ELSEVIER

Oscillations in cell biology

Karsten Kruse and Frank Jülicher

Oscillations play an important role in many dynamic cellular processes. They can emerge as the collective dynamic behavior of an ensemble of interacting components in the cell. Examples include oscillations in cytoskeletal structures such as the axonemes of cilia. Spontaneous oscillations of mechano-sensitive hair bundles have been shown to give frequency selectivity and amplification to mechano-sensation. In some bacteria, oscillations of Min proteins are important for division site selection. Genetic oscillators form the basis of circadian clocks. All these oscillations share many general features. Models and theoretical approaches are essential for an understanding of the principles underlying these dynamic cellular processes.

Addresses
Max Planck Institut für Physik komplexer Systeme, Nöthnitzer Str. 38, 01187 Dresden, Germany

Corresponding authors: Kruse, K (karsten@mpipks-dresden.mpg.de) and Jülicher, F (julicher@mpipks-dresden.mpg.de)

Current Opinion in Cell Biology 2005, **17**:20–26

This review comes from a themed issue on
Cell structure and dynamics
Edited by Anthony A Hyman and Jonathon Howard

Available online 15th December 2004

0955-0674/$ – see front matter

DOI 10.1016/j.ceb.2004.12.007

Introduction

Cells are dynamic systems (see glossary) that constantly alter their state and are able to generate morphological changes and motion. Such dynamic phenomena arise from the interplay of cellular components such as the gene expression machinery, interacting proteins and cellular structures including the cytoskeleton. It is an important challenge to understand how dynamic behaviors emerge in a cell. One would like to identify general principles that underlie the cellular organization and permit the existence of dynamic behaviors related to cellular functions. Systems biology addresses such questions by studying how functional biological units can exhibit complex behaviors, which result from the architecture of the system rather than from specific properties of isolated components.

Spontaneous oscillations represent the simplest example of complex dynamics and hence oscillating systems are ideally suited for a theoretical analysis of the interactions and dynamic properties of a complex system. Here, we discuss recent progress in the study of oscillations in cell biology.

Nonlinear oscillators

Active oscillators can generate spontaneous oscillations, which continue indefinitely. This is in contrast to passive oscillators such as the strings of a piano, where oscillations die down. In the case of spontaneous oscillations, a variable of the system changes periodically in time. The shape of oscillations can be sinusoidal or follow a different periodic function. Oscillations are characterized by their amplitude and their phase. The amplitude is the maximal value the variable attains during a period; the phase indicates the state of the oscillator relative to the beginning of a period. Spontaneous oscillations occur only in nonlinear dynamic systems that are open (i.e. there is a continuous flow of energy through the system from its environment) [1]. Biological systems fall in this category and in general are able to exhibit oscillations [2].

Oscillations of cytoskeletal structures

The generation of forces and motion in cells is mediated by active processes in the cytoskeleton. Active cytoskeletal structures can undergo oscillating instabilities, where a non-oscillating state becomes unstable and is replaced by an oscillating one, if system parameters are changed. A prototype system is the generation of oscillations by molecular motors [3]. A single motor, which generates a force along a filament, will attain a stable displaced state when acting on an elastic spring. If a large number of motors act together, this state can under certain conditions become unstable with respect to oscillatory motion. A collection of motors can suddenly lose their grip on the filaments on which they act via a rupture process in which the initial detachment of a few motors induces the subsequent detachment of the remaining motors. If this collective detachment is followed by a renewed build-up of force, oscillatory motion is generated. To study whether and how such oscillations occur requires a mathematical description of the dynamics of the system, taking into account the physical properties of the coupled elements. A theoretical analysis, for example an analyis of the dynamics of small perturbations (linear stability analysis) or numerical calculations, can reveal the physical mechanisms underlying oscillation generation and permit the calculation of oscillation frequencies and amplitudes. A general mechanism of oscillation generation in motors is related to a dynamic instability in the force–velocity relationship (see glossary) of motor collections that has been suggested on theoretical grounds [4]. The concept of a dynamic instability in the force–velocity

Glossary

Collective dynamic behavior
Behavior of a system that emerges from the interactions of a large number of components and in which all components take part. Isolated components cannot show this behavior.

Compressive nonlinearity
A response which increases less than linearly with the stimulus strength.

Dynamic instability
If the parameters of a dynamic system are changed, a dynamic state that initially was stable with respect to perturbations can lose stability. In this case a new state becomes stable. The points at which the stability of dynamic states change are called dynamic instabilities.

Dynamic system
In a mathematical context, a dynamic system is a set of deterministic equations for the time-evolution of several variables. After long times a dynamic system displays one of a few possible types of dynamic states such as a steady state, oscillations or chaos. The dynamic equations typically depend on parameters that qualitatively influence the dynamic states of the system. For a general introduction, see [1]. In a more general context a dynamic system evolves according to specific rules.

Force–velocity relationship
A force-generating system such as a motor protein advancing on a cytoskeletal filament can be characterized by a force–velocity relationship indicating the average velocity the system generates while acting against a specified force. The signature of a dynamic instability in the force–velocity curve is an abrupt change of the mean velocity as a function of the force and hysteresis.

Noisy oscillation
The oscillating state of a system that is subject to fluctuations in amplitude and phase.

Non-linear dynamic system
A dynamical system is nonlinear if the sum of two solutions to the equations is not solution. Non-linearities appear if different components of a system interact.

Relaxation oscillations
A dynamic system with a discontinuous dynamic instability that exhibits hysteresis can show relaxation oscillations. These oscillations occur if a slow feedback process brings the system periodically across the instability (see [2]).

Self-organization
Emergence of a spatio-temporal pattern as a collective dynamic behavior. Such pattern-generation requires a continuous energy input to the system.

Spontaneous oscillation
Periodically varying state of a dynamic system in the absence of external forcing that is attained irrespective of initial conditions. Spontaneous oscillations only exist in nonlinear dynamic systems and persist with finite amplitude.

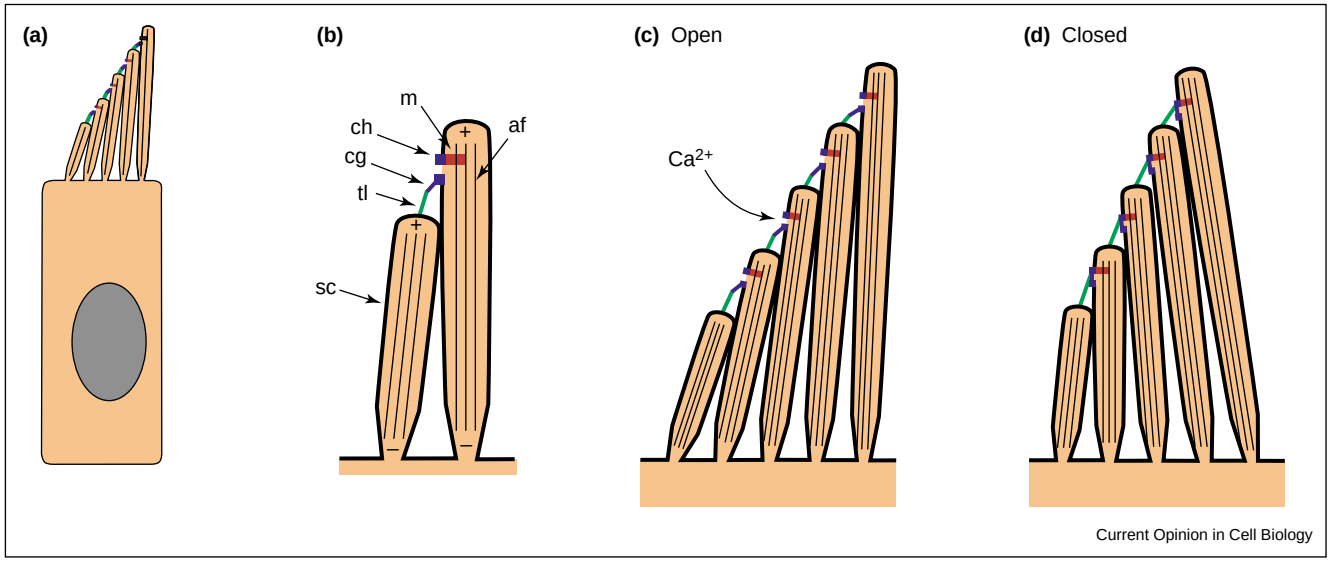
Thermal fluctuations
Fluctuations are rapid and irregular variations on the molecular scale which result from intermolecular interactions. Thermal fluctuations are fluctuations which occur in a system at thermodynamic equilibrium. An example is the random Brownian motion of small particles in a fluid.

curve of a motor collection can provide a framework for the understanding of unconventional types of motility such as the bidirectional motion of filaments observed in motility assays investigating NK11 mutants of NCD motors [5,6]. Individual NK11 molecules are unable to generate directed motion. However, groups of these mutants can move microtubules in one direction for several seconds and then reverse direction. Spontaneous oscillations have also been observed during asymmetric cell divisions. In this case, the spindle poles exhibit periodic motion and it has been proposed that this phenomenon results from an interplay between astral microtubules and cortical force generators [7,8,9•].

Mechanical oscillations can be of direct importance for the biological function of a cytoskeletal system. An example of this is provided by the dynamics of axonemes. These are elastic bundles of microtubule doublets that form the motile elements of eucaryotic cilia. Force generation by dynein motors leads to the sliding of microtubule doublets relative to each other, resulting in bending deformations of the bundle. The finding that active force-generating systems have the tendency to undergo oscillating instabilities if they act on elastic elements suggests that motors and microtubules can generate oscillations in the axoneme without any other element being necessary, since the bending elasticity of the microtubules provides an elastic element to which motors are coupled [10,11]. Wave-like patterns could thus result from the self-organization of dynein motors and microtubules [11,12]. Muscle oscillations, as observed in the flight muscles of many insects, could similarly result from oscillating instabilities of sarcomeres [13].

The fact that oscillations in force-generating systems represent a general phenomenon can be further illustrated by the motion of some bacteria, such as *Listeria monocytogenes*. This bacterium propels itself in an infected cell by polymerizing an actin gel on its surface [14]. This gel material grows in the form of a comet, which trails the cell. While the velocity of the generated motion is typically constant, some mutants advance in a saltatory manner [15]. Theoretical analysis suggests that these oscillations emerge by a dynamic instability of the force-generating system based on the sudden rupture of the gel from the bacterium's surface and rapid subsequent relaxation of the gel [16,17]. *In vitro* experiments using latex beads coated with the VCA protein, which is a subdomain of the Wiskott–Aldrich syndrome protein (WASP), have supported this view and demonstrated that this oscillating instability can be induced by varying the bead size [18].

Figure 1



The signal transduction apparatus of auditory hair bundles. **(a)** Schematic representation of a hair cell. Hairs cells are characterized by a hair bundle consisting of stereocilia. **(b)** The stereocilia (sc) contain bundles of actin filaments (af) with their plus-end directed towards the stereocilia tip. They are connected by elastic tip links (tl) to their neighbors. Deformations of the bundle induce the opening of ion channels (ch) by mechanical action on the channel gate (cg). The tension in the tip links is controlled by myosin motors (m). During spontaneous oscillations, the system changes periodically between two extreme situations shown in (c) and (d). **(c)** Channels are open, tip-links extended. Ca^{2+} enters the stereocilia via ion channels and down-regulates the myosin motors. **(d)** Channels are closed, tip-links relaxed. The motors are upregulated by a falling Ca^{2+} concentration.

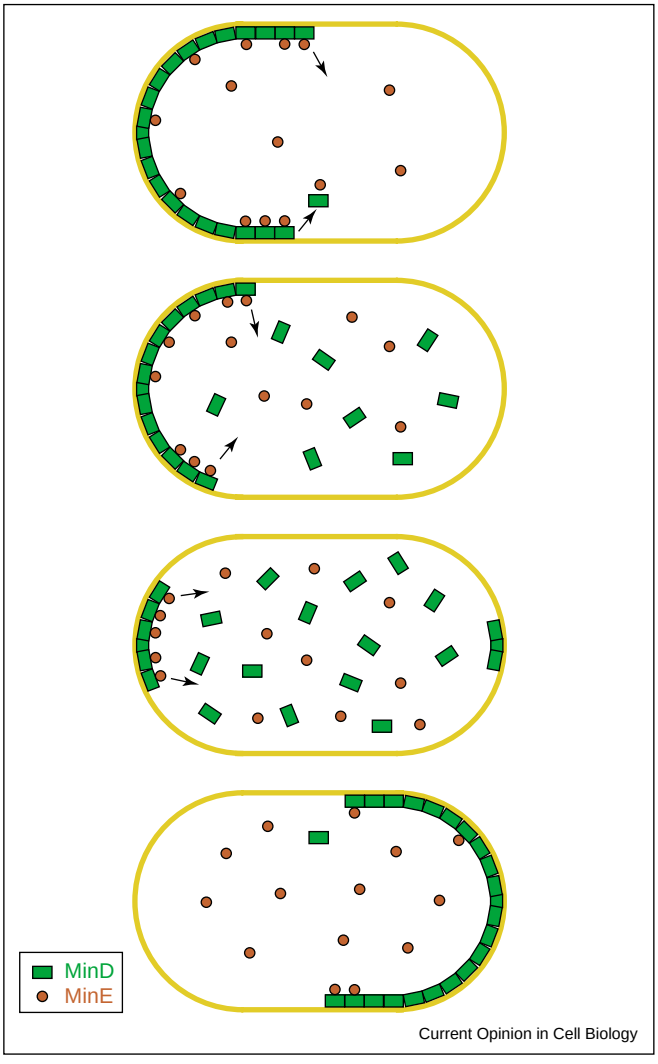
Spontaneous oscillations of auditory hair bundles

Hair cells are the mechanosensors in the hearing organs of vertebrates and can amplify mechanical stimuli using active processes [19]. The sensory element, the hair bundle, consists of about 50 rod-like extensions called stereocilia. Shear deformations of the hair bundle induce the opening of mechanosensory ion channels and subsequently a change in the membrane potential (see Figure 1). It has recently been shown that in the bullfrog sacculus the hair bundles display spontaneous movements, which are noisy oscillations (see glossary) [20–24,25••]. These spontaneous oscillations are driven by active processes, including the interaction of adaptation motors, possibly myosin-1c or myosin-VIIa, with actin filaments in the stereocilia [25••,26,27]. The combined system — the motors, the mechanosensitive ion channels and the feedback provided by Ca^{2+} concentration regulating the motor activity — can undergo an oscillating instability. This can be shown by a theoretical analysis of simple models of the transduction apparatus in the hair bundle [25••,28,29•]. The existence of spontaneous oscillations modifies the mechanical properties of the hair bundle and makes it most sensitive just at the frequency at which spontaneous movements occur. Furthermore, stimulation at this frequency with a periodically varying force leads to a response amplitude that exhibits a compressive nonlinear behavior (see glossary) [30]. A compressive nonlinearity is characteristic of the active amplifier in vertebrate hearing. Near an oscillatory instability, non-linear oscillators exhibit in general a compressive nonlinearity if stimulated at their oscillation frequency. Therefore they provide a framework to describe active amplification [31,32]. Theoretical analysis shows that the spontaneous oscillations provide the hair bundle with a frequency-selective, amplified response to mechanical stimuli. Fluctuations resulting from the stochastic action of motors and the stochastic opening and closing of channels as well as from thermal fluctuations generate the noise in the observed oscillations. These fluctuations strongly influence the hair bundle's mechanical response to stimuli [29•].

Oscillations in bacteria

In some cases, spatiotemporal oscillations are used to structure cells spatially. Division of the rod-like bacterium *Escherichia coli* occurs perpendicular to its long axis in the cell center, resulting in two equal daughter cells. The location of the division septum is determined by a ring consisting of FtsZ, a bacterial analog of tubulin. The positioning of this Z-ring in the cell center results from the spatial distribution of the DNA and of proteins of the Min system. This system consists of three proteins, MinC, MinD and MinE, of which MinC is an inhibitor

Figure 2

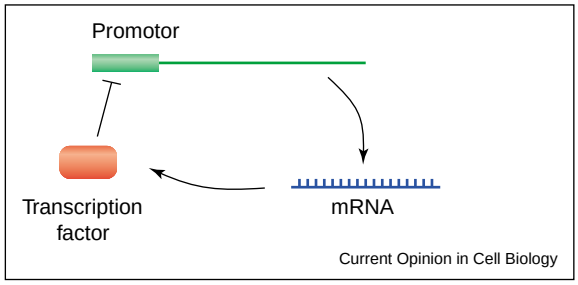


Schematic representation of Min oscillations in *E. coli*. MinD (green) is localized on the inner bacterial membrane (yellow) on one side of the cell, where it aggregates. MinE (red) induces disassembly of the MinD aggregates and detachment of MinD molecules into the cytoplasm. MinD then assembles on the membrane of the opposite side of the cell and the process is repeated.

of Z-ring formation. Membrane-associated MinC and MinD rapidly oscillate from pole to pole [33–35] (see Figure 2). Therefore both poles experience large concentrations of MinC while at the cell center its concentration remains relatively low, resulting in the suppression of Z-ring formation at the poles. The oscillations are generated by MinD and MinE, the former of which binds to the membrane and aggregates into filaments [36,37,38•]. MinC co-localizes with MinD but is not essential for oscillations. Several mechanisms which could lead to the observed oscillations via dynamic instabilities have been discussed theoretically [39–42]. A central element of all these mechanisms is the recruitment of MinE to the membrane by MinD and the MinE-induced detachment of MinD from the membrane. The formation of MinD filaments has been suggested to be a further necessary element [41,42].

MinD is involved in the spatial regulation of cell division in many bacteria, but oscillations of this protein have been reported in only a few. It belongs to the large ParA subfamily of bacterial proteins, most of which are associated with DNA segregation [43]. Other members of this family that have been observed to show pole-to-pole oscillations are ParA in *E. coli* [44–46] and Soj in *Bacillus subtilis* [47,48]. The function of the ParA and Soj oscillations are not known. In general, however, spatiotemporal oscillations provide the bacterium with information about its geometry and thus represent a general means to assess large-scale properties of a cell by molecular processes.

Figure 3



Genetic oscillations are often generated by negative feedback resulting from a transcription factor repressing the promotor of its own gene. The feedback involves the production of mRNA as an intermediate. Because of the time lag between repression and mRNA production, the protein level can change periodically.

Genetic oscillations

Gene expression is regulated by transcription factors which themselves are gene products. The resulting networks of genetic interactions represent interconnected dynamical systems, which generally can undergo oscillating instabilities. Genetic oscillations are observed in a growing number of systems.

The best-studied examples of genetic oscillators are circadian clocks [49] and cell cycle oscillators [50]. More recently, oscillations involved in the segmentation of vertebrates [51] and oscillations of the tumor suppressor p53 [52,53••] and of the NFκB-IκBα signaling module [54] have received attention. To obtain a fundamental understanding of oscillatory gene expression, it has proved valuable to use simplified systems and to focus on general mechanisms [55]. Theoretical work could provide models for genetic oscillators and even predict oscillatory behaviors [52]. The simplest case of a feedback oscillator is represented by a single gene, its product and the corresponding mRNA (see Figure 3). If the gene product inhibits transcription of the mRNA, the gene expression can oscillate if the time between the beginning of transcription and the end of translation can be represented by a time delay in the self-inhibitory system [56•]. This mechanism has been proposed to provide the basis for segmentation oscillations [57]. Furthermore, the p53–Mdm2 and the NFκB–IκBα systems can successfully be described using this framework. Oscillators based on auto-inhibition with time-delay possess the remarkable property that the oscillation period is mainly determined by the time delay and depends only weakly on the average protein expression rates [56•].

Networks forming circadian clocks typically involve more components than just a protein and its mRNA [49]. These clocks must work faithfully against various backgrounds in different stages of the cell cycle and under different environmental conditions (e.g. variations in food supply or temperature). One way to achieve robustness with respect to varying conditions is through cell–cell communications. In cyanobacteria, evidence has been found that oscillations in individual cells maintain their amplitude and temporal period over a long time [58••]. In such systems robustness could be achieved by relaxation oscillations (see glossary). [59,60].

Conclusions

Investigation of the dynamics of complex systems has shown that the interplay of many components in chemical, mechanical and/or genetic networks readily leads to oscillatory behaviors as a consequence of self-organization. From this point of view the widespread occurrence of oscillations in cell biology is therefore no surprise. Cellular oscillations can be of direct importance for biological functions such as axonemal beat, hair bundle oscillations and circadian clocks. Oscillations may in some cases have no function and simply reflect the dynamic properties of a system.

The study of oscillations in cell biology provides valuable information about the organization of cellular processes. Oscillations are the simplest case of dynamical processes found in complex systems. The key characteristics of this dynamic state can be quantitatively determined in experiments. The emergence of oscillations in a complex system is subtle as it depends crucially on the dynamic properties of the interacting components and their collective behaviors. Therefore, theoretical approaches are an essential tool in the study of cellular oscillations. The focus on cellular oscillations using a combination of theory and experiment represents a first step in the development of a systematic approach for the study of the self-organization and function of cellular systems.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Strogatz SH: *Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry, and Engineering.* Reading, Mass: Addison-Wesley; 1994.

2. Murray JD: *Mathematical Biology*. edn 3. Berlin: Springer; 2002.

3. Jülicher F, Prost J: **Spontaneous oscillations of collective molecular motors**. *Phys Rev Lett* 1997, **78**:4510-4513.

4. Jülicher F, Prost J: **Cooperative molecular motors**. *Phys Rev Lett* 1995, **75**:2618-2621.

5. Endow SA, Higuchi H: **A mutant of the motor protein kinesin that moves in both directions on microtubules**. *Nature* 2000, **406**:913-916.

6. Badoual M, Jülicher F, Prost J: **Bidirectional cooperative motion of molecular motors**. *Proc Natl Acad Sci USA* 2002, **99**:6696-6701.

7. Grill SW, Gonczy P, Stelzer EH, Hyman AA: **Polarity controls forces governing asymmetric spindle positioning in**

the *Caenorhabditis elegans* embryo. *Nature* 2001, **409**:630-633.

8. Colombo K, Grill SW, Kimple RJ, Willard FS, Siderovski DP, Gonczy P: **Translation of polarity cues into asymmetric spindle positioning in *Caenorhabditis elegans* embryos**. *Science* 2003, **300**:1957-1961.

9. • Grill SW, Howard J, Schäffer E, Stelzer EH, Hyman AA: **The distribution of active force generators controls mitotic spindle position**. *Science* 2003, **301**:518-521.
The authors estimate the number of cortical force generators that act on aster fragments generated by centrosome disintegration and show that a larger number act on the posterior side as compared to the anterior side. These force generators and their interactions with microtubules play a key role in spindle positioning and oscillations.

10. Brokaw CJ: **Molecular mechanism for oscillation in flagella and muscle**. *Proc Natl Acad Sci USA* 1975, **72**:3102-3106.

11. Camalet S, Jülicher F: **Generic aspects of axonemal beating**. *N J Phys* 2000, **2**:1-23.

12. Brokaw CJ: **Computer simulation of flagellar movement VIII: coordination of dynein by local curvature control can generate helical bending waves**. *Cell Motil Cytoskeleton* 2002, **53**:103-124.

13. Vilfan A, Duke T: **Synchronization of active mechanical oscillators by an inertial load**. *Phys Rev Lett* 2003, **91**:114101.

14. Theriot JA, Mitchison TJ, Tilney LG, Portnoy DA: **The rate of actin-based motility of intracellular *Listeria monocytogenes* equals the rate of actin polymerization**. *Nature* 1992, **357**:257-260.

15. Lasa I, Gouin E, Goethals M, Vancompernolle K, David V, Vanderkerkhove J, Cossart P: **Identification of two regions in the N-terminal domain of ActA involved in the actin comet tail formation by *Listeria monocytogenes***. *EMBO J* 1997, **16**:1531-1540.

16. Gerbal F, Chaikin P, Rabin Y, Prost J: **An elastic analysis of *Listeria monocytogenes* propulsion**. *Biophys J* 2000, **79**:2259-2275.

17. Prost J: **The physics of *Listeria* propulsion**. In *Physics of biomolecules and cells.* Edited by Flyvbjerg H, Jülicher F, Ormos P, David F. EDP Sciences; 2001:215-236.

18. Bernheim-Groswasser A, Wiesner S, Golsteyn RM, Carlier MF, Sykes C: **The dynamics of actin-based motility depend on surface parameters**. *Nature* 2002, **417**:308-311.

19. Hudspeth A: **Mechanical amplification of stimuli by hair cells**. *Curr Opin Neurobiol* 1997, **7**:480-486.

20. Crawford AC, Fettiplace R: **The mechanical properties of ciliary bundles of turtle cochlear hair cells**. *J Physiol* 1985, **364**:359-379.

21. Martin P, Hudspeth AJ: **Active hair-bundle movements can amplify a hair cell's response to oscillatory mechanical stimuli**. *Proc Natl Acad Sci USA* 1999, **96**:14306-14311.

22. Hudspeth AJ, Choe Y, Mehta AD, Martin P: **Putting ion channels to work: mechanoelectrical transduction, adaptation, and amplification by hair cells**. *Proc Natl Acad Sci USA* 2000, **97**:11765-11772.

23. Fettiplace R, Ricci AJ, Hackney CM: **Clues to the cochlear amplifier from the turtle ear**. *Trends Neurosci* 2001, **24**:169-175.

24. Manley GA, Kirk DL, Koppl C, Yates GK: ***In vivo* evidence for a cochlear amplifier in the hair-cell bundle of lizards**. *Proc Natl Acad Sci USA* 2001, **98**:2826-2831.

25. •• Martin P, Bozovic D, Choe Y, Hudspeth AJ: **Spontaneous oscillation by hair bundles of the bullfrog's sacculus**. *J Neurosci* 2003, **23**:4533-4548.
This work provides a systematic study of spontaneous hair bundle oscillations under various conditions and shows that these observations are consistent with a simple model of hair bundle mechanics.

26. Holt JR, Gillespie SK, Provance DW, Shah K, Shokat KM, Corey DP, Mercer JA, Gillespie PG: **A chemical-genetic strategy implicates myosin-1c in adaptation by hair cells**. *Cell* 2002, **108**:371-381.

27. Kros CJ, Marcotti W, van Netten SM, Self TJ, Libby RT, Brown SD, Richardson GP, Steel KP: **Reduced climbing and increased slipping adaptation in cochlear hair cells of mice with Myo7a mutations**. *Nat Neurosci* 2002, **5**:41-47.

28. Vilfan A, Duke T: **Two adaptation processes in auditory hair cells together can provide an active amplifier**. *Biophys J* 2003, **85**:191-203.

29. • Nadrowski B, Martin P, Jülicher F: **Active hair-bundle motility harnesses noise to operate near an optimum of mechanosensitivity**. *Proc Natl Acad Sci USA* 2004, **101**:12195-12200.
This is a theoretical study of signal amplification by spontaneously oscillating hair bundles. The authors show that fluctuations strongly influence the mechanical properties of hair bundles and need to be considered in a quantitative description.

30. Martin P, Hudspeth AJ: **Compressive nonlinearity in the hair bundle's active response to mechanical stimulation**. *Proc Natl Acad Sci USA* 2001, **98**:14386-14391.

31. Camalet S, Duke T, Jülicher F, Prost J: **Auditory sensitivity provided by self-tuned critical oscillations of hair cells**. *Proc Natl Acad Sci USA* 2000, **97**:3183-3188.

32. Eguiluz VM, Ospeck M, Choe Y, Hudspeth AJ, Magnasco MO: **Essential nonlinearities in hearing**. *Phys Rev Lett* 2000, **84**:5232-5235.

33. Raskin DM, de Boer PA: **Rapid pole-to-pole oscillation of a protein required for directing division to the middle of *Escherichia coli***. *Proc Natl Acad Sci USA* 1999, **96**:4971-4976.

34. Hu Z, Lutkenhaus J: **Topological regulation of cell division in *Escherichia coli* involves rapid pole to pole oscillation of the division inhibitor MinC under the control of MinD and MinE**. *Mol Microbiol* 1999, **34**:82-90.

35. Raskin DM, de Boer PA: **MinDE-dependent pole-to-pole oscillation of division inhibitor MinC in *Escherichia coli***. *J Bacteriol* 1999, **181**:6419-6424.

36. Hu ZL, Gogol EP, Lutkenhaus J: **Dynamic assembly of MinD on phospholipid vesicles regulated by ATP and MinE**. *Proc Natl Acad Sci USA* 2002, **99**:6761-6766.

37. Suefuji K, Valluzzi R, RayChaudhuri D: **Dynamic assembly of MinD into filament bundles modulated by ATP, phospholipids, and MinE**. *Proc Natl Acad Sci USA* 2002, **99**:16776-16781.

38. • Shih YL, Le T, Rothfield L: **Division site selection in *Escherichia coli* involves dynamic redistribution of Min proteins within coiled structures that extend between the two cell poles**. *Proc Natl Acad Sci USA* 2003, **100**:7865-7870.
The authors observe helical MinD structures in living *E. coli*. These structures are independent of helices in the bacterium that are formed by other proteins. Their findings show that Min oscillations are a cytoskeletal phenomenon involving filament dynamics.

39. Meinhardt H, de Boer PA: **Pattern formation in *Escherichia coli*: a model for the pole-to-pole oscillations of Min proteins and the localization of the division site**. *Proc Natl Acad Sci USA* 2001, **98**:14202-14207.

40. Howard M, Rutenberg AD, de Vet S: **Dynamic compartmentalization of bacteria: accurate division in *E. coli***. *Phys Rev Lett* 2001, **87**:278102.

41. Kruse K: **A dynamic model for determining the middle of *Escherichia coli***. *Biophys J* 2002, **82**:618-627.

42. Huang KC, Meir Y, Wingreen NS: **Dynamic structures in *Escherichia coli*: spontaneous formation of MinE rings and MinD polar zones**. *Proc Natl Acad Sci USA* 2003, **100**:12724-12728.

43. Lutkenhaus J, Sundaramoorthy M: **MinD and role of the deviant Walker A motif, dimerization and membrane binding in oscillation**. *Mol Microbiol* 2003, **48**:295-303.

44. Ebersbach G, Gerdes K: **The double par locus of virulence factor pB171: DNA segregation is correlated with oscillation of ParA**. *Proc Natl Acad Sci USA* 2001, **98**:15078-15083.

45. Hunding A, Ebersbach G, Gerdes K: **A mechanism for ParB-dependent waves of ParA, a protein related to DNA segregation during cell division in prokaryotes**. *J Mol Biol* 2003, **329**:35-43.

46. Ebersbach G, Gerdes K: **Bacterial mitosis: partitioning protein ParA oscillates in spiral-shaped structures and positions plasmids at mid-cell**. *Mol Microbiol* 2004, **52**:385-398.

47. Marston AL, Errington J: **Dynamic movement of the ParA-like Soj protein of *B. subtilis* and its dual role in nucleoid organization and developmental regulation**. *Mol Cell* 1999, **4**:673-682.

48. Quisel JD, Lin DC, Grossman AD: **Control of development by altered localization of a transcription factor in *B. subtilis***. *Mol Cell* 1999, **4**:665-672.

49. Dunlap JC: **Molecular bases for circadian clocks**. *Cell* 1999, **96**:271-290.

50. Tyson JJ, Chen K, Novak B: **Network dynamics and cell physiology**. *Nat Rev Mol Cell Biol* 2001, **2**:908-916.

51. Pourquie O: **The segmentation clock: converting embryonic time into spatial pattern**. *Science* 2003, **301**:328-330.

52. Bar-Or RL, Maya R, Segel LA, Alon U, Levine AJ, Oren M: **Generation of oscillations by the p53–Mdm2 feedback loop: a theoretical and experimental study**. *Proc Natl Acad Sci USA* 2000, **97**:11250-11255.

53. •• Lahav G, Rosenfeld N, Sigal A, Geva-Zatorsky N, Levine AJ, Elowitz MB, Alon U: **Dynamics of the p53–Mdm2 feedback loop in individual cells**. *Nat Genet* 2004, **36**:147-150.

This is an experimental study of oscillations of the tumor suppressor p53 in individual living cells. Oscillations result from a simple feedback mechanism and provide evidence for a digital response of p53 expression to cell damage.

54. Hoffmann A, Levchenko A, Scott ML, Baltimore D: **The IκB-NF-κB signaling module: temporal control and selective gene activation**. *Science* 2002, **298**:1241-1245.

55. Goldbeter A: **Computational approaches to cellular rhythms**. *Nature* 2002, **420**:238-245.

56. • Monk NAM: **Oscillatory expression of Hes1, p53, and NF-κB driven by transcriptional time delays**. *Curr Biol* 2003, **13**:1409-1413.

The author shows that time delays could play a key role in the generation of oscillations in genetic feedback systems.

57. Lewis J: **Autoinhibition with transcriptional delay: A simple mechanism for the zebrafish somitogenesis oscillator**. *Curr Biol* 2003, **13**:1398-1408.

58. •• Mihalcescu I, Hsing W, Leibler S: **Resilient circadian oscillator revealed in individual cyanobacteria**. *Nature* 2004, **430**:81-85.

The authors study circadian oscillators in bacteria. In an individual bacterium, these oscillations have strong temporal stability characterized by a correlation time of several months. After this time, the imprecision of this clock is one cycle or 24h.

59. Barkai N, Leibler S: **Circadian clocks limited by noise**. *Nature* 2000, **403**:267-268.

60. Vilar JMG, Kueh HY, Barkai N, Leibler S: **Mechanisms of noise-resistance in genetic oscillators**. *Proc Natl Acad Sci USA* 2002, **99**:5988-5992.