INTERFACE FOCUS

royalsocietypublishing.org/journal/rsfs

Introduction

Cite this article: Tyson JJ, Csikasz-Nagy A, Gonze D, Kim JK, Santos S, Wolf J. 2022 Time-keeping and decision-making in living cells: Part I. *Interface Focus* **12**: 20220011. https://doi.org/10.1098/rsfs.2022.0011

Accepted: 8 March 2022

One contribution of 5 to a theme issue 'Time-keeping and decision-making in living cells; Oscillations and Synchronization (Part I)'.

Subject Areas:
systems biology

Keywords:
molecular regulatory networks, feedback loops, mathematical modelling, multi-rhythmicity, entrainment, circadian rhythms

Author for correspondence:
John J. Tyson
e-mail: tyson@vt.edu

Downloaded from https://royalsocietypublishing.org/ on 20 May 2022

Time-keeping and decision-making in living cells: Part I

John J. Tyson[1], Attila Csikasz-Nagy[2], Didier Gonze[3], Jae Kyoung Kim[4,5], Silvia Santos[6] and Jana Wolf[7,8]

[1]Department of Biological Sciences, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, USA
[2]Faculty of Information Technology and Bionics, Pázmány Péter Catholic University, 1088 Budapest, Hungary
[3]Unit of Theoretical Chronobiology, Université Libre de Bruxelles, 1050 Brussels, Belgium
[4]Department of Mathematical Sciences, KAIST, Daejeon 34141, South Korea
[5]Biomedical Mathematics Group, Institute for Basic Science, Daejeon 34126, South Korea
[6]Quantitative Stem Cell Biology Laboratory, The Francis Crick Institute, London NW1 1AT, UK
[7]Mathematical Modeling of Cellular Processes, Max Delbrück Center for Molecular Medicine, 13125 Berlin, Germany
[8]Department of Mathematics and Computer Science, Free University, 14195 Berlin, Germany

JJT, 0000-0001-7560-6013; AC-N, 0000-0002-2919-5601; DG, 0000-0002-9800-2412; JKK, 0000-0001-7842-2172; SS, 0000-0002-2906-7888; JW, 0000-0003-3254-5868

To survive and reproduce, a cell must process information from its environment and its own internal state and respond accordingly, in terms of metabolic activity, gene expression, movement, growth, division and differentiation. These signal–response decisions are made by complex networks of interacting genes and proteins, which function as biochemical switches and clocks, and other recognizable information-processing circuitry. This theme issue of *Interface Focus* (in two parts) brings together articles on time-keeping and decision-making in living cells—work that uses precise mathematical modelling of underlying molecular regulatory networks to understand important features of cell physiology. Part I focuses on time-keeping: mechanisms and dynamics of biological oscillators and modes of synchronization and entrainment of oscillators, with special attention to circadian clocks.

1. Introduction

Living cells are remarkably effective and adaptable information-processing systems (IPSs) that receive information from the cell's external environment and internal conditions, integrate concurring and conflicting signals, figure out appropriate responses and induce their implementation (figure 1). As in a digital computer, cellular IPSs rely on the dynamics of molecular 'switches' and biological 'clocks', but rather than solid-state electronic devices, these biochemical switches and clocks are made up of genes, proteins and metabolites interacting by reaction, diffusion and transport in a tiny volume (approx. 10^{-12} l) of gel-like cytoplasm [1–5]. Cellular IPSs are autonomous, analogue and massively parallel and often knocked about by stochastic fluctuations among the limited numbers of molecules in such small volumes. Nonetheless, their responses are remarkably successful in supporting the survival, growth, repair and reproduction of cells. A grand challenge of molecular systems biology is to understand how cellular IPSs work (basic science), how to fix them when they malfunction (health science) and how we might re-engineer them to our specifications (biotechnology).

The theoretical foundation for understanding time-keeping and decision-making in molecular regulatory networks was crafted in the 1960s and early 1970s by the pioneering work of Goodwin [6], Higgins [7], Griffith [8,9], Roessler [10], Thomas [11] and others. Over the next 30 years, much progress was made in uncovering design principles of cellular control systems and carrying out novel experimental tests of theoretical ideas. This history has been documented in great detail in research monographs by Segel [12], Goldbeter [13],

© 2022 The Authors. Published by the Royal Society under the terms of the Creative Commons Attribution License http://creativecommons.org/licenses/by/4.0/, which permits unrestricted use, provided the original author and source are credited.

THE ROYAL SOCIETY PUBLISHING

Downloaded from https://royalsocietypublishing.org/ on 20 May 2022

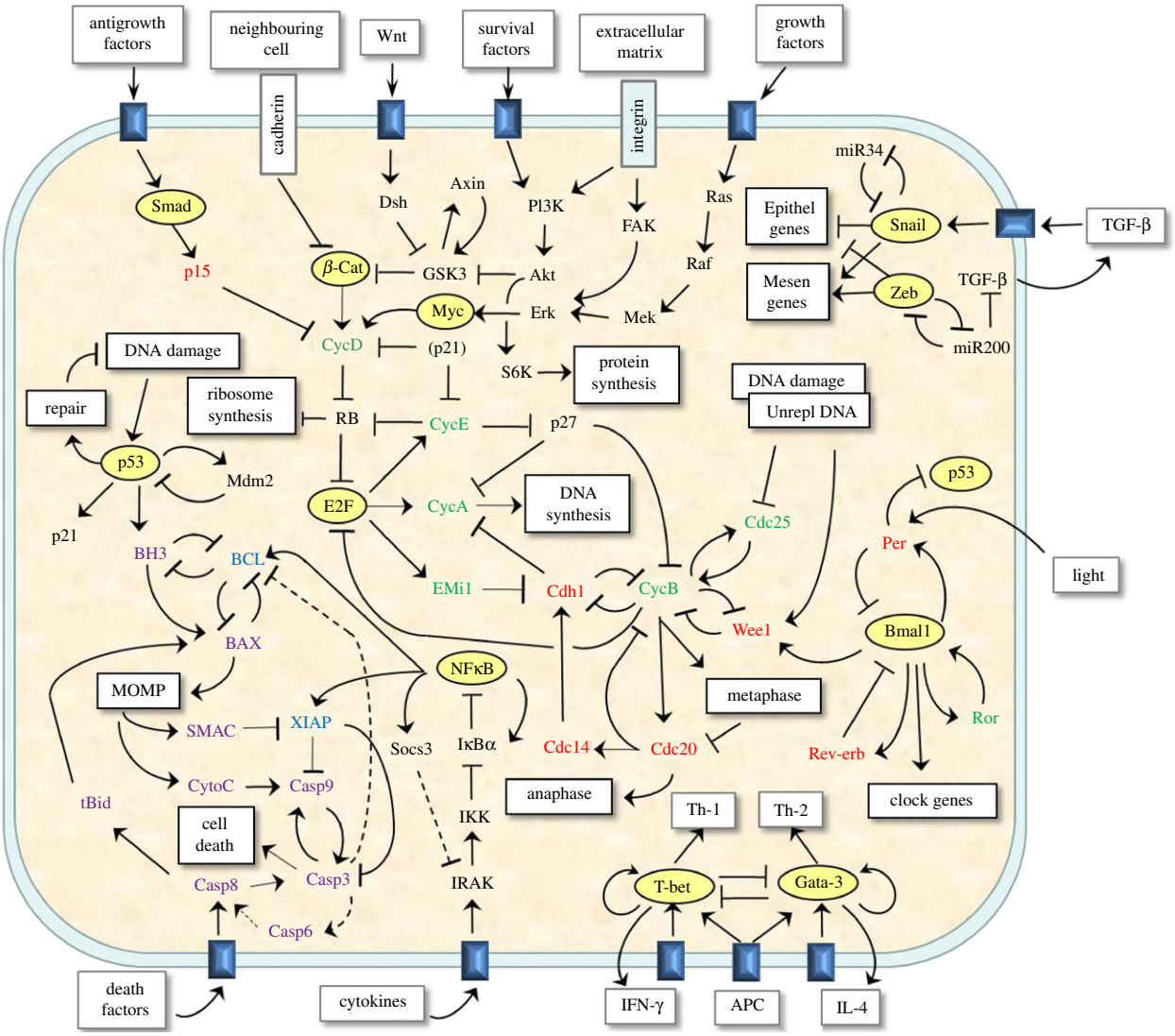


Figure 1. Some components of the information-processing system (IPS) in a mammalian cell. External signals (e.g. growth factors, death factors, cytokines, etc.) and internal signals (e.g. DNA damage, unreplicated DNA, mitochondrial outer membrane permeability—MOMP) are decoded through a cell's IPS—a complex network of interacting genes and proteins—to determine the best course of action for the cell given this information. Appropriate cellular responses include cell growth and division, cell differentiation, phase resetting of the circadian clock, cell cycle arrest, damage repair or cell death. The signals along the top provide input to cell growth (ribosome synthesis and protein synthesis) and division (DNA synthesis, mitosis). To the left, we see the DNA-damage response, mediated by p53, culminating (if it cannot be repaired) in cell death (apoptosis). Bottom left is the extrinsic cell death response through Caspase 8. Bottom middle is cytokine activation of the master transcription factor NFκB. Bottom right is one example of T-helper cell differentiation, mediated by the transcription factors T-bet and Gata-3. On the lower right is the core circadian clock (Per/Bmal1/Rev-erb/Ror), and the upper right is a schematic of the epithelial/mesenchymal differentiation decision pathway.

Alon [14], Keener & Sneyd [15] and Ferrell [16] and briefly by Tyson *et al*. [17] in a supplemental issue of *Journal of the Royal Society Interface* on 'biological switches and clocks'. As a follow-up to that issue, *Interface Focus* is presenting a two-part collection of articles on the theme of 'time-keeping and decision-making in living cells'.

Part I focuses on time-keeping, in particular on mechanisms of biological oscillators, on synchronization of intercommunicating oscillators and on entrainment to external driving rhythms, with particular emphasis on circadian rhythms. Jiménez *et al*. [18] lead off the collection with a valuable survey of entrainment among biological oscillators, focusing on six representative examples: the circadian clock, the cell cycle, mitotic exit (Cdc14 endocycles), cardiac pacemaker cells (Ca^{2+}/cyclic AMP (cAMP) oscillations), glycolytic oscillations and inflammatory responses (nuclear factor-κB (NFκB) oscillations). Next, Goldbeter & Yan [19] present a masterly review of multi-rhythmicity (two or more simultaneously stable oscillatory states in models of biochemical reaction networks) and multi-synchronization (two or more simultaneously stable modes of synchronization of coupled biological oscillators). Examples are drawn from cAMP signalling, circadian rhythms and cell cycle oscillations. Burckard *et al*. [20] provide new results on the synchronization of peripheral circadian clocks by intercellular communication between two cells or in small clusters of cells. In the final contribution, Jeong *et al*. [21] investigate the role of multiple modes of transcriptional repression in generating many of these rhythms. By modelling three mechanisms of transcriptional repression—repressor R may bind to activator A on promoter P to block transcription (R:A:P is transcriptionally inactive), R binding to A may displace A from the promoter (R + A:P → R:A:P → R:A + P) and R binding to A may sequester A from P (R:A prevents A from binding to P)—they show that synergistic interactions of the three modes generate ultrasensitive transcriptional responses and robust oscillations.

Part II will focus on decision-making in cell differentiation, development and cell cycle progression.

Downloaded from https://royalsocietypublishing.org/ on 20 May 2022

2. Other recent developments in time-keeping

Because this theme issue presents only a few snapshots of the immense progress that has been made on biological clocks since the 2008 collection, we review here some other recent developments.

As might be expected, considerable progress has been made in understanding the molecular mechanisms underlying circadian rhythms. Firstly, some new models of mammalian clock, taking into account interactions among the principal clock genes (*Per1*, *Per2*, *Cry1*, *Cry2*, *Clock*, *Bmal1*, *Rev-erbα* and *Rorα*), have been remarkably successful in accounting for the physiological properties of circadian rhythms in wild-type and mutant cell lines [22–24]. These mathematical models have proven their usefulness in applications to chronotherapy [25–28], wearable devices [29,30] and diagnostic tools [31,32]. The development of multi-scale circadian models, linking intra- and intercellular dynamics, has been pursued by DeWoskin *et al*. [33,34]. Other theoretical studies have revealed some general features of the molecular architecture of circadian clocks. Maeda & Kurata [35] showed that the dual-feedback structure found in living organisms supports a robust and entrainable oscillator. The roles of feedback and other design principles in the robustness of oscillations were analysed in many studies (e.g. Kim & Forger [24], Tsai *et al*. [36], Hafner *et al*. [37], Ananthasubramaniam [38] and Baum *et al*. [39]). By fitting models to experimental data, Herzel and co-workers [40,41] identified the important control loops at play in the suprachiasmatic nucleus (SCN) and peripheral organs. In particular, they have identified a three-component negative feedback loop (*Cry1* –| *Per2* –| *Rev-erbα* –| *Cry1*) as a dominant source of oscillations in their models [42]. Ko *et al*. [43] have highlighted the possible role of noise in generating self-sustained circadian rhythms. Notably, the mystery of temperature compensation of the circadian clock has been cleared up by a recognition of the temperature-dependent properties of the phospho-switch that regulates PERIOD-2 (PER2) protein phosphorylation by casein kinase-1 and its subsequent degradation, after polyubiquitination by beta-transducin repeats-containing protein (βTrCP) [44–46].

Intercellular coupling and synchronization of circadian clocks have also been the subject of many publications. Bernard *et al*. [47] showed that robust, self-sustained circadian oscillations can emerge from a heterogeneous network of damped oscillators through intercellular coupling. Hafner *et al*. [37] suggested that heterogeneity of circadian clocks in the SCN decreases the sensitivity of the network to brief perturbations while simultaneously improving its adaptation to long-term entrainment signals. Recent studies found that the heterogeneous responses of master and slave clock neurons to entrainment signals are critical for strong, adjustable circadian rhythms [48]. Studies by Vasalou *et al.* [49,50] and by Ananthasubramaniam *et al*. [51] have focused on the roles of neurotransmitters in synchronizing circadian oscillators in the SCN. Meanwhile, Webb *et al*. [52] further investigated the synchronization of weak, heterogeneous oscillators to produce robust circadian rhythms.

The interplay of circadian clocks and metabolism has received much attention. Using a combination of mathematical modelling and experiments in *Neurospora crassa*, Dovzhenok *et al*. [53] found an additional negative feedback loop that maintains circadian period over a wide range of glucose conditions. Woller *et al*. [54] introduced metabolic sensors into a mathematical model of the mammalian circadian clock to study the effects of diet (normal, high-fat, fasting) on clock function. Woller & Gonze [55] used a clock model to show how conflicting zeitgebers (light and food intake) disrupt the phase relations of core clock genes, leading to metabolic complications such as hyperglycaemia. Bae & Androulakis [56,57] developed models to study the impact of the circadian clock on insulin secretion and gluconeogenesis, showing how external signals (light/dark cycles and feeding/fasting cycles) affect metabolism over the course of a day. In a different vein, Rao *et al*. [58] used a model of the hypothalamus–pituitary–adrenal axis and the sleep/wake cycle to explore the influence of sleep deficiency on daily rhythms of cortisol release.

We also draw your attention to some additional studies of interactions between the circadian clock and the cell division cycle, based on the unexpected discovery by Matsuo *et al*. [59] that transcription of the cell cycle gene *Wee1* is upregulated by an E-box, which binds to the master transcription factor BMAL1 : CLOCK. Zamborszky *et al*. [60] used mathematical modelling to show how the circadian clock, by gating *Wee1* expression, would generate quantized cell cycle times and cell division sizes. Later, Gerard & Goldbeter [61] found entrainment bands (at 24 h and 48 h) for a cell cycle model (without size control) driven by a 24 h rhythm of BMAL1 : CLOCK. On the experimental side, Feillet *et al*. [62] found multiple modes of entrainment and phase locking between cell divisions and the circadian rhythms in mouse fibroblasts whose clock phases were synchronized by a pulse of dexamethasone, which can be observed and modelled also on the single cell level [63]. And, Matsu-Ura *et al*. [64], using dual luciferase reporters for cell cycle and circadian oscillators, observed 2 : 1 entrainment (i.e. 12 h cell division cycles) in mouse intestinal organoids. In a different vein, Gotoh *et al*. [65] used mathematical models to gain insight into the coupling of the circadian clock to the DNA damage checkpoint (i.e. the interactions between PER2 and p53 proteins).

Finally, we review recent proposals that the cell division cycle is a 'clock-shop' of autonomous (independent) oscillators entrained to one another. It is commonly thought that cell cycle events (DNA replication, mitosis, cell division) are controlled by a 'master programme' based on fluctuations of cyclin-dependent kinases (Cdks) and their immediate regulators [66,67]. However, it is now established that many cell cycle events continue in a repetitive fashion even when the Cdk programme is blocked by mutations. For example, periodic processes that continue more-or-less on schedule in mutant (non-dividing) strains of budding yeast include budding and mating projections [68], DNA endoreplication [69], spindle pole body re-duplication [70], gene transcription [71], Cdc14 release from the nucleolus (a marker of mitotic exit) [72,73] and metabolic oscillations (NADPH fluctuations) [74]. Also, periodic centriole biogenesis (Polo kinase-4 oscillations) has been observed in mutant fruit fly embryos [75]. Furthermore, chromosome endoreduplication [76] and basal body (centriole) amplification [77] are characteristics of certain terminally differentiated (non-dividing) cells. These observations support the 'clock-shop' hypothesis [71,72,78], although there are opposing opinions [73,79,80]. In the future, we may expect continued debate on the possible roles of 'autonomous clocks' in cell cycle progression.

Altogether, these recent studies and many others have contributed greatly to our understanding of the molecular regulatory mechanisms underlying biological oscillations

Downloaded from https://royalsocietypublishing.org/ on 20 May 2022

and of their advantageous properties, such as robustness, tunability, entrainment and temperature compensation. Also, we now have a better appreciation of the—often non-intuitive—dynamics resulting from the interplay between clocks and clock-controlled processes. This progress has revolutionized our interpretation of experimental observations and our vision of future progress in health science and biotechnology.

3. In memoriam

The theoretical foundations of time-keeping and decision-making by the molecular regulatory networks in living cells were laid out in the 1970s and 1980s by a small band of physical chemists, biochemists, chemical engineers and mathematical biologists. Unfortunately, many of these pioneering scientists have passed away and are sorely missed. In conclusion, we would like to recognize their contributions to the field.

Joel E. Keizer (1942–1999). As a physical chemist, Joel Keizer made fundamental contributions to the theory of non-equilibrium thermodynamics before turning his attention to the application of dynamical systems theory to problems in cell physiology, most notably complex bursting oscillations in pancreatic β-cells and Ca^{2+} waves in fertilized eggs [81,82].

Benno Hess (1922–2002). As director of a Max-Planck-Institute in Dortmund, Germany, Benno Hess directed a large group of biochemists and mathematical modellers exploring the molecular mechanisms of glycolytic oscillations in yeast cells [83].

Arthur T. Winfree (1942–2002). An engineer by training, Art Winfree turned his creative mind to the dynamics of oscillations and wave propagation in living organisms. His predictions of 'phase singularities' in circadian rhythms and cardiac physiology revolutionized our understanding of these fields [84,85].

Rene Thom (1923–2002). The purest of pure mathematicians, Rene Thom was among the first persons to recognize the relevance of bifurcations of vector fields to temporal and spatial organization in living organisms [86,87].

Ilya Prigogine (1917–2003). The 1977 Nobel Prize in Chemistry was awarded to Ilya Prigogine for his fundamental insights on far-from-equilibrium thermodynamics, most notably on 'dissipative structures' (temporal oscillations and spatial patterns) in living organisms [88].

Lee A. Segel (1932–2005). A world-renowned applied mathematician, Lee Segel made major contributions to the theory oscillations, pattern formation and wave propagation in living cells [89,90].

Reinhart Heinrich (1946–2006). A physicist who moved into biochemistry, Reinhart Heinrich combined modelling of specific cellular systems with a search for general principles. As one of the founding intellects behind metabolic control theory, he upset the paradigm of 'rate-limiting' steps in biochemistry by showing, in quantitative detail, how flux control is distributed across all enzymes in a metabolic network [91].

Brian Goodwin (1931–2009). A Canadian émigré who got his PhD at the University of Edinburgh under Conrad Waddington, Brian Goodwin had a lifelong interest in development and evolution and was a leading figure in the renaissance of mathematical biology in the 1960s. His pioneering work on biochemical oscillators is reverberating to this day [92].

Christopher Zeeman (1925–2016). A leading English mathematician and early convert to Thom's theory of singularities of vector fields, Christopher Zeeman applied 'catastrophe theory' in creative ways to a wide variety of phenomena in biology, as well as other fields [93,94].

Rene Thomas (1928–2017). The Belgian biochemist Rene Thomas was an early proponent of 'logical modelling' of biochemical reaction networks (i.e. modelling by Boolean functions). Early on he recognized the importance of negative feedback in generating biochemical oscillations and positive feedback in creating biological switches [95].

Gregoire Nicolis (1939–2018). A chemical physicist at the Free University of Brussels, Gregoire Nicolis led a team of talented and creative younger scientists in the application of Prigogine's abstract ideas about non-equilibrium thermodynamics and 'dissipative structures' to real-world problems in chemistry, physics and biology [96,97].

George F. Oster (1940–2018). After an unusual start in the merchant marines and nuclear physics, George Oster studied biophysics and applied his massive intellect to a theoretical understanding of some of the toughest problems in molecular cell biology, including morphogenesis, pattern formation and molecular motors [98,99].

Garrett M. Odell (1943–2018). Trained in applied mathematics and theoretical mechanics, Garry Odell took an abrupt turn to mathematical biology, where he made many remarkable contributions to our understanding of chemotaxis, embryogenesis, molecular motors, gene regulatory networks and cytoskeletal mechanics [100].

Data accessibility. This article has no additional data.

Authors' contributions. J.J.T.: writing—original draft, writing—review and editing; A.C.-N.: writing—review and editing; D.G.: writing—review and editing; J.K.K.: writing—review and editing; S.S.: writing—review and editing; J.W.: writing—review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Competing interests. We declare we have no competing interests.

Funding. We received no funding for this study.

References

1. Bray D. 1995 Protein molecules as computational elements in living cells. *Nature* **376**, 307–312. (doi:10.1038/376307a0)
2. McAdams HH, Shapiro L. 1995 Circuit simulation of genetic networks. *Science* **269**, 650–656. (doi:10.1126/science.7624793)
3. Arkin AP. 2000 Signal processing by biochemical reaction networks. In *Self-organized biological dynamics, nonlinear control* (ed. J Walleczek), pp. 112–144. Cambridge, UK: Cambridge University Press.
4. Tyson JJ, Chen KC, Novak B. 2003 Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell. *Curr. Opin. Cell Biol.* **15**, 221–231. (doi:10.1016/S0955-0674(03)00017-6)
5. Navlakha S, Bar-Joseph Z. 2011 Algorithms in nature: the convergence of systems biology and computational thinking. *Mol. Syst. Biol.* **7**, 546. (doi:10.1038/msb.2011.78)

Downloaded from https://royalsocietypublishing.org/ on 20 May 2022

6. Goodwin BC. 1965 Oscillatory behavior in enzymatic control processes. *Adv. Enzyme Regul.* **3**, 425–438. (doi:10.1016/0065-2571(65)90067-1)
7. Higgins J. 1967 Theory of oscillating reactions. *Ind. Eng. Chem.* **59**, 19–62. (doi:10.1021/ie50689a006)
8. Griffith JS. 1968 Mathematics of cellular control processes. II. Positive feedback to one gene. *J. Theor. Biol.* **20**, 209–216. (doi:10.1016/0022-5193(68)90190-2)
9. Griffith JS. 1968 Mathematics of cellular control processes. I. Negative feedback to one gene. *J. Theor. Biol.* **20**, 202–208. (doi:10.1016/0022-5193(68)90189-6)
10. Roessler OE. 1972 Basic circuits of fluid automata and relaxation systems. *Z. Naturforsch.* **27**, 332–343.
11. Thomas R. 1973 Boolean formalization of genetic control circuits. *J. Theor. Biol.* **42**, 563–585. (doi:10.1016/0022-5193(73)90247-6)
12. Segel LA. 1980 *Mathematical models in molecular and cellular biology*. Cambridge, UK: Cambridge University Press.
13. Goldbeter A. 1996 *Biochemical oscillations and cellular rhythms*. Cambridge, UK: Cambridge University Press.
14. Alon U. 2007 *An introduction to systems biology: design principles of biological circuits*. Boca Raton, FL: Chapman & Hall/CRC.
15. Keener J, Sneyd J. 2009 *Mathematical physiology. I. Cellular physiology*, 2nd edn. New York, NY: Springer.
16. Ferrell Jr JE. 2022 *Systems biology of cell signaling: recurring themes and quantitative models*. Boca Raton, FL: CRC Press.
17. Tyson JJ, Albert R, Goldbeter A, Ruoff P, Sible J. 2008 Biological switches and clocks. *J. R. Soc. Interface* **5**(Suppl. 1), S1–S8. (doi:10.1098/rsif.2008.0179.focus)
18. Jiménez A, Lu Y, Jambhekar A, Lahav G. 2022 Principles, mechanisms and functions of entrainment in biological oscillators. *Interface Focus* **12**, 20210088. (doi:10.1098/rsfs.2021.0088)
19. Goldbeter A, Yan J. 2022 Multi-synchronization and other patterns of multi-rhythmicity in oscillatory biological systems. *Interface Focus* **12**, 20210089. (doi:10.1098/rsfs.2021.0089)
20. Burckard O, Teboul M, Delaunay F, Chaves M. 2022 Cycle dynamics and synchronization in a coupled network of peripheral circadian clocks. *Interface Focus* **12**, 20210087. (doi:10.1098/rsfs.2021.0087)
21. Jeong EM, Song YM, Kim JK. 2022 Combined multiple transcriptional repression mechanisms generate ultrasensitivity and oscillations. *Interface Focus* **12**, 20210084. (doi:10.1098/rsfs.2021.0084)
22. Mirsky HP, Liu AC, Welsh DK, Kay SA, Doyle III FJ. 2009 A model of the cell-autonomous mammalian circadian clock. *Proc. Natl Acad. Sci. USA* **106**, 11 107–11 112. (doi:10.1073/pnas.0904837106)
23. Relogio A, Westermark PO, Wallach T, Schellenberg K, Kramer A, Herzel H. 2011 Tuning the mammalian circadian clock: robust synergy of two loops. *PLoS Comput. Biol.* **7**, e1002309. (doi:10.1371/journal.pcbi.1002309)
24. Kim JK, Forger DB. 2012 A mechanism for robust circadian timekeeping via stoichiometric balance. *Mol. Syst. Biol.* **8**, 630. (doi:10.1038/msb.2012.62)
25. Hesse J, Martinelli J, Aboumanify O, Ballesta A, Relogio A. 2021 A mathematical model of the circadian clock and drug pharmacology to optimize irinotecan administration timing in colorectal cancer. *Comput. Struct. Biotechnol. J.* **19**, 5170–5183. (doi:10.1016/j.csbj.2021.08.051)
26. Hill RJW, Innominato PF, Levi F, Ballesta A. 2020 Optimizing circadian drug infusion schedules towards personalized cancer chronotherapy. *PLoS Comput. Biol.* **16**, e1007218. (doi:10.1371/journal.pcbi.1007218)
27. Kim DW, Chang C, Chen X, Doran AC, Gaudreault F, Wager T, DeMarco GJ, Kim JK. 2019 Systems approach reveals photosensitivity and PER2 level as determinants of clock-modulator efficacy. *Mol. Syst. Biol.* **15**, e8838. (doi:10.15252/msb.2019883)
28. Brown LS, Doyle III FJ. 2020 A dual-feedback loop model of the mammalian circadian clock for multi-input control of circadian phase. *PLoS Comput. Biol.* **16**, e1008459. (doi:10.1371/journal.pcbi.1008459)
29. Huang Y, Mayer C, Cheng P, Siddula A, Burgess HJ, Drake C, Goldstein C, Walch O, Forger DB. 2021 Predicting circadian phase across populations: a comparison of mathematical models and wearable devices. *Sleep* **44**, zsab126. (doi:10.1093/sleep/zsab126)
30. Serkh K, Forger DB. 2014 Optimal schedules of light exposure for rapidly correcting circadian misalignment. *PLoS Comput. Biol.* **10**, e1003523. (doi:10.1371/journal.pcbi.1003523)
31. Wittenbrink N *et al.* 2018 High-accuracy determination of internal circadian time from a single blood sample. *J. Clin. Invest.* **128**, 3826–3839. (doi:10.1172/JCI120874)
32. Anafi RC, Francey LJ, Hogenesch JB, Kim J. 2017 CYCLOPS reveals human transcriptional rhythms in health and disease. *Proc. Natl Acad. Sci. USA* **114**, 5312–5317. (doi:10.1073/pnas.1619320114)
33. DeWoskin D, Myung J, Belle MD, Piggins HD, Takumi T, Forger DB. 2015 Distinct roles for GABA across multiple timescales in mammalian circadian timekeeping. *Proc. Natl Acad. Sci. USA* **112**, E3911–E3919. (doi:10.1073/pnas.1420753112)
34. DeWoskin D, Geng W, Stinchcombe AR, Forger DB. 2014 It is not the parts, but how they interact that determines the behaviour of circadian rhythms across scales and organisms. *Interface Focus* **4**, 20130076. (doi:10.1098/rsfs.2013.0076)
35. Maeda K, Kurata H. 2012 A symmetric dual feedback system provides a robust and entrainable oscillator. *PLoS ONE* **7**, e30489. (doi:10.1371/journal.pone.0030489)
36. Tsai TY, Choi YS, Ma W, Pomerening JR, Tang C, Ferrell Jr JE. 2008 Robust, tunable biological oscillations from interlinked positive and negative feedback loops. *Science* **321**, 126–129. (doi:10.1126/science.1156951)
37. Hafner M, Koeppl H, Gonze D. 2012 Effect of network architecture on synchronization and entrainment properties of the circadian oscillations in the suprachiasmatic nucleus. *PLoS Comput. Biol.* **8**, e1002419. (doi:10.1371/journal.pcbi.1002419)
38. Ananthasubramaniam B, Herzel H. 2014 Positive feedback promotes oscillations in negative feedback loops. *PLoS ONE* **9**, e104761. (doi:10.1371/journal.pone.0104761)
39. Baum K, Politi AZ, Kofahl B, Steuer R, Wolf J. 2016 Feedback, mass conservation and reaction kinetics impact the robustness of cellular oscillations. *PLoS Comput. Biol.* **12**, e1005298. (doi:10.1371/journal.pcbi.1005298)
40. Korencic A, Kosir R, Bordyugov G, Lehmann R, Rozman D, Herzel H. 2014 Timing of circadian genes in mammalian tissues. *Sci. Rep.* **4**, 5782. (doi:10.1038/srep05782)
41. Pett JP, Kondoff M, Bordyugov G, Kramer A, Herzel H. 2018 Co-existing feedback loops generate tissue-specific circadian rhythms. *Life Sci. Alliance* **1**, e201800078. (doi:10.26508/lsa.201800078)
42. Pett JP, Korencic A, Wesener F, Kramer A, Herzel H. 2016 Feedback loops of the mammalian circadian clock constitute repressilator. *PLoS Comput. Biol.* **12**, e1005266. (doi:10.1371/journal.pcbi.1005266)
43. Ko CH *et al.* 2010 Emergence of noise-induced oscillations in the central circadian pacemaker. *PLoS Biol.* **8**, e1000513. (doi:10.1371/journal.pbio.1000513)
44. Zhou M, Kim JK, Eng GW, Forger DB, Virshup DM. 2015 A period2 phosphoswitch regulates and temperature compensates circadian period. *Mol. Cell* **60**, 77–88. (doi:10.1016/j.molcel.2015.08.022)
45. Masuda S, Narasimamurthy R, Yoshitane H, Kim JK, Fukada Y, Virshup DM. 2020 Mutation of a PER2 phosphodegron perturbs the circadian phosphoswitch. *Proc. Natl Acad. Sci. USA* **117**, 10 888–10 896. (doi:10.1073/pnas.2000266117)
46. Narasimamurthy R, Hunt SR, Lu Y, Fustin JM, Okamura H, Partch CL, Forger DB, Kim JK, Virshup DM. 2018 CK1delta/epsilon protein kinase primes the PER2 circadian phosphoswitch. *Proc. Natl Acad. Sci. USA* **115**, 5986–5991. (doi:10.1073/pnas.1721076115)
47. Bernard S, Gonze D, Cajavec B, Herzel H, Kramer A. 2007 Synchronization-induced rhythmicity of circadian oscillators in the suprachiasmatic nucleus. *PLoS Comput. Biol.* **3**, e68. (doi:10.1371/journal.pcbi.0030068)
48. Jeong EM, Kwon M, Cho E, Lee SH, Kim H, Kim EY, Kim JK. 2022 Systematic modeling-driven experiments identify distinct molecular clockworks underlying hierarchically organized pacemaker neurons. *Proc. Natl Acad. Sci. USA* **119**, e2113403119. (doi:10.1073/pnas.2113403119)
49. Vasalou C, Henson MA. 2011 A multicellular model for differential regulation of circadian signals in the core and shell regions of the suprachiasmatic nucleus. *J. Theor. Biol.* **288**, 44–56. (doi:10.1016/j.jtbi.2011.08.010)
50. Vasalou C, Herzog ED, Henson MA. 2011 Multicellular model for intercellular synchronization in circadian neural networks. *Biophys. J.* **101**, 12–20. (doi:10.1016/j.bpj.2011.04.051)

Downloaded from https://royalsocietypublishing.org/ on 20 May 2022

51. Ananthasubramaniam B, Herzog ED, Herzel H. 2014 Timing of neuropeptide coupling determines synchrony and entrainment in the mammalian circadian clock. *PLoS Comput. Biol.* **10**, e1003565. (doi:10.1371/journal.pcbi.1003565)
52. Webb AB, Taylor SR, Thoroughman KA, Doyle III FJ, Herzog ED. 2012 Weakly circadian cells improve resynchrony. *PLoS Comput. Biol.* **8**, e1002787. (doi:10.1371/journal.pcbi.1002787)
53. Dovzhenok AA, Baek M, Lim S, Hong CI. 2015 Mathematical modeling and validation of glucose compensation of the neurospora circadian clock. *Biophys. J.* **108**, 1830–1839. (doi:10.1016/j.bpj.2015.01.043)
54. Woller A, Duez H, Staels B, Lefranc M. 2016 A mathematical model of the liver circadian clock linking feeding and fasting cycles to clock function. *Cell Rep.* **17**, 1087–1097. (doi:10.1016/j.celrep.2016.09.060)
55. Woller A, Gonze D. 2018 Modeling clock-related metabolic syndrome due to conflicting light and food cues. *Sci. Rep.* **8**, 13641. (doi:10.1038/s41598-018-31804-9)
56. Bae SA, Androulakis IP. 2019 Mathematical modeling informs the impact of changes in circadian rhythms and meal patterns on insulin secretion. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **317**, R98–R107. (doi:10.1152/ajpregu.00230.2018)
57. Bae SA, Androulakis IP. 2018 Mathematical analysis of circadian disruption and metabolic re-entrainment of hepatic gluconeogenesis: the intertwining entraining roles of light and feeding. *Am. J. Physiol. Endocrinol. Metab.* **314**, E531–E542. (doi:10.1152/ajpendo.00271.2017)
58. Rao R, Somvanshi P, Klerman EB, Marmar C, Doyle III FJ. 2021 Modeling the influence of chronic sleep restriction on cortisol circadian rhythms, with implications for metabolic disorders. *Metabolites* **11**, 483. (doi:10.3390/metabo11080483)
59. Matsuo T, Yamaguchi S, Mitsui S, Emi A, Shimoda F, Okamura H. 2003 Control mechanism of the circadian clock for timing of cell division in vivo. *Science* **302**, 255–259. (doi:10.1126/science.1086271)
60. Zamborszky J, Hong CI, Csikasz Nagy A. 2007 Computational analysis of mammalian cell division gated by a circadian clock: quantized cell cycles and cell size control. *J. Biol. Rhythms* **22**, 542–553. (doi:10.1177/0748730407307225)
61. Gerard C, Goldbeter A. 2012 Entrainment of the mammalian cell cycle by the circadian clock: modeling two coupled cellular rhythms. *PLoS Comput. Biol.* **8**, e1002516. (doi:10.1371/journal.pcbi.1002516)
62. Feillet C *et al.* 2014 Phase locking and multiple oscillating attractors for the coupled mammalian clock and cell cycle. *Proc. Natl Acad. Sci. USA* **111**, 9828–9833. (doi:10.1073/pnas.1320474111)
63. Bieler J, Cannavo R, Gustafson K, Gobet C, Gatfield D, Naef F. 2014 Robust synchronization of coupled circadian and cell cycle oscillators in single mammalian cells. *Mol. Syst. Biol.* **10**, 739. (doi:10.15252/msb.20145218)
64. Matsu-Ura T *et al.* 2016 Intercellular coupling of the cell cycle and circadian clock in adult stem cell culture. *Mol. Cell* **64**, 900–912. (doi:10.1016/j.molcel.2016.10.015)
65. Gotoh T, Kim JK, Liu J, Vila-Caballer M, Stauffer PE, Tyson JJ, Finkielstein CV. 2016 Model-driven experimental approach reveals the complex regulatory distribution of p53 by the circadian factor Period 2. *Proc. Natl Acad. Sci. USA* **113**, 13 516–13 521. (doi:10.1073/pnas.1607984113)
66. Nurse P. 1990 Universal control mechanism regulating onset of M-phase. *Nature* **344**, 503–508. (doi:10.1038/344503a0)
67. Tyson JJ, Novak B. 2013 Irreversible transitions, bistability and checkpoint controls in the eukaryotic cell cycle: a systems-level understanding. In *Handbook of systems biology* (eds AJM Walhout, M Vidal, J Dekker), pp. 265–285. San Diego, CA: Academic Press.
68. Haase SB, Reed SI. 1999 Evidence that a free-running oscillator drives G1 events in the budding yeast cell cycle. *Nature* **401**, 394–397.
69. Simmons Kovacs LA, Mayhew MB, Orlando DA, Jin Y, Li Q, Huang C, Reed SI, Mukherjee S, Haase SB. 2012 Cyclin-dependent kinases are regulators and effectors of oscillations driven by a transcription factor network. *Mol. Cell* **45**, 669–679. (doi:10.1016/j.molcel.2011.12.033)
70. Haase SB, Winey M, Reed SI. 2001 Multi-step control of spindle pole body duplication by cyclin-dependent kinase. *Nat. Cell Biol.* **3**, 38–42. (doi:10.1038/35050543)
71. Orlando DA, Lin CY, Bernard A, Wang JY, Socolar JE, Iversen ES, Hartemink AJ, Haase SB. 2008 Global control of cell-cycle transcription by coupled CDK and network oscillators. *Nature* **453**, 944–947. (doi:10.1038/nature06955)
72. Lu Y, Cross FR. 2010 Periodic cyclin-Cdk activity entrains an autonomous Cdc14 release oscillator. *Cell* **141**, 268–279. (doi:10.1016/j.cell.2010.03.021)
73. Manzoni R, Montani F, Visintin C, Caudron F, Ciliberto A, Visintin R. 2010 Oscillations in Cdc14 release and sequestration reveal a circuit underlying mitotic exit. *J. Cell Biol.* **190**, 209–222. (doi:10.1083/jcb.201002026)
74. Papagiannakis A, Niebel B, Wit EC, Heinemann M. 2017 Autonomous metabolic oscillations robustly gate the early and late cell cycle. *Mol. Cell* **65**, 285–295. (doi:10.1016/j.molcel.2016.11.018)
75. Aydogan MG *et al.* 2020 An autonomous oscillation times and executes centriole biogenesis. *Cell* **181**, 1566–1581.e1527. (doi:10.1016/j.cell.2020.05.018)
76. Brody TB. 1996 Genes involved in tissue and organ development: polytene chromosomes, endoreduplication and puffing. In *The interactive fly*.
77. Meunier A, Azimzadeh J. 2016 Multiciliated cells in animals. *Cold Spring Harb. Perspect. Biol.* **8**, a028233. (doi:10.1101/cshperspect.a028233)
78. Mofatteh M, Echegaray-Iturra F, Alamban A, Dalla Ricca F, Bakshi A, Aydogan MG. 2021 Autonomous clocks that regulate organelle biogenesis, cytoskeletal organization, and intracellular dynamics. *eLife* **10**, e72104. (doi:10.7554/eLife.72104)
79. Rahi SJ, Pecani K, Ondracka A, Oikonomou C, Cross FR. 2016 The CDK-APC/C oscillator predominantly entrains periodic cell-cycle transcription. *Cell* **165**, 475–487. (doi:10.1016/j.cell.2016.02.060)
80. Novak B, Tyson JJ. In press. The oscillation of mitotic kinase governs cell cycle latches. *Curr. Biol.*
81. Hastings A. 2001 In memoriam: Joel E. Keizer. *J. Theor. Biol.* **210**, 133–139. (doi:10.1006/jtbi.2001.2329)
82. Cheer A, Mogilner A, Stuchebrukhov A. 1999 In Memoriam: Joel E. Keizer. See https://senate.universityofcalifornia.edu/_files/inmemoriam/html/joelekeizer.html.
83. Engelhard M, Mueller SC. 2003 Benno Hess (1922–2002): from chemistry to biophysics and self-organization. *Angew. Chem. Int. Ed.* **42**, 2330. (doi:10.1002/anie.200390466)
84. Tyson JJ, Glass L. 2004 Arthur T. Winfree (1942–2002). *J. Theor. Biol.* **230**, 433–439. (doi:10.1016/j.jtbi.2004.04.042)
85. Strogatz S. 2003 Arthur Taylor Winfree. *Phys. Today* **56**, 74. (doi:10.1063/1.4776726)
86. Johnson G. 2002 Rene Thom, 79, inventor of catastrophe theory, dies. *The New York Times*. See https://www.nytimes.com/2002/11/10/world/rene-thom-79-inventor-of-catastrophe-theory-dies.html.
87. Ekelund I. 2002 Rene Thom (1923–2002). *Nature* **420**, 758. (doi:10.1038/420758a)
88. Chang K. 2003 Ilya Prigogine, 86, Nobelist for study of complexity, dies. *The New York Times*. See https://www.nytimes.com/2003/05/30/world/ilya-prigogine-86-nobelist-for-study-of-complexity-dies.html.
89. Keshet L, Perelson A. 2006 A tribute to Lee Segel. *Bull. Math. Biol.* **68**, 969–980. (doi:10.1007/s11538-006-9134-4)
90. Levin S, Hyman JM, Perelson AS. 2005 Obituary: Lee Segel. *SIAM News*. See https://archive.siam.org/news/news.php?id=10.
91. Kirschner MW. 2006 Reinhart Heinrich (1946–2006). *Nature* **444**, 700. (doi:10.1038/444700a)
92. Gonze D, Ruoff P. 2021 The Goodwin oscillator and its legacy. *Acta Biotheor.* **69**, 857–874. (doi:10.1007/s10441-020-09379-8)
93. Stewart I. 2016 Sir Christopher Zeeman obituary. *The Guardian*. See https://www.theguardian.com/education/2016/feb/24/sir-christopher-zeeman-obituary.
94. Rand DA. 2016 Memories of Professor Sir Christopher Zeeman. Warwick Knowledge Centre. See https://warwick.ac.uk/newsandevents/knowledgecentre/science/maths-statistics/zeeman/memories/.
95. Thieffry D, Kaufman M. 2019 Prologue to the special issue of JTB dedicated to the memory of Rene Thomas (1928–2017): a journey through

biological circuits, logical puzzles and complex dynamics. *J. Theor. Biol.* **474**, 42–47. (doi:10.1016/j.jtbi.2019.04.021)

96. Basios V. 2019 Founding complexity science: the work of Gregoire Nicolis. See https://www.sci.unich.it/mmcs2019/slides/basios.pdf.
97. Nicolis G. 1995 *Introduction to nonlinear science*. Cambridge, UK: Cambridge University Press.
98. Mogilner A. 2018 In memoriam: George Oster, UC Berkeley, 1940–2018. *Mol. Biol. Cell* **29**, 1411–1412. (doi:10.1091/mbc.E18-04-0235)
99. Nuzzo R. 2006 Profile of George Oster. *Proc. Natl Acad. Sci. USA* **103**, 1672–1674. (doi:10.1073/pnas.0509056103)
100. von Dassow G, Munro E. 2018 Garrett Mitchell Odell. Center for Cell Dynamics. See http://celldynamics.org/celldynamics/eulogy/index.html.

Downloaded from https://royalsocietypublishing.org/ on 20 May 2022