1. Introduction

This two-part collection of articles on ‘time-keeping and decision-making in living cells’ covers various examples of the mechanisms by which cells and organisms receive and integrate signals from many sources, figure out how the organism should respond and then elicit the appropriate response. Unlike digital computers, these information-processing systems (IPS) are autonomous, analogue and massively parallel, and their responses are remarkably successful in supporting the survival, growth, repair and reproduction of living organisms. Molecular, cellular and organismal biologists, in collaboration with mathematical and computational biologists, have made remarkable progress in understanding how living IPS work. Some of these recent successes are reviewed in this collection.

Part I focused 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. Jimenez et al. [1] provided a valuable survey of entrainment among biological oscillators, focusing on the circadian clock, the cell cycle, cardiac pacemaker cells, glycolytic oscillations and inflammatory responses. Goldbeter & Yan [2] presented a masterly review of multi-rhythmicity (two or more simultaneously stable oscillatory states) and multi-synchronization (two or more simultaneously stable modes of synchronization), with examples drawn from cyclic AMP signalling, circadian rhythms and cell cycle oscillations. Burckard et al. [3] provided new results on the synchronization of peripheral circadian clocks by intercellular communication between two cells or in small clusters of cells. And Jeong et al. [4] investigated the role of multiple modes of transcriptional repression in generating many of these rhythms.

Part II focuses on decision-making in cell differentiation, development and cell cycle progression. Sáez et al. [5] use ideas from dynamical systems theory to turn Waddington’s ‘landscape’ metaphor of cell fate decisions into quantitative and predictive models that can shed light on the underlying biology (figure 1a). For instance, they identify just two distinct ways for a cell to choose between alternate fates: the ‘binary choice’ landscape and the ‘binary flip’ landscape. They go on to study three-attractor landscapes and beyond, and to consider how to incorporate experimental data with dynamics. Robert et al. [6] investigate potential sources of heterogeneity required to induce cell differentiation in early mammalian embryos, using a multi-cellular model of Nanog-Gata6-Fgf4 interactions (figure 1b).
attribute the observed characteristics to cell-to-cell variability in gene expression, most notably Nanog expression. Diegmiller et al. [7] study the dynamics of cell division and differentiation in small clusters of cells that make up germline cysts, which ultimately mature into an oocyte and surrounding support cells (figure 1c). They propose a minimal cell cycle oscillator model for generating the cell lineage tree (CLT) of a cyst and discuss how CLTs of varying topologies can arise. Such clonal clusters of connected cells are found in almost all lineages of eukaryotes, and the cytoplasmic bridges that connect such cells are thought to have played a key role in the evolution of multi-cellularity. Tyson & Novak [8] use mathematical models to study the roles of time-keeping and decision-making during progression through the eukaryotic cell cycle. Their models, based on the well-known cyclin-dependent kinase (CDK) control system (figure 1d), account for both clock-like CDK oscillations during early embryonic cell divisions and switch-like CDK-arrested states (checkpoints) during somatic cell cycles. Lastly, Nam et al. [9] review a graph-based approach to biochemical reaction dynamics, called ‘the linear framework’ (figure 1e). In this approach, the nonlinear kinetics of a network of biochemical reactions is decomposed into a coupled set of graphs, each of which has linear dynamics, and the steady states of the network can be expressed as rational algebraic functions of the parameters. The linear framework, which encompasses systems both at thermodynamic equilibrium and away from equilibrium, provides a sound theoretical foundation for modelling the post-translational modifications that underlie many biochemical mechanisms of time-keeping and decision-making in living cells.

2. Decision-making in cell physiology

2.1. Early studies

Experimental and theoretical studies of decision-making by bistable molecular circuits go back many years, at least to the observations of Novick & Weiner [10] on the ‘all-or-none’ behaviour of the lac operon (figure 2a) and later mathematical models by Griffith [11], Thomas [12] and Santillán & Mackey [13]. In cell cycle studies, Solomon et al. [14] observed an abrupt activation of CDK activity, which was later attributed to bistability in a mathematical model of the feedback control of CDK (figure 2b) [15], and bistable behaviour was demonstrated experimentally by Sha et al. [16] and Pomerening et al. [17]. Nasmyth [18] proposed that—quite generally—progression through the eukaryotic cell cycle involves irreversible switching between two ‘self-maintaining’ states: low CDK activity (G1 phase) and high CDK activity (S-G2-M phases). The origin of this behaviour is the mutual antagonism between CDKs and their ‘enemies’ (stoichiometric inhibitors and cyclin-degrading pathways; figure 2c), as made clear later by mathematical modelling [19]. Ferrell & Machleder [20] observed an ‘all-or-none’ maturation response of frog oocytes to progesterone
treatment, which they attributed to bistability in the MAP kinase signalling pathway (figure 2d). Yates et al. [21] and later van den Ham & de Boer [22] studied the phenotypic polarization of helper T cells with nonlinear differential equations based on the regulatory properties of master transcription factors (mutual inhibition and self-activation (MISA); figure 2e). van den Ham & de Boer found up to four stable steady states: naive cell (both factors off), Th1 cell (Tbet on), Th2 cell (Gata3 on) and dual-expressing cell (both factors on). The same motif was introduced by Huang et al. [23] to model the differentiation of blood cell progenitors into erythroid and myeloid cell lineages. Chickarmane et al. [24] modelled the differentiation of embryonic stem cells in terms of two basic transcription factors (Oct4-Sox2 dimer and Nanog) that mutually activate each other, creating a bistable switch with the transcription factors being either ON or OFF. Perkins & Swain [25] and Balázsi et al. [26] have reviewed optimal decision-making in noisy environments.

The common themes of these early studies are that (i) cells make decisions by flipping between coexisting stable steady states (bistability or multi-stability) and (ii) multiple stable steady states are generated by biochemical reaction networks with mutual inhibition and/or self-activation [27]. We see these themes repeated over and over again in more recent developments, with interesting twists.

### 2.2. Bistability and multi-stability in models of stem cell differentiation

The differentiation of pluripotent embryonic stem cells and of blood cell progenitors has long fascinated mathematical biologists (e.g. an early review by Laurent & Kellersohn [28]). MISA motifs are hallmarks of the study by Chickarmane & Peterson [29] on the differentiation of stem cell, trophoectoderm and endoderm lineages; figure 3a. They found that, as the signal is varied, the control system may exhibit four different steady states: trophoectoderm, endoderm, stem cell and ‘differentiated’ stem cell. Later, Chickarmane et al. [30] used a similar model to study the role that stochastic noise in gene expression plays in the differentiation process, concluding that Nanog heterogeneity is the deciding factor in stem cell fate. In the meantime, in a study of Nanog expression in mouse embryonic stem cells, Kalmar et al. [31] observed two populations of cells: HER cells (high Nanog, relatively stable) and LN cells (low Nanog, relatively unstable but more likely to differentiate). To account for their observations, they proposed a model of noise-driven excitability (figure 3b; an activator–inhibitor motif rather than a MISA motif).

Mutual inhibition between mRNA and microRNA has been proposed by Tian et al. [32] as a mechanism for bistable switches in cell fate decisions (figure 3c). They applied this idea to the epithelial-to-mesenchymal transition (EMT) in embryonic development [33] with a mathematical model based on two bistable switches (figure 3d) controlling the expression of the transcription factors Snail and Zeb. At low TGFβ (the inducer of EMT), Snail and Zeb are turned off, and the cell is expressing epithelial genes. At intermediate TGFβ, Snail and Zeb are turned on partially, and the cell is not secreting TGFβ (partial EMT state). At higher levels of (paracrine) TGFβ, the cell turns on Snail and Zeb fully and starts secreting TGFβ, which locks the cell in the mesenchymal state by autocrine signalling, even if the external TGFβ signal drops substantially.

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[34] and Hong et al. [35–37], who used MISA motif models to understand in more detail the differentiation of CD4+ T cells into multiple lineages and into hybrid cells expressing multiple cytokines.

2.3. Multi-cell/multi-scale modelling

Up to this point, we have attributed cell differentiation to bistability and multi-stability at the single-cell level, based on MISA motifs in the underlying control circuits. In a fascinating paper, Stanoev et al. [38] recently proposed a conceptually different dynamical mechanism in which cell types emerge and are maintained collectively by cell–cell communication as a novel inhomogeneous state of the coupled system. They showed how spatial patterns of cell differentiation (inhomogeneous steady states) arise in a population of cells as cell number increases. Robust proportions of differentiated cells emerge spontaneously and recover reliably after perturbations.

De Mot et al. [39] proposed a multi-cellular model for the differentiation of the inner cell mass into epiblast and primitive endoderm based on tristability in the Nanog–Gata6–Fgf4 network (figure 1b). The model was later extended to account for cell division [40]. Saiz et al. [41] proposed a related model that further highlights the role of Fgf4 signalling between cells in the cell fate decision and in the embryo’s response to perturbations in lineage composition. An important aspect of embryonic development is the coupling of mechanics to gene expression in the context of cellular tissue that is increasing in cell number due to division. Extending their model of Cdx2/Oct4 and Nanog/Gata3 interactions (figure 3a) to include mechanical forces and cell division, Krupinski et al. [42] have attacked this problem in the context of pattern formation in the mammalian blastocyst. Their multi-cell/multi-scale approach is a powerful tool to model how cells move within the embryo in response to mechanical forces and how cell positions influence cell fates (the formation of trophectoderm and of endoderm).

Macklin et al. [43] presented a multi-scale model of solid tumour growth, which illustrated the potential of mathematical modelling to understand complex interactions of cell proliferation, extracellular matrix degradation, angiogenesis and nutrient availability on the ability of solid tumours to expand. Populations of budding yeast cells growing on sucrose were studied by Dai et al. [44]. The population was maintained by daily dilution with fresh medium. Because sucrose is hydrolysed to glucose and fructose externally, the cells benefit from neighbours (called the Allee effect in population biology), and if the daily dilution factor is too large, the population undergoes a catastrophic collapse from a stable population density to extinction. The ‘tipping point’ is a saddle-node bifurcation, and close to this point the population should become more vulnerable to fluctuations (loss of resilience), which they demonstrated experimentally. In bacterial biofilms, a different type of vulnerability arises from a conflict between interior and peripheral cells. Peripheral cells protect interior cells from chemical attack but, at the same time, starve interior cells of nutrients. Liu et al. [45] showed that biofilm cells resolve this conflict by periodically halting growth to increase nutrient availability to interior cells. The oscillations, observed period 2–3 h, are due to Hopf bifurcations in the mathematical model.

2.4. Cell cycle modelling: checkpoints, variability and travelling waves

Cell cycle modelling has moved in several directions over the past decade. Regarding mammalian cell cycle regulation, Gérard & Goldbeter [46,47] presented a limit-cycle model of the CDK control system and assessed its merits. Weis et al. [48] confronted a published bistable switch model of CDK controls [49,50] with novel quantitative data on cyclin A2 and cyclin B1 accumulation, which suggested some
modifications to the published model. Heldt et al. [51] presented a model of light-responsive size control of DNA replication in *Chlamydomonas*, to explain the unusual ‘multiple-fission’ mode of cell division in this green alga. Li et al. [52] presented an elaborate, stochastic, spatio-temporal model of the asymmetric cell division cycle of *Caulobacter crescentus*, an alphaproteobacterium. Deterministic modelling of the budding yeast cell cycle has become more comprehensive. Palumbo et al. [53] presented a detailed model of the G1–S transition, based on multi-site phosphorylation of Whi5, an inhibitor of transcription of cyclin genes. Kraikivski et al. [54] presented a model of the budding yeast cell cycle (from start to finish) that tracks the dynamics of approximately 60 molecular species by a set of differential-algebraic equations. The model was fitted to the observed phenotypes of 263 mutant strains of budding yeast with 98% success (six strains could not be correctly simulated). Stochastic modelling has also progressed; the latest model by Barik et al. [55] provides excellent quantitative fit to observed measurements of cell cycle variability in wild-type cells and approximately 20 mutant strains. In particular, the model accounts for ‘partial viability’ of some mutant strains, which is a property that cannot be explained by a deterministic model. Other recent papers have explored the roles of checkpoints in the cell cycle, for example, the DNA damage checkpoint [56–58], the spindle assembly checkpoint [59], mitotic entry and exit [60] and the restriction point [61]. Comprehensive Boolean (discrete logical) models of the budding yeast cell cycle have also been proposed, starting with Fauré et al. [62] and pursued subsequently by Münzner et al. [63] at a ‘genome scale’ and by Howell et al. [64] to incorporate spatial effects into a logical model of mitotic exit.

Because the activation of MPF (a cyclin-CDK dimer) is a bistable switch (figure 2b), Novak & Tyson [65] predicted that ‘trigger’ waves of MPF activation would propagate in syncytial (i.e. multi-nucleate) tissues at a speed of 10–100 µm min⁻¹. Twenty years later, these waves were observed definitively by Chang & Ferrell [66] in frog egg extracts supplemented with sperm nuclei. The waves travelled at approximately 50 µm min⁻¹.

### 2.5. Synthetic regulatory circuits

The age of synthetic genetic regulatory networks was inaugurated by the ground-breaking papers of Gardner et al. [67]—the genetic toggle switch, and Elowitz & Leibler [68]—the repressilator. Stricker et al. [69] created the first robust, tunable, synthetic gene oscillator, based on an activator–inhibitor motif (like figure 3b), in *E. coli* cells. Tigges et al. [70] created a tunable synthetic oscillator in a mammalian cell with a transcriptional control circuit encoding both positive and time-delayed negative feedback loops. Danino et al. [71] showed that a population of oscillating cells could be synchronized by global intercellular coupling, which was introduced by cloning the *Vibrio* quorum sensing machinery into their oscillating *E. coli* strain. Zhang et al. [72] designed and implemented a synthetic NF-κB oscillator in budding yeast cells, based on RelA (a nuclear factor κB protein) and IκBε (an inhibitor of RelA).

Matsuda et al. [73] studied ‘cell-type bifurcation’ of Chinese hamster ovary cells that were engineered with a basic transcriptional repression circuit based on Delta-Notch signalling between cells supplemented with an intracellular self-activation circuit whereby Notch induces expression of Lfng (Lunatic Fringe) and Lfng activates Notch. The population consisted of a mixture of Delta-expressing cells (low Notch and Lfng) and Lfng-expressing cells (low Delta and high Notch).

Sekeine et al. [74] have engineered a reaction–diffusion pattern network in human embryonic kidney cells using the Nodal–Lefty signalling system, which satisfies—in principle—the requirements of Turing pattern formation: Nodal activates the production of both Nodal and Lefty, Lefty inhibits the activity of Nodal, and the diffusion range of Lefty (the inhibitor) is approximately 3.5 times longer than Nodal (the activator). Nonetheless, the authors propose that the patterns they observe are not Turing patterns but ‘solitary localized structures’ caused by an excitable or bistable reaction–diffusion system with a rapidly diffusing inhibitor. In this mechanism, Nodal foci are formed by short-range self-activation and further propagation of Nodal activation is stopped by long-range inhibition.

The potential for synthetic decision-making has been greatly expanded by two publications. Gordley et al. [75] showed how slow-acting, synthetic bistable switches (in yeast cells) can be selectively tuned by fast-acting, synthetic phospho-regulons. Zhu et al. [76] introduced ‘MultiFate’ technology for creating synthetic circuits that support controllable and expandable multi-stability in mammalian cells. MultiFate circuits are created from synthetic zinc-finger transcription factors that enable homodimer-dependent self-activation and heterodimer-dependent cross-inhibition. The MultiFate-2 circuit is the MISA motif introduced in figure 2c; it readily generates bistability and tristability in a controllable fashion. MultiFate-3 cells can generate up to seven stable steady states.

### 2.6. Pattern formation in bistable systems

Shortly after fertilization, the *C. elegans* zygote establishes an anterior–posterior gradient of PAR proteins in the cell cortex. In modelling this phenomenon, Goehring et al. [77] found that passive advection of PAR proteins by transient actomyosin-driven flow in the cell cortex can serve as a mechanical trigger for the formation of a persistent spatial pattern in a reaction–diffusion system exhibiting bistability. Bistability in their model is generated by mutually antagonistic interactions between ‘anterior’ and ‘posterior’ PAR proteins.

All above-ground plant tissues originate from stem cell divisions in shoot apical meristems (SAM). Stem cells, in the central zone of SAM, express the transcription factor WUSCHEL, which upregulates its own inhibitors, encoded by CLAVATA genes. Spontaneous emergence of a central zone is often modelled by a Turing mechanism, for example [78], but Battogtokh [79] has shown that pattern formation in a bistable system gives a better description of the nucleation and confinement of the stem cell domain. His proposal for SAM patterning closely resembles patterning in the Nodal–Lefty system developed by Sekine et al. [74].

### 2.7. Programmed cell death

Apoptosis is an interesting cell fate decision whereby, in response to severe stress, a cell commits ‘suicide’. Crucially, this decision, once made, must be irreversible, and a one-way bistable switch is ideally suited to this end. Following
on early models of irreversible apoptosis in mammalian cells [80–83], Ziraldo & Ma [84] presented a mathematical model of the apoptotic switch in the fruit fly and discussed the role of feedback topology on the reversibility or irreversibility of the switch. Autophagy (self-feeding) is another interesting cellular stress response, whereby a cell breaks down its own macromolecules to obtain energy and raw materials for survival purposes. By design, autophagy is reversible, so that the cell can recover if the stress is removed soon enough. If the stress is too intense, autophagy (which can be lethal if taken too far) is usually coordinated with the intrinsic apoptotic death pathway. Kapuy et al. [85] have modelled this crosstalk between apoptosis and autophagy and the positive feedback loop that makes the apoptosis switch irreversible.

3. Conclusion
Altogether, the studies reviewed in Parts I and II of this Special Issue have contributed greatly to our understanding of the molecular mechanisms underlying biological information processing, giving us a deeper appreciation of the—often non-intuitive—dynamical interplay of biochemical switches and clocks and the life-sustaining processes that they support. The progress resulting from the development, analysis and application of mathematical models has revolutionized our interpretation of experimental observations and renewed our vision of future possibilities in health science and biotechnology.

Data accessibility. This article has no additional data.

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References

1. Jimenez J, 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)
2. 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)
3. Burckard O, Teboul M, Delaunay F, Chaves M. 2022 Special Issue have contributed greatly to our understanding of landscapes of cell fate decisions. J. Theor. Biol. 210, 249–263. (doi:10.1016/j.jtbi.2002.0013)
4. Dupont G, Gonze D. 2022 Initial source of bistability in the early mammalian embryo. Proc. Natl Acad. Sci. USA 115, 10637–10642. (doi:10.1073/pnas.1809087115)
5. 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)
6. Thomas R. 1991 Regulatory networks seen as asynchronous automata. J. Theor. Biol. 153, 1–23. (doi:10.1016/0022-5193(90)90350-9)
7. Balazsi G, van Oudenaarden A, Collins JJ. 2011 Strategies for cellular decision-making. Proc. Natl Acad. Sci. USA 108, 10641–10646. (doi:10.1073/pnas.1103822108)
8. Tyson JJ, Novak B. 2002 Time-committing and decision-making in the cell cycle. J. Theor. Biol. 220, 2000075. (doi:10.1016/j.jtbi.2001.07.075)
9. Nam K-M, Martinez-Corral R, Gunawardena J. 2022 The linear framework: using graph theory to reveal the algebra and thermodynamics of biomolecular systems. Interface Focus 12, 20220013. (doi:10.1098/rsfs.2022.0013)
10. Novick A, Weiner M. 1957 Enzyme induction as an all-or-none phenomenon. Proc. Natl Acad. Sci. USA 43, 553–566. (doi:10.1073/pnas.43.7.553)
11. Thomas R, Ari R. 1990 Cyclin activation of p34cdc2. Science 249, 346–351. (doi:10.1126/science.2493461)
12. Huang S, Guo YP, May G, Enver T. 2007 Bifurcation dynamics in lineage-commitment in bipotential progenitor cells. Dev. Biol. 305, 655–713. (doi:10.1016/j.ydbio.2007.02.036)
13. Nycin C, Tyson JJ. 2003 Hysteresis drives cell-cycle transitions in Xenopus laevis egg extracts. Proc. Natl Acad. Sci. USA 100, 975–980. (doi:10.1073/pnas.0235349100)
14. Sha W, Moore J, Chen K, Lassaletta AD, Yi CS, Tyson JJ, Sible JC. 2003 Hysteresis drives cell-cycle transitions in Xenopus laevis egg extracts. Proc. Natl Acad. Sci. USA 100, 975–980. (doi:10.1073/pnas.0235349100)
15. Pomerening JR, Sontag ED, Ferrell Jr JE. 2003 Bistability in the activation of Cdc2. J. Theor. Biol. 220, 2000075. (doi:10.1016/j.jtbi.2002.0013)
16. Thomas R. 1991 Positive feedback to one gene. J. Theor. Biol. 153, 1–23. (doi:10.1016/0022-5193(90)90350-9)
17. Thomas R, Ari R. 1990 Cyclin activation of p34cdc2. Science 249, 346–351. (doi:10.1126/science.2493461)
18. Chang C-H, Kirschner MW. 1990 Cyclin activation of p34cdc2. Science 249, 346–351. (doi:10.1126/science.2493461)
19. Tyson JJ, Novak B. 2001 Regulation of the eukaryotic cell cycle: molecular antagonism, hysteresis, and irreversible transitions. J. Theor. Biol. 210, 249–263. (doi:10.1016/j.jtbi.2001.2293)
20. Bellamy J, Fitchette IM, Machleder EM. 1998 The biochemical basis of an all-or-none cell fate switch in Xenopus oocytes. Science 280, 895–898. (doi:10.1126/science.280.5365.895)
21. Yates A, Callard R, Stark J. 2004 Combining cytokine signalling with T-bet and GATA-3 regulation in Th1 and Th2 differentiation: a model for cellular decision-making. J. Theor. Biol. 231, 181–196. (doi:10.1016/j.jtbi.2004.06.013)
22. van den Ham HJ, de Boer RJ. 2008 From the two-dimensional Th1 and Th2 phenotypes to high-dimensional models for gene regulation. Int. Immunol. 20, 1269–1277. (doi:10.1093/intimm/dxn093)
71. Danino T, Mondragon-Palomino O, Tsimring L, Hasty J. 2010 A synchronized quorum of genetic clocks. *Nature* **463**, 326–330. (doi:10.1038/nature08753)

72. Zhang ZB, Wang QY, Ke YX, Liu SY, Ju JQ, Lim WA, Tang C, Wei P. 2017 Design of tunable oscillatory dynamics in a synthetic NF-κB signaling circuit. *Cell Syst.* **5**, 460–470 e465. (doi:10.1016/j.cels.2017.09.016)

73. Matsuda M, Koga M, Woltjen K, Nishida E, Ebisuya M. 2015 Synthetic lateral inhibition governs cell-type bifurcation with robust ratios. *Nat. Commun.* **6**, 6195. (doi:10.1038/ncomms7195)

74. Sekine R, Shibata T, Ebisuya M. 2018 Synthetic mammalian pattern formation driven by differential diffusivity of Nodal and Lefty. *Nat. Commun.* **9**, 5456. (doi:10.1038/s41467-018-07847-x)

75. Gordley RM, Williams RE, Bashor CJ, Toettcher JE, Yan S, Lim WA. 2016 Engineering dynamical control of cell fate switching using synthetic phospho-regulators. *Proc. Natl Acad. Sci. USA* **113**, 13 528–13 533. (doi:10.1073/pnas.1610973113)

76. Zhu R, Del Rio-Salgado JM, García-Ojalvo J, Elowitz MB. 2022 Synthetic multistability in mammalian cells. *Science* **375**, eabg9765. (doi:10.1126/science.abg9765)

77. Goehring NW, Trong PK, Bois JS, Chowdhury D, Nicola EM, Hyman AA, Grill SW. 2011 Polarization of PAR proteins by advective triggering of a pattern-forming system. *Science* **334**, 1137–1141. (doi:10.1126/science.1208619)

78. Fujita H, Toyokura K, Okada K, Kawaguchi M. 2011 Reaction–diffusion pattern in shoot apical meristem of plants. *PLoS ONE* **6**, e18243. (doi:10.1371/journal.pone.0018243)

79. Battogtokh D. 2015 Domain nucleation and confinement in agent-controlled bistable systems. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* **91**, 032713. (doi:10.1103/PhysRevE.91.032713)

80. Eissing T, Conzelmann H, Gilles ED, Allgower F, Bullinger E, Scheurich P. 2004 Bistability analyses of a caspase activation model for receptor-induced apoptosis. *J. Biol. Chem.* **279**, 36 892–36 897. (doi:10.1074/jbc.M404893200)

81. Legewie S, Bluthgen N, Herzel H. 2006 Mathematical modeling identifies inhibitors of apoptosis as mediators of positive feedback and bistability. *PLoS Comput. Biol.* **2**, e120. (doi:10.1371/journal.pcbi.0020120)

82. Bagci EZ, Vodovotz Y, Billiar TR, Ermentrout GB, Bahar I. 2006 Bistability in apoptosis: roles of Bax, Bcl-2, and mitochondrial permeability transition pores. *Biophys. J.* **90**, 1546–1559. (doi:10.1529/biophysj.105.068122)

83. Zhang T, Brazhnik P, Tyson JJ. 2009 Computational analysis of dynamical responses to the intrinsic pathway of programmed cell death. *Biophys. J.* **97**, 415–434. (doi:10.1016/j.bpj.2009.04.053)

84. Ziraldo R, Ma L. 2015 A mathematical model for apoptotic switch in *Drosophila*. *Phys. Biol.* **12**, 056003. (doi:10.1088/1478-3975/12/5/056003)

85. Kapuy O, Vinod PK, Mandl J, Banhegyi G. 2013 A cellular stress-directed bistable switch controls the crosstalk between autophagy and apoptosis. *Mol. Biosyst.* **9**, 296–306. (doi:10.1039/C2MB25261A)