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# Synthesiology
English edition

**Establishing reliability in vibration measurement and its international equivalency**

**High performance thermoelectrics for power generation using earth-abundant and low toxicity elements**

**Challenges to the development of the world's first nondestructive inspection system**

**Toward overcoming neurodegenerative disease by the circadian molecular clock study**



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National Institute of Advanced Industrial Science and Technology (AIST)

## Highlights of the Papers in *Synthesiology*

*Synthesiology* is a journal that describes the objectives, specific scenarios, and procedures of research activities that attempt to utilize the results in society, in particular, the process of synthesis and integration of elemental technologies for practical application. To allow the readers to see the value of the papers in a glance, the highlights of the papers that characterize *Synthesiology* have been extracted.

***Synthesiology* Editorial Board**

**Establishing reliability in vibration measurement and its international equivalency**
***—Development of national metrology standards for vibration, acceleration, shock measurement and progress on international comparisons—***
**Takashi USUDA *et al.***
This paper describes the activities over 20 years starting from 1995, to establish the national standard for mechanical vibration measurement and related acceleration and shock measurements. International comparisons were conducted through collaboration with the metrology institutes of various countries, concurrent with the development of highly reliable calibration technology, and the targeted frequency range was expanded gradually from 0.1 Hz to 10 kHz.

**High performance thermoelectrics for power generation using earth-abundant and low toxicity elements**
***—Toward developing an innovative waste heat recovery system—***
**Michihiro OHTA**
This is a description of the author's consistent research strategy in which the aim was the diffusion of thermoelectric power generation technology to utilize waste heat energy, from original material development, modularization, and to social implementation, while cooperating with research institutions in Japan and overseas. It does not stop only at technological development, but addresses venture establishment and the standardization of the evaluation method.

**Challenges to the development of the world's first nondestructive inspection system**
***—Development of an inspection system with laser ultrasound and a cold cathode X-ray source—***
**Bo WANG *et al*.**
This is a report of a case study where a venture company developed and commercialized two first-in-the-world nondestructive inspection devices, using the technological potential nurtured at AIST, including the laser ultrasound visualization technology and the small cold cathode X-ray source technology. With the objective of extending their use to social and industrial infrastructures, the product development continues and the work of standardization is also being done.

**Toward overcoming neurodegenerative disease by the circadian molecular clock study**
***—My 30 year history in a national institute—***
**Norio ISHIDA**
This article chronologically presents the author's genetic level research for the biological clock that spans over 30 years. It describes how genetic research, in which the main subject is the fruit fly *Drosophila*, led to the findings in mammalian clock genes and then to human disease research, including the relationship with the research community in the background.

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# Synthesiology – English edition Vol.10 No.2 (Feb. 2018)

# Contents

# Establishing reliability in vibration measurement and its international equivalency

## — Development of national metrology standards for vibration, acceleration, shock measurement and progress on international comparisons —

**Takashi USUDA[1*], Akihiro OOTA[2], Hideaki NOZATO[2] and Wataru KOKUYAMA[2]**

**[Translation from *Synthesiology*, Vol.10, No.2, p.50–62 (2017)]**

The metric system and primary national metrology standards are necessary, but not sufficient for obtaining measurement equivalency. Recently, national metrology institutes of various countries including NMIJ/AIST of Japan are participating in international comparisons to confirm equivalency of their measurement capabilities, under a mutual recognition of arrangement (MRA). In this report, we describe progress on improving vibration measurement at NMIJ/AIST, along with global activities for establishing MRA. We also discuss future issues for improving vibration measurement.

*Keywords* : Vibration, acceleration, shock, calibration, metrology standard, equivalency evaluation, inter comparison, international standardization

## 1 Introduction

### *1.1 Outline of the vibration measurement and the necessity of calibration*

Vibration is closely connected to human physiology and living conditions through natural phenomena such as earthquakes as well as industrial products including buildings, aircraft, railways, and automobiles. Also, vibration in machines may reduce their functions and cause failure, and may lead to problems in occupational safety or accidents. Vibration measurement was positioned as important technology from the early stage of mechanical technology, and its importance is increasing as humans enjoy the benefits of science and technology while maintaining safe and comfortable environment.

The person (or device) conducting vibration measurement must be placed at a point from which it does not move within the spatial coordinate (the fixed point). As shown in Fig. 1, such a fixed point can be simulated by a seismic system consisting of a spring and a mass. The mass keeps its place (fixed point) against vibration due to inertia. By detecting the relative displacement between the mass and the object, or the inertial force acting on the mass, it is possible to measure the quantity of vibration. In the actual detection mechanism, various elements are involved such as conductive coils (displacement), strain gauges (strain), and load cells (force). In this paper, we shall generally call such a seismic system vibration detector as a vibrometer. The seismometer for earthquakes, the accelerometer used in inertial navigation of aircraft, and the acceleration sensor installed in smart phones are also vibrometers.

On the other hand, as it can be projected from Fig. 1, while the mass can stay at a fixed point as long as the vibration amplitude is small enough, the mass will not be able to stay at the fixed point due to the restoring force of the spring when the vibration surpasses a certain level. Such a property is determined by the stiffness of the spring, the natural vibration when considered as a mass-spring model, and the viscous element (damping) that absorbs vibration though this is abbreviated in Fig. 1. The vibrometer manufacturers optimize the above parameters for specific uses such as measurement of earthquakes, vibration of structures such

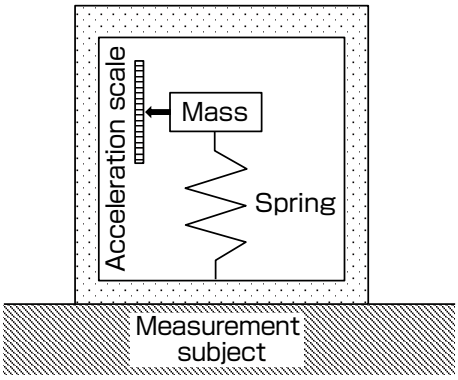


**Fig. 1 Seismic system vibrometer**

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as bridges or buildings, mechanical vibration, or collision phenomena (Fig. 2).

Whether a vibrometer has the property as designed must be checked by calibration. Calibration can be achieved by applying vibration of arbitrary frequency to a vibrometer, and then measuring the displacement with a laser interferometer and, at the same time, measuring the electric output from the vibrometer. The calibration result is given as the electric output against the unit vibration input (displacement, velocity, or acceleration). Figure 3 shows such a calibration device for a vibrometer.[1] Needless to say, the entire calibration device must be thoroughly vibration-isolated to prevent any effect of extraneous vibrations.

Calibration using such a laser interferometer is called primary calibration because it is linked directly to the definition of length. Conducting relative calibration of other vibrometers using a primary-calibrated vibrometer as the reference standard is called secondary calibration. A vibrometer that is primary-calibrated at AIST becomes the standard for vibrometer production companies and private calibration laboratories, and many vibrometers will undergo secondary calibration. Secondary-calibrated vibrometers are used in various kinds of application such as in vibration tests or in seismometers. The unbroken connection between the national standards and on-site vibrometers through calibration is called measurement traceability (Fig. 4).

### *1.2 Activities around international consistency for measurement and the responses of Japan*

Since the 1990s, with the end of the Cold War and the integration of Europe as the European Union, globalism accelerated, and there was demand for the internationalization of technological standards that were applied within each nation. In 1995, under the World Trade Organization (WTO),

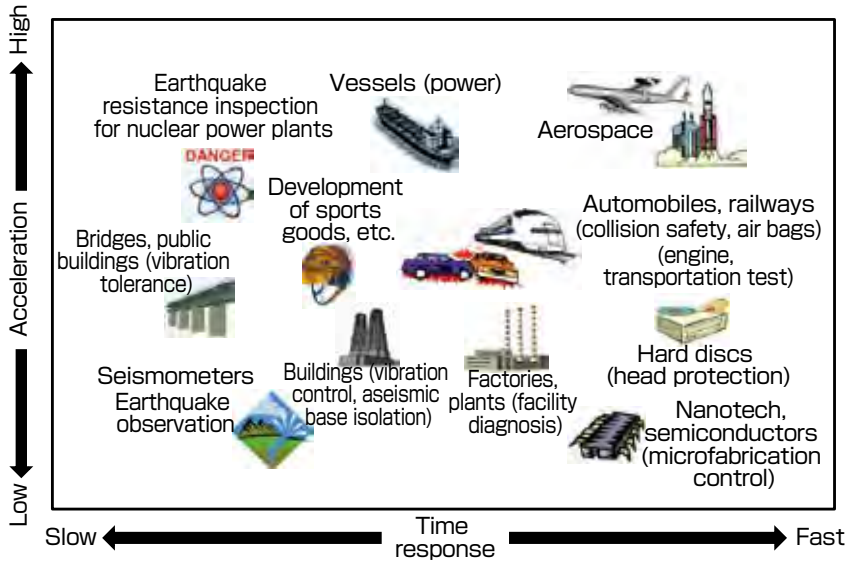


**Fig. 2 Fields in which vibration measurement is in demand and the characteristics of vibrations**

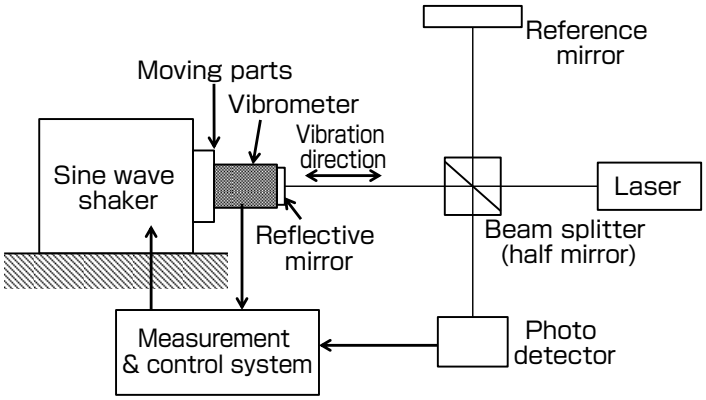


**Fig. 3 Vibrometer calibration device**

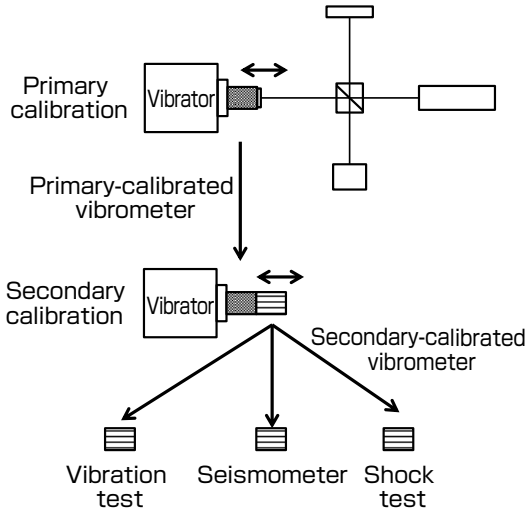


**Fig. 4 Traceability in vibrometer calibration**

the Agreement on Technical Barriers to Trade (TBT) was concluded, and countries were required to set technological standards, as exemplified by the international standards of the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC), and they had to mutually recognize such standards. For measurement standards, from a system where traceability[2] was maintained by the national metrology institute (NMI) who establishes national primary standards, the shift was made to a system of evaluating the equivalency of national measurement standards under the Metre Convention. In 1999, a memorandum for Mutual Recognition Arrangement (called the CIPM-MRA, adding the acronym for Comité International des Poids et Mesures that drafted the memorandum)[3] was signed, to conduct equivalency evaluation by international comparison and to publish the results.

The types and ranges of international comparison necessary for equivalency evaluation were to be discussed by the Consultative Committee consisting of the Metre Convention members. For vibration, the Consultative Committee for Acoustics, Ultrasound and Vibration (CCAUV) was established in 1998,[4] and the first discussions for international comparison for vibrometers began.

Until about the middle of the 1990s, the calibration of vibrometers at the Japanese NMI (at the time, it was the National Research Laboratory of Metrology, the Agency of Industrial Science and Technology) was conducted only for low vibration frequency (4 to 90 Hz; later revised to 80 Hz) for environmental assessment to measure ground vibration under construction, and the users and manufacturers of other fields conducted their own calibration. At the National Research Laboratory of Metrology, the "Review Committee for Traceability of Vibration and Acceleration" (hereinafter, the Review Committee) for vibrometers was organized by 13 Japanese companies starting in FY 1995. For two years and a half, the Review Committee conducted a survey of the demand for calibration. As a result, it was agreed that due to the necessities for vibration tests, automobile collision tests, and others, in addition to the conventional 80 Hz ceiling as the national standard for vibrometer calibration, vibration frequency range up to 5 kHz and acceleration amplitude of 1–100 $m/s^2$ should be set as quickly as possible. It was also recognized that phase lags (phase shift character) of vibration accelerometer output was an important reference value.

In this paper, the development of a vibrometer calibration method in Japan and the international movement in equivalency evaluation will be discussed, setting 1995 as a starting point. The configuration of the paper is as follows.

In Chapter 2, the establishment of the national standard for vibrometer calibration up to 5 kHz that was accomplished by 2000 and the response to the first international comparison will be explained.

In Chapter 3, the establishment of the national standard for vibrometer calibration up to 10 kHz and the response to the second international comparison that was conducted around 2010 will be explained.

In Chapter 4, the establishment of the national standard for vibrometer calibration up to 0.1 Hz and the response to the third international comparison that was conducted around 2015 will be explained.

In Chapter 5, the establishment of the national standard for shock calibration and the equivalency evaluation to centrifuge acceleration calibration will be explained.

Chapter 6 will be the summary of this paper and future prospects.

## 2 Establishment of the national standard for vibrometer calibration up to 5 kHz and the response to the first international comparison

In this chapter, the establishment of the national standard for vibrometer calibration up to 5 kHz that was agreed upon by the Review Committee and the response to the first international comparison will be explained.

### *2.1 Scenario for the R&D*

The laser interferometer used as the calibration device shown in Fig. 3 is called the Michelson type, and is the most basic format for displacement measurement. The light emitted from the laser source has coherent wavelength and phase. Its optical path is divided by a beam splitter, and the beams are introduced into the reference mirror and the vibrometer. A reflective mirror is installed at the edge of the vibrometer that is to be calibrated, and the displacement of the vibrometer can be measured as the optical path difference of the two beams. The interfering light intensity changes periodically for each 0.5 wavelength of an optical path difference, and this can be detected by an optical detector. Therefore, for example, if the helium-neon laser of wavelength of 632.8 nm is used as the light source, the interfering light intensity repeats the light-dark cycle every 316.4 nm, and the resolution at submicrometer level can be achieved relatively easily. Moreover, for the measurement of static displacement, it is possible to obtain higher resolution by interpolating the interfering light intensity, but it is difficult to obtain high resolution in the environment of vibration, which essentially is in conflict with making precise measurement.

On the other hand, since displacement, velocity, and acceleration are in calculus relationships with each other, if the vibration is in sine wave, the relationship with vibration frequency is as given in Fig. 5. At 5 kHz that was agreed

as the upper limit of the vibration frequency by the Review Committee, the displacement amplitude will be about 100 nm (at acceleration amplitude of 100 m/s$^2$), and the improvement of the resolution is essential.

However, in the vibration environment, the interfering light intensity itself fluctuates due to the shift of the optical axis arising from vibration, and it is not possible to increase the resolution by interpolating the intensity as it can be done for static displacement measurement. Also, the information obtained from the interferometer shown in Fig. 3 is only for amplitude, and this does not allow the evaluation of the output difference (phase) from the vibrometer and the vibration in the time domain.

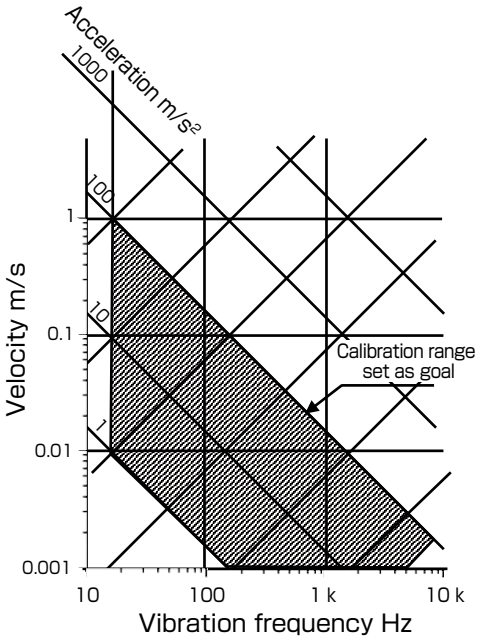


**Fig. 5 Relationship of displacement, velocity, and acceleration in sine wave vibration and their calibration range**

The technological goal is to achieve calibration of vibration at acceleration amplitude of 1–100 m/s$^2$ up to a vibration frequency range of 5 kHz, along with phase property evaluation. In conducting the equivalency evaluation by international comparison, it is necessary to conduct uncertainty evaluation. It is also necessary for the system to have robustness and stability that can withstand the rigors of routine calibration work.

### *2.2 Selection and development of the elemental technologies*

The calibration device is mainly composed of the following:

- Laser interferometer
- Vibrator
- Controller and electric measurement system

Of these, it was mandatory to newly develop the laser interferometer due to the necessity for phase shift evaluation and the required calibration range. On the other hand, since it was difficult to develop a mechanical element of a vibrator with reliability and durability in a short time, we used a commercially available product for which the evaluation was established at the time (we used an electrodynamic vibrator in which the moving parts were supported by leaf springs). Since the performance of interface and personal computers (PC) have improved rapidly, a PC was used as the controller, a multipurpose voltmeter and a frequency counter were used for an electric measurement system, and the system could be sufficiently flexible to meet the demands for future performance improvement. Needless to say, it was necessary to prepare and evaluate the calibration environment such as control of humidity and temperature, as well as a vibration isolation table that sufficiently eliminated extraneous vibration. Figure 6 shows the principle of the developed interferometer.

The interferometer is a modified Michelson type. The laser beam from the light source (He-Ne laser, wavelength of

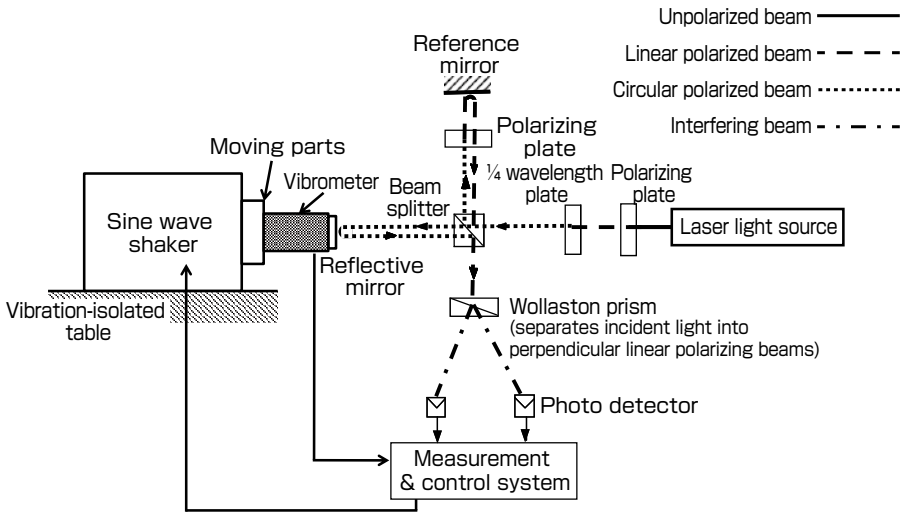


**Fig. 6 Developed laser interferometer**

632.8 nm) is linearly polarized by a polarizing plate. Then, it passes through the 1/4 wavelength plate and becomes circular-polarized. Next, it is separated into a measurement beam and a reference beam by an unpolarized beam splitter. The reference beam is reflected by a reference mirror, and is linearly polarized by a polarizing plate. The measurement beam is reflected by the reflecting mirror installed at the edge of the vibrometer, and interferes with the reference beam. The Interfering light is separated by a Wollaston prism into a quadrature beam where the phase differs by 90°. The polarized beam components are detected by the two optical detectors.

Figure 7 shows the relationship between vibration acceleration and the detected interference signal. In circular polarization, an interference signal in the polarization direction that differs in phase by 90° is obtained, and therefore, when the vibrometer to be calibrated moves, the signals from the two optical detectors will be as shown in Fig. 7 right. As the vibration direction inverts, the output of the interferometer inverts and the vibration direction can be determined. By demodulating the two outputs with an appropriate algorithm, the wavelength of the displacement (and velocity and acceleration that are its differential signals) of the vibrometer is obtained. By comparing this result with the electric output from the vibrometer, calibration and evaluation of the phase shift become possible. With this interferometer, there is an advantage that because displacement is demodulated from the phases of two interfering signals, the deterioration of interpolation accuracy can be reduced even if the interfering beam intensity itself fluctuates due to the shift of the optical axis. Figure 8 shows the external appearance of the developed calibration device.[5]

### *2.3 Execution of the first international comparison and the results*

International comparison is conducted by measuring a common device called the transfer standard at the NMIs of the participating countries, and then comparing the results. During the development of the calibration equipment explained in the previous subchapter, the first international comparison was planned by CCAUV. The items examined included the determination of the measurement range, the selection of a transfer standard, the setting of measurement

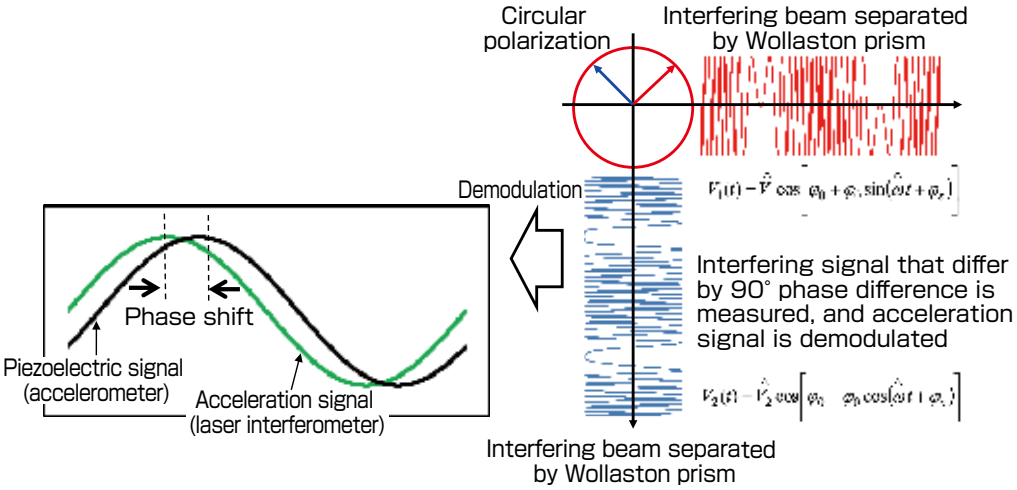


**Fig. 7 Detected interfering signal**

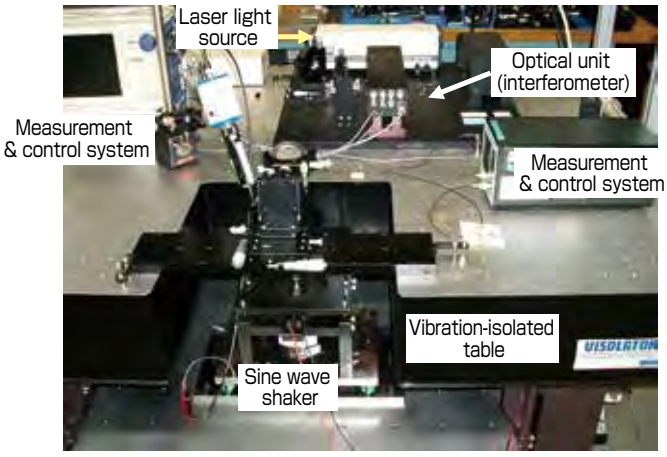


**Fig. 8 Developed calibration device for vibrometer up to 5 kHZ**

conditions, the processing method of the measurement results, the preliminary adjustment of participating institutes, and others. After the discussions at CCAUV, the Physikalisch-Technische Bundesanstalt (PTB), the German NMI, was entrusted to be the pilot laboratory that would be responsible for the management of the international comparison, and details were reviewed led by PTB. One of the authors was a visiting scientist to PTB at the time, and was able to participate in the discussions for determining the measurement conditions. The topic that became particularly important in the measurement conditions was the range of the vibration frequency. Some participating institutes requested measurement up to 10 kHz, but it was agreed to compare the measurement results up to 5 kHz only because the stability and high frequency characteristic of the transfer standard were not sufficiently investigated. The international comparison was conducted by 12 participating institutes from 2000 to 2001.[6] In this international comparison, the vibrometer with a piezoelectric element was employed as the transfer standard, and its sensitivity (piezoelectric output per unit output) was calibrated. Figure 9 shows the results of some of the participants in this international comparison.

The vertical axis shows the calibration value of the transfer standard, while the horizontal axis shows the vibration frequency. It is shown that the sensitivity increases due to the effect of the resonance vibration of the seismic system as the frequency increases. The measurement results of the participating institutes are processed statistically along with the uncertainty, and the key comparison reference value, which is the value estimated to have the highest certainty in this international comparison, is determined. If the measurement results of each participant fall in the reference value within the range of uncertainty, it will be proof of international equivalency. The calibration results of AIST was good. However, some participants showed deviation of 1 % or higher as shown in Fig. 9. Since the uncertainty at which the participating institutes conducted self-evaluation was around 0.5 %, this result forced the total review of the calibration equipment for some NMIs. Also, since there was a tendency that the deviation among participants increased at a higher vibration frequency, the necessity of an international comparison at a higher frequency was recognized.

## 3 Establishment of the national standard for vibrometer calibration up to 10 kHz and the response to the second international comparison

When the first international comparison was conducted, the Measurement Standards and Intellectual Infrastructure Plan was created under the 2nd Science and Technology Basic Plan (approved by the Cabinet on March 30, 2001), and the world's highest level intellectual infrastructure was to be organized by about 2010. The organization of the metrology standard was assigned to the National Metrology Institute of Japan, AIST. For the calibration of the vibrometer, since the vibration measurement of 5 kHz or more was being done in industry, the goal was set at the establishment of a national standard up to 10 kHz. In this chapter, the establishment of the national standard for vibrometer calibration up to 10 kHz and the response to the second international comparison will be explained.

### *3.1 Scenario of the R&D*

As shown in Fig. 5, when the vibration frequency applied to the vibrometer is increased, the displacement amplitude is inversely proportional to the square of the vibration frequency when the acceleration value is kept constant. Therefore, when the acceleration amplitude of 100 m/s$^2$ is maintained, the displacement amplitude is 100 nm at 5 kHz, while it decreases to 25 nm that is 1/4 of that value at 10 kHz. Since such small displacement amplitude surpassed the calibration capacity of the device described in Chapter 2, a totally new laser interferometer was necessary. For the vibrator that generates motion, even linear vibration cannot be produced using an electrodynamic vibrator in which the moving parts are supported by conventional leaf springs, due

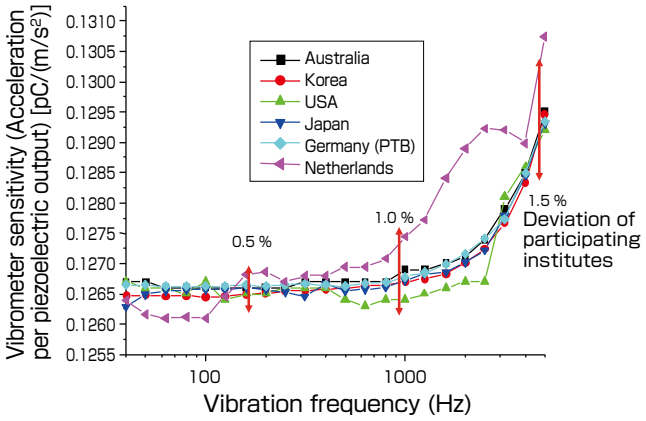


**Fig. 9 An example of the results of the first international comparison for vibrometer calibration**

to the effects of vibration strain and parasitic vibration.[7][8] Therefore, a new vibrator with superior stability, including a solid actuator such as a magnetostriction element became necessary. For an electric measurement system, reviews were done since advanced sampling was necessary. For calibration capacity, considering the requests from the Japanese industry and looking at the actual calibration conducted at advanced industrial countries such as Germany, the goal was set at expanded calibration uncertainty of 0.3 %–1.0 %.

### *3.2 Selection and development of elemental technologies*

Due to the requirements mentioned in the previous subchapter, a totally new laser interferometer was developed. The technological characteristic was to double the optical path difference compared to the conventional one by introducing a catoptric system. Specifically, two types of laser interferometers, one with twofold optical paths and another with fourfold optical paths, were fabricated, and their properties and operabilities were investigated.[9] Figure 10 shows the optical arrangement and details of the optical path of the developed fourfold optical path laser interferometer.

The characteristic is, as shown in Fig. 10(a), that the resolution increases as the measurement beam introduced to the vibrometer is folded back four times through the fourfold optical path system. This is achieved by controlling and selecting the polarization direction of the beam by combining the optical elements, and the details are shown in Fig. 10(b). Laser beam that enters from (1) is separated into reference and measurement beams by the reflective and transmitting surfaces (2) of the polarizing beam splitter, and the measurement beam is reflected on the measurement surface (3) of the vibrometer. The reflected beam reflects off the reflective surfaces (4) (5) of the corner mirror, and then is reflected again on the measurement surface (6) of the vibrometer. The beam is reflected in numerical order as indicated in Fig. 10(b), is finally combined with the reference beam, and interference occurs.

Since the interfering beam output itself is detected as a quadrature beam as shown in Fig. 7, it is possible to reproduce the vibration wavelength by appropriate demodulation. The major advantage of this interferometer is that a special reflective mirror such as a corner cube mirror is not necessary to measure the subject, and the optical path difference can be doubled with a flat-reflective mirror. In the vibration range of 10 kHz, all parts are subject to elastic deformation, and therefore it is desirable that the vibrating parts have simple structures as much as possible, and such a characteristic that allows simplification of the structure contributes greatly in reducing the uncertainty of calibration. When this interferometer was evaluated, it was confirmed that amplitude displacement up to 16 nm that greatly surpassed the planned 25 nm could be detected.

A twofold optical path laser interferometer was fabricated and evaluated similarly, and it was confirmed that amplitude displacement up to 25 nm could be detected as originally planned. Based on these results, considering the technical level of the calibration personnel and efficiency of work time when this technology was applied to actual calibration work, and reviewing the technological issues such as the S/N ratio of the interfering light signals and operability of the optical axis alignment, we decided to employ the twofold optical path laser interferometer.

For the vibrator, an electrodynamic vibrator, in which the moving parts are supported by leaf springs, just as in the calibration equipment for 5 kHz maximum that was developed in Chapter 2, and a piezoelectric vibrator, in which the moving parts are supported by solid actuators and air bearings, were considered as candidates. In this calibration condition where the vibration amplitude reaches several tens of nm level, the parasitic oscillation in the direction outside the intended vibration may reach a relatively non-negligible size in the leaf spring supported type, and this method was eliminated. The piezo and magnetostriction elements were strong candidates, but it was found that the strain in the vibration wavelength was large, and they were inappropriate

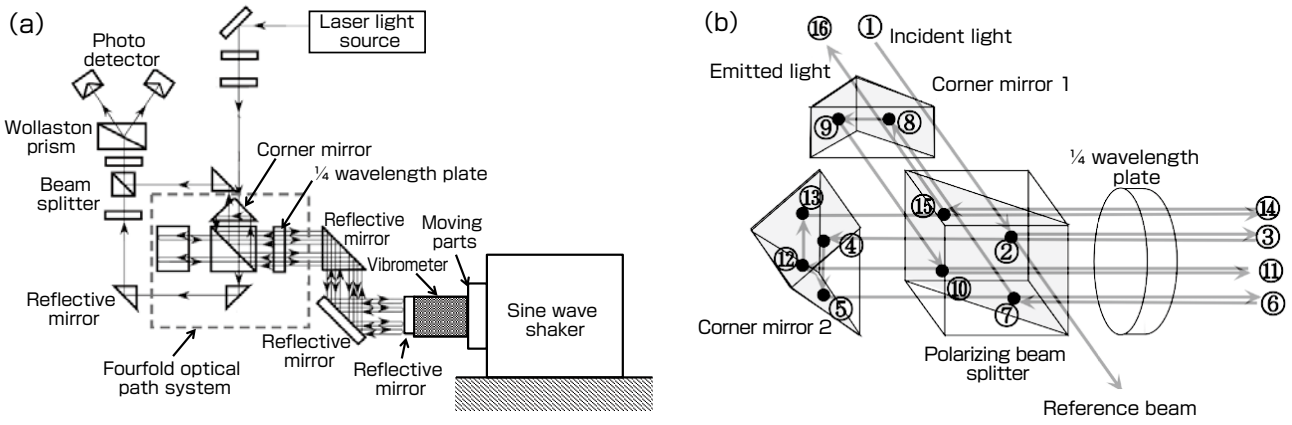


**Fig. 10 Configuration of the developed laser interferometer and its optical path arrangement**
(a) Optical path arrangement diagram, (b) Optical path of measurement light

for calibration. Finally, the electrodynamic vibrator where the moving parts are supported by air bearings was employed. The calibration equipment with maximum of 10 kHz thus developed is shown in Fig. 11.[10]

### *3.3 Execution of the second international comparison and the results*

After the first international comparison of the vibrometer calibration explained in Subchapter 2.3, CCAUV decided to conduct the second international comparison. From the necessity to evaluate the equivalency at a high vibration frequency, it was decided that the calibration range would be up to 10 kHz, and the phase shift of the vibrometer that was essential information in modal analysis and automatic control would also be evaluated and compared. The international comparison was conducted by 15 participating institutes from 2009 to 2012.[11] The pilot laboratory was PTB of Germany as in the first international comparison.

Figure 12 is an example of the calibration result at 10 kHz. In the figure, the key comparison reference value is set at the origin, and the deviation of participating NMIs is shown in the vertical axis. The error bars are the stated uncertainties

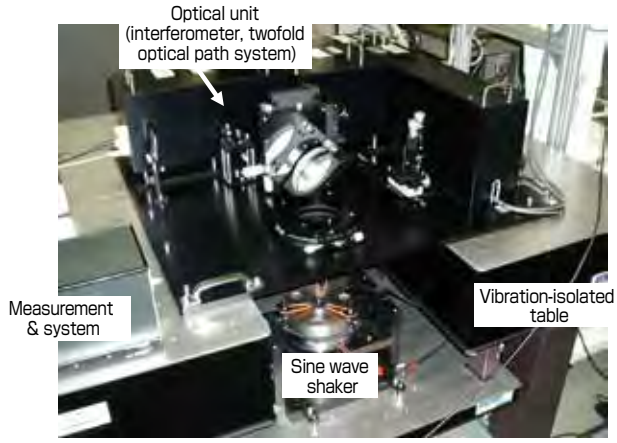


**Fig. 11 Developed calibration device for vibrometer up to 10 kHz**

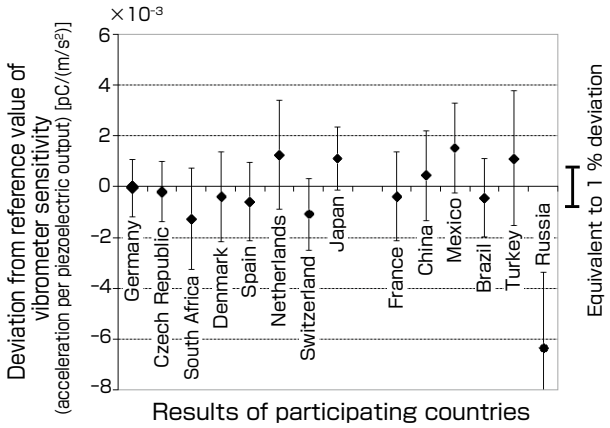


**Fig. 12 An example of the results of the second international comparison for vibrometer calibration**

of NMIs. The size of deviation does not directly indicate the superiority of the NMIs, but compared to the first international comparison results where the deviation of participating NMIs reached several percent, the deviation of all institutes (except Russia) was about 1 %. Also, the values were mutually consistent in the uncertainty range, and it could be seen that the equivalency of calibration results of the countries was satisfied for a high vibration frequency range. On the other hand, in the process of measurement by participating institutes, it was observed that the sensitivity of the transfer standard changed (Fig. 12 is the result where such a change was corrected by regression analysis). The sensitivity change of the transfer standard is a problem that greatly damages the reliability of international comparison. Currently, CCAUV is engaging in discussions on the selection of an appropriate transfer standard and the handling of the transfer standard during transportation, in order to start a new international comparison after 2017.

## 4 Establishment of the national standard for vibrometer calibration up to 0.1 Hz and the response to the third international comparison

Chapters 2 and 3 mainly discussed the expansion of the calibration capacity to a high vibration frequency range. However, as shown in Fig. 2, vibrometers are used in observation of earthquakes (in seismometers) and in monitoring the vibration of bridges and other structures. These vibrations may range from several tens of Hz to a low vibration frequency of about 0.1 Hz. Recently, it has been reported that although earthquake resistance of buildings increases, the low frequency (long-period) seismic waves lead to large shakes due to the introduction of flexible structures in high-rise buildings. The vibrometer calibration at a low vibration frequency range is similarly important. In this chapter, the establishment of the national standard for such a low vibration frequency and the result and response to the third international comparison will be explained.

### *4.1 Scenario of the R&D*

The topic of the reliability of the vibration measurement in a low vibration frequency range is particularly a matter of concern in Japan that is an earthquake prone country, and the introduction of calibration equipment to facilitate evaluation of seismometers has been done since the old National Research Laboratory of Metrology days. Figure 13 is the external appearance of such equipment. The moving parts supported by air bearings vibrate over 360 nm strokes by an electrodynamic linear motor.[12] As shown in Fig. 5, when the vibration frequency decreases, the acceleration generated decreases even if the same displacement amplitude is maintained, and the acceleration amplitude that can be generated by this equipment is in the range of 0.03 $m/s^2$–20 $m/s^2$. When the displacement at large amplitude is generated at such small acceleration, the strain of the acceleration

waveform becomes relatively large due to the non-uniformity of movement, and this increases the uncertainty of the calibration results. Therefore, generation of sine waves where the waveform strain is decreased to 1 % or less is achieved by employing air bearings that have extremely small friction. On the other hand, for the laser interferometer, the sensitivity of the vibrometer and phase assessment are made possible by basically using the modified Michelson interferometer as presented in Chapter 2.

### *4.2 Selection and development of elemental technologies*

For vibrometer calibration in a low frequency range, in general, only small acceleration can be generated due to the limitation of vibration strokes. The vibrometer output signal is small against the generated acceleration, the S/N ratio deteriorates, and this increases the uncertainty. Therefore, a digital filter, where the S/N ratio is increased and the uncertainty is decreased by filter-processing the obtained signal on the computer, was employed.[13]

Although the digital filter itself was not a new method, the calculation load was large because it was necessary to take in several gigabytes of data per session and conduct a demodulation process if one wished to obtain several dozen waveforms needed for filtering at 0.1 Hz (10 sec cycle). However, due to the increased capacity of computers in the past few years, the processing became possible in realistic time.

Through a series of development and optimization, the performance of uncertainty of 0.15 % and phase shift of 0.05° was achieved at 0.1 Hz.

### *4.3 Execution of the third international comparison and the results*

On the other hand, CCAUV was conducting international comparisons mostly in the high vibration frequency range. This was because the high frequency range was the priority in industrial vibration measurement, and the low frequency vibrometers were mostly used in special cases such as in seismometers or in inertial navigation for aircraft. Also, such vibrometers could be converted to military use such as for intercontinental ballistic missiles, and it was considered not in the best interest for conducting international comparison.

Against such a background, there were earthquake related disasters in several countries including Japan, and there was a surge in interest for vibrometer calibration at a low frequency range. Also, after the establishment of CCAUV in 1998 and the following two international comparisons, there was increased interest in vibration measurement in the international community, as well as understanding for the importance of international comparisons. Therefore, the third international comparison where the minimum vibration frequency was set at 0.1 Hz was conducted from 2013 to 2015, using the low frequency vibrometer as a transfer device, and 14 NMIs participated.

Figure 14 shows an example of the international comparison results, and shows the equivalency among institutes for 0.1 Hz.[14] As in Fig. 12, the key comparison reference value is set at the origin, and the deviations of participating NMIs are shown in the vertical axis. The error bars are the stated uncertainties of each institute.

Of the 14 NMIs that participated, only eight institutes, including China, Germany, Denmark, South Africa, Mexico, Australia, Singapore, and Japan, were able to make the most difficult measurement of 0.1 Hz, and the other six institutes withdrew their data. The result submitted by AIST had the smallest uncertainty among the eight institutes, and was consistent with the key comparison reference value. However, the meaning of this result will be discussed at CCAUV in the future, including the stability of the transfer standard.

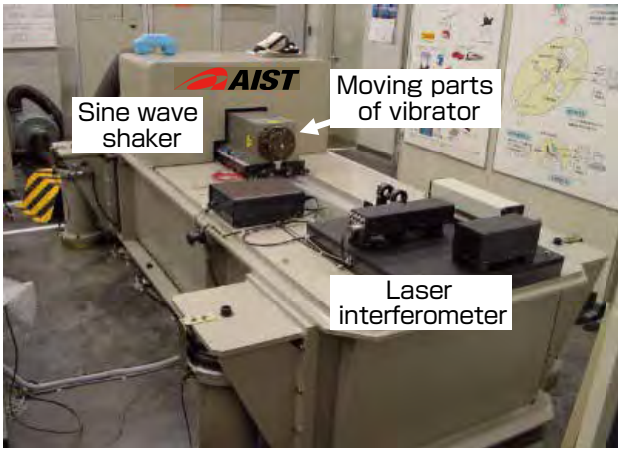


**Fig. 13 Developed calibration device for vibrometer with minimum frequency 0.1 Hz**

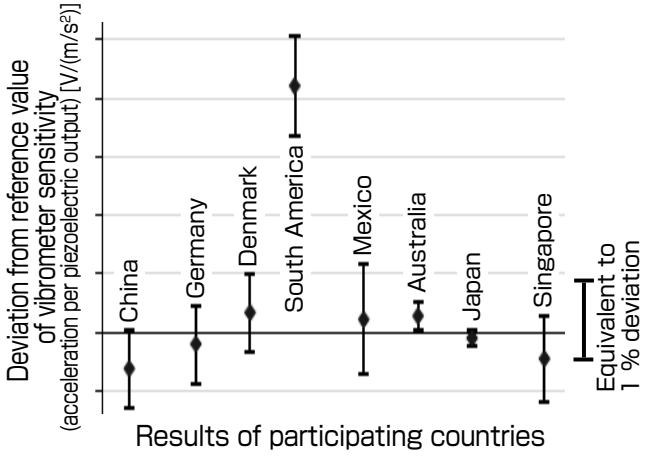


**Fig. 14 An example of the results of the third international comparison for vibrometer calibration**

## 5 Establishment of the national standard for shock calibration and the consistency evaluation to centrifugal acceleration calibration

Through the technological development and participation to international comparisons explained up to this point, the National Metrology Institute of Japan, AIST can provide vibrometer calibration from 0.1 Hz to 10 kHz for which a certain level of international equivalency is guaranteed.

On the other hand, for collision safety performance evaluation for automobiles, measurement of acceleration range of several hundred m/s$^2$ to several thousand m/s$^2$ are being conducted, and at this range, vibrometer evaluation with a vibrator that generates sine waves is no longer possible. In this chapter, the national standard for shock calibration that was developed to meet such demands will be explained. The consistency evaluation with centrifuge calibration that is frequently used in industry and the work on its ISO standardization will also be explained.

### *5.1 Scenario of the R&D*

In control engineering and mechanics, Dirac's delta function $\delta(x)$ is known as the function that mathematically expresses shock input. The delta function is a function where infinite value is given at one point, and all other points are 0, or 1 when integrated in the range of $[-\infty, \infty]$ (Fig. 15).

When the delta function is converted to frequency range, a certain value can be given to all frequency components. That is, the delta function is a signal that includes all frequency components evenly, and is an ideal input when evaluating the vibration frequency property of a subject to be controlled and its mechanical elements. If such a function can be generated as a motion (shock acceleration rate), it is possible to evaluate the frequency property of the vibrometer through all ranges. However, in reality, it is impossible to generate such a motion. On the other hand, the frequency property and sensitivity are optimized according to the demands on the vibrometer that is to be evaluated. If a shock input of unnecessarily wide range is given, the S/N ratio of the evaluation may deteriorate, and at times, the vibrometer itself may be destroyed. Therefore, technology to generate the mechanical shock acceleration with desired peak value and duration is necessary.

The technology for generating high-level acceleration includes the reflection of elastic waves proposed by B. Hopkinson,[15] and the calibration of a vibrometer using this principle has been reported in the past.[16] However, the elastic waves are characterized by the physical property called elasticity. There were problems that the peak acceleration and duration were restricted, and the peak value of generated acceleration was too high compared to the demand.

Therefore, as the technology to generate shock acceleration, momentum replacement by collision of rigid bodies is used. Figure 16 is the schematic diagram of the principle of shock acceleration generation of the elastic waves and rigid body collision. In rigid body collision, the hammer to which the kinetic energy is applied collides with the anvil to which the vibrometer to be evaluated is attached. The momentum of the hammer is replaced by the anvil, and half sine wave acceleration is generated. The peak value and duration of acceleration can be controlled to a degree by the momentum given to the hammer or by placing a buffering material such as rubber between the hammer and the anvil.

### *5.2 Selection and development of the elemental technologies*

For the stable generation of shock acceleration by rigid

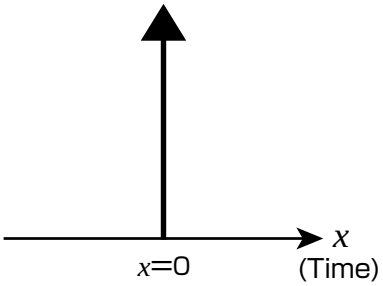


**Fig. 15 Delta function when there is infinite value at x=0**

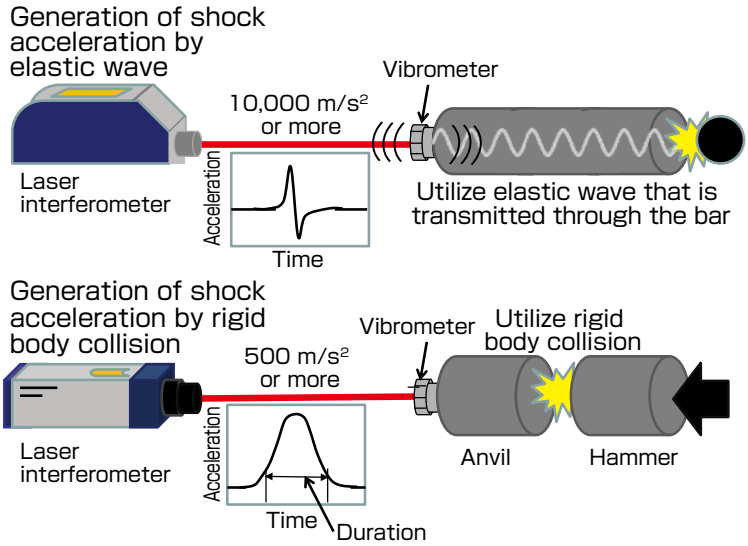


**Fig. 16 Generation of shock acceleration and calibration of vibrometer**

body collision, it is desirable that the anvil and hammer move without friction in the direction of the motion, and the freedom of motion is allowed only in the direction of the motion. Therefore, the structure is comprised of a metal rod anvil and hammer supported by air bearings. The anvil and hammer can move freely in the longitudinal direction of the metal rod owing to the air bearings, and are bound in the radial direction by the rigidity of the air film created by air bearings. As a result, the vibration other than in the longitudinal direction is inhibited, and this contributes to the improvement of the S/N ratio. The buffering material made of urethane rubber is attached between the anvil and the hammer, and the hammer accelerated by compressed air applies half sine wave acceleration to the anvil and to the vibrometer through the elasticity of the buffering material.

For the interferometer, initially, a laser interferometer categorized as homodyne, where the interfering light intensity periodically changes for every optical path difference of 0.5 wavelength, was used up to the previous chapter, but later, a heterodyne laser interferometer, which provides interfering signals from scattered light from the measurement subject and does not require a reflective mirror, was employed. A heterodyne interferometer is a device that detects the velocity signal by conducting heterodyne detection of scattered light from the measurement subject that undergoes Doppler shift depending on velocity. The difference frequency regarding heterodyne detection was several tens of MHz, and conventionally, it was mainly analog detection. Therefore, gain reduction corresponding to frequency and phase shift in the demodulation of vibration waveforms could not be avoided, and this was unsuitable for calibration. However, due to improved performance and increased capacity of the waveform memory (A/D conversion and data logger) in recent years, it became possible to digitize all signals. In this system, the vibration waveform is demodulated based on all digitized signals. Figure 17 shows the developed calibration equipment.[17]

Figure 18 is the acceleration waveform obtained from the developed equipment, and the output waveform from the vibrometer obtained by its acceleration input. The peak value (Ap) of acceleration reaches 3000 m/s$^2$. The property of the vibrometer can be calibrated from the ratio of the peak value of acceleration and the peak value (Vp) of the vibrometer output.

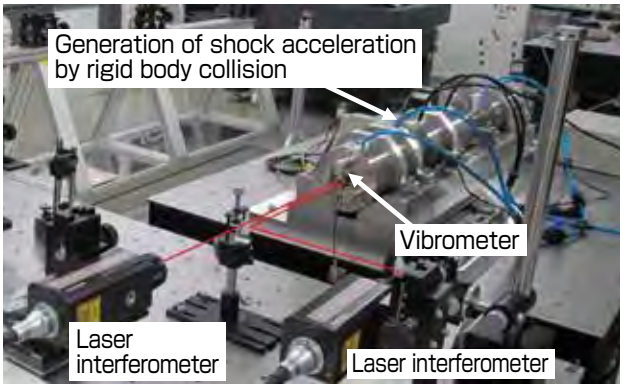


**Fig. 17 Developed shock calibration device**

The international comparison of shock acceleration is being discussed by CCAUV, and it will soon be started as CCAUV. V-K4 with China and Japan as joint pilot laboratories.

### *5.3 Consistency evaluation with the centrifuge calibration and issuance of the ISO standard*

Through the development explained in the previous subchapter, the national standard for amplitude linearity evaluation of vibrometers was established. Acceleration can also be generated by centrifugal force. In Japan, through the efforts of companies, inexpensive and high performance strain gauges are widely available, and vibrometers that use strain gauges as the detection mechanism of seismic systems are widely used. A strain gauge has sensitivity for DC components, and its calibration is done against constant acceleration such as centrifugal force. In contrast, in Europe and the US, vibrometers that use piezoelectric elements as the detection mechanism are widely used. This has low

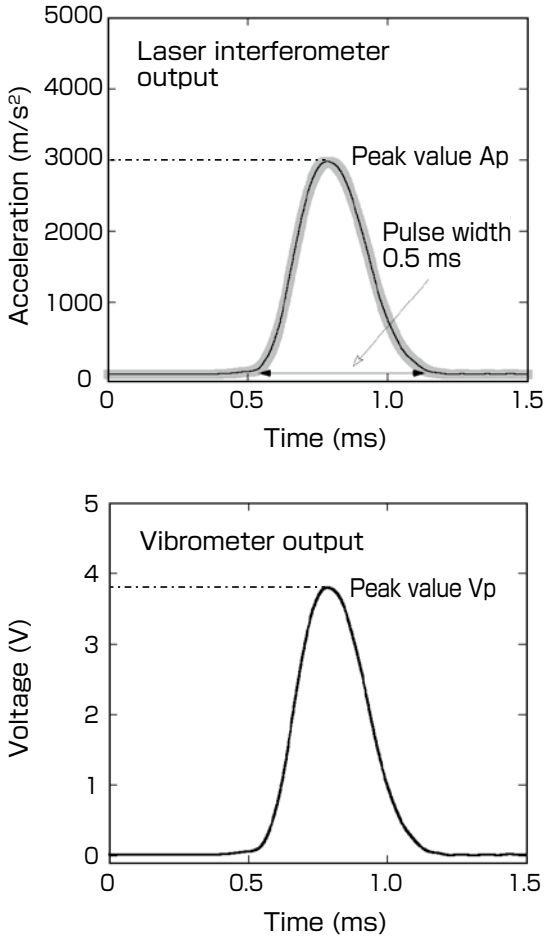


**Fig. 18 Acceleration waveform obtained from the shock calibration device and output from the vibrometer**

sensitivity for the DC components, and calibration by shock acceleration is generally done. The two calibration devices and the outline of generated acceleration are shown in Fig. 19.

In the centrifuge calibration, calibration is done by calculating the applied acceleration by the distance from the center of the rotation of the vibrometer, and then calculating the ratio of applied acceleration and vibration output. In contrast, in shock calibration, shock acceleration is applied to the vibrometer to be calibrated by hitting with a hammer, and calibration is done by the output ratio against the reference vibrometer attached to the same axis. Both are simple methods, but it cannot be said immediately that the two calibration results are equivalent. Until now, the problem of safety evaluation in automobile collision among different countries never surfaced. However, with the rise in interest for safety evaluation, the equivalency of measurement devices used in evaluation and traceability started to be questioned. Therefore, the adequacy evaluation of the centrifuge calibration method and ISO standardization were assigned to Japan. To obtain agreement of other countries that mainly engage in shock calibration, it was necessary to present the test results that investigated the adequacy of the centrifuge calibration.

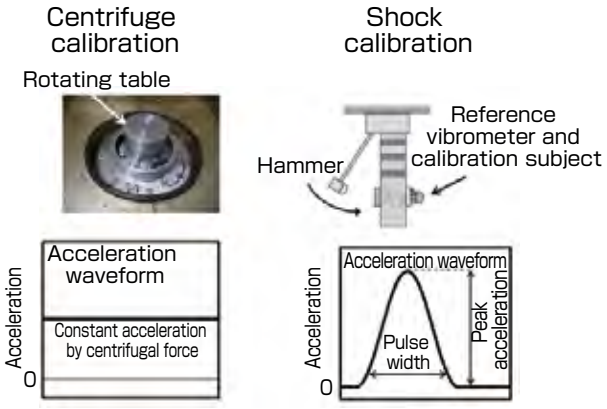


**Fig. 19 Calibration method for large amplitude acceleration used in industry**

Therefore, AIST and the major Japanese automobile companies collaborated on the revision of the international standard[18] for centrifuge calibration of the strain gauge vibrometer, and at the same time, evaluated the technological adequacy of centrifuge calibration. Kyowa Electronic Instruments Co., Ltd., Toyota Technical Development Corporation, Japan Automobile Research Institute, and Nissan Creative Services Co., Ltd. collaborated in this evaluation. The same vibrometer was calibrated using the centrifuge calibration device possessed by the companies, and the results were compared with the results of AIST's shock acceleration calibration device. The results of centrifuge calibration at four organizations matched the calibration results of AIST in the uncertainty range, and all results fell in the certainty (1.8 %) of shock measurement required by the standard for road-bound vehicles collision tests.[19] Therefore, the equivalency of the shock calibration device of AIST and the centrifuge calibration device of the four organizations were confirmed, and the technological efficacy of centrifuge calibration was demonstrated. Based on these results, the revised standard of centrifuge calibration was issued as ISO.[20] By using the strain gauge vibrometer that is evaluated by the calibration method in accordance to ISO when conducting the safety evaluation for automobile collision tests, the barrier against the Japanese automobile manufacturers in exporting their products can be reduced. Also, regarding the back data for centrifuge calibration without time change that the automobile industry had been accumulating over the years, this gives the technological evidence that matches the shock calibration that incurs time change like the actual collision tests.

## 6 Summary and prospects

In this paper, the establishment of the national standard for vibrometer calibration in Japan over 20 years since the middle of 1990s is explained. The activities for the establishment of international equivalency that was done concurrently are explained through international comparison and ISO standardization. Figure 20 is the summarized

| Research goal→ | Calibration up to 0.1 Hz | Calibration up to 5 kHz | Calibration up to 10 kHz | Shock acceleration calibration |
|---|---|---|---|---|
| Demand and background of development | ·Evaluation of seismometer reliability<br>·Vibration reduction<br>·Aseismic base isolation | ·Basic national standard necessary for vibration tests | ·World top class vibration test<br>·Safety evaluation | ·Safety evaluation<br>·Equivalency in frequency and time ranges |
| Elemental technology | ·Hydrostatic bearing<br>·Long word memory<br>·Signal processing | ·Homodyne interferometer<br>·Signal processing | ·Homodyne interferometer and technology to double optical path difference<br>·Signal processing | ·Acceleration generation by rigid body collision<br>·Heterodyne interferometer<br>·Digital demodulation |
| Measures for diffusion and ripple effect | ·Provision of standard<br>·Contribution to international comparison | ·Provision of standard<br>·Contribution to international comparison | ·Provision of standard<br>·Contribution to international comparison | ·Provision of standard<br>·Contribution to international comparison<br>·Proposal and setting of international standard |

**Fig. 20 Major items of this paper and the R&D scenario**

scenario of the items described in this paper.

When the international equivalency of metrology standards became an issue after the discussion at WTO, internationally, CCAUV was established and the discussions on equivalency evaluation started. Fortunately, in Japan, the development of national standards was being organized after a survey for such needs and its results. Excellent manufacturers existed in Japan for the mechanical elements such as laser light sources, optical elements, and air bearings, and the most advanced elemental technologies could be utilized for standard development. It was also fortunate that the authors were at the pilot laboratory of international comparisons during the equivalency evaluation period, and were able to observe the process from an international perspective. Also, we were able to contribute to the internationalization of Japanese industrial products and test results by using the developed national standard as tools to evaluate the equivalency of the calibration results that were originally done at the laboratory level, and issue the results as ISO.

On the other hand, the demand for measurement range is further expanding in both frequency and amplitude. Through the advances in micro-electro-mechanical systems (MEMS) based on semiconductor microfabrication, vibration sensors and angular velocity sensors (gyroscopes) can be manufactured at low cost and can be installed in smart phones. Also, multi-axis sensors that allow detection of vibration in multiple directions and hybrid sensors integrated with gyro are widely used. These sensors are, in general, called the inertial sensors, and the development of their calibration method is an important issue. While there was no space in this paper for their description, the authors' group is working on the development of a calibration device for gyro (Fig. 21).[21] On the other hand, it is not realistic to continue infinite development of calibration devices. As discussed in the equivalency evaluation and international standardization of centrifuge calibration, it is necessary to clarify the equivalency of existing technology, and to maintain the measurement reliability through standardization.

Looking at the situation overseas, the advancement of emerging NMIs is significant against a background of economic growth in Asia. Under such circumstances, the emerging NMIs tend to seek adequacy of their own calibration results through international comparisons. While international comparisons may be the most direct evidence of equivalency evaluation, as a prerequisite, it is important that each institute engage in self-evaluation of calibration results. If self-evaluation is not done and systemic deviation is not addressed, reference value calculated statistically from the results of the NMIs may deteriorate. When several organizations start to use the same commercial product, the inclination of that device may become a bias and will have an effect. In such a case, it may no longer be an evaluation of equivalency, but may become a repeatability evaluation for the same device. As a member of an advanced NMI, we must not lose the stance of originally developing standards from elemental technology. We shall continue working with organizations in Japan, establish reliability of inertial measurement including vibration, and maintain leadership in the international stage.

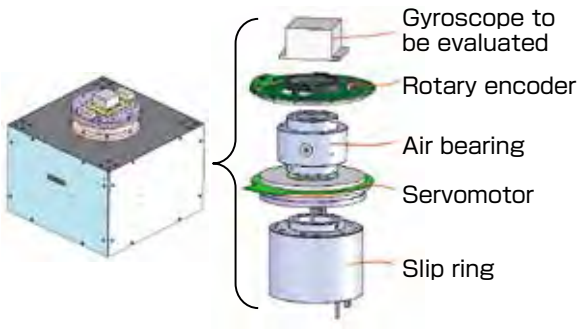


**Fig. 21 Gyro calibration device**

In this paper, the main discussion was our effort on vibration measurement, but the demand on measurement is expected to deepen in the future, and the pursuit of precision will not stop. At the same time, the equivalency of measurement results will be further in demand due to the spreading globalism. To maintain the universality and invariance of measurement in such technological and regional expansion, mutual understanding based on the spirit of free and scientific criticism among NMIs is essential. In the field of metrology standard, the spirit of mutual criticism (review) based on scientific evidence is established as a culture in the form of international comparison. At the same time, the spirit of mutual help and reliance with which we manage the multinational project of international comparison is firmly established. We shall conclude this paper by mentioning that in this age when transparency and reliability are being challenged as the competition in science and technological development becomes fierce, the culture and mechanism built by the NMIs may provide a hint for how to advance science and technology as common assets of humankind.

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## Discussions with Reviewers

### 1 Overall

**Comment (Mitsuru Tanaka, AIST)**

The paper provides an overview of the technological development in national metrology standards necessary to objectively present the reliability of vibration acceleration measurement in Japanese industries on site, both within and outside Japan, and the process of obtaining international consistency. It also addresses the establishment of standard approval for a practical sensor performance. The explanations of various elemental technologies capture the main point well, and the impact of this measurement on industry is presented in an easy-to-understand manner. Through the understanding of the research results and their achievements, the readers will be able to readily grasp the scenario and have high expectations for gyro measurement that is being developed by the authors.

**Comment (Norimitsu Murayama, AIST)**

This paper presents the elemental technologies and how they need to be combined to establish the national standard, giving the example of national standard development for vibration, acceleration, and shock measurement. I think the content is worthy of publication in *Synthesiology.*

### 2 Ready-to-understand explanation about utilizing the results in the industrial world

**Comment (Norimitsu Murayama)**

I think the value of this paper will increase if you specifically describe how the national standards are used in the industrial world. Also, I think you should address the relationship and linkage between the national standard and the calibration work that is actually done on site.

**Answer (Takashi Usuda)**

As you indicated, I added the last paragraph on how the national standard is provided and utilized in “1.1 Outline of the vibration measurement and the necessity for calibration,” and added Fig. 4.

### 3 Future scenario

**Comment (Mitsuru Tanaka)**

For the calibration of the shock acceleration sensor, you say that the equivalency will be checked through international comparison in the future. The scenario for monochromatic frequency vibration has been already established, where confirmation has been done by international comparison and it will support the measurement reliability in the industrial world. Compared to this, the story of shock acceleration sensor calibration is still in progress and almost in its final stretch. Still more, for the calibration of static acceleration, you are applying the prospective results of this shock acceleration sensor. If that is so, what is the basis of AIST’s confidence in being successful with the final problem solving, and why did the ISO experts of other countries approve of the issuance of a standard based on the prospective success of a particular country? I don’t think this is merely a collusive relationship, but it is also not an agreement among the colleagues in an academic society. You mention the effect of your stay in Germany and other explanations in the final part of the summary. What about adding a description about the mutual trust relationship in a paragraph?

**Answer (Takashi Usuda)**

I added the final paragraph as a possible scenario in the last part of “6 Summary and prospects.”

# High performance thermoelectrics for power generation using earth-abundant and low toxicity elements

## — Toward developing an innovative waste heat recovery system —

**Michihiro OHTA**

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We have successfully realized greater thermoelectric performance through nanotechnology and developed alternative materials that are more abundant and less toxic than the conventional materials. These studies were conducted in collaboration with domestic and overseas research institutions. A comprehensive effort to all aspects of thermoelectrics, *i.e.* from materials to module, has realized high-performance and environmentally friendly technologies. A startup company was founded in order to develop the thermoelectric market for these technologies. This article describes the research and development strategies employed to achieve practical use of thermoelectric power generation.

*Keywords* : Thermoelectric power generation, nanostructuring, element strategy, technology transfer, international collaborative research

## 1 Introduction

While it may not be easy to notice in daily life, a massive amount of waste heat is generated by many sources, such as vehicles, industrial processes, computers. According to a statistical study by the Lawrence Livermore National Laboratory, 66.4 % of primary energy supplied in the United States in 2016 was rejected; only 30.8 % of this energy was used for human activities.[1] Because energy eventually becomes heat, unused energy primarily takes the form of waste heat. A similar situation was found in the estimated energy flow in Japan in 1998, where the amount of waste heat reached 66 % of the primary energy.[2] Since the primary energy in Japan in 1998 was $18 \times 10^{18}$ J according to the Energy White Paper of Agency for Natural Resources and Energy,[3] the amount of waste heat in this case can be represented as $12 \times 10^{18}$ J. We lose an enormous amount of energy in the form of waste heat. Therefore, an important strategy that can diminish a serious global energy crisis and environmental burden is improving thermal energy management. Thermoelectrics[Term1] can provide a new approach to this problem. An enormous amount of unused waste heat can be directly converted to useful electricity by using thermoelectric generators. This article describes our longstanding efforts to advance thermoelectric technologies.

Thermoelectrics have only been found in niche applications, for example for use in space exploration. From the 1950s to the present, when space probes explore dark areas without sunlight, radioisotope thermoelectric generators (RTGs) have been used to supply power to the probes.[4] In RTGs, heat released as a result of radioactive decay has been used as the heat source for thermoelectrics. These thermoelectric generators have decades of proven reliability as mission critical applications in space missions. The current focus of energy and environmental sustainability has recently begun to promote the development of commercial thermoelectric applications. If thermoelectric modules[Term2] with a conversion efficiency of 12 % harvest waste heat from exhaust gases in a vehicle, fuel efficiency is estimated to increase by 7 %.[5] In these cases, thermoelectric modules are placed on a vehicle's exhaust pipe surface after the catalytic converters. The surface temperature reaches ~720 K.

There are obvious differences in thermoelectric performance requirements for space and commercial uses. Improved thermoelectric conversion efficacy is required for commercial applications. Further, thermoelectric materials, the key technology in thermoelectrics, should be composed mainly of earth-abundant and low toxicity elements. To realize thermoelectric waste heat recovery, it is necessary to develop thermoelectric modules and associated peripherals, such as a system for the harvesting of waste heat and the transport of heat to modules. It is then important to accumulate operating experience to validate the prototypes. It is also essential to develop rules and guidelines for these processes, including standards for efficiency evaluation. In collaboration with researchers in the National Institute of Advanced Industrial

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Science and Technology (AIST) (of which the author is a member) and at domestic and overseas research institutes, he has steadily addressed the technical challenges of thermoelectrics in interdisciplinary studies that span several research fields. Our longstanding efforts and future strategies are shown in Fig. 1. This article discusses an improvement in thermoelectric conversion efficacy through nanostructuring, the development of thermoelectric materials composed of earth-abundant and low toxicity elements, and the establishment of a startup for developing the thermoelectric market. Further study on the prototype validation is being undertaken.

## 2 Enhancement in thermoelectric performance through nanotechnology under international collaboration

### *2.1 Technical barriers between the development of thermoelectric materials and modules*

Solid-state devices based on thermoelectrics can directly convert temperature difference (heat) between the hot and cold sides of thermoelectric materials into useful electrical energy through a physical phenomenon called the Seebeck effect. An enhancement in the performance of thermoelectric materials is principally required to achieve high efficiency in thermoelectric modules; therefore, the development of high-performance thermoelectric materials is the most popular field in thermoelectrics. Yet, the development of high-temperature electrodes and the design of electrical and thermal circuits are also important for module fabrication but are low profile fields in thermoelectrics. Extensive efforts have been devoted to enhancing materials performance; however, there has been little effort made to apply this progress in the materials to module development.

To overcome technical barriers, an integrated approach combining materials development and module fabrication has been conducted under international collaboration supported as part of the Japan-United States Cooperation Project for Research and Standardization of Clean Energy Technologies (Japan-United States Clean Energy Cooperation, FY2010–FY2014) funded by the Ministry of Economy, Trade and Industry (METI). As a result, we have successfully demonstrated exceptionally high performance in materials and corresponding high conversion efficiency in the modules.

### *2.2 Development of thermoelectric materials and modules through technological interaction between Japan and the United States*

Good thermoelectric materials need to possess two key properties: low electrical resistivity and low thermal conductivity. Low electrical resistivity (*i.e.*, high electrical conductivity) results in high electrical output because of reduced Joule heating. The thermal conductivity must be low to inhibit heat flow and maintain the temperature difference across materials. Recall that electric power is induced through the temperature difference in thermoelectrics. However, both electrical and thermal transport property needs lead to a conflict in material design. Metals typically exhibit low electrical resistivity but high thermal conductivity. Typical glasses exhibit low thermal conductivity but high electrical resistivity. Therefore, metals and glasses show poor thermoelectric properties. One strategy to optimize these conflicting material properties is based on the concept of a phonon glass–electron crystal (PGEC).[6] In a PGEC material, an electron crystal region allows efficient transmission of charge carriers while inhibiting the heat flow in a phonon glass region. Before the end of the 20th century, it was difficult to realize this concept.

In 2000, then-President Bill Clinton launched the National Nanotechnology Initiative to boost the United States' competitiveness in nanotechnology. As in other fields, attempts had been made to end the trade-off between electrical and thermal transport properties through nanotechnology to enhance performance in thermoelectrics. For almost all

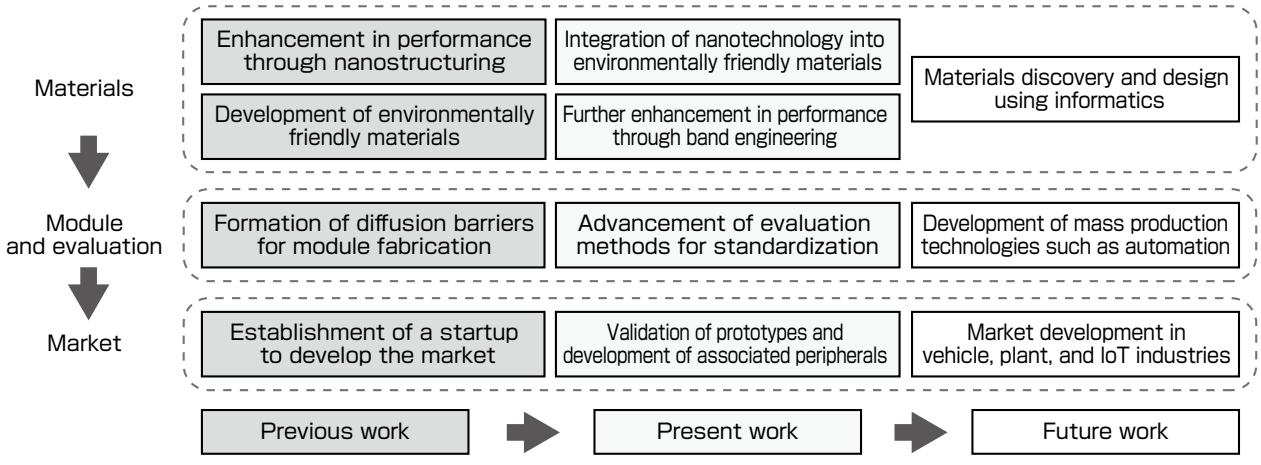


**Fig. 1 The author's longstanding studies and future strategies in thermoelectrics**
Interdisciplinary studies combining materials, module, and market development.

fields including thermoelectrics, nanotechnology initially got a boost from the development of low-dimensional materials, such as zero-dimensional quantum dots, one-dimensional nanowires, and two-dimensional nanolayer films. Thermoelectric materials used in products are normally three-dimensional bulk forms aimed to distribute the temperature difference across materials; therefore, in this early stage, thermoelectrics benefited little from nanotechnology. Single-phase lead telluride (PbTe)-based thermoelectric materials have been used in several space missions. In 2004, a team led by Mercouri Kanatzidis of Michigan State University (present affiliations: Argonne National Laboratory (ANL) and Northwestern University (Northwestern Univ.)) successfully embedded nanoscale secondary phases (nanostructures) in PbTe bulk through the addition of silver (Ag), bismuth (Bi), and extra tellurium (Te).[7] The insertion of nanostructures causes the effective scattering of heat-carrying phonons and correspondingly reduces the lattice thermal conductivity, enhancing the thermoelectric figure of merit *ZT*.[Term3] Scientific validation of this process took a lot of time and effort because of difficulty in the forming of nanostructures in bulk materials. Recently, several groups including the present team have demonstrated that high performance is observed with the reduction in lattice thermal conductivity through nanostructuring.

Around the same time (FY2002–FY2006), a Japanese national project called the Development for Advanced Thermoelectric Conversion Systems was conducted under the support of New Energy and Industrial Technology Development (NEDO). The author does not know the details because this project was launched prior to his joining AIST. More resources had been devoted to the development of thermoelectric systems than to the development of thermoelectric materials, because this project began before the trend toward nanotechnology.[8] In this project, AIST researchers, Haruhiko Obara and Atsushi Yamamoto, developed thermoelectric modules and measurement systems and accumulated necessary knowledge in AIST.[9]

As mentioned above, Kanatzidis *et al*. first demonstrated that the insertion of nanostructures in bulk thermoelectric materials causes an enhancement in the figure of merit. AIST researchers have successfully developed thermoelectric modules and measurement systems. Since FY2010, in a five-year project under the Japan-United States Clean Energy Cooperation funded by METI, a team of researchers from AIST, ANL, and Northwestern Univ. have developed a high efficacy thermoelectric module based on nanostructured materials by combining both technologies. Figure 2 shows an overview of this joint research. To promote technological interaction, the author had joined the Kanatzidis group at ANL and Northwestern Univ. as a visiting scholar for one year and two months from 2011 to 2012. This stay has led to close coordination with colleagues at these institutions and the consequent achievement of innovative results.

### *2.3 Improvement in the thermoelectric figure of merit through insertion of nanostructures in bulk materials*

The nanostructuring of bulk thermoelectric materials was not investigated in detail before the present study. Under the Japan-United States Clean Energy Cooperation, the experimental condition of melt growth process for PbTe was thermodynamically investigated, allowing for the formation of nanostructures. As shown in Fig. 3(a), nanostructures were embedded in PbTe possessing p-type electrical transport properties through the addition of a very small amount (2.0 at.%) of Mg and the optimization of heating and cooling rates and holding temperature and time in the preparation process.[10] It is well known that sodium (Na) is an acceptor for PbTe. In this study, we doped 4.0 at.% sodium (Na) to yield a suitable p-type carrier concentration for thermoelectric properties.

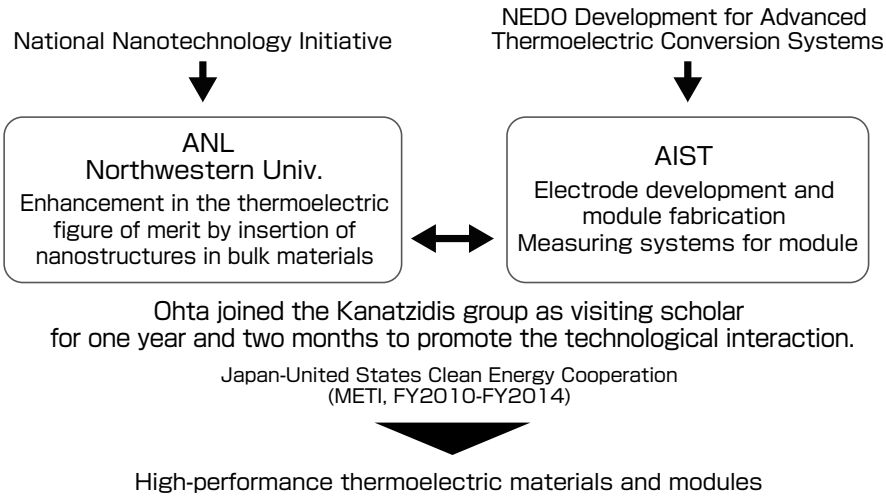


**Fig. 2 International joint research between AIST, ANL, and Northwestern Univ. has led to development of high-performance thermoelectric materials and modules.**

Figures 3(b) and (c) show a schematic representation of phonon scattering and charge carrier transmission and simplified energy band diagrams, respectively, in the nanostructured thermoelectric materials. The lattice strain fields surrounding nanostructures, induced by the addition of Mg, effectively scatter the nano-order wavelength phonons, resulting in reduced lattice thermal conductivity (Fig. 3(b)). Nonetheless, the lattice strain fields have only a small effect on the system's electrical transport properties. This is most likely due to the coherent (endotaxial) nature of the interface between the nanostructure and the PbTe matrix. In other words, the charge carriers, holes in this case, can propagate without significant scattering in a defect-free interface between two endotaxial components. Moreover, the small valence-band offset between the nanostructures and the PbTe matrix allows for seamless charge carrier transmission[Term4][11] (Fig. 3(c)). Further, the nanostructure is too big for scattering of the charge carriers. A mean free pass of the charge carriers is typically shorter than that of phonons. An important finding here is that the nanostructures induced through the addition of Mg in p-type PbTe selectively reduce lattice thermal conductivity and maintain excellent electrical transport properties, dramatically enhancing the thermoelectric figure of merit *ZT*. A *ZT* of 1.6 at 780 K achieved for $(Pb_{0.94}Mg_{0.02}Na_{0.04})Te$ is 1.8 times higher than that achieved without nanostructures (Fig. 4).[10]

The nanostructured PbTe developed is stable. In this study, the ingots of nanostructured PbTe were hand-ground to fine powders; the samples were then sintered at 773 K for 1h under a uniaxial pressure of 30 MPa in a vacuum ($7.0 \times 10^{-3}$ Pa). The nanostructures are maintained after sintering (Fig. 5(a)).[12] As shown in Fig. 5(b), an energy dispersive spectroscopy analysis carried out on the nanostructures confirmed the clear presence of Mg and the absence of Pb and Na. It is noted here that this high performance was maintained in the sintered compacts, which are favorable for processing into thermoelectric modules.

In this article, we focus on the enhancement in thermoelectric performance of p-type PbTe through nanostructuring. We have shown that the performance of n-type PbTe doped with lead iodide ($PbI_2$) is enhanced through the same nanostructuring approach.[13]

### *2.4 Comprehensive development from materials to modules: achieving the world's highest level of conversion efficiency*

We have successfully enhanced the *ZT* value of both p and n-type PbTe through nanostructuring. The articles describing these results and observations have been published in high impact journals.[10]–[13] This progress in nanostructured thermoelectric materials aroused our interest in future work in materials science. However, in this work, we advanced the development of thermoelectric modules using newly developed nanostructured materials, aiming to inspire innovation in thermoelectric applications. One of the important missions of AIST is to bridge the gap between basic research and commercial production;

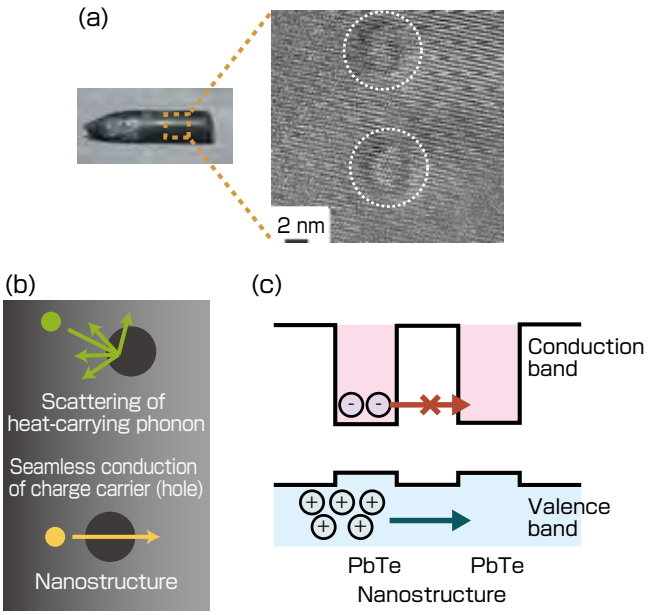


**Fig. 3 (a) Typical photograph and high-magnification transmission electron microscopy image of the melt-grown ingot of p-type $(Pb_{0.94}Mg_{0.02}Na_{0.04})Te$,[10] (b) conceptual diagram of the enhancement in the thermoelectric figure of merit *ZT* through nanostructuring, and (c) expected band alignment of nanostructure in the p-type PbTe matrix.[11]**
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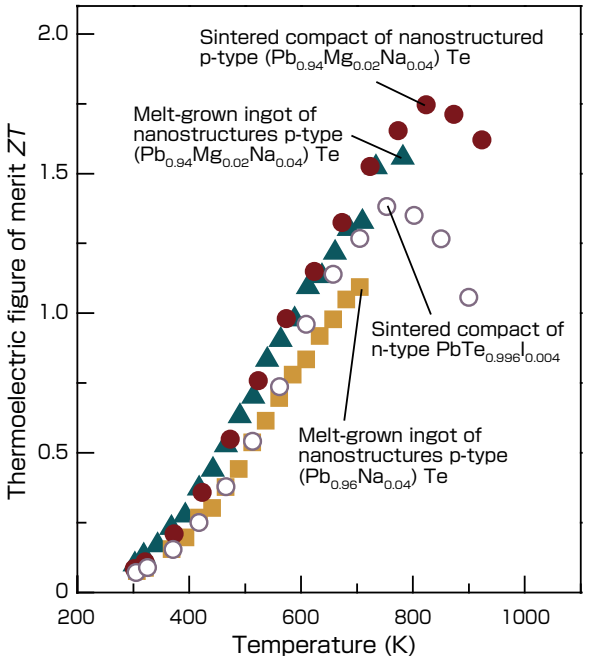


**Fig. 4 Temperature dependence of the thermoelectric figure of merit *ZT* for the melt-grown ingots and sintered compacts of p- and n-type PbTe[10][12]**

therefore, the author decided to respond to industrial and social expectations for thermoelectrics. In this study, he took advantage of the existing knowledge of thermoelectric modules and measurement systems developed at AIST in the previous NEDO project.

A thermoelectric module is composed mainly of thermoelectric materials and electrodes. The electrodes should have low electrical resistivity to efficiently extract electrical energy from the materials and a high thermal conductivity to efficiently provide heat to the materials. The hot side of the module is subject to high temperatures, such as 720 K in vehicle applications. In high temperatures, the diffusion of atoms generally occurs at the interface between different materials, *i.e.*, thermoelectric materials and electrodes, reducing the module's efficiency. Therefore, in module development, it is particularly important to prevent interface diffusion. Single-phase PbTe is one of the traditional thermoelectric materials. It has been reported that for single-phase PbTe an iron (Fe)-based diffusion barrier formed between the thermoelectric materials and the electrodes prevents interface diffusion.[14] However, in the case of nanostructured PbTe, a high electrical resistance layer has been found to form in the Fe-based diffusion barrier between the thermoelectric materials and the electrodes. In this study, we investigated several Fe-based alloys and mixtures as possible diffusion barriers. As a result, a cobalt (Co)-Fe based diffusion barrier has been successfully developed to improve electrical and thermal contact between the nanostructured PbTe materials and the electrodes.[12]

Figures 6(a) and (b) show the single-stage module fabricated in this study. In this module, we used the sintered compacts of nanostructured $(Pb_{0.94}Mg_{0.02}Na_{0.04})Te$ for p-type legs, $Pb(Te_{0.996}I_{0.004})$ for n-type legs, and a mixture of Co-Fe for the diffusion barriers. As shown in Fig. 4, the *ZT* of $(Pb_{0.94}Mg_{0.02}Na_{0.04})Te$ and Pb $(Te_{0.996}I_{0.004})$ are ~1.8 at 810 K and ~1.4 at 750 K, respectively. The cross section of thermoelectric elements composed of the legs and the diffusion barriers is 2.0 mm × 2.0 mm. The lengths of the thermoelectric legs and diffusion barriers are 2.2 mm and 0.3 mm, respectively; the total length of the legs is 2.8 mm. The module comprises eight p–n couples (sixteen elements) interconnected by copper (Cu) electrodes. As listed in Table 1, the maximum power output and maximum conversion

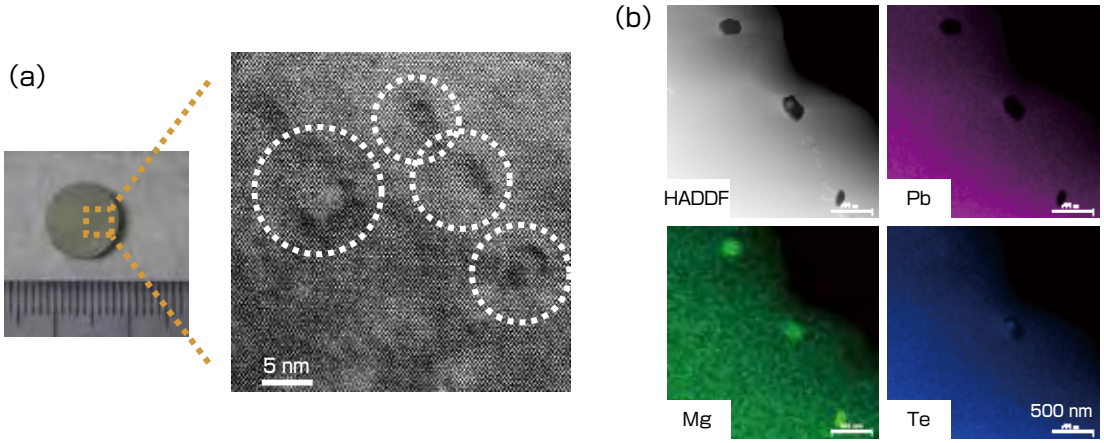


**Fig. 5 (a) Typical appearance and high-magnification transmission electron microscopy image[12] and (b) energy-dispersive X-ray elemental mapping of the sintered compact of p-type $(Pb_{0.94}Mg_{0.02}Na_{0.04})Te$.[12]**
(a) and (b) Reproduced with permission.[12] Copyright 2016 Royal Society of Chemistry

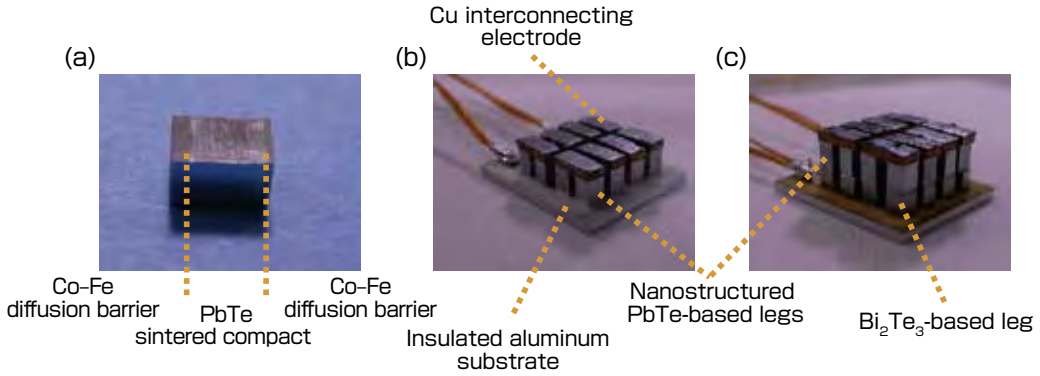


**Fig. 6 Nanostructured PbTe-based (a) thermoelectric element, (b) single-stage thermoelectric module, and (c) two-stage (segmented) thermoelectric module using $Bi_2Te_3$[12]**
(b) and (c) Reproduced with permission.[12] Copyright 2016 Royal Society of Chemistry

**Table 1. Measured and simulated values of the maximum power output and maximum conversion efficiency of single- and two-stage thermoelectric modules[12]**

| | Hot-side temperature (K) | Cold-side temperature (K) | Maximum power output (W) | | Maximum conversion efficiency (%) | |
|---|---|---|---|---|---|---|
| | | | Measured value | Simulated value | Measured value | Simulated value |
| Single-stage thermoelectric module | 873 | 303 | 3.55 | 4.71 | 8.8 | 12.2 |
| Two-stage thermoelectric module | 873 | 283 | 2.34 | 2.55 | 11 | 15.6 |

efficiency achieved are 3.55 W and 8.8 %, respectively, at a hot-side temperature of 873 K and a cold-side temperature of 303 K.

The sintered compact of PbTe shows a high *ZT* over the temperature range of 573 K to 973 K and a low *ZT* below at temperatures below 573 K (Fig. 4). Therefore, conventional bismuth telluride ($Bi_2Te_3$), which shows a high *ZT* (~1.0) at 373 K, was used in the cold-side thermoelectric elements to develop a two-stage (segmented) thermoelectric module (Fig. 6(d)).[12] The module also comprises eight p–n couples. The size of the PbTe-based thermoelectric elements is the same as that of the single-stage type. The $Bi_2Te_3$-based thermoelectric elements are 2.0 mm long, 2.0 mm wide, and 2.0 mm tall. The improvement in performance on the cold-side boosts maximum power output. The very high value of 11 % is achieved at a hot-side temperature of 873 K and a cold-side temperature of 283 K (Table 1). If this two-stage module is used for a waste heat recovery system in vehicles, as mentioned above, fuel efficiency is estimated to increase by 7 %.

The power generation characteristics of our nanostructured PbTe-based modules were investigated in a three-dimensional finite-element simulation using the measured thermoelectric properties of the legs and the diffusion barrier.[12] As listed in Table 1, the simulations predict that the maximum conversion efficiency of the single- and two-stage modules would reach 12.2 % and 15.6 %, respectively. The comparison between the simulated and the measured values shows that the differences in maximum power output and maximum conversion efficiency are due to the large contact resistances at the interfaces between the legs and the interconnecting electrodes and heat losses such as radiation which do not contribute to power generation. Therefore, as a next step, we will focus on the further optimization of interfaces and geometrical configuration in order to achieve a maximum conversion efficiency significantly greater than 11 %.

When the author started studying thermoelectrics in 2002, it was challenging to develop a module with a greater than 10 % efficiency. Thermoelectric generators are semiconductor-based devices. Similarly, solar photovoltaics semiconductors convert solar energy into electricity. The photovoltaic market expanded after solar cell efficiency reached 10 %. Although thermoelectric and photovoltaic technologies cannot be directly compared, when the efficiency of semiconductor-based thermoelectric modules exceeds 10 %, this likely promotes the growth of the market. Of course, it is necessary to combine the associated peripherals with high-efficiency thermoelectric modules and technically validate the prototypes for realizing a thermoelectric waste heat recovery system, as discussed in Chapter 5. In collaboration with the researches from ANL and Northwestern Univ., and Osaka University, the author has recently focused on engineering electrical properties in thermoelectric materials to enhance performance. Materials science is actually the author's primary field. This work has been supported as part of the Development of Thermal Management Materials and Technology funded by NEDO.

## 3 Substitution of rare and toxic elements: environmentally friendly thermoelectric sulfides

### *3.1 Advantages of thermoelectric sulfides and the difficulty of their preparation*

The exceptionally high thermoelectric figure of merit in materials and corresponding high efficiency in modules achieved in this work probably meet those required by commercial markets. Unfortunately, the PbTe-based thermoelectric materials mainly consist of the toxic element Pb and the scarce and expensive element Te. The use of Pb is tightly restricted not only in Japan but also worldwide. The abundance of Te in Earth's crust is low (0.005 ppm), comparable to that of platinum (Pt). Note that the toxicity of Pb has no direct relation to the toxicity of PbTe. The restriction of the use of PbTe should be considered carefully because the high toxicity of Pb is not a sufficient reason for this restriction. It is necessary to scientifically investigate the toxicity of PbTe; however, this takes a great deal of time and effort. At this stage, the use of PbTe is hard to be accepted

in the market. Therefore, to explore the market, efforts to develop environmentally friendly thermoelectric materials and modules using less toxic and more earth-abundant elements should be considered in parallel with efforts to develop PbTe-based materials and modules.

Numerous alternative materials to PbTe have recently been investigated. Among these are sulfide systems, which we have studied for over ten years. Thermoelectric sulfides would be widely accepted in society because of the abundance and low toxicity of sulfur (S). Moreover, both sulfur and tellurium belong to the chalcogen family in the periodic table; therefore, sulfides and tellurides tend to have similar chemical and physical properties. Finally, the electronegativity of S is less than that of oxygen (O), which also belongs to the same element group. This means that sulfides generally have low electrical resistivity. However, there are difficulties to developing thermoelectric sulfides. For example, it is difficult to control the chemical reaction for synthesizing sulfides because of the large difference in vapor pressure between metals and sulfur.

This study has made attempts to develop the synthesis and processing of thermoelectric sulfides. For example, in collaboration with a team led by Shinji Hirai of the Muroran Institute of Technology (Muroran IT), several sulfide systems have been successfully prepared through sulfurization.[15]–[21] Because carbon disulfide ($CS_2$) is a powerful sulfurizing agent, we have used it for sulfurization. The $CS_2$ sulfurization leads to the low temperature formation of sulfides. The thermodynamic investigations on the synthesis and processing of sulfides have brought about the development of various thermoelectric sulfides. For instance, rare-earth sulfides have been developed for n-type high-temperature applications (above 873 K).[16][17] The titanium disulfide developed is a candidate for n-type intermediate-temperature thermoelectric applications (~673 K).[18] Layered sulfides have been developed as high-temperature thermoelectric materials. In this system, the charge carrier type (p or n) is tunable through the change in the chemical composition.[19][21] p-type Chevrel-phase sulfides exhibit high potential for high-temperature applications.[22][23] However, as summarized in Fig. 7, the thermoelectric figure of merit *ZT* has been limited to 0.6 for these systems.

There are limitations on the development of thermoelectric sulfides through studies based only on inorganic chemistry. We fully acknowledge that studies of condensed matter are also required to look for promising systems within the very large sulfide family. An integration of chemistry and physics is obviously needed for thermoelectric study. The author has noted the benefits of such integration through direct experience. Since 2010, he has collaborated with the following condensed matter physicists, who have investigated the thermoelectric sulfides: Koichiro Suekuni of the Japan Advanced Institute of Science and Technology (JAIST) (at Hiroshima University (Hiroshima Univ.) from 2013 to 2016 and since then at Kyushu University (Kyushu Univ.)), Mikio Koyano of JAIST, and Toshiro Takabatake of Hiroshima Univ. To promote the development of thermoelectric sulfides through joint research, the following three strategies have been integrated into the substitution of Te for S, which is a key direction of AIST studies.[24] In the first strategy, the crystal structure of thermoelectric sulfides should belong to a cubic system, because high valley degeneracy in electronic bands is conducive to a high thermoelectric power factor and a high corresponding power output. In the second strategy, the thermoelectric sulfides should have a complex crystal structure such as a large unit cell containing a large number of atoms, because structural complexity enables low lattice thermal conductivity. The third strategy is to use chemically stable minerals as references for developing thermoelectric sulfides. To carry out these strategies, we have focused on copper (Cu)-containing sulfides; these would be widely

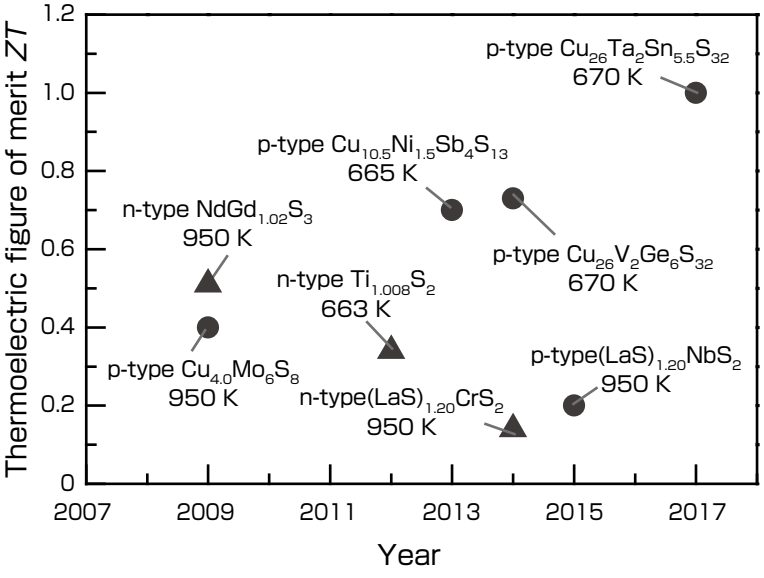


**Fig. 7 Thermoelectric sulfides developed in this study:**
rare-earth sulfide $NdGd_{1.02}S_3$,[16] titanium disulfide $Ti_{1.008}S$,[18] layered sulfides $(LaS)_{1.20}CrS_2$[19] and $(LaS)_{1.20}NbS_2$,[21] Chevrel-phase sulfide $Cu_{4.0}Mo_6S_8$,[22] tetrahedrite $Cu_{10.5}Ni_{1.5}Sb_4S_{13}$,[26] and colusites $Cu_{26}V_2Ge_6S_{32}$[29] and $Cu_{26}Ta_2Sn_{5.5}S_{32}$[31]

accepted in society because of their abundance and low toxicity of S and Cu.

### 3.2 Successful development of new thermoelectric tetrahedrites

Thermoelectric sulfides have been explored through the four strategies mentioned above. In 2012, JAIST researchers found low lattice thermal conductivity at room temperature in $Cu_{12}Sb_4S_{13}$, whose chemical composition is similar to a sulfosalt mineral called tetrahedrite.[25] In 2013, a team of researchers from JAIST, AIST, and RIKEN successfully enhanced the *ZT* of the thermoelectric tetrahedrites at around 673 K by substituting Ni for Cu.[26] These systems are excellent candidates for use in vehicle applications. In this study, materials were first developed for thermoelectrics by physicists at JAIST. Inorganic chemists at AIST investigated the processing for the preparation of these materials. At RIKEN, the crystal structure was examined using synchrotron radiation at SPring-8.

Thermoelectric tetrahedrites exhibit a PGEC behavior, namely, low electrical resistivity and low lattice thermal conductivity. The crystal structure of tetrahedrites belongs to a cubic system. The concentration of the charge carrier can be tuned by substituting Ni for Cu, resulting in an improved thermoelectric power factor.[26] Lattice thermal conductivity is low, below 0.5 W $K^{-1}$ $m^{-1}$ over the temperature range of 300 K to 673 K (Fig. 8). To understand lattice thermal conductivity, the synchrotron powder X-ray diffraction data measured were used to carry out crystal structure refinements. The result reveals the low-energy vibration of some Cu atoms in the crystal structure.[26] The vibration effectively scatters phonons, yielding the low lattice thermal conductivity. The enhancement in the *ZT* achieved have come both from the improvement in power factors and the reduction in lattice thermal conductivity. In $Cu_{10.5}Ni_{1.5}Sb_4S_{13}$, the *ZT* reaches ~0.7 at 665 K as shown in Fig. 7.

At the same time, a team led by Donald Morelli of Michigan State University has also successfully developed thermoelectric tetrahedrites.[27] In 2015, they demonstrated high *ZT* ~ 1.03 at 723 K in $Cu_{10.5}Ni_{1.0}Zn_{0.5}Sb_4S_{13}$.[28] The successful development of tetrahedrites in these studies has proven our strategies, demonstrating the potential of sulfides for thermoelectrics. The high *ZT* achieved in the Cu-containing sulfide has significant impacts for the thermoelectric community. The citation of our paper on the thermoelectric tetrahedrite[26] is greater than 90 (accessed July 2017). However, the high toxicity of antimony (Sb) in tetrahedrites is an obstacle to practical use.

### 3.3 Materials development and module fabrication in colusites

Since our strategies have been demonstrated through the development of tetrahedrites, we have continued to explore thermoelectric sulfides based on mineral-based systems under joint research. In 2014, we demonstrated that Pb, Te, and Sb-free thermoelectric sulfides $Cu_{26}V_2M_6S_{32}$ (M = Ge, Sn) called colusites show a high *ZT* at around 673 K.[29] Colusites also crystallize in a cubic structure. Like tetrahedrites, the high *ZT* in colusites arises from their metal-like high power factor and glass-like low lattice thermal conductivity. As shown in Fig. 8, the lattice thermal conductivity of $Cu_{26}V_2Ge_6S_{32}$ is low, below 0.5 W $K^{-1}$ $m^{-1}$ over the temperature range of 300 K to 673 K. It remains an open question why colusites show low lattice thermal conductivity. To address this question, lattice thermal conductivity is compared between colusite and sulvanite. The chemical composition of sulvanite is

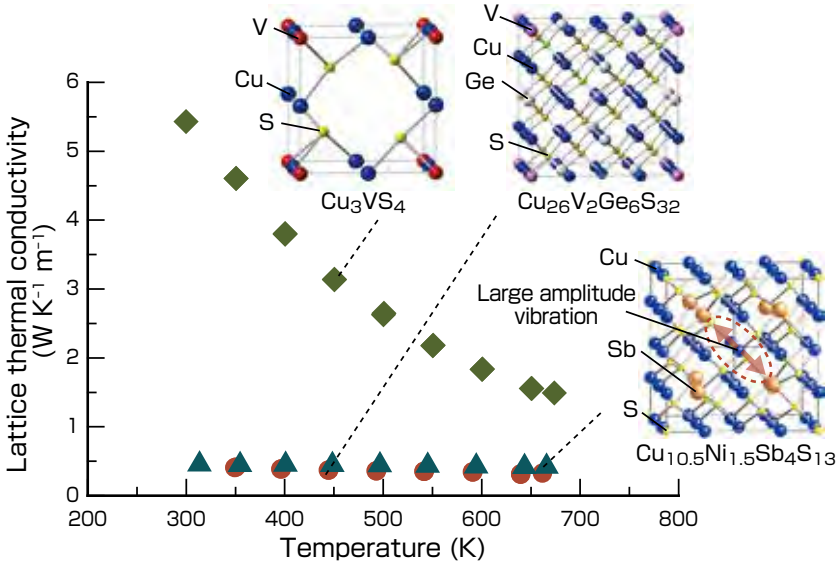


**Fig. 8 Temperature dependence of thermal conductivity for tetrahedrite $Cu_{10.5}Ni_{1.5}Sb_4S_{13}$,[26] colusites $Cu_{26}V_2Ge_6S_3$,[29] and sulvanite $Cu_3VS_4$,[29] along with their crystal structures.**

$Cu_3VS_4$ ($Cu_{24}V_8S_{32}$), similar to that of colusite $Cu_{26}V_2Ge_6S_{32}$. Both of these sulfides belong to a cubic system. On the other hand, there is a large difference in the number of atoms per unit cell between $Cu_{26}V_2Ge_6S_{32}$ (66 atoms) and $Cu_3VS_4$ (8 atoms). As shown in Fig. 8, the lattice thermal conductivity of $Cu_3VS_4$ is higher than that of $Cu_{26}V_2Ge_6S_{32}$. For example, the room-temperature value of $Cu_3VS_4$ is ten times as high as that of $Cu_{26}V_2Ge_6S_{32}$. This comparison implies that the much lower lattice thermal conductivity in $Cu_{26}V_2Ge_6S_{32}$ is due to its structural complexity, including the large number of atoms per unit cell.

A certain company pointed out that there is still concern regarding the oxidation of V for production processes and practical use, because V-oxides are toxic. We have therefore reworked our strategy using the periodic table of elements to address the problem. Like in the substitution of S for Te, an attempt was made to substitute the low toxicity elements Nb and Ta for V in colusites.[30] The Nb and Ta-substituted samples have been successfully prepared without a significant change in the processing, because all the elements belong to the same element family. The important finding here is that high thermoelectric performance is maintained with full substitution of Nb and Ta for V. Therefore, it can be said that the fully substituted colusites are environmentally friendly thermoelectric materials. In our recent study, the concentration of charge carriers can be tuned by changing the Sn content, leading to an improved thermoelectric power factor.[31] As a result, the *ZT* has been enhanced to 1.0 for $Cu_{26}Ta_2Sn_{5.5}S_{32}$ at 670 K. In PbTe, nanostructuring is proven to result in the dramatic enhancement of *ZT*; therefore, further study is currently in progress to boost the thermoelectric performance of colusites through nanostructuring (Fig. 1). This work has been supported as part of the International Joint Research Program for Innovative Energy Technology funded by METI. We will also promote the development of materials using data-driven study such as materials informatics (Fig. 1).

We have not only enhanced the materials performance of colusite systems but have also fabricated a thermoelectric module for practical use. Au-based diffusion barriers have been developed in our recent study. Figure 9 shows the recently fabricated colusite-based thermoelectric elements.

## 4 Establishment of a startup through technology transfer from AIST for developing the market

Thermoelectrics have recently received increasing attention with growing concerns over the global energy crisis and associated environmental burdens. As a result, there is increased need in downstream and end-user companies to test thermoelectric prototypes with their products. We possess high-efficiency thermoelectric modules and environmentally friendly materials developed at AIST. The studies are now in progress to improve their mechanical properties and chemical stability. There is also increased demand to evaluate thermoelectric products and buy measurement systems in upstream and manufacturing companies. We have mastered the measurement of thermoelectric materials and modules. As shown in Fig. 10, the seeds created by AIST seem to match the needs of industry. However, for AIST, it is hard to sufficiently meet demands from industry for various reasons, such as the difficulty of mass production. To bridge this gap, we had to create a new framework beyond the activities of AIST. One possibility was to transfer technologies from AIST to an established company. However, negotiations broke down because almost all companies did not have enough certainty in regard to how the thermoelectric market would grow. Furthermore, the author hoped to introduce the technologies into the market himself, improving them through feedback from the market. In June 2016, a startup company named Mottainai Energy was founded through transfer of technologies from AIST. The author is now the technical advisor to Mottainai Energy while he continues to work for AIST as a senior researcher.

Although it is difficult for a startup company to survive in Japan, two reasons prompted the establishment of

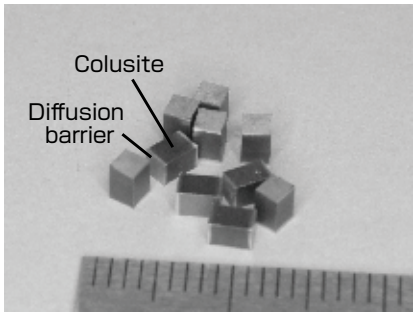


**Fig. 9 Colusite-based thermoelectric elements. Au-based diffusion barriers are formed on both sides.**

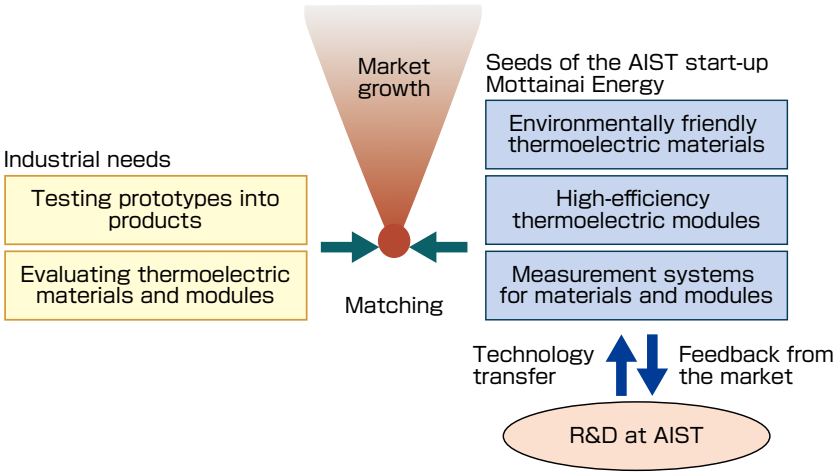


**Fig. 10 Industrial needs and the AIST startup's seeds in thermoelectrics.**

the Mottainai Energy. The first reason has already been mentioned above. And here is the second reason. In Japan, several national projects supported by METI, the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and related agencies are now in progress. In this project, many companies and research institutes, including AIST, have focused on various subjects covering the basics and applications of thermoelectrics. Almost all of these projects target the development of applications for large markets such as the vehicle market. Because thermoelectrics provide new approaches to improving energy, in the future thermoelectric markets will grow and provide benefits and returns to government and the companies who invest in them. On the other hand, the use of thermoelectrics is currently limited to space applications such as RTGs; therefore, the quality of products is expected to gradually improve for commercial markets. The first market for thermoelectrics is probably small. US startups have initially introduced niche products such as outdoor gear to small markets. In Japan, there are less projects and support for targeting niche applications. Mottainai Energy, to keep up with world trends, aims to first develop niche applications for commercial markets and then grow the market in Japan.

Taking into consideration the factors mentioned above, the following main products are being developed through Mottainai Energy: High-efficiency thermoelectric modules and environmentally friendly materials will be supplied for downstream and end-user companies. Measurement systems and services will be supplied for upstream and manufacturing companies. The supply of the former provides a good opportunity to inform people about thermoelectrics, thereby developing the market. In the latter, the measurement systems and services improve the reliability of products at each company, as mentioned in Chapter 5. The company passed its first anniversary without deviation from its original purposes during the writing of this article.

## 5 Challenges in prototype validation and advanced measurements

To develop the thermoelectric market, we have focused on the following studies, in addition to the materials and module developments discussed above: prototypes should be made and validated to promote commercialization and implementation. Common measurement methods must be established as part of the rules. For prototype validation, the design and development of a system of technical integration between the thermoelectric module and associated peripherals, particularly for vehicles, are needed to meet growing industrial demand. As an example of associated peripherals, a heat exchanger is needed to transfer heat from waste heat sources to thermoelectric modules. Moreover, it is necessary to validate the thermoelectric system in a vehicle test bench for finding and solving technical problems. Like the materials and module developments, the project is being promoted in international collaboration with researchers who are familiar with vehicles.

For measurements, common methods must be established as standard before the wide spread of thermoelectrics. If the thermoelectric efficiency of modules is measured with different methods and systems of each company and country, it is easy to imagine that the lack of compatibility will cause confusion. A measurement method and system for thermoelectric modules were developed at AIST in collaboration with Japanese companies and research institutes before the author joined AIST.[9] The efficiency of ~370 modules was measured through the AIST system for the past decade. The AIST system has become a de facto standard in Japan. On the other hand, because the modules have been used in space missions for many years, other high-quality measurement systems were developed for this field. Therefore, the joint research between AIST and research institutes for space programs will lead to the development of high-accuracy measurement systems. Specifically, there are plans for cross-checking of the measurement systems, to be performed by a team led by A. Yamamoto, who is mainly responsible for the development of the AIST system. The members of this team would include the author and experts from space technology research institutes and equipment manufacturing companies. The measurement of heat flow and the reduction of the effect of thermal radiation will be particularly improved through cross-checking.

An example of the collaboration in prototype validation and advanced measurement is the joint research between AIST and the German Aerospace Center (DLR) supported as part of the International Joint Research Program for Innovative Energy Technology funded by METI. The DLR research covers transportation and energy as well as aeronautics and space. The DLR is therefore an appropriate collaboration partner for both prototype validation and advanced measurement. On 19 March 2017, AIST and DLR concluded a memorandum of understanding (MOU) to start joint research. The author will steadily improve thermoelectric technologies through various frameworks, including through the AIST and DLR joint research.

## 6 Conclusion

Although the author's interdisciplinary activities from materials development to startup establishment have made an impact on thermoelectrics, the growth of the market remains a distant goal. His effort will continue to be devoted to achieving this goal, using current knowledge, including the discussions in this journal, *Synthesiology*. The importance of international collaboration, interdisciplinary study, and technology transfer addressed in this paper was already recognized through various past discussions. The important aim of this work was to integrate these discussions in the

development of the study. Each knowledge element has been deeply understood in full research proposed by AIST after a great deal of discussion. The author believes that the discussion of the full research should be shifted to the integration and advancement of elements of knowledge.

## 7 Acknowledgments

The author expresses my deep appreciation to Prof. Mercouri Kanatzidis, Senior Researcher at ANL and Professor at Northwestern Univ., and Dr. Priyanka Jood, Researcher at ATSI, for plentiful stimulating discussions in the development of PbTe-based thermoelectric materials. The author is sincerely grateful to Prof. Koichiro Suekuni, Associate Professor at Kyushu Univ., Prof. Shinji Hirai, Professor at Muroran IT., Prof. Toshiro Takabatake, Professor at Hiroshima Univ., and Prof. Mikio Koyano, Professor at JAIST, for productive collaboration on the development of thermoelectric sulfides. The author also thanks Dr. Haruhiko Obara, Deputy Director General at AIST, and Mr. Atsushi Yamamoto, Group Leader at AIST, for lending their expertise on thermoelectric module and their evaluations in PbTe and sulfide. Mr. Hirotaka Nishiate, CEO at Mottainai Energy, made enormous contribution to starting the company. The author would like to thank his colleagues for in-depth discussions and the postdoctoral fellows for strenuous efforts. Their names appear in the various publications cited in this article. The work was supported as part of Japan-United States Cooperation Project for Research and Standardization of Clean Energy Technologies funded by METI, International Joint Research Program for Innovative Energy Technology funded by METI, and Development of Thermal Management Materials and Technology funded by NEDO. Financial support from JSPS KAKENHI Grant Number 25420699, Thermal and Electric Energy Technology Foundation, and Iketani Science and Technology Foundation also are gratefully acknowledged.

## Terminologies

Term 1. Thermoelectrics: Figure a shows an electric circuit consisting of two dissimilar materials. In this case, one is an electrode and the other is a semiconductor thermoelectric material. When one of the two junctions is heated, the voltage $V$ is produced in electric circuits by the temperature difference dT: $V = SdT$. The phenomenon and proportionality constant, $S$, are known as the Seebeck effect and Seebeck coefficient, respectively. A thermoelectric generator directly converts heat into electricity through the Seebeck effect.

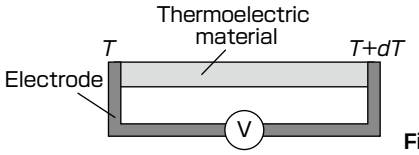


**Fig. a Seebeck effect**

Term 2. Thermoelectric module: Figure b shows the thermoelectric module made from one couple of p- and n-type thermoelectric materials. The charge carriers of the p- and n-type materials are positively-charged holes and negatively-charged electrons, respectively. Both charge carriers, holes and electrons, diffuse from the hot side to the cold side. As a result, the electrical current flows form the cold side of n-type material to that of p-type material by passing through the interconnecting electrode. Thermoelectric modules normally contain many couples. For example, the modules shown in Figs. 6(b) and (c) contain eight p-n couples. The power output and conversion efficiency obtained changes with the electrical load. The power output reaches a maximum (maximum power output) when the impedance is matched between the load and the internal resistance. In conversion efficiency, the maximum value (maximum conversion efficiency) slightly shifts from the value at the impedance matching because of the effect of heat.

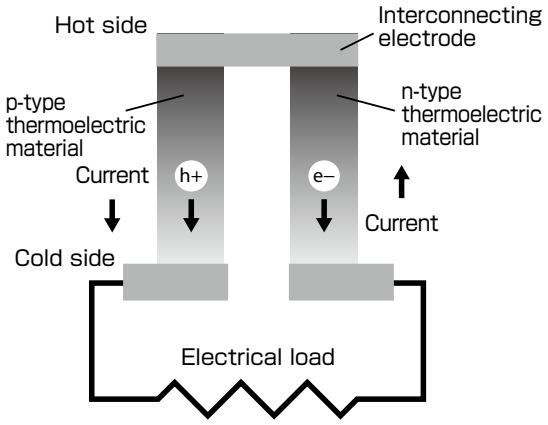


**Fig. b Thermoelectric module made from one couple of p- and n-type thermoelectric materials**

Term 3. Thermoelectric figure of merit: The performance of a thermoelectric material is determined by the thermoelectric figure of merit $ZT$, defined as $ZT = S^2T/\rho\kappa$, where $T$ is the temperature, $S$ is the Seebeck coefficient, $\rho$ is the electrical resistivity, and $\kappa$ is the thermal conductivity. The performance of a thermoelectric material increases with increasing $ZT$. Their units are $T$ [K], $S$ [V $K^{-1}$], $\rho$ [Ω m], and $\kappa$ [W $K^{-1}$ $m^{-1}$], respectively. Thermal conductivity arises from two sources, phonons and charge carriers; therefore, it is the sum of lattice (lattice thermal conductivity, $\kappa_{lat}$) and electronic (electronic thermal conductivity, $\kappa_{el}$) contributions: $\kappa = \kappa_{lat} + \kappa_{el}$. A high Seebeck coefficient and low electrical resistivity lead to a high-power output. Low thermal conductivity, particularly low lattice thermal

conductivity, helps to maintain the temperature difference.

Term 4. Band offset: In this case, this means the energy difference between the top of the valence bands in dissimilar materials.

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## Author

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Michihiro Ohta received his Ph.D from the Kyushu Institute of Technology in 2002. He was a postdoctoral fellow at the National Institute for Materials Science and the Muroran Institute of Technology before joining the National Institute of Advanced Industrial Science and Technology (AIST) in 2006. He has been a senior researcher at AIST since 2013. He was a visiting scholar at Argonne National Laboratory and Northwestern University from 2011 to 2012. Ohta is also a technical advisor at the startup company, Mottainai Energy, founded in 2016. He has led several thermoelectric projects, including a program supported by the International Joint Research Program for Innovative Energy Technology funded by the Ministry of Economy, Trade and Industry (METI), Japan.

## Discussions with Reviewers

### 1 Overall

**Comment (Toshihiko Kanayama, AIST)**

This paper discusses the author's consistent strategy to work from original materials development and module fabrication to social implementation for thermoelectrics. The content of this article meets the editorial policy of *Synthesiology*. International collaboration with a team of experts from various research institutes has been actively conducted, achieving meaningful results. This article gives a good example for others.

**Comment (Shigeki Naitou, AIST)**

The utilization of unused heat energy will greatly contribute to energy conservation and have significant effects on industries' activities, including power generation, steel, vehicle, and chemical industries. Therefore, this study will play an important role in society. The author's concept and the design of R&D and the efforts to establish a startup for social implementation meets the editorial policy of *Synthesiology*.

### 2 Industrial significance of thermoelectrics

**Comment (Shigeki Naitou)**

Thermoelectric waste heat recovery in industries including power generation, steel, vehicle, and chemicals should be discussed in more detail. With regards to social implementation, the future outlook should be provided in this article. Public support would be received through improvement in the outlook to be shared with these industries.

**Answer (Michihiro Ohta)**

A technology roadmap for thermoelectric waste heat recovery in industrial use should be provided as you indicated. For the introduction of thermoelectrics, it is necessary to develop associated peripherals such as a heat exchanger as well as thermoelectric materials and modules. For example, a heat exchanger should be designed and developed for each product. We have started to develop a thermoelectric system, including a heat exchanger, for use in vehicles, as mentioned in Chapter 5. Figure 1 and relevant sentences have been modified to clarify the importance of developing the associated peripherals as well as the thermoelectric technologies.

### 3 Social implementation

**Comment (Toshihiko Kanayama)**

The important point of this work is that the establishment of the startup and the development of advanced measurements, as well as the development of materials and modules, have been promoted for social implementation and the spread of thermoelectrics. There is a need for more concrete discussion of the establishment of the startup and the development of advanced measurements in Chapters 4 and 5, respectively. The startup's business activities and missions should be particularly emphasized in Chapter 4. In Chapter 5, the author should address how advanced measurements and prototype validations will be developed through international collaboration with research institutes and companies. These discussions would help to clarify the author's intentions.

**Answer (Michihiro Ohta)**

As suggested by the reviewer, the startup's activities and missions have been included in Chapter 4. Moreover, future plans and the purpose of international collaboration have been added to Chapter 5. However, because both activities are at an early stage, these discussions need to be deepened in further work. On the other hand, the profound discussions on the materials and module development in previous works have been provided in Chapters 2 and 3.

### 4 Configuration and properties of the thermoelectric module

**Comment (Toshihiko Kanayama)**

An explanation for the configuration of the thermoelectric module is needed to better understand the discussion in this article. I recommend that the schematic representation of the basic configuration is shown in a figure and an explanation is added to the text. The reasons why both p- and n- type semiconductors are needed in the module should be particularly noted.

In addition, the meaning of the following technical terms used is unclear. Definitions and explanations should be added: a) Nanostructure: Because this generally has a very broad meaning, a definition should be provided. b) Bulk: This technical term is used in specific fields. c) Maximum power output: The meaning of maximum is unclear. d) Maximum conversion efficiency: The meaning of maximum and conversion efficiency should be explained.

**Answer (Michihiro Ohta)**

Thank you for your valuable suggestions. In term 2 of Terminologies, the configuration of thermoelectric module, maximum power output, and maximum conversion efficiency have been explained. The meaning of nanostructure and bulk has been defined in the main text.

# Challenges to the development of the world's first nondestructive inspection system

## — Development of an inspection system with laser ultrasound and a cold cathode X-ray source —

**Bo WANG, Junji TAKATSUBO, Norio SAITO*, Xiaojun LIU and Shuichi SUZUKI**

**[Translation from *Synthesiology*, Vol.10, No.2, p.75–86 (2017)]**

The social and industrial infrastructure built for the 1964 Tokyo Olympics, during a period of high economic growth, has become old. This infrastructure urgently needs inspection for the success of the 2020 Tokyo Olympics. As an AIST Start-up, we are conducting research and development of a new nondestructive inspection system based on the world's first visualization technology using laser ultrasound and compact X-ray technology with carbon nanostructure cold cathode X-rays. Here we describe various challenges for its development.

*Keywords*: Nondestructive inspection, laser ultrasound, X-ray inspection, visualization, miniaturization, image processing, secular change

## 1 Introduction

Currently, Japan is facing a problem of aging social and industrial infrastructures that were built during the rapid economic growth period. Various inspection devices are used for the maintenance inspection of such infrastructures, but in most cases, these products are imported from overseas.

As a technology transfer venture company of AIST, we are spending our efforts to research, develop, and achieve product realization of new nondestructive inspectors to inspect the social and industrial infrastructures, and to make contribution to safety and security.

One of our efforts is a laser ultrasonic visualization inspector (LUVI). This is a device by which thermal stress ultrasound is generated by laser-scanning the surface of the object to be inspected, and the behavior of ultrasound propagation is visualized. It is the first of its kind in the world. This device has the characteristics that follow: (1) it allows nondestructive inspection of objects with complex shapes, and (2) it allows inspection of objects at high speed from a distance.

Another effort is a compact X-ray inspector that fits in the palm of a hand, can be driven even by dry cell batteries, and is equipped with a small power-saving cold cathode X-ray tube. This device has the characteristics that it is compact and lightweight, can generate X-ray instantly without preheating, is power-saving so it can be driven by an AA battery, and has a long lifespan.

In this report, the development of LUVI and a dry-cell-operated compact X-ray inspector, as well as their application to various inspections will be explained.

## 2 LUVI and its application to nondestructive inspection

Laser ultrasound is a technology to generate ultrasound in an object and to conduct inspection without contact, using laser beams. The sending/receiving of ultrasound can be done in a nondestructive manner from a distance, and this enables inspection of objects that were difficult to inspect using conventional devices, including objects of complex shapes, large surface areas, or those located in high temperature or in high places. Therefore, it is expected to be a new inspection device for aircraft, automobiles, plants, thermal and nuclear power stations, electronic parts, as well as social infrastructures such as steel bridges.

LUVI that our company developed, as seen in Fig. 1, is a device that visualizes the propagation of ultrasound as moving images by laser-scanning the surface of an object to be inspected. This is a novel device, where, if there is a defect in an object, ripples can be observed as if a spring is gushing to the water surface, and this can be easily recognized by a person even though he/she may not be an inspection specialist.[1]

## 3 Visualization principle

The characteristic of this visualization method is the

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measurement of ultrasonic propagation images by scanning the oscillating (sending) side, rather than the receiving side of the ultrasound. This assumes that there is reciprocity of ultrasound propagation (the receiving waveform does not change if the direction of sending/receiving is reversed). For example, as shown in Fig. 2 top, when ultrasound transmission/reception is conducted by placing an angle beam transmission transducer A and a normal reception transducer B with a defect (spherical groove with curvature radius of 20 mm and depth of 4 mm) in the middle, and if the transmission/reception properties of the two transducers are the same, the waveform, where the signal is sent to A from an ultrasound pulsar and received at B, and the waveform, where the signal is sent to B and received at A, should almost be the same as shown in Fig. 2 bottom. Therefore, as shown in Fig. 3 top, in the case of a PZT transducer, the measurement


**Fig. 1 Laser ultrasonic visualization inspector and an example of visualized image**
(There are two simulated defects at the arrow points on the surface of the stainless elbow with thickness 6 mm)

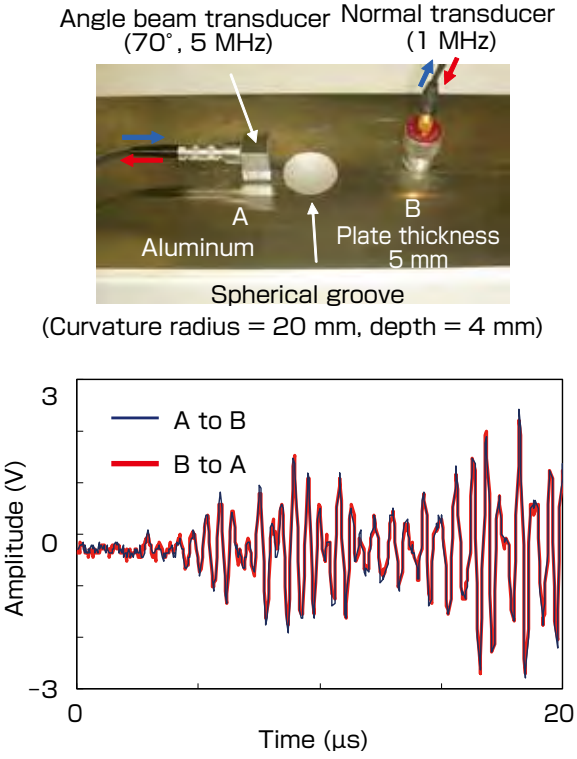



**Fig. 2 Reciprocity of ultrasound propagation**

system can be considered equivalent even if the direction of transmission/reception are reversed regardless of the incident direction of ultrasound or the presence of a defect. Applying this to the measurement system of PZT and a laser, as shown in Fig. 3 bottom, it can be considered that the measurement system in which the thermally excited ultrasound is generated by a laser and received by a PZT transducer, and the measurement system where ultrasound is generated by a PZT transducer and received by a laser probe that has the same property as laser oscillation are equivalent. Since the measurement system where the ultrasound oscillation point is scanned with a laser and is received by a PZT transducer attached to a fixed point can be considered equivalent to the measurement system where the ultrasound produced at a PZT transducer at a fixed point is received while scanning the laser probe, it is possible to obtain moving images of ultrasound sent from a PZT transducer at a fixed point, if the receiving amplitude at each laser scanning point is displayed as images in time series by conducting brightness (color) modulation. In the conventional measurement method in which the laser probe of the receiving side is scanned, there was limitation that the laser beam had to be introduced perpendicularly to the inspection object by maintaining a constant focal length. However, in the case of laser scanning on the sending side, there is almost no limitation in the focal length or incident angle, and the laser beam can be moved freely at high speed, and this enables visualization of ultrasound traveling through three-dimensional objects.

## 4 Laser ultrasonic visualizing inspector (LUVI)

Figure 4 shows the configuration of LUVI. It has the mechanism where a laser, a galvanometer mirror, and a high-speed A/D converter are synchronized using a personal computer (PC), and a pulse laser is used for high-speed scanning in lattice form over the surface of an inspection object. Then, weak ultrasonic waves are excited by heat strain. In "contact measurement," this ultrasound propagation signal is detected by piezoelectric reception sensors (maximum eight sensors) attached to the object. In "noncontact measurement," it is detected using a laser

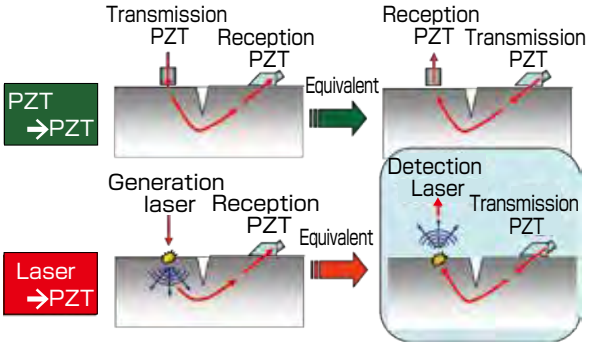



**Fig. 3 Fig Comparison of reciprocities of PZT-PZT transceiver system and laser-PZT transceiver system**

Doppler vibrometer that enables noncontact reception. The signal is then amplified using an ultralow noise amplifier, and is recorded on a PC hard disk using a high-speed A/D converter. By reconstructing the multiple ultrasound propagation signals that travel from the laser scanning point to the reception sensors by the reciprocity theorem of ultrasound propagation, visualization of ultrasound generated from the reception sensor as moving images is made possible.

## 5 Types of LUVI

As shown in Fig. 5, LUVI can be used for "contact measurement" where a reception sensor comes in contact, and for "noncontact measurement" where the laser probe is used.

Here, the characteristics of LUVI are listed.

1. It is easy to understand by non-experts because moving images are displayed.
2. Complexly shaped objects (curved or uneven surfaces) can be inspected since it is noncontact scanning.
3. A wide range can be quickly inspected since high-speed scanning is done by mirrors.
4. It is effective in inspection of dangerous places (radioactive, high temperature, or high places) since it is noncontact inspection.
5. Web camera images can be superimposed and displayed on the moving images.
6. The abnormal area that is shown on the measurement image can be marked by a guide beam on the surface, and the location of defects can be checked in real time.

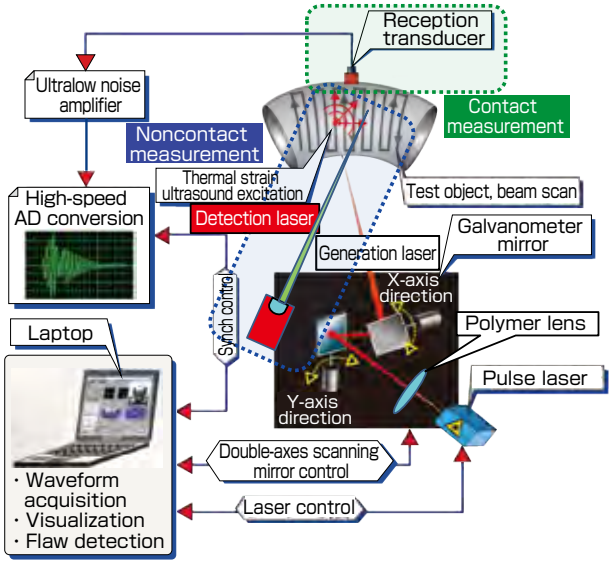



**Fig. 4 Configuration of the laser ultrasonic visualization inspector (LUVI)**

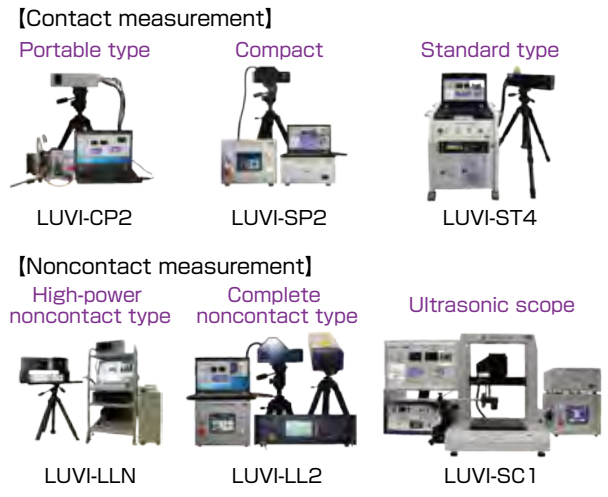



**Fig. 5 Contact measurement and noncontact measurement LUVI**

## 6 Examples of application to nondestructive inspection

### *6.1 Inspection of welded parts (T-shaped welded joint)*

Next, as a case study of application of LUVI to welded parts, an example of high-speed imaging at laser scanning rate of 5,000 points/sec is presented.[2]

Figure 6 shows an image of a T-shaped welded joint (SS400 material) with width of 100 mm. This was measured using LUVI under the following measurement conditions:

(1) Scanning rate of 1,000 Hz; scanning pitch of 0.8 mm
(2) Scanning rate of 5,000 Hz; scanning pitch of 0.8 mm
(3) Scanning rate of 5,000 Hz; scanning pitch of 1.5 mm

In practice, a pulse laser of wavelength of 1064 nm scanned the T-shaped welded part with a simulated crack, signals were detected, measurement images were analyzed, and internal flaw echoes were visualized on the spot. The results are shown in Fig. 7.

Since the welded part itself is a large defect, many false echoes are generated. Therefore, it is difficult to identify defect echoes, but the identification becomes easier if ultrasound propagation is visualized.

**Fig. 6 T-shaped welded joint (defect in welded corner part)**

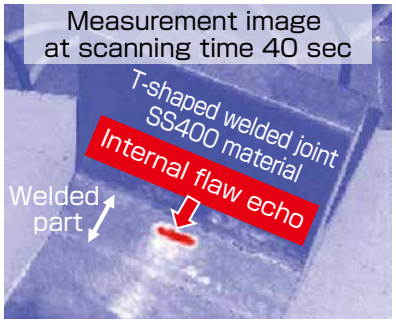
The following results were obtained under the following conditions:

(1) Scanning rate of 1,000 Hz and scanning pitch of 0.8 mm, scanning time was 40 sec;
(2) Scanning rate of 5,000 Hz and scanning pitch of 0.8 mm, scanning time was 3 sec; and
(3) Scanning rate of 5,000 Hz and scanning pitch 1.5 mm, scanning time was 2 sec.

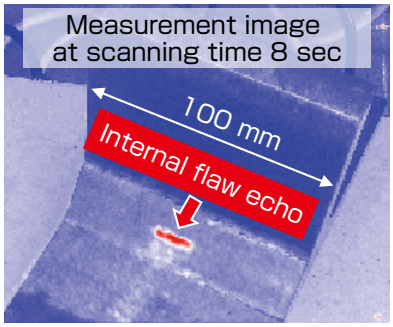
From the results, the following was observed:

(1) When scanning rate was 1,000 Hz and scanning pitch was 0.8 mm, scanning time was 40 sec, but
(3) At scanning rate of 5,000 Hz and scanning pitch of 1.5 mm, scanning time was 2 sec.

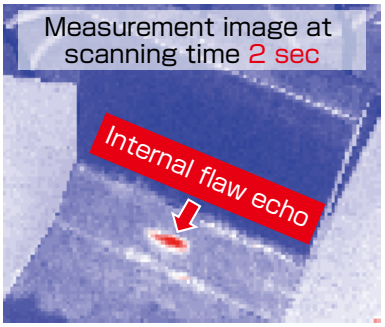
Looking at Fig. 7, the internal flaw echo is clearly detected even when the scanning time is 2 seconds in (3). Therefore, quick inspection was achieved at a short time of 2 sec, even at the welded part that is difficult to identify at laser scanning rate of 5,000 points/sec.[3]




① Scanning rate 1,000 Hz; scanning pitch 0.8 mm




② Scanning rate 5,000 Hz; scanning pitch 0.8 mm




③ Scanning rate 5,000 Hz; scanning pitch 1.5 mm

**Fig. 7 High-speed imaging of ultrasound propagation**

### *6.2 CFRP inspection (aircraft fan blade)*

Figure 9 is an ultrasonic propagation image of an aircraft fan blade (about 1.5 m in length) made of carbon fiber reinforced plastic (CFRP). An ultrasonic sensor was attached to the backside of the fan blade, and a pulse laser scanned the blade surface at a pitch of 3 mm from a distance of 1.5 m. The measurement time was 50 sec (scanning rate of 2,000 Hz). Since the decay of ultrasound is great in CFRP, a vertical sensor of low frequency (100 kHz) was used as the ultrasound sensor. Although there was no significant defect in this inspection object, it was possible to measure ultrasound that propagated throughout the surface of the fan blade using one sensor. Such CFRP inspection is being applied to automobiles as well as aircraft.

### *6.3 Noncontact measurement (insulator)*

The above-mentioned results were for cases where a PZT reception transducer was used in contact measurement, and the following are examples of visualization using a noncontact laser probe.

Since there is danger of electrocution with a high-voltage insulator, a reception transducer cannot be attached directly to an insulator, and there is a need for inspection by noncontact measurement. Therefore, using an insulator with

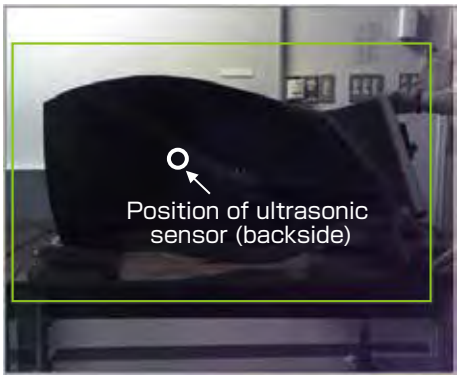



**Fig. 8 CFRP aircraft fan blade**

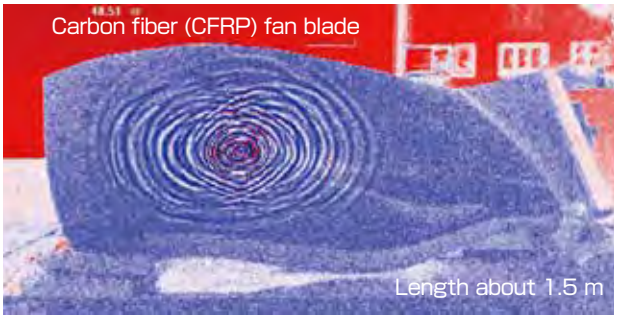



**Fig. 9 Ultrasound propagation image of the CFRP aircraft fan blade**

a slit flaw as shown in Fig. 10 right, noncontact measurement of a slit flaw was attempted as shown in Fig. 10 left.

The slit flaw echo measurement is shown in Fig. 11. Since detection sensitivity decreases in noncontact measurement compared to contact measurement, one spot was irradiated five times and the average was taken. Echoes from the slit flaw and traveling waves of ultrasound that spread from the irradiation point of the laser probe can be observed.

### *6.4 Inspection of social infrastructures (steel bridges)*

The application of nondestructive inspection to industrial infrastructures was discussed above, but the urgent issue for Japan is the inspection of aging social infrastructures. We are trying to develop defect inspection technology by a noncontact and nondestructive method, particularly for effective and remote detection of cracks that occur in steel bridges, using laser ultrasound, and are trying to save manpower and to simplify inspection work as well as to increase inspection accuracy.

An actual steel bridge inspection is shown in Fig. 12. As shown in Fig. 12 right, an inspection device (LUVI) was placed on an inspection vehicle, the laser scanned the welded part of the stiffener of the main girder upper flange, and a contact sensor was attached. Then, visualization measurement of fatigue cracks using ultrasonic echoes was attempted.

Figure 13 right is the crack echo observed by measuring the frame part shown in Fig. 13 left. Here, it is important to note that it is possible to measure the propagation of ultrasound as a moving image, even when laser scanning is done on the inspection surface of the steel bridge that is covered by a coating film. If there is a crack, the ripple wave echoes can be seen in the measurement image, and the presence of the crack and its size under the coating film can be determined.

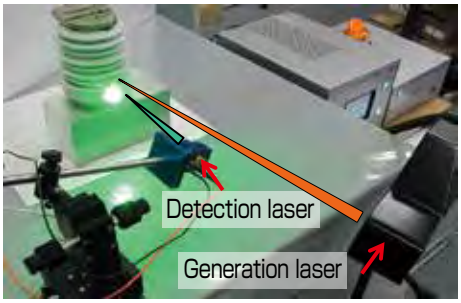




**Fig. 10 Insulator with cracks**

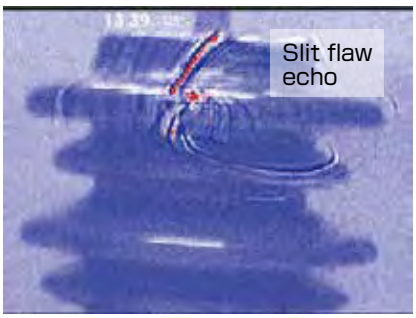



**Fig. 11 Noncontact measurement image of the insulator with cracks**


**Fig. 12 Scene of fatigue crack inspection in the welded part of a steel bridge**

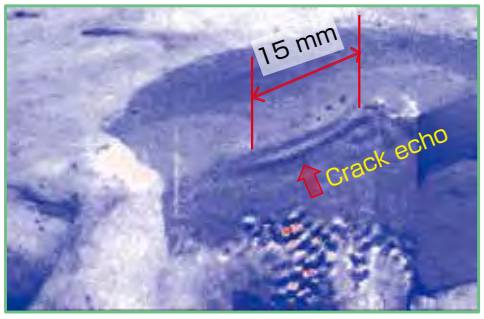



**Fig. 13 Fatigue crack echo of the welded part of steel bridge**

Since this is noncontact scanning by a laser, the echo can be observed quickly and remotely for a wide inspection surface or complex shaped parts such as corner welded parts.

## 7 Future of laser ultrasound technology

LUVI is gaining attention as an innovative technology that allows inspection that was conventionally considered difficult, including the following: the inspection of curved objects such as plant pipes, aircraft engine blades, or rocket boosters; the inspection of narrow or uneven parts such as automobile engine blocks or transmission cases; the inspection in radioactive environment such as nuclear power plants; the inspection under high temperature such as during welding; the inspection in high places such as tunnels or steel bridges; and the inspection of CFRP materials in aircraft and automobiles. It is being introduced to various places now.

## 8 Dry-cell-operated compact X-ray inspector and its application to nondestructive inspection

Using a carbon nanostructure cold cathode X-ray tube[4] that was researched at AIST, we developed[5] and formed into a product[6][7] an X-ray inspector with output of 60 kV, 100 kV, 120 kV, and 150 kV. Particularly, a palm-sized compact X-ray inspector that can conduct practical inspection with one AA battery is a type that has never been seen before. This enables on-site inspection by allowing the X-ray inspectors in places where formerly such a device could not be taken. Here, specific application of these X-ray inspectors to various fields will be described.

## 9 Cold cathode X-ray tube that can be operated with a dry cell

Carbon nanostructure used in our compact X-ray inspector and its cold cathode electron source are shown in Fig. 14.

As shown in this photograph, the carbon nanostructure cold cathode electron source is in the shape of a conifer tree. It is thick at the substrate side, and the resistance to field force is strong. This is because when the substrate side is thick, just like a tree, even if it gradually erodes at the top, the thickness on the substrate side allows the structure to be less affected by electric fields and is resilient just like the thick trunk of a tree. Therefore, it is characterized by having a long lifespan compared to the filaments and heaters of a Hot cathode electron source that is used commonly in X-ray tubes. A cold cathode X-ray tube equipped with a carbon nanostructure cold cathode electron source is shown in Fig. 15.

**Table 1. Comparison of the Hot cathode x-ray tube and the cold cathode X-ray tube**

| Hot cathode X-ray tube | Cold cathode X-ray tube |
|---|---|
|  |  |
| (1) Hot electrons emitted from filament<br>(2) Preheating of filament and standby power necessary<br>(3) Must wait until the filament temperature reaches a certain level<br>(4) Needs preheating and running cost is high<br>(5) Large and heavy power source unit, cumbersome handling<br>(6) Filament lifespan is a problem | (1) Field emission by cold cathode carbon nanostructure<br>(2) Preheating of filament and standby power are not necessary<br>(3) Pulse action allows instant start-up of X-ray tube<br>(4) Operable with dry cells, running cost is inexpensive<br>(5) Compact/lightweight can be achieved for entire X-ray generator<br>(6) Long lifespan of 10 million shots due to carbon nanostructure |

The cold cathode X-ray tube shown in Fig. 15 has the length of about two or three AA batteries. Many electrons are emitted due to a field emission phenomenon from the tip of the carbon nanostructure cold cathode electron source shown in Fig. 14. Since there is no heater or filament in this X-ray tube, preheating and aging are unnecessary, and X-rays can be irradiated immediately. Since it consumes power only during X-ray generation, it is energy saving and can be operated with one AA battery.

Table 1 shows a comparison with a Hot cathode X-ray tube,

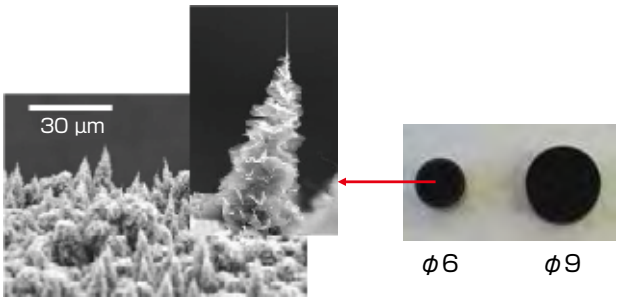



**Fig. 14 Carbon nanostructure (left) and cold cathode electron source (right)**

**Fig. 15 Cold cathode X-ray tube equipped with carbon nanostructure cold cathode electron source**

Fig. 16 shows the internal structure of a Hot cathode X-ray tube, and Fig. 17 shows the internal structure of a cold cathode X-ray tube.

A Hot cathode electron source needs preheating and standby voltage to emit Hot electrons, and this requires corresponding circuits that make the whole device large and heavy. In comparison, a cold cathode electron source emits field electrons as soon as voltage is applied, can provide instant irradiation, and does not require preheating or standby voltage. Therefore, the device has the advantage of being energy-saving, small, and lightweight.

## 10 AA-battery-operated compact X-ray inspector

Figure 18 shows a dry-cell-operated compact X-ray inspector that is palm-sized, which was realized by the installation of the above-mentioned cold cathode X-ray tube. This device boosts the voltage of one AA battery (1.5 V) several stages through its originally developed booster circuit, and boosts it 40,000 times up to tube voltage 60 kV. This allows the irradiation of X-rays at tube voltage of 60 kV with one AA battery, from a device with thickness of 70 mm or less and weight of 1.8 kg.

This compact and lightweight device is capable of irradiating about 100 shots of pulse X-rays at 50 ms per shot with one AA battery. When used as an actual nondestructive inspector, it will be equipped with two 7.2 V small lithium ion batteries of width 2 cm × length 3 cm × thickness 1 cm. The booster factor is optimized, and the number of pulses that can be irradiated is about 5,000 shots.

The effective focal size of the X-rays is 1 mm, and this is small compared to the effective focal size of 3 mm for X-ray inspectors equipped with a general Hot filament X-ray tube. Therefore, a high-resolution image can be obtained even when imaging is done at a short distance from an object.

## 11 Compact X-ray inspector for pipes

### *11.1 Compact X-ray source*

At industrial plant sites, the space between pipes is about 10 cm, and therefore, it was difficult to insert a conventional X-ray source device into this space. We set the thickness of the X-ray source to 7 cm, and set out to fabricate a device that can irradiate X-rays from the gap between the pipes.[8]

Figure 19 shows a compact X-ray source that we developed with thickness of 7 cm. This X-ray source uses the above-mentioned cold cathode X-ray tube as its X-ray tube, and has tube voltage of 150 kV and maximum tube current of 2 mA, though it is compact and lightweight at thickness of

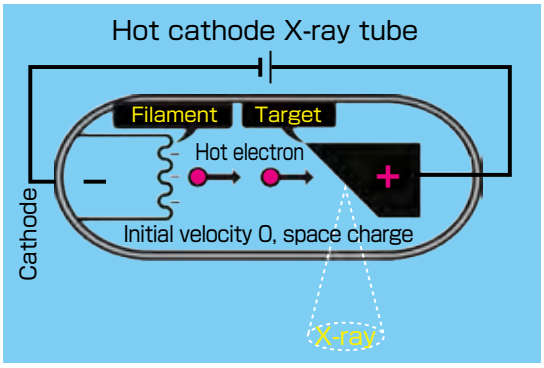



**Fig. 16 Internal structure of the Hot cathode X-ray tube**

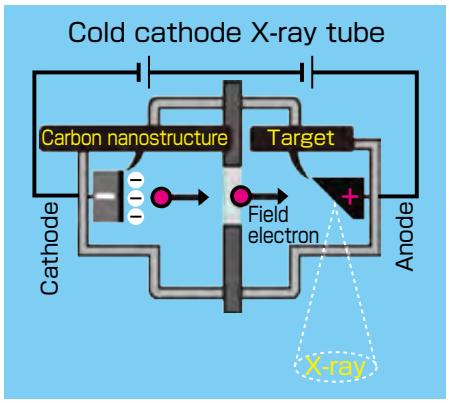



**Fig. 17 Internal structure of the cold cathode X-ray tube**

**Fig. 18 Dry-cell-operated compact X-ray inspector that fits on a palm**

**Fig. 19 Compact X-ray source**

7 cm and weight of 6 kg. It employs a controller to enable X-ray inspection of tubes in high or narrow space from a distant place in the plant. The X-ray can be irradiated from a distance of 20 m to obtain a detector image. This allows safe and efficient inspection by workers. Since it is battery operated, it does not require a 100 V power source, and it is suitable for use on site.

### *11.2 Developed device*

Figure 20 shows our developed compact X-ray inspector for pipes. This device has a controller that allows irradiation of X-rays from a distance of 20 m. It consists of a compact X-ray source of thickness of 7 cm, a thin detector of width of 5 cm, and a personal computer for control and display. This device is compact, lightweight, portable, and mobile, and the inspection can be conducted by placing it between pipes wrapped with insulating material.

To inspect pipes using this device, we newly developed a cold cathode X-ray tube and a booster circuit, and achieved output of 150 kV. As the tube voltage reached 150 kV, we used our original solid mold as the insulating mold to ensure portability. To keep the thickness of the X-ray source to 7 cm, the high-voltage circuit was downsized and highly integrated, and was enclosed in the body. Using a controller, photography conditions such as tube voltage, tube current, pulse width, and pulse frequency can be changed depending on the diameter and thickness of the pipes, and X-rays can be irradiated from a place 20 m away from the X-ray source. From the control/display PC, the operator can irradiate X-rays by pushing the X-ray irradiation button on the screen, data from the detector can be read, image processing can be done, and photographed images can be displayed in real time. The displayed images can be adjusted for brightness and contrast, and zoom and size can also be displayed.

### *11.3 Thickness reduction inspection of pipes*

The X-ray source has thickness of 7 cm and weight of 6 kg. It is placed between pipes, is battery operated, and irradiates X-rays in a horizontal direction. It can irradiate pulse X-rays of pulse width of 30–200 ms at tube voltage of 100–150 kV, using a controller from a 20 m distance.

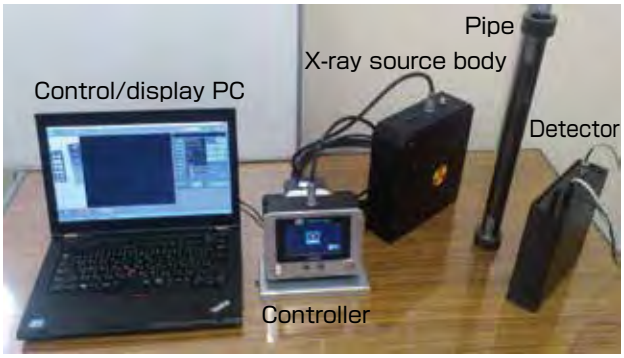



**Fig. 20 Compact X-ray inspector for pipes**

The effective focal size is 1 mm, and a high-resolution image can be obtained even if X-rays are irradiated right near the pipes that are wrapped with insulating material. Figure 21 shows an example of a size display of an object that simulates a thickness reduced pipe. The image shows an eroded end of a simulated thickness reduced pipe. The external diameter of this pipe was 34 mm, the thickness was 6.8 mm, and the thinning depth of the protruding part was 1.8 mm. The conditions for photography were tube voltage of 140 kV, tube current of 1 mA, pulse width of 100 ms, and 1 pulse.

The comparison of the displayed thinning depth of the protruding part and the actual measurement values was as follows:

Actual value: Protrusion length of 21.0 mm, protrusion depth of 1.8 mm

Displayed value: Protrusion length of 21.09 mm, protrusion depth of 1.83 mm

From these values, the differences between the actual value and the displayed value were 0.09 mm for protrusion length and 0.03 mm for protrusion depth, and the possibility of thickness loss measurement in piping inspection was confirmed.

## 12 Compact X-ray inspector for power lines

### *12.1 Current situation and issues in power line inspection*

With the 2020 Tokyo Olympics on the horizon, the maintenance of social and industrial infrastructures has become an urgent issue for Japan. Among such infrastructure maintenance, power lines and their inspection are extremely important for ensuring power supply.

However, there was no effective inspection method for power lines. For the inspection of high-voltage power lines, the inspector must climb up to the lines and visually check them. This method involves danger of work in high places, moreover, the power must be stopped, and it is difficult to conduct safe and efficient inspection.

Therefore, to solve this problem, we developed a compact X-ray inspector that combines a dry-cell-operated compact X-ray source with the above-mentioned cold cathode X-ray tube and a flat panel detector (FPD),[Term] and are working on

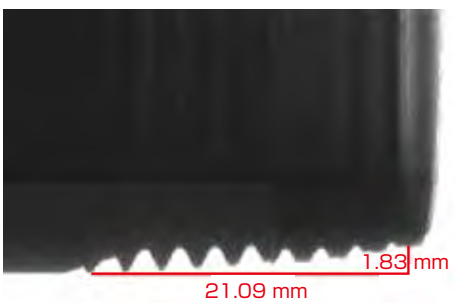



**Fig. 21 Example of display of pipe size**

promoting its practical use.

### *12.2 Compact X-ray inspector for power lines*

The compact X-ray inspector for power lines with a cold cathode X-ray tube is shown in Fig. 22.

For this device, an X-ray tube and a booster circuit were newly developed to obtain 70–120 kV that is necessary for power line inspection, by increasing the tube voltage of the 60 kV compact X-ray inspector that was described earlier.

This device is comprised of an X-ray inspector part and a control/display PC, and the former is comprised of a compact X-ray source and FPD. In actual inspection, the power line to be inspected is placed between the compact X-ray source and FPD of the X-ray inspector part, the lid is closed so the power line is held and fixed, and X-rays are irradiated to conduct inspection.

The photography condition can be set using the control panel of the X-ray inspector unit, at tube voltage of 70–120kV, pulse width of 20–100 ms, and pulse frequency of 1–100. Of course, this setting can also be done from the control/display PC.

During actual inspection, X-rays are irradiated by operation on the PC screen, the transmission image is detected by FPD, the signals are transferred to the PC through LAN cables, and the transmission image is displayed on the PC screen using image display software.

Here, the device shown in Fig. 22 is used for power lines or any objects that are in wire form, but for objects of other shapes, the main body without a hole, as shown in Fig. 23, can be used for research in combination with an appropriate X-ray source. By switching the frame body, various objects can be inspected, and this allows expansion of the range of inspection. In fact, objects up to a size of width 260 mm × depth 80 mm × height 170 mm can be placed in the frame body. The frame body size of this device is 270 × 270 × 180 mm, the weight is 20 kg, and it can be transported by one person.[9]

The frame body of the X-ray inspector part has been lead insulated to keep the leakage dose rate of X-rays to 0.6 μSv/h or less, and a wide range of inspection for power lines and other objects can be done at laboratories and offices by a person without qualification for operation chief of work with X-rays. This device is compact, lightweight, and portable so it can be taken to the site, and allows quick inspection of power lines or other objects.

### *12.3 Image of power line inspection*

X-rays were irradiated at tube voltage 100 kV, 50 ms, and 1 pulse using this device, and the image of a power line photographed under this condition is shown in Fig. 24.

The transmission image of Fig. 24 shows parts of copper wire and aluminum strand wire lines well and clearly. This software can conduct various image processing, enlargement and reduction at real time on screen, display histograms, and

**Fig. 22 Compact X-ray inspector for power lines**

**Fig. 23 Compact X-ray inspector for research**

**Fig. 24 Image of a power line**

adjust brightness and contrast.

The FPD of this device is capable of digital output and can immediately display the photography results, and an object can be re-photographed several times at different conditions. Therefore, the object can be inspected at optimal photo conditions, and the defect parts can be identified and the degree of corrosion can be quantified easily. The detection area of this FPD is 10.2 × 15.3 cm and pixel pitch is 99 μm, and these figures lie in the practical range of an inspector for power lines with thickness of about 10–40 mm.

### *12.4 Self-propelled compact X-ray inspector for power lines*

In a project of the Kanto Bureau of Economy, Trade and Industry, we developed a self-propelled compact X-ray inspector for power lines as shown in Fig. 25.

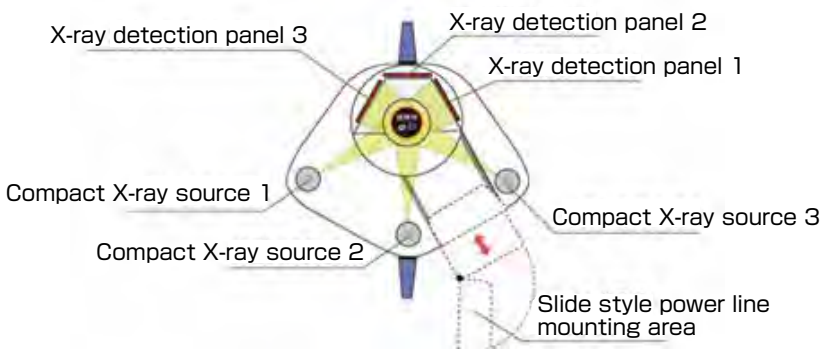
This self-propelled compact X-ray inspector for power lines has three sets of compact X-ray sources and X-ray detection panels arranged in the top and bottom parts opposed to each other, as shown in the diagram of the internal structure in Fig. 25. This allows photography of the entire circumference of power lines at once. The developed device underwent self-propelled trials targeting simulated power lines of an electrical wire manufacturer, and good results were obtained. In the future, tests will be done on real power lines. We hope to make contribution to the maintenance of power infrastructure through such power line inspection. We plan to widen application to those other than power companies, such as inspection of ropes of suspended bridges or the inspection of wires of elevators.

## 13 Conclusion

In this report, we discussed the development and application of the laser ultrasonic visualization inspector and the dry-cell-operated compact X-ray inspector. The LUVI is starting to be used in screening and inspection of social and industrial infrastructures. Currently, to enhance its diffusion, we are

Scene of self-propulsion test on power line

Three-direction photo image of power line




Arrangement within the device

**Fig. 25 Self-propelled compact X-ray inspector for power lines**

working on the standardization of this technology through the Japan Standards Association. We are also working on the domestic production of laser light sources.

For dry-cell-operated compact X-ray inspectors, other than the nondestructive inspection described here,[10] we are developing a portable chest X-ray photography device for home medical care[11] and a device that can display tomosynthesis imagery by conducting X-ray photography from four directions using an irradiation head equipped with four X-ray sources. Through such efforts, we are working to diffuse the technologies of AIST from Tsukuba to the world.

## 14 Acknowledgements

For this development, we received enormous cooperation from Hiroshi Tsuda, Principal Research Manager; Nobuyuki Toyama, Group Leader; and Ryoichi Suzuki, Prime Senior Researcher of AIST. We express our deep gratitude.

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## Terminologies

Term Flat panel detector (FPD): Planar X-ray detector used in X-ray photo-imaging device.

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## Authors

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## Discussion with Reviewers

### 1 Overall

**Comment (Ken'ichi Fujii, AIST)**

Response to aging of the social and industrial infrastructures is a major social issue, and therefore, I think the value of this report that explains the development of new inspection technology is high. This report describes two technologies, visualization technology by laser ultrasound and compact X-ray technology by carbon nanotube structure cold cathode X-rays.

**Comment (Keiichi Ikegami, AIST)**

This report discusses a case study in which a venture company utilizes the technological potentials of a public research institute, including laser ultrasound visualization technology and compact cold cathode X-ray source technology, to develop and commercialize two types of nondestructive inspectors, both of which are the first in the world. The practical effectiveness that is the appeal point of the products is presented through demonstration. This report is very instructive in considering the commercialization of technological potential in a synthesiological manner, and is worthy of publication in *Synthesiology*.

### 2 Visualization technology by laser ultrasound

**Question & Comment (Ken'ichi Fujii)**

You provide detailed descriptions of the social demands and the examples of application of this technology, but there are no details about the scanning method of pulse lasers. You simply mention "lattice form" in Chapter 3, and there are no technical details.

I think you should provide explanation for the technical concept, "reciprocity theorem," of ultrasound propagation. The readers will be aided in understanding the uniqueness of this technology if you provide explanation about the principles and methods for visualization of moving image information.

**Answer (Junji Takatsubo)**

For the reciprocity theorem, we provided explanation by adding a new chapter "3 Visualization principle."

### 3 Compact X-ray technology by carbon nanotube structure cold cathode X-ray

**Question & Comment (Ken'ichi Fujii)**

You provide explanation on the characteristics of the carbon nanotube structure cold cathode X-ray source in Chapter 8, but I couldn't understand why it is more advantageous than the Hot cathode electron source that is used in general X-ray tubes. Particularly, can you explain why resistance against field force increases when the substrate side is thicker?

**Answer (Norio Saito)**

The Hot cathode electron source requires preheating and standby voltage to emit Hot electrons. More circuits become necessary, and accordingly, the device tends to become large and heavy. In contrast, the cold cathode electron source emits field electrons as soon as the voltage is applied, thus enabling instant irradiation. It does not require preheating or standby voltage, and that makes it energy saving, compact, and lightweight. Also, when the substrate side is thick, even if the tip gradually erodes due to

the effect of electric fields, the thick substrate side is less affected and its resilience increases.

**Comment (Ken'ichi Fujii)**

The measurement principle has become more understandable, since you added a new chapter, Chapter 3 (Visualization principle), as well as Fig. 2 (Reciprocity of the ultrasound propagation) and Fig. 3 (Comparison between the reciprocities of PZT-PZT transceiver system and laser-PZT transceiver system). Also, the advantages became clear, as you added the characteristic when the carbon nanotube structure is used in the cold cathode source. I expect that your device will contribute further in dealing with the aging of social and industrial infrastructures, through further downsizing and weight reduction.

## 4 Scenario

**Question & Comment (Keiichi Ikegami)**

For the "scenario" that is considered highly important in *Synthesiology*, you mention that your development is "based on the compact X-ray technology using carbon nanostructure cold cathode X-rays and the world's first visualization technology by laser ultrasound among the nondestructive inspection technologies developed at AIST." What are your thoughts and background that turned you to these two particular technologies?

**Answer (Bo Wang, Junji Takatsubo, and Norio Saito)**

Laser ultrasound has excellent properties [(1) it can be easily used by an untrained person since it is displayed as moving images, (2) it is capable of inspecting any complexly shaped objects since it is noncontact scanning, and (3) a wide range can be inspected quickly since it is high-speed scanning using mirrors] that are unseen in conventional ultrasound inspection technology. We thought a new field of inspection could be cultivated, and embarked on product realization of a device that is portable and easily operable. The assumption is based on the voices of the inspection market that "only about 10–20 % of the places we'd like to inspect can be inspected with the current nondestructive inspector, because we're inspecting only the places which can be inspected."

For the carbon nanostructure cold cathode X-ray, there was a demand that one wished to inspect the changes, corrosion, and damage over time of objects with a compact and lightweight device that can be transported to the spot to conduct inspection on site. Therefore, we incorporated carbon nanostructures that were being developed originally as light source to the cold cathode electron source of the X-ray tube, and succeeded in achieving practical level X-ray output. Moreover, compared to the Hot cathode, there were many advantages including the following: it is compact and lightweight, requires no preheating or standby voltage, can conduct instant irradiation, is energy saving so it can be operated by a dry cell, and has a long lifespan.

## 5 Approach when overcoming difficulties

**Question & Comment (Keiichi Ikegami)**

Even if you obtain the basic technology through technological transfer from AIST, it doesn't mean that you've made a product that is acceptable to the market. For example, in the case of LUVI, in research, parts such as a laser and a piezoelectric receiving sensor may be selected focusing only on performance at a public research institute, but in case of commercialization, I imagine it was necessary to select and combine optimal parts while considering cost. What were the difficulties that arose during the process, and what kind of background and approach did you have when overcoming the difficulties?

**Answer (Bo Wang, Junji Takatsubo, and Norio Saito)**

In the development of LUVI, we were forced to spend time on improving the synchronizing precision of laser irradiation, mirror scanning, waveform recording, reduction of electric noise during single measurement, and development of extraction algorithms for defect echoes from the measured images. On the other hand, there was a dilemma that the cost would increase if the performance and precision were increased, and we struggled on how to make an inexpensive, light, small, and tough product while satisfying the users in performance and precision.

For the carbon nanostructure cold cathode X-ray, the components including the carbon nanostructure cold cathode electron source, the cold cathode X-ray tube to which it is incorporated, and the circuit that is operated by dry cells did not exist, and we had to create them for the first time in the world. It was trial-and-error and repetition of prototyping and experimenting, and it was a continuous challenge while building on our findings. Using those findings, we continued development toward practical application, from low tube voltage to higher tube voltage.

## 6 Ultralow loss multistage booster circuit in the cell-operated compact X-ray inspector

**Question & Comment (Keiichi Ikegami)**

Regarding the cell-operated compact X-ray inspector, I think the development of an ultralow loss multistage booster circuit must have been a major hurdle. For plant piping inspection, I believe you had the choice of installing a large power source in the controller side (that can be placed at a distance of 20 m from the X-ray source), but what were your thoughts and background that made you opt for downsizing the power source as well? Also, did you encounter major difficulties in developing the booster circuit?

**Answer (Bo Wang and Norio Saito)**

We initially started the development of a cell-operated compact X-ray inspector because there was a demand for a compact and lightweight X-ray source that fit in the narrow space between the plant pipes. The demand was also that it ran on dry cells or battery units, so it could be used on site even without an AC 100 V power source, while being compact and lightweight. Therefore, the booster circuit was made as a multistage system that could boost the voltage from about 1.5 V of one dry cell to about 60 to 100 kV. We repeated the prototyping and experimenting until the desired tube voltage was obtained, and finally arrived at an ultralow loss multistage booster circuit.

## 7 Work on new fields

**Question & Comment (Keiichi Ikegami)**

In developing the self-propelled compact X-ray inspector for power lines, I think the weight reduction and setting three sets of FPD and X-ray sources to photograph the entire circumference at once would have been conflicting elements. I imagine that the new development of a booster circuit was one way to overcome this difficulty, but did you have any other innovation such as in the selection of parts? Also, the self-propelling mechanism seems to belong to a field different from the one that your company specializes, but was there any difficulty in its development?

**Answer (Norio Saito)**

For the development of a self-propelled compact X-ray inspector for power lines, first, several years were taken to downsize the carbon nanostructure cold cathode X-ray tube. Since the existing detector was too big, we obtained three detector elements and worked hard on originally developing the detection circuit. Through such efforts, we were able to downsize the device even with three sets. Also, through new development of the circuit, we could efficiently drive the three sets. For the self-propelling mechanism, it was a new challenge, and we selected a compact and optimal motor by driving torque, and created simulated power lines within the company to ensure control during scanning. We placed the device on this mechanism and conducted experiments to perfect the device.

# Toward overcoming neurodegenerative disease by the circadian molecular clock study

## — My 30 year history in a national institute —

**Norio ISHIDA**

**[Translation from *Synthesiology*, Vol.10, No.2, p.87–99 (2017)]**

The mammalian clock gene, *Period2*, was discovered by my research group studying clock genes in 1998. I summarize the progress of understanding the circadian clock molecular mechanism after this discovery. Our group has demonstrated the importance of glycogen synthase kinase 3-dependent phosphorylation of *Period2* and its nuclear transfer and E4BP4 (*vrille*) negative transcriptional regulation, as well as *Clock/Bmal*, *Period/Cry* E-box dependent negative feedback loop. A role of myo-inositol for elongation of the circadian clock was uncovered through collaboration on ice plant projects with Tsujiko Co., Ltd, Shiga prefecture. When we started the molecular study of the circadian clock, we only considered the daily rhythm. Fortuitously, our research on the peripheral clock mechanism (PPAR*α*) revealed a new mechanism of seasonal clocks, which can count photoperiods to adapt to winter (torpor). Our generation of researchers entered Japanese national institutes during a period called "the basic research shift era." But, basic research grants were cut significantly during the 24 to 25 year period after we joined the institutes, and our research mission was abruptly changed to applied science. After several years of frustration and contemplation, we gave up studies using mice and concentrated on using *Drosophila* to reduce costs and save time. Consequently, we found a causative role of sleep abnormality around a young age in two neurodegenerative (Gaucher's and Parkinson's) diseases by using fly models. I summarize an application for the molecular mechanism of neurodegenerative disease. I am greatly thankful that I was able to spend more than 30 years on the study of molecular circadian clocks with the people who have been involved, from when I started as a researcher in 1986 at the Fermentation Research Institute of the Agency of Industrial Science and Technology to the present day at AIST.

*Keywords*: Circadian clock, clock gene, transcriptional factor, sleep, neurodegenerative disease, Gaucher's disease, Parkinson's disease

## 1 Beginning of circadian clock gene research

The author joined the Fermentation Research Institute, the Agency of Industrial Science and Technology in 1986, after strong insistence and recommendation by Group leader Youji Mitsui of the Animal Cell Research Laboratory. At his lab, they were looking for a person with skills for animal gene cloning since they wanted to investigate the vascular endothelial cell growth factor. I had a couple of offers from national universities at that time, but I decided on this lab because it seemed they would allow me to do whatever I wanted to do. Immediately after I joined, I worked like a worker ant from early morning to midnight for isolating and sequencing various clones, but I could not pick out the target gene. Unable to just watch our hard work, the Group leader recruited a student, Shinichiro Nishimatsu (currently, Kawasaki Medical School), from Dr. Kazuo Murakami's lab at the University of Tsukuba. However, in less than three months, we received reports of the successful FGF cloning from two places, one in Japan and the other in USA, and my first project was terminated. While I was filled with a sense of defeat, there was a paper published in *Nature*[1] by Mike Young's group that a specific RNA sequence similar to a *Drosophila* clock gene, *Period*, was detected in birds, mice, and humans. This paper got me excited. That is because the research of genes involved in behavior was the reason I jumped into this field. Furthermore, it was my dream to study behavior from genes ever since I became interested in psychology and behavior science in high school. At that time, for circadian clock genes, the *Period* gene of *Drosophila* was cloned for the first time in 1984, but it was a total mystery why such a gene could affect complex behavior. Therefore, I immediately shifted the target to clone circadian clock genes in mammals, and embarked on the labor of isolating and sequencing candidate clones every day. However, the sequences I obtained were all an RNA repetitive sequence (ACNGGC) of a specific RNA region partially similar to the *Period* gene, and I was unable to obtain the targeted *Period* homologous gene composed of 1,100 or more amino acids from mice. Looking back, this seemed to be the noncoding RNA that is the current megatrend in molecular biology. Excellent colleagues who joined the Biological Clock Group during this time included the following people: Miwa Matsui (*in situ* hybridization); Masae Kurama (diurnal expression of endothelin); Kaname Saida (cloning of endothelin family); Koichiro Kako [establishment of EMSA method and a role

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of CRE for clock ; currently, lecturer at Life Science Center of Tsukuba Advanced Research Alliance (TARA)], a post-doc from Dr. Eisuke Munekata's lab at the Department of Applied Biology, University of Tsukuba; Motoo Watanabe from Mitsubishi Chemical Corporation; and Satoru Suzuki who graduated from the open university of Japan while he was a technical support staff in my lab.

## 2 Background of the biological clock research

When we started circadian rhythm research, most of the study was done in the field of physiology and anatomy, and the study at molecular and gene levels was very much behind. The master clock that governs the 24-hour rhythm in mammals is located in the brain region called the suprachiasmatic nucleus (SCN) in the hypothalamus. This nomenclature was given because it is situated directly above the optic chiasm. It is located right above the region where the left and right optical nerves cross each other in the brain. The SCN tissue consisting of about $10^4$ cells receives input from the optical nerves. (This is why light can entrain the phase of the clock to an environmental phase.) The output of SCN includes the pineal body (main producer of melatonin), the satiety center, the feeding center, the thermoregulatory center, and the autonomous nervous system. The firing frequency of individual nerve cells in the SCN is high during the day and low at night. It has been gradually discovered that there is a 24-hour rhythm in the hormone secretion from the SCN, but it was totally unknown which molecule (gene product) is required for the generation of such a 24-hour rhythm in mammals.

As mentioned above, this mystery has been unraveled through the advances in *Drosophila* molecular biology. It has now been discovered that in *Drosophila*, various gene products are involved in the generation of the 24-hour rhythm, as shown in Table 1, including the *Period* gene, using the forward genetic approach where genes of mutations of *Drosophila* that show rhythm abnormality are analyzed.

The clock gene is defined as the gene that affects the behavioral circadian rhythm (phenotype includes arrythmic, long period, short period, or all of the above) when there is a mutation in one gene. Please refer to the original paper for the description of phenotypes of individual clock genes (Table1). One of the important characteristics of such clock genes is 24 hours-rhythmic expression of the gene products (mRNA or proteins) in our body. I present as an example the rat *per2* gene that we isolated for the first time in the world.[2] Surprisingly, we found that the circadian clock gene, rat *per2* gene, expressed not only in the central pacemaker clock (SCN) in the brain, but also in other tissue such as stomach, liver, kidneys, as well as blood cells, hair cells, and nail cells. (We called these present in places other than the brain peripheral clocks.)[3] It is obvious that such peripheral clocks are controlled by the SCN, because

**Table 1. Circadian Clock gene in *Drosophila* (fly) and humans**
Most of the biological clock genes except for the *Clock* gene, surprisingly, were discovered from the fly.

| *Drosophila* gene | Human genes |
|---|---|
| *Period* | *Period1* |
| | *Period2* |
| | *Period3* |
| *Timeless* | Not applicable |
| *Timeout/Timeless 2* | *Timeless* |
| *Cryptochrome* | *Cryptochrome 1* |
| | *Cryptochrome 2* |
| *Clock (Jerk)* | *Clock* |
| | *NPAS2/MOP4* |
| *Cycle* | *Bmal1/MOP3* |
| | *Bmal2/MOP9/CLIF* |
| *Doubletime* | Casein kinase 1 epsilon |
| | Casein kinase 1 delta |
| *Shaggy* | Glycogen synthase kinase 3$\beta$ |
| Phosphatase 2A | Not applicable |
| *Slim* | *FWD1/β-TrCP* |
| *Brill* | *E4BP4* |
| *Pearl Domain 1* | *CBP* |
| *Ultra Spiracle* | *Coup-TF* |
| *Clockwork Orange* | *Dec1, Dec2* |
| *Twin of Eyeless* | *PAX6* |
| Not applicable | Protein kinase G type 2 |
| *Ataxin 2* | *Ataxin 2* |
| Not applicable | *FBXL3, 21* |
| *Jetlag* | *FBXL15* |
| *Kissmet* | *CHP7 (Chromatin helicase DNA-binding protein 7)* |
| *Unfulfilled* | *NR2E3* |
| Not applicable | *RORα* |
| *E75* | *Rev-erbα, Rev-erbβ* |

the rhythmic expression of peripheral clock genes is abolished after the lesion of SCN and the fact that when the organs are cultured, the peripheral organs such as liver, kidneys, and heart lose their rhythmic gene expression in a few days while the SCN cells possess automaticity and the 24-hour rhythm is not lost for a long time. In our bodies, not only every cell, but also the expression of circadian clock genes showed a 24-hour rotation.

## 3 Circadian clock gene *Period2* is a period determining factor for mammalian behavior

The molecular mechanism of the circadian clock in mammals is shown by the transcription-translation feedback loop of clock gene products including *Period* (Fig. 1b). The main idea of this molecular mechanism is based on the *Drosophila* model (Fig. 1a). The *Drosophila* clock mutant *Period* was isolated by Ronald Konopka and Seymour Benzer in 1971.[4] Dr. Benzer unfortunately passed away in November 2007. He was the strongest candidate for the Nobel Prize in the field of circadian clocks. He can be considered the true founder of this field, as he moved from the field of physics and created the basic notion of the first generation of molecular biology along with Francis Crick and Sydney Brenner. That is because at that time when the behavioral trait was thought to

be determined by multiple factors, he proposed the one gene-one behavior theory which continues to shine. Such a unique bold hypothesis had emerged from his background in physics as a first generation of molecular biologist applying phage molecular genetics. In the early days, Dr. Benzer discovered the linearity of genes and the qualitative difference (cistron) of point mutation using the T4 phage. Benzer was one of the first scientists to rise to prominence in the field of behavioral molecular biology. Later, the *Period* gene was cloned in 1984 by the J Hall group and the M Young group (2017Nobel Prize), and it was found that one amino acid mutation in a different position produced phenotypes for short period, long period, and arrhythmic periods (stop codon).[5]

After a long period of dark ages, the existence of period homologous genes in mammals came into light again in the latter half of the 1990s after the Genome Project of human and rodents was completed. During this time, we won a NEDO grant, and many post-docs worked in my Group [Tomoko Kuroiwa, Marek Banasik, Toshiyuki Hamada (currently, Associate Professor, Hokkaido University), Yutaka Sadakane (currently, Professor, Suzuka University of Medical Science), Zhi-Qiang Qu (currently, Professor, Qingdao University), Naoto Hayasaka, and Norihiko Yamazaki]. At last we identified the rat *Period2* (*rper2*) gene with the Kazusa DNA Research Institute and discovered its 24-hour oscillatory expression in peripheral organs.[2] The greatest contributors to that paper were Takahiro Nagase (Kazusa DNA Research Institute) and Katsuhiko Sakamoto (currently, Associate Professor of Insect Function Studies, Faculty of Agriculture, Kobe University), who was a post-doc in my laboratory. In the competition with the United States, the paper almost made it to *Science* but was turned down right before publication. Quite unwillingly, we sent our paper to the *Journal of Biological Chemistry*, and surprisingly enough it was accepted in Rapid Communication in one week. Because of the collaboration with the Kazusa DNA Research Institute, we were able to take lead in the *Period* gene cloning for humans and rats, but for mice *period* gene, we were secondary to Dr. Yoshiyuki Sakaki of the University of Tokyo and Dr. CC Lee of the University of Texas.[5] There were three homologs (*per1*, *per2*, and *per3*) of the *Drosophila Period* gene in mammals including humans, and it was later revealed that *per2* was deeply involved in the behavioral clock function. Accidentally, we were very lucky enough to start on the analysis of *per2*. Mice lacking these genes were created, and it was found that individually, *per1* was for short period rhythms, and *per3* had hardly any phenotypes [later, it was found that *per3* was involved in delayed sleep phase syndrome (DSPS)[6] and in peripheral clocks of lungs and adrenal glands]. However, *per2 gene knock out* mice or overexpressed *per2* transgenic mice showed a drastic phenotype of arrhythmic behavior in the conditions of constant dark or constant light, respectively. Moreover, while not observed in *per1*-destroyed mice, in *per2 gene knock out* mice, the oscillatory expression of other important clock genes *Bmal1* was lost in the SCN. From this fact, *per2* was considered to be an important factor that controls the oscillatory expression of other clock genes. Moreover, we discovered the bipolar nuclear localization sequence[Term 1] in *rper2* amino acids sequence.[7] Therefore, Koyomi Miyazaki, who was then employed as a member of staff scientists in our lab after working as a post-doc, and others prepared the *rper2* gene that deletes this nuclear localization sequence (NLS). When the NLS deleted *rper2* was overexpressed in COS1 cells,[Term 2] we found that the *Cry1*[Term 4] and *per2* nuclear localization was inhibited by trapping in the cytoplasm.[7] Therefore, we attempted to create a transgenic (TG) mouse with normal *rper2 overexpressors*, and another with NLS deleted *rper2 overexpressors*.[8] As a result, the NLS deleted *rper2 overexpressor* mouse showed long period, while normal *rper2 overexpressor* mouse showed short period in the circadian behavior rhythm. This work was the first example in my laboratory where observation *in vitro* was reproduced *in vivo*.

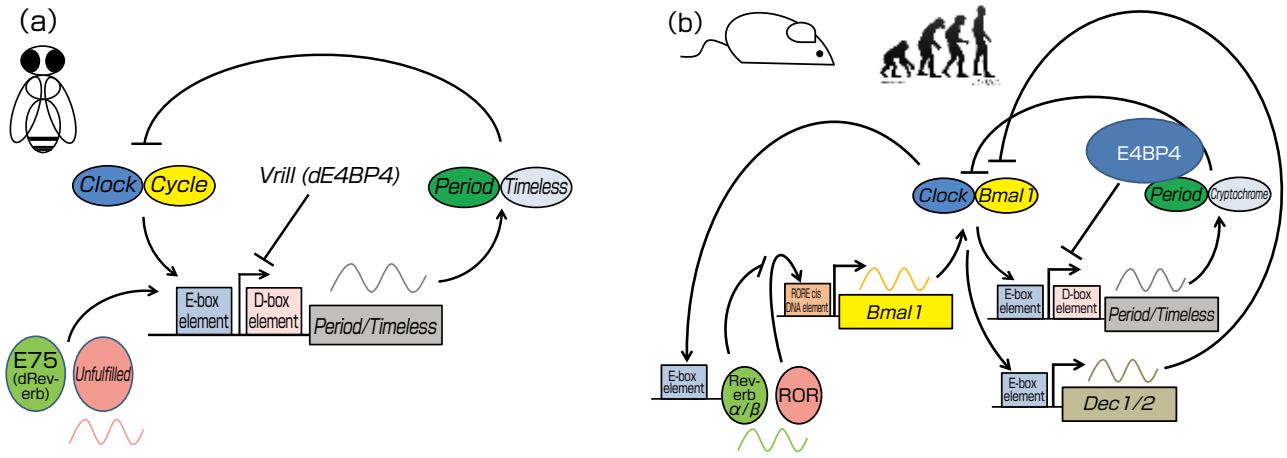



**Fig. 1 Compared biological clock molecular model for *Drosophila* (a) and mammals (b)**
In both species, a negative feedback model of clock gene transcription with extremely similar sequences occurs.

Immuno-staining the nuclear translocation suggests ion of *per2* was delayed in the long period type. We believe that the period was extended due to the delay of nuclear localization of regulating proteins such as *Period* and *Cry*, as shown in Fig. 1b. Moreover, it was observed that the *rper2*-overexpressed mice might have high body temperature and high wakefulness in active phase which suggests that the brain region other than the SCN might be involved in these phenomenon. Later, Chisato Iidaka (current name Chisato Kinoshita; Department of Pharmacology, Teikyo University School of Medicine), who joined our Group as a graduate student at the Tokyo Institute of Technology, discovered that glycogen synthase kinase-3$\beta$ (GSK-3$\beta$) was a factor that promoted the nuclear localization of *per2*.[9] The GSK-3$\beta$ directly binds to *per2*, causes phosphorylation, and promotes nuclear localization. This pathway explained well the action mechanism of LiCl that was effective against depression. That is, when LiCl causes the self-phosphorylation of GSK-3$\beta$, it becomes inactive and delays the nuclear localization of *per2*, and this extends the period of activity. This pathway is attracting attention of researchers developing anti-depressant drugs as a target for new drug discovery. Recently, Kazuki Sakata, a graduate student at the University of Tsukuba, *et al.* found that high concentration of inositol extended the period of courtship rhythm and locomotor rhythm in *Drosophila*.[10] Myoinositol, an ingredient derived from ice plants (*Mesembryanthemum crystallinum*) grown in a plant factory of Tsujiko Co. Ltd. of Shiga Prefecture, was discovered originally by us during the screening for a substance that affects Drosophila mating rhythm. Myoisitol is highly expected to be an antidepressant in the future.

The mystery of GSK-3$\beta$ was found in *Drosophila*. ATP-mediated protein kinase B (AKT, also called PKB), which was known in the signal pathway of nutrition stimulation, inhibited the nuclear localization of clock gene product *Timeless* through the target of rapamycin (TOR) pathway.[11] In AKT-overexpressed flies, TOR-S6 kinase in the central pacemaker of the fly brain was activated, then the glycogen synthase kinase-3$\beta$ (SGG) was phosphorylated, and inhibited the nuclear localization of clock gene product *Timeless*. In summary, nutrients signal from food delayed the peripheral clock, then the peripheral clock affected the central pacemaker in the brain by a feedback mechanism. This feedback mechanism is also common in mammals.

## 4 Rhythm disorder and clock gene mutation

Sleep-wake rhythm syndrome in humans include the advanced sleep phase syndrome (ASPS), the delayed sleep phase disorder (DSPS), and the non-24-hour sleep-wake syndrome. These syndromes occur on a familial basis, but the causal gene was totally unknown. However, in 2001, linkage analysis was carried out of a family of ASPS in Utah, USA, and the responsible gene was mapped to Chromosome 2. Finally, it was identified that the 662nd serine of *hper2* gene product was replaced by glycine[12] (Fig. 2). This is the binding region of casein kinase I$\varepsilon$ (CKI$\varepsilon$), and particularly the first serine on the N-terminal side is thought to be an important amino acid in initiating phosphorylation. The main function of *per2* is thought to be phase delay, and it is assumed that the mutation at the phosphorylation site causes the loss of the function of *per2* protein and the phase of circadian rhythm is advanced. At the same time as this discovery, Ebisawa and our group found an example where valine mutated into glycine in the *hper3* region of an amino acid very close to the casein kinase I$\varepsilon$ phosphorylation site, in the DSPS family line.[13] In both family lines, the change in one amino acid of a sequence of a clock gene product affects the entrain function. Recently, it is becoming clear that clock gene sequence polymorphism is involved in the nocturnal/diurnal tendencies in humans and mice. Also, we succeeded in making a model mouse with nocturnal tendencies from the mutant strain of the *Clock* gene. As the age of personalized medicine arrives in the future, the importance of the genetic background of an individual's sleep rhythm will be increasing.

## 5 Factors affecting the *Period2* rhythmic expression

As mentioned in this paper, the 24-hour rhythmic expression of *per2* is very important in maintaining the biological rhythm in mammals, and the main regulatory point is transcription. Until now, CACGTT, a non-canonical E-box,[Term 6] was known as the cis sequence[Term 5] involved in the *per2* mRNA rhythmic expression. Tomoya Ohno, who joined our Group as a graduate student at Life Science and Technology, Tokyo Institute of Technology(TIT) because I was a visiting professor at TIT, biochemically identified that the bZIP transcription factor[Term 7] E4BP4 (*Drosophila vrille* homolog) had an inhibitory effect on *per2* rhythmic expression (Fig. 1b).[14] As a result of detailed analysis, he found there were two E4BP4 binding sites, the A-site[Term 9] and the B-site,[Term 10] near the *mper2* promoter[Term 8] DNA region. When a mutation was made into these two sequence sites, the *per2* rhythmic

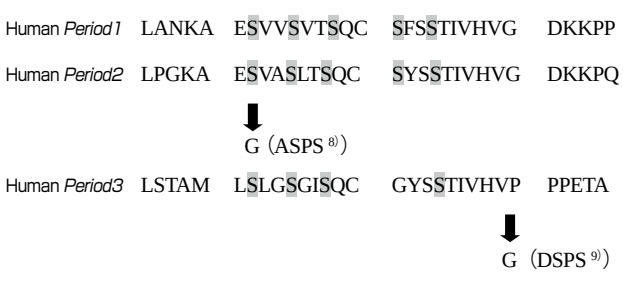



**Fig. 2 Mutated amino acids in hPERIOD protein in human abnormal +rhythm syndrome**

Serines (S) in the region are target amino acids of phosphorylation by casein kinase I, and this region is important for the phase regulation of circadian rhythm. The arrows point to amino acid mutation in advanced sleep phase syndrome (ASPD) and delayed sleep phase syndrome(DSPS).

expression was inhibited specific to the B-site. Moreover, circadian time-specific binding was confirmed at the B-site by both a gel retardation assay and the ChIP method. Finally, the *per2* promoter rhythmic expression activity was compared with the mutation to the A-site, the B-site, and the E2-box by the luciferase activity using the real-time monitoring system. Interestingly, the 24-hour oscillation was not lost in the single mutation of E2, but it was proven at a cellular level that the 24-hour oscillation disappeared with the mutation to both the E2-box and the B-site. Conventionally, the importance of the A-site only was reported *in vitro*,[14] but in a complex system such as oscillatory expression, it is important to conduct analysis by introducing to a cellular or an *in vivo* level system. Since the oscillatory expression was maintained in the single mutation of E2-box, it became clear that the *per2* oscillation could not be explained only by the negative feedback model of *Clock/Bmal1* and *per/Cry*. Moreover, we found that the E4BP4 bound with *per2* and *Cry2* in the cell.[15] From these facts, we proposed a new model for a negative transcription-regulating factor complex for biological clocks (Fig. 1b). In this new model, these complexes go through nuclear localization in circadian time specific manner, and *per2* and *Cry2* complex target the *Clock/Bmal*, while E4BP4 complex targets the B-site (D-box) to negatively regulate the transcription. There are several reports that E4BP4 is important in the 24-hour oscillatory expression of phosphatidylcholine transporter Mdr2,[16] cytochrome P4503A4 (CYP3A4) involved in drug catabolism, and cholesterol 7$\alpha$-hydroxylase (Cyp7$\alpha$) that is involved in bile acid synthesis. Therefore, it is thought that the transcription factor E4BP4 acting negatively on the 24-hour rhythm transcript is important in peripheral circadian clocks, particularly in liver rhythm formation.

## 6 Biological clock regulation by chromatin

This chromatin topic was tackled by Yoshiaki Onishi (currently, AIST Kansai), who specializes in chromatin biochemistry and who moved from a different group in AIST. The *Bmal1* which formed the heterodimer with a circadian clock gene product CLOCK protein is an extremely important protein that causes the 24-hour oscillation of the biological rhythm, and consists of the negative feedback loop. However, why this gene is transcribed through 24-hour oscillation remained a mystery. First, Transcriptional rhythmic regulation of *Bmal1* gene was accomplished by the binding of clock transcription factor REV-ERB$\alpha$ and ROR$\alpha$ to upstream region of *Bmal1* gene, using various deleted DNA constructs. Onishi further found that the intranuclear matrix protein SAF-A (also called hnRNPU) bind rhythmically at the downstream of the cis element RORE, to control the transcription.[17] That is, the state of chromatin around *Bmal1* gene was widely open or closed. As SAF-A has been reported to involve in the regulation of the c-Mycc-Max complex, *Bmal1* will become very important in controlling cancer cells in the future.

## 7 Different functions of peripheral clock (Haradokei) and central clock in *Drosophila* and mammals

Until recently, most of the relationships between the peripheral clock (Haradokei) and the central clock was studied in mammals, but an interesting study has been published by Sehgal *et al*. using *Drosophila*.[18] In *Drosophila*, the tissue that has both the functions of liver and fat tissues of humans is called the fat body (Fig. 3). Using genetic engineering methods to transfer the dominant negative type *Clock* gene so that the biological clock function in the fat body was lost, a fly that was very weak against fasting (i.e. quick to starve to death) was created because its glycogen storage was significantly decreased. Therefore, this fly would feed frequently during the night. Interestingly, such abnormality was not seen in the $CLK^{JRK}$ fly that had *Clock* gene mutation throughout the body. Therefore, they hypothesized that there must be different effects of clock genes on the central clock and peripheral clock, and created a fly in which the *Clock* gene function was lost specifically in the central pacemaker. As a result, the glycogen storage increased in the fat body, and the fly became stronger against fasting compared to a normal fly. Through this experiment, it was shown that the functions of the peripheral clock (Haradokei) and the central pacemaker were different, as observed in mammals. Unfortunately, in this paper, the direct relationship between the clock gene and glycogen storage was not demonstrated, but this point was proven using mammals by Ryosuke Doi (currently, Astellas Tsukuba Research Center), who was a graduate student at the University of Tsukuba of which I was a professor. I shall describe the glycogen study.[19]

The most important organ for glycogen storage and for maintaining blood glucose levels is liver in mammals. It was known in the 1970s that there was a circadian rhythm in the glycogen synthase that was the rate-limiting enzyme in glycogen synthesis. In later molecular biology analysis, it was

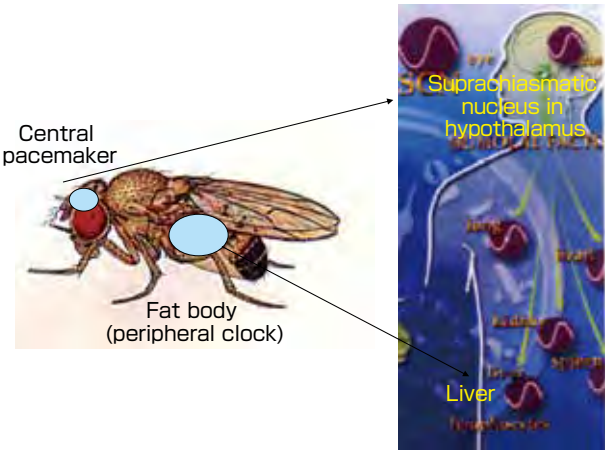



**Fig. 3 Fat body, the organ corresponding to human liver in *Drosophila* (fly)**
The central pacemakers in *Drosophila* are located in the lateral neurons in the brain.

clarified that the glycogen synthase 2 (Gys2) was expressed mainly in the liver, and its family glycogen synthase 1 was expressed in muscles, nerves, and fat. Doi *et al.* looked at the rhythmic expression regulating the mechanism of Gys2 in the liver. First, the rhythmic expression of genes involved in glucose metabolism was investigated in the normal mouse and the mouse with mutation in the *Clock* gene (Cl/Cl) using the real-time PCR method. As a result, abnormalities were seen in the *Clock*-mutant mouse for the rhythm expression of phosphoenolpyruvate carboxykinase (Pepck), glucose-6-phosphate, glucose transporter 2, and others. The most interesting difference was the almost complete disappearance of the expression rhythm of Gys2 mRNA in Cl/Cl mice. On the other hand, there was no significant difference in glycogen phosphorylase, which was the rate-limiting enzyme of glycogen breakdown, between the normal and the *Clock*-mutant mice. The data indicate that the glycogen storage rhythm in the liver was under the rate limitation of glycogen synthesis but not in the breakdown. Moreover, arrythmicity was detected not only in Gys2 mRNA but also in the Gys2 protein level in *Clock*-mutant mice. Furthermore, the data suggests that this glycogen rhythm was not dependent on insulin or glucagon levels that changed depending on food. From these facts, it was considered that the Gys2 rhythm was an endogenous[Term 3] regulatory expression of mRNA. We hypothesized that it might be directly controlled by clock gene products, and searched the genome sequence for the cis element binding to clock gene products. Since we could not find typical rhythm cis elements in about 3 kb of the 5' upstream region, after trial-and-error, we found two E-box elements in tandem in the first intron of the Gys2 gene. By making mutations into these two E-box elements, it was shown that both elements contributed equally by using the *in vitro* reporter assay and the chromatin immune-precipitation method from the liver extract. It was thought that these elements might function *in vivo*. Therefore, we addressed this point by investigating the effect on rhythm oscillation using the real-time reporter assay method. Using the *mper2*-dLuc as a positive control, E1, E2, and both were mutated and compared. As a result, both of E1 and E2 mutations were most attenuated. From this experiment, we showed that glycogen synthesis rate-limiting enzyme Gys2 was regulated rhythmically at a transcription level through the two E-box elements recognized by *Clock* and *Bmal*. We think the Gys2 gene was one of the output from the peripheral clock. This is the first data in the world that showed that the glycogen metabolism was under the direct control of the molecular clock. Haruhisa Kawasaki (Institute for Chronobiology, Foundation for Advancement of International Science), who joined our group after returning from studying in the United States, advanced this study, and found that C/EBP$\alpha$, an important transcription factor involved in glycogen storage in fetal liver, was also regulated by core feedback loop through the E-box element in the upstream region of C/EBP$\alpha$ gene.[20]

## 8 Three cis elements that comprise the circadian clock

As input of the circadian clock system, various elements other than light are being found. That is because the concept of peripheral clocks in all tissues has become established because of the discovery of the rhythmic clock gene expression in all tissues. The most recent peripheral clock model is shown in Fig. 4.[21] The cholesterol in food and HEME (hemoglobin) supplied from blood are becoming very important, as they have been considered to be important factors that synchronize with the circadian clock in liver and other internal organs. Cholesterol positively controls clock proteins *Clock* and *Bmal* through the transcription factor ROR dependent RORE binding, while HEME negatively controls *Clock* and *Bmal gene* through the transcription factor REV-ERB (Figs. 1 and 4).[1] A recent paper showed

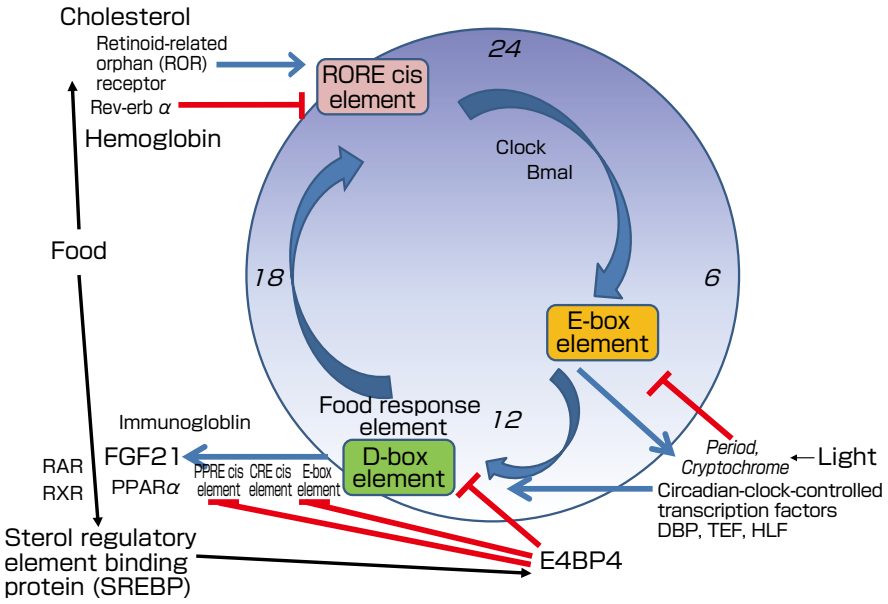



**Fig. 4 Circadian clock synchronization with various environmental factors such as light, food, and fat**
ROR, Rev-erb, *Clock*, *Bmal*, *Period*, and *Cryptochrome* (*Cry*) are clock genes. DBP, TEF, HLF, E4BP4, PPAR, RAR, RXR, and SREBP are circadian-clock-controlled transcription factors. RORE, E, D, CRE, and PPRE are target DNA sequences (cis element) for the transcription factor binding.

that when a ligand-binding site of ROR$\alpha$ is expressed in an insect cell, cholesterol coprecipitates with ROR$\alpha$. Moreover, from X-ray crystal analysis, the possibility of ROR$\alpha$ ligand being cholesterol is indicated, because cholesterol sulfate and 25-hydroxycholesterol bind to this ligand-binding site of ROR$\alpha$. On the other hand, in chronobiology, what is in the upstream of clock proteins *Clock* and *Bmal* is the big issue, and this is being solved. These clock proteins *Clock* and *Bmal*, other than regulating *Period* and *Cry* in the core loop, regulate the transcription factors DBP, TEF, and HLF as output, bind with the nine-base sequence called the D-box, and create a large 24-hour rhythm in the peripheral cells (Fig. 4). Recently, fasting-induced hormone, FGF21, was reported as the factor that had this D-box in its regulatory sequence.

Katsutaka Oishi, who was employed as a research scientist from research technician of the Biological Clock Group, previously conducted genome-wide expression analysis using clock-mutant mice. He discovered the peroxisome proliferator-activated receptor $\alpha$ (PPAR$\alpha$) that was a nuclear receptor and fatty acid as ligand, among the genes that was rhythmic expression regulated by clock gene products in the liver, and also discovered that fatty acid breakdown ($\beta$-oxidation) occurred specifically during the night via this PPAR$\alpha$.[22][23] Moreover, It was found that FGF21 was expressed with a large circadian rhythm, when fibrate, a ligand of peroxisome proliferator receptor α, was administered to the abdominal cavity of the mouse.[24] We also reported that fasting by the fibrate (particularly the catabolization of fatty acid) advanced the circadian rhythm in the body and enhanced the fluctuation of the FGF21 rhythm.

Since this phenomenon is not observed in PPAR$\alpha$KO mice, it was considered to be dependent on the peroxisome proliferator response element (PPRE). However, when a ketone diet (a diet method of ingesting high fat and low carbohydrates) was carried out, FGF21 was increased without depending on PPAR$\alpha$. That suggests a pathway for inducing FGF21 without depending on PPRE. Recently, it was reported that not only the known PPRE but also new D-boxes and E-boxes were discovered through the detailed analysis of the mouse FGF21 promoter (Fig. 4). More interesting is the fact that the transcription factor E4BP4 suppressed both the *Bmal/Clock*-dependent transcription and the PPARα-dependent transcription at the same time. That the E4BP4 regulated the *Bmal/Clock*-dependent transcription was easily predictable, because we had already made a complex with E-box (cis element consisting of CACCTG) dependent negative regulators, *Period2* and *Cry* with oE4BP4.[8] However, it is very interesting that E4BP4 suppressed the PPRE-dependent transcription with PPAR$\alpha$ at the same time. This indicates that the suppression of rhythmic transcription of E4BP4 is much more powerful than we initially thought, acts on E-boxes and PPRE as well as D-boxes, and plays the role of a major brake on the peripheral clock. It is known that E4BP4 negatively controls the transcription targeting genes of the D-box with an insulin dependent manner after a meal. As mentioned in Chapter 5, the mechanism in which transcription factor E4BP4 acts negatively on the formation of 24-hour rhythm transcription is very important particularly in liver function. There is a report that E4BP4 is activated on time-specific light stimuli and induced at transcription factor SREBP in bird pineal body. The effects of light and food are very complex even in one gene expression. This is a field that needs further attention.

In humans, there was an interesting report that blood FGF21 was expressed in circadian rhythm following fatty acid rhythms.[25] In the same paper, they showed that FGF21 was induced by unsaturated fatty acid like linoleic acid rather than saturated acid like palmitic acid, using human hepatocarcinoma-derived cell HepG2. More surprisingly, when the circadian rhythm of FGF21 was compared in normal and obese (having BMI 25 or over) humans, the amplitude of rhythm was very small in obese humans[25] (Fig. 5). In the future, by studying the diurnal dynamics of such fasting-induced hormone FGF21, it may become possible to prevent obesity and aging by increasing the amplitude of rhythm. Recently, it was reported that FGF21 was induced from brown adipose cells when Swiss mice were kept in low temperature. FGF21 is studied as the factor that induces hibernation and diurnal torpor, and please refer to other reviews for details.[26] In summary, nuclear receptor PPARα binds with PPRE in the liver during fasting, and transcription factor ATF2 binds to CRE in brown adipose cells during low temperature to induce FGF21. However, in the case of a ketone diet when FGF21 is induced without PPAR$\alpha$ pathway, the pathways through D-boxes and CRE are important for this induction. (Fig. 4). By analyzing FGF21 induction comprehensively, the relationship between fasting and fat metabolism will become clearer in the future.[26][27]

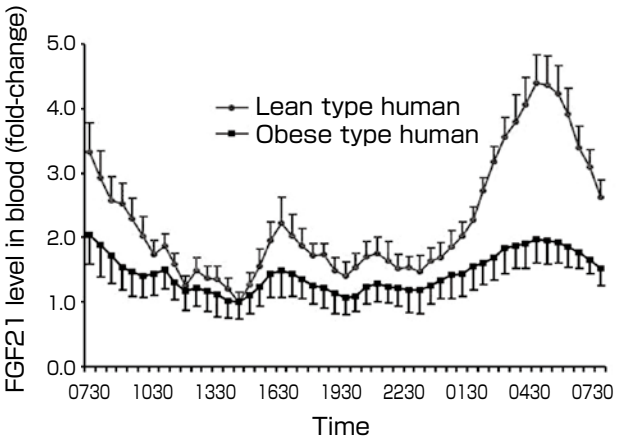



**Fig. 5 Three peaks of circadian rhythm of the fasting-induced hormone, FGF21 in humans[25]**
Clear circadian rhythm is detected in lean humans compared to obese humans.

## 9 Basic model of biological clock learned from *Drosophila*

As mentioned above, we learned of almost all the actors (molecules) and the relationships (pathways) from *Drosophila* (Table 1). Though quite late in the game, I decided to study the *Drosophila* system. Earlier, every time I ran into Dr. Sumihare Noji (currently, President, Tokushima University), at the Molecular Biology Society of Japan, he recommended me to introduce *Drosophila* system studies. Coincidentally, Director Tatsuo Katsura of the National Institute of Bioscience and Human Technology (currently, AIST) recommended a co-professorship of the University of Tsukuba to me, and it became possible to take in more students at the lab. At that time, Tetsuya Okada joined our Ishida Group of Clock Gene, AIST with the recommendation of Dr. Michiko Ohtomi of Toho University. Dr. Ohtomi had been studying the biological clock for a long time, and was a student under Dr. Takeo Deguchi (Tokyo Metropolitan Institute of Gerontology), who studied diurnal rhythm of melatonin in the pineal body. Later, Okada moved and received tutelage of Dr. Osamu Hayaishi, who was the President of the Osaka Bioscience Institute famous for sleep and prostaglandin study, but Dr. Hayaishi passed away at 2015. Here, I was in trouble, as I had never done *Drosophila* genetics before. I looked for someone who was experienced in *Drosophila* genetics and found Takehide Murata in Riken Tsukuba. He had directly learned molecular genetics from Dr. Teiichi Tanimura (currently, School of Science, Kyushu University) who identified the *Timeless* (named Ritsu) gene in *Drosophila* in Japan. After Okada studied at Riken for a while, he discovered the E-box, as well as the *vrille*/E4BP4 gene product binding element responsible for the rhythmic expression in the upstream region of *Drosophila* clock gene *Timeless* in our laboratory[28] Later, Takaomi Sakai (currently, School of Science and Engineering, Tokyo Metropolitan University) joined our group as a post-doc from Dr. Yuzuru Oguma's lab at the College of Biological Sciences, University of Tsukuba, and the *Drosophila* clock gene research was rapidly accelerated in my laboratory. Sakai was interested in the female mating behavior because he worked on it during graduate school, and found that this female mating behavior showed circadian rhythm depending on clock genes.[29] More interestingly, he discovered a diversity of female mating rhythms in different fly species. Therefore, he set up a hypothesis that such time specific mating is effective in species differentiation driven by reproductive isolation. To test this hypothesis, Izumi Nishinokubi, who was employed as a technical support member from Dr. Kenji Tomioka's lab at Okayama University, carried on the experiment. The clock gene *Timeless* was isolated from *Drosophila ananassae*, transferred to the *Timeless* null mutant fly of *Drosophila melanogaster*, and this *ananassae timeless gene*, was regulated by a heat shock promoter. The result was not so simple as to reproduce the mating circadian behavior of *D. ananassae* with a replacement of one clock gene (we got an intermediate of *D. ananassae* and *D. melanogaster*), but we obtained an unexpected by-product where the locomotor rhythm of diurnal fly could be changed to nocturnal by shifting the expression period of the *Timeless* protein by 12 hours.[30] This result supports a recent ecological experiment where mice could be changed from nocturnal to diurnal by environmental adaptation. It is my pleasant memory that I wrote a review, "Time, love and species," where I discussed these findings.[31] As mentioned earlier, the discoverer of the Period gene, Dr. Benzer passed away, but his book "*Time, Love, Memory*" became a bestseller in the United States. During the age from Sakai to Nishinokubi, we mainly studied the time specificity of female mating receptivity in circadian behavior. Then, Yasutaka Hamasaka, who got his degree in Sweden, joined our Ishida Group of Clock Gene. When I talked with him, he was interested in the brain neural connection of close-proximity (CP) rhythm, in which the male pursued the female fly. An American group started a new CP rhythm system using a CCD camera, after seeing our first paper in the *Proceedings of the National Academy of Science*.[32] This system had much better throughput than the arranged marriage method used by Sakai, and we incorporated this method. Hamasaka created various *Drosophila* with destroyed biological clock region in the brain, by utilizing a molecular genetic method (such as causing cell death in certain nerves only). As a result, we identified the center for close-proximity rhythm in *Drosophila*, and clarified that males stopped pursuing females when the brain area called evening oscillator was deleted.[33] Since this center became active during summer, it is most likely related to seasonal rhythms. Later, we attempted to develop an automating machine for close-proximity rhythm, locomotor and sleep rhythm. Jointly with Taisei Co., Ltd., we introduced moving image analysis of IR camera, and Takahiro Suzuki, a post-doc at the graduate school of the University of Tsukuba, created a program in C language. The device was named Automated Circadian System (AutoCircaS) (Fig. 6). The prototype of AutoCircaS was assembled uniting many parts that lay in the corner of our lab as junk, and Taisei and Suzuki (who set up a venture company Shigray Inc.) brushed up AutoCircaS as a selling product. For this accomplishment, AutoCircaS was awarded one of the Chiba Prefecture Monozukuri big prize in 2016.

One day, I received a call from Masami Shimoda (National Institute of Agrobiological Sciences), an old friend of mine, and he asked for our help to figure out why a *Drosophila* fly that lacked a gene for a certain mental disease was showing abnormal behavior. According to him, there was a *Drosophila* family gene (*dfmr1*) of fragile X syndrome[Term 11] that was accompanied by mental retardation in humans. Furthermore, there were three family genes in mammals, but only one homologous gene in flies. I thought this would be very easy to analyze, and conducted behavioral analysis, and found that the locomotor rhythm was strikingly arrythmic. Shimoda rescued the normal *dfmr1* genes of the mutant fly (Fig. 7), and found that the behavior of the fly became normal, the core clock

gene oscillation was maintained, and the eclosion rhythm showed normal.[34] This experiment indicated that the *dfmr1* gene possessed output functions from central pacemaker tolocomotor behavior. Later, it was clarified that poor growth of nerve cells was a common cause of disease in humans and *Drosophila*. As mentioned here, the *Drosophila disease* model contributes to the research of neurodegenerative disease with unknown mechanisms.

Schizophrenia is a disease that is most difficult among the psychiatric disease. Recently, through genetic analysis of a family with frequent occurrences of schizophrenia in Scotland, the disrupted-in-schizophrenia1 (DISC1) gene was reported to show frequent mutual translocation of Chromosome 1 and Chromosome 11. For DISC1, we worked jointly with Masami Shimoda mentioned earlier, Katsuo Furukubo-Tokunaga of the University of Tsukuba, and Akira Sawa of Johns Hopkins School of Medicine, to analyze behavior for expressing human DISC1 in *Drosophila*.[35] As a result, the human DSIC1 transgenic *Drosophila* showed tendency to have longer sleep time.

## 10 Essence of dementia learned from *Drosophila* genetics

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer disease, accompanied by so-called dementia symptoms, and is a major social issue confronting the current longevity society. As the *Drosophila* model for familial Parkinson disease, transgenic fly expressing human mutant $\alpha$-synuclein[Term 12] is famous and published in *Nature* and other journals. Using this *Drosophila* model for Parkinson disease, we found that sleep disorder preceded behavioral abnormality such as tremors. Recently, there was a report that patients with a hetero variant of Gaucher disease[Term 13] causal gene had 28 times more risk for Parkinson disease.[36] That is, the Gaucher disease causative gene is the most risk factor for Parkinson disease. However, the molecular mechanism is currently unknown. If this mechanism can be solved from the clock and sleep gene pathway, we can develop new treatment methods from new perspectives.

Takahiro Suzuki (currently, Shigray Inc.), who was a graduate student ( the University of Tsukuba) in Ishida Group of Clock Gene, AIST, succeeded in creating a model animal by transforming a variant human Gaucher disease gene in a *Drosophila* compound eye.[37] Gaucher disease is a lysosome disease[Term 14] that is specified as one of diseases in the Research on Measures for Intractable Diseases Project of the Ministry of Health, Labour and Welfare. Due to a genetic mutation, the activity of enzymes called glucocerebrosidase is lost before birth. Therefore, glucocerebroside which is a substrate of this enzyme cannot be transferred into ceramides, and the substrate accumulates in the liver, spleen, bones, nerves, and others. The gene of glucocerebrosidase was firstly cloned in USA by Dr. Shoji Tsuji (currently, Faculty of Medicine, the University of Tokyo) *et al.* in 1986. Many patients with human Gaucher disease die in childhood, and a complete cure of this disease is extremely difficult even today. Suzuki *et al.* set out to create a model *Drosophila* for Gaucher disease, and expressed this human variant glucocerebrosidase gene in *Drosophila* using a compound-eye-specific driver, and found a formation abnormality in the compound eye. With further detailed molecular biological analysis, we clarified that this eye morphological abnormality was caused by endoplasmic reticulum (ER) stress. Therefore, ambroxol, a chaperone drug thought to reduce endoplasmic


**Fig. 6 New automated behavior analyzer for small animals**
AutoCircaS (Automated Circadian System) enables measurement of rhythms for sleep, locomotor, and courtship (mating) behavior in *Drosophila*. The software was created by Takahiro Suzuki of Shigray Inc.

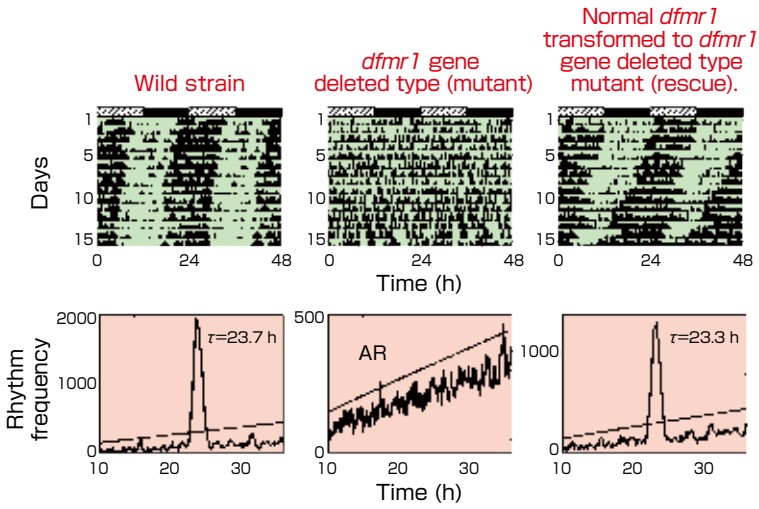



**Fig. 7 Restored circadian rhythm is detected after transformation of a normal *dfmr1* gene in *Drosophila* mental retardation gene, *dfmr1* B55 mutant.**

reticulum (ER) stress[Term 15] was administered, and the above eye abnormality and ER stress were reduced (Fig. 8). From these data, we concluded that human Gaucher disease involved not only the accumulation of enzyme substrates as explained conventionally, but was a molecular mechanism of ER stress caused by mutant proteins themselves.

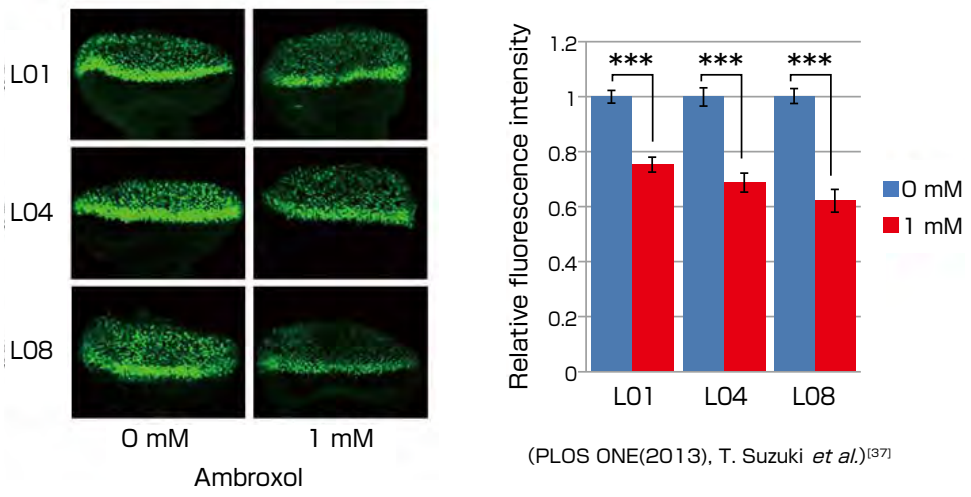
To link such neurodegenerative molecular mechanism to Parkinson disease and to propose a treatment method, we recently succeeded in creating a Gaucher disease model *Drosophila* where human mutant glucocerebrosidase was expressed throughout the body, as well as in specific sites. We recently succeeded in creating a disease model *Drosophila* that had both Parkinson disease and Gaucher disease because *Drosophila* allowed creation of models faster and easier than with mice.

We recently developed the second generation of the Garcher disease model *Drosophila*. This was a model in which a Minos-insertion mutation[Term 17] was introduced into a GBA homologous gene[Term 16] in *Drosophila*. This mutant showed accumulation of hydroxyl glucocerebroside, an enzyme substrate, as observed in the Gaucher patients. By analyzing the gene expression in this second generation of Garucher disease model *Drosophila*, the increased expression of several genes (factors) for autophagy[Term 18] related Parkinson disease was observed. It was shown that this Gaucher disease model *Drosophila* had a short lifespan, and showed motor dysfunction as well as sleep disorder.[38] Interestingly enough, in the new Gaucher model *Drosophila* and the Parkinson disease model *Drosophila*, sleep disorder was found in the young age (corresponding to about the late 20s to 30s in humans). From this fact, in neurodegenerative disease accompanying dementia, it is important to prevent sleep disorder in the young generation. These results may lead to the development of new treatments, early diagnosis, and prevention of neurodegenerative disease accompanying dementia including Parkinson disease and Gaucher disease. We are still continuing drug screening using the dementia model *Drosophila* mentioned above.

## 11 Conclusion

The clock gene research at AIST was started by using mice and cell strains, but in the mice system, two years were necessary to manipulate one gene by genetic engineering, and the maintenance of mice and cultivation of the cell line were expensive. In the latter phase at AIST, we ran out of budget, and therefore, changed our research system to flies and mammalian cell cultures only. The merit of the *Drosophila* system is that it has a short life-span of about 60 days, the stock facilities for normal and all genetic variants are available all over the world, and the researchers and organizations in fly society are very friendly and any mutants are supplied readily by an e-mail request. We have succeeded in creating useful mutant fly lines for the development of new treatments for neurodegenerative disease such as dementia at AIST. Using such new mutants, primary screening of dementia drugs is still going on and we are receiving small funding from companies. Looking back at the 30 years of scientist life at a national research institute(AIST), I am very grateful that I can continue my work with many collaborators, participants including young students. and with the cooperation of many company people. I was unable to mention the names of all the collaborators, however, I express my deepest thanks here for the 30 years.

Now, a big stream of the science funding in Japan tends toward application, and there is an economical demand that science be immediately useful. It is becoming difficult to study basic science in national research institutes and universities. However, real innovation in science and technology comes from pure basic research, particularly for antibody medicine in Japan. In the future, I hope national




(PLOS ONE(2013), T. Suzuki *et al.*)[37]

**Fig. 8 Ambroxol is effective for Gaucher disease model *Drosophila*.**
After ambroxol treatment in food, the protein level of ER stress maker, Xbp-1 (green), decreased significantly.

agencies and ministries nurture real organizers with good judgement (mekiki in Japanese) over cross-sectional basic research so that bioscience in Japan does not decline.

The author established the Institute for Chronobiology in the Foundation for Advancement of International Science (FAIS) (3-24-16 Kasuga, Tsukuba) in April 2016. Here, we are continuing our basic research on clock genes, sleep, and neurodegenerative disease. I hope you might drop in and talk to us at my new laboratory if you stop by at Tsukuba Science City. While proofreading this article, the 2017 Nobel Prize in Physiology or Medicine was awarded to "Discoveries of Molecular Mechanisms Controlling the Circadian Rhythm." I would like to say congratulations to Drs. Jeffrey C. Hall, Michael Rosbash, Michael W. Young who are my good old friends and teachers in this field.

## Terminologies

Term 1. Bipolar nuclear localization sequence: a special amino acid sequence region within a protein to transport a specific protein from the cytoplasm to the nucleus..

Term 2. COS cell: A cell line name, which comes from SV40 transformed renal fibroblast cells of African Green Monkey. Since it shows good expression efficiency of foreign genes, it is often used in transient expression of proteins.

Term 3. Endogenous: In general, a situation where the root or cause of a phenomenon exists within itself.

Term 4. *Cry*: Blue-light photoreceptor protein that was originally discovered in plants. Later, it was found in many animals including humans.

Term 5. Cis element: Also called cis-acting element. Existing in the vicinity of the gene, gene transcription (reading of RNA from DNA) is modulated when a regulating protein binds to this site. This region itself does not synthesize proteins, and it is solely for binding with other proteins (a transcription factor).

Term 6. TE2-box: When an E-box sequence is categorized, it can be divided into the canonical E-box CAGNTG sequence and the second E-box. CACGTT sequence was named E2-box. An E-box is a DNA sequence to which transcription factors such as *Clock* and *Bmal* can bind and activate transcription. In Fig. 1, it is referred to as E cis element.

Term 7. bZIP transcription factor: bZIP (basic zipper protein) is one of the motifs of a secondary protein structure, and has the ability to bind with DNA.

Term 8. *mper2* promoter: Transcription factor binding region in the upstream of mouse *Period2* gene.

Term 9. A-site: DNA sequence for the binding with E4BP4 transcription factors on the upstream region of *Period2* gene.

Term 10. B-site: DNA sequence for the binding with E4BP4 transcription factors on the downstream region of *Period2* gene.

Term 11. Fragile X syndrome: Mental retardation disease that is accompanied by low IQ. This syndrome has been confirmed to be genetic. The branching of nerve cells is defective.

Term 12. Variant $\alpha$-synuclein: Missense mutation of a protein comprised of 140 amino acid residues coded by the SNCA gene. This protein mutation is the cause of familial Parkinson's disease.

Term 13. Variant Gaucher disease: Disease discovered by a French physician, Philippe Gaucher. Due to a genetic factor, the activity of enzymes called glucocerebrosidase (GBA) is low, since it is deficient or lacking from birth. Glucocerebroside (glucolipid) cannot be broken down into ceramides and Glucocerebroside accumulates in the liver, spleen, or bone. In severe cases like type III, patients die by age 2.

Term 14. Lysosome disease: A general name for congenital metabolic disorder where enzyme substances accumulate in the body as waste products, because enzymes related to lysosome are lacking.

Term 15. Endoplasmic reticulum (ER) stress: Proteins that were not folded into a normal higher-order structure (unfolded protein) accumulate in the endoplasmic reticulum, and this causes stress on the cells. Since ER stress inhibits normal physiological functions of the cells, the cells have a mechanism to avoid such stress and to maintain normal conditions called homeostasis.

Term 16. GBA homologous gene: GBA stands for glucocerebrosidase, the causal gene for Gaucher disease in humans. The gene has similar DNA sequence as well as similar function as human's. This DNA was found in *Drosophila*, and this is called the GBA homologous gene.

Term 17. Minos insertion mutation: The genetic engineering technique used frequently in *Drosophila*. Insertion mutation using movable genetic element can affect specific gene function. The property of transposons can move over chromosomal DNA and insert genomes at random.

Term 18. Autophagy: One of the mechanisms of the cell to break down junk proteins within the cell. It is also called, self-eating. Dr. Yoshinori Ohsumi of the Tokyo Institute of Technology received the Nobel Prize for Physiology and Medicine in 2016 for discovering this mechanism.

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# Editorial Policy

*Synthesiology* Editorial Board

## Objective of the journal

The objective of *Synthesiology* is to publish papers that address the integration of scientific knowledge or how to combine individual elemental technologies and scientific findings to enable the utilization in society of research and development efforts. The authors of the papers are researchers and engineers, and the papers are documents that describe, using "scientific words," the process and the product of research which tries to introduce the results of research to society. In conventional academic journals, papers describe scientific findings and technological results as facts (i.e. factual knowledge), but in *Synthesiology*, papers are the description of "the knowledge of what ought to be done" to make use of the findings and results for society. Our aim is to establish methodology for utilizing scientific research result and to seek general principles for this activity by accumulating this knowledge in a journal form. Also, we hope that the readers of *Synthesiology* will obtain ways and directions to transfer their research results to society.

## Content of paper

The content of the research paper should be the description of the result and the process of research and development aimed to be delivered to society. The paper should state the goal of research, and what values the goal will create for society (Items 1 and 2, described in the Table). Then, the process (the scenario) of how to select the elemental technologies, necessary to achieve the goal, how to integrate them, should be described. There should also be a description of what new elemental technologies are required to solve a certain social issue, and how these technologies are selected and integrated (Item 3). We expect that the contents will reveal specific knowledge only available to researchers actually involved in the research. That is, rather than describing the combination of elemental technologies as consequences, the description should include the reasons why the elemental technologies are selected, and the reasons why new methods are introduced (Item 4). For example, the reasons may be: because the manufacturing method in the laboratory was insufficient for industrial application; applicability was not broad enough to stimulate sufficient user demand rather than improved accuracy; or because there are limits due to current regulations. The academic details of the individual elemental technology should be provided by citing published papers, and only the important points can be described. There should be description of how these elemental technologies are related to each other, what are the problems that must be resolved in the integration process, and how they are solved (Item 5). Finally, there should be descriptions of how closely the goals are achieved by the products and the results obtained in research and development, and what subjects are left to be accomplished in the future (Item 6).

## Subject of research and development

Since the journal aims to seek methodology for utilizing the products of research and development, there are no limitations on the field of research and development. Rather, the aim is to discover general principles regardless of field, by gathering papers on wide-ranging fields of science and technology. Therefore, it is necessary for authors to offer description that can be understood by researchers who are not specialists, but the content should be of sufficient quality that is acceptable to fellow researchers.

Research and development are not limited to those areas for which the products have already been introduced into society, but research and development conducted for the purpose of future delivery to society should also be included.

For innovations that have been introduced to society, commercial success is not a requirement. Notwithstanding there should be descriptions of the process of how the technologies are integrated taking into account the introduction to society, rather than describing merely the practical realization process.

## Peer review

There shall be a peer review process for *Synthesiology*, as in other conventional academic journals. However, peer review process of *Synthesiology* is different from other journals. While conventional academic journals emphasize evidential matters such as correctness of proof or the reproducibility of results, this journal emphasizes the rationality of integration of elemental technologies, the clarity of criteria for selecting elemental technologies, and overall efficacy and adequacy (peer review criteria is described in the Table).

In general, the quality of papers published in academic journals is determined by a peer review process. The peer review of this journal evaluates whether the process and rationale necessary for introducing the product of research and development to society are described sufficiently well.

In other words, the role of the peer reviewers is to see whether the facts necessary to be known to understand the process of introducing the research finding to society are written out; peer reviewers will judge the adequacy of the description of what readers want to know as reader representatives.

In ordinary academic journals, peer reviewers are anonymous for reasons of fairness and the process is kept secret. That is because fairness is considered important in maintaining the quality in established academic journals that describe factual knowledge. On the other hand, the format, content, manner of text, and criteria have not been established for papers that describe the knowledge of "what ought to be done." Therefore, the peer review process for this journal will not be kept secret but will be open. Important discussions pertaining to the content of a paper, may arise in the process of exchanges with the peer reviewers and they will also be published. Moreover, the vision or desires of the author that cannot be included in the main text will be presented in the exchanges. The quality of the journal will be guaranteed by making the peer review process transparent and by disclosing the review process that leads to publication.

Disclosure of the peer review process is expected to indicate what points authors should focus upon when they contribute to this journal. The names of peer reviewers will be published since the papers are completed by the joint effort of the authors and reviewers in the establishment of the new paper format for *Synthesiology.*

## References

As mentioned before, the description of individual elemental technology should be presented as citation of papers published in other academic journals. Also, for elemental technologies that are comprehensively combined, papers that describe advantages and disadvantages of each elemental technology can be used as references. After many papers are accumulated through this journal, authors are recommended to cite papers published in this journal that present similar procedure about the selection of elemental technologies and the introduction to society. This will contribute in establishing a general principle of methodology.

## Types of articles published

*Synthesiology* should be composed of general overviews such as opening statements, research papers, and editorials. The Editorial Board, in principle, should commission overviews. Research papers are description of content and the process of research and development conducted by the researchers themselves, and will be published after the peer review process is complete. Editorials are expository articles for science and technology that aim to increase utilization by society, and can be any content that will be useful to readers of *Synthesiology.* Overviews and editorials will be examined by the Editorial Board as to whether their content is suitable for the journal. Entries of research papers and editorials are accepted from Japan and overseas. Manuscripts may be written in Japanese or English.

## Required items and peer review criteria (January 2008)

| | Item | Requirement | Peer Review Criteria |
|---|---|---|---|
| 1 | Research goal | Describe research goal ("product" or researcher's vision). | Research goal is described clearly. |
| 2 | Relationship of research goal and the society | Describe relationship of research goal and the society, or its value for the society. | Relationship of research goal and the society is rationally described. |
| 3 | Scenario | Describe the scenario or hypothesis to achieve research goal with "scientific words". | Scenario or hypothesis is rationally described. |
| 4 | Selection of elemental technology(ies) | Describe the elemental technology(ies) selected to achieve the research goal. Also describe why the particular elemental technology(ies) was/were selected. | Elemental technology(ies) is/are clearly described. Reason for selecting the elemental technology(ies) is rationally described. |
| 5 | Relationship and integration of elemental technologies | Describe how the selected elemental technologies are related to each other, and how the research goal was achieved by composing and integrating the elements, with "scientific words". | Mutual relationship and integration of elemental technologies are rationally described with "scientific words". |
| 6 | Evaluation of result and future development | Provide self-evaluation on the degree of achievement of research goal. Indicate future research development based on the presented research. | Degree of achievement of research goal and future research direction are objectively and rationally described. |
| 7 | Originality | Do not describe the same content published previously in other research papers. | There is no description of the same content published in other research papers. |

# Instructions for Authors

*"Synthesiology" Editorial Board*
*Established December 26, 2007*

*Revised April 1, 2017*

## 1 Types of articles submitted and their explanations

The articles of *Synthesiology* include the following types:
• Research papers, reports, commentaries, roundtable talks, and readers' forums
Of these, the submitted manuscripts of research papers, reports, and commentaries undergo review processes before publication. The roundtable talks are organized, prepared, and published by the Editorial Board. The readers' forums carry writings submitted by the readers, and the articles are published after the Editorial Board reviews and approves. All articles must be written so they can be readily understood by the readers from diverse research fields and technological backgrounds. The explanations of the article types are as follows.

① Research papers
A research paper rationally describes the concept and the design of R&D (this is called the scenario), whose objective is to utilize the research results in society, as well as the processes and the research results, based on the author's experiences and analyses of the R&D that was actually conducted. Although the paper requires the author's originality for its scenario and the selection and integration of elemental technologies, whether the research result has been (or is being) already implemented in society at that time is not a requirement for the submission. The submitted manuscript is reviewed by several reviewers, and the reviewers will recommend whether the manuscript should be accepted, revised, or declined. The author completes the final draft based on the discussions with the reviewers. Views may be exchanged between the reviewers and authors through direct contact (including telephone conversations, e-mails, and others), if the Editorial Board considers such exchange necessary.

② Reports
A report describes a development example of technology which has practical value as well as an example of new technology which has been put to practical use. It contains 1) the aim, 2) the process of development (the course to the goal), and 3) the outcomes. The submitted manuscript is checked by the Editorial Board. The authors will be contacted if corrections or revisions are necessary, and the authors complete the final draft based on the Board members' comments.

③ Commentaries
Commentaries describe the thoughts, statements, or trends and analyses on how to utilize or spread the results of R&D to society. Although the originality of the statements is not required, the commentaries should not be the same or similar to any articles published in the past. The submitted manuscripts will be checked by the Editorial Board. The authors will be contacted if corrections or revisions are necessary, and the authors complete the final draft based on the Board members' comments.

④ Roundtable talks
Roundtable talks are articles of the discussions or interviews that are organized by the Editorial Board. The manuscripts are written from the transcripts of statements and discussions of the roundtable participants. Supplementary comments may be added after the roundtable talks, if necessary.

⑤ Readers' forums
The readers' forums include the readers' comments or thoughts on the articles published in *Synthesiology*, or articles containing information useful to the readers in line with the intent of the journal. The forum articles may be in free format, with 1,200 Japanese characters or less. The Editorial Board will decide whether the articles will be published.

## 2 Qualification of contributors

There are no limitations regarding author affiliation or discipline as long as the content of the submitted article meets the editorial policy of *Synthesiology*, except authorship should be clearly stated. (It should be clearly stated that all authors have made essential contributions to the paper.)

## 3 Manuscripts

### *3.1 General*

3.1.1 Articles may be submitted in Japanese or English.
Accepted articles will be published in *Synthesiology* (ISSN 1882-6229) in the language they were submitted. All articles will also be published in *Synthesiology - English edition* (ISSN 1883-0978). The English edition will be distributed throughout the world approximately four months after the original *Synthesiology* issue is published. Articles written in English will be published in English in both the original *Synthesiology* as well as the English edition. Authors who write articles for *Synthesiology* in Japanese will be asked to provide English translations for the English edition of the journal within 2 months after the original edition is published.
3.1.2 Research papers should comply with the structure and format stated below, and reports and commentaries should also comply with the same structure and format except subtitles and abstracts are unnecessary.
3.1.3 Research papers should only be original papers (new literary work).
3.1.4 Research papers should comply with various guidelines of research ethics

### *3.2 Structure*

3.2.1 The manuscript should include a title (including subtitle), abstract, the name(s) of author(s), institution/contact, main text, and keywords (about 5 words).
3.2.2 Title, abstract, name of author(s), keywords, and institution/

contact shall be provided in Japanese and English.
3.2.3 The manuscript shall be prepared using word processors or similar devices, and printed on A4-size portrait (vertical) sheets of paper. The length of the manuscript shall be, about 6 printed pages including figures, tables, and photographs.
3.2.4 Research papers, reports, and commentaries shall have front covers and the category of the articles (research paper, report, or commentary) shall be stated clearly on the cover sheets.
3.2.5 The title should be about 10–20 Japanese characters (5–10 English words), and readily understandable for a diverse readership background. Research papers shall have subtitles of about 15–25 Japanese characters (7–15 English words) to help recognition by specialists.
3.2.6 The abstract should include the thoughts behind the integration of technological elements and the reason for their selection as well as the scenario for utilizing the research results in society.
3.2.7 The abstract should be 300 Japanese characters or less (125 English words). The Japanese abstract may be omitted in the English edition.
3.2.8 The main text should be about 9,000 Japanese characters (3,400 English words).
3.2.9 The article submitted should be accompanied by profiles of all authors, of about 200 Japanese characters (75 English words) for each author. The essential contribution of each author to the paper should also be included. Confirm that all persons who have made essential contributions to the paper are included.
3.2.10 Discussion with reviewers regarding the research paper content shall be done openly, and the Editorial Board will edit the highlights of the review process to about 3,000 Japanese characters (1,200 English words) or a maximum of 2 pages with the names of the reviewers disclosed. The edited discussion will be attached to the main body of the paper as part of the article. Regarding the reports and the commentaries, discussion with the Editorial Board members will be opened at the Board's discretion. In this case, the Editorial Board will edit the discussion to about 800 Japanese characters (less than half a page) with the names of the Board members disclosed.
3.2.11 If there are reprinted figures, graphs or citations from other papers, prior permission for citation must be obtained and should be clearly stated in the paper, and the sources should be listed in the reference list. A copy of the permission should be sent to the Publishing Secretariat. All verbatim quotations should be placed in quotation marks or marked clearly within the paper.

### *3.3 Format*

3.3.1 The headings for chapters should be 1, 2, 3…, for subchapters, 1.1, 1.2, 1.3…, for sections, 1.1.1, 1.1.2, 1.1.3, for subsections, 1.1.1.1, 1.1.1.2, 1.1.1.3.
3.3.2 The chapters, subchapters, and sections should be enumerated. There should be one line space before each paragraph.
3.3.3 Figures, tables, and photographs should be enumerated. They should each have a title and an explanation (about 20–40 Japanese characters or 10–20 English words), and their positions in the text should be clearly indicated.
3.3.4 For figures, image files (resolution 350 dpi or higher) should be submitted. In principle, the final print will be in black and white.
3.3.5 For photographs, image files (resolution 350 dpi or higher) should be submitted. In principle, the final print will be in black and white.
3.3.6 References should be listed in order of citation in the main text.

Journal—[No.] Author(s): Title of article, Title of journal (italic), Volume(Issue), Starting page–Ending page (Year of publication).
Book—[No.] Author(s): Title of book (italic), Starting page–Ending page, Publisher, Place of Publication (Year of publication).
Website—[No.] Author(s) name (updating year): Title of web page, Name of website (may be omitted If the name of the website is the same as that of the author(s)), URL, Access date.

## 4 Submission

One printed copy or electronic file (Word file) of manuscript with a checklist attached should be submitted to the following address:

*Synthesiology* Editorial Board
c/o Public Relations Information Office, Planning Headquarters, National Institute of Advanced Industrial Science and Technology(AIST)
Tsukuba Central 1, 1-1-1 Umezono, Tsukuba 305-8560
E-mail: synthesiology-ml@aist.go.jp
The submitted article will not be returned.

## 5 Proofreading

Proofreading by author(s) of articles after typesetting is complete will be done once. In principle, only correction of printing errors is allowed in the proofreading stage.

## 6 Responsibility

The author(s) will be solely responsible for the content of the contributed article.

## 7 Copyright

The copyright of the articles published in "*Synthesiology*" and "*Synthesiology English edition*" shall belong to the National Institute of Advanced Industrial Science and Technology(AIST).

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# Letter from the editor

Starting this fiscal year, we have revised part of the submission rules and have established a new category called "Report." This category is for "articles reporting cases of practical realization of new technologies and cases of technological developments that may possibly lead to innovation." In this issue, we publish the first Report, "Challenges to the development of the world's first nondestructive inspection system," that describes the activities of a venture company. The objective of *Synthesiology* is to accumulate specific case studies of the ways by which the results of basic research are utilized in society. It is rare that such activities are conducted by a small organization, but generally, it is conducted through collaboration among a number of institutions. Venture companies are important players that engage in the final stages of product realization, but normally, they are not involved in the basic research itself, but concentrate mainly on product realization. With the new establishment of the Report category, it became possible to accept submissions of reports that do not include the whole course of development starting all the way from basic research. I hope this will help increase articles on case studies of practical realization by venture companies and others.

The four articles in this issue all describe the activities covering a long period. "Establishing reliability in vibration measurement and its international equivalency" took over 20 years, and "High performance thermoelectrics for power generation using earth-abundant and low toxicity elements" describes a seven-year activity. These were not activities done by AIST alone, but the collaboration with other institutions in Japan and overseas played a crucial role. The aforementioned venture company was established in 2005 for the purpose of practical realization of AIST technology. Adding the period of technological development at AIST, the Report describes the results over several years. "Toward overcoming neurodegenerative disease by the circadian molecular clock study" describes activities spanning 30 years as indicated by the subtitle. For the practical realization of a technology, it is necessary to consider the requirements that are acceptable to society, in addition to the integration of multiple elemental technologies from different fields. That is the reason why multi-disciplinary collaboration must be done over many years.

What are the conditions necessary for the creation of innovation? I hope the articles in this issue may provide hints for answering this question.

(Toshihiko KANAYAMA, Executive Editor)

# Aim of *Synthesiology*
## — Utilizing the fruits of research for social prosperity —

There is a wide gap between scientific achievement and its utilization by society. The history of modern science is replete with results that have taken life-times to reach fruition. This disparity has been called the *valley of death*, or the *nightmare stage*. Bridging this difference requires scientists and engineers who understand the potential value to society of their achievements. Despite many previous attempts, a systematic dissemination of the links between scientific achievement and social wealth has not yet been realized.

The unique aim of the journal *Synthesiology* is its focus on the utilization of knowledge for the creation of social wealth, as distinct from the accumulated facts on which that wealth is engendered. Each published paper identifies and integrates component technologies that create value to society. The methods employed and the steps taken toward implementation are also presented.




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## Highlights of the Papers in *Synthesiology*

### Research papers



### Report



### Commentary





*"Synthesiology-English edition" is a translated version of "Synthesiology," which is published quarterly, ISSN 1882-6229, by AIST. Papers or articles published in "Synthesiology-English edition" appear approximately four months after the publication of the original "Synthesiology."*

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