

1 Model Development

We consider analysis of equations (1)–(3) presented in the Main Text. To recap, we define two dependent variables, $p(t)$ and $n(t)$, that are functions of time, t , and represent numbers of molecules of cytoplasmic clock protein and NICD, respectively. Although we do not explicitly describe the transcription of clock genes, we impose known transcriptional logic of clock gene expression in the mouse PSM to define the production rate of clock protein, i.e.

$$f(n, p) = \frac{\frac{n}{K_n}}{1 + \left(\frac{p}{K_p}\right)^2}. \quad (1)$$

This functional form captures the principles that NICD is necessary for transcription and clock protein represses transcription. We assume that the logic of transcriptional activation is such that the balance between clock protein and NICD sets the overall transcription rate.

The governing equations are given by

$$\frac{dp}{dt} = k_1 f(n(t - T_1), p(t - T_1)) - k_2 p(t), \quad (2)$$

$$\frac{dn}{dt} = k_3 f(n(t - T_2), p(t - T_2)) - k_4 n(t), \quad (3)$$

and all rate constants are assumed to be positive. The delay T_1 represents the time taken for changes in cytoplasmic protein number to affect the next round of protein synthesis (delays arising as a result of transcription, splicing and transport). The difference between T_2 and T_1 represents the additional time that elapses between the emergence of clock protein in the cytoplasm and the release of NICD from the cell membrane.

We rescale the dependent variables such that

$$\hat{p} = \frac{p}{K_p} \quad \hat{n} = \frac{n}{K_n}, \quad (4)$$

and, defining the parameters

$$\gamma_1 = \frac{k_1}{P} \quad \gamma_2 = \frac{k_3}{M}, \quad (5)$$

the governing equations are given by

$$\frac{d\hat{p}}{dt} = \gamma_1 \hat{f}(\hat{n}(t - T_1), \hat{p}(t - T_1)) - k_2 \hat{p}(t), \quad (6)$$

$$\frac{d\hat{n}}{dt} = \gamma_2 \hat{f}(\hat{n}(t - T_2), \hat{p}(t - T_2)) - k_4 \hat{n}(t), \quad (7)$$

where

$$\hat{f}(\hat{n}, \hat{p}) = \frac{\hat{n}}{1 + \hat{p}^2}. \quad (8)$$

For convenience, we now drop the hatted notation.

We seek the steady-states of equations (6)–(7) and find that they are given by the expressions

$$p_{ss} = 0, \quad \sqrt{\frac{\gamma_2}{k_4} - 1} \quad (9)$$

$$n_{ss} = 0, \quad \frac{\gamma_2 k_3}{\gamma_1 k_4} \sqrt{\frac{\gamma_2}{k_4} - 1}, \quad (10)$$

Hence if

$$\gamma_2 < k_4, \quad (11)$$

the trivial steady state is the only real steady state and it is linearly stable. If

$$\gamma_2 > k_4 \quad (12)$$

the trivial steady state becomes unstable and the non-trivial steady-state is real.

2 Model parameters

In order to determine model parameters we have used estimates from previous works and fitted parameters so that the model yields experimentally reasonable levels of molecules.

It has previously been assumed that the half life of clock repressor Hes7 is approximately 25 minutes [2]. We assume this value in order to determine the decay constant for Hes7 protein. Given the observations of NICD decay presented in the Main Text we set the NICD half life to be 12 minutes.

The IC50 constants are chosen based on previous estimates for the repression of Hes7 [3]. Note that in the rescaled model equations these parameters are absorbed into the production constants γ_1 and γ_2 hence do not qualitatively affect model behaviour. In previous models of the somitogenesis clock ([e.g. 3]) the number of mRNA molecules is explicitly defined and two delays are defined to represent processes such as transcription, splicing and export of mRNA to the cytoplasm and the translation of mRNA into the protein. As the goal of this model is to study the effect of protein half lives on the clock period, here we do not explicitly account for mRNA but the delays are incorporated in the parameter T_1 .

For the second delay parameter T_2 we assume that the release of NICD into the cytoplasm is downstream of protein, hence $T_2 > T_1$. Based upon observations of the relative positions of NICD and other clock components (data not shown) we approximate that this additional delay is 30 minutes. We choose the production rate k_1 such that there are order thousands of molecules as in previous studies [3]. The NICD production rate was then chosen to insure stable oscillations.

Parameter	Value	Unit
k_1	400	min^{-1}
k_2	0.03	min^{-1}
k_3	20	min^{-1}
k_4	0.06	min^{-1}
K_P	40	Nondimensional
K_N	40	Nondimensional
τ_1	40	min
τ_2	70	min

Table 1: Parameter values used to solve equations (2)–(3).

3 Numerical solution

Numerical solutions of equations (2)–(3) were calculated using Matlab’s delay differential equation solver ‘dde23’. In order to numerically calculate the oscillator period, initial histories $\{[p(t), n(t)] = [0, 1]; -T_2 < t < 0\}$ were applied and the numerical solution were computed until oscillations reached dynamic equilibrium. Hopf bifurcation were identified using the freely available package DDEBif [1].

References

- [1] Koen Engelborghs, Tatyana Luzyanina, and Giovanni Samaey. DDE-BIFTOOL v. 2.00: a Matlab package for bifurcation analysis of delay differential equations. *TW Reports*, page 61, 2001.
- [2] Yukiko Harima, Yoshiki Takashima, Yuriko Ueda, Toshiyuki Ohtsuka, and Ryoichiro Kageyama. Accelerating the tempo of the segmentation clock by reducing the number of introns in the *hes7* gene. *Cell reports*, 3(1):1–7, 2013.
- [3] Julian Lewis. Autoinhibition with transcriptional delay: a simple mechanism for the zebrafish somitogenesis oscillator. *Current Biology*, 13(16):1398–1408, 2003.