**2008 Lecture on Nonlinear Physics**

**Graduate School of Science**

**Kyoto University**

**Subject：Theories of Life**

**Teacher：Masatoshi Murase**

**Office: Yukawa Institute for Theoretical Physics**

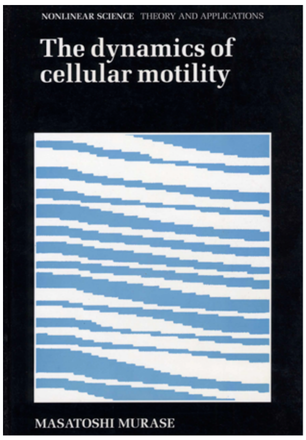
**E-mail: murase@yukawa.kyoto-u.ac.jp**

## No.1　Background and Introduction

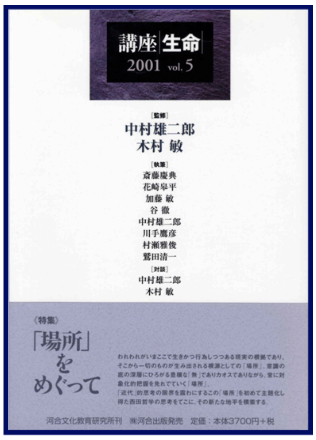
A challenging problem that has puzzled biologists for over 100 years is how cilia and flagella produce such a variety of spatio-temporal bending patterns.  In some species, the development of propagating waves is a typical phenomenon, which is believed to be useful for locomotion.  Many theoretical models have been proposed to account for these ordered motions.  In other species, however, it seems more important to consider the advantage of the disordered motions which lead to intermittent beating and reversal of the direction of wave propagation.  Unfortunately, no attempt has been made to account for these modes of motion in previous theoretical models.

I will propose here quite new mathematical models of cilia and flagella.  These models can account for not only the ordered motion but also the disordered behaviour.  From a structural point of view, it is possible to understand the essential difference between the two modes of motion.

**Books** ①（１９９２）　②　（２０００）　③　（２００１）








① http://hdl.handle.net/2433/49765

② http://hdl.handle.net/2433/48889

③ http://hdl.handle.net/2433/48889

① This book presents new ideas and theories that account for oscillatory contraction in muscle and the various modes of flagellar and ciliary movements. Despite the great variety of dynamical behaviours, attempts have been made to model some of the specific modes, though not to account for the overall properties. I have tried to develop theoretical models and to interpret nearly all of the dynamical behaviours in terms of these models.

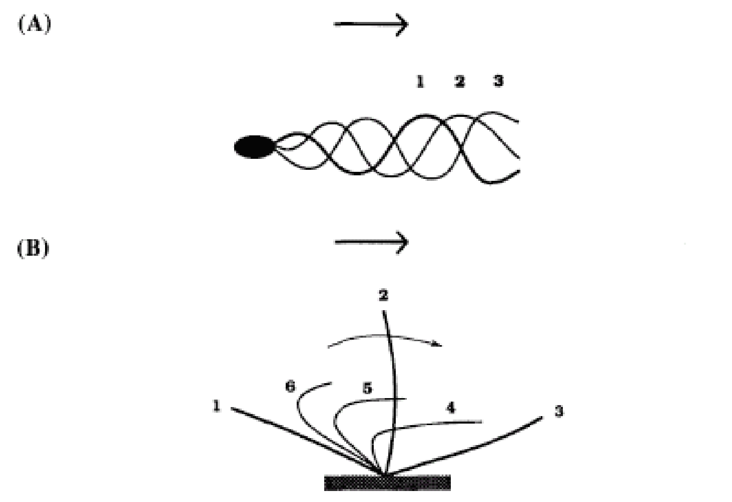
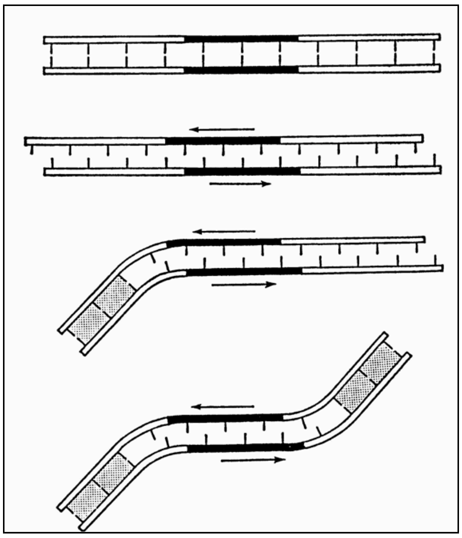
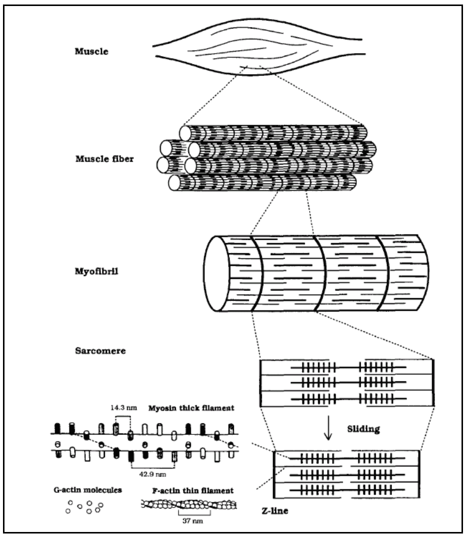



Figure 4.1 Typical beating patterns of flagella and cilia. (A): Successive waves with sustained amplitude (1 – 3) propagated toward the tip of a flagellum move water and thus propel the sperm head forward. (B): The beating cycle of a cilium consists of the effective stroke (1 – 3) in which the extended cilium moves rapidly toward one side by making an 'oar-like' movement, and the recovery stroke (4 – 6) in which the cilium moves more slowly back by propagating a bend from the base to the tip. The effective stroke occurs more or less in one plane. The recovery stroke swings either in the same plane or out of the plane. The arrows indicate the water flow caused by activity of the organelles.

*Maatoshi Murase "The Dynamics of Cellular Motility" Wiley (1992), p90*






Flagella

Muscle

Shingyoji et al. Nature 265, 279-270 (1977) ; *Murase "The Dynamics of Cellular Motility" (1992), p32*

② The book “Life as History” (Kyoto University Press, 2000) is written in Japanese. What is life? Despite the advanced studies of science, we have not yet answered this problem satisfactorily. What is worse, it is a double problem that we cannot realize how we are deeply influenced by the traditional way of Western thinking in attacking the original problem. Dichotomy of subject (or endo) and object (or exo), together with reductionism, specifies more and more the detailed components of a living system and in turn requires the reproducibility that the living system shows the same responses to the same stimuli under the same conditions. The dichotomy perspective of this kind, which has been central to modern science, stands on the assumption that opposites are mutually exclusive and even contradictory. Contrary to this dichotomy perspective, there is an alternative complementarity perspective typical of Eastern philosophy. The complementarity perspective actually suggests that opposites are not mutually exclusive, but merely complementary with one another; that is, the opposites are thought to be only the different aspects of the same wholeness. This means that there is no clear distinction between subject (endo) and object (exo). As the reproducibility principle that the same events occur under the same conditions is often violated, we must pay much attention to the transients during the past history of life. On the basis of this complementarity idea, therefore, we would be encouraged to have a holistic view by integrating fragments of knowledge at various component levels and time scales during the life history. In this sense, we need a new synthesis of Western science and Eastern philosophy instead of considering either of them separately. Only then, it is possible to attack the long-standing problem: what is life? Along this line, a process of endo-exo circulation was introduced as an essential paradigm of life. As a living organism is engaged in challenges from both its internal and external environments, it contains unlimited conflicts and oppositions, which in turn must be the driving force for its evolution and development. It is such dynamics that can give rise to identity of the living organism. The present book deals with many problems such as aging, cancer, evolution and development.

③ The book “Mind” (Kawai Press) is written in Japanese. What is mind? What is identity? How can we describe the identity of life? In the present book, I discussed the development of mind and the aging of mind. Essentially, mind can be understood as a process of endo-exo circulation. Such a process leads to an emergent symbol called Mandala. The identity of life was represented by Mandala.

## Papers


① Masatoshi Murase. (2008) Endo-exo circulation as a key process of evolution
http://hdl.handle.net/2433/49154

② Masatoshi Murase (2008) Environmental pollution and health: an interdisciplinary study of the bioeffects of electromagnetic fields Sansai (Kyoto University)
http://hdl.handle.net/2433/49793

④ Masatoshi Murase (1996) “Alzheimer’s Disease as Subcellular ‘Cancer’ : The Scale Invariant Principles Underlying the Mechanisms of Aging” *Prog. Theor. Phys.* **95**, 1-36 (1996).
http://hdl.handle.net/2433/48880

# International Symposium organized by Masatoshi Murase

**Nishinomiya-Yukawa International & Interdisciplinary Symposium on "What is Life? The Next 100 Years of Yukawa's Dream" Kyoto, 2007 (Chair: Masatoshi Murase)**

http://ocw.kyoto-u.ac.jp/en/index.htm


| | 10/15(Mon) | 10/16(Tue) | 10/17Wed) | 10/18(Thu) | | 10/19(Fri) | | 10/20(Sat) |
|---|---|---|---|---|---|---|---|---|
| 9:00 \| 9:15<br>9:15 \| 10:00 | S.Nara<br>M. Murase *Kyoto Univ.* Opening address<br>Nobuhiro Minaka *NIAES* Historical reasoning and abductive inference in phylogenetic reconstruction | K. Kaneko<br>Seunghwan Kim *APCTP* A few problems on functional self-organization in brain | K. Kato<br>Kunihiko Kaneko *Univ. Tokyo* Consitency principe in biological dynamical system: Plasticity, robustness, and genotype-phenotype relationship* | Y. P. Gunji<br>Susumu Goto *Kyoto Univ. Network perspective in bioinformatics*<br>Kiyoshi Miyagawa *Univ. Tokyo* Radiation and anti-cancer drug: How to cope with DNA damage? | 9:00 \| 9:20<br>9:20 \| 10:20 | I. Tsuda<br>Toshio Yokoyama *Kyoto Univ. The Premodern Japanese Approach to Life: Sharing the World with Non-Humans*<br>Aage R.Moller *Univ. Texas* Plasticity of the brain: For good and bad* | 9:00 \| 9:40 | Y. P. Gunji<br>Saburo Matsui *Kyoto Univ.* Faith Ethics for Sustainable Development |
| 10:15 \| 11:15 | S.Nara<br>Alex Mogilner *U. C. Davis* Sorting of polar filaments by multiple motor action | H. Kook<br>I. Tsuda, Y. Yamaguti, S. Kuroda, Y. Fukushima and M. Tsukada *Hokkaido Univ* A mathematical model for the hippocampus: towards the understanding of episodic memory and imagination* | K. Kato<br>Hiroyuki Takeda *Univ. Tokyo* Coupled oscillators in vertebrate segmentation | D. Deamer<br>Akio Kanai *Keio Univ.* Importance of periodicity in the genetic information and a new hypothesis of the tRNA evolution* | 10:35 \| 11:35 | A. Kanai<br>David Deamer *U. C. Santa Cruz* Self-assembly processes in the prebiotic environment | 9:50 \| 10:50 | R. Pinaud<br>Donald W. Pfaff *Rockefeller Univ.* The central neural foundations of awareness and self-awareness* |
| 11:30 \| 12:30 | S.Nara<br>Toshio Yanagida *Osaka Univ.* Single molecule study for elucidating the mechanism involved in utilizing fluctuations by biosystems | A. R. Moller<br>Tsutomu Murata *NICT, Brain Proj.* Creativity and Consciousness of the Human Brain | K. Kato<br>Vidyanand Nanjundiah *Indian Institute of Science* How important is genetic relatedness for social behaviour? | R. Rucker<br>Mark van Atten *CNRS, Paris* The foundations of mathematics as a study of life* | 11:45 \| 12:45 | Y. Takagi<br>Robert Arking *Wayne State Univ.* Why and how we age, and is that process modifiable?* | 11:00 \| 12:00 | K. Nishimura<br>Naoko Tosa *Kyoto Univ.* Computing of Japanese Culture |
| 14:45 \| 15:45 | S. Kim<br>Yukio-Pegio Gunji *Kobe Univ.* A minimal cell model showing both amoebic movement and network formationl* | Poster Session | L. Salford<br>John Evans *Cambridge University* Vertebrate growth and form: A whole-body approach | Free time | 14:15 \| 15:15 | C. Becker<br>Motohiro Yoritomi *Shuchiin Univ.* The multiple implications and functions in Mandalas* | 13:30 \| 14:10<br>14:20 \| 15:20 | J. Evans<br>Masami Ishido *Nat. Inst. Env.* The modification of biocellular chemical reactions by physico-chemical stimulants in the environment<br>Leif G. Salford Lund Univ. The mammalian brain in the electromagnetic fields designed by man* |
| 16:00 \| 17:00 | R. Arking<br>Luciano Floridi *Oxford Univ.* What is bioinformation? | K. Yoshimura<br>Yoshiaki Omura, MD, ScD *New York Medical College* Non-invasive quick diagonisis and safe & effective treatment of intractable medical problems: Anti-aging and anti-cancer | T. Murata<br>Mitsuhiko Shionoya *Univ. Tokyo* Nanoscopic Molecular Architectures in Supra-molecular Science | 16:15-17:15<br>S. Tsokolov<br>Franz Halberg *University of Minnesota* Life's waves in space-time in and around us | 15:40 \| 16:30 | A. Mogilner<br>Junji Takabayashi *Kyoto Univ.* Leaf volatile ecology: multitrophic interaction networks mediated by leaf volatiles* | 15:40 \| 16:30 | V. Nanjundiah<br>Carl Becker *Kyoto Univ.* Life from the Outside/Life from the Inside* |
| 17:30 \| 18:30 | K. Kaneko<br>Raphael Pinaud *Univ. of Rochester* Neural basis of vocal communication in songbirds* | Y. Miyake<br>Kuniaki Otsuka *Tokyo Women College Med.* Biological clocks in the life and its clinical use | M. van Atten<br>Rudy Rucker *San Jose State University* Life as a gnarly computation | T. Hondou<br>Hajime Kimata *Moriguchi-Keijinkai Hospital* Environmental stress and atopic dermatitis: Cure with steroid-free treatment and mutual trust* | 16:45 \| 17:45 | D. W. Pfaff<br>Nicholas Humphrey *London Univ.* The necessity of consciousness. Why human zombies would be an evolutionary dead end. | 16:45 \| 17:45 | S. Tsokolov<br>Tetsuro Matsuzawa *Kyoto Univ.* Chimpanzee mind: The evolutionary basis of human mind* |
| 18:45 \| 21:00 | Reception | | | | 18:45 \| 21:00 | Reception | 17:45 \| 17:50 | Masatoshi Murase *Kyoto Univ.* Closing address |
| 20:00 \| 20:45 | | Y. Miyake<br>Gentaro Taga *Univ. Tokyo* Being and Becoming Human: A dynamical systems perspective on development of brain and behavior* | K. Ebina<br>Yoshihiro Miyake *Tokyo Inst. Tech.* Co-creation of presence and its application to human interface* | S. Tanaka<br>Shoji Itakura *Kyoto Univ. Understanding other's mind: Approach from the Developmental Cybernetics* | | | | |

**Mastoshi Murase** (http://www2.yukawa.kyoto-u.ac.jp/~murase/eng/) became an associate professor at the Yukawa Institute for Theoretical Physics, Kyoto University, in 1992. He received a PhD degree from the University of Tokyo, Department of Pharmaceutical Sciences, in 1987. Positions held overseas include a period as a visiting scientist in the Physiology Department at Duke University Medical Centre from 1987 to 1988, and an associate professorship in the Department of Mathematics of the University of California at Davis from 1990 to 1991. He chaired an international symposium entitled, *"What is Life? The Next 100 Years of Yukawa's Dream"*, held in 2007 at Kyoto University, to commemorate the centenary of the birth of Hideki Yukawa. The proceedings of this symposium will appear as a *Progress of Theoretical Physics Supplement* in 2008 (Kyoto University: Yukawa Institute for Theoretical Physics). He

can be contacted by email at murase@yukawa.kyoto-u.ac.jp.

**Introduction**

One of the important problems in biology is to clarify the mechanisms underlying self-organization at various levels. From a thermodynamic point of view, self-organizating phenomena are likely to occur in non-equilibrium open systems close to or beyond instability of a stationary state (Nicolis and Prigogine, 1977). States possessing such properties are called dissipative structures (Prigogine et al., 1969). Their occurrence depends on (i) specific nonlinear dynamics taking place in each subsystem (i.e. each part of the system), and (ii) the way the subsystems couple.

An example of self-organizating phenomena occurs in a nervous system. Under space clamp conditions, where the state of the nerve membrane is spatially uniform or homogeneous, the nervous system exhibits temporal orders such as excitability, oscillations and multiple steady-state transitions in the form of all-or-none responses to external stimuli. If one removes the spatially homogeneous condition, to take into account the electrotonic coupling of nearby regions of the membrane, the system is no longer uniformly stable; instead, space-dependent patterns like action potentials can appear.

Self-organizating phenomena are also observed in biochemical systems, such as metabolic pathways. Under the spatially homogeneous conditions, when the medium is well stirred, time-dependent properties of concentration like excitability and oscillations appear. Without continuous stirring we must take into account diffusion, and the system gives rise to space-dependent travelling patterns known as chemical waves.

Another example is seen in a mechano-chemical system, such as muscle, cilia or flagella. This system not only exhibits excitability and oscillations, but also shows bending waves. Like electrotonic and diffusion coupling, an elastic coupling is responsible for the generation of space-dependent traveling patterns. It seems that these three biological systems may share, in spite of their detailed differences, common principles for the self-organization of spatio-temporal structures. The key requirements for these properties seem to be: (i) the excitable and/or oscillatory dynamics operating as a functional unit (or subsystem); and (ii) an attractive type of interaction between the units (or subsystems).

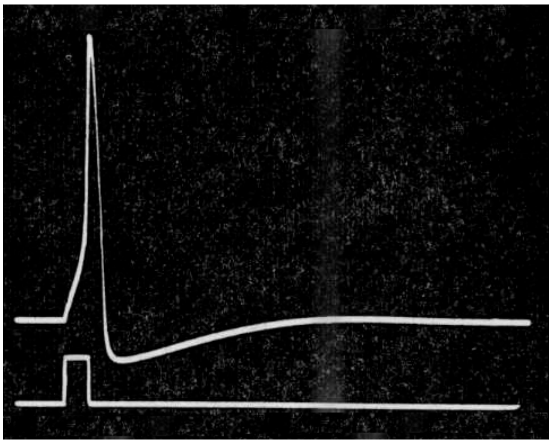
Recent theoretical and experimental studies, however, have revealed that the above two requirements are not always met. Under spatially homogeneous conditions, the nervous and biochemical systems show complex temporal patterns such as chaos and bursting oscillations. It will not be surprising if the mechano-chemical system shows similarly complex behaviours, though they have not been studied yet.

Much more complex dynamical behaviours occur when there is a repulsive type of interaction in addition to the attractive type. Under these conditions self-turbulization phenomena of spatio-temporal structures appear in the one-dimensional case, which leads to spatio-temporal chaos. The most interesting point is that the total system exhibits chaos through two functionally different interactions, even though an individual subsystem persists with its ordered temporal structure in isolation. Some spatio-temporal irregular behaviours have been observed in the flagellar system. These irregular behaviours may probably be interpreted in terms of the destabilization process similar to that found in the self-turbulization phenomena.

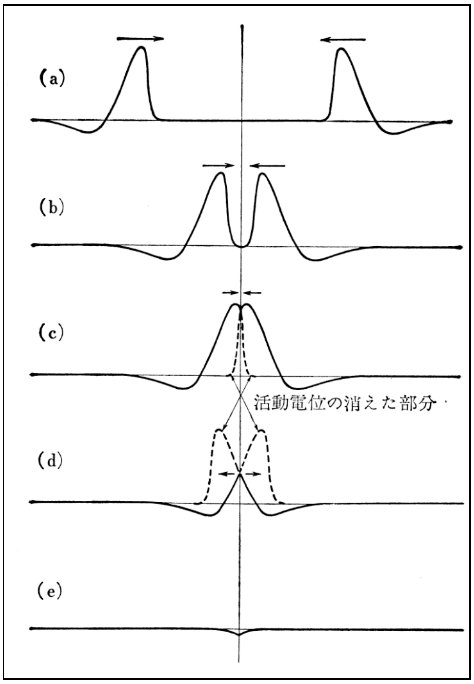
The mechano-chemical systems considered in this book provide various types of behaviours. These behaviours are worth studying not only from a physiological, but also from a theoretical point of view. Before considering this system, it is instructive to survey some of the mechanical and biological models which exhibit various types of order and disorder.

*Maatoshi Murase "The Dynamics of Cellular Motility" Wiley (1992), p1*

## (1) The nerve excitation and annihilation of two waves traveling in the opposite directions



Action potential due to a current stimulation

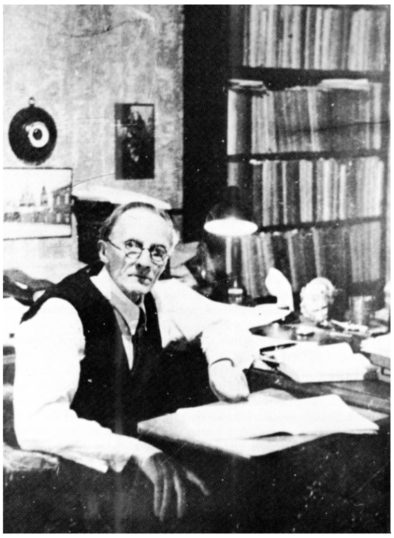



Annihilation of two impulses on collision

Gen Matsumoto “Nerve excitation” Maruzen (1981) 106, 81

## (2) The Belousov-Zhabotinski (BZ) reaction

The Belousov-Zhabotinski reaction is one of the best-studied oscillatory chemical processes.



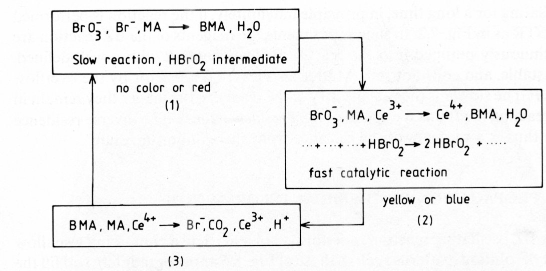
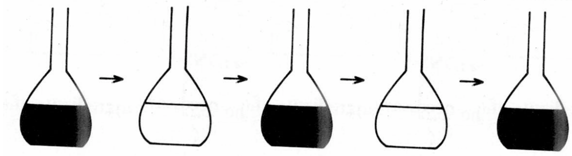
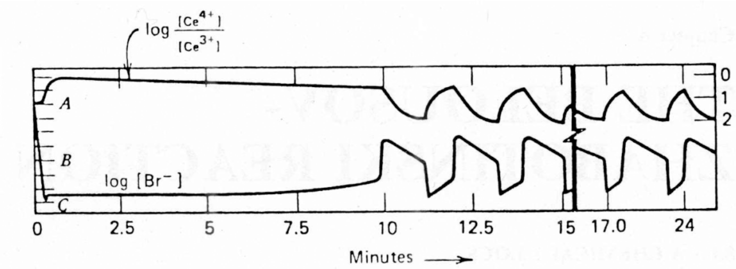


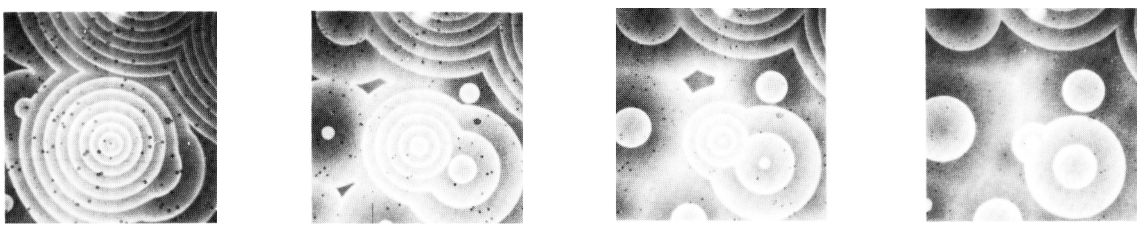

**Fig. 8.4.** The key intermediates of the BZ reaction. Some twenty elementary steps are needed for the description of the BZ reaction. In order to explicate the oscillating behavior, they are classified into three stages.

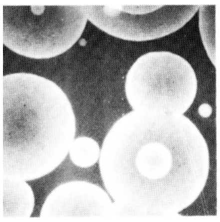


*Left: Arthur T. Winfree “When Time Breaks Down” Princeton Univ. Press (1987), p162*
*Right: A. Babloyantz “Molecules, Dynamics, and Life” Wiley (1986), p155 (top), 159 (bottom)*




*Left: Arthur T. Winfree “When Time Breaks Down” Princeton Univ. Press (1987), p172*
*Right: A. Babloyantz “Molecules, Dynamics, and Life” John Wiley & Sons (1986), p156*





There are four snapshots taken 1 minute apart and a fifth somewhat later. Waves erupt periodically from about ten pacemaker nuclei scattered about the dish in the end only those of shortest period suvive.

*Arthur T. Winfree "When Time Breaks Down" Princeton University Press (1987), p167*

## (3) The Mechano-chemical system

### Oscillatory contraction in muscle

Insects fly by beating their wings up and down. Their wing-beat frequencies range from about 5 Hz for butterflies to about 1000 Hz for mosquitos. The wing-movements of some insects result from oscillatory contraction of antagonistic pairs of direct flight muscles, while others are produced by indirect flight muscles. The direct muscles are inserted into the wing base so that the wing-movements are directly caused by these muscles. The indirect muscles occur in the thorax and they are not connected to the wing base; by distortions of the thorax, the wing-movements are indirectly produced.

Upon the arrival of motor nerve impulses, the muscle cell membrane is excited and causes a contraction. Usually a single nerve impulse or its associated muscle membrane excitation causes a single muscle contraction. Muscles of this type are called synchronous. Pringle (1949), however, found that specialized insect flight muscle contracts several times in response to a single electrical stimulu. Such muscles are described as asynchronous. A nerve impulse is necessary to initiate contractions, but subsequent contractions result from intrinsic properties of the muscle itself. Further nervous stimulation is necessary only to maintain the excited state of the muscle. Asynchronous muscle is, therefore, capable of oscillating at very high frequencies.

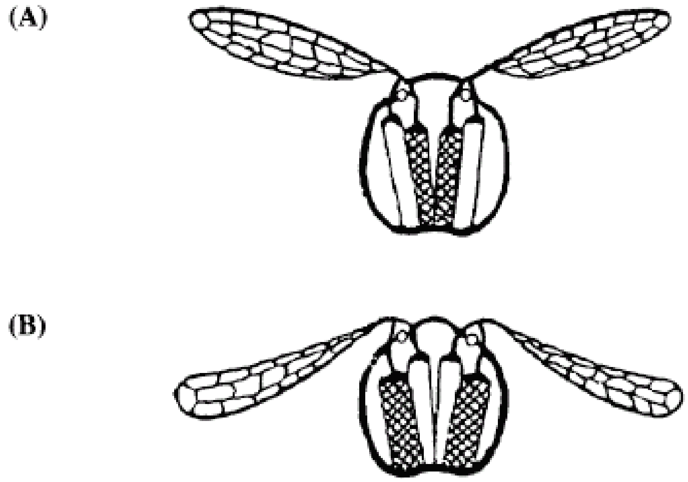



Figure 2.1 Synchronous, direct flight muscles of the type found in dragonflies. The thorax sections show that antagonistic pairs of flight muscles are directly connected to the wing base. The hinges are represented by black circles with white centres. (A): Contraction of the inner pair of muscles raises the wings and stretches the antagonistic pair. (B): Contraction of the outer pair of muscles lowers the wings and stretches the inner pair. Modified from Davydov (1982). Reprinted with permission.

*Masatoshi.Murase "The Dynamics of Cellular Motility" Wiley (1992), p30*

**Synchronous muscle and asynchronous muscle**

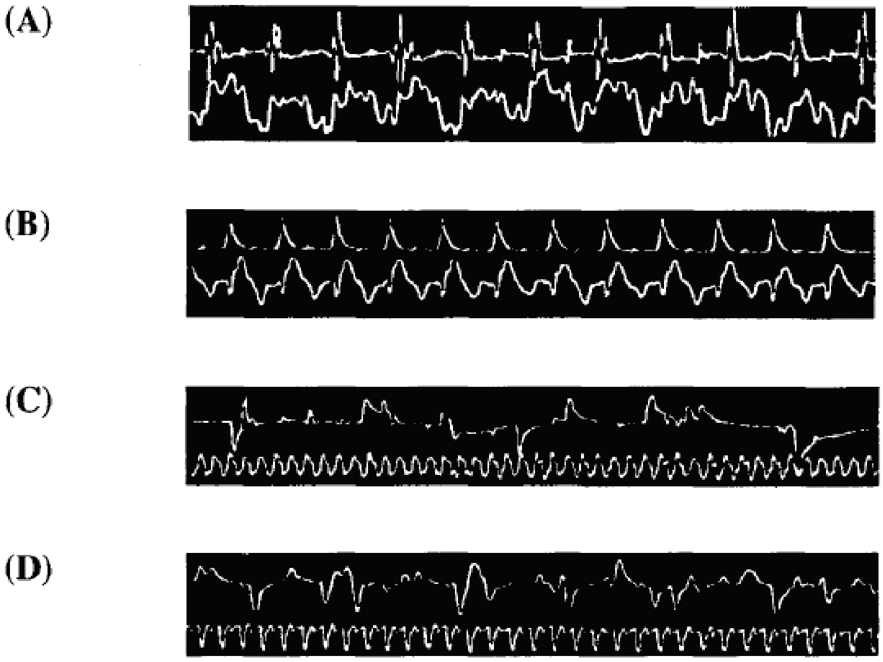



Figure 2.3 Electrical (upper trace) and mechanical (lower trace) records from the thorax of various insects. (A), (B) Synchronous type; (C), (D) asynchronous type. (A) Cockroach; (B) moth; (C) fly; (D) wasp. The wing-beat frequencies are 25, 43.5, 155 and 120 Hz for (A), (B), (C) and (D), respectively. Whereas the wing-beat frequency of insects with synchronous flight muscles is low, not more than about 100 Hz, the frequency is high in insects with asynchronous muscles. From Pringle (1957). Reprinted with permission.

*Masatoshi.Murase "The Dynamics of Cellular Motility" Wiley (1992), p31*

## Free-oscillation

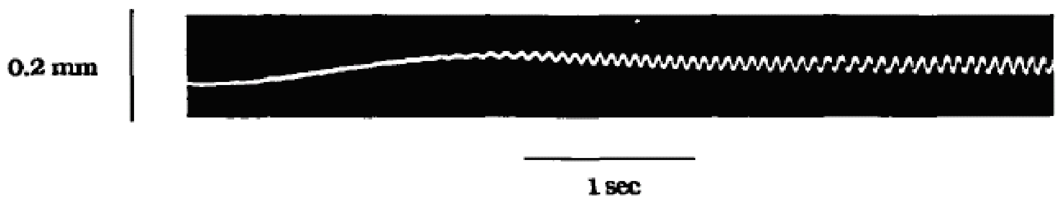



Figure 2.9 Free oscillation of glycerinated insect muscles. This oscillation requires a steady level of free calcium. From Jewell and Rüegg (1966). Reprinted with permission of the Royal Society.

*Masatoshi.Murase "The Dynamics of Cellular Motility" Wiley (1992), p38*

**Synchronization in flagella**

It has been observed that two or more nearby flagella, originally beating with different frequencies, tend to beat with a common frequency and wavelength due to mechanical coupling via moving fluid near the flagella. Such behaviour is typical of a certain class of nonlinear oscillators and is called synchronization.

As pointed out by Gray (1928), a well-known example of this phenomenon is given by two pendulum clocks hung on a common support. Because each clock transmits its vibrations to the support and at the same time receives from the support vibrations set up by the other, the pendulum of the slower clock is forced to swing by the faster clock resulting in acceleration of its vibrations. This example is simpler than the case of flagella because clocks counting time give rise to only 'temporal' synchronization whereas flagella generating bending waves exhibit both 'temporal' and 'spatial' synchronization.

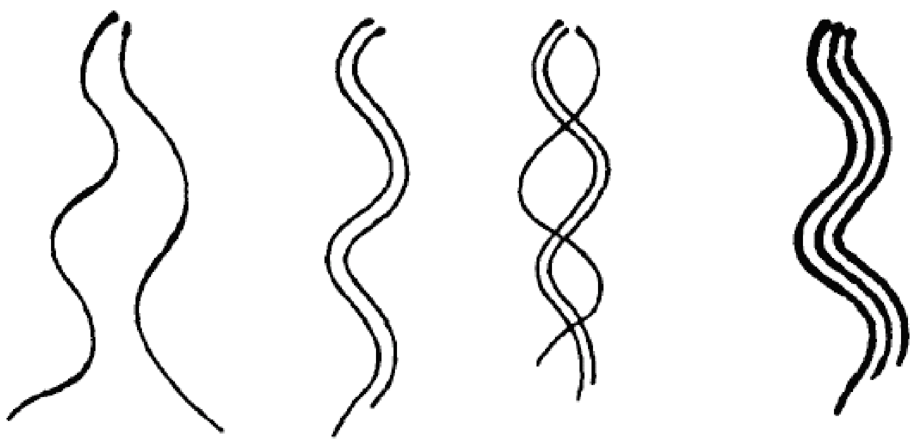


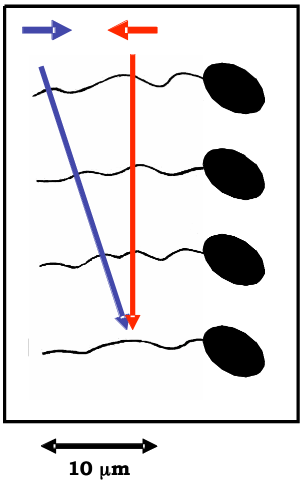
Figure 4.24 *Spirochaeta balbianii* exhibiting synchronism and metachronism. Each individual flagellum has a different waveform. When positioned close to each other, their movements tend to be coordinated by hydrodynamic interaction. Forces generated in the transverse direction (horizontal direction in the figure) presumably exceed those in the main axis of the flagellum (vertical direction in the figure). As a result, synchronization occurs parallel to the transverse forces. Metachronal waves propagate perpendicular to the direction of synchronization. From Gray (1928). Reprinted with permission.

Top Left, right, and bottom: *M.Murase "The Dynamics of Cellular Motility" Wiley (1992), p30, 31, 125*

## Non-anihilating waves

In abnormal conditions where the viscosity of the medium is increased (Holwill, 1965) or some chemical agent is added (Alexander and Burns, 1983), it is found that two waves travel in opposite directions. When the two waves pass each other the flagellum appears to be frozen. The following wave propagates along the flagellum from tip to base (Holwill, 1965).

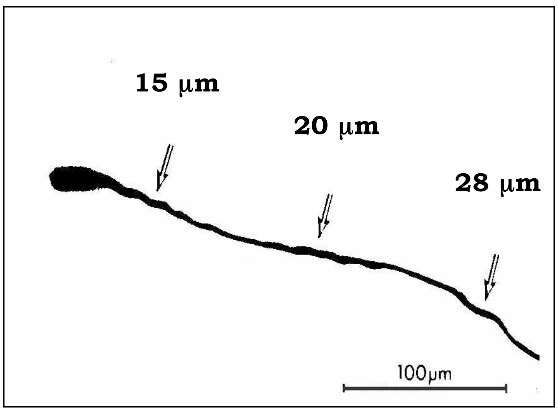
Two waves propagating in the opposite directions do not annihilate upon collision.




The motion of *Strigomonas Oncopelti.*
*M. E. J. Holwill J. Exp. Biol. 42, 125-137 (1965)*

## Spatio-temporal irregularity

A long (800 μm-long) cricket sperm flagellum shows complex dynamics.




Different sections have different wavelengths and different frequencies.
*R. Rikmenspoel Biophys. J. 23, 177-206 (1978)*

## Reversal of the direction of propagating waves

The distally propagating waves, typical of flagella of protozoa and spermatozoa, propel the cell through a medium. However, flagella of trypanosomatids, Crithidia oncopelti (Holwill, 1965) or Leishmania (Alexander and Burns, 1983), show an unusual ability to propagate bending waves from either the base or the tip. Normally these flagella propagate bending waves from tip to base, by which the cell is pulled in the direction of the flagellum.

Since there are no special structures at the tip that are initiating the tip-to-base bending waves, the reversal of the direction of propagating waves remains a mystery to be solved. Attempts have been made to solve the mystery by isolating the flagellum from the cell by laser irradiation (Goldstein et al., 1970; Goldstein, 1974). Interestingly, the amputated flagellar segments could beat, not only from the tip or the irradiated point, but also first from the tip and then from the irradiated point (Fig. 4.21) or vice versa. This indicated that the influence of the cell was not important in the reversal of wave propagation.

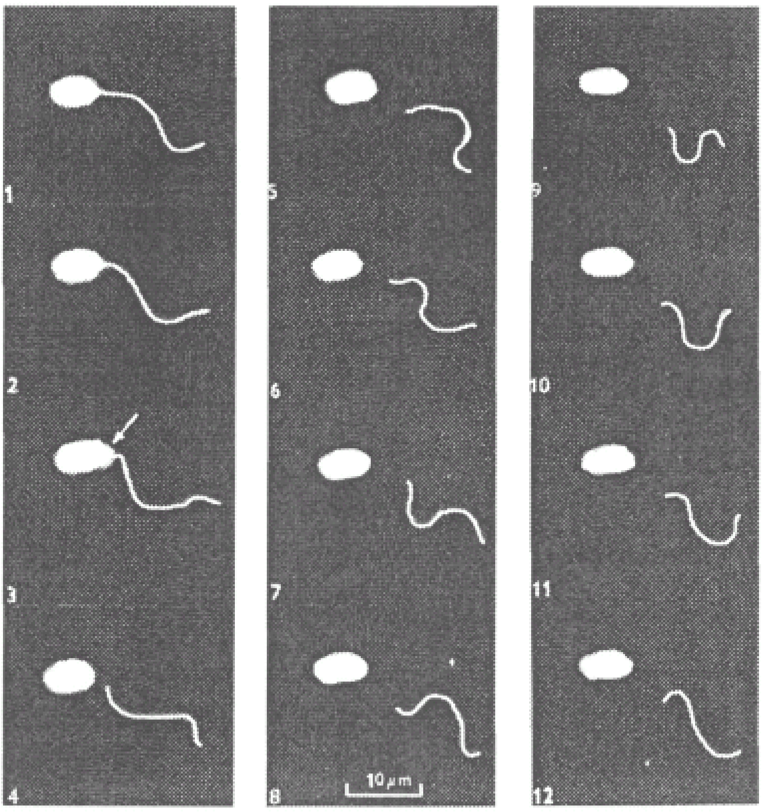



Figure 4.21 Selected frames illustrating the effect of laser radiation on a flagellum of *Crithidia oncopelti*. Panels 1 and 2: Tip-to-base waves are observed before irradiation. Panels 3 and 4: The laser beam hits a basal region. The flagellum is completely severed from the cell. The disturbance produced by the laser beam is indicated by the arrow. Panels 5–8: After irradiation, bends continue to propagate from the tip of the isolated flagellum. Panels 9–12: At a later time (about 1 s), bends are now traveling toward the tip. Elapsed time (ms): Panel 1, 0; 2, 10; 3, 20; 4, 30; 5, 120; 6, 160; 7, 200; 8, 230; 9, 900; 10, 930; 11, 970; 12, 1020. From Goldstein *et al.* (1970). Reprinted with permission of the Company of Biologists Ltd.

*Maatoshi Murase "The Dynamics of Cellular Motility" Wiley (1992), p122*