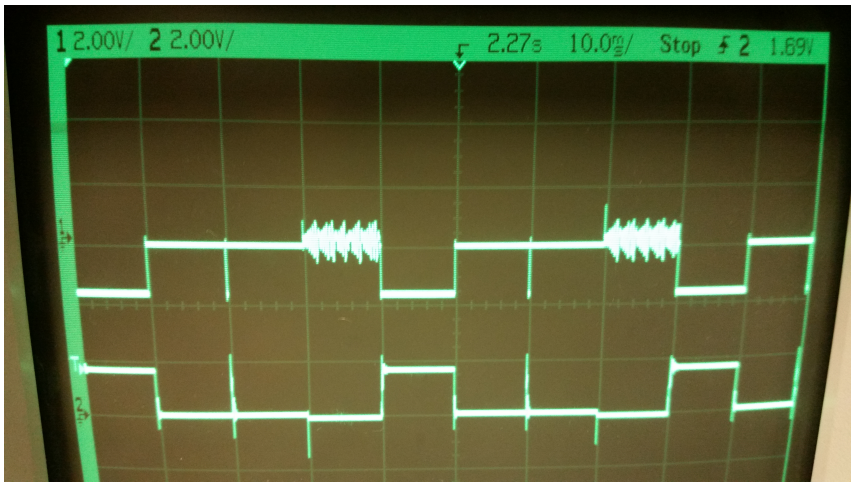


- Designed new version of chaotic RS flip-flop
- Built physical realization
- Simulations agree with the experiments
- Components caught on fire (oops)
- Testing the possibility of chaotic encryption

Modeling Thresholds

Experimental results:





Let ξ and η represent the threshold voltages

$$\begin{aligned} \xi_{n+1} &= f(I_1, I_2, \xi_n), \\ \eta_{n+1} &= g(I_3, I_4, \eta_n); \end{aligned} \tag{2}$$

What we know from direct observation:

$$\begin{aligned} f(0,0,0) &= 0 & f(1,0,1) = f(0,1,1) &= 1 & f(1,1,\star) &= \star, \\ g(0,0,-1) &= -1 & g(1,0,0) = g(0,1,0) &= 0 & g(1,1,\star) &= \star. \end{aligned} \tag{3}$$

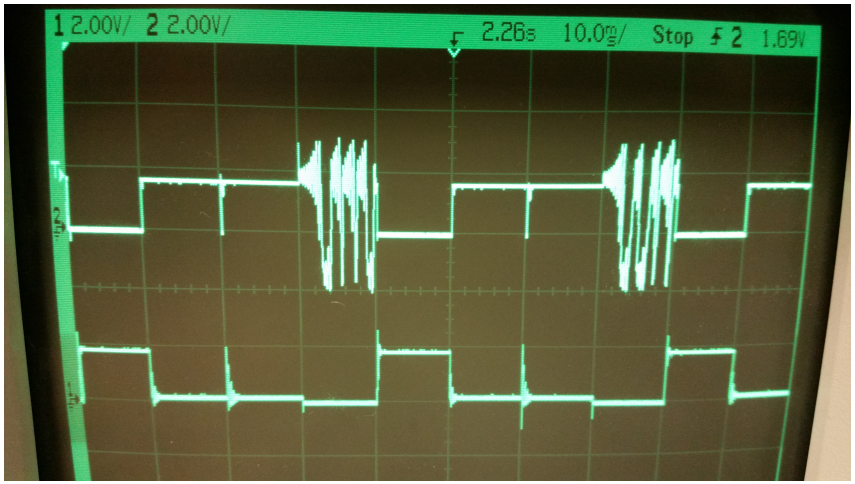
Assumptions

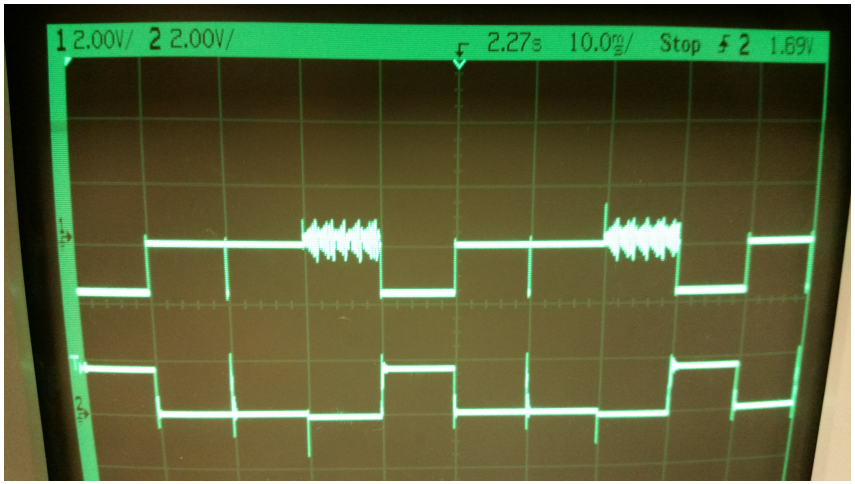
To satisfy the above observations we let

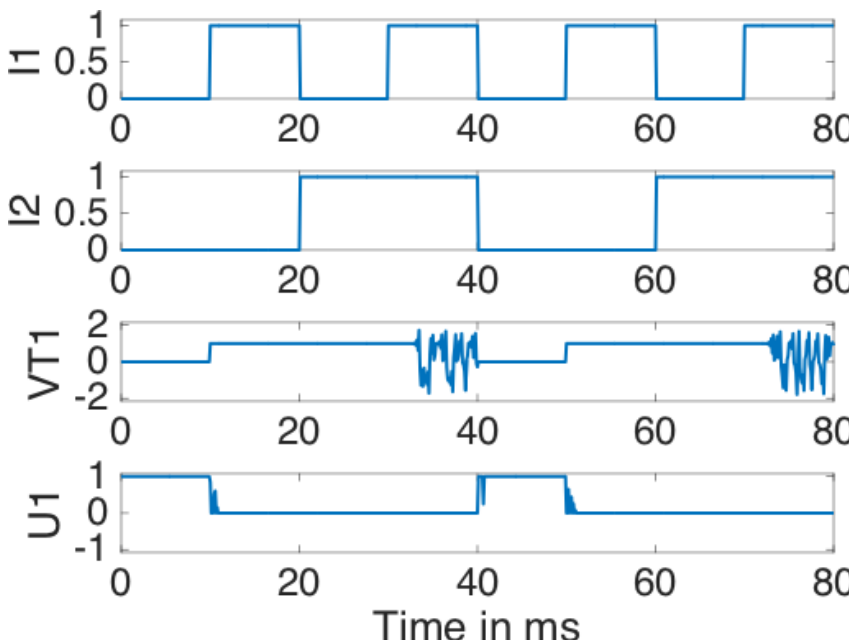
$$\begin{aligned} f(I_1, I_2, x_1) &:= |I_1 - I_2| + I_1 I_2 y_f(x_1), \\ g(I_3, I_4, x_2) &:= |I_3 - I_4| - 1 + I_3 I_4 y_g(x_2); \end{aligned} \tag{4}$$

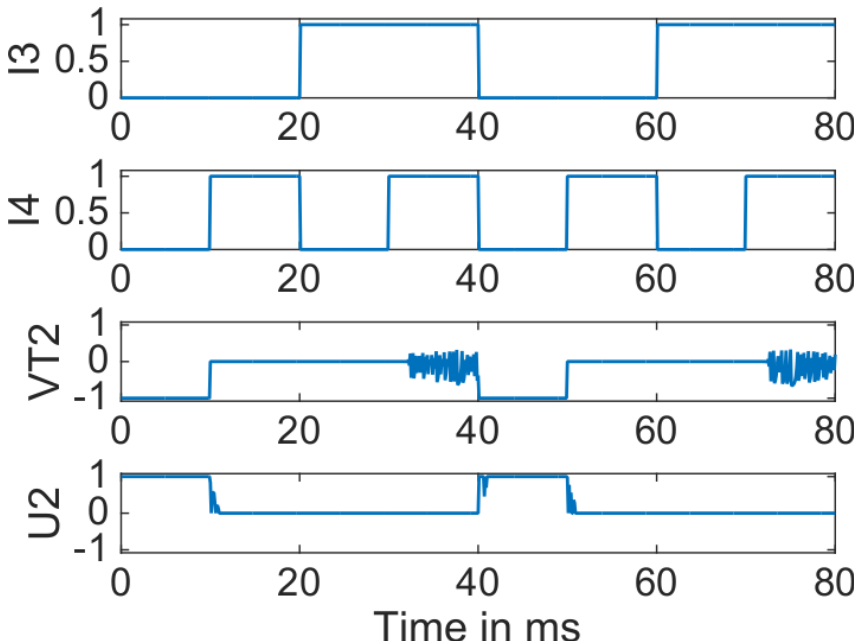
- y are combinations or modifications of tent maps.
- $y_g - 1$ has a f.p. at $x = 0$.
- y_f has two nonzero f.p.'s near ± 1.

Simulations vs. Experiments









Current and future work

- Develop a capacitor-based (rather than our TCU-based) model and compare.
- Build neuronal analogs.
- Model microfluidic circuits.

Walking in confined geometry

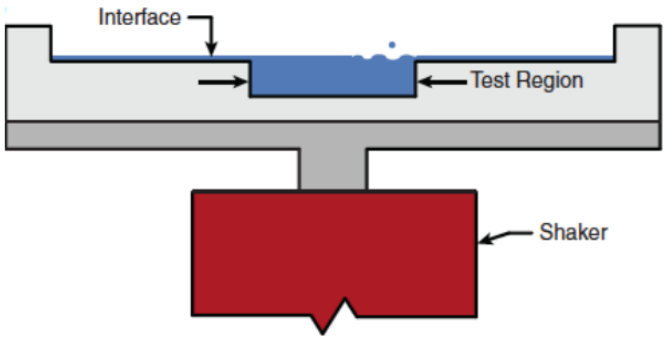


Figure: [Harris *et al.*, PRE 2013]

("Free" Space)

Figure: `http://math.mit.edu/~bush/?page_id=252`

- (Couder *et al.Nature* (2005)) observed walking dynamics.
- Groups at Paris, MIT, and others have made significant experimental and theoretical contributions since.
- Analogous to wave-particle duality.
- Can produce quantum-like behavior.

Walking in rotating frame

(Corral)

Figure: `http://math.mit.edu/~bush/?page_id=252`

Discrete Dynamical Model

Originally developed by Gilet (PRE 2014).

$$\begin{bmatrix} w_{n+1} \\ x_{n+1} \end{bmatrix} = \begin{bmatrix} \mu[w_n + \Psi(x_n)] \\ x_n - C w_n \Psi'(x_n) \end{bmatrix} \quad (5)$$

Simplifying assumptions:

- Droplet shifted proportionally to the gradient of the wave field.
- Droplet moving in a straight line.
- Only one eigenmode is excited in a confined geometry.

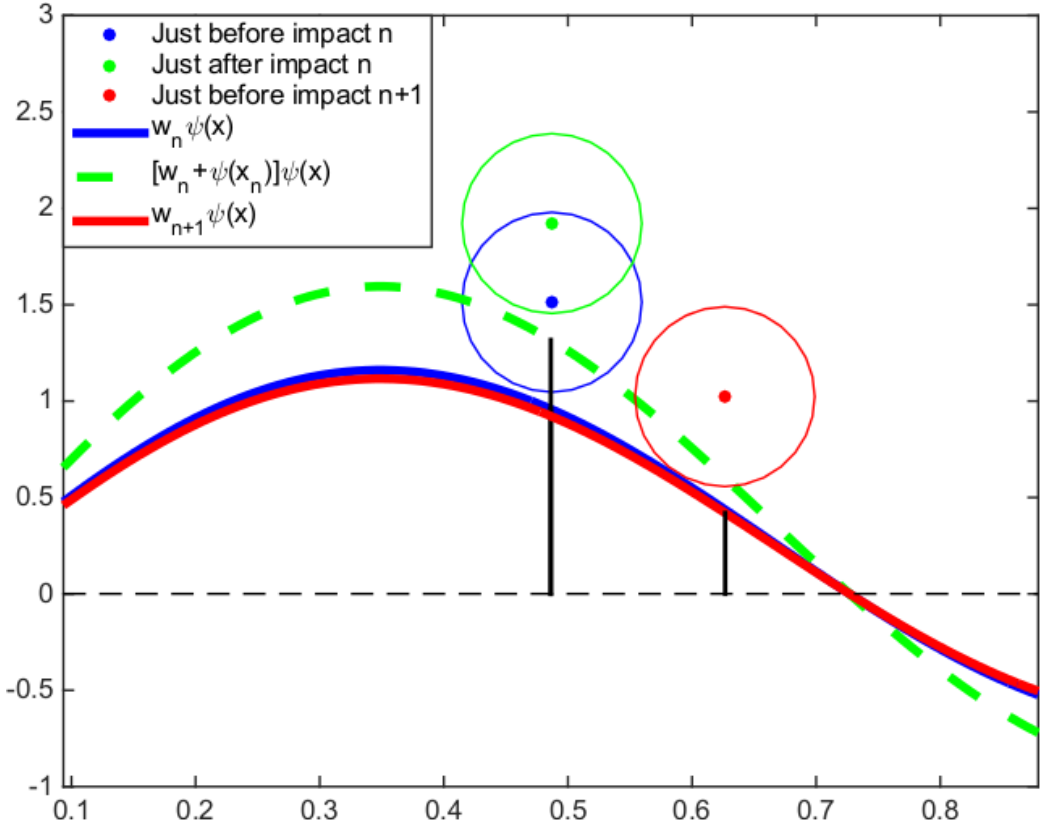


Figure: Source: [Rahman and Blackmore, CSF 2016]

Simulations

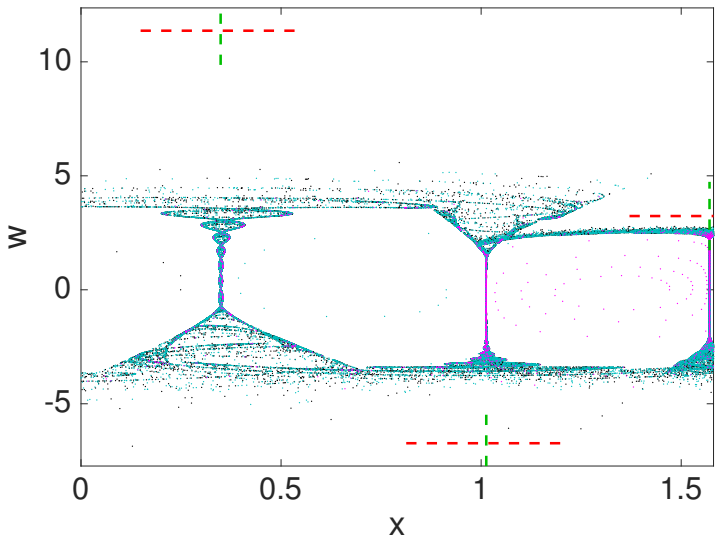


Figure: $\mu = 0.94$

(Chaos)

Confining the walker

$$w(n+1) = \mu[w_n + \Psi(x_n)] \qquad x(n+1) = [x_n - Cw_n\Psi'(x_n)] \mod 2\pi$$

$$\Psi(x,\beta) = \frac{\cos\beta}{\sqrt{\pi}} \sin 3(x - pi/2) + \frac{\sin\beta}{\sqrt{\pi}} \sin 5(x - pi/2)$$

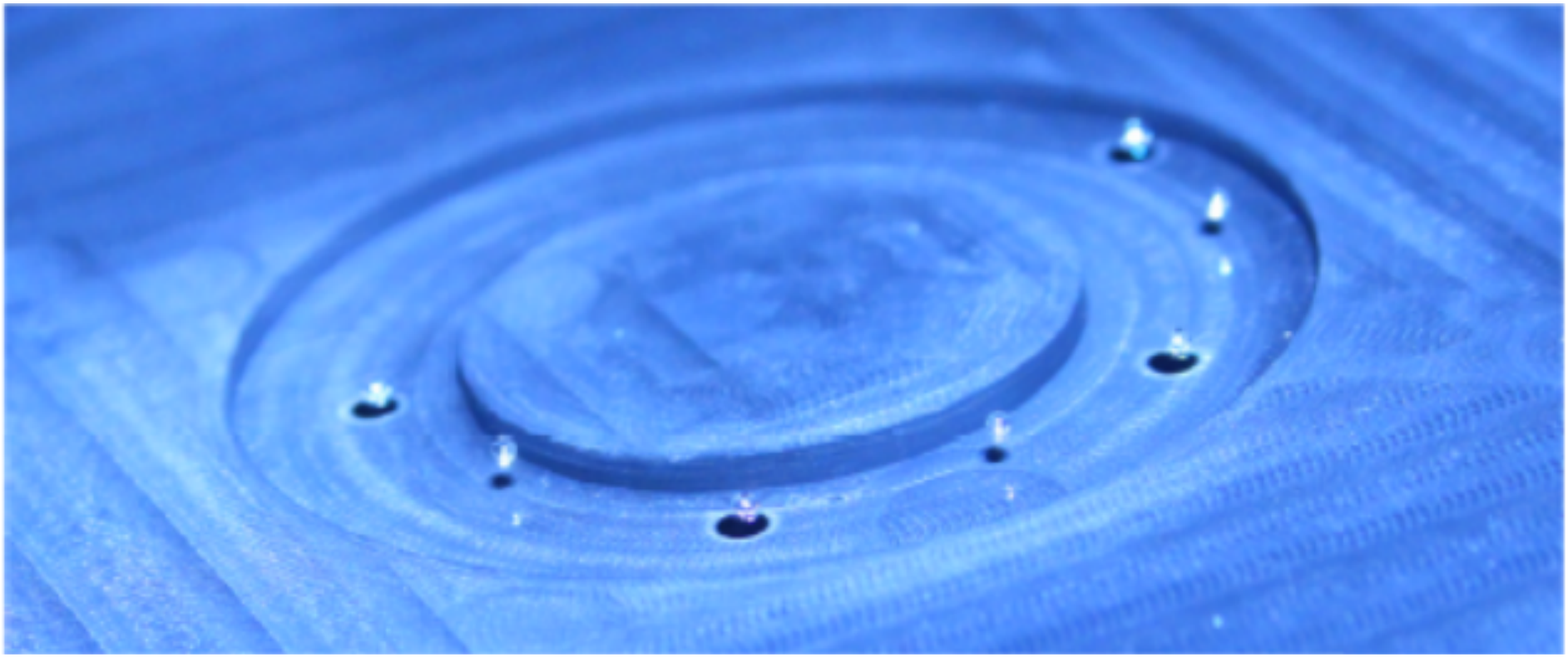


Figure: Source: [Filoux, Hubert, Vanderwalle. *Phys. Rev. E*(2015)]

Current and future work

- Working on kicked rotator - like model on the annulus.
- Working on model for elliptical corral.
- Connections between dynamics and statistics.

Drug diffusion: Story time

Two Bengalis, a grant, and Reddit.

- Souparno's NIH grant on individualized treatment.
- Lots of procrastination.
- Redditors write bad science headlines.

Drug diffusion: Story time

Two Bengalis, a grant, and Reddit.

- This title is much better.
- Using alcohol to treat solid tumors.

Development of enhanced ethanol ablation as an alternative to surgery in treatment of superficial solid tumors

Robert Morhard ✉, Corrine Nief, Carlos Barrero Castedo, Fangyao Hu, Megan Madonna, Jenna L. Mueller, Mark W. Dewhirst, David F. Katz & Nirmala Ramanujam

Scientific Reports **7**, Article number: 8750 (2017)
doi:10.1038/s41598-017-09371-2

Received: 05 May 2017
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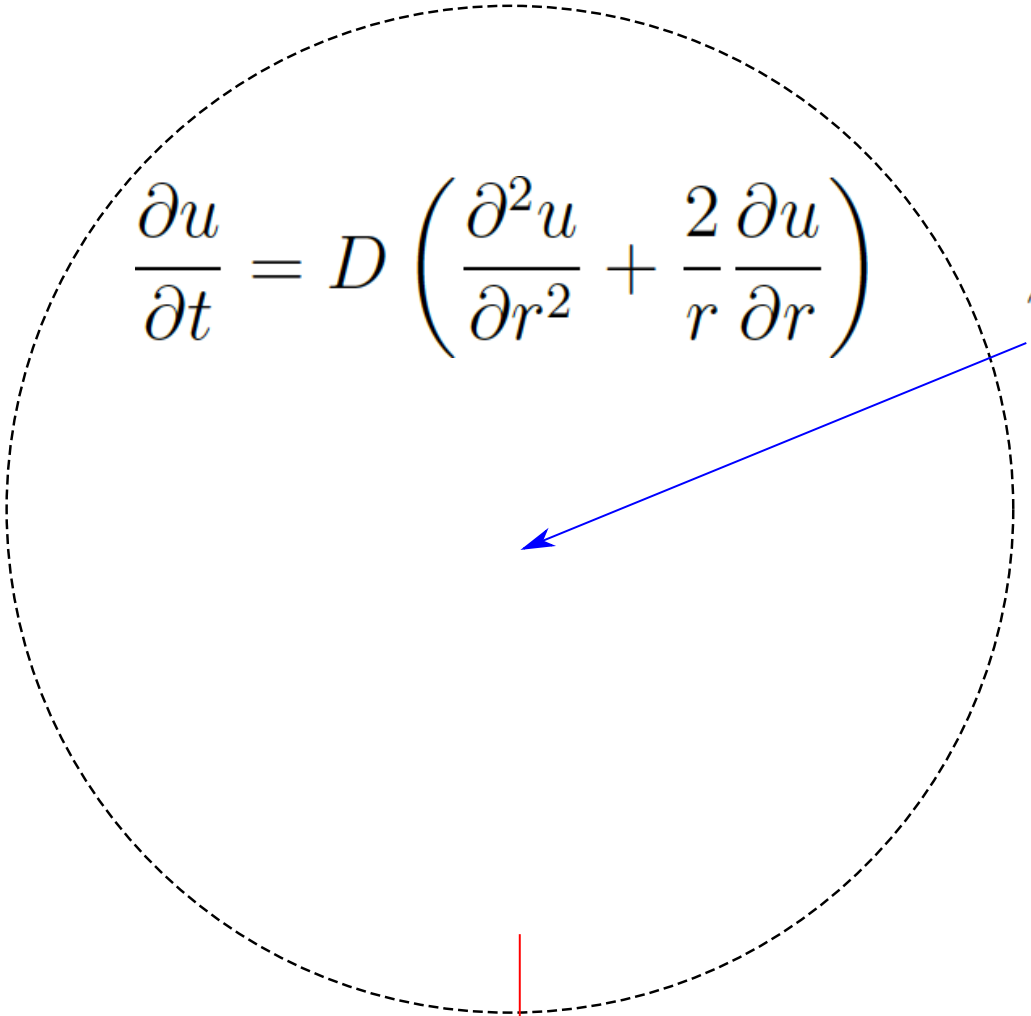
Published online: 18 August 2017

Simplest possible mechanistic model

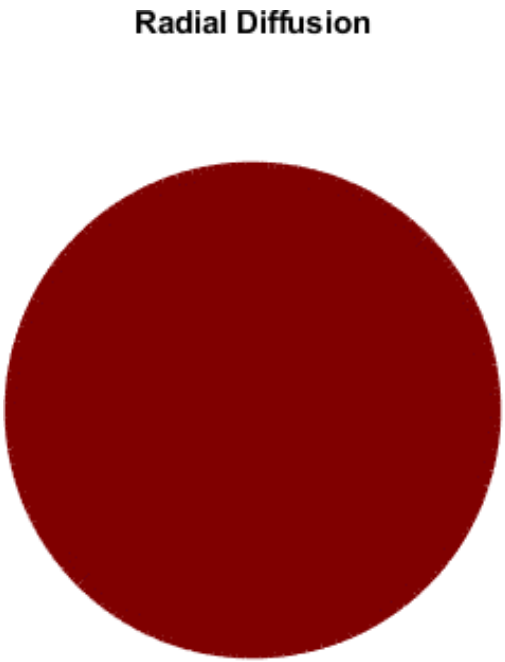
Assumptions:

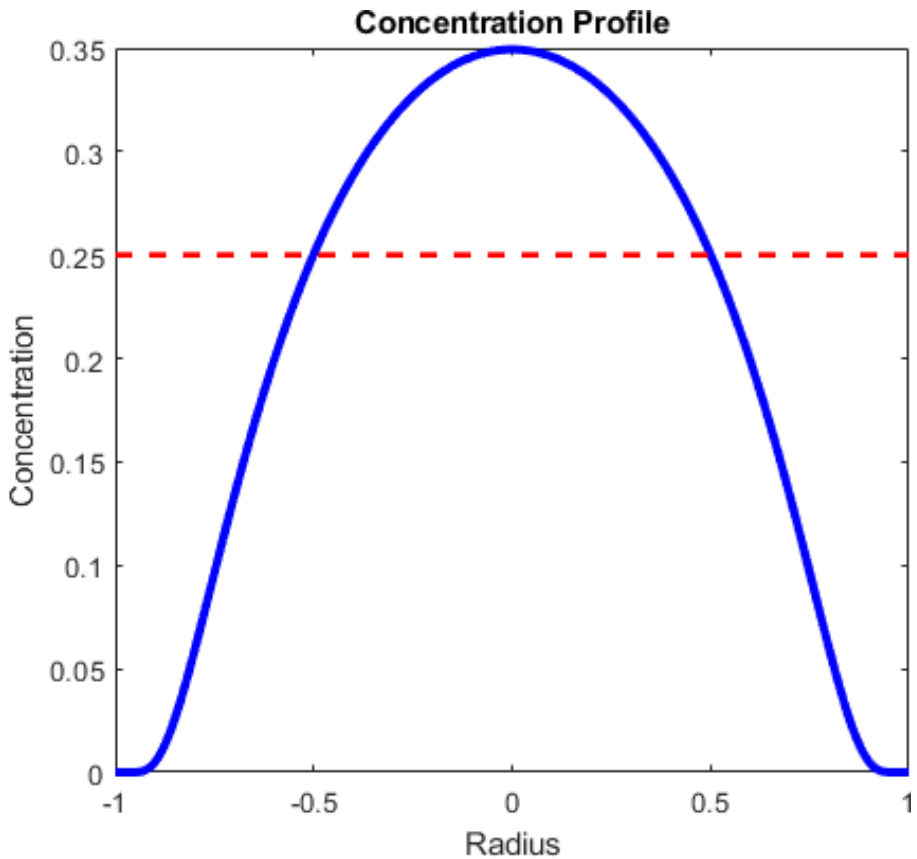
- Spherical solid tumor.
- Diffusion with constant diffusivity.
- Leaky boundary.
- Injection into the center.
- Diffusion begins after injection ends.
- There exists a minimum drug concentration required to kill a cell.

Simplest possible mechanistic model



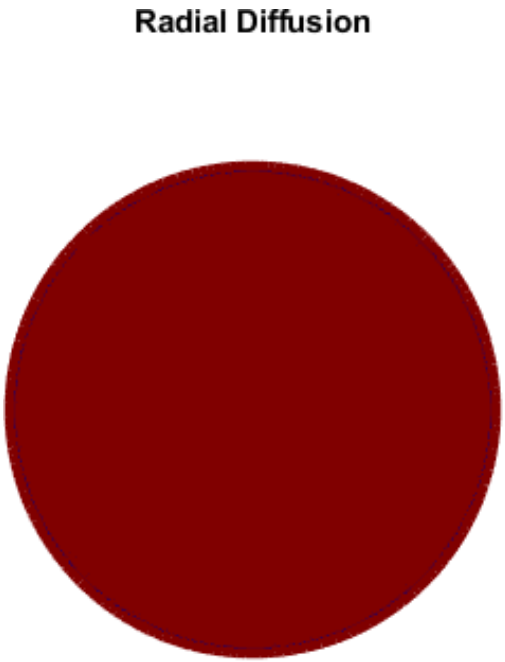
Cell death

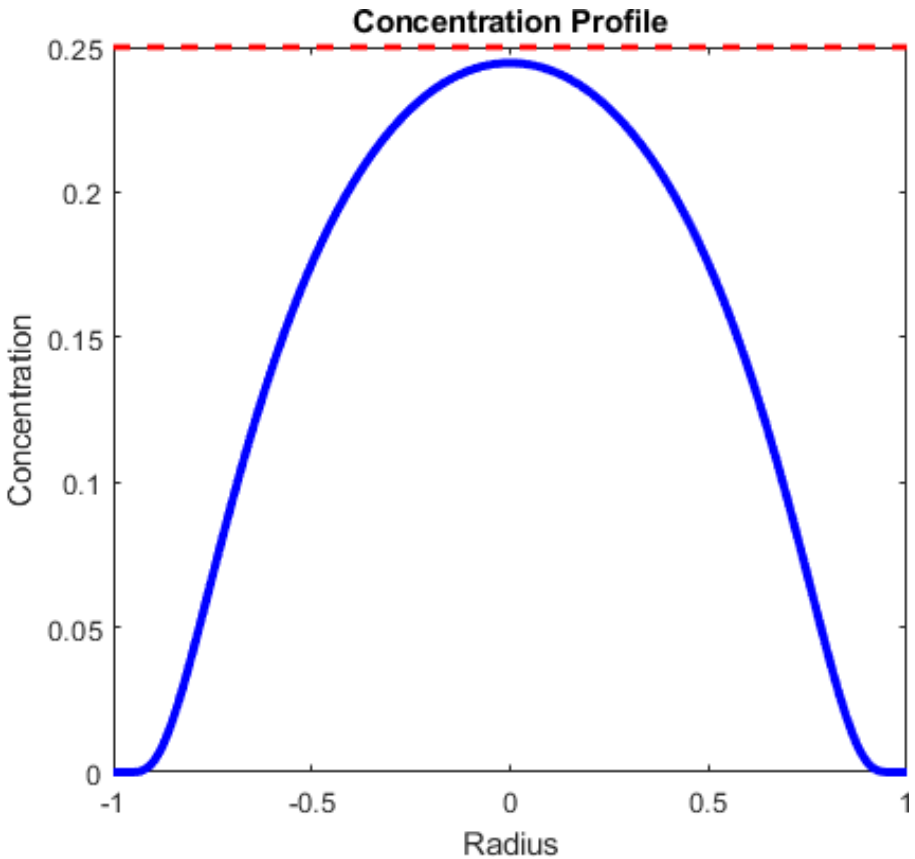

Radial Diffusion


Concentration Profile
Concentration
Radius
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
-1
-0.5
0
0.5
1

Diffusion

No ablation



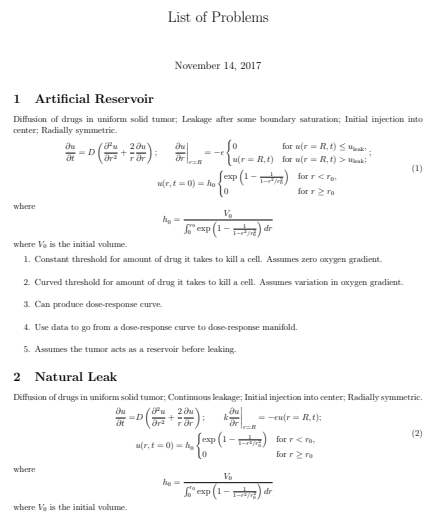


(Partial Ablation)

(Full Ablation)

Current and future work

- Model the relationship between time and threshold.
- Using statistics to connect the model with population data.
- Making individualized predictions.
- Analyze our other models.



List of Problems

November 14, 2017

1 Artificial Reservoir

Diffusion of drugs in uniform solid tumor; Leakage after some boundary saturation; Initial injection into center; Radially symmetric.

$$\frac{\partial u}{\partial t} = D\left(\frac{\partial^2 u}{\partial r^2} + \frac{2}{r}\frac{\partial u}{\partial r}\right); \quad \left.\frac{\partial u}{\partial r}\right|_{r=R} = -\epsilon\begin{cases}0 & \text{for } u(r=R,t) \le u_{\text{leak}},\\ u(r=R,t) & \text{for } u(r=R,t) > u_{\text{leak}};\end{cases}$$
$$u(r,t=0) = h_0\begin{cases}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right) & \text{for } r < r_0,\\ 0 & \text{for } r \ge r_0\end{cases} \tag{1}$$

where

$$h_0 = \frac{V_0}{\int_0^{r_0}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right)dr}$$

where V_0 is the initial volume.

1. Constant threshold for amount of drug it takes to kill a cell. Assumes zero oxygen gradient.
2. Curved threshold for amount of drug it takes to kill a cell. Assumes variation in oxygen gradient.
3. Can produce dose-response curve.
4. Use data to go from a dose-response curve to dose-response manifold.
5. Assumes the tumor acts as a reservoir before leaking.

2 Natural Leak

Diffusion of drugs in uniform solid tumor; Continuous leakage; Initial injection into center; Radially symmetric.

$$\frac{\partial u}{\partial t} = D\left(\frac{\partial^2 u}{\partial r^2} + \frac{2}{r}\frac{\partial u}{\partial r}\right); \quad k\left.\frac{\partial u}{\partial r}\right|_{r=R} = -\epsilon u(r=R,t);$$
$$u(r,t=0) = h_0\begin{cases}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right) & \text{for } r < r_0,\\ 0 & \text{for } r \ge r_0\end{cases} \tag{2}$$

where

$$h_0 = \frac{V_0}{\int_0^{r_0}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right)dr}$$

where V_0 is the initial volume.

1. Constant threshold for amount of drug it takes to kill a cell. Assumes zero oxygen gradient.
2. Curved threshold for amount of drug it takes to kill a cell. Assumes variation in oxygen gradient.
3. Can produce dose-response curve.
4. Use data to go from a dose-response curve to dose-response manifold.

3 Buffer Zone

Diffusion of drugs in uniform solid tumor; Leakage on some buffered boundary; Initial injection into center; Radially symmetric

$$\frac{\partial u}{\partial t} = D\left(\frac{\partial^2 u}{\partial r^2} + \frac{2}{r}\frac{\partial u}{\partial r}\right); \quad \left.\frac{\partial u}{\partial r}\right|_{r=R_{\text{soft}}} = -\epsilon u(r=R_{\text{soft}},t);$$
$$u(r,t=0) = h_0\begin{cases}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right) & \text{for } r < r_0,\\ 0 & \text{for } r \ge r_0\end{cases} \tag{3}$$

where

$$h_0 = \frac{V_0}{\int_0^{r_0}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right)dr}$$

where V_0 is the initial volume.

1. Assumes no leak threshold, but rather diffusion up to some buffer and leakage after.
2. Constant threshold for amount of drug it takes to kill a cell. Assumes zero oxygen gradient.
3. Curved threshold for amount of drug it takes to kill a cell. Assumes variation in oxygen gradient.
4. Can produce dose-response curve.
5. Use data to go from a dose-response curve to dose-response manifold.

4 Absorption – Diffusion

~~Diffusion of drugs and absorption in uniform solid tumor; Leakage after some boundary saturation; Initial injection into center; Radially symmetric.~~

$$\frac{\partial u}{\partial t} = D\left(\frac{\partial^2 u}{\partial r^2} + \frac{2}{r}\frac{\partial u}{\partial r}\right) - \gamma u; \quad \left.\frac{\partial u}{\partial r}\right|_{r=R} = -\epsilon\begin{cases}0 & \text{for } u(r=R,t) \le u_{\text{leak}},\\ u(r=R,t) & \text{for } u(r=R,t) > u_{\text{leak}};\end{cases}$$
$$u(r,t=0) = h_0\begin{cases}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right) & \text{for } r < r_0,\\ 0 & \text{for } r \ge r_0\end{cases} \tag{4}$$

~~where~~

$$h_0 = \frac{V_0}{\int_0^{r_0}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right)dr}$$

~~where V_0 is the initial volume.~~

1. ~~Constant threshold for amount of drug it takes to kill a cell. Assumes zero oxygen gradient.~~
2. ~~Curved threshold for amount of drug it takes to kill a cell. Assumes variation in oxygen gradient.~~
3. ~~Can produce dose-response curve.~~
4. ~~Use data to go from a dose-response curve to dose-response manifold.~~

5 Off-center Injection

Diffusion of drugs and absorption in nonuniform solid tumor; Leakage after some boundary saturation; Initial injection off center center;

$$\frac{\partial u}{\partial t} = D(r,\theta,\phi)\nabla^2 u - \gamma u; \quad \left.\frac{\partial u}{\partial r}\right|_{r=R} = -\epsilon\begin{cases}0 & \text{for } u(r=R,t) \le u_{\text{leak}},\\ u(r=R,t) & \text{for } u(r=R,t) > u_{\text{leak}};\end{cases}$$
$$u(r,t=0) = h_0\begin{cases}\exp\left(1-\frac{1}{1-(r-r_{\text{inj}})^2/r_0^2}\right) & \text{for } |r-r_{\text{inj}}| < r_0,\\ 0 & \text{for } |r-r_{\text{inj}}| \ge r_0\end{cases} \tag{5}$$

where

$$h_0 = \frac{V_0}{\int_0^{r_0}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right)dr}$$

where V_0 is the initial volume.

1. Constant threshold for amount of drug it takes to kill a cell. Assumes zero oxygen gradient.
2. Curved threshold for amount of drug it takes to kill a cell. Assumes variation in oxygen gradient.
3. Can produce dose-response curve.
4. Use data to go from a dose-response curve to dose-response manifold.

6 Drugs and Oxygen Diffusion

Diffusion of drugs and oxygen in uniform solid tumor; Leakage after some boundary saturation; Initial injection into center; Radially symmetric.

$$\frac{\partial u_{\text{drug}}}{\partial t} = D_{\text{drug}}\left(\frac{\partial^2 u_{\text{drug}}}{\partial r^2} + \frac{2}{r}\frac{\partial u_{\text{drug}}}{\partial r}\right);$$
$$\left.\frac{\partial u_{\text{drug}}}{\partial r}\right|_{r=R} = -\epsilon_{\text{drug}}\begin{cases}0 & \text{for } u_{\text{drug}}(r=R,t) \le u_{\text{drug leak}},\\ u_{\text{drug}}(r=R,t) & \text{for } u_{\text{drug}}(r=R,t) > u_{\text{drug leak}};\end{cases} \tag{6}$$
$$\frac{\partial u_{\text{oxygen}}}{\partial t} = D_{\text{oxygen}}\left(\frac{\partial^2 u_{\text{oxygen}}}{\partial r^2} + \frac{2}{r}\frac{\partial u_{\text{oxygen}}}{\partial r}\right);$$
$$\left.\frac{\partial u_{\text{oxygen}}}{\partial r}\right|_{r=R} = -\epsilon_{\text{oxygen}}\begin{cases}0 & \text{for } u_{\text{oxygen}}(r=R,t) \le u_{\text{oxygen leak}},\\ u_{\text{oxygen}}(r=R,t) & \text{for } u_{\text{oxygen}}(r=R,t) > u_{\text{oxygen leak}};\end{cases} \tag{7}$$

Initial conditions:

$$u_{\text{drug}}(r,t=0) = h_{\text{drug}}\begin{cases}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right) & \text{for } r < r_0,\\ 0 & \text{for } r \ge r_0\end{cases}; h_{\text{drug}} = \frac{V_{\text{drug}}}{\int_0^{r_0}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right)dr}$$

where V_{drug} is the initial volume of the drug itself and

$$u_{\text{oxygen}}(r,t=0) = h_{\text{oxygen}}\begin{cases}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right) & \text{for } r < r_0,\\ 0 & \text{for } r \ge r_0\end{cases}; h_{\text{oxygen}} = \frac{V_{\text{oxygen}}}{\int_0^{r_0}\exp\left(1-\frac{1}{1-r^2/r_0^2}\right)dr}$$

where V_{oxygen} is the initial volume of the oxygen.

1. Assume a superposition between oxygen and drug after injection.
2. Oxygen profile will determine kill threshold of the drug.
3. Can produce dose-response curve.
4. Use data to go from a dose-response curve to dose-response manifold.
5. Use optimization techniques to maximize efficacy with least toxicity.

7 Coupled Population and Concentration Model

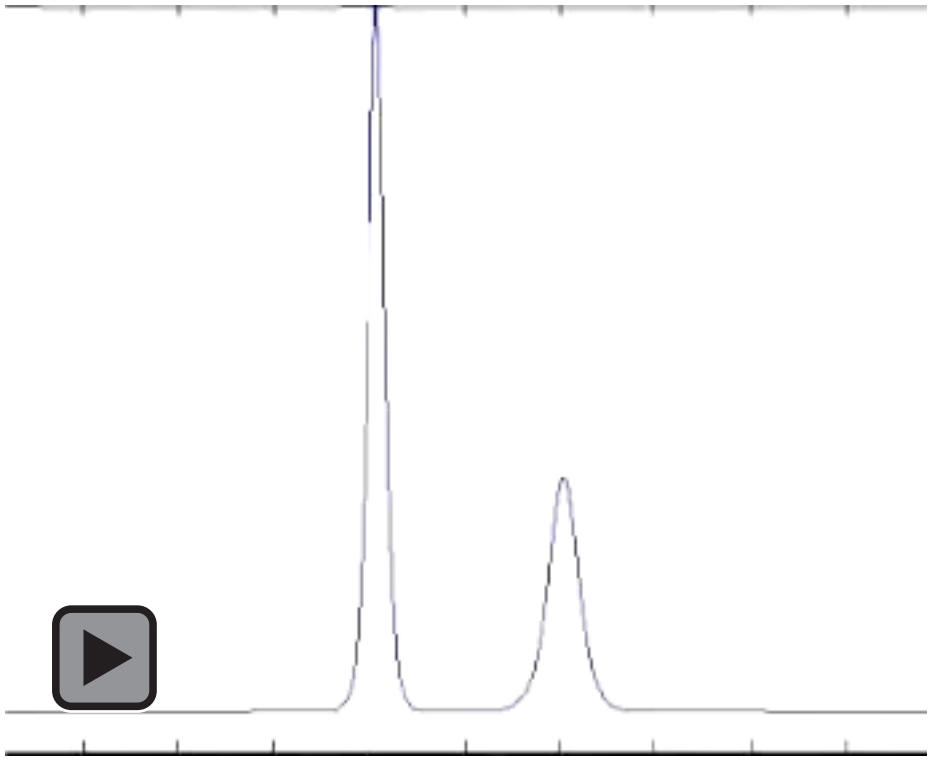
8 Polydispersed Tumor

What came first, the experiment or the model?

Solitary Waves

- First discovered by John Scott Russell.
- Not just water waves;
  - Generally solitary waves are solutions to non-linear evolutionary PDEs that translate at a constant speed while maintaining it's profile.

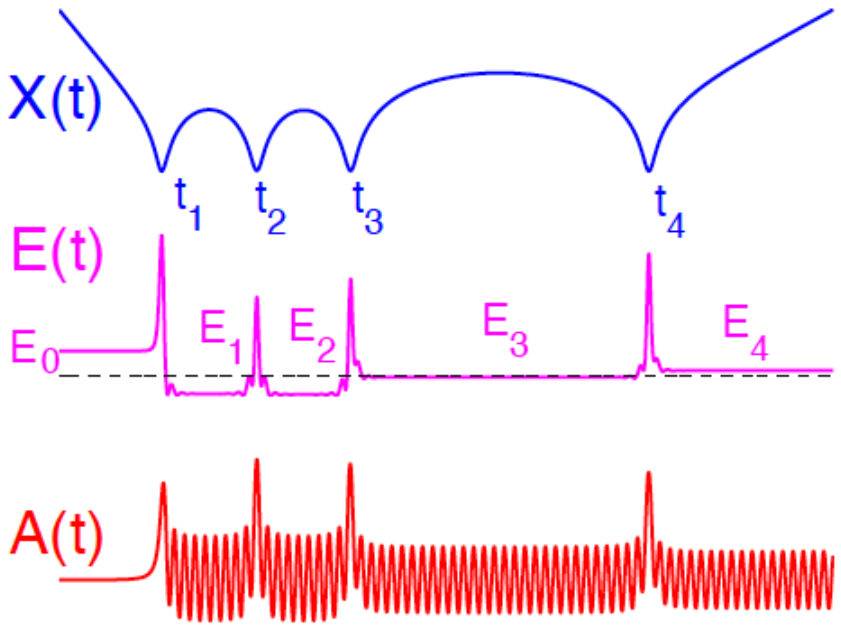
History

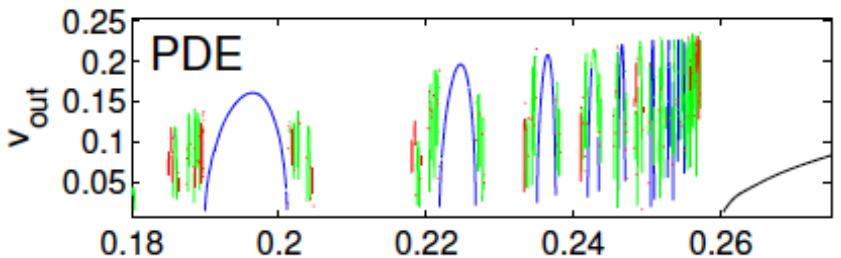


- Kruskal-Zabusky(1960): Solitary waves of KdV ($u_t + 6uu_x + u_{xxx} = 0$) preserve shape and velocity after collisions.
- Soon after similar studies on NLS ($iu_t + u_{xx} + |u|^2 u = 0$) and Sine-Gordon ($u_t t - u_x x + \sin u = 0$).
  - "Easy" because they are completely integrable.

History

- In the 70s and 80s many studies on φ^4 ($\varphi_{tt} - \varphi_{xx} + \varphi - \varphi^3 = 0$) were conducted.
  - Much more difficult because it's not integrable.
  - Many numerical experiments on kink-antikink (colliding in a special way) solutions (some observations dubbed "chaotic scattering").





Recent History

- Reduction of PDE (φ^4) to a system of ODEs that approximates the behavior.

$$
\begin{aligned}
&m\ddot{X}(t) + U'(X) + cAF'(X) = 0, \\
&\ddot{A}(t) + \omega^2 A + cF(X) = 0; \\
&U(X) = e^{-2X} - e^{-X},\ F(X) = e^{-X}
\end{aligned}
\tag{6}
$$

where X is the position of the center of a wave and A is the amplitude.

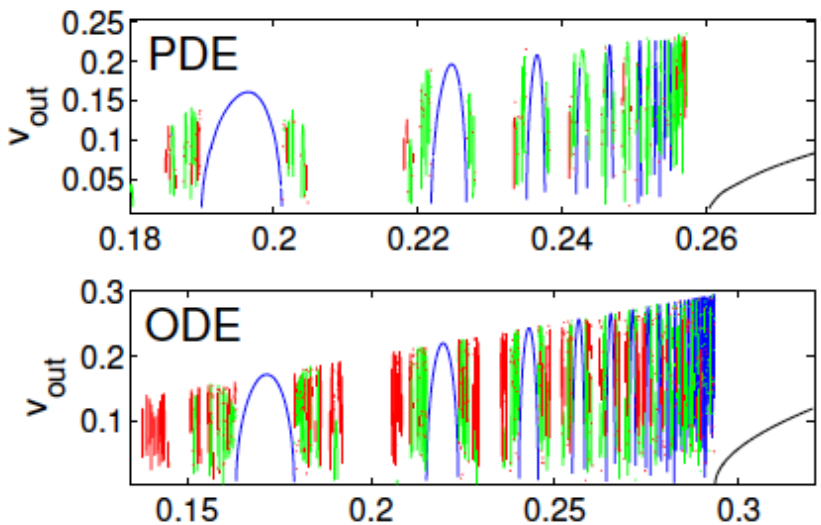
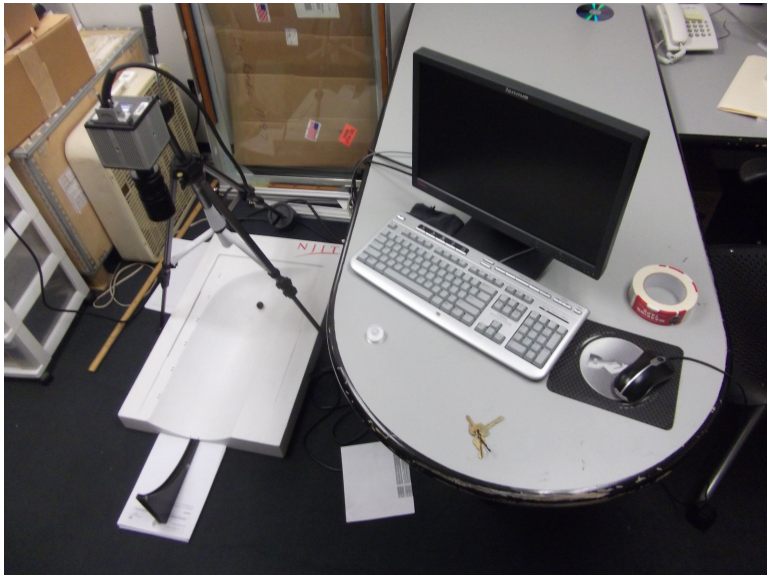


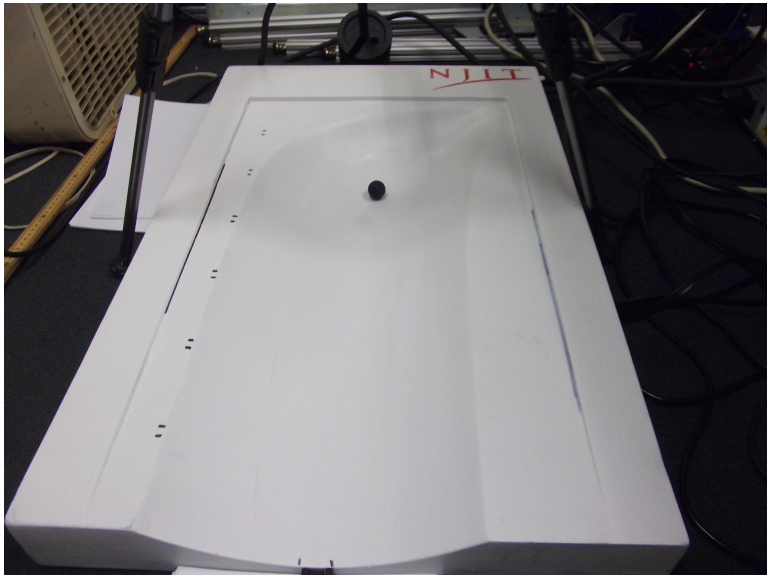
Figure: Source: [Goodman and Haberman. *Phys. Rev. Lett.*(2007)]

Experiment

Source: [Goodman, Rahman, Bellanich, Morrison. *Chaos* (2015)]

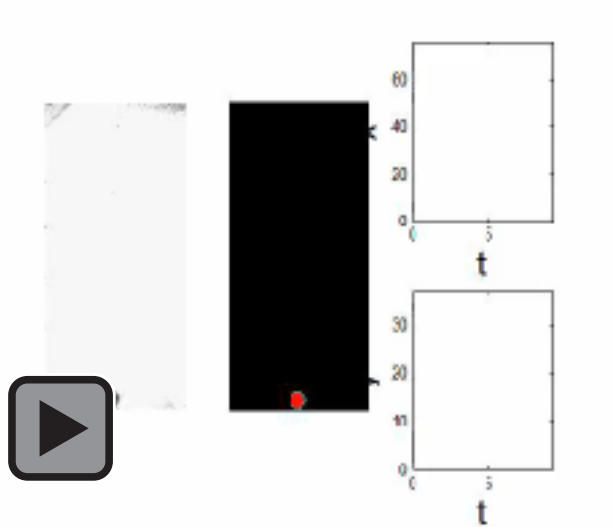
Experimental set up:



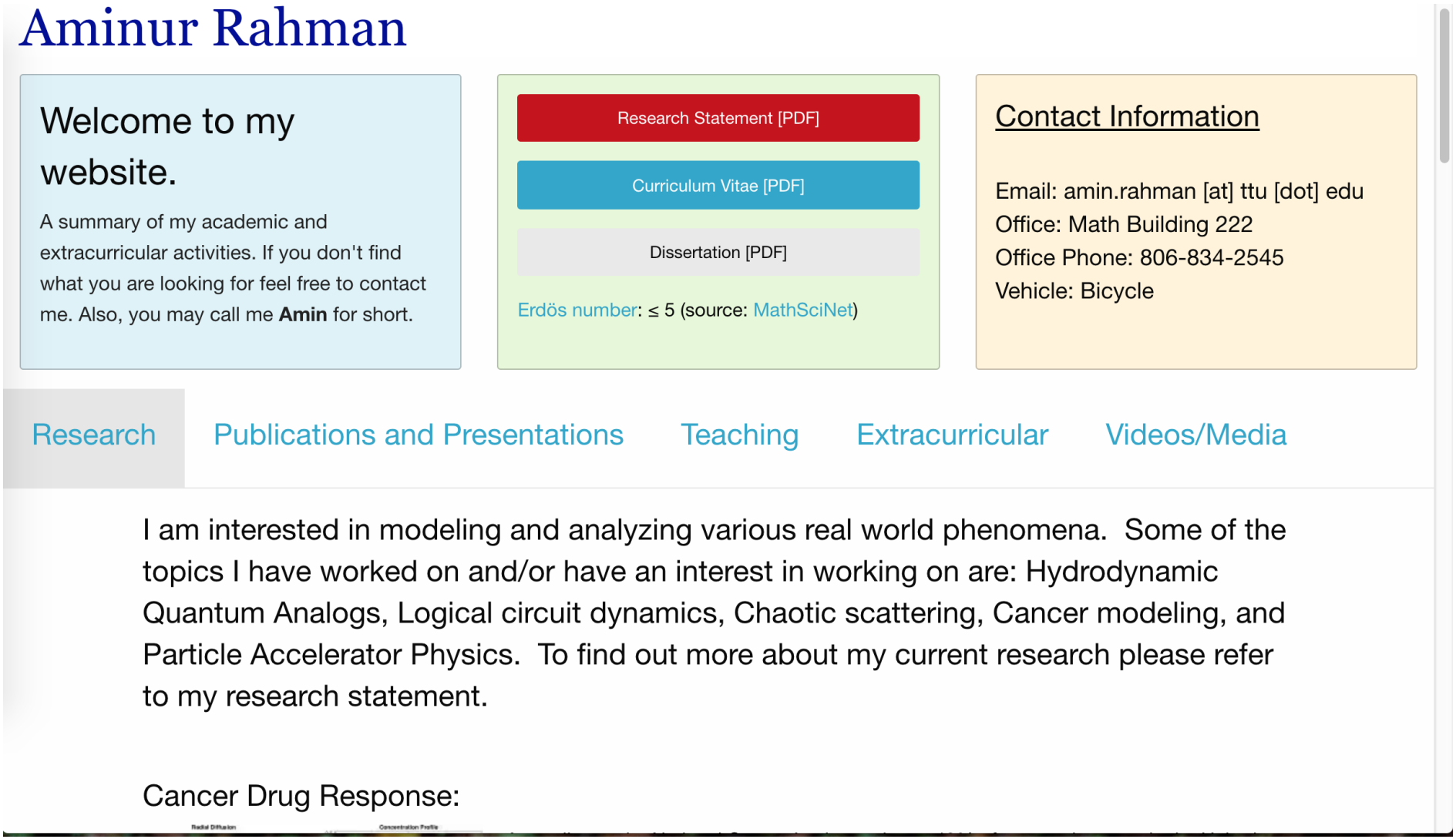


Movies:

(1-bounce movie)



If anyone is interested in knowing more about my work please visit my website: `myweb.ttu.edu/aminrahm`



And, thank you for your attention!