

# Estudio in silico de la dinámica espacio-temporal de la somitogénesis

## Examen de Doctorado

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Sinodales:

- Dr. Jesús G. Rodríguez González
- Dr. Daniel P. Sánchez Herrera
- Dr. Bruno A. Escalante Acosta
- Dr. Víctor F. Breña Medina

13 de julio 2021

# Introducción



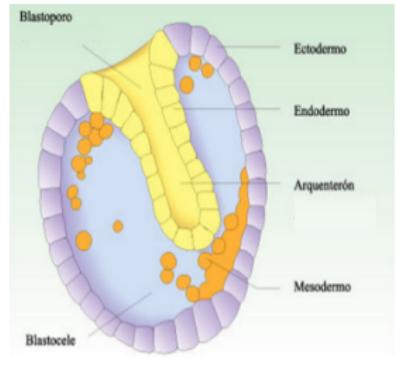
# Introducción



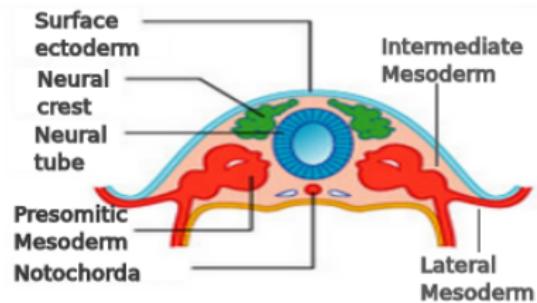
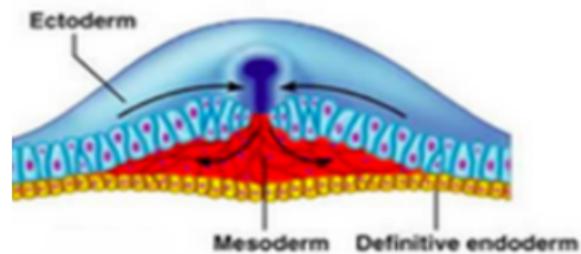
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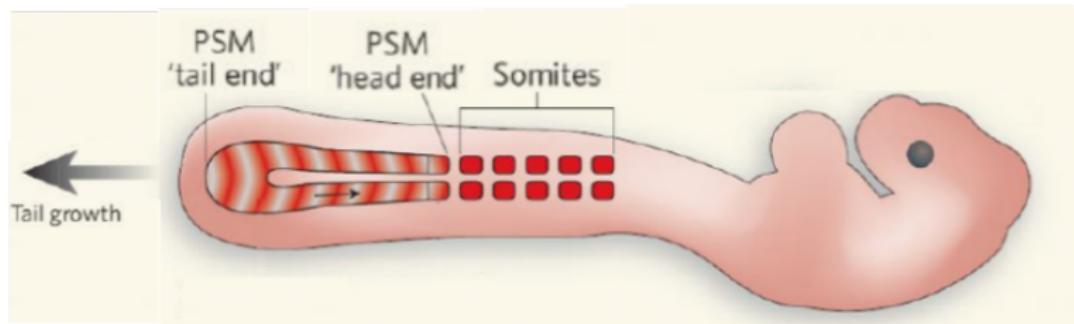
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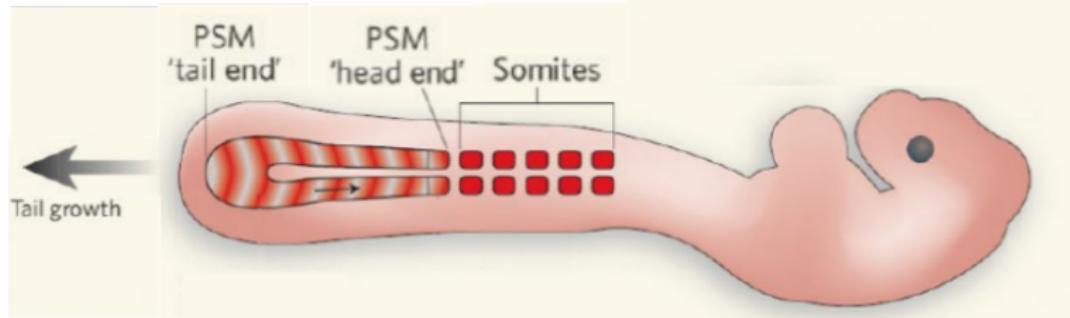
# Gastrulación



# Somitogénesis



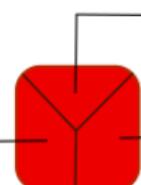
# Somitogénesis



— Esclerotoma —— Vertebras, costillas  
y cartílago.

— Miotoma —— Músculos de la  
caja torácica y  
extremidades

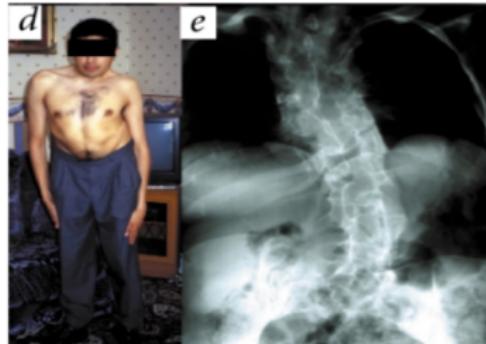
— Dermatoma —— Dermis del área  
dorsal



Somitos

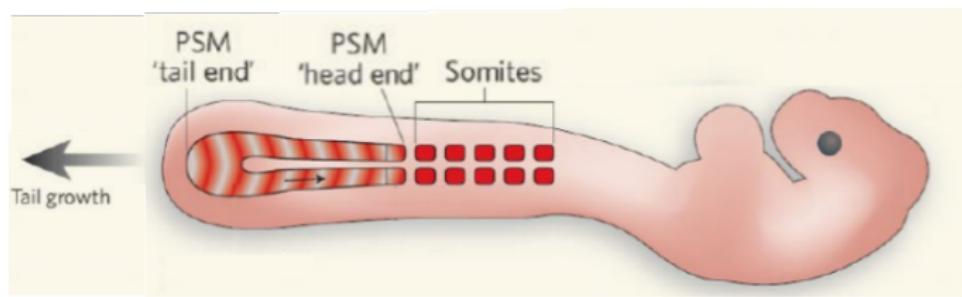
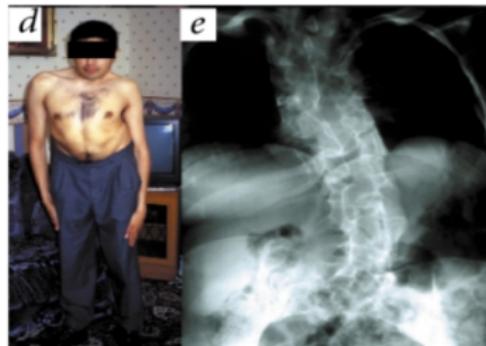
# somitogénesis

Michael P. Bulman<sup>1\*</sup>, Kenro Kusumi<sup>2\*</sup>, Timothy M. Frayling<sup>1</sup>, Carole McKeown<sup>3</sup>, Christine Garrett<sup>4</sup>, Eric S. Lander<sup>5</sup>, Robb Krumlauf<sup>2</sup>, Andrew T. Hattersley<sup>1</sup>, Sian Ellard<sup>1</sup> & Peter D. Turnpenny<sup>6</sup>

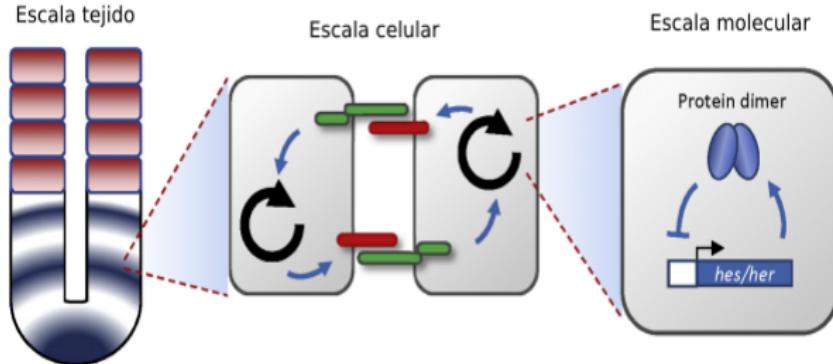


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# Antecedentes



## A Cell Cycle Model for Somitogenesis: Mathematical Formulation and Numerical Simulation

J. R. COLLIER,\* D. McINERNEY,† S. SCHNELL,‡ P. K. MAINI,§,|| D. J. GAVAGHAN,  
P. HOUSTON\*\* AND C. D. STERN††

## Adding Adhesion to a Chemical Signaling Model for Somite Formation

Nicola J. Armstrong, Kevin J. Painter\*, Jonathan A. Sherratt

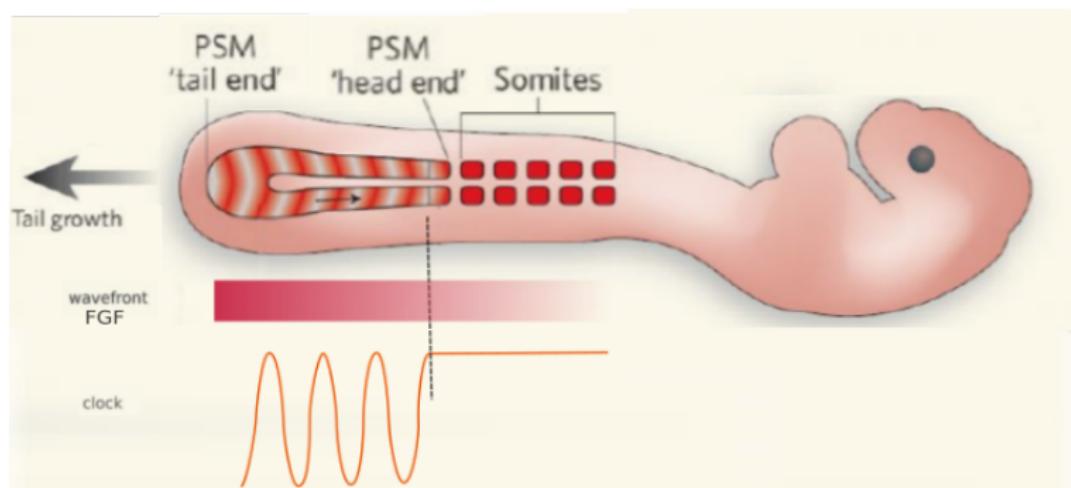
A mechanical perspective on vertebral segmentation

L. Truskinovsky <sup>a,\*</sup>, G. Vitale <sup>a,b</sup>, T.H. Smit <sup>c</sup>

# Modelo de reloj y frente de onda

## A Clock and Wavefront Model for Control of the Number of Repeated Structures during Animal Morphogenesis

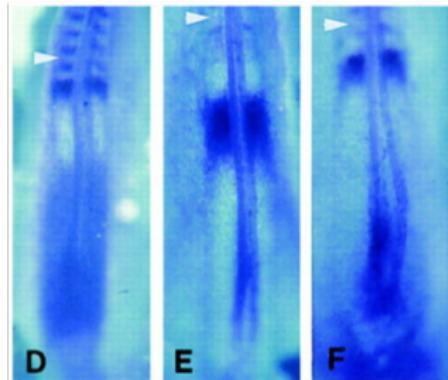
J. COOKE† E. C. ZEEMAN



# Antecedentes modelo de reloj y frente de onda

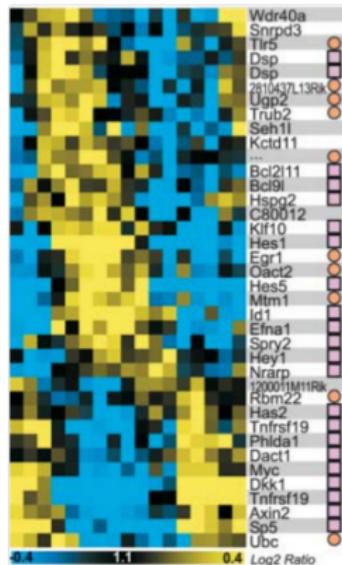
## Avian hairy Gene Expression Identifies a Molecular Clock Linked to Vertebrate Segmentation and Somitogenesis

Isabel Palmeirim<sup>1</sup>, Domingos Henrique<sup>2</sup>✉, David Ish-Horowicz<sup>2</sup>, Olivier Pourquié<sup>3</sup>✉

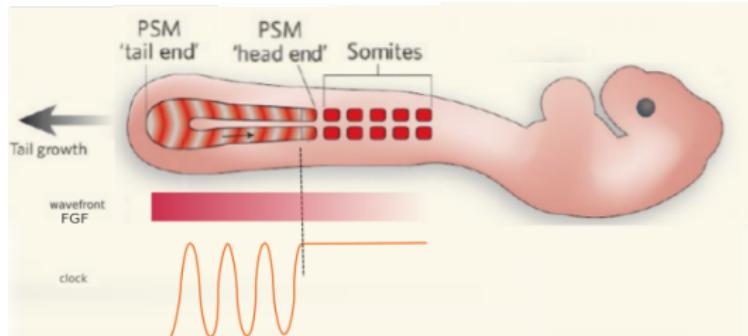


## A Complex Oscillating Network of Signaling Genes Underlies the Mouse Segmentation Clock

Mary-Lee Dequéant,<sup>1,2,3</sup> Earl Glynn,<sup>3</sup> Karin Gaudenz,<sup>3</sup> Matthias Wahl,<sup>1,3</sup> Jie Chen,<sup>4</sup> Arcady Mushegian,<sup>3</sup> Olivier Pourquié<sup>1,2,3\*</sup>

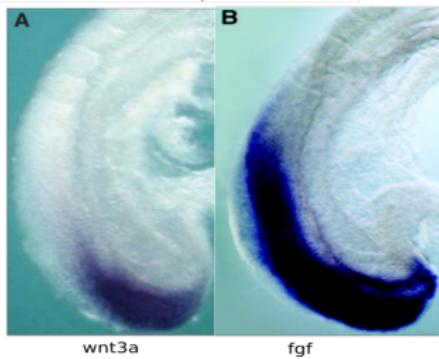


# Gradientes de concentraciones candidatos a ser el FO



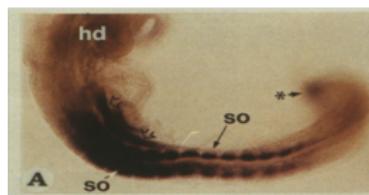
## Signaling Gradients during Paraxial Mesoderm Development

Alexander Aulehla<sup>1</sup> and Olivier Pourquié<sup>1,2,3</sup>



Restricted expression and retinoic acid-induced downregulation of the retinaldehyde dehydrogenase type 2 (RALDH-2) gene during mouse development.

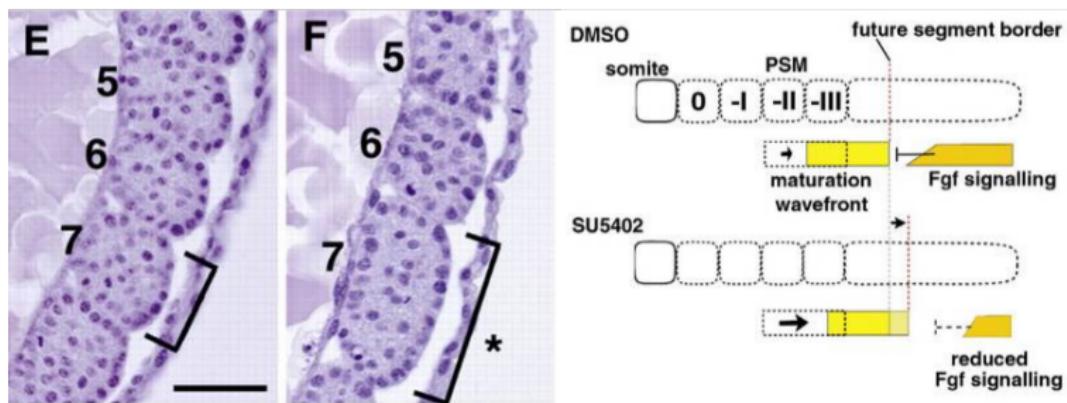
Karen Niederreither,  
Peter McCaffery,  
Ursula C. Drager,  
Pierre Chambon,  
Pascal Dolle.



# Antecedentes modelo de reloj y frente de onda

## Fgf/MAPK signalling is a crucial positional cue in somite boundary formation

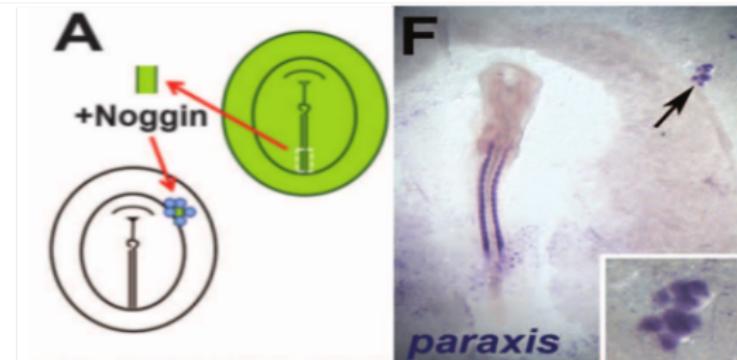
Atsushi Sawada, Minori Shinya, Yun-Jin Jiang, Atsushi Kawakami, Atsushi Kuroiwa, Hiroyuki Takeda



# Antecedentes modelo de reloj y frente de onda

## Somites Without a Clock

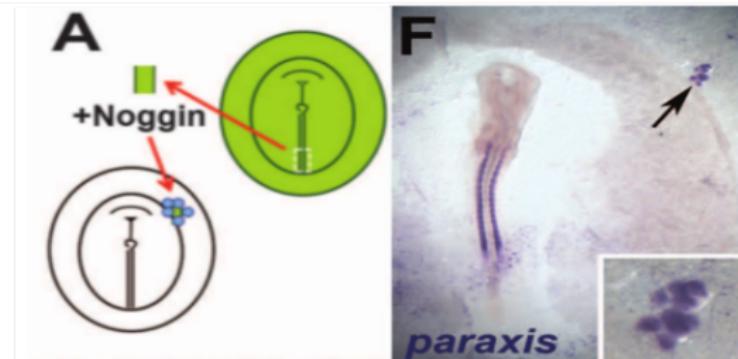
Ana S. Dias,<sup>1\*</sup> Irene de Almeida,<sup>1\*</sup> Julio M. Belmonte,<sup>2</sup> James A. Glazier,<sup>2</sup> Claudio D. Stern<sup>1†</sup>



# Antecedentes modelo de reloj y frente de onda

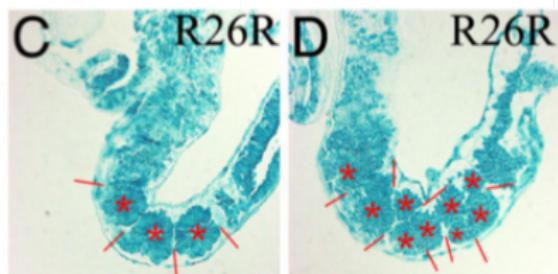
## Somites Without a Clock

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**FGF4 and FGF8 comprise the wavefront activity that controls somitogenesis**

L. A. Naiche, Nakisha Holder<sup>1</sup>, and Mark Lewandoski<sup>2</sup>



## **Pattern formation in biology: a comparison of models and experiments**

Hans Meinhardt

Max-Planck-Institut für Entwicklungsbiologie, Spemannstr. 35, D74 Tübingen, Federal Republic of Germany

## **THE CHEMICAL BASIS OF MORPHOGENESIS**

By A. M. TURING, F.R.S. *University of Manchester*

(Received 9 November 1951—Revised 15 March 1952)

# Modelos de reacción-difusión

## Pattern formation in biology: a comparison of models and experiments

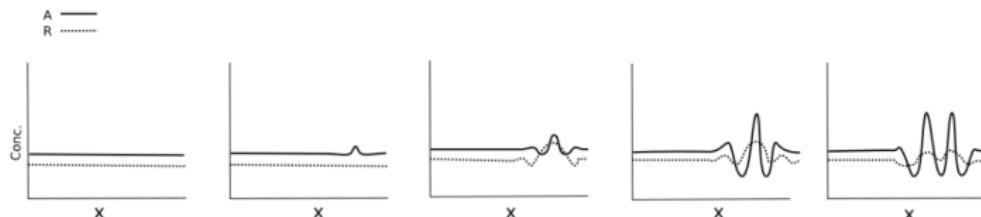
Hans Meinhardt

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## THE CHEMICAL BASIS OF MORPHOGENESIS

By A. M. TURING, F.R.S. *University of Manchester*

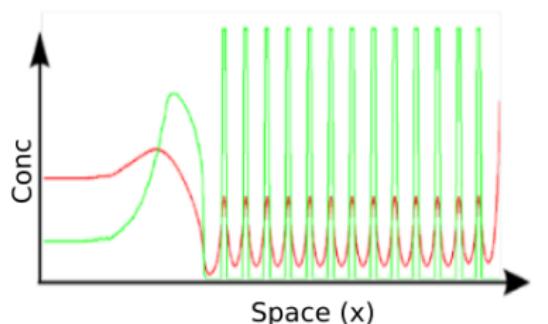
(Received 9 November 1951—Revised 15 March 1952)



Article

## Cell Systems

### A Local, Self-Organizing Reaction-Diffusion Model Can Explain Somite Patterning in Embryos

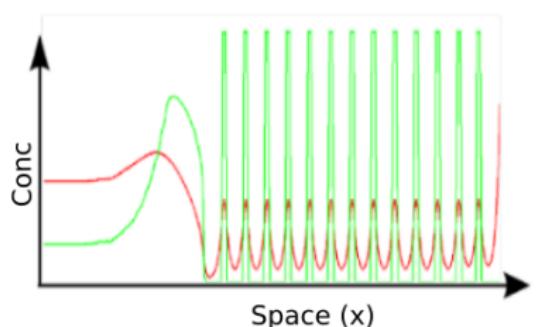


#### Authors

James Cotterell,  
Alexandre Robert-Moreno,  
James Sharpe

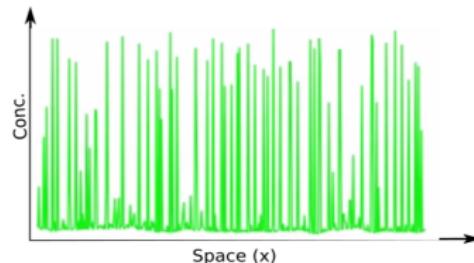
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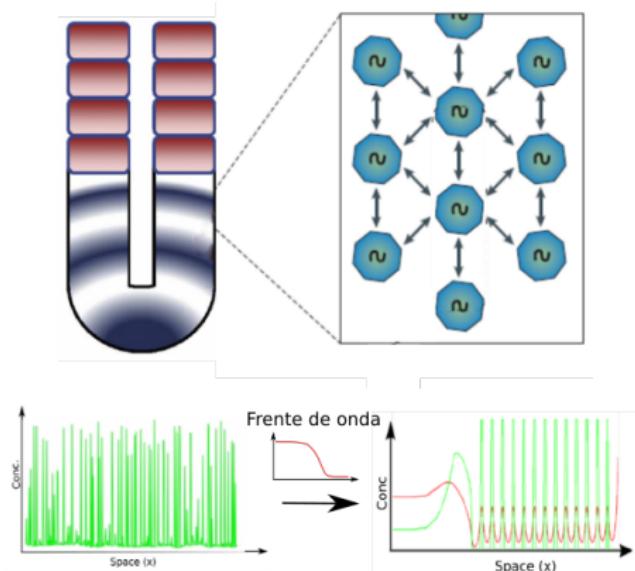


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James Sharpe



# Planteamiento del problema



- Tamaño de la red
- Número de conexiones
- Fuerza de conexión
- Variabilidad

# Hipótesis

## Hipótesis

La robustez espacio-temporal de la somitogénesis es afectada por interacciones a escala del tejido e interacciones a escala celular.

# Objetivos

## Objetivo General

Estudiar la dinámica espacio-temporal de la somitogénesis mediante dos modelos a diferente escala, uno a escala del tejido y otro a escala celular.

# Objetivos

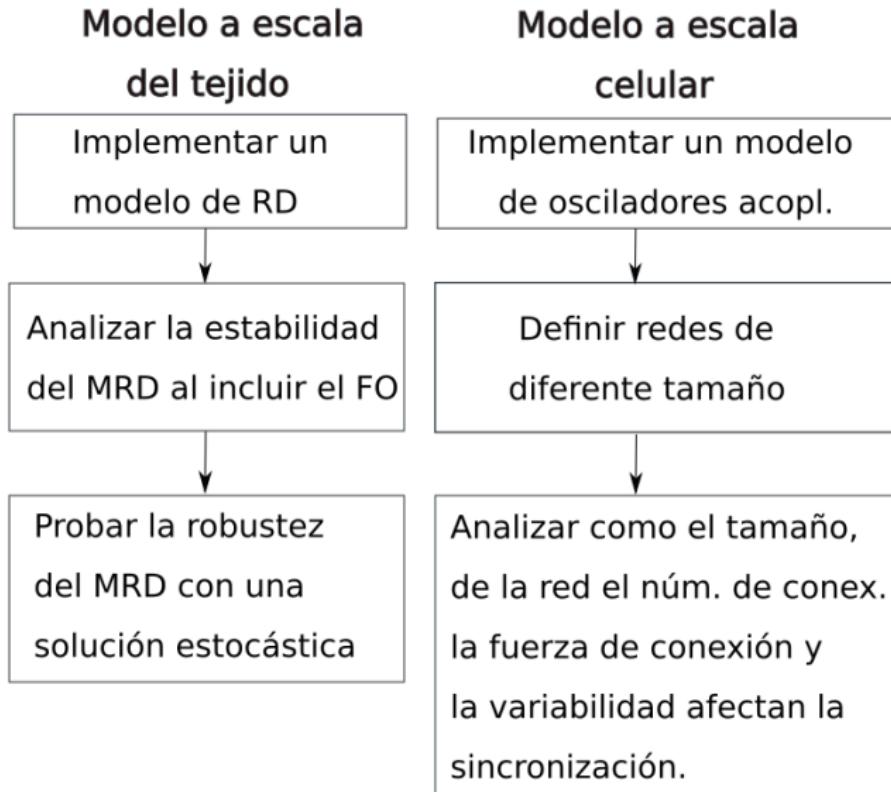
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Estudiar la dinámica espacio-temporal de la somitogénesis mediante dos modelos a diferente escala, uno a escala del tejido y otro a escala celular.

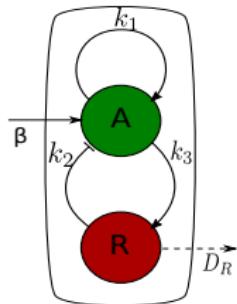
## Objetivos Particulares

- Estudiar la somitogénesis con un modelo a escala del tejido y analizar su estabilidad para caracterizar su robustez ante diferentes variaciones.
- Estudiar con un modelo a escala celular como el número de células, el nivel de conectividad, la fuerza de conexión y la variabilidad celular afectan la sincronización de las células del MPS.

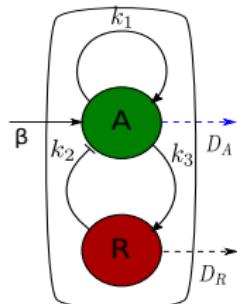
# Metodología



# Desarrollo del modelo

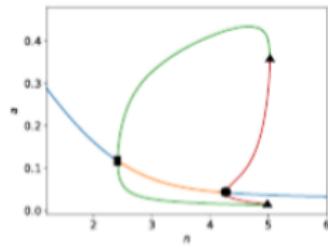
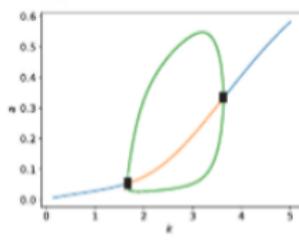
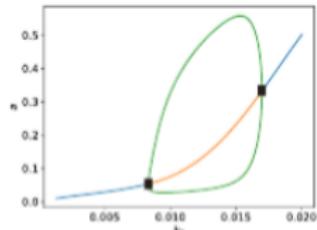
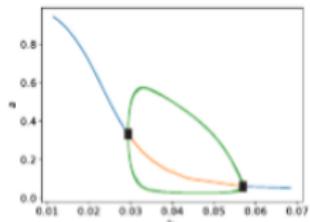
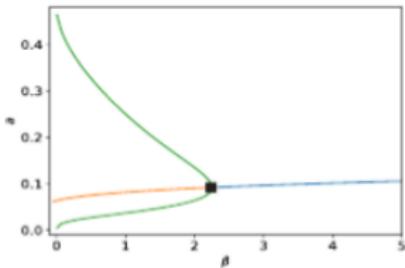


$$\begin{aligned}\frac{\partial A}{\partial t} &= \Phi \left( \frac{k_1 A - k_2 R + \beta}{1 + k_1 A - k_2 R + \beta} \right) - A \\ \frac{\partial R}{\partial t} &= \frac{k_3 A}{1 + k_3 A} + D_R \nabla^2 R - R\end{aligned}$$



$$\begin{aligned}\frac{\partial A}{\partial t} &= \frac{\beta + (A/k_1)^n}{1 + (A/k_1)^n + (R/k_2)^n} + D_A \nabla^2 A - A \\ \frac{\partial R}{\partial t} &= \frac{A/k_3}{1 + A/k_3} + D_R \nabla^2 R - R\end{aligned}$$

# Estimación de los parámetros

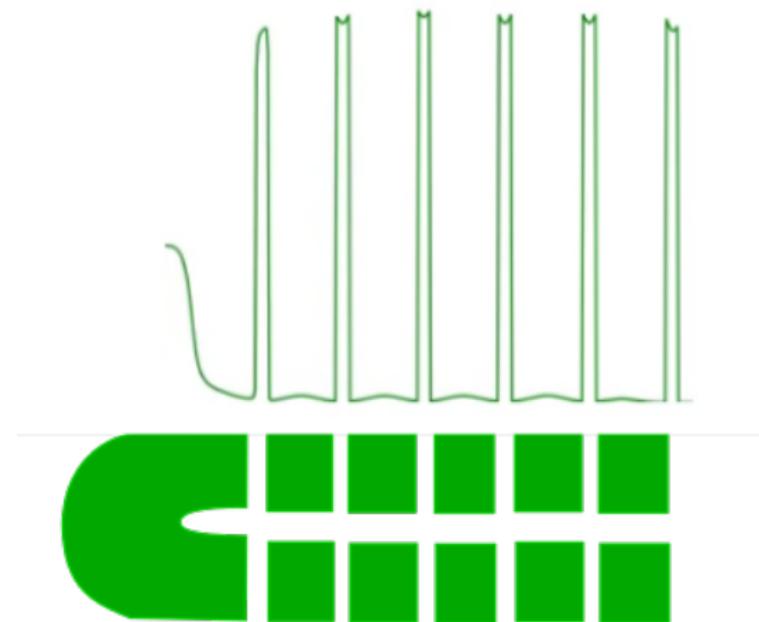


Parámetro	Intervalo
$k_1$	0.03-0.057
$k_2$	0.0085-0.017
$k_3$	1.65-3.65
$n$	2.4-4.2
$\beta$	.001-2.3

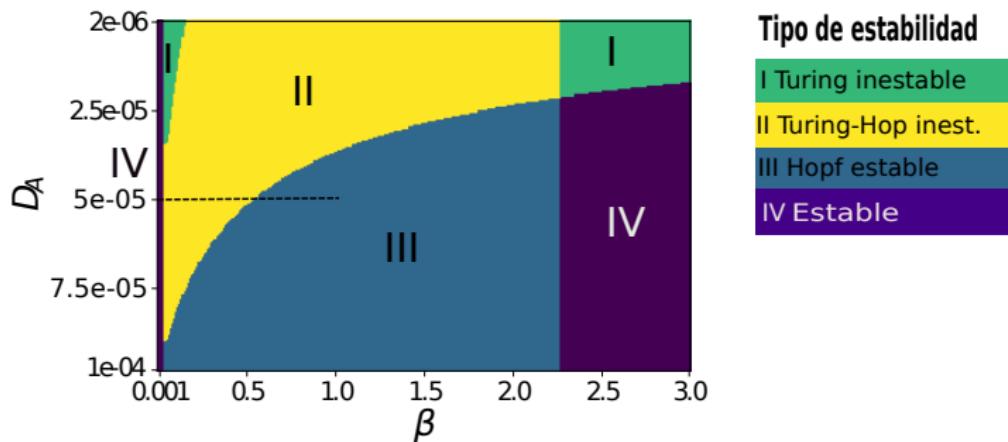
## Resultados. Validación del modelo.

$$k_1 = 0.05, k_2 = 0.01, k_3 = 2.0, \beta = 0.5, n = 3.0, D_R = 0.0025$$

## Resultados. Validación del modelo.

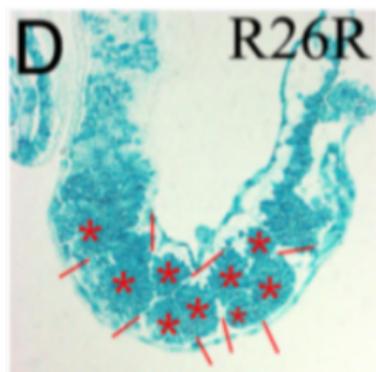
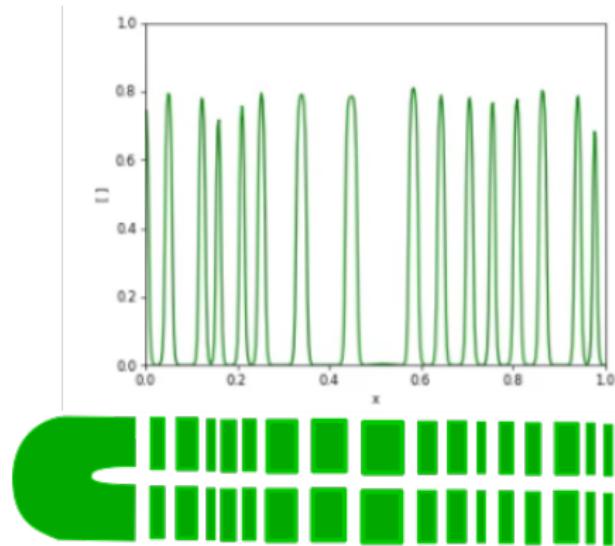


# Análisis de estabilidad espacio-temporal



# Resultados con $\beta = 0.1$

# Resultados $\beta = 0.1$



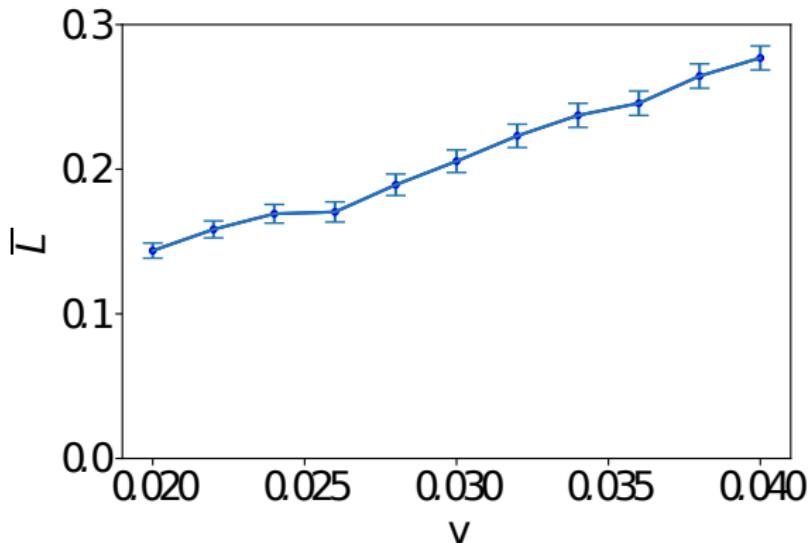
# Resultados con $\beta = 0.7$

## Efecto del FO v= 0.02

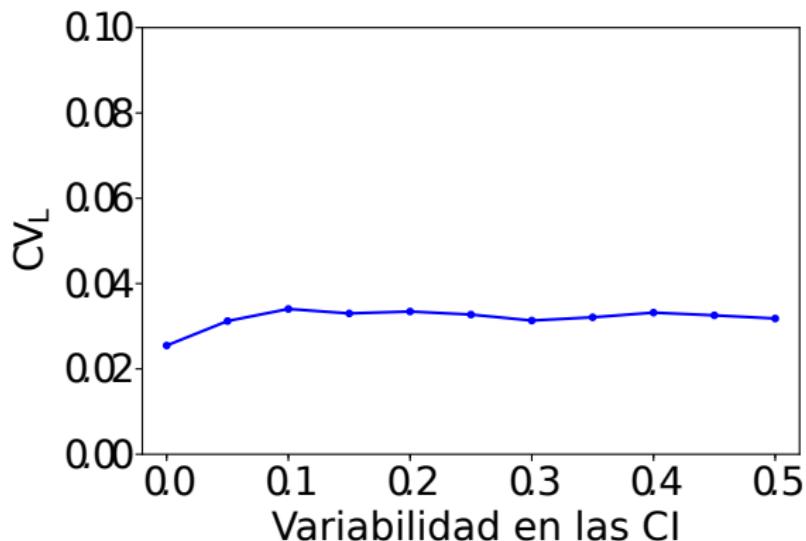
$$\beta = f(x, vt) = \frac{k^n}{k^n + (x - vt)^n}$$

# Efecto del FO con $v=0.04$

# Tamaño de los somitas en función de la velocidad del FO



# Robustez del tamaño de los somitas en función de la variabilidad en las CI

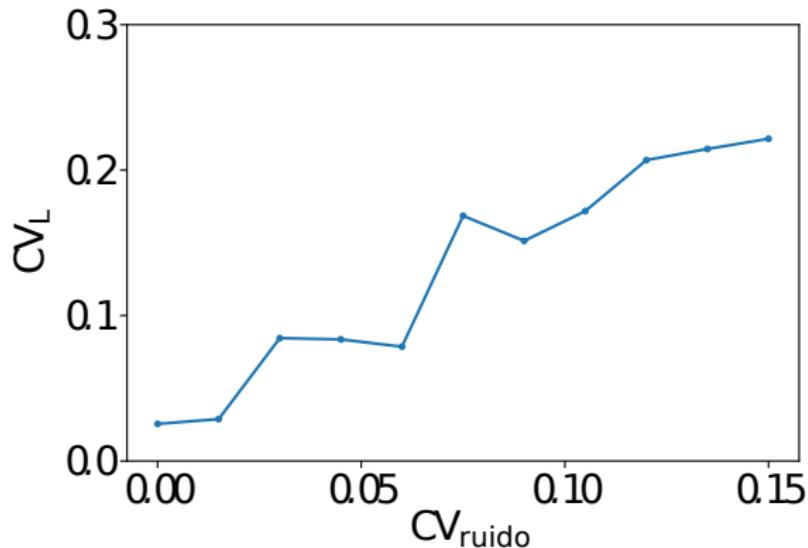


## Robustez al ruido con CV=5%

$$\begin{aligned}\frac{\partial A}{\partial t} &= \frac{\beta + (A/k_1)^n + R/k_2}{1 + (A/k_1)^n + (R/k_2)^n} + -A + D_A \nabla^2 A + C_V \bar{A} dW \\ \frac{\partial R}{\partial t} &= \frac{A/k_3}{1 + A/k_3} - R + D_R \nabla^2 R + C_V \bar{R} dW\end{aligned}$$

## Robustez al ruido con CV=10%

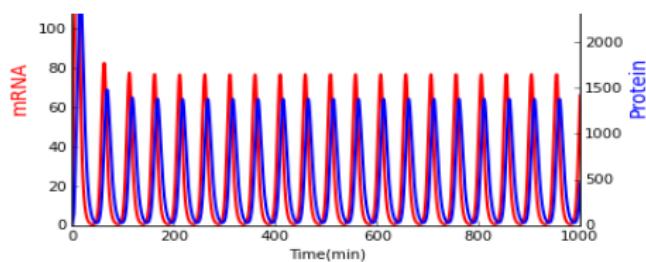
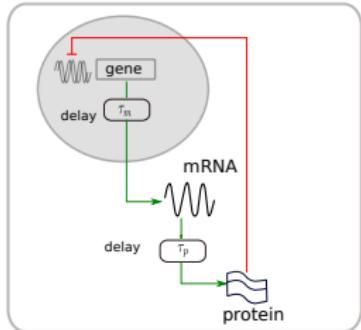
# Robustez del tamaño de los somitas en función del ruido



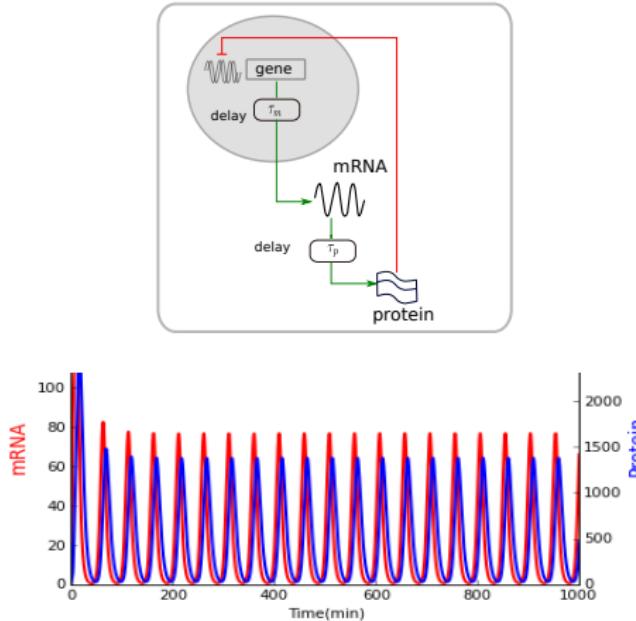
# Discusión MET

- El acoplamiento del frente de onda con el modelo a escala del tejido permiten eliminar la sensibilidad así como la dependencia de las condiciones iniciales, sin embargo, no son suficientes para explicar la robustez que exhibe la somitogénesis.
- Es posible que las interacciones a corto alcance involucradas en la sincronización de las células del MPS contribuyan en la robustez.

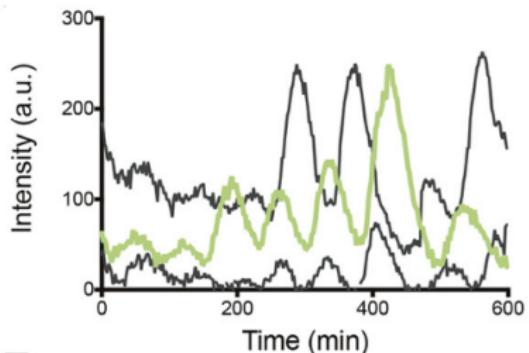
# Estudio a Escala celular, reloj de segmentación



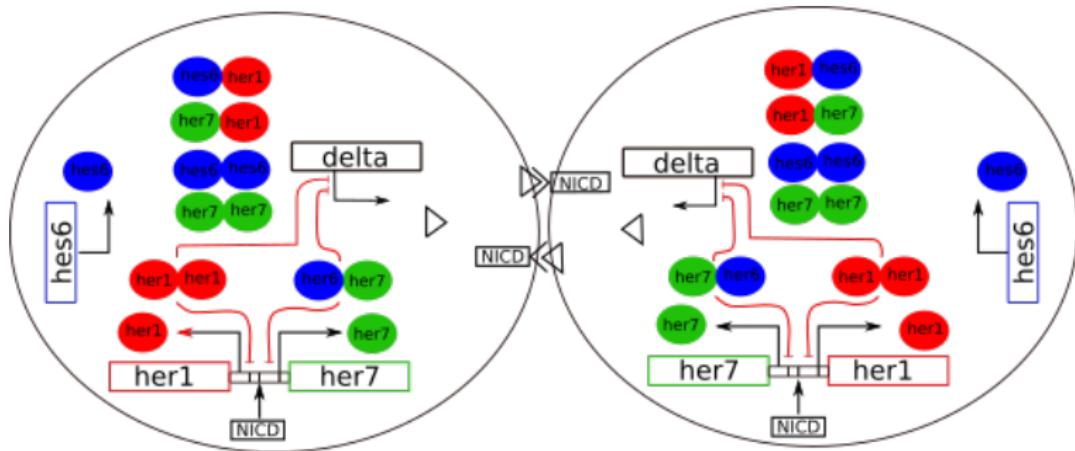
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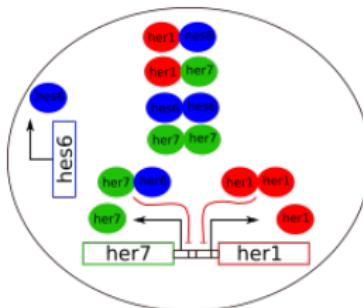
Modificado de Alexis B Webb et. al. (2016)



# Vía Delta-Notch y sincronización



# Desarrollo del modelo a escala celular



C. Schroter et. al. (2012). *Topology and Dynamics of the Zebrafish Segmentation Clock Core Circuit*

$$\frac{dH_1(t)}{dt} = \rho_1 \frac{1}{1 + (\frac{H_{11}(t-\tau_1)}{k_{11}} + \frac{H_{76}(t-\tau_1)}{k_{76}})^2} - c_1 H_1(t)$$

$$- 2a_{11} H_1(t)^2 + 2b_{11} H_{11}(t) - a_{16} H_1(t)H_6(t) + b_{16} H_{16}(t) - a_{17} H_1(t)H_7(t) + b_{17} H_{17}(t)$$

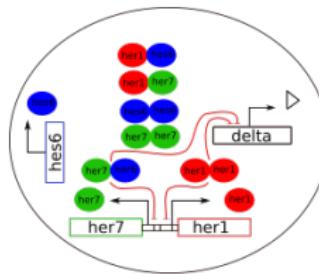
$$\frac{dH_6(t)}{dt} = \rho_6 - c_6 H_6(t)$$

$$- 2a_{66} H_6(t)^2 + 2b_{66} H_{66}(t) - a_{16} H_1(t)H_6(t) + b_{16} H_{16}(t) - a_{67} H_6(t)H_7(t) + b_{67} H_{67}(t)$$

$$\frac{dH_7(t)}{dt} = \rho_7 \frac{1}{1 + (\frac{H_{11}(t-\tau_7)}{k_{11}} + \frac{H_{76}(t-\tau_7)}{k_{76}})^2} - c_7 H_7(t)$$

$$- 2a_{77} H_7(t)^2 + 2b_{77} H_{77}(t) - a_{76} H_7(t)H_6(t) + b_{76} H_{76}(t) - a_{17} H_1(t)H_7(t) + b_{17} H_{17}(t)$$

# Modelo base con proteína Delta



$$\frac{dH_1(t)}{dt} = \rho_1 \frac{1}{1 + (\frac{H_{11}(t-\tau_1)}{k_{11}} + \frac{H_{76}(t-\tau_1)}{k_{76}})^2} - c_1 H_1(t)$$

$$- 2a_{11} H_1(t)^2 + 2b_{11} H_{11}(t) - a_{16} H_1(t)H_6(t) + b_{16} H_{16}(t) - a_{17} H_1(t)H_7(t) + b_{17} H_{17}(t)$$

$$\frac{dH_6(t)}{dt} = \rho_6 - c_6 H_6(t)$$

$$- 2a_{66} H_6(t)^2 + 2b_{66} H_{66}(t) - a_{16} H_1(t)H_6(t) + b_{16} H_{16}(t) - a_{67} H_6(t)H_7(t) + b_{67} H_{67}(t)$$

$$\frac{dH_7(t)}{dt} = \rho_7 \frac{1}{1 + (\frac{H_{11}(t-\tau_7)}{k_{11}} + \frac{H_{76}(t-\tau_7)}{k_{76}})^2} - c_7 H_7(t)$$

$$- 2a_{77} H_7(t)^2 + 2b_{77} H_{77}(t) - a_{76} H_7(t)H_6(t) + b_{76} H_{76}(t) - a_{17} H_1(t)H_7(t) + b_{17} H_{17}(t)$$

$$\frac{dD(t)}{dt} = \rho_D \frac{1}{1 + (\frac{H_{11}(t-\tau_D)}{k_{11}} + \frac{H_{76}(t-\tau_D)}{k_{76}})^2} - c_D D(t)$$

# Normalización del modelo

$$a_{\mu\nu} = a, b_{\mu\nu} = b, c_{\mu\nu} = c, k_{\mu\nu} = k$$

$$\alpha = ak/c, \beta = b/c, \gamma_i = \rho_i \delta / ck, s = ct$$

$$H_{\mu\nu}(t) = \delta H_\mu(t) H_\nu(t), \delta = (\alpha/(1 + \beta))^{1/2}$$

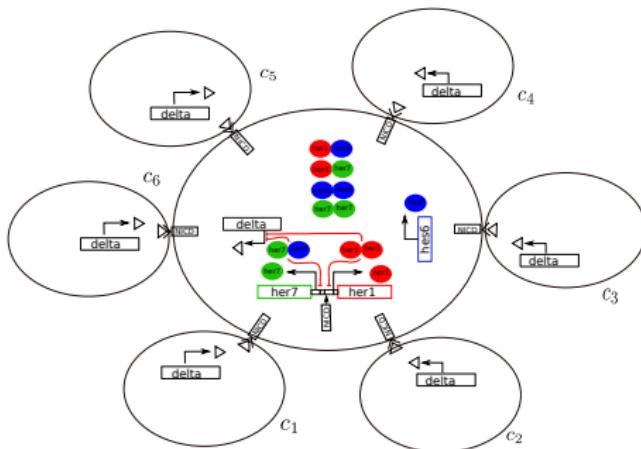
$$\frac{dh_1(s)}{ds} = \gamma_1 \frac{1}{1 + (h_1(s - \tau_1))^2 + h_7(s - \tau_1)h_6(s - \tau_1))^2} - h_1(s) - \delta(h_1(s)(2h_1(s) + h_6(s) + h_7(s)))$$

$$\frac{dh_6(s)}{ds} = \gamma_6 - h_6(s) - \delta h_6(s)(h_1(s) + 2h_6(s) + h_7(s))$$

$$\frac{dh_7(s)}{ds} = \gamma_7 \frac{1}{1 + (h_1(s - \tau_7))^2 + h_7(s - \tau_7)h_6(s - \tau_7))^2} - h_7(s) - \delta(h_7(s)(h_1(s) + h_6(s) + 2h_7(s)))$$

$$\frac{dD(s)}{ds} = \gamma_D \frac{1}{1 + (h_1(s - \tau_D))^2 + h_7(s - \tau_D)h_6(s - \tau_D))^2} - D(s)$$

# Ecuaciones para la interacción entre varias células



$$\frac{dh_1(s)}{ds} = \gamma_1 \frac{1}{1 + (h_1(s - \tau_1))^2 + h_7(s - \tau_1)h_6(s - \tau_1))^2} (g(\sum_j D_j)) - h_1(s) - \delta(h_1(s)(2h_1(s) + h_6(s) + h_7(s)))$$

$$\frac{dh_6(s)}{ds} = \gamma_6 - h_6(s) - \delta h_6(s)(h_1(s) + 2h_6(s) + h_7(s))$$

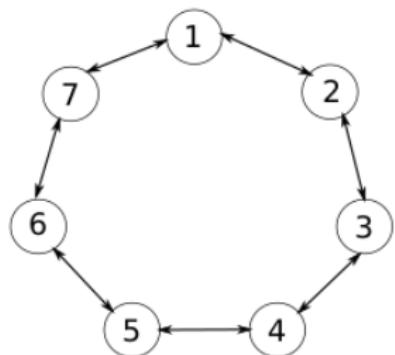
$$\frac{dh_7(s)}{ds} = \gamma_7 \frac{1}{1 + (h_1(s - \tau_7))^2 + h_7(s - \tau_7)h_6(s - \tau_7))^2} (g(\sum_j D_j)) - h_7(s) - \delta(h_7(s)(h_1(s) + h_6(s) + 2h_7(s)))$$

$$\frac{dD(s)}{ds} = \gamma_D \frac{1}{1 + (h_1(s - \tau_D))^2 + h_7(s - \tau_D)h_6(s - \tau_D))^2} - D(s)$$

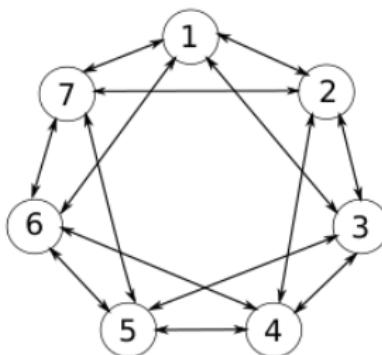
$$g(D) = \frac{D^2}{k_D^2 + D^2}$$

# Niveles de conexión

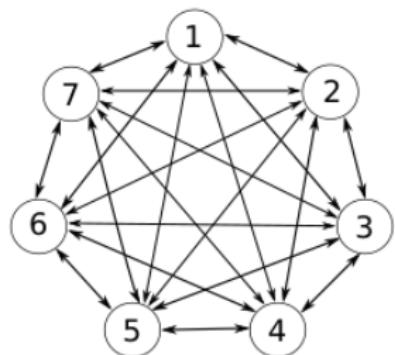
Nivel 1



Nivel 2



Nivel 3



## Parámetro de Orden y parámetros del modelo.

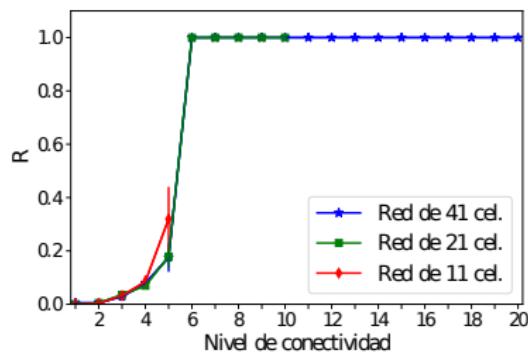
$$R = \frac{Var(M)}{Var(b_i)}$$

# Parámetro de Orden y parámetros del modelo.

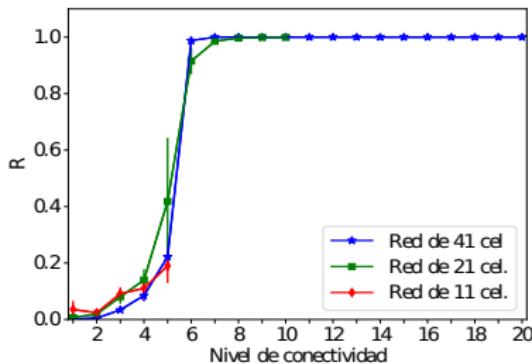
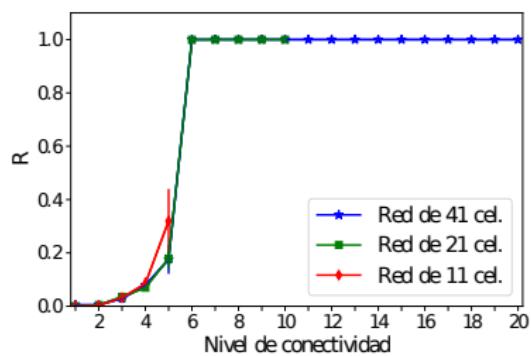
$$R = \frac{\text{Var}(M)}{\text{Var}(b_i)}$$

Parámetro	Valor	Ref.
$\gamma_1$	10.0	Scrotter et al.
$\gamma_6$	25.0	Scrotter et. al.
$\gamma_7$	10.0	Scrotter et. al
$\gamma_D$	2.0	Ahmet et. al.
$\delta$	1.0	Scrotter et. al.
$\tau_1$	1.02	Scrotter et. al.
$\tau_7$	1.00	Scrotter et. al.
$\tau_D$	0.85	Scrotter et. al.
$k_D$	1.0	Ahmet et. al.

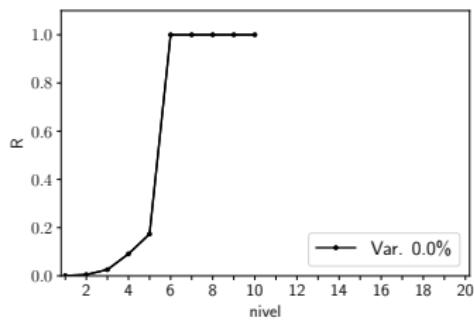
# Efecto del tamaño de la red y el número de conexiones en la sincronización



# Efecto del tamaño de la red y el número de conexiones en la sincronización

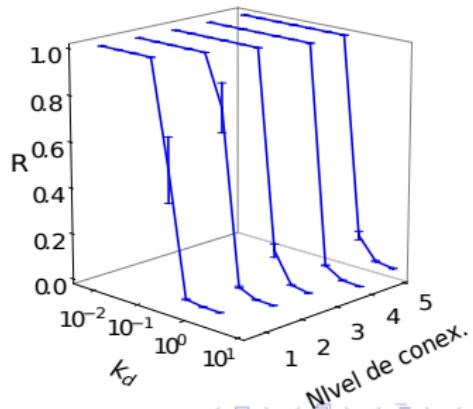


# Progresión de la sincronización

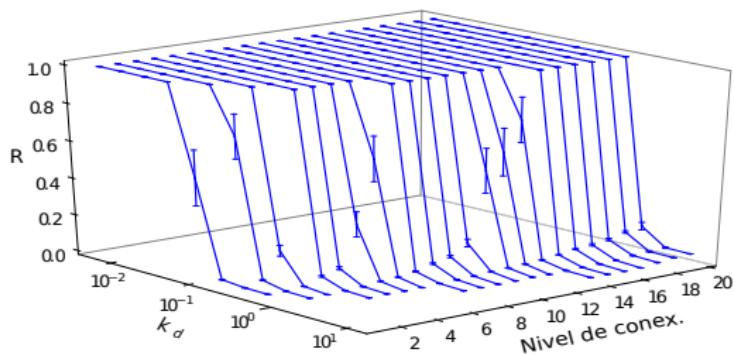
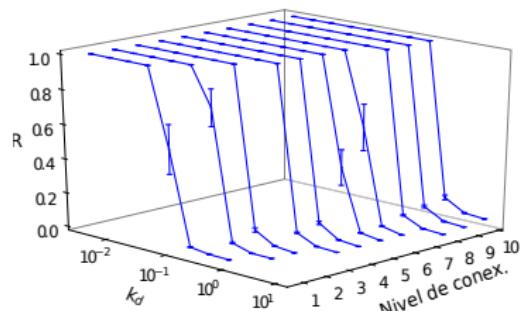


# Efecto de la fuerza de conexión en la sincronización. 11 cel.

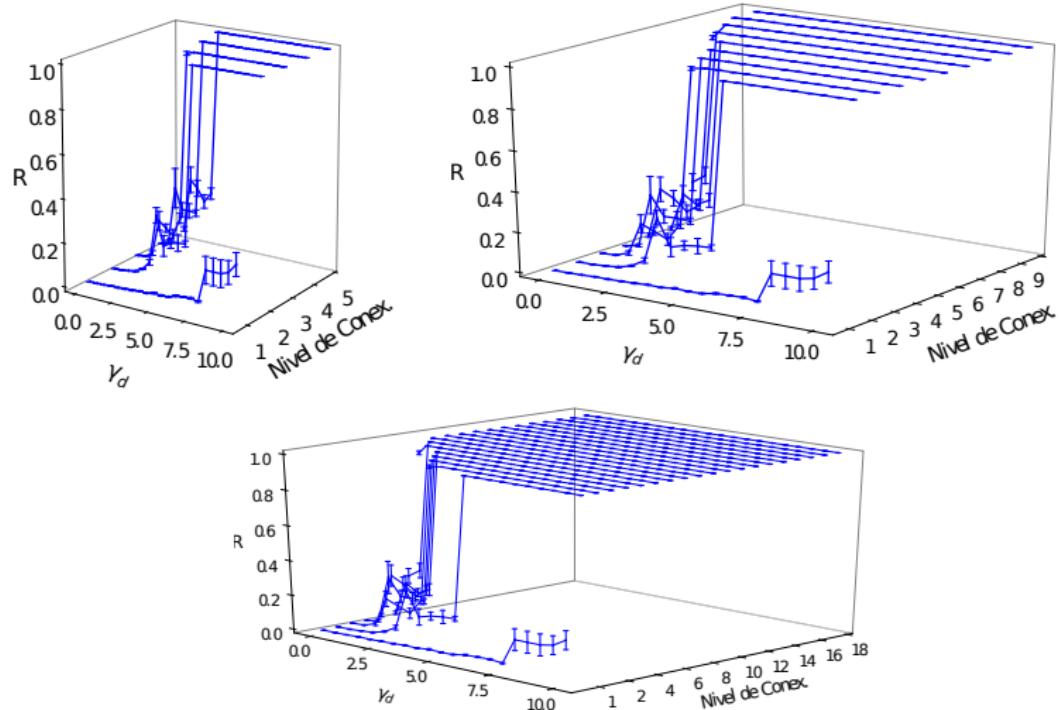
$$g(D) = \frac{D^2}{k_D^2 + D^2}; k_D = \frac{k_{disoc}}{k_{asoc}}$$



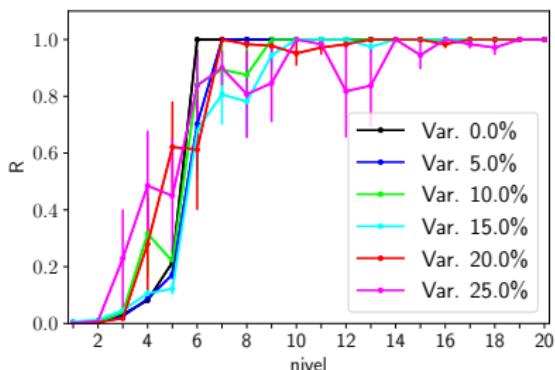
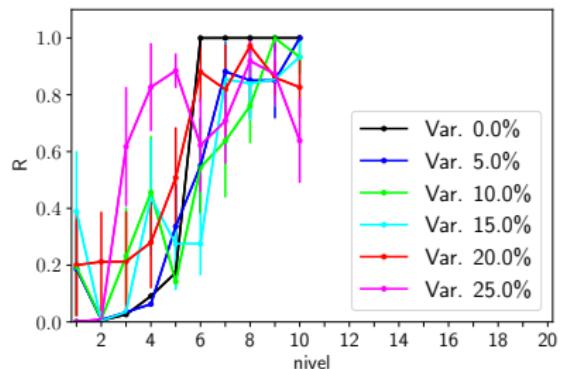
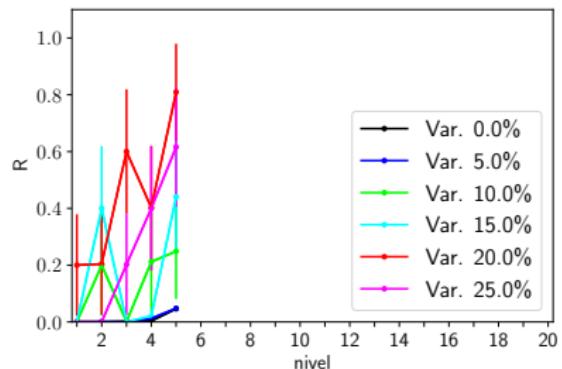
# Efecto de la fuerza de conexión en la sincronización. 21 y 41 cel.



# Efecto del parámetro $\gamma_D$ en la sincronización



# Robustez de la sincronización ante la variabilidad en las células del MPS.



## Discusión modelo escala celular

- Se requiere de una cantidad mínima de células para que se dé la sincronización.
- La disminución de la fuerza de conexión tiene un efecto negativo en la sincronización, pero este efecto es revertido al aumentar el número de conexiones.
- El incremento en el número de células da robustez a la sincronización ante la variabilidad.

# Conclusiones

- Para explicar la robustez observada en la somitogenesis es necesario considerar las interacciones tanto a escala celular como a escala del tejido.

# Perspectivas

- Plantear un modelo de reacción-difusión basado en las interacciones de las vías Wnt, FGF y Notch para identificar los posibles componentes que plantea el modelo a escala del tejido.

# Gracias.