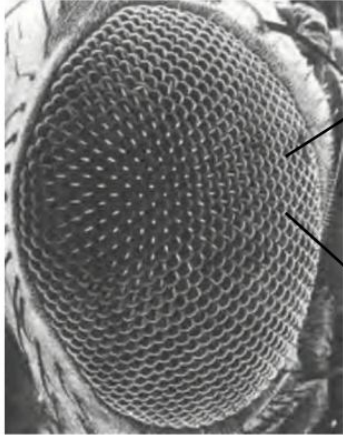


# Pattern Formation in Biology

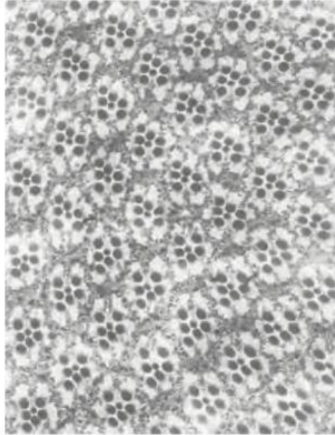
Sho Takeshita

# Cell Differentiation



Phillips "Physical Biology of the Cell"

50  $\mu\text{m}$



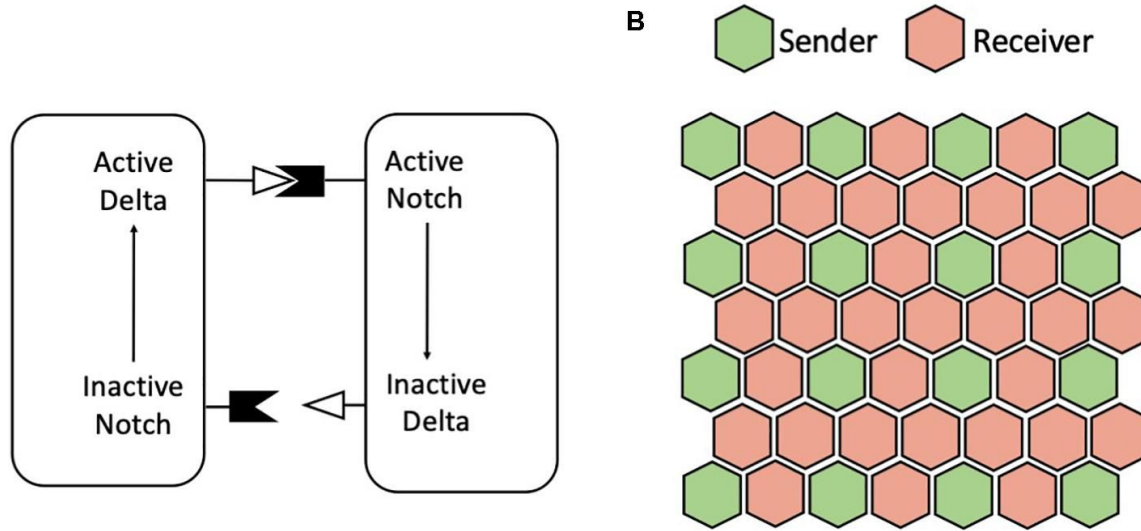
5  $\mu\text{m}$

Drosophila Eye differentiation

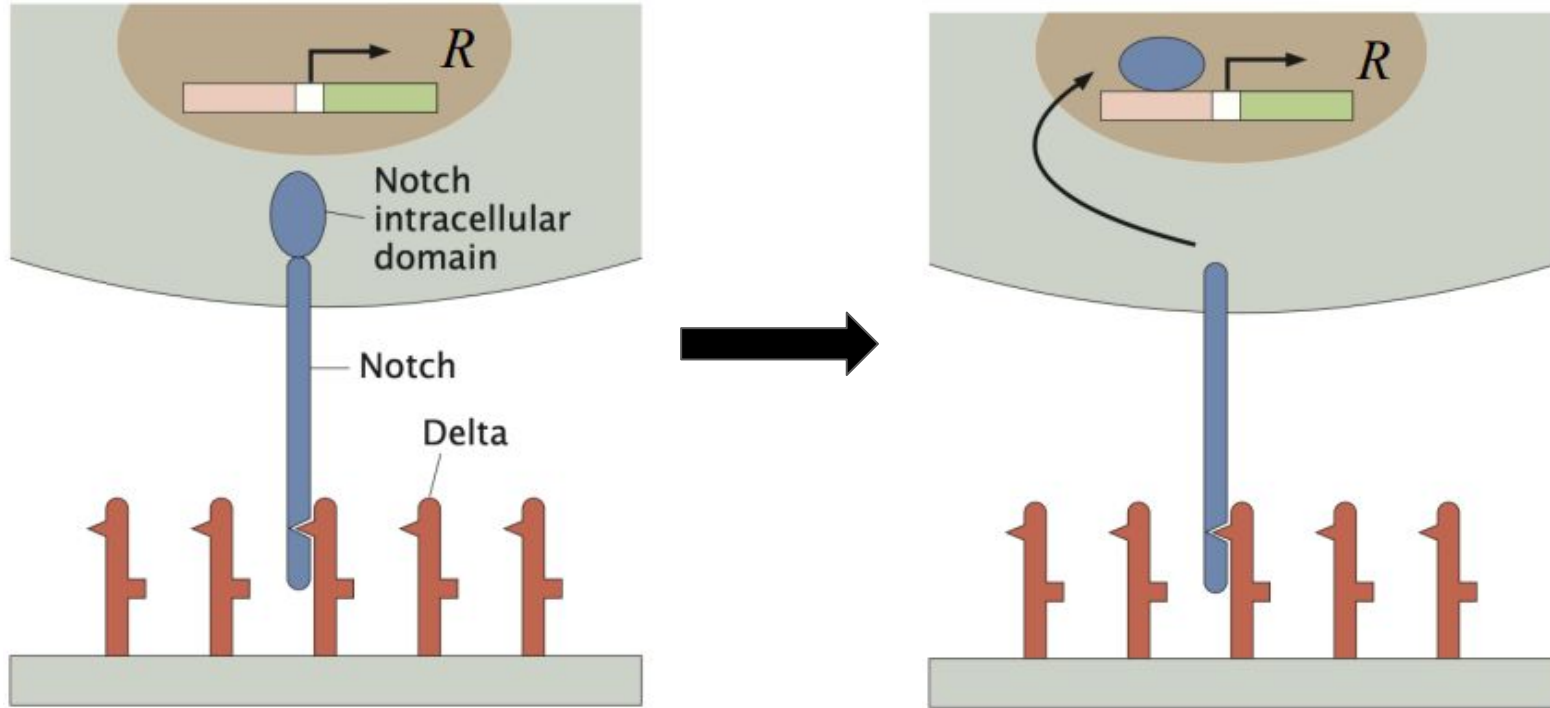
Ommatidia - composed of 20 cell types

Creates pattern from uniform cells

# Pattern formation through Notch-Delta lateral inhibition



## Continued



# Goal

To simulate the Notch-Delta pattern formation mechanism to gain insights on what happens under various conditions

See if mutual inhibition may lead to pattern formation in the absence of cooperativity

# Mathematical Model

$$\dot{N}_i = \beta_N - N_i$$

$$\dot{D}_i = \beta_D \frac{1}{1 + R_i^m} - D_i$$

$$\dot{R}_i = \beta_R \frac{(N_i \langle D_j \rangle_i)^p}{k_{RS}^p + (N_i \langle D_j \rangle_i)^p} - R_i$$

Dimensionless

N,D,R are concentrations in a given cell i

$\beta$  is maximum rates of synthesis of N,D,R

$\langle D_j \rangle_i$  is average of D of neighbors to cell i

m and p represent the cooperativity

$k_{RS}$  is the Michaelis-Menten constant

# Assumptions and Limitations and Applications

Assumes no mutual inhibition

Works well with  $mp > 1$

Cooperativity is not shown to occur in real systems

Limited to 2 outcomes

Does not take into account pathways that sequentially contribute to differentiation

# Code of Equations

```
def normalinhibition(bn,bd,br,ncells,dcells,rcells,m,p,krs):  
    davg = np.roll(dcells,1)  
    davg += np.roll(dcells,-1)  
    davg /= 2.  
  
    nnew = bn - ncells  
    dnew = bd * (1 / (1 + (rcells**m))) - dcells  
    rnew = br * (((ncells*davg)**p) / ((krs**p) + ((ncells*davg)**p))) - rcells  
  
    return nnew,dnew,rnew
```



# Simulation Code

```
def simulate_normal(Tmax, Nday, bn, bd, br, ncells, dcells, rcells, m, p, krs):  
    Nhistory = [np.array(ncells)]  
    Dhistory = [np.array(dcells)]  
    Rhistory = [np.array(rcells)]  
    n=np.array(ncells)  
    d=np.array(dcells)  
    r=np.array(rcells)  
    Nsteps=int(Tmax)*Nday  
    dt = 1./Nday  
    for k in range(Nsteps):  
        nd,dd,rd = normalinhibition(bn,bd,br,n,d,r,m,p,krs)  
        n += nd*dt  
        d += dd*dt  
        r += rd*dt  
        if k%100==0:  
            Nhistory.append(np.array(n))  
            Dhistory.append(np.array(d))  
            Rhistory.append(np.array(r))  
  
    return np.array(Nhistory),np.array(Dhistory),np.array(Rhistory)
```

# Parameters

2 cells

```
ncells = np.array([2.,1.9])  
dcells = np.array([10.,10.])  
rcells = np.array([30.,30.])
```

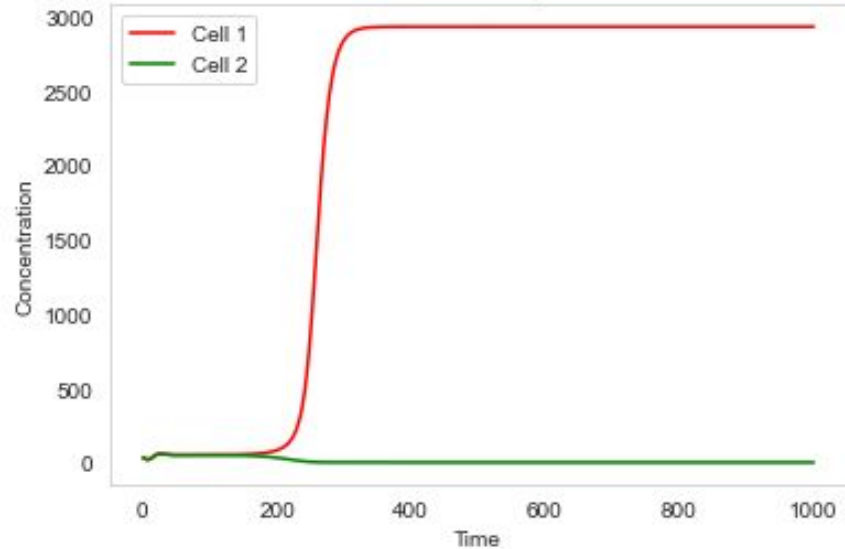
10 cells

```
ncells = np.array([2.,2.,1.9,2.,2.,2.,2.,2.,2.,2.])  
dcells = np.array([10.,10.,10.,10.,10.,10.,10.,10.,10.,10.])  
rcells = np.array([30.,30.,30.,30.,30.,30.,30.,30.,30.,30.])
```

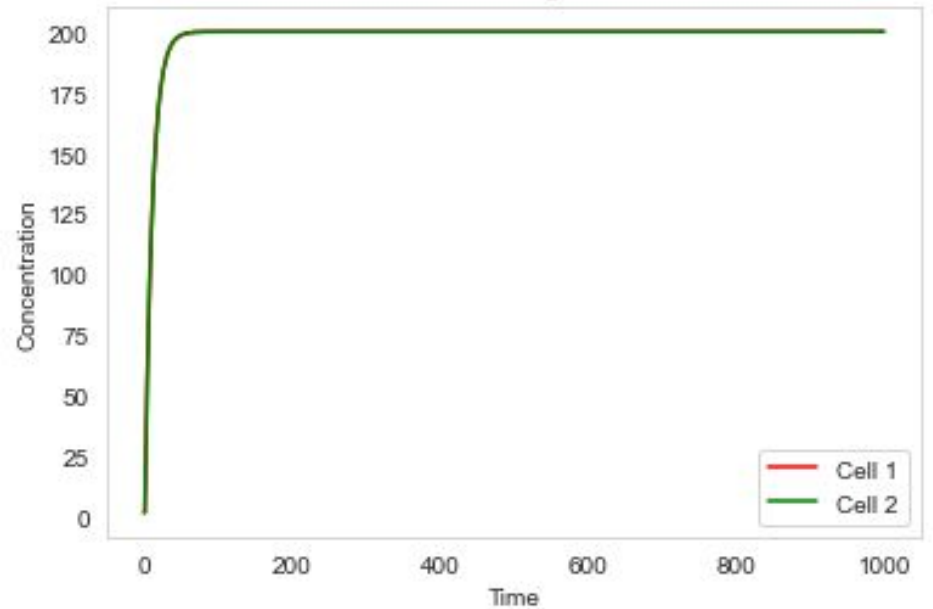
```
bn=200  
bd = 1000  
br = 3000  
krs = 30000
```

## 2 neighboring cells normal inhibition where $m = 1$ and $p = 2$

Repressor Concentration from Simulating 2 Cells with Normal Inhibition

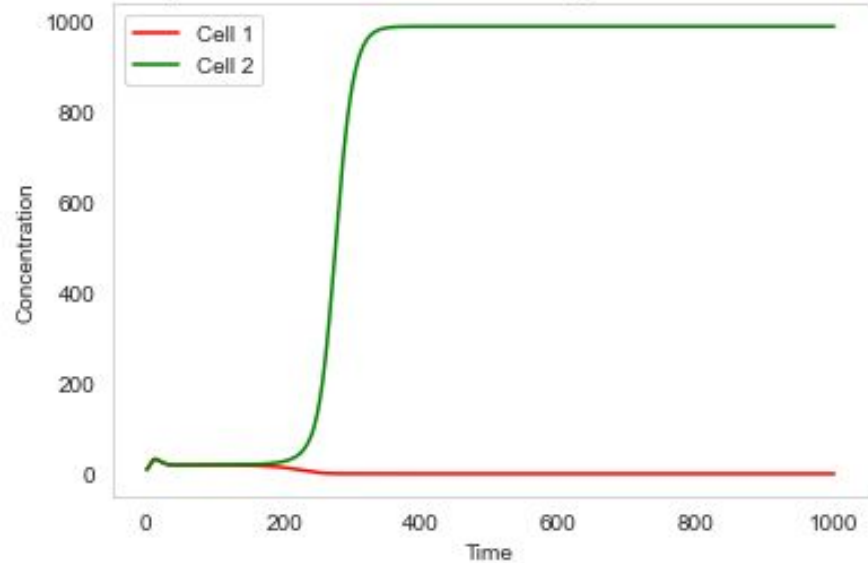


Notch Concentration from Simulating 2 Cells with Normal Inhibition

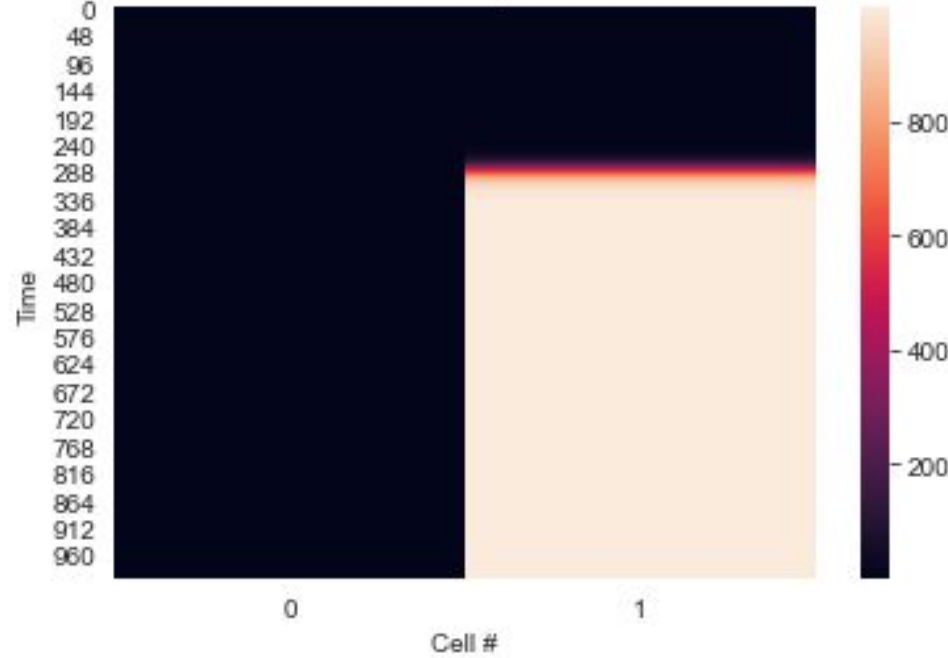


## 2 neighboring cells normal inhibition where $m = 1$ and $p = 2$

Delta Receptor Concentration from Simulating 2 Cells with Normal Inhibition

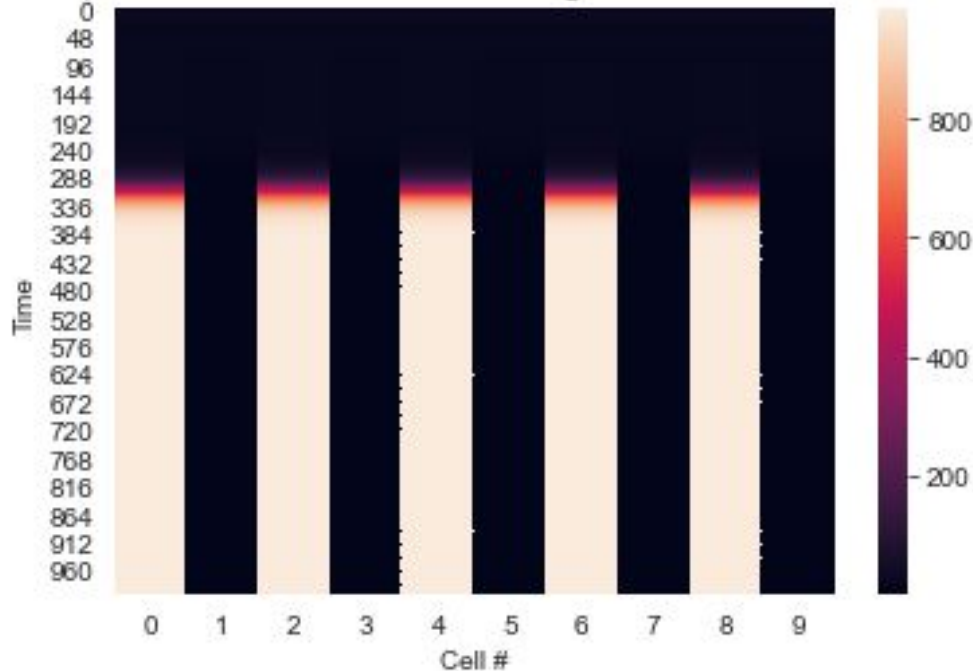


Delta Concentration from Simulating 2 Cells with Normal Inhibition



# Array of 10 cells normal inhibition where $m = 1$ and $p = 2$

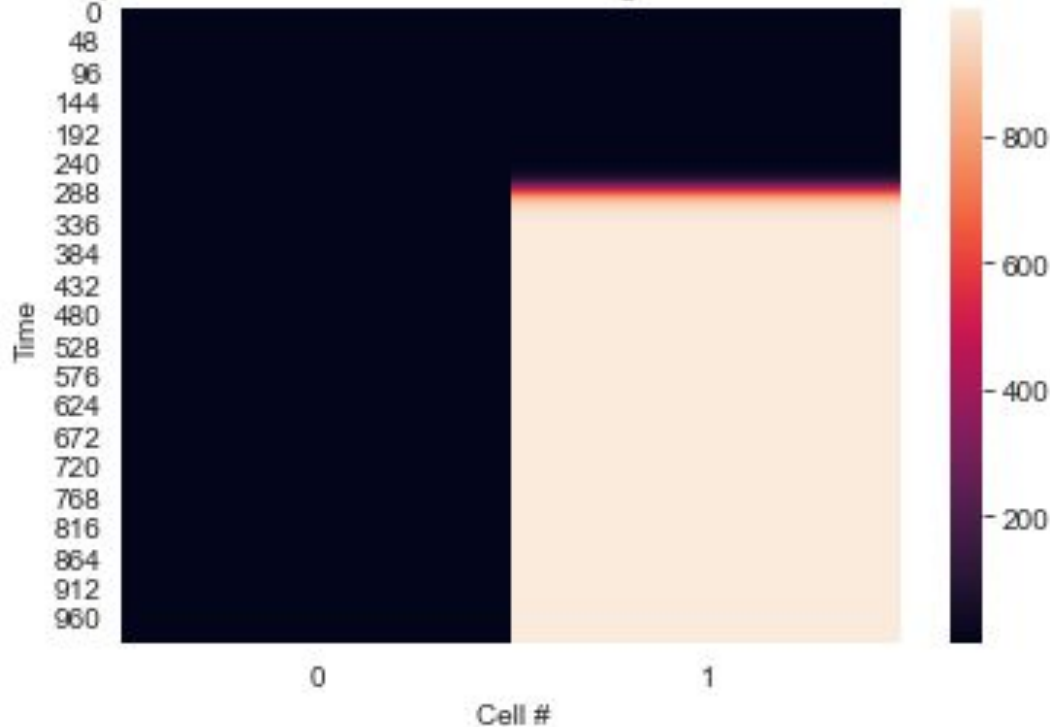
Delta Receptor Concentration from Simulating 10 Cells with Normal Inhibition



Slight difference between cell neighbours will self-amplify, generating a spatial pattern of inhomogeneity (Goriely et al., 1991; Heitzler & Simpson, 1991; Sternberg, 1993)

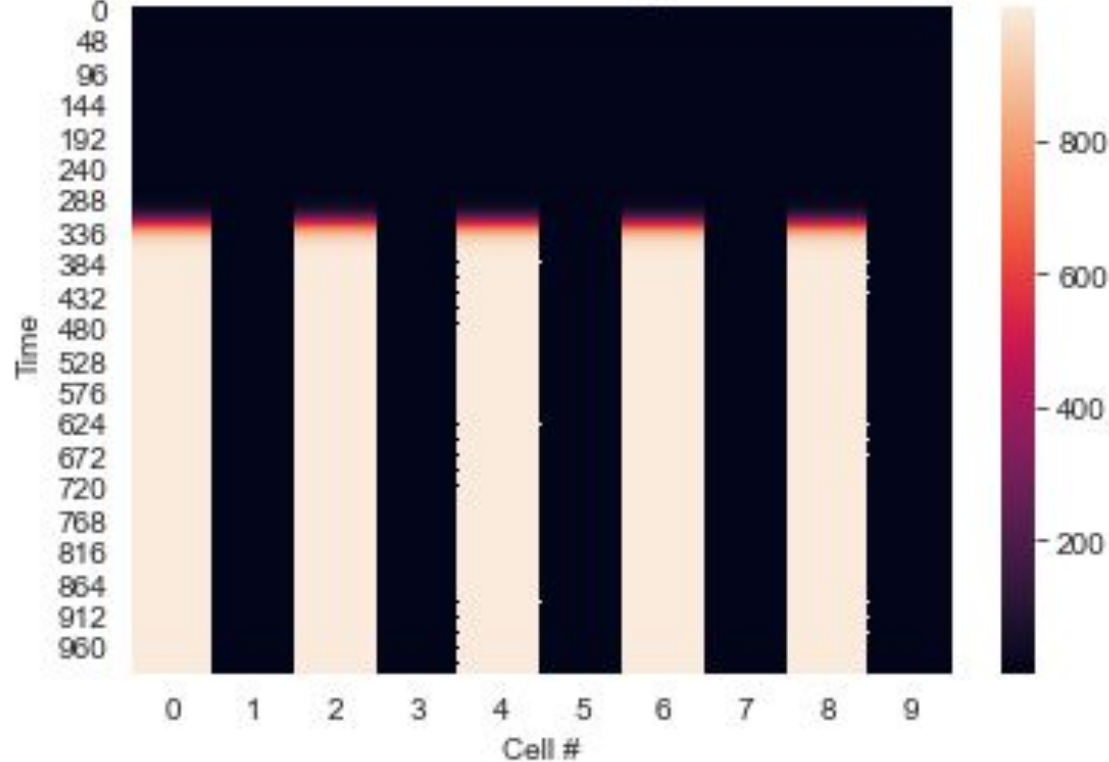
2 neighboring cells normal inhibition where  $m = 2$  and  $p = 1$

Delta Receptor Concentration from Simulating 2 Cells with Normal Inhibition



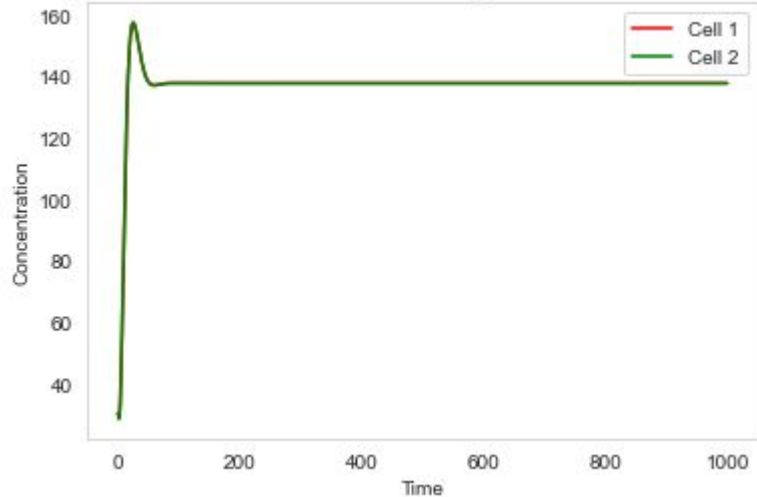
Array of 10 cells normal inhibition where  $m = 2$  and  $p = 1$

Delta Receptor Concentration from Simulating 10 Cells with Normal Inhibition

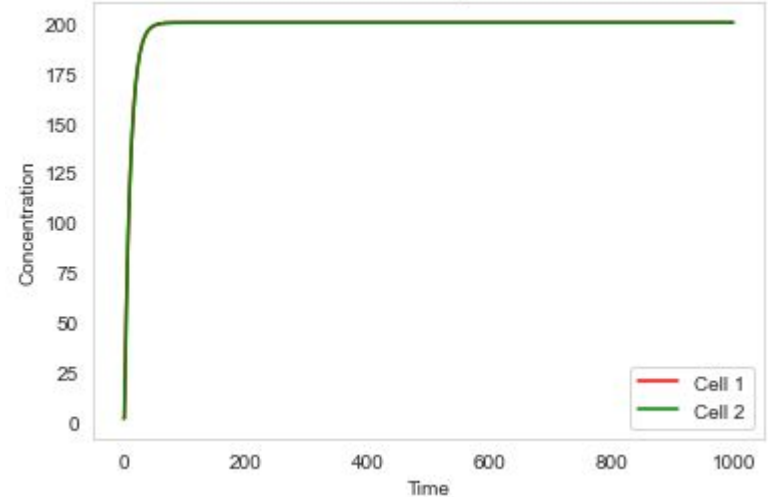


## 2 neighboring cells normal inhibition where $m = 1$ and $p = 1$

Repressor Concentration from Simulating 2 Cells with Normal Inhibition



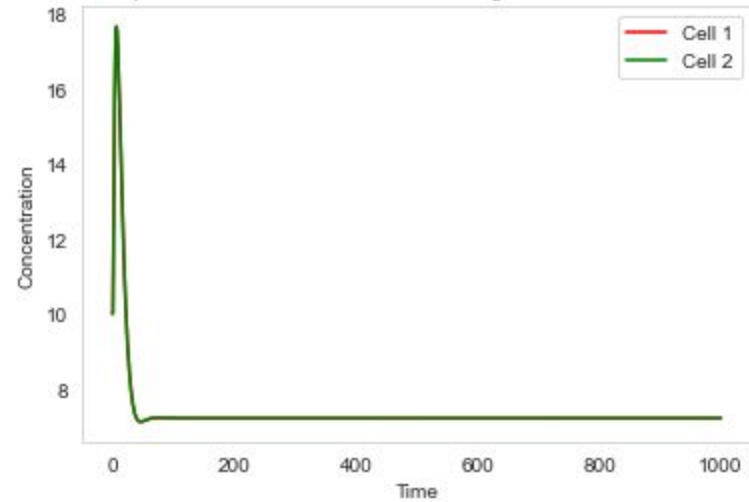
Notch Concentration from Simulating 2 Cells with Normal Inhibition



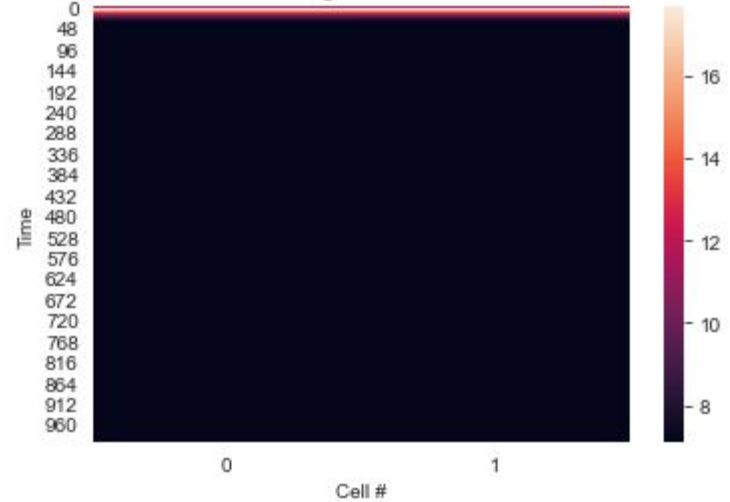


## 2 neighboring cells normal inhibition where $m = 1$ and $p = 1$

Delta Receptor Concentration from Simulating 2 Cells with Normal Inhibition

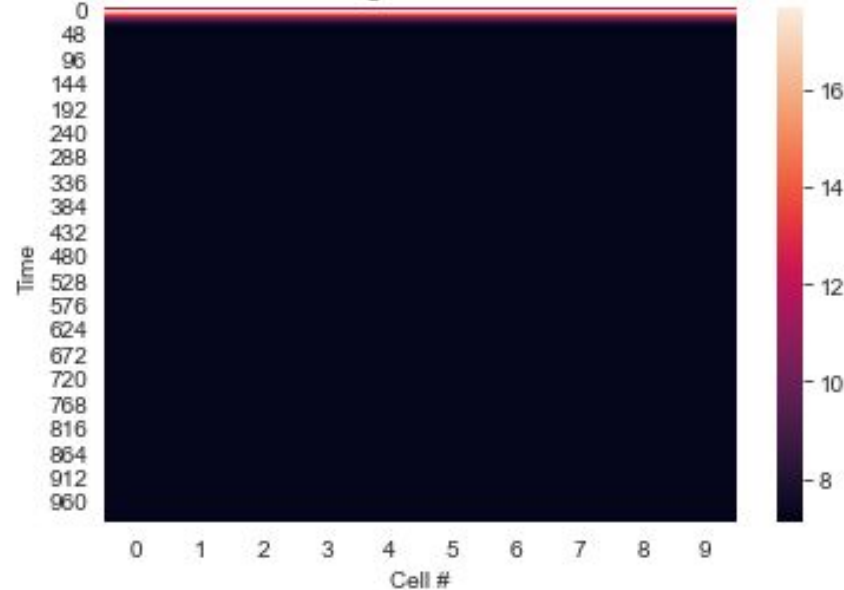


Delta Receptor Concentration from Simulating 2 Cells with Normal Inhibition and no Cooperativity



# Array of 10 cells normal inhibition where $m = 1$ and $p = 1$

Delta Receptor Concentration from Simulating 10 Cells with Normal Inhibition and no Cooperativity



$mp$  must be  $> 1$

(E. Plahte, J. Math. Biol. 43, 411 (2001))

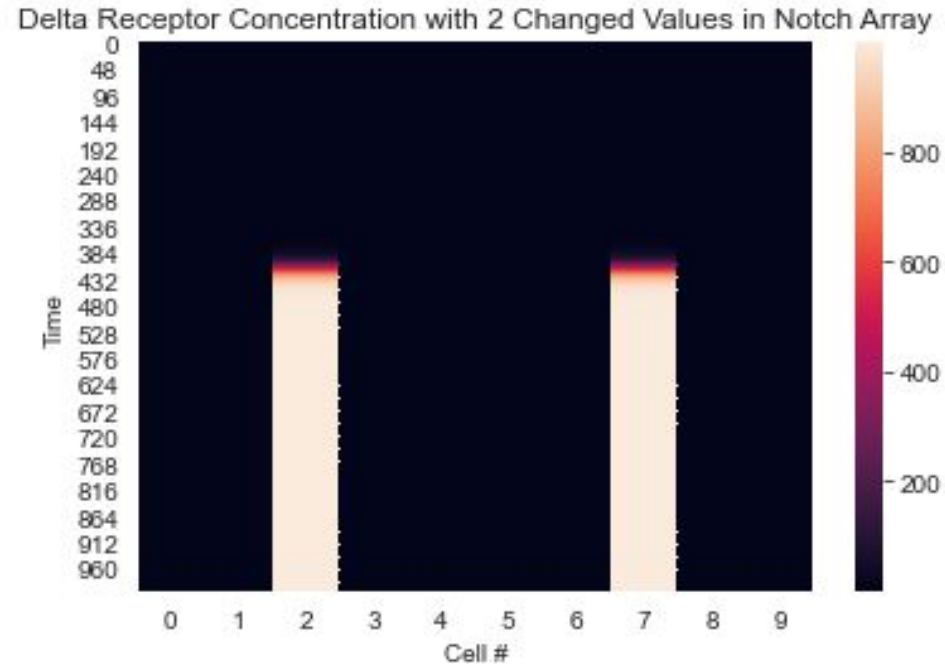
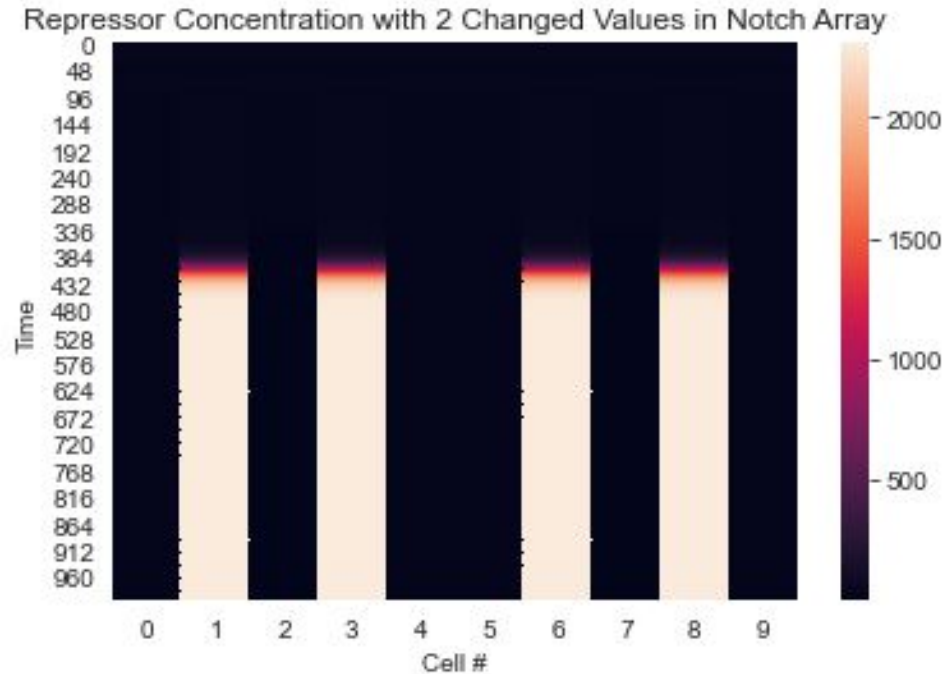
# Why no differentiation?

No cooperativity and no mutual inhibition

Without either there is no way to achieve a Delta concentration difference

Essentially both cells repress each other

# Weird results when 2 values in notch array are changed $m = 2$ and $p = 1$



```
ncells = np.array([2., 2., 1.9, 2., 2., 2., 2., 1.9, 2., 2.])
```

# Adding Mutual Inhibition

Mutual inhibition is where cells can actively suppress each other

Normal inhibition fails to cause differentiation when the product of cooperativities  $m_p=1$  (no cooperativity)

## With Mutual Inhibition

$$\dot{N}_i = \beta_N - N_i - N_i \langle D_j \rangle_i - N_i \frac{D_i}{\kappa_c}$$

$\kappa_c$  is the cis-inhibition parameter

$$\dot{D}_i = \beta_D \frac{1}{1 + R_i^m} - D_i - \langle N_j \rangle_i D_i - N_i \frac{D_i}{\kappa_c}$$

N and D are activated concentrations

$$\dot{R}_i = \beta_R \frac{(N_i \langle D_j \rangle_i)^p}{k_{RS}^p + (N_i \langle D_j \rangle_i)^p} - R_i$$

# Assumptions and Limitation and Applications

Works well with  $mp=1$

Limited to 2 outcomes

Does not take into account pathways that sequentially

Assumes Notch and Delta a mutually exclusive - high level of Notch expression inhibits Delta expression and vice versa - leads to either high or low delta

# Mutual Inhibition Code

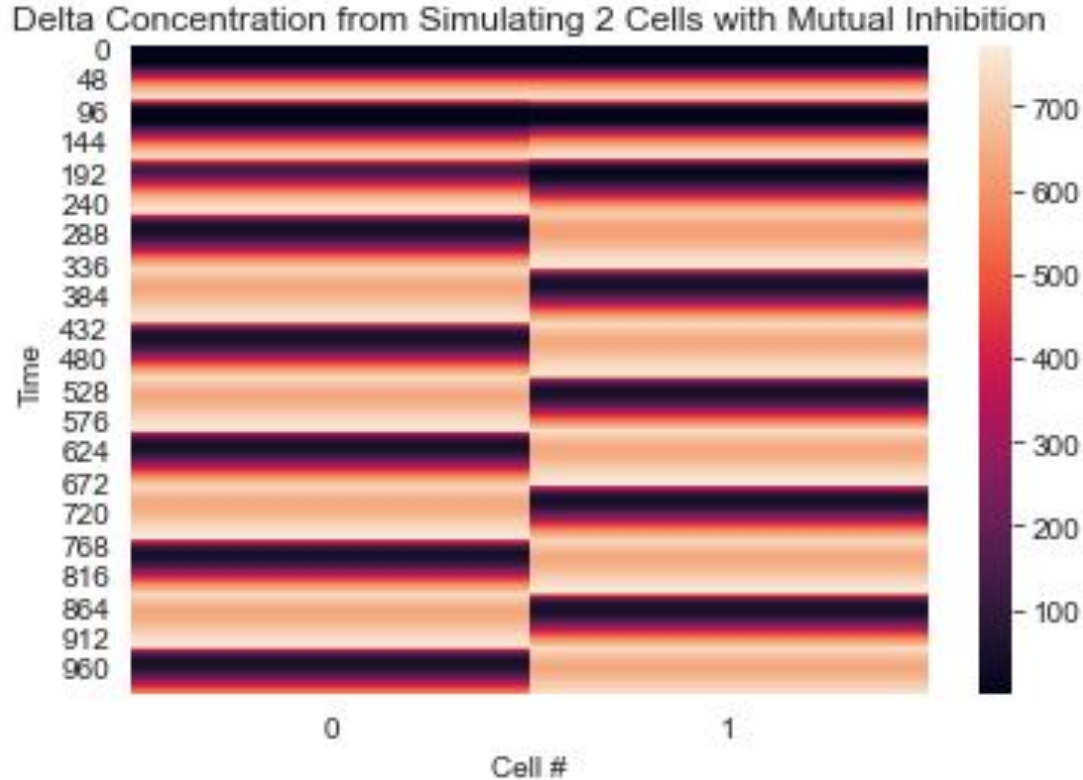
```
def mutualinhibition(bn,bd,br,ncells,dcells,rcells,m,p,krs,kc):  
  
    davg = np.roll(dcells,1)  
    davg += np.roll(dcells,-1)  
    davg /= 2.  
    navg = np.roll(ncells,1)  
    navg += np.roll(ncells,-1)  
    navg /= 2.  
  
    #      bn - ncells - (ncells*davg) - (ncells*(dcells/kc))  
    nnew = bn + ncells*( -1 - davg - (dcells/kc))  
  
    #      bd*(1 / (1 + (rcells**m))) - dcells - navg*dcells - ncells*(dcells/kc)  
    dnew = bd*(1 / (1 + (rcells**m))) + dcells*( -1 - navg - (ncells/kc))  
  
    ndpow = (ncells*davg)**p  
    #      br*(((ncells*davg)**p) / ((krs**p) + ((ncells*davg)**p))) - rcells  
    rnew = br*(ndpow / ((krs**p) + ndpow)) - rcells  
  
    return nnew,dnew,rnew
```



# Simulation Code

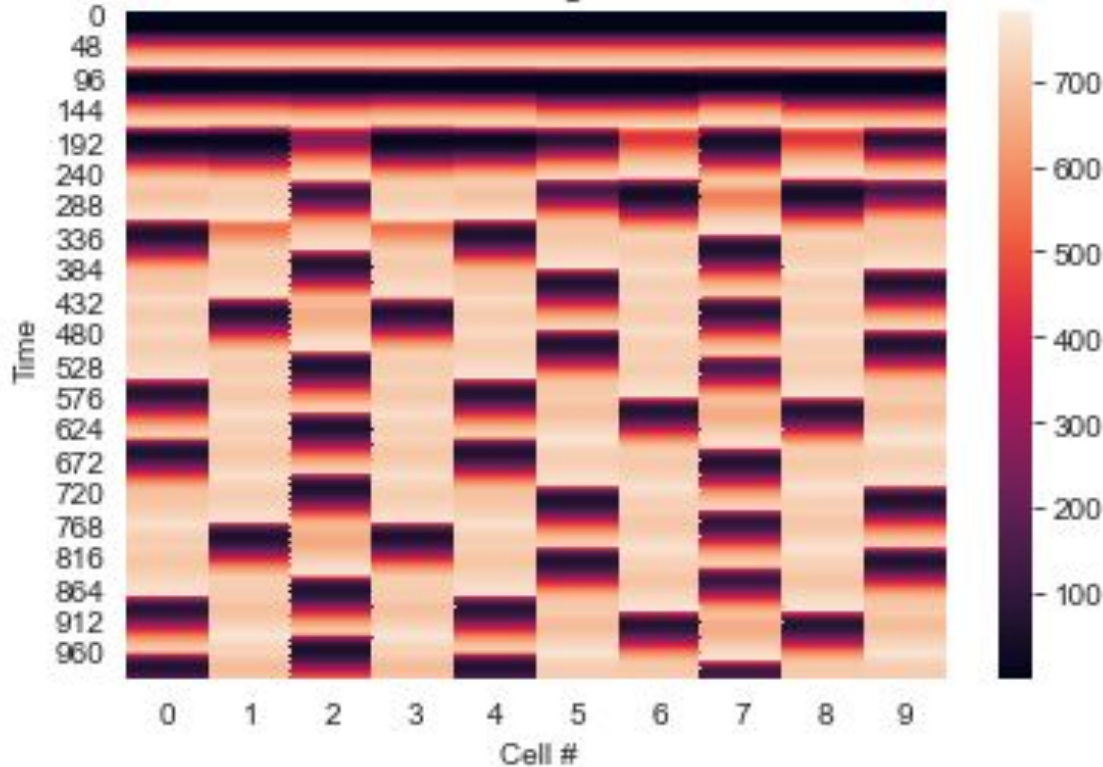
```
def simulate_mutual(Tmax,Nday,bn,bd,br,ncells,dcells,rcells,m,p,krs,kc):  
    Nhistory = [np.array(ncells)]  
    Dhistory = [np.array(dcells)]  
    Rhistory = [np.array(rcells)]  
    n=np.array(ncells)  
    d=np.array(dcells)  
    r=np.array(rcells)  
    Nsteps=Tmax*Nday  
    Nsteps = int(Nsteps)  
    dt = 1./Nday  
    for k in range(Nsteps):  
        nd,dd,rd = mutualinhibition(bn,bd,br,n,d,r,m,p,krs,kc)  
        n += nd*dt  
        d += dd*dt  
        r += rd*dt  
        if k%100==0:  
            Nhistory.append(np.array(n))  
            Dhistory.append(np.array(d))  
            Rhistory.append(np.array(r))  
  
    return np.array(Nhistory),np.array(Dhistory),np.array(Rhistory)
```

2 neighboring cells normal inhibition where  $m = 1$  and  $p = 2$



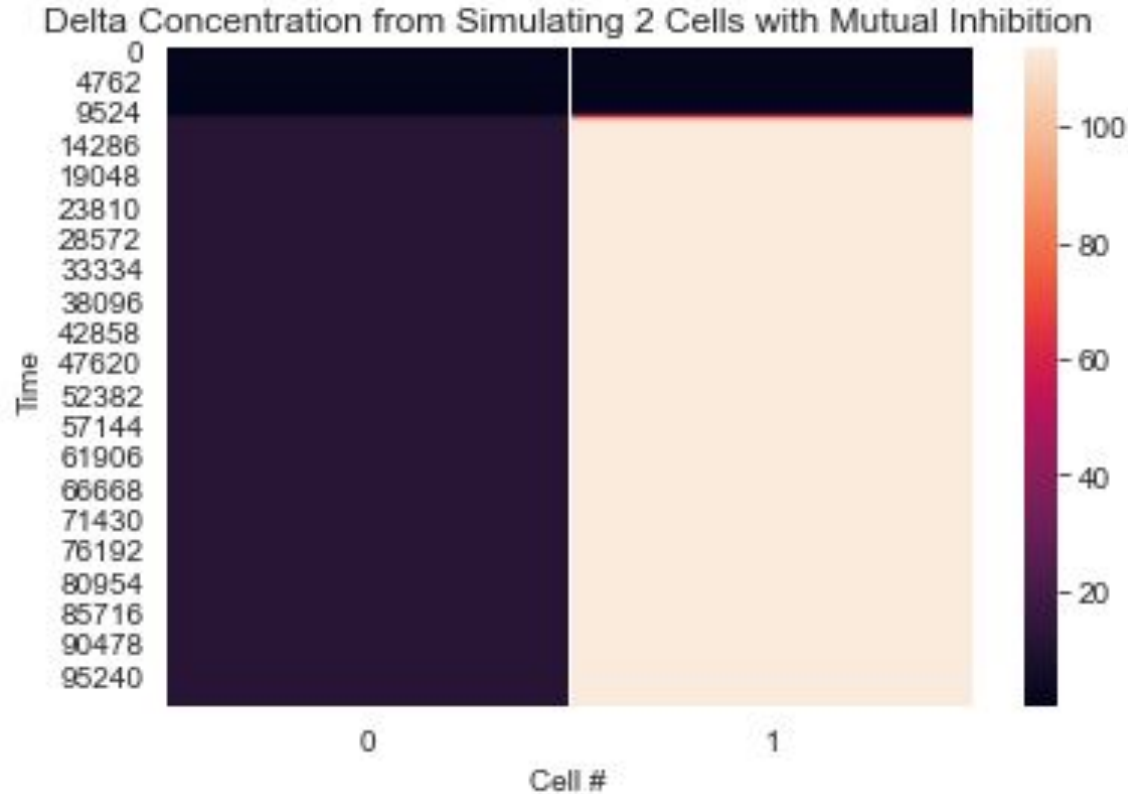
# Array of 10 cells mutual inhibition where $m = 1$ and $p = 2$

Delta Concentration from Simulating 10 Cells with Mutual Inhibition

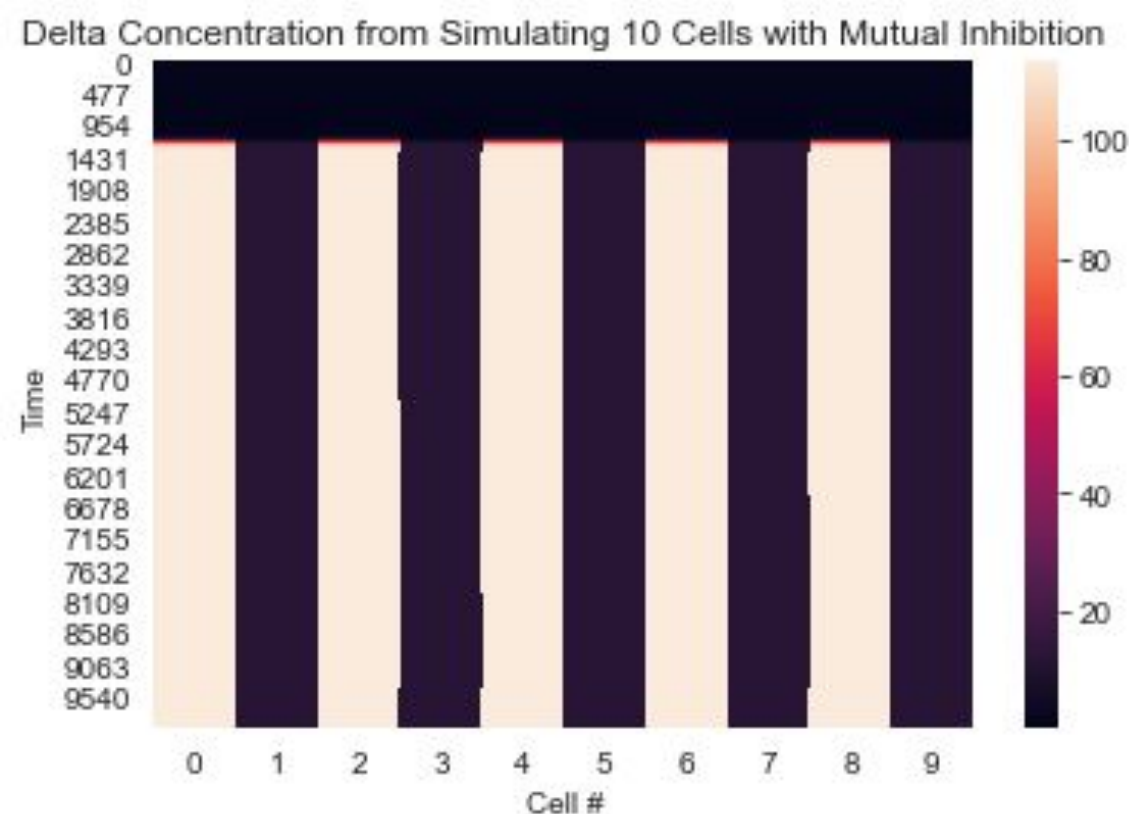


Does not work the best for  $mp > 1$   
Limitation

2 neighboring cells mutual inhibition where  $m = 1$  and  $p = 1$

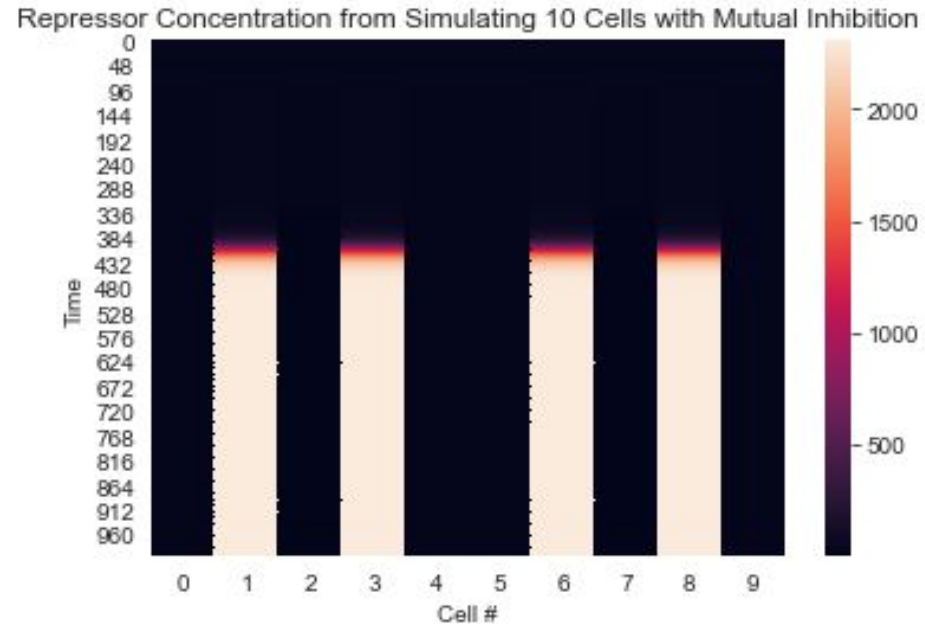
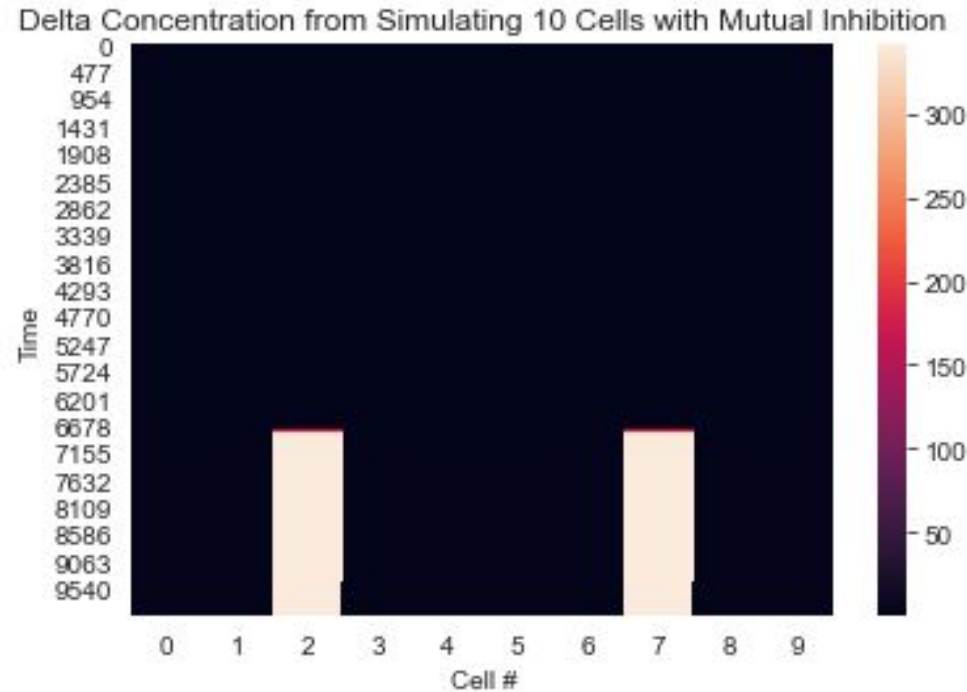


# Array of 10 cells mutual inhibition where $m = 1$ and $p = 1$



No evidence for strongly cooperative transactivation (Spriznak et al., 2010)

# Weirdness presented again in Mutual Inhibition with 2 changed values



# Summary

Normal and Mutual inhibition can simulate pattern formation to an extent

Limitations for each

Cannot rule out cooperativity, but mutual inhibition occurs

Initial values and cooperativity affect simulations the most