Universality in kinetic models of circadian rhythms in *Arabidopsis thaliana*

Yian Xu · Masoud Asadi-Zeydabadi · Randall Tagg · Orrin Shindell

Received: 30 November 2020 / Revised: 20 July 2021 / Accepted: 6 October 2021 / Published online: 18 October 2021
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract

Biological evolution has endowed the plant *Arabidopsis thaliana* with genetically regulated circadian rhythms. A number of authors have published kinetic models for these oscillating chemical reactions based on a network of interacting genes. To investigate the hypothesis that the *Arabidopsis* circadian dynamical system is poised near a Hopf bifurcation like some other biological oscillators, we varied the kinetic parameters in the models and searched for bifurcations. Finding that each model does exhibit a supercritical Hopf bifurcation, we performed a weakly nonlinear analysis near the bifurcation points to derive the Stuart–Landau amplitude equation. To illustrate a common dynamical structure, we scaled the numerical solutions to the models with the asymptotic solutions to the Stuart–Landau equation to collapse the circadian oscillations onto two universal curves—one for amplitude, and one for frequency. However, some models are close to bifurcation while others are far, some models are post-bifurcation while others are pre-bifurcation, and kinetic parameters that lead to a bifurcation in some models do not lead to a bifurcation in others. Future kinetic modeling can make use of our analysis to ensure models are consistent with each other and with the dynamics of the *Arabidopsis* circadian rhythm.

Keywords Circadian rhythms · *Arabidopsis thaliana* · Hopf bifurcation · Stuart–Landau equation

Mathematics Subject Classification 37M20 · 37N25 · 92B25 · 92D10

1 Introduction

Adapting to the 24-h light–dark cycle caused by the rotation of the Earth, plants have evolved endogenous circadian rhythms that control many of their biological functions...
Circadian rhythms are genetically regulated chemical reactions inside cells that cause chemical concentrations to rise and fall with daily periodicity. Over the past 15 years, eleven papers have proposed chemical kinetic models to govern the circadian oscillations in the laboratory plant *Arabidopsis thaliana* (Locke et al. 2005a, b, 2006; Zeilinger et al. 2006; Pokhilko et al. 2010, 2012, 2013; Fogelmark and Troein 2014; Ohara et al. 2015; Foo et al. 2016; De Caluwé et al. 2016). These sets of differential equations specify gene-interactions that were deduced through genetic experiments and include chemical reaction rate constants that were estimated by fits to experimental time series data (Bujdoso and Davis 2013; Chew et al. 2014; Johansson and Köster 2019).

As knowledge about the genetic regulation of circadian rhythms has increased, the models have become larger and more complicated: the original model of a two-gene feedback loop has seven differential equations and 28 parameters (Locke et al. 2005a), while the largest model of 12 genes has 35 differential equations with 122 parameters (Fogelmark and Troein 2014). Recent efforts have aimed to reduce the mathematical complexity of these models while retaining their dynamical features (Foo et al. 2016; De Caluwé et al. 2016; Tokuda et al. 2019; Foo et al. 2020).

Another body of literature studying circadian rhythms in *Arabidopsis* has focused on the spatiotemporal patterns formed when the genetic expression of individual cells are coupled together in the tissues of a live plant (Fukuda et al. 2007; Wenden et al. 2012; Fukuda et al. 2013; Endo et al. 2014; Takahashi et al. 2015; Endo 2016; Gould et al. 2018). Some studies employed phenomenological models like the Stuart–Landau amplitude equation (Fukuda et al. 2007) and the related Kuramoto coupled phase oscillator model (Kuramoto 1984; Takahashi et al. 2015; Gould et al. 2018). These coarse-grained descriptions are useful because they reduce the complicated dynamics of interacting gene networks with many rate constants to simple dynamical forms that contain only one or a few parameters. The parameters can then be fit to experimental results, a process recently proposed as a tool in agricultural engineering projects (Anpo et al. 2018).

In the present work, we employ a weakly nonlinear analysis method, the *Reductive Perturbation Method* (RPM) of Kuramoto (1984), to cast the *Arabidopsis* models into a two-dimensional form that is universally valid in systems poised near a Hopf bifurcation. The success of this approach is based on the fact that the published models are situated near supercritical Hopf bifurcation points in parameter space, a fact that may have biological significance: a nonlinear oscillator tuned near a Hopf bifurcation exhibits a resonance response when it is forced near its natural frequency (Mora and Bialek 2011; Munoz 2018). This mechanism confers sensitivity to some other biological oscillators, like the hair cells of the cochlea in the ears of humans (Eguíluz et al. 2000; Hudspeth et al. 2010) and frogs (Ospeck et al. 2001).

Near a Hopf bifurcation, the nonlinear equations governing the chemical oscillations may be linearized about a fixed point to give an approximate two-dimensional oscillating solution with a complex amplitude. The complex amplitude is governed by the Stuart–Landau equation whose parameter values are derived from a higher order expansion of the nonlinear system, and are therefore functions of the rate constants without free parameters (Hassard et al. 1981; Guckenheimer and Holmes 1983; Kuramoto 1984).
We perform the RPM calculation on the published circadian rhythms models for two reasons. The first is to show how to calculate the parameters appearing in the Stuart–Landau equation directly from the kinetic rate constants in the chemical kinetic models. This calculation suggests experimental routes to drive bifurcations in circadian rhythms by manipulating kinetic parameters, a useful method in pattern formation experiments and plant engineering projects. The second reason is to quantify the essential dynamical features that models should aim to capture in addition to the oscillation period: the eigenvalues of the linearized system indicate whether the model is post-bifurcation or pre-bifurcation; the dependence of the eigenvalues on the kinetic rate constants show which rate constants lead to bifurcation; and the error between the perturbation solution and numerical solution to the full kinetic equations provides a measure of the proximity of the model to Hopf bifurcation. These dynamical quantities should be consistent between models and with the circadian rhythms of the organism.

Our paper is organized into two sections. In the Methods and Results section we summarize the Reductive Perturbation Method and show how to apply it to one of the circadian rhythms models. Then we illustrate the universal structure underlying the kinetic models. Finally, in the Discussion we point out inconsistencies between the kinetic models and suggest experimental and modeling approaches that could give additional information about the chemical dynamics of the *Arabidopsis* circadian rhythm.

### 2 Methods and results

#### 2.1 Hopf bifurcations in the circadian rhythms models

The *Arabidopsis* circadian rhythms models we considered are sets of coupled, nonlinear, first-order, ordinary differential equations. All of these models explicitly incorporate time dependence as a 24-h periodic function. To investigate the dynamics of the endogenous chemical oscillations, we chose to make the differential equations autonomous by assuming perpetual darkness (Tokuda et al. 2019) or perpetual illumination (Fukuda et al. 2013). The autonomous equations may be expressed in the general form,

$$\frac{dx}{dt} = f(x; \mu) \quad (1)$$

where $x$ is an $n$-dimensional vector of chemical concentrations associated with the circadian reactions, $f$ is a nonlinear $n$-dimensional vector-valued function specifying the chemical reactions in a model, and $\mu$ is a function of one of the rate constants in the reaction equations. Using the kinetic rate constants as bifurcation parameters differs from previous work that studied time delay models for circadian rhythms and used the time delay constant as a Hopf bifurcation parameter (Xiao and Cao 2008).

Each of the circadian rhythms models we studied exhibits a supercritical Hopf bifurcation. Near $\mu = 0$, with $\mu$ suitably defined, the system of equations Eq. (1)
possesses a fixed point, i.e., a constant solution \( X_0 \) that satisfies

\[
f(X_0; \mu) = 0
\]  

(2)

At the bifurcation point \( \mu = 0 \), the fixed point switches linear stability: in the pre-bifurcation region \( \mu < 0 \), \( X_0 \) is stable, and in the post-bifurcation region \( \mu > 0 \), \( X_0 \) is unstable. When the system is post-bifurcation, in addition to an unstable fixed point, it possess a stable limit cycle, i.e., a linearly stable periodic solution \( X(t) \) that satisfies

\[
\frac{dX}{dt} = f(X; \mu), \quad X(t) = X(t + T)
\]  

(3)

for some period \( T \). The limit-cycle dynamics near a Hopf bifurcation belong to a dynamical universality class: for \( \mu \gtrapprox 0 \), the amplitude of the limit cycle oscillations scales in proportion to \( \sqrt{\mu} \) and the frequency in proportion to \( \mu \). These properties enable an approximation to the amplitude and frequency of the limit cycle that is valid near the bifurcation point.

For a concrete example from the literature, we consider here the original model (L2005a) presented in Locke et al. (2005a), which assumes a single negative feedback interaction between two core circadian genes: \textit{LATE ELONGATED HYPO-COTYL} (\textit{LHY}), which is partially redundant with \textit{CIRCADIAN CLOCK ASSOCIATED 1}, and \textit{TIMING OF CAB EXPRESSION 1} (\textit{TOC1}) (Alabadí et al. 2001). A bifurcation diagram for L2005a is displayed in Fig. 1(f) in Tokuda et al. (2019), where the reaction rates given in the caption of Fig. 4 of Locke et al. (2005a). We use this same parameter set in the analysis presented in this subsection and the next. As the transcription rate of \textit{LHY} is varied in perpetual darkness, a supercritical Hopf bifurcation occurs.

In Fig. 1a, we compare the bifurcation diagram for the levels of \textit{LHY} mRNA calculated analytically with RPM (discussed in more detail in the next subsection) to the numerical solution obtained using the differential equation solver MATLAB ODE15s (Shampine and Reichelt 1997). The \textit{LHY} transcription rate is normalized so that a value of unity corresponds to the fitted parameter value 7.5038 nM/h (Tokuda et al. 2019). In Fig. 1b, we compare the frequency of oscillations calculated analytically with the results obtained numerically. At the biological value of the \textit{LHY} transcription rate, the RPM calculation matches the amplitude and frequency determined by the numerical solution to the system of differential equations to within 0.86% for the amplitude and 0.45% for the frequency. In the Supplementary Materials, we show bifurcation diagrams for concentration and frequency of the other post-bifurcation models; as a measure of how close each model is poised to bifurcation we calculate the percent differences in amplitude and frequency between the numerical calculation and the RPM calculation at the fitted parameter values reported for each model.

2.2 Reductive perturbation method and the Stuart–Landau amplitude equation

In dynamical systems that undergo a Hopf bifurcation, an approximate two-dimensional periodic solution, valid near the bifurcation point, may be derived
Fig. 1 Bifurcation in a concentration and b frequency of circadian oscillations in a model (L2005a) poised near a supercritical Hopf bifurcation. The transcription rate of \( \text{LHY} \) is normalized such that the estimated biological value is unity; the bifurcation occurs at 0.9785. a The central branch is the fixed point, which is stable to the left of 0.9785 (closed circles) and unstable to the right (open circles). The upper and lower branches are the maximum and minimum values of \( \text{LHY} \) mRNA limit cycle oscillations, calculated numerically (closed blue circles) and perturbatively (orange line). b The limit cycle frequency is calculated numerically (blue hash marks) and perturbatively (orange line) (color figure online)

(Hassard et al. 1981; Kuramoto 1984). This stems from the fact that one pair of complex conjugate eigenvalues of the Jacobian matrix have positive real parts, while all the other eigenvalues have negative real parts. The two eigenmodes associated with the former dominate the long-time behavior of the system, as the modes associated with the latter decay to zero.

The system of equations Eq. (1) may be linearized about the fixed point \( \mathbf{X}_0 \), to give

\[
\frac{d \mathbf{u}}{dt} = \mathbf{L} \mathbf{u}, \quad \mathbf{u} = \mathbf{x} - \mathbf{X}_0, \quad L_{ij} = \left. \frac{\partial f_i}{\partial x_j} \right|_{(\mathbf{X}_0, \mu)}
\]

(4)

where \( \mathbf{u} \) is the deviation from the fixed point and \( \mathbf{L} \) is the Jacobian matrix. At the bifurcation point \( \mu = 0 \), the Jacobian matrix possesses \( n \) eigenvalues with \( n \) associated eigenvectors (the systems we studied had no repeated eigenvalues), with two of the eigenvalues purely imaginary. Thus, at bifurcation,

\[
\mathbf{L}_0 \mathbf{U} = i \omega_0 \mathbf{U}
\]

(5)

where \( \mathbf{L}_0 \) is the Jacobian matrix evaluated at \( \mu = 0 \) and \( \mathbf{U} \) is the eigenvector corresponding to the eigenvalue \( i \omega_0 \), with the complex conjugate eigenvector \( \mathbf{U} \) corresponding to the eigenvalue \( -i \omega_0 \). Near the bifurcation point in the post-bifurcation region, the linearized system has two eigenvalues with positive real parts that dominate the dynamics of system, as the remaining \( n - 2 \) eigenvalues have strictly negative real parts. There is the approximate eigenvalue equation

\[
(\mathbf{L}_0 + \mu \mathbf{L}_1) \mathbf{U} = (i \omega_0 + \mu \lambda_1) \mathbf{U}, \quad \lambda_1 = \sigma_1 + i \omega_1, \quad \sigma_1 > 0
\]

(6)

where \( \mathbf{L}_1 \) is the first-order term of the Taylor expansion of \( \mathbf{L} \) about \( \mu = 0 \), and \( \lambda_1 \) is the first-order term in the Taylor series about \( \mu = 0 \) of the eigenvalue of \( \mathbf{L} \) whose zeroth-order term is \( i \omega_0 \), with \( \sigma_1 \) the real part and \( \omega_1 \) the imaginary part. For \( \mu \gtrsim 0 \), the solution \( \mathbf{x}(t) \) takes the approximate form
Fig. 2 Time series (a) and phase space plot (b) are calculated numerically (ODE) and perturbatively (RPM) for a model (L2005a) poised near a supercritical Hopf bifurcation

\[
x = X_0 + \sqrt{\mu} \left[ W(t) e^{i\omega_0 t} + \bar{W}(t) e^{-i\omega_0 t} \right]
\]  

(7)

where \( W \) is a complex amplitude, with \( \bar{W} \) the complex conjugate, that evolves according to the Stuart–Landau equation

\[
\frac{dW}{dt} = \mu \left( \lambda_1 W - g |W|^2 W \right), \quad g = g' + ig'', \quad g' > 0
\]  

(8)

The complex number \( g \) is a function of the higher order expansion coefficients of Eq. (1). We refer to Kuramoto (1984) for the details leading to Eqs. (7) and (8). Equation (8) can be split into two equations by setting \( W(t) = R(t) e^{i\Theta(t)} \), with \( R(t) \) and \( \Theta(t) \) both real, which lead to the asymptotic quantities

\[
R_s = \lim_{t \to \infty} R = \sqrt{\frac{\sigma_1}{g'}},
\]

(9)

\[
\omega_s = \lim_{t \to \infty} \frac{d\Theta}{dt} = \left( \omega_1 - g'' R_s^2 \right)
\]

The limit cycle in the post-bifurcation region is thus approximately given by

\[
x = X_0 + \sqrt{\mu} R_s \left[ U e^{i(\omega_0+\mu\omega_s)t} + \bar{U} e^{-i(\omega_0+\mu\omega_s)t} \right]
\]  

(10)

which describes an elliptical orbit in a two-dimensional subspace of \( \mathbb{R}^n \). In Fig. 2a, we compare the time series given by the limit cycle prediction of Eq. (10) to the numerically computed solution for the mRNA concentration of the central gene LHY.

The phase differences between different chemical species in the circadian system, which are important to biological function (Locke et al. 2005a), can be estimated directly from the eigenvector \( U \). In Fig. 2b, we plot phase space diagrams for LHY protein and LHY mRNA oscillations. The phase difference between the pair of chemical species deviates from those obtained from numerical solutions; as a fraction of \( 2\pi \) the absolute value of the difference in phase difference is 0.003. In the Supplementary
Fig. 3 Amplitude (upper) and frequency (lower) of limit cycle oscillations for ten models of *Arabidopsis* circadian rhythms are collapsed onto universal functions of the bifurcation parameter $\mu$. The limit cycle amplitude and frequency calculated numerically with ODE solvers are scaled with the asymptotic solutions to the Stuart–Landau equation. Data for each model is shown up to the value of $\mu$ that they diverge from one of the universal curves by 10%

Materials, we show time series and phase space plots for the other post-bifurcation models.

### 2.3 Scaling and data collapse

The parameters appearing in the Stuart–Landau equation, which result from the values of the kinetic rate parameters in the circadian reactions, set natural scales for the chemical oscillations in the circadian rhythms models. Exactly at the bifurcation point, the system exhibits zero amplitude oscillations about the fixed point $X_0$ with frequency $\omega_0$. As the system deviates from the bifurcation point with increasing $\mu$, the limit cycle amplitudes of the oscillating chemicals increase in proportion $\sqrt{\mu}R_s$ while their frequency changes from $\omega_0$ by $\mu\omega_s$. There is an arbitrariness in the calculation of these parameters, however, as the eigenvectors in Eq. (5) are unique only up to a multiplicative constant. To set an exact scale, we chose to normalize the eigenvectors by the component with the largest modulus, which sets $\sqrt{\mu}2R_s$ as an upper bound for the chemical oscillation amplitudes. With this definition, Eq. (10) implies that the amplitude $A$ and frequency $\omega$ for the largest amplitude chemical species in the limit cycle regime can be collapsed onto parameter-free curves near $\mu = 0$:

$$\frac{A}{2R_s} = \sqrt{\mu},$$

$$\frac{\omega - \omega_0}{\omega_s} = \mu$$

In Fig. 3, we show the amplitude $A$ and frequency $\omega$ of circadian oscillations in perpetual illumination for ten of the eleven models determined using MATLAB ODE solvers (Shampine and Reichelt 1997) scaled by $R_s$ and $\omega_s$ into the forms of Eq. (11). We neglected the model given in Locke et al. (2006) because the reported parameter set
gave two pairs of complex eigenvalues with positive real parts. In the Supplementary Materials, we collapse data from the same ten models in perpetual darkness, and show the collapsed data for each model separately.

For each system, we had to decide which rate parameter to use to define $\mu$, as each system contains more than one parameter whose variation leads to a Hopf bifurcation. To choose which was appropriate, we referenced research that suggests the circadian rhythms in Arabidopsis are sensitive to the degradation rates of mRNA (Yakir et al. 2007). Thus we confined ourselves to using chemical degradation rates as bifurcation parameters.

Of the models we analyzed, the majority employ Michaelis-Menten kinetics (Murray 2013) to govern the degradation rates of mRNA and protein. A few models use constant degradation rates. We varied the maximum degradation rates in the Michaelis-Menten kinetics or the constant degradation rates one at a time while keeping all other parameters constant. Whenever the variation of one of these parameters led to a Hopf bifurcation, we defined the parameter value at bifurcation as $m_c$. Motivated by the original work of Stuart (Stuart 1958), we further defined a dimensionless bifurcation parameter,

$$\mu_m = \frac{m_c - m}{m_c}$$

For each model, we investigated the amplitude and frequency scaling (Eq. (11)) for each $\mu_m$. As each $\mu_m$ increased from zero, the scaled quantities deviated from the universal curves. For the purpose of illustration, we present results in Fig. 3 using the bifurcation parameter $\mu$ defined to be the $\mu_m$ that was largest when the one of the two scaled quantities deviated from the predicted value by ten percent. We note that we did not find a single degradation rate that led to a bifurcation in all the models.

3 Discussion

In this work, we demonstrated that the published dynamical systems models for circadian rhythms in Arabidopsis thaliana possess supercritical Hopf bifurcations. We further employed the Reductive Perturbation Method (RPM) of Kuramoto (1984) to derive an approximate two-dimensional form for the chemical oscillations of the models in the post-bifurcation region of parameter space with a complex amplitude governed by the Stuart–Landau equation. By scaling the amplitude and frequency of the numerical limit cycle solutions with the asymptotic solutions to the Stuart–Landau equation, we showed that all the models possess a common phase space near the Hopf bifurcation.

There are nevertheless significant differences between the models that warrant discussion. Each of the models we investigated contain many rate parameters that were fit to experimental data. The results of these fits vary. Some of the systems we studied are situated on the pre-bifurcation side of a Hopf bifurcation, and others on the post-bifurcation side. Moreover, rate constants that lead to a Hopf bifurcation when varied in some models do not lead to a Hopf bifurcation when varied in other models.
We can suggest a possible experimental path to address whether *Arabidopsis* circadian oscillations are post-bifurcation or pre-bifurcation; namely, by driving a plant with a periodic light signal at the free-running frequency over a range of weak intensities. The oscillation amplitude of a pre-bifurcation system should increase linearly with the light intensity while the oscillation amplitude of a post-bifurcation system should not change. In the Supplementary Materials, we show numerical amplitude response curves for both sinusoidal and square-wave forcing.

A second way the models differ is in how close each is to the Hopf bifurcation with their given parameter values, which we measured by comparing the numerical solution to the RPM approximation. The limit cycle amplitude in the model from Locke et al. (2005a) presented in the “Methods and results” section matched the RPM calculation to within 0.8% while the limit cycle amplitude from Pokhilko et al. (2010) shown in Supplementary Materials differed from the RPM calculation by 45.02%. Despite all the differences in the models, including that the genetic network architecture and numerical values of rate constants differed significantly, we showed the dynamical structure of all the models near the bifurcation point is the same. This should be useful in future efforts to fit experimental data close to a supercritical Hopf bifurcation. An experiment that measures a bifurcation curve by varying an external parameter could yield the eigenvalues, eigenvectors, and parameters appearing in Eq. (10). Those quantities could then be used to verify the accuracy of the parameter choices in a particular kinetic model.

Our method of analysis may find application in agricultural engineering projects that use coarse-grained models as valid approximations to weakly nonlinear dynamics to describe an organism-level response to an external stimulus. By using RPM, we are able to arrive at a coarse-grained form, i.e., the Stuart–Landau equation, as a function of the underlying details of the circadian gene network. The driven Stuart–Landau equation predicts a resonance response of the oscillations that is most pronounced at the Hopf bifurcation point (Eguíluz et al. 2000). This resonance behavior near bifurcation suggests a possible engineering program where the chemical kinetics of the organism is tuned, perhaps by varying temperature, to be near the bifurcation point and then driven with a small amplitude (i.e., a low power), sinusoidal light source.

Finally, in recent experiments the circadian oscillations in the cyanobacterium *Synechococcus elongatus* were shown to exhibit a supercritical Hopf bifurcation with temperature as the bifurcation parameter (Murayama et al. 2017). It has long been noted that commonalities exist in the circadian rhythms of disparate organisms (Pittendrigh 1960). We tentatively suggest that close proximity to a supercritical Hopf bifurcation may be an additional property favored in the evolutionary development of circadian rhythms. If this suggestion is true, then as we have demonstrated by using the *Reductive Perturbation Method*, circadian rhythms can be cast into a generic mathematical form given by the Stuart–Landau equation.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00285-021-01677-0.

**Acknowledgements** The authors would like to thank Harry L. Swinney for a critical reading of the manuscript and helpful conversations. This research was funded by Trinity University with a Murchison Fellowship to Y.X. and start-up funds to O.S.
Code availability  The MATLAB code to replicate the calculations in this work is available on GitHub at https://github.com/oshindel/Reductive-Perturbation-Method-A.-thaliana.

Declarations

Conflict of interest  The authors declare that they have no conflict of interest.

References

Alabadi D, Oyama T, Yanovsky MJ, Harmon FG, Más P, Kay SA (2001) Reciprocal regulation between
toc1 and lhy/cca1 within the Arabidopsis circadian clock. Science 293(5531):880–883
Anpo M, Fukuda H, Wada T (2018) Plant factory using artificial light: adapting to environmental disruption
and clues to agricultural innovation. Elsevier
Bujdoso N, Davis SJ (2013) Mathematical modeling of an oscillating gene circuit to unravel the circadian
clock network of Arabidopsis thaliana. Front Plant Sci 4:3
Chew YH, Smith RW, Jones HH, Seaton DD, Grima R, Halliday KJ (2014) Mathematical models light up
plant signaling. Plant Cell 26(1):5–20
De Caluwé J, Xiao Q, Hermans C, Verbruggen N, Leloup JC, Gonze D (2016) A compact model for the
complex plant circadian clock. Front Plant Sci 7:74
Eguíluz VM, Ospeck M, Choe Y, Hudspeth A, Magnasco MO (2000) Essential nonlinearities in hearing.
Phys Rev Lett 84(22):5232
Endo M (2016) Tissue-specific circadian clocks in plants. Curr Opin Plant Biol 29:44–49
Endo M, Shimizu H, Nohales MA, Araki T, Kay SA (2014) Tissue-specific clocks in Arabidopsis show
asymmetric coupling. Nature 515(7527):419–422
Fogelmark K, Troein C (2014) Rethinking transcriptional activation in the Arabidopsis circadian clock.
PLoS Comput Biol 10(7):e1003,705
Foo M, Somers DE, Kim PJ (2016) Kernel architecture of the genetic circuitry of the Arabidopsis circadian
system. PLoS Comput Biol 12(2):e1004,748
Foo M, Bates DG, Akman OE (2020) A simplified modelling framework facilitates more complex repre-
sentations of plant circadian clocks. PLoS Comput Biol 16(3):e1007,671
Fukuda H, Nakamichi N, Hisatsune M, Murase H, Mizuno T (2007) Synchronization of plant circadian
oscillators with a phase delay effect of the vein network. Phys Rev Lett 99(9):098–102
Fukuda H, Murase H, Tokuda IT (2013) Controlling circadian rhythms by dark-pulse perturbations in
Arabidopsis thaliana. Sci Rep 3:1533
Gould PD, Domijan M, Greenwood M, Tokuda IT, Rees H, Kozma-Bognar L, Hall AJ, Locke JC (2018)
Coordination of robust single cell rhythms in the Arabidopsis circadian clock via spatial waves of
gene expression. Elife 7(e31):700
Guckenheimer J, Holmes P (1983) Local bifurcations. In: Nonlinear oscillations, dynamical systems, and
bifurcations of vector fields. Springer, pp 117–165
Hassard BD, Kazarinoff ND, Wan YH (1981) Theory and applications of Hopf bifurcation, vol 41. CUP
Archive
Hudspeth A, Jülicher F, Martin P (2010) A critique of the critical cochlea: Hopf’s bifurcation is better than
none. J Neurophysiol 104(3):1219–1229
Johansson M, Köster T (2019) On the move through time—a historical review of plant clock research. Plant
Biol 21:13–20
Kuramoto Y (1984) Chemical oscillations, waves, and turbulence. Springer-Verlag, Berlin
Locke JC, Millar AJ, Turner MS (2005a) Modelling genetic networks with noisy and varied experimental
data: the circadian clock in Arabidopsis thaliana. J Theor Biol 234(3):383–393
Locke JC, Southern MM, Kozma-Bognár L, Hibberd V, Brown PE, Turner MS, Millar AJ (2005b) Extension
of a genetic network model by iterative experimentation and mathematical analysis. Mol Syst Biol
1(1):0013
Locke JC, Kozma-Bognár L, Gould PD, Fehér B, Kevei E, Nagy F, Turner MS, Hall A, Millar
AJ (2006) Experimental validation of a predicted feedback loop in the multi-oscillator clock of
Arabidopsis thaliana. Mol Syst Biol 2(1):59
Millar AJ (2016) The intracellular dynamics of circadian clocks reach for the light of ecology and evolution. Annu Rev Plant Biol 67:595–618
Mora T, Bialek W (2011) Are biological systems poised at criticality? J Stat Phys 144(2):268–302
Munoz MA (2018) Colloquium: criticality and dynamical scaling in living systems. Rev Mod Phys 90(3):031,001
Murayama Y, Kori H, Oshima C, Kondo T, Iwasaki H, Ito H (2017) Low temperature nullifies the circadian clock in cyanobacteria through Hopf bifurcation. Proc Natl Acad Sci 114(22):5641–5646
Murray J (2013) Mathematical biology. Biomathematics. Springer, Berlin
Ohara T, Fukuda H, Tokuda IT (2015) An extended mathematical model for reproducing the phase response of Arabidopsis thaliana under various light conditions. J Theor Biol 382:337–344
Ospeck M, Eguíluz VM, Magnasco MO (2001) Evidence of a Hopf bifurcation in frog hair cells. Biophys J 80(6):2597–2607
Pittendrigh CS (1960) Circadian rhythms and the circadian organization of living systems. In: Cold Spring Harbor symposia on quantitative biology, vol 25. Cold Spring Harbor Laboratory Press, pp 159–184
Pokhilko A, Hodge SK, Stratford K, Knox K, Edwards KD, Thomson AW, Mizuno T, Millar AJ (2010) Data assimilation constrains new connections and components in a complex, eukaryotic circadian clock model. Mol Syst Biol 6(1):416
Pokhilko A, Fernández AP, Edwards KD, Southern MM, Halliday KJ, Millar AJ (2012) The clock gene circuit in Arabidopsis includes a repressilator with additional feedback loops. Mol Syst Biol 8(1):574
Pokhilko A, Mas P, Millar AJ (2013) Modelling the widespread effects of toc1 signalling on the plant circadian clock and its outputs. BMC Syst Biol 7(1):23
Shampine LF, Reichelt MW (1997) The matlab ode suite. SIAM J Sci Comput 18(1):1–22
Stuart JT (1958) On the non-linear mechanics of hydrodynamic stability. J Fluid Mech 4(1):1–21
Takahashi N, Hirata Y, Aihara K, Mas P (2015) A hierarchical multi-oscillator network orchestrates the Arabidopsis circadian system. Cell 163(1):148–159
Tokuda IT, Akman OE, Locke JC (2019) Reducing the complexity of mathematical models for the plant circadian clock by distributed delays. J Theor Biol 463:155–166
Wenden B, Toner DL, Hodge SK, Grima R, Millar AJ (2012) Spontaneous spatiotemporal waves of gene expression from biological clocks in the leaf. Proc Natl Acad Sci 109(17):6757–6762
Xiao M, Cao J (2008) Genetic oscillation deduced from Hopf bifurcation in a genetic regulatory network with delays. Math Biosci 215(1):55–63
Yakir E, Hilman D, Hassidim M, Green RM (2007) Circadian clock associated 1 transcript stability and the entrainment of the circadian clock in Arabidopsis. Plant Physiol 145(3):925–932
Zeilinger MN, Farré EM, Taylor SR, Kay SA, Doyle FJ (2006) A novel computational model of the circadian clock in Arabidopsis that incorporates prr7 and prr9. Mol Syst Biol 2(1):58

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.