# How mathematics helps unraveling the mystery behind somitogenesis

*Peng Feng*

DEPARTMENT OF **MATHEMATICS**

University of Central Florida, October 29th, 2010

# Outline

1. Introduction
   - Somite Formation
   - Early Mathematical Models
   - Mathematical Model

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2. Thoeretical Results
   - Hopf Bifurcation Without Discrete Delay
   - Hopf Bifurcation With Discrete Delay

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   - Early Mathematical Models
   - Mathematical Model
2. Thoeretical Results
   - Hopf Bifurcation Without Discrete Delay
   - Hopf Bifurcation With Discrete Delay
3. Methods Applied

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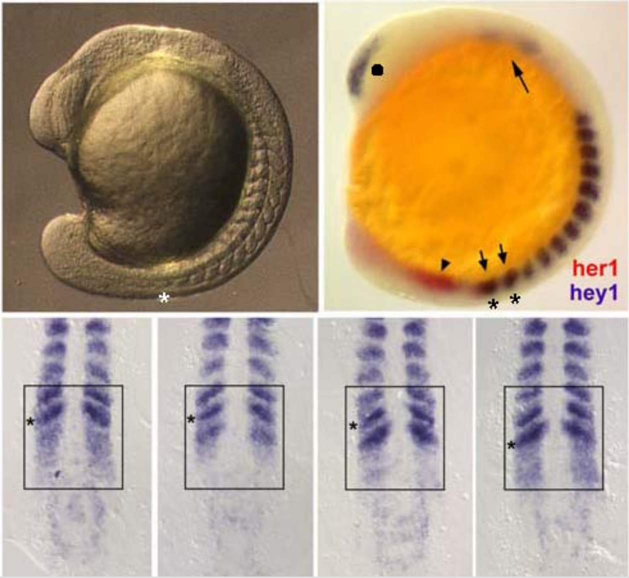
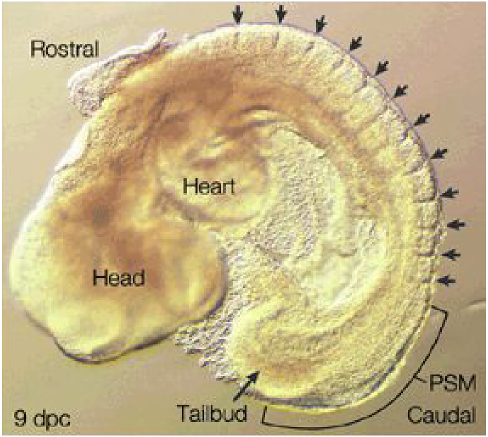
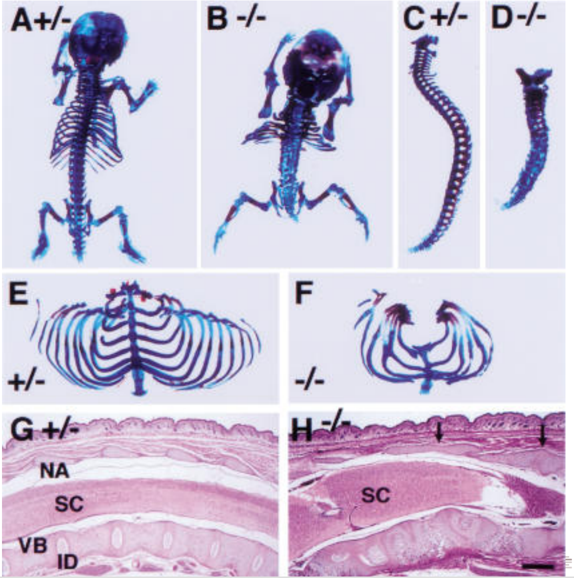
# Somite Formation(Zebrafish Embryo)



# Somite Formation(Mouse Embryo)



# Laboratory Findings



# Early Mathematical Models

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- Molecular Clock Model, Palmeirim et al., 1997

# Schematic Sketch of Gene Regulating Network

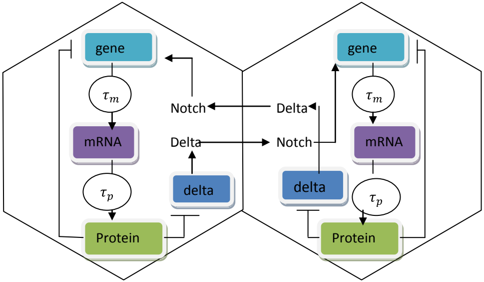


Figure: Schematic representation of communication among cells

# A Simpler Diagram

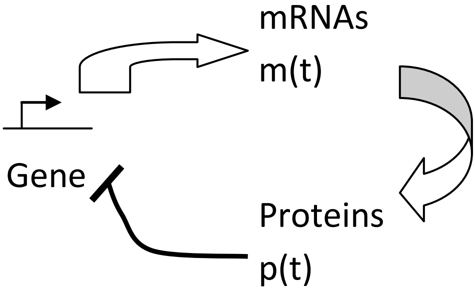


Figure: Schematic representation of gene regulation: Gene is transcribed into mRNA which is translated into protein. By binding to the promoter of the gene the protein represses further transcription of gene.

# A Simple yet Illuminating Model

$$\begin{cases} \frac{dp}{dt} = am(t-\tau_p) - bp(t), \\ \frac{dm}{dt} = f(p(t-\tau_m)) - cm(t), \end{cases} \tag{1}$$

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- Movement of the protein between the cytoplasm and nucleus is neglected
- The delay takes a discrete, well-defined value

## Steady States and Local Stability

Let $r = \tau_m/\tau_p$

### Theorem

*When $c > \frac{ka}{b\theta}\frac{n-1}{n}\sqrt[n]{n-1}$, $E^* = (p^*, m^*)$ is asymptotically stable for all $r \geq 0$. When c is small, there exists a critical value $r_0$ such that the steady state $E^*$ is asymptotically stable for $r \in [0, r_0)$ and unstable for $r > r_0$, where*

$$r_0 = \frac{1}{\xi_+}\arccos\left\{\frac{\xi_+^2 - bc\tau_p^2}{bc_1\tau_p^2}\right\} - 1, \tag{2}$$

*and*

$$\xi_+^2 = -\frac{1}{2}(b^2+c^2)\tau_p^2 + \frac{1}{2}\tau_p^2[(b^2-c^2)^2 + 4b^2c_1^2]^{1/2} \tag{3}$$

## Lemma

*Consider the equation*

$$\lambda^2 + a\lambda + e + (c\lambda + d)e^{-\lambda r} = 0, \tag{4}$$

*where a, b, c, d and e are real numbers. Let the hypotheses:*

- *(A1)* $a + c > 0$,
- *(A2)* $e + d > 0$,
- *(A3)* $c^2 - a^2 + 2e < 0$ *and* $e^2 - d^2 > 0$ *or* $(c^2 - a^2 + 2e)^2 < 4(e^2 - d^2)$,
- *(A4)* $e^2 - d^2 < 0$ *or* $c^2 - a^2 + 2e > 0$ *and* $(c^2 - a^2 + 2e)^2 = 4(e^2 - d^2)$.

*(a) if A1, A2 and A3 hold, then all roots of Eq.(4) have negative real parts for all* $r \geq 0$.
*(b) If A1, A2 and A4 hod, then there exists* $r_0 > 0$ *such that, when* $r \in [0, r_0)$ *all roots of (4) have negative real parts, when* $r = r_0$*, Eq.(4) has a pair of purely imaginary roots* $\pm i\xi_+$*, and for* $r > r_0$ *(4) has at least one root with positive real part. Here* $r_0$ *and* $\xi_+$ *are given by*

# Hopf Bifurcation

## Theorem

*When* $c < \frac{ka}{b\theta}\frac{n-1}{n}\sqrt[n]{n-1}$*, there exists* $\epsilon_0 > 0$ *such that for each* $0 \leq \epsilon < \epsilon_0$*, Eq.(1)have a family of periodic solutions* $p_\epsilon(t)$ *with period* $T(\epsilon)$*. Moreover, for the parameter* $r = r(\epsilon)$*,* $p_0(t) = E^*$*,* $T(0) = \frac{2\pi}{\xi_+}$ *and* $r(0) = r_0$*, where* $r_0$ *and* $\xi_+$ *are given in Eq.(2) and Eq.(3), respectively.*

# A More Realistic Mathematical Model

$$\begin{cases} \frac{dp}{dt} = am(t-\tau_p) - bp(t), \\ \frac{dm}{dt} = \int_{-\infty}^{t} g(t-s)f(p(s))ds - cm(t), \end{cases} \tag{5}$$

$\tau_p$: time lag between the initiation of the translation and the appearance of a mature protein; $b$ and $c$ represent the degradation rates of proteins and mRNAs, respectively; $a$ is the translation constant.

$$f(p) = \frac{k\theta^h}{\theta^h + p^h}, g(t) = \alpha e^{-\alpha t}(Weak\ \ Kernel), g(t) = \alpha^2 t e^{-\alpha t}(Strong\ \ Kernel).$$

# Theoretical Results

## Theorem (Weak Kernel Without Discrete Delay)

*If (i)* $bc < ad$ *or*
*(ii)*$bc > ad$, $(b+c)^2 + ad > 2(b+c)\sqrt{bc}$ *and* $\alpha > \alpha_0$ *where* $\alpha_0$ *is given by*

$$\alpha_0 = \frac{ad - (b+c)^2 + \sqrt{\Delta}}{2(b+c)}, \text{with } \Delta = [(b+c) - \sqrt{bc}]^2 - (bc - ad).$$

*then the steady-state solution* $(p^*, m^*)$ *is asymptotically stable.*
*If* $bc > ad$, $(b+c)^2 + ad > 2(b+c)\sqrt{bc}$ *and* $\alpha \in [0, \alpha_0)$*, then the steady state is unstable. Hopf bifurcation occurs when* $\alpha = \alpha_0$*.*

# Theoretical Results

## Theorem (Strong Kernel Without Discrete Delay)

*If* $(2b + ad/b)^2 > 4b^2$*, then* $(p^*, m^*)$ *is locally asymptotically stable for* $\alpha \in (0, \alpha_1) \cup (\alpha_2, +\infty)$ *and is unstable for* $\alpha \in (\alpha_1, \alpha_2)$*.* $\alpha_1$*,* $\alpha_2$ *are given by*

$$\alpha_1 = \frac{1}{2}[C_5 - \sqrt{C_5^2 - 4b^2}],\ \alpha_2 = \frac{1}{2}[C_5 + \sqrt{C_5 - 4b^2}]$$

*with* $C_5 = (2b + ad/b)$*.* $\alpha_1$ *and* $\alpha_2$ *are Hopf bifurcation values. If* $(2b + ad/b)^2 < 4b^2$*, then* $(p^*, m^*)$ *is always asymptotically stable.*

## Theoretical Results

### Theorem (Weak Kernel With Discrete Delay)

*If $bc < -ad$, and $\omega_+$ is the least simple root of equation (6),*

$$\omega^6 + (A^2 - 2B)\omega^4 + (B^2 - 2AC)\omega^2 + C^2 - D^2 = 0 \tag{6}$$

*then a Hopf bifurcation occurs as $\tau_p$ passes through*
$\tau_0 = \frac{1}{\omega_+} \arccos\left\{\frac{A\omega_+^2 - C}{D}\right\}$. *Here*

$$A = b + c + \alpha,\ C = \alpha bc,\ D = -\alpha ad.$$

## Theoretical Results

### Theorem (Strong Kernel With Discrete Delay)

*(i) If* $B^2 - C^2 > 0,\ -A^2 + 2B < 0$ *or* $(-A^2 + 2B)^2 < 4(B^2 - C^2)$*, then the steady state* $(p^*, m^*)$ *is asymptotically stable for all discrete delays;*

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# Weak Kernel with Discrete Delay

Define

$$w(t) = \int_{-\infty}^{t} \alpha e^{-\alpha(t-s)} f(p(s)) ds.$$

The original system then becomes

$$\frac{dp}{dt} = am(t - \tau_p) - bp(t),$$

$$\frac{dm}{dt} = w(t) - cm(t),$$

$$\frac{dw}{dt} = \alpha(f(p(t)) - w(t)).$$

The linearized system takes the form:

$$\frac{dP}{dt} = aM(t - \tau_p) - bP(t),$$

$$\frac{dM}{dt} = W(t) - cM(t),$$

$$\frac{dW}{\ldots}$$

## Weak Kernel with Discrete Delay

Expanding this expression, we arrive at the following characteristic equation

$$\lambda^3 + A\lambda^2 + B\lambda + C + De^{-\tau_p\lambda} = 0,$$

where

$$A = b + c + \alpha,\ B = \alpha(b + c) + bc,\ C = \alpha bc,\ D = -\alpha ad > 0.$$

## Weak Kernel with Discrete Delay

Let $\lambda = \xi + i\omega$ be a solution to this quasi-polynomial characteristic equation. We can rewrite the equation in terms of the real and imaginary parts as

$$\xi^3 - 3\xi\omega + A\xi^2 - A\omega^2 + B\xi + C + De^{-\xi\tau_p}\cos(\omega\tau_p) = 0$$
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$$-A\omega^2 + C + D\cos(\xi\tau_p) = 0$$
$$-\omega^3 + B\omega - D\sin(\omega\tau_p) = 0$$

Thus

$$(-A\omega^2 + C)^2 + (-\omega^3 + B\omega)^2 = D^2.$$

Or equivalently,

$$\omega^6 + (A^2 - 2B)\omega^4 + (B^2 - 2AC)\omega^2 + C^2 - D^2 = 0 \qquad (7)$$

Applying the next Lemma, we show that there is no real root to this equation when $C^2 - D^2 > 0$.

## Lemma

*The cubic equation*

$$x^3 + a_1 x^2 + a_2 x + a_3 = 0$$

*has at least one single positive root when* $a_3 > 0$ *if and only if*
*(1) Either* $a_1 < 0$, $a_2 \geq 0$, $a_1^2 > 3a_2$ *or* $a_2 < 0$;
*and*
*(2)* $\frac{4}{27}a_2^3 - \frac{1}{27}a_1^2 a_2^2 + \frac{4}{27}a_1^3 a_3 - \frac{2}{3}a_1 a_2 a_3 + a_3^3 < 0$

Let $\omega_+$ be the solution to (7). We denote

$$F(\lambda, \tau_p) = \lambda^3 + A\lambda^2 + B\lambda + C + De^{-\tau_p \lambda}. \tag{8}$$

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At $\tau_p = \tau_0$, $\lambda = i\omega_+$, it follows that

$$\frac{d}{d\tau_p} Re(\lambda)|_{\tau_p=\tau_0} = \frac{\omega_+^2(3\omega_+^4 + 2(A^2 - 2B)\omega_+^2 + B^2 - 2AC)}{P^2 + Q^2}, \quad (9)$$

where

$$P = -3\omega_+^2 + B + \tau_0(-A\omega_+^2 + C),$$

and

$$Q = 2A\omega_+ + \tau_0(-\omega_+^3 + B\omega_+).$$

## Linear Chain Trick

Let

$$w_2(t) = \int_{-\infty}^{t} \alpha^2 (t-s) e^{-\alpha(t-s)} f(p(s)) ds$$

and

$$w_1(t) = \int_{-\infty}^{t} \alpha e^{-\alpha(t-s)} f(p(s)) ds,$$

we have the following equivalent system

$$\frac{dp}{dt} = am(t-\tau_p) - bp(t),$$

$$\frac{dm}{dt} = w_2(t) - cm(t),$$

$$\frac{dw_2}{dt} = \alpha(w_1(t) - w_2(t)),$$

$$\frac{dw_1}{dt} = \alpha(f(p(t)) - w_1(t)).$$

## Characteristic Equation

The associated characteristic equation to the linearized system is

$$\begin{vmatrix} -b-\lambda & ae^{-\tau_p\lambda} & 0 & 0 \\ 0 & -c-\lambda & 1 & 0 \\ 0 & 0 & -\alpha-\lambda & \alpha \\ -\alpha d & 0 & 0 & -\alpha-\lambda \end{vmatrix} = 0.$$

Expansion of the above equation yields

$$(b+\lambda)(c+\lambda)(\alpha+\lambda)^2 + \alpha^2 ade^{-\tau_p\lambda} = 0.$$

## Simplification

Assuming $b = c$, the characteristic equation then becomes

$$(b+\lambda)(\alpha+\lambda) = \pm\alpha\sqrt{adi}e^{-\lambda\tau_p/2}.$$

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The characteristic equation then takes the following form

$$\lambda^2 + A\lambda + B \pm Cie^{-\bar{\tau}\lambda} = 0.$$

## Analysis of the Roots

Let

$$\xi_+ = \sqrt{\frac{1}{2}(-A^2+2B) + [1/4(-A^2+B)^2 - (B^2-C^2)]^{1/2}}.$$

and

$$\tau_{n,1}^+ = \frac{1}{\xi_+}\arcsin\left(\frac{\xi_+^2 - B}{C}\right) + \frac{2n\pi}{\xi_+}.$$

Let

$$\xi_- = \sqrt{\frac{1}{2}(-A^2+2B) - [1/4(-A^2+B)^2 - (B^2-C^2)]^{1/2}},$$

and

$$\tau_{n,2}^+ = \frac{1}{\xi_-}\arcsin\left(\frac{\xi_-^2 - B}{C}\right) + \frac{2n\pi}{\xi_-}.$$

## Analysis of the Roots

Let

$$\eta_+ = \sqrt{\frac{1}{2}(-A^2 + 2B) + [1/4(-A^2 + B)^2 - (B^2 - C^2)]^{1/2}}.$$

and

$$\bar{\tau} = \tau_{n,1}^- = -\frac{1}{\eta_+}\arcsin(\frac{\eta_+^2 - B}{C}) + \frac{2n\pi}{\eta_+}.$$

Let

$$\eta_- = \sqrt{\frac{1}{2}(-A^2 + 2B) - [1/4(-A^2 + B)^2 - (B^2 - C^2)]^{1/2}},$$

and

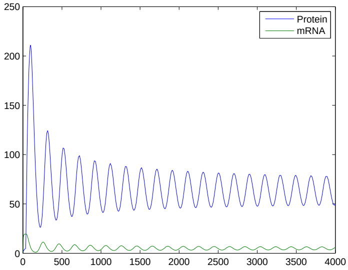
$$\tau_{n,2}^- = -\frac{1}{\eta_-}\arcsin(\frac{\eta_-^2 - B}{C}) + \frac{2n\pi}{\eta_-}.$$

## Parameters

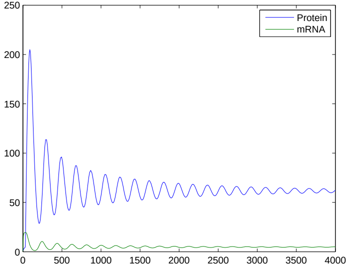
Table: Estimated parameters for hes7 gene.

| Parameter | Value | Description |
|---|---|---|
| $a$ | 0.45 molecules/min | translation constant |
| $b$ | 0.0347 or 0.0231 molecules/min | 0.0347 for wild-type and 0.0231 for Hes7K14R |
| $c$ | 0.231 molecules/min | mRNA degradation rate |
| $k$ | 4.5 molecules/cell$\cdot$ min | critical protein concentration |
| $h$ | 2.6 | Hill coefficient |
| $\theta$ | 40 molecules | DNA dissociation constant |
| $\tau_p$ | 20-40 min | Translation delay |
| $\alpha$ | controlled | |

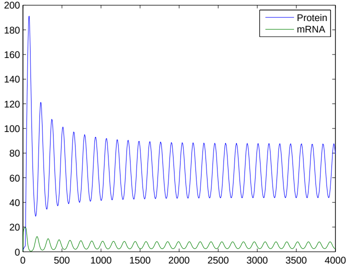
# Sustained Oscillation $\tau_p = 35$, $\alpha = 2/40$

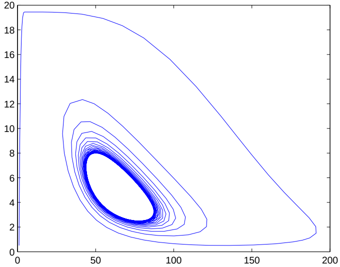


# Damped Oscillation $\tau_p = 30$, $\alpha = 2/40$

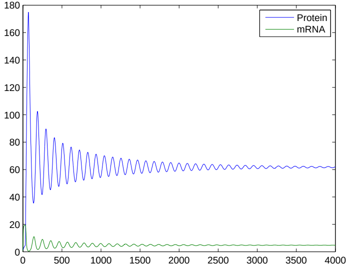


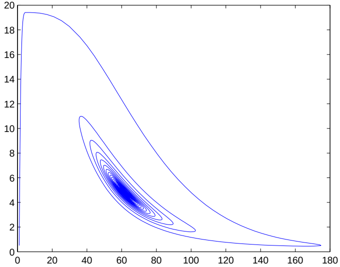
# Sustained Oscillation for Large Distributed Delay $\tau_p = 30$, $\alpha = 2/15$



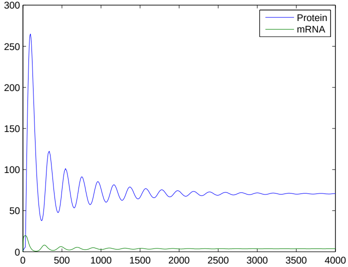



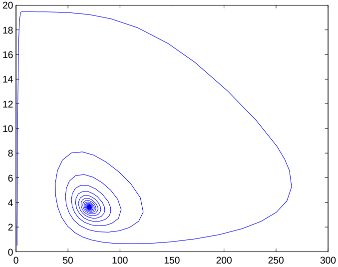
# Stability Switch When $\alpha$ Increases $\tau_p = 30$, $\alpha = 2$



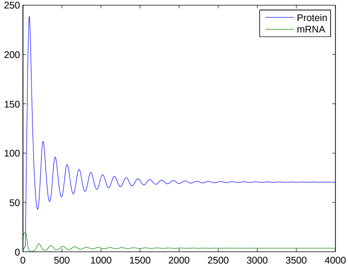



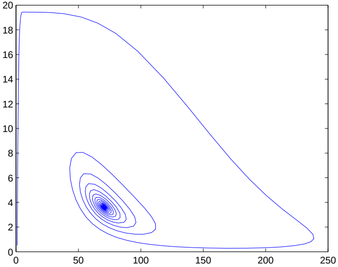
# Damped Oscillation for mutant Hes7K14R $\tau_p = 35$, $\alpha = 2/40$, $b \approx 0.0231$



# Damping oscillation for mutant Hes7K14R $\tau_p = 30$, $\alpha = 2/15$,$b \approx 0.0231$



# Future Directions

- Explore the role of Delta-Notch pathway;

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- Consider the effect of diffusion of cells during early stage of embryos.

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