Coupling Hair Follicle Cycles to Produce Traveling Waves

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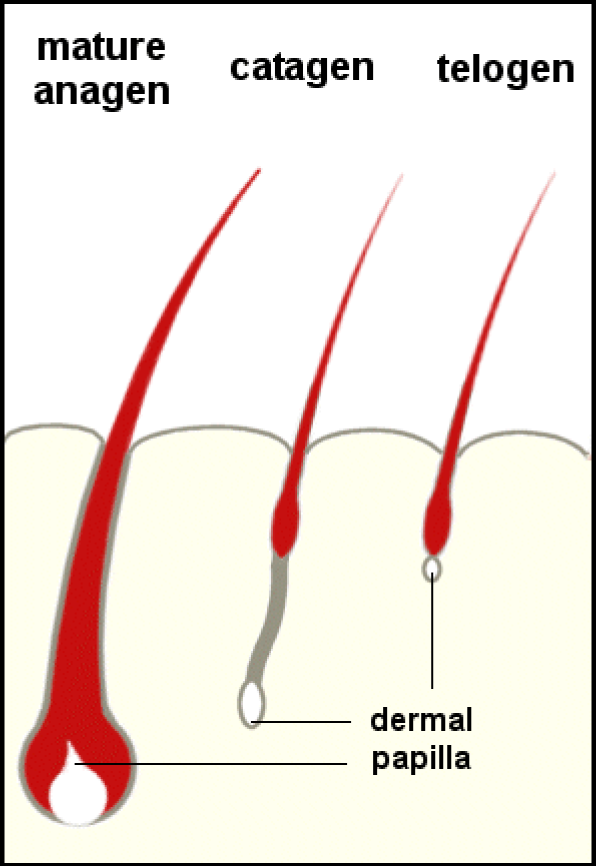
Examples of Biological Synchronization

- Pacemaker cells in the heart
- Discharging of brain cells during epileptic seizures
- Women's menstrual cycles
- Hair growth in rodents – motivation for this study

Suzuki, *et al.*

The Hair Follicle Cycle

- Begins with catagen – apoptosis
- Telogen – rest, exogen usually occurs in this phase
- Anagen – growth, longest phase



www.keratin.com/aa/aa008.shtml

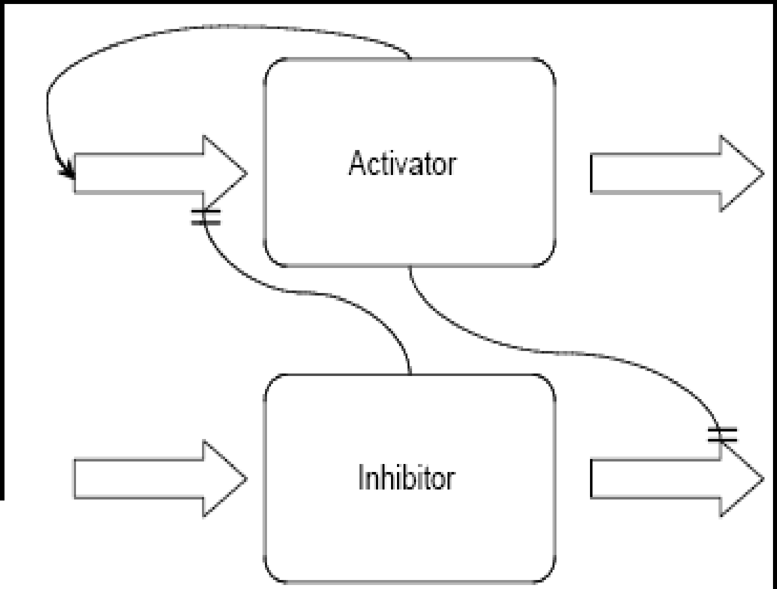
Objectives

- Simulate the hair follicle cycle with two models.
  - Activator/ inhibitor
  - Substrate/ depletion
- Create networks of follicle oscillators via different modes of coupling
  - To observe the effects of certain variables
  - To produce synchronization.

The Activator/Inhibitor Model

x – autocatalytic activator

y – inhibitor



$$\frac{dx}{dt} = \frac{\varepsilon^2 + x^2}{1 + x^2} \cdot \frac{1}{1+y} - ax$$

Fall, *et al.*

$$\tau \frac{dy}{dt} = b - \frac{y}{1 + cx^2}$$

The Substrate/Depletion Model

x – product

y - reactant

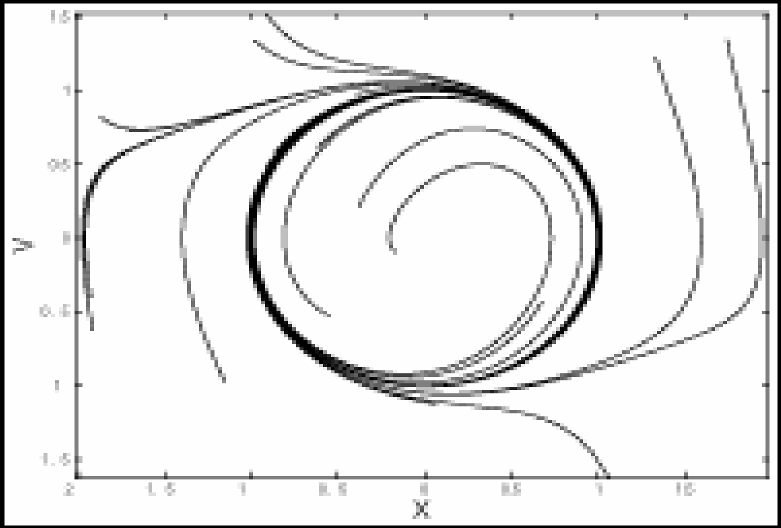
$$dx/dt = \frac{v(y-x)(\varepsilon^2 + x^2)}{1+x^2} - x$$

$$dy/dt = k - x$$

Fall, *et al.*

Hopf Bifurcation

- Fixed point loses stability as the eigenvalues cross the imaginary axis of the complex plane
- Stable limit cycle



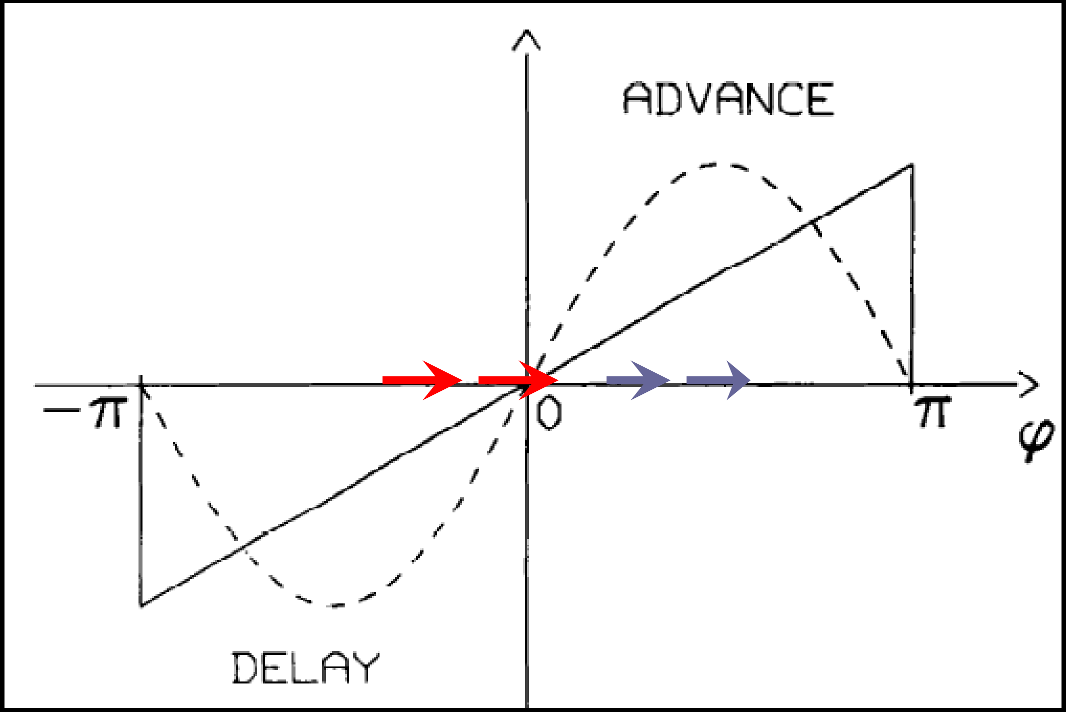
Perturbations and the Interaction Function (H)

$$\frac{d\theta}{dt} = 2\pi / T_0 + \beta \sin(\omega t - \theta)$$

$$\omega = 2\pi / T$$

Phase difference between oscillator and stimulator

$$\phi = \omega t - \theta$$

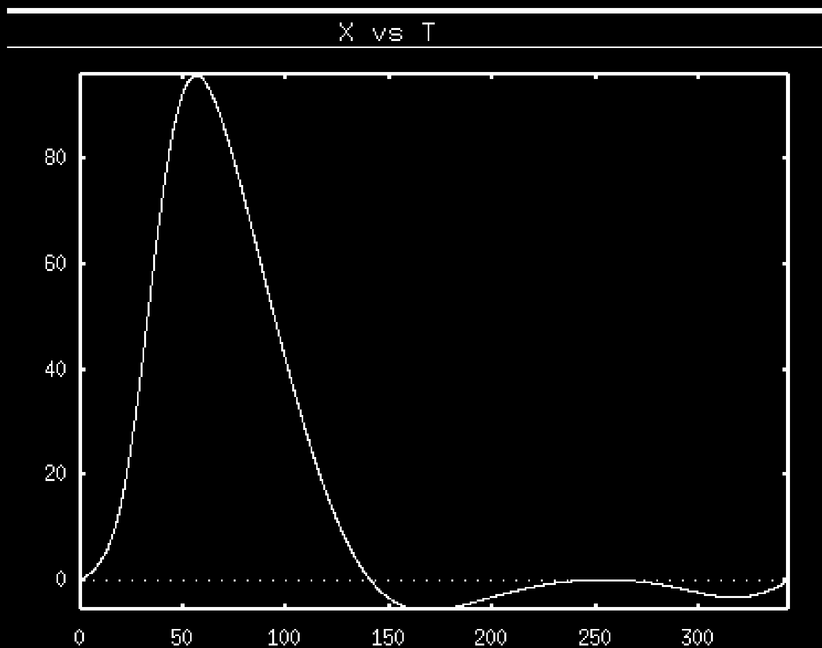


Averaging

- Z(t) – response function
- G(x) – type of coupling
  - Diffusive coupling x'-x
  - Bath coupling f((x+0.01*x',y)-f(x,y))/0.01
- H(Φ) – interaction function; coupling as a function of phase difference between oscillators

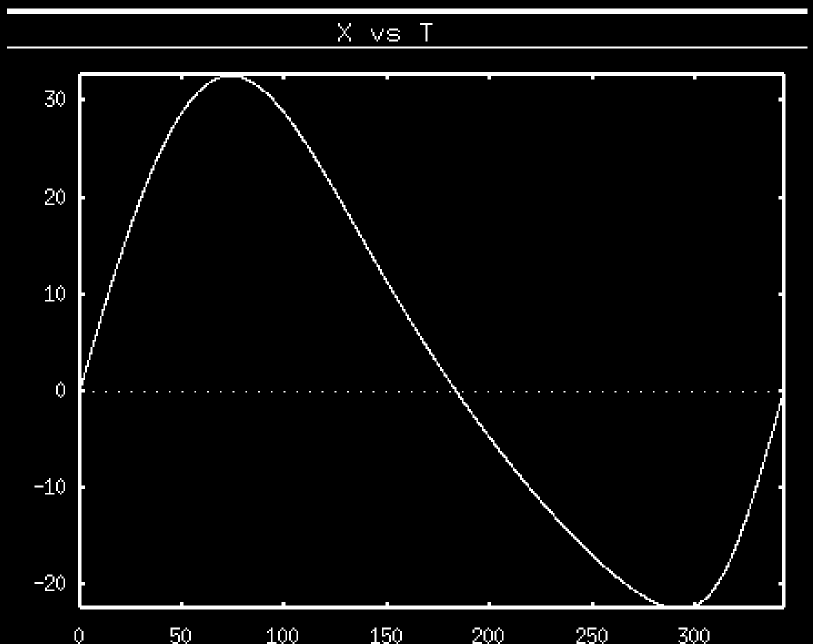
$$H_1(\phi) = \frac{1}{T}\int_0^T Z(t)\cdot G_1(X_0(t+\phi), X_0(t))\, dt$$

Diffusive coupling function via the activator



$$H(\phi) = 17 + 12\cos\theta - 18\cos 2\theta - 11\cos 3\theta + 31\sin\theta + 16\sin 2\theta - 3\sin 3\theta$$

Diffusive coupling function via the inhibitor



$$H(\phi) = 4 - 2\cos\theta - 2\cos 2\theta + 26\sin\theta + 5\sin 2\theta + \sin 3\theta$$

Network Equation

- 20 oscillators in the network
- Optional gradient (ε)
- Coupling strength (a) – must be weak

$$x_1 = 1 + ah(x_2 - x_1)$$

gradient

$$x_{2..19} = 1 - \frac{(j-1)\varepsilon}{20} + a\left(h(x_{j-1} - x_j) + h(x_{j+1} - x_j)\right)$$

$$x_{20} = 1 - \frac{19\varepsilon}{20} + ah(x_{19} - x_{20})$$

Neighbor influence

1-D Arrays

- Kind of coupling
  - Via x or y variable
  - Via diffusive or bath coupling
- Coupling constant (a)
- Diffusion limit (number of neighbors)
- Heterogeneity (ε)

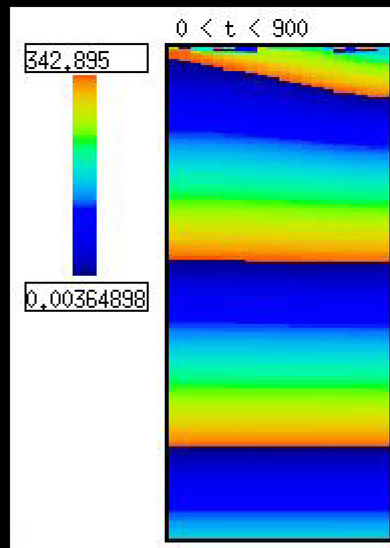
$$x_{2..19} = 1 - \frac{(j-1)\varepsilon}{20} + a\left(h(x_{j-1} - x_j) + h(x_{j+1} - x_j)\right)$$

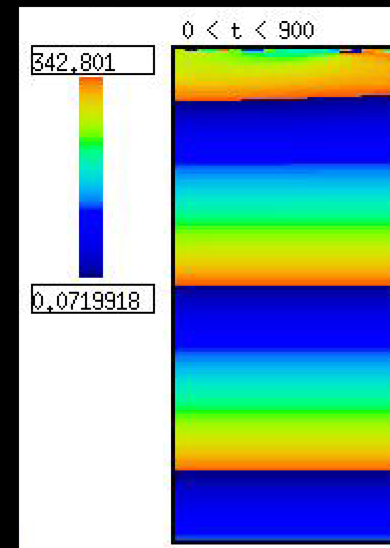
Types of Coupling (ε = 0, 2 nearest neighbors)

Activator | Inhibitor

Diffusive Coupling

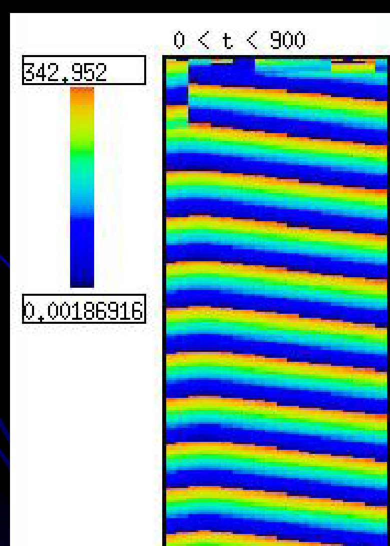
a = 1



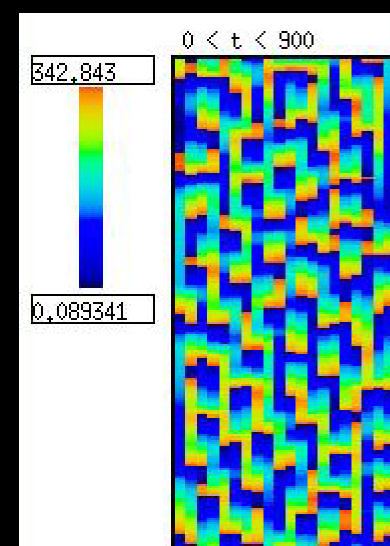


Bath Coupling

a = 5



Sine component is too small



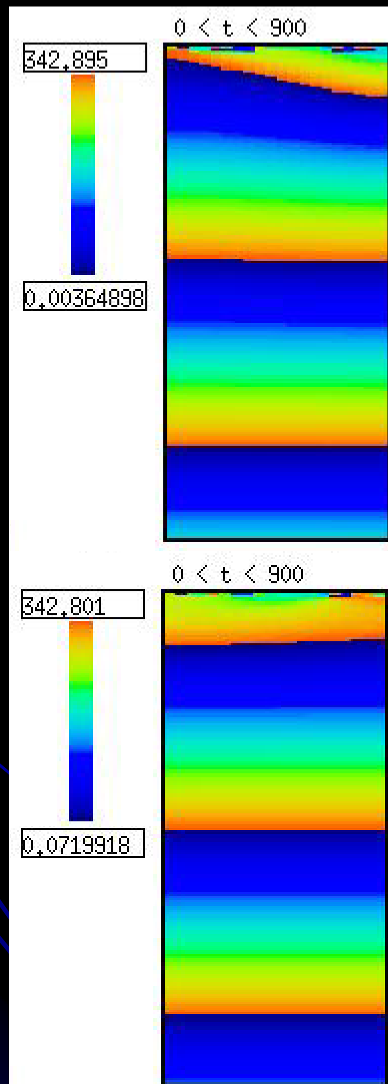
Coupling Constant (ε = 0, 2 nearest neighbors, diffusive coupling)

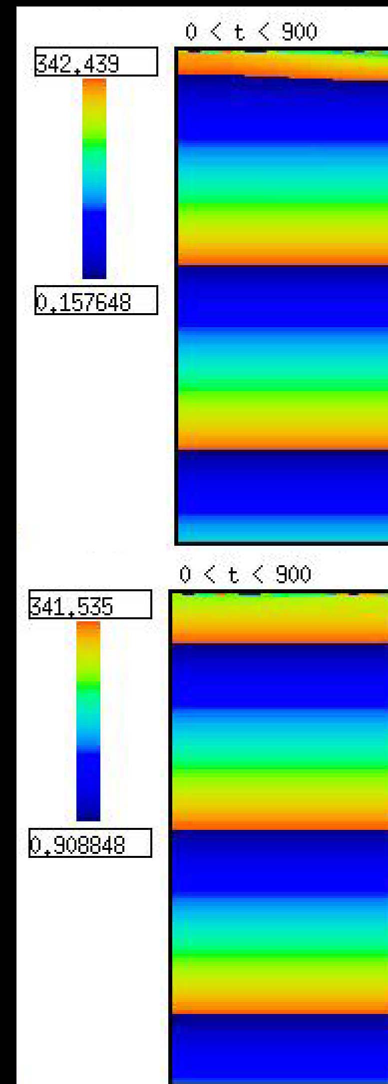
a = 1

a = 5

Activator

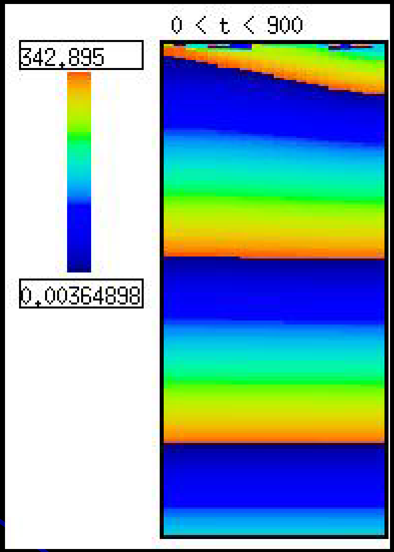
Inhibitor



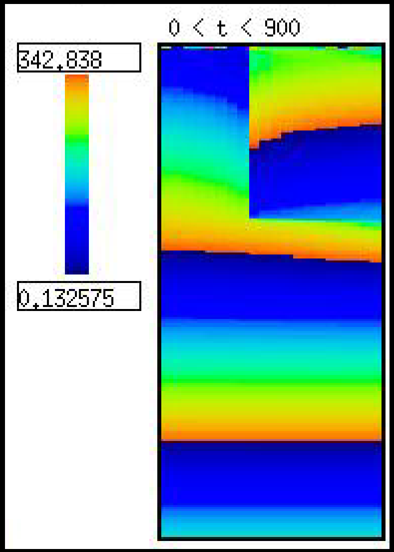


Diffusion Limit (a = 1, ε = 0, diffusive coupling via activator)

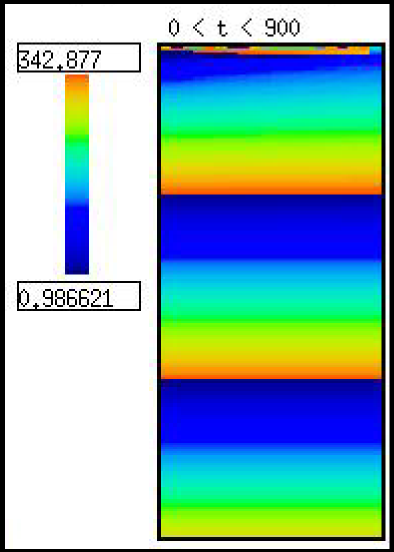
2 neighbors



4 neighbors



6 neighbors



Introducing Heterogeneity (a = 1, diffusive)

eps = -1 eps = 1 eps = 5

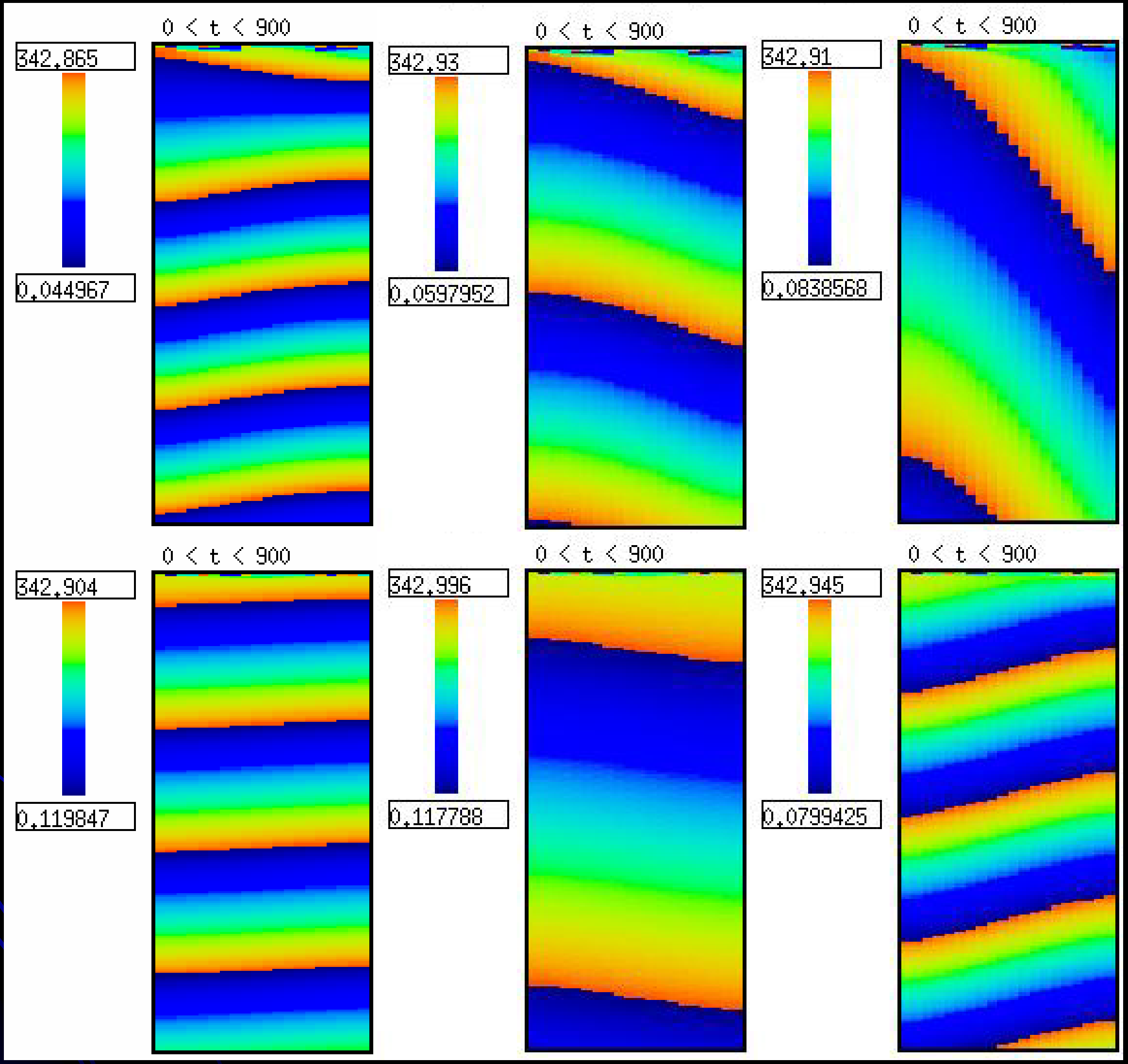
Activator

2 nearest neighbors

Inhibitor

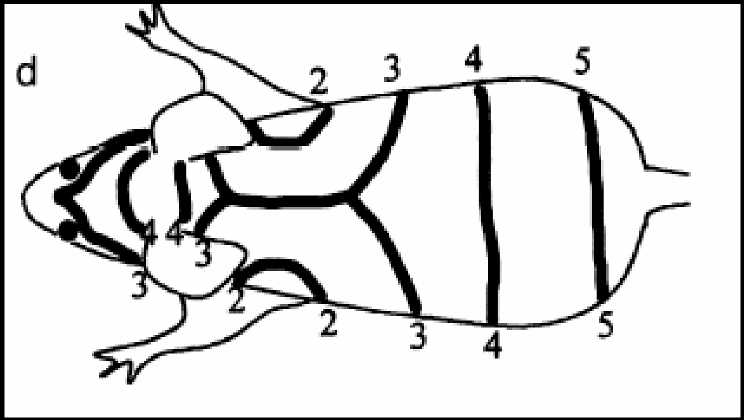
4 nearest neighbors

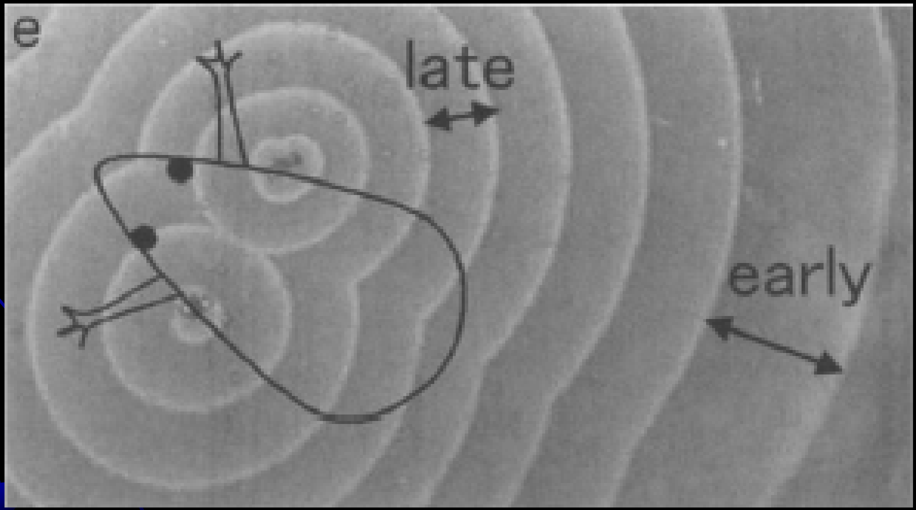
(same phenomena for 6 neighbors)



2-D Arrays

- Using Fourier approximation
- Simulates actual traveling waves in the mouse





Suzuki, *et al.*

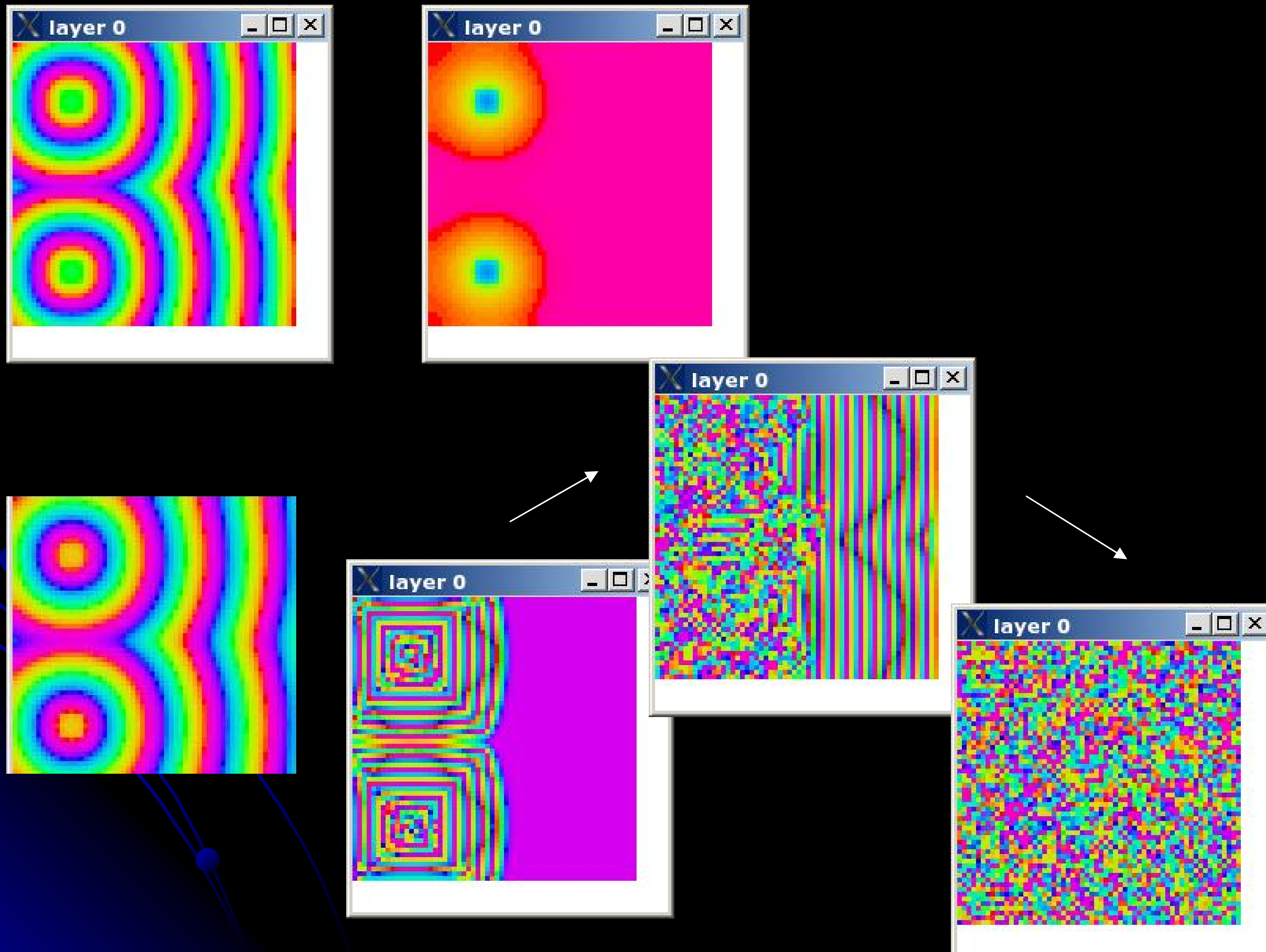
2-D Arrays

Activator

Inhibitor

Diffusive

Bath

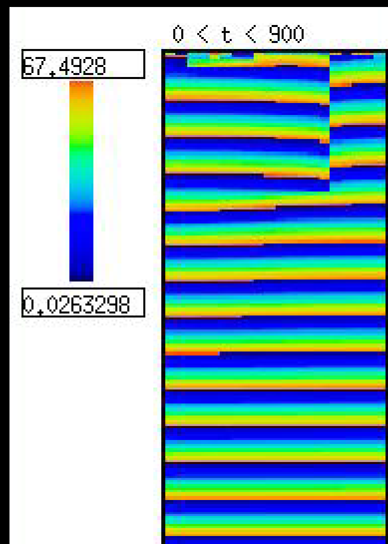


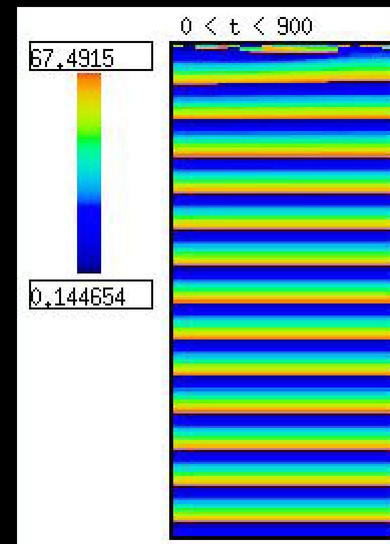
Types of Coupling (a=1, eps=0, 2 nearest neighbor)

via product

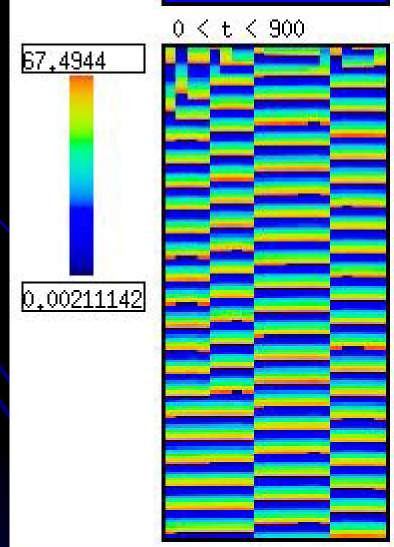
via reactant

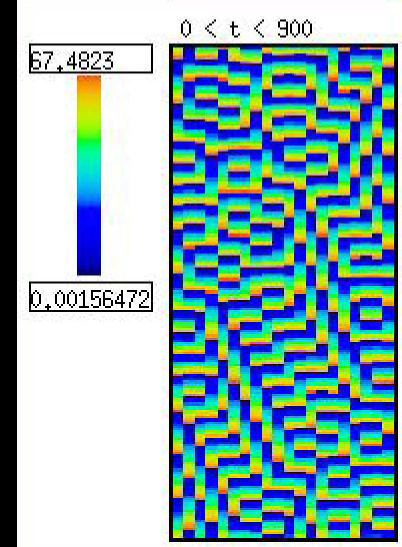
Diffusive coupling





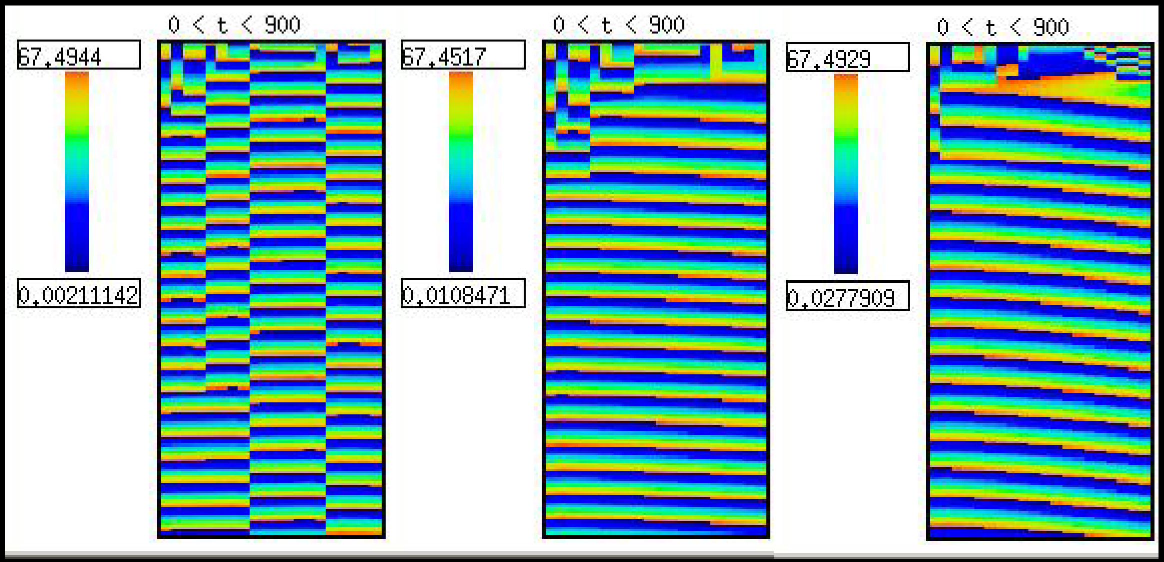
Bath coupling





Adding a gradient induces synchronization for bath coupling via product

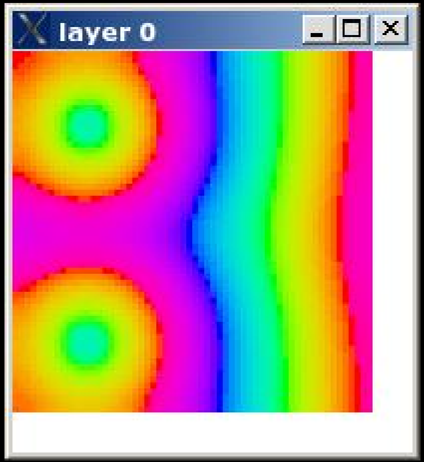
eps = 0 eps = 1 eps = 5



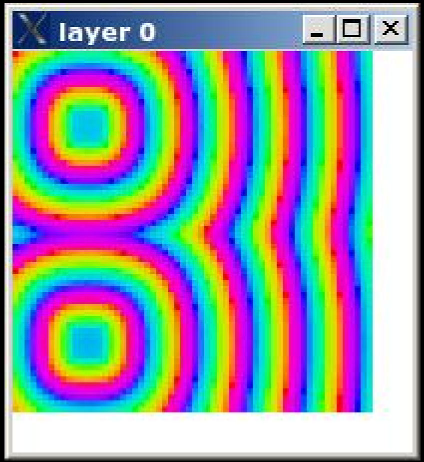
2-D Arrays

Diffusive coupling via

Product



Reactant



Bath coupling did not produce any patterns.

Results Summary – Types of Coupling

- Only 4 networks synchronized for both 1 and 2 D arrays.

	AI Model	1-D Array	2-D Array	SD Model	1-D Array	2-D Array
Diffusive	Activator	*	*	Product	*	*
	Inhibitor	*		Reactant	*	*
Bath	Activator	*	*	Product	*	
	Inhibitor			Reactant		

Results Summary - Variables

- 1-D Arrays
  - The only coupling mode which never synchronized was bath coupling via the reactant.
  - Changing the gradient can induce traveling waves, reverse wave direction and produce synchrony.
  - The coupling constant and the diffusion limit are proportional to synchronization speed.
  - 4 nearest neighbor coupling can initially produce unusual patterns.
- 2-D Arrays

Conclusions

- The hair follicle cycle could be represented by either model.
- Most likely networks are those which synchronize for 1 and 2 D networks.
  - Diffusive coupling via activator, product, and reactant
  - Bath coupling via activator

Who cares??

Acknowledgments

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References

- Edelstein- Keshet, Leah. Mathematical Models in Biology, 1st ed. Boston: McGraw Hill, 1988.
- Ermentrout, G.B. and J. Rinzel. “Beyond a pacemaker’s entrainment limit: phase walk-through.” *Am J Physiol Regulatory Integrative Comp Physiol. 246 (1984): 102-106.*
- Fall, Christopher P., *et. al.,* eds. Computational Cell Biology. New York: Springer-Verlag, 2002.
- Maini, Philip K. “How the mouse got its stripes.” *PNAS* 100:17(2003): 9656-9657.
- Paus, Ralf and Kerstin Foitzik. “In search of the ‘hair cycle clock’: a guided tour.” *Differentiation*. 72(2004):489-511.
- Suzuki, Noboru, *et al.* “Traveling strips on the skin of a mutant mouse.” *PNAS*. 100:17 (2003): 9680-9685.