Technologies to Watch in 2021

2021/01

Mitsui & Co. Global Strategic Studies Institute
Technology Foresight Center, Technology & Innovation Studies Div.

Introduction

In January of each year, MGSSI's Technology Foresight Center identifies and selects technologies that deserve particular attention during the year, and provides a forward-looking overview of those technologies and insights. This year, the center focuses on: (1) prime editing, (2) super clocks, (3) EUV lithography, and (4) invasive BMI.

Prime editing is positioned as the third generation of genome editing, which won the Nobel Prize last year, and is a technology that realizes safer gene therapy by transferring RNA information to DNA using reverse transcriptase. **Super clocks** are an important fundamental digital technology for the realization of an IoT society that links cyberspace and physical space, and connects people, things, and data to achieve total optimization through AI and other means. **EUV lithography** is a miniaturization manufacturing technology for semiconductor integrated circuits used in smartphones and wearable devices, which was also subject to regulation during the US-China trade friction. Although Taiwanese manufacturers have leaped to public attention, Japanese companies underpin many of the elemental technologies for manufacturing equipment and materials. **Invasive Brain Machine Interface (BMI)** technology directly inputs and outputs electrical signals to and from the brain through surgery and other means. By combining the progress of brain science research with AI technology, the aim is to apply the technology to the treatment of mental disorders and prosthetic engineering for the disabled, and further to human augmentation through the integration of humans and machines.

We also analyzed the global patent application trends for the four themes discussed in this report.

Yutaka Abe, Technology Foresight Center

Prime Editing
— Third-generation genome editing technology —

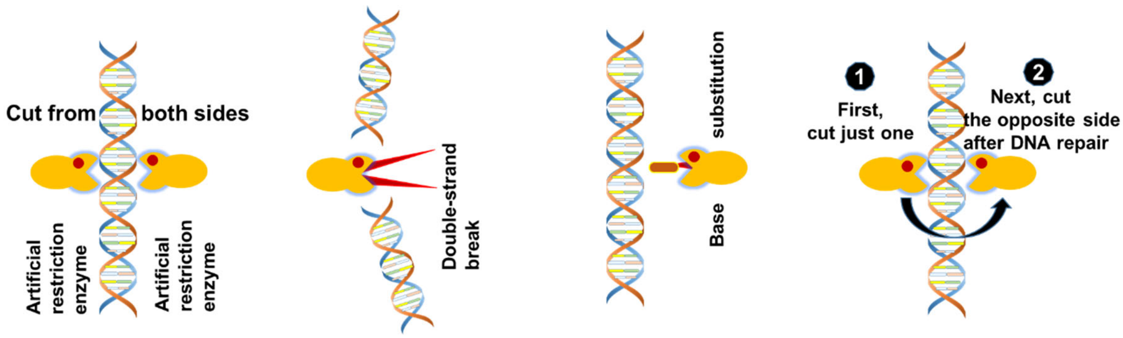
What is Prime Editing?

Prime editing is a genome editing technology. In terms of the transition in substances (enzymes) used to edit the genome, prime editing is positioned as the third generation.

First, let us review a brief history of genome editing technology. Genome editing technology began in 1996 with the introduction of **Zinc-Finger Nuclease (ZFN)**, an artificial restriction enzyme. Then, with the introduction of **Transcription Activator-Like Effector Nuclease (TALEN)** in 2010 and **CRISPR-Cas9** and **RNA editing** in 2012, genome editing took the world of life sciences by storm and quickly spread to other industries such as agriculture, fisheries, and livestock farming. In particular, CRISPR-Cas9 was awarded the Nobel Prize in Chemistry (2020), for bringing about changes comparable to those of the Ford Model T (mass-produced automobile) in manufacturing and land transportation[1]. Genome editing is still being researched and developed at a furious pace, and CRISPR-Cas9 derivative technologies have been announced one after another[2]. As shown in Figure 1, new genome editing methods that edit the double-helix structure of DNA without cutting it have emerged, and these new genome editing methods were reported in November 2020 as "The Dawn of the CRISPR-Free Genome Editing Era —The Development of Genome Editing Technology—"[3]. Of these, **Prime Editing** is attracting particular attention.

Figure 1: Classification of generation by changes in enzymes used for genome editing

1st generation	2nd generation	3rd generation	
Artificial nuclease		Base editing enzyme (Deaminase)	Reverse transcriptase single-stranded break enzyme (Cas9 nickase)
Artificial restriction enzyme (DNA-binding protein)	Nucleolytic enzyme (Guide RNA complex)		
ZFN (1996) TALEN (2010)	CRISPR-Cas9 (2012) CRISPR-Cas3 (2019)	RNA editing (2012) Mitochondrial DNA editing (2020)	Prime editing (2019)

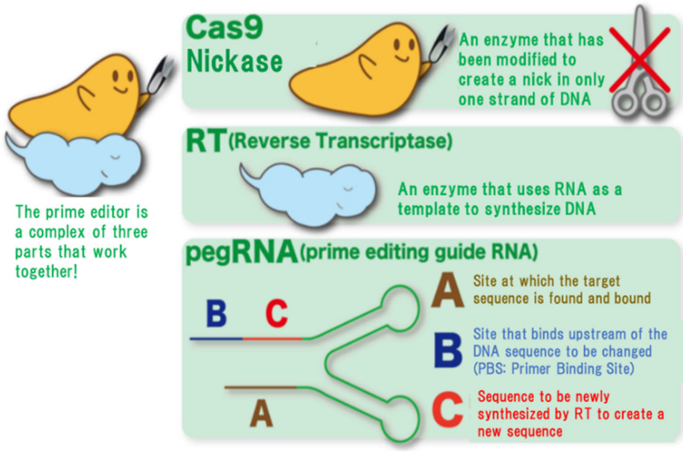


Source: Compiled by MGSSI

[1]*WIRED*, Crispr Isn't Enough Any More. Get Ready for Gene Editing 2.0, December 26, 2017 https://www.wired.com/story/whats-next-for-crispr/
[2]CRISPR-Cas9 DNA Base-Editing and Prime-Editing https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7503568/
[3]Mitsui & Co. Global Strategic Studies Institute
https://www.mitsui.com/mgssi/en/report/detail/__icsFiles/afieldfile/2021/01/18/2011pm_abe_e.pdf

Prime editing is a method whereby instead of severing two strands of DNA at once such as with CRISPR-Cas9, only one strand of DNA is cut and edited by an artificial enzyme called **Cas9 nickase**, and when finished, the other strand is cut and edited in the same way (cutting only one strand can suppress the expression of DNA repair mechanisms / immune functions). After cutting only the single strand, **reverse transcriptase (RT)** is used to transcribe the information to be edited into DNA. Reverse transcriptase, as the name implies, is an enzyme that transcribes RNA information into DNA in the opposite direction to the central dogma flow. Prime editing is a technology to edit the genome as desired by using **Prime Editing Guide RNA (pegRNA)**, a complex of Cas9 nickase, reverse transcriptase, and RNA to carry it to the editing site (Figure 2).

Figure 2: Tools for prime editing



Prime editing is an up-and-coming technology published in *Nature* in October 2019[4], and is the result of the work of Professor David R. Liu and his colleagues at the Broad Institute of MIT and Harvard, who developed **RNA editing** and **mitochondrial DNA editing**, shown in Figure 1[5]. According to this paper, along with the development of prime editing technology, the effectiveness of genome editing of genes related to genetic diseases (sickle cell syndrome, lysosome disease, and human prion disease) was confirmed using human cells to verify the editing effect. After analysis and evaluation of this pilot study, they report that up to 89% of known genetic variants associated with human diseases can be corrected by prime editing.

Since prime editing can edit the desired content while compensating for the shortcomings and limitations of conventional editing technologies such as CRISPR-Cas9 and single base editing, it is attracting interest for its full-scale application to gene therapy, which has been anticipated from the outset with genome editing. For example, in the case of sickle cell syndrome, upon which Professor Liu and his colleagues conducted trials, it is known that the hemoglobin gene is abnormal, and as shown in Figure 3, editing the genetic information A (adenine) to T (thymine) may correct the hemoglobin abnormality and heal sickle cell syndrome.

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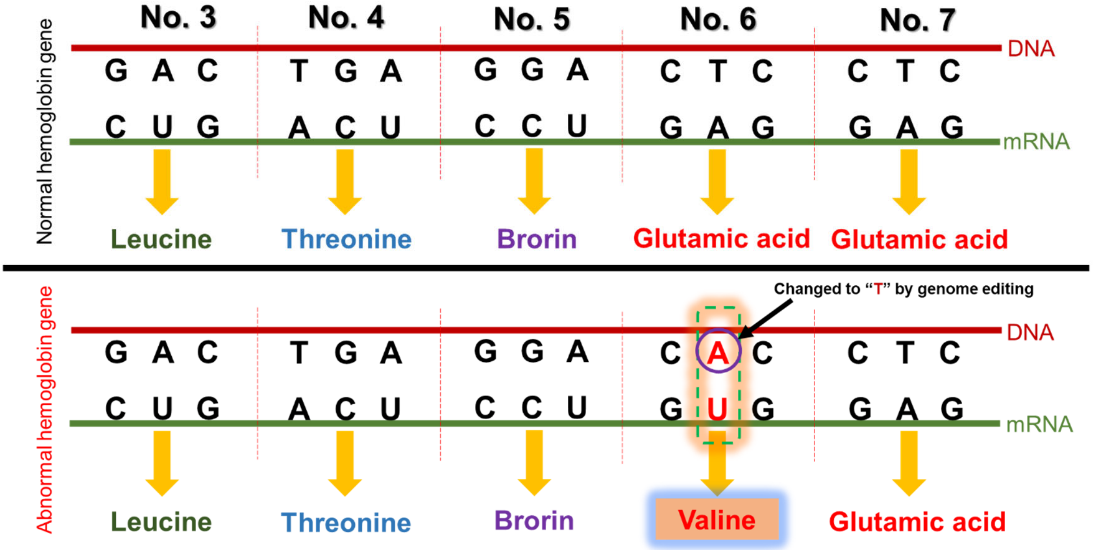
[4]*Nature*, October 21, 2019, Search-and-Replace Genome Editing Without Double-Strand Breaks or Donor https://www.nature.com/articles/s41586-019-1711-4 (Nature volume 576, pages 149–157)

[5]Professor Liu founded Prime Medicine, a company that deploys prime editing technology. On October 31, 2019, the company signed a licensing agreement with Beam Therapeutics, which is developing a business related to base editing technology as a co-founder. The two companies will collaborate on genome-editing gene therapy in the field of genetic disease.

Figure 3: Abnormalities in the hemoglobin gene in sickle cell syndrome



Source: Compiled by MGSSI

Promising Field of Application - Gene Therapy

Gene therapy is a medical technology for the treatment of diseases whose genes are abnormal. The dramatic reduction in the cost of genetic analysis has led to significant advances in the study of genetically-induced diseases. As the mechanisms of genetic diseases become clearer, genome editing, which can edit genes, holds great promise. However, gene therapy stalled when hematopoietic stem cell gene therapy carried out from 2002 onwards patients developed leukemia one after another. Thereafter, since 2010, successful clinical trials have been conducted, and with the emergence of **chimeric antigen receptor T-cell (CAR-T) therapy**, which is a genetically engineered cancer therapy, gene therapy has come back into the spotlight. Currently, clinical studies are being conducted to apply genome editing to gene therapy.

Genome editing in the medical field is used as a technology to edit specific genes into meaningless gene sequences, to destroy (knock-out) functions, to repair abnormal genes, or to replace them with intended genes (knock-in). There are about 50 clinical trials registered on ClinicalTrials.gov (according to a search result for "Gene Editing"), the clinical trial registration site of the U.S. National Institutes of Health (NIH), and the content of the trials is knock-in/knock-out and other forms of genetic modification. Most genetic diseases are caused by mutations of only a single base, and are not subject to the originally expected clinical trials of genome editing. In addition, there are concerns about unintended genetic alterations (off-target) when genes are cut and edited, as it is in the case of CRISPR-Cas9, and such status quo has prevented gene therapy from becoming full-scale.

Prime editing has been attracting attention as a technology that can overcome the challenges of conventional genome editing as described above. Not only knock-in/knock-out, but also base editing is possible. Other than prime editing, there is epigenome editing, which is the indirect manipulation of genes by chemically altering them, but its functions are limited, and the flexibility of prime editing, which can respond to the editing methods required for genome editing, is highly valued. In addition, as shown in Figure 2, prime editing employs a more complex method than existing genome editing, so support tools that can appropriately and quickly design substances to be used for editing are important. At the Broad Institute of MIT and Harvard, a separate research group to the one above has already developed an IT tool called **PrimeDesign** that enables rapid design and optimization of pegRNA, and has made it available free of charge. There also are other IT tools available (Figure 4), and an environment to promote the use of prime editing is being set up.

Figure 4: Prime editing design tools

No.	Prime editing tool	Overview (website, GitHub)
1	PrimeDesign	pegRNA design tools http://primedesign.pinellolab.org/
	Code release (GitHub) -> https://github.com/pinellolab/PrimeDesign Docker download required	
2	PrimeVar	PrimeVar is bundled with PrimeDesign. About 68,300 genetic diseases that can be repaired by prime editing are extracted from the ClinVar database of genetic diseases and a searchable database of corresponding pegRNA/ncRNA is created https://drugthatgene.pinellolab.partners.org/primevar
3	DeepPE	Prime Editing prediction tool for editing efficiency (for PE2) http://deepcrispr.info/DeepPE
	Code release (GitHub) -> https://github.com/hkimlab-PE/PESupplementaryCode Prime Editing 2 (PE2) efficiency analysis code & DeepPE service code (language: Python)	
4	pegFinder	pegFinder is a pegRNA design support tool developed by Yale University School of Medicine http://pegfinder.sidichenlab.org/
	Code release (GitHub) -> https://github.com/rdchow/pegfinder	

Source: Compiled by MGSSI

Future Prospects

The research group at the Broad Institute has intended from the outset to use prime editing for gene therapy, and as previously mentioned, up to 89% of genetic variants can be corrected by prime editing. PrimeVar, shown in Figure 3, has compiled a database of pegRNAs corresponding to about 68,300 human genetic diseases that are likely to be repairable by prime editing, and made it available. The research group is also developing improved versions of prime editing, and has published **Prime Editing 2 (PE2)** and **Prime Editing 3 (PE3),** and is improving them for full-scale gene therapy.

Problems also exist with this kind of prime editing. pegRNAs are twice the size of CRISPR-Cas9 molecules because they use multiple biological substances to reliably edit the genome, so a drug delivery system to deliver these macromolecules to the target cells is important. However, further technological breakthroughs are still needed. Another problem common to genome editing as well as prime editing is gene therapy targeting germ cells.

Cells are classified into somatic cells and germ cells. Germ cells are cells that repeatedly divide to create new life. Although gene therapy by genome editing of germ cells has not been approved, if an abnormality is known in advance through genetic testing, editing the genes of germ cells before birth will increase the possibility of preventing congenital genetic diseases. This will ensure that the unborn child will be free of disease, and society can expect a reduction in medical, nursing, and education costs. In 2018, a Chinese researcher announced that twin girls had been born after he applied gene therapy to fertilized eggs. However, there has been insufficient discussion on whether children whose fertilized eggs have been genetically edited will really grow up healthy, what will be done if abnormalities caused by gene editing are found after they grow up, and whether they will suffer social disadvantages such as discrimination. Of particular consideration is the fact that gene editing of a fertilized egg is passed on to the next generation and beyond.

However, genome editing, especially prime editing, is considered to be a promising technology for the treatment not of fertilized eggs but for the various diseases caused by genes already mentioned above. In addition to the technology, there are other hurdles to overcome, such as regulations, intellectual property, and the cost of treatment, but the advent of prime editing is a ray of hope for gene therapy for the goal of curing genetic diseases. Against this background, COVID-19 (virus name: SARS-CoV-2) occurred at the end of 2019, when prime editing was announced. The disease quickly spread around the world, and had a huge impact on society and the economy, including urban lockdowns. Then the world witnessed the extremely rapid development of the COVID-19 vaccine, leading to inoculation. In particular, RNA vaccines are being administered to humans for the first time in history. Thus, the global spread of COVID-19 may have drastically changed the state of medicine in the future, as vaccine development, which normally takes about 10 years, will be greatly shortened and simplified. Today, we have promising technologies such as prime editing, which is effective for gene therapy, and the hope is that we can make progress in our efforts to overcome genetic diseases.

Study of patent application trends regarding prime editing (genome editing technology)

Super Clocks
— Core Technology Supporting a New Digital Age —

Yutaka Abe, Technology Foresight Center

What are Super Clocks?

Super clocks are next-generation clocks that exceed **cesium atomic clocks** in accuracy**.** Originally, one second was determined as one 86,400th of the length of a day, but now it is defined as the length of time it takes for the electromagnetic waves emitted and absorbed by the cesium in a cesium atomic clock to oscillate 9,192,631,770 times[6]. Since its invention in 1955, the cesium atomic clock has been used to establish a universal standard time, and industrial systems such as electric power, finance, communications, and transportation operate based on this precise time information. Now, in the 21st century, **super clocks** that exceed cesium atomic clocks in accuracy are being developed in the West, in China, and in Japan. The super clock is 1,000 times more accurate than a cesium atomic clock. Such a high accuracy makes it possible to measure the difference in the passage of time, for example, by comparing a clock at 0 meters above sea level with a clock 1 centimeter higher. The time on a clock at an altitude of 0 meters will advance ever so slightly slower than a clock at a height of 1 centimeter. This is because, as Einstein's theory of relativity shows, gravity becomes weaker for every additional centimeter of separation. A super clock can measure such extremely subtle changes in time. It is believed that these ultra-high-precision super clocks can be applied to the exploration of underground resources, such as veins of heavy metals and movement of magma deep underground, as well as to the monitoring of volcanic and subterranean activity. Professor Hidetoshi Katori of the University of Tokyo calls this kind of sensing using super clocks **relativistic sensing.** The effectiveness of relativistic sensing has already been proven, and the difference in the progression of clocks at the ground level of the Skytree and the 450 meter observation deck has been successfully measured[7].

This paper will introduce two technologies: the **optical lattice clock**, which is a Japanese original technology and the most promising candidate to be used when the definition of one second is updated at General Conference on Weights and Measures in 2026, and the **nuclear clock**, which is still in the basic research stage but is expected to surpass the atomic clock in accuracy and be equal to or more accurate than the optical lattice clock.

(1) Optical lattice clock

An optical lattice clock is a super clock proposed by Professor Katori of the University of Tokyo in 2001, and as the name suggests, it is a clock that uses laser light. Current atomic clocks determine a second by energizing a cesium atom and measuring the frequency of its oscillation. During this measurement, the measurement and calculation are repeated a million times to minimize the error and a highly accurate period can be obtained. This is a time-consuming and

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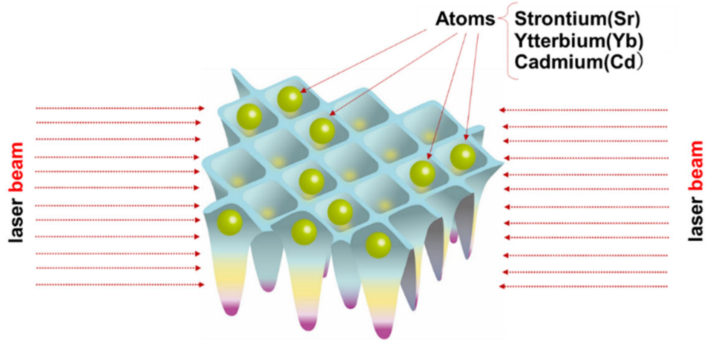
[6]http://www.spring8.or.jp/ja/news_publications/research_highlights/no_99/

[7]Japan Science and Technology Agency (JST), World-First Success in Developing a Portable Optical Lattice Clock with 18-Digit Accuracy [in Japanese], https://www.jst.go.jp/pr/announce/20200407/index.html

cumbersome process. The optical lattice clock takes a different approach. Here, a large number (one million) of atoms are trapped in the interference pattern of light emitted from multiple lasers (optical lattice), and the frequencies emitted by these atoms are measured at once, eliminating the need for repeated measurements and calculations. In addition, as shown in Figure 1, trapping atoms in an optical lattice eliminates external physical influences, making it an excellent technique for obtaining an extremely precise period.

Figure 1: Schematic of an optical lattice



When opposing laser beams are superimposed, the two beams interfere with each other positively and negatively, creating a lattice-like interference pattern as shown above. This traps one million atoms.

Source: Compiled by MGSSI

(2) Nuclear clock

An atomic clock uses the entire atom including the nucleus and the surrounding electrons, while a nuclear clock uses only the nucleus to obtain an accurate period. Along with uranium, thorium (atomic number 90) is used as the atomic fuel for the nuclear clock. In particular, the nucleus of the isotope thorium-229 is known to change its nuclear state at the lowest energy compared to other nuclei. Using this property, research is underway to obtain an exact period by measuring the change in state of a thorium nucleus when a small amount of energy is given to it. The nucleus of thorium is less susceptible to external factors due to the presence of a group of electrons orbiting around it, and it is believed to have the potential to achieve an accuracy about 100 times higher than that of an optical lattice clock. The optical lattice clock is described as a "practically accurate clock" with a deviation of one second in 15 billion years, which is the same as the age of the universe, but the nuclear clock is a "truly accurate clock" with an expected deviation of one second in 300 billion years, which far exceeds this[8].

Promising Fields of Application

Two promising fields of application for the super clock will be discussed: **Finance,** and **Positioning, Navigation and Timing (PNT).** PNT will be explained in two parts: **Positioning and Navigation** and **Time Synchronization**.

(1) Finance

The most promising field of application of the original function of the super clock, that is, as a clock, is in finance, which

[8] Akihiro Yoshimi, Research Institute for Interdisciplinary Science, Okayama University, 229Th Nuclear Ultra-Low Energy Levels and Their Application to High-Precision Nuclear Clocks [in Japanese] http://www2.riken.jp/lab/molecule/member/kato/2019BG2/abstract/ I-3-Yoshimi.pdf

is symbolized by ultra-high speed trading. Of particular attention is a digitalized legal tender known as Central Bank Digital Currency (CBDC). The core technology of the CBDC is the blockchain. The blockchain has been implemented in the virtual currency Bitcoin. It is a system that makes the details of financial transactions open and practically impossible to tamper with. Since Bitcoin is traded around the world, strict time management (a universal clock function, and a time synchronization function to ensure the timing of transaction processing as described below) is inherently necessary. However, since blockchains do not have a time management function, they have the disadvantage of generating multiple transaction histories in different parts of the world (called the forking problem). CBDCs are legal tender, so a universal and precise clock will be important to solve the blockchain forking problem. This would currently be an atomic clock, but in the future would be universal clock provided by a super clock.

(2) Positioning and Navigation

In addition to clocks, there is a field of application of super clocks called **PNT.** PNT is an acronym for **Positioning, Navigation and Timing**, or **time synchronization.** Positioning and navigation are the means by which one reaches a destination while verifying where one is on the earth while moving. Currently, the mainstream method of positioning and navigation is to use radio waves from positioning satellites orbiting the earth, such as GPS satellites or quasi-zenith satellites, to locate and confirm ones' current position while moving. Positioning satellites are equipped with atomic clocks (Figure 2 shows the status of research and development of next-generation atomic clocks to be installed in positioning satellites in various countries). Latitude, longitude, and height (elevation) are calculated based on precise time signals transmitted by three to four positioning satellites.

Figure 2: Research and development status of atomic clocks onboard positioning satellites

Country	GNSS[*1]	Organization	Atomic clock in development	Launch	Notes
US	GPS[*2]	NASA[*6]/JPL[*7] (Jet Propulsion Laboratory)	Mercury ion atomic clock (MAFS[*14])	2019	Demonstrated as a spare clock for GPS-III after demonstration unit verification
		AFRL[*8] (U.S. Air Force Research Laboratory)	Laser cooled Cs (cesium) Optical Rb (rubidium)	2023	Mounted on NTS[*17]-3 (lifetime 1 year) Plans to demonstrate using Clock slot for experiments in GPS-III
Russia	GLONASS[*3]	Роскосмос[*9] (ROSCOSMOS)	hydrogen maser	2023	To be installed in High-Orbit GLONASS (6 units)
Europe	Galileo[*4]	European Space Agency ESA[*10]	Hydrogen maser + Laser cooled Cs	2020	ACES[*18] (demonstrated in the European module of the space station)
		ESA/G2G[*11]	Hydrogen maser RAFS[*15] ensemble (ONCLE[*16])	2019-	For 2nd generation Galileo (2025~) Europe also has an R&D plan to launch an onboard optical lattice clock around 2020
China	BeiDou	CAST[*12] (China Academy of Space Technology)	Hydrogen maser RAFS	2018	Constellation of 30 satellites completed in June 2020 Operations to cover the entire globe commenced
India	IRNSS[*5]	Indian Space Research Organisation ISRO[*13]	RAFS	Undecided	To be installed in 2nd Generation IRNSS (NIC[*5]) (2018-2023?)

*1: Global Navigation Satellite System
*2: Global Positioning System
*3: GLObal NAvigation Satellite System
*4: Galileo
*5: Indian Regional Navigation Satellite system (Navigation Indian Constellation)
*6 : National Aeronautics and Space Administration
*7: Jet Propulsion Laboratory
*8: Air Force Research Laboratory
*9: ROSCOSMOS (Roscosmos State Corporation for Space Activities)
*10: European Space Agency
*11: Galileo 2nd Generation
*12: China Academy of Space Technology
*13: Indian Space Research Organisation
*14: Mercury Atomic Frequency Standard
*15: Rubidium Atomic Frequency Standard
*16: ONe CLock Ensemble
*17: Navigation Technology Satellite
*18: Atomic Clock Ensemble in Space

Source: Quasi-Zenith Satellite System Strategy Office, Cabinet Office, Japan, with addition by MGSSI

As a concrete example of social implementation, the map information of car navigation systems and smartphones show the current location, which has become an indispensable tool in daily life, and a transportation system that enables unmanned automatic driving will be a future development of this. In order to fully realize unmanned automatic driving, which is referred to as Level 5, measurement precision of centimeters or less is considered necessary, but this is difficult for the current accuracy of atomic clocks to achieve. Since super clocks' accuracy exceeds that of atomic clocks, enabling measurement of centimeters or less, which makes them an essential technology for realizing a next generation transportation system.

(3) Time Synchronization

From within the fields of application of super clocks (positioning, navigation, and time synchronization), time synchronization refers to the matching of the times and coordinated operation of multiple systems and all sensors/information devices connected to them. This time synchronization can be compared to the metronome used in music. A metronome is a tool that taps out a regular beat in order to match the tempo of various instruments and provide a marker for the timing of the performance of each instrument. The super clock is the metronome of industrial systems, and embodies a more precise real-time control of the entire system by generating signals with a tempo (synchronization) that ranges in accuracy from the level of seconds to picoseconds (10^{-12} sec / a trillionth of a second), depending on the needs and specifications of the system[9]. Although we are not aware of it in our daily lives, this is an important mechanism that is fundamental to the social and industrial systems that support our lives. In addition to the aforementioned financial sector, there is a wide range of industries in which this precise time synchronization will become increasingly important, including electric power, broadcasting, advanced manufacturing, transportation, and telecommunications (Figure 3).

Figure 3: Industry sectors that require precise time synchronization (PNT)

Industry	PNT ◎: Essential ○: Very useful			Overview
	Time synchronization	Positioning	Navigation	
Finance	◎	○		Securities (ultra-fast trading), currency exchange, settlement, distributed ledger (blockchain)
Telecommunications	◎			Base station synchronization, time division multiplexing, time synchronization, frequency synchronization
Broadcasting	◎	○	○	Broadcasting equipment, 4K/8K broadcasting, signal synchronization, live/IP*1 remote production
Energy	◎	○		Substation synchronization, transmission management, digital grids, smart meter synchronization
Manufacturing	◎	○	○	Control system synchronization, sensor synchronization, smart factories, logistics coordination
Transportation	◎	◎	◎	Vehicle operation management, railroad power transmission management, air/marine navigation, manufacturing coordination
Architecture	○	○ Indoor		Seismic sensor synchronization, BIM*2⇔IoT*3, digital twin (urban virtualization)
Medicine	◎	In ○ hospitals	○ Guidance	Medical device synchronization, medical sensor synchronization, medical records, machine learning data rectification

*1: Internet Protocol *2: Building Information Modeling *3: Internet of Things

Source: Compiled by MGSSI, based on data from Enabler.

[9] For more information on new synchronization environments using optical lattice clocks, see Ultra-High-Precision Digital Twin Derived From Atomic Clock Chip [in Japanese] (Motoaki Hara, Senior Researcher, Applied Electromagnetic Research Institute, National Institute of Information and Communications Technology) in the July 2020 issue of Nikkei Electronics.

Future Prospects

The progression of digital transformation has led to entire social systems becoming digitized, and previously unconnected systems are now linked to each other. In order to realize a digital society in which many systems mutually and intricately cooperate to manage social functions, super clocks will keep exact time and generate precise synchronization signals. Currently, at the forefront of ICT, attention is shifting from information processing using electrons to photonics, which uses photons, the fastest medium in the physical world, to develop information processing technology that can carry out analysis, processing, and control at the almost instantaneous speed of light. Super clocks are likely to be positioned as a technology that can control the future systems of society, which will process at the speed of light, because they are accurate enough to capture the changes in time delay caused by gravity.

Study of patent application trends regarding super clocks

Next-Generation EUV Lithography
— The Semiconductor Manufacturing Method to Revive Moore's Law —

Reina Ogawa, Consumer Innovation Dept., Technology & Innovation Studies Div.

What is Next-Generation EUV Lithography?

Next-generation EUV lithography[10] is the successor to EUV lithography, a technology used to manufacture cutting-edge semiconductors that has been subject to export restrictions to China as trade friction between the United States and China intensifies. In this section, we will review the basics of what semiconductors are, why miniaturization is important, and what EUV lithography is, and then introduce the elemental technologies that will make next-generation EUV lithography a reality.

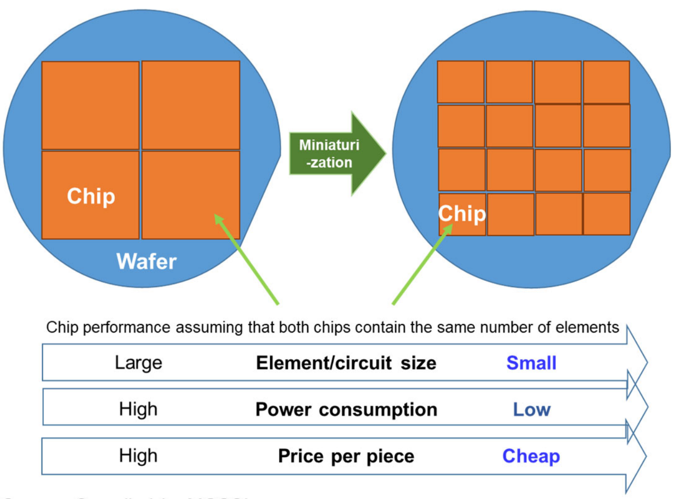
What is a Semiconductor?

A semiconductor is broad term for semiconductor integrated circuit (see the column on semiconductor integrated circuits). These are made up of semiconductor elements and circuits, and their performance is defined by their miniaturization.

Why do Semiconductors Aim for Miniaturization?

Smartphones have maintained an easy to handhold size, even though their functions, such as the ability to enjoy videos in comfort, continue to improve with the release of each new model. If the battery is fully charged in the morning, a smartphone can be used until nightfall without running out of power. Moreover, in many cases, the retail price remains unchanged despite the improved performance. , Smartphones have thus become widespread, and this has largely been achieved due to smaller semiconductors processing information efficiently with lower power, and the continued reduction of manufacturing costs, in other words, miniaturization. An image of miniaturization is shown in Figure 1.

Figure 1: Semiconductor miniaturization



Source: Compiled by MGSSI

Column: What are semiconductor integrated circuits exactly?

We will introduce the semiconductors relevant to the process of taking and saving a photo with a smartphone. Every time you turn on the power, start the camera, or touch the shutter on the display, the DRAM and processor, which are the semiconductors that serve as the brain of the smartphone, are at work. DRAM (also called volatile memory) stores processing in the short-term. Processors (also called “logic”) analyze and process information. According to the information handled, different processors are used, such as CPUs, GPUs, and FPGAs in servers and the like. A semiconductor that acts as the long-term memory, and is the place where the photos taken in this way are stored is SSD (non-volatile memory).

When discussing GAFA and other IT companies, the focus tends to be on their services, but they also own infrastructure such as servers for processing the large amount of information that users type during searches, and data centers for storing it, which contain a large number of semiconductors. IT companies such as GAFA, have continued to replace or increase the number of new servers as they have grown in recent years, and are large customers for semiconductor manufacturers.

[10] Abbreviation for Extreme Ultraviolet Lithography.

As miniaturization advances, more elements can be placed on a single wafer, so less material is needed to make a chip with the same performance. As a result, the price of chips goes down. If we compare the number of elements per unit area, the number increases with miniaturization, which means that more information can be processed and stored in the same area.

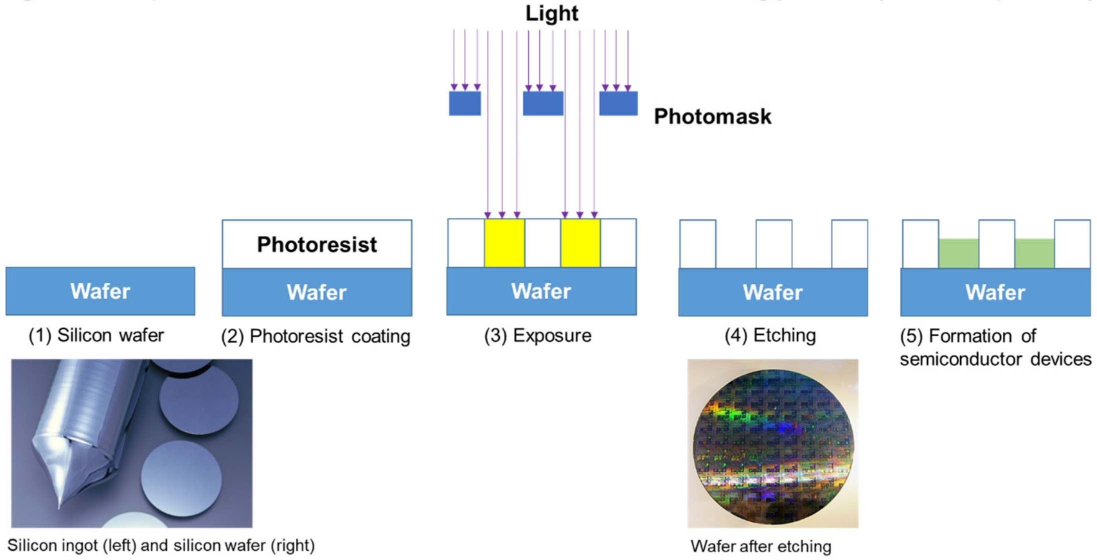
Moore's Law, an empirical prediction of how this miniaturization will progress, specifically shows that the density of integrated circuits will double in 18 months.

With the prospect of a dramatic increase in the amount of data handled due to the spread of 5G and IoT, performance improvement through miniaturization is becoming the key to product differentiation, especially for processors and DRAM. **Lithography is a key technology for miniaturization because it is a technique for drawing circuits in semiconductor manufacturing.** EUV lithography is undergoing further development as a technology that will extend the life of Moore's Law beyond the limits of previous generations of lithography technology.

How are Semiconductors Fabricated?

Semiconductors are manufactured by matching and combining many elemental technologies. The front-end process, which is directly related to miniaturization, manufactures semiconductors through the following process (Figure 2). Steps (1)-(4) of the diagram are relevant to EUV lithography.

Figure 2: Simplified schematic of the semiconductor manufacturing process (front-end process)



Source: Compiled by MGSSI. Photos: Shin-Etsu Chemical website (left), Wikipedia (right)

(1) Silicon ingots[11] are processed into thin sheets to produce silicon wafers (hereinafter referred to as wafers).

(2) Photoresist[12] is applied to the wafer.

(3) The pattern[13] is drawn by exposing the photoresist to light through the photomask[14].

(4) Etching[15].

(5) Semiconductor elements are formed by injecting boron or phosphorus into the wafer surface. Each of these semiconductor elements is responsible for processing or storage.

(6) If there are multiple layers, steps (2) through (5) are repeated for the number of layers, and then a metal film (electrode) is formed in inert gas plasma to finish the chip. The resulting chip is then inspected to make sure there are no problems.

This is followed by the manufacturing process (back-end process) where the chips formed on the wafer are separated and completed into components (packages) that can be shipped to customer manufacturers downstream in the supply chain.

For the front-end of the semiconductor manufacturing process, including EUV lithography, Japanese companies hold the large share of the technology needed for the most advanced manufacturing processes, from wafers, photoresists, and masks to inspection equipment. Typical examples are shown in Figure 3.

Figure 3: Japanese companies providing important materials and technologies for front-end processes, including current-generation EUV lithography

Material/Technology	Examples of Japanese companies
Wafer	Shin-Etsu Chemical
Light source	Gigaphoton
Masks, materials for masks, and manufacturing equipment	AGC, Shin-Etsu Chemical, HOYA, Toppan Printing, JEOL
Mask inspection system related	Lasertec
Photoresist, Photoresist materials, developing solution, abrasives, etc.	Tokyo Ohka Kogyo, JSR, Shin-Etsu Chemical, Sumitomo Chemical, Fujifilm, Toyo Gosei, Osaka Organic Chemical Industry
Coater/developer, polishing equipment, etc.	Tokyo Electron, SCREEN Semiconductor Solutions
Semiconductor inspection equipment	Advantest, Hitachi High-Tech

Source: Compiled by MGSSI

[11] A member of silicon processed into the shape of an elongated lump.

[12] A substance that changes chemically or physically when exposed to light. A photoresist that leaves the pattern of areas that have been exposed to light is called a positive photoresist; conversely, a photoresist that leaves the pattern of areas that have not been exposed to light is called a negative photoresist.

[13] A pattern formed by the difference between areas that are exposed to light and areas that are not.

[14] A member that has parts that absorb light and parts that do not, thereby producing parts of the photoresist that are exposed to light and parts that are not. The simplification of the photomask in Figure 2 is for the generation before EUV. The photomask for EUV will have a different shape, the details of which are discussed later.

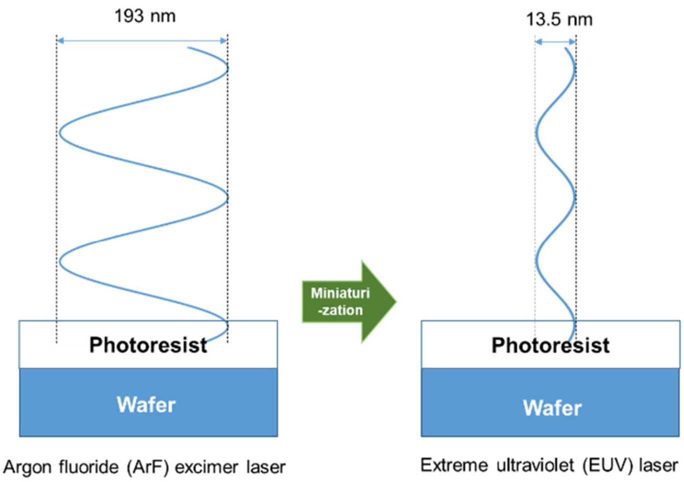
[15] The process of removing photoresist that is not needed for the pattern.

What is the Light Used in EUV lithography?

Figure 4 shows an image of different wavelengths of light (laser) used in lithography. The shorter the wavelength, the finer the pattern that can be drawn.

EUV lithography uses a light called extreme ultraviolet light, which has a wavelength of 13.5 nm. This has made it possible to draw even finer circuits than the 193 nm wavelength of the previous generation technology, the argon fluoride (ArF) excimer laser. Both the current generation EUV and the next generation EUV use extreme ultraviolet light with a wavelength of 13.5 nm.

Figure 4: Different wavelengths of light used in lithography

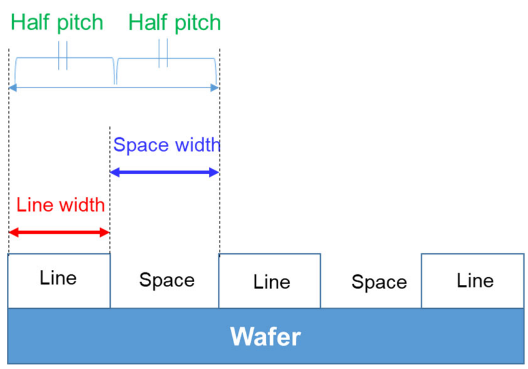


Source: Compiled by MGSSI

Miniaturization index — technology node

The index of miniaturization is often discussed in terms of the logic technology node. The technology node is traditionally expressed in terms of half-pitch (Figure 5), which is the value obtained by adding the width of the line where the circuit or element is placed to the width of the space where nothing is placed, and dividing by two. However, in recent years, there has been a discrepancy between the half-pitch and technology node values, partly because half-pitch and logic performance no longer match due to advances such as 3D wiring technology for stacking circuits.

Figure 5: Schematic of half-pitch



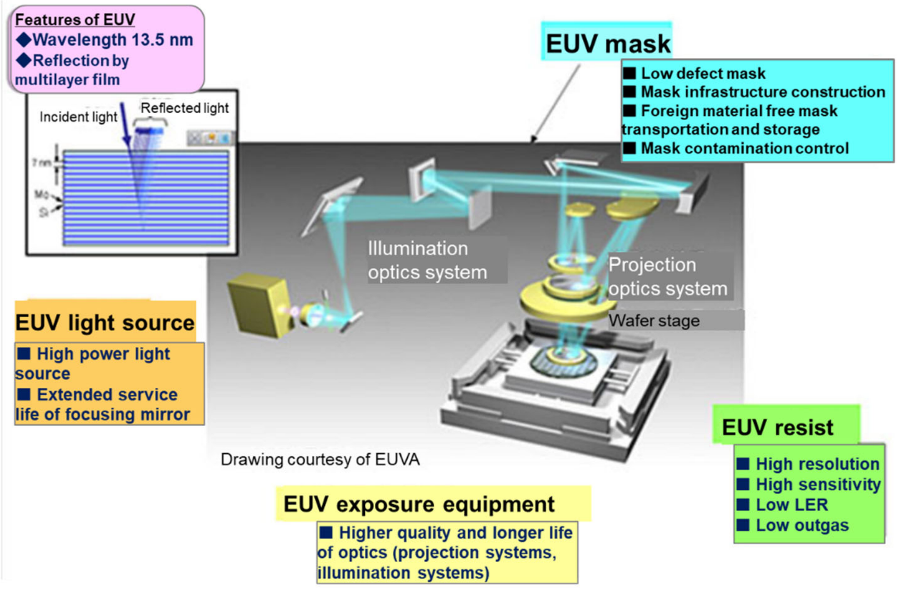
Source: Compiled by MGSSI

The current technology node is referred to as the 5 nm generation, and was made possible by current generation EUV lithography. An advance to the next generation of EUV lithography will result in a 3 nm generation. 2021 will be the year of technology development for the launch of 3 nm generation mass production in 2022.

Elemental technologies driving next-generation EUV lithography

Figure 6 shows an overview of EUV lithography. Since the method of controlling the light up to the point where the EUV light hits the wafer is very different from ArF and other light used in lithography to date, the members and materials used must be changed accordingly. In terms of the fact that the wavelength of the light used remains the same, many of the elemental technologies of the next generation EUV lithography will also be realized as an extension of current generation EUV lithography. The following is an overview of the elemental technologies that will change significantly between the current generation and the next generation.

Figure 6: Overview of EUV lithography



Source: NEDO website (https://www.nedo.go.jp/activities/ZZJP_100028.html)

(1) Lithography equipment

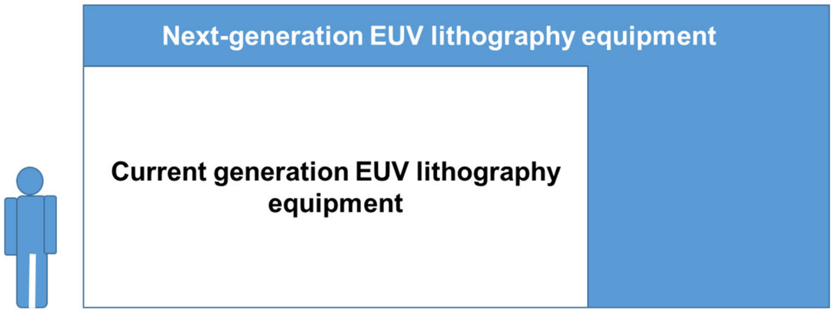
Lithography equipment prepares EUV light in a condition suitable for lithography and irradiates it onto the wafer. The only supplier is ASML (Netherlands), which was established as a joint venture between the trading company ASM International (Netherlands), and Philips (Netherlands).

Since ASML was a member of EUV LLC, which is at the core of the development of EUV lithography technology in the US and has an extensive patent portfolio related to the technology, it is assumed that some of the lithography equipment contains technology originating from the US. This may be the reason behind why the US has urged ASML to ban the export of EUV lithography equipment to China.

EUV light is generated by laser ablation of tin droplets. Since 13.5 nm EUV light is absorbed by most materials, the space where the light leaves from the source and flies to hits the wafer must be a vacuum. Since the light emitted by the light source does not have an aligned wave direction, it should be aligned by illumination optics system before being applied to the mask. The magnification of the EUV light reflected from the mask is adjusted by the projection optics system. Mirrors of dozens of layers of molybdenum and silicon thin film, which can reflect EUV light, alternately coated on a wafer are used for the illumination optics system, mask, and projection optics system, rather than convex lenses like those on magnifying glasses.

Carl Zeiss SMT (Germany) is in charge of the development and manufacture of the optics of the lithography equipment. The parameter related to miniaturization in optics is the numerical aperture (NA), and the larger the NA value, the more miniaturization is possible. The current generation has an NA of 0.33, but the next generation is being developed to increase to 0.55. Next-generation EUV lithography equipment for prototyping and evaluation are scheduled to be shipped by ASML to several joint development partners in 2021. To increase the NA, it is necessary to use larger lenses, so the next generation of lithography equipment will be even larger (Figure 7). The price of one current-generation EUV lithography system is also expensive, ranging from JPY 12.5 to 20 billion, but the price of a mass-produced next-generation EUV lithography system is expected to be about as much as JPY 48 billion per unit.

Figure 7: Size of current-generation EUV lithography equipment and next-generation EUV lithography equipment



Source: Compiled by MGSSI with reference to ASML presentation materials for the 2018 EUVL Workshop

(2) Photoresist

Photoresist is precisely applied to the wafer using a device called a coater. Photoresists need to be sensitive enough to undergo sufficient changes in chemical structure when exposed to EUV light. Currently, resin photoresists based on the photoresist design technology of the previous generation are used, but in the next generation and beyond, the use of metal-based resists, nanoparticulate resists, and other photoresists based on a completely different design concept to the resin-based resists used to date are being considered.

(3) Manufacturing technology

Taiwan Semiconductor Manufacturing Company (TSMC) was the first company to successfully mass produce processors using EUV lithography. Established in 1987, TSMC is a foundry that manufactures semiconductors. Mr. Morris Chang, the founder of TSMC, is a professional in the field of outsourced semiconductor manufacturing, having been contracted by IBM to manufacture semiconductors that IBM had designed but could not produce while he was working for Texas Instruments (US). TSMC has published on its website the secrets to eliminating yield issues, a key point in the mass production application of EUV lithography. This is achieved through steady efforts to identify the source of foreign particles on the mask by analyzing the composition of each particle, and to improve processes to prevent the generation of particles. It is not simply a matter of buying manufacturing equipment and raw materials and pressing a switch to mass produce. The essence of advanced semiconductor manufacturing, including EUV lithography, lies in manufacturing technology.

In the ArF process, it was a three-way contest between TSMC, Samsung (Korea), and Intel (US), but with the current generation of EUV, Intel has dropped out, and Samsung is now in hot pursuit of TSMC, which has a commanding lead.

Promising Fields of Application

Mobile devices

The first lithography tool for the current generation of EUV lithography volume production was shipped by ASML (Netherlands) in 2016. Four years have passed since then, and products equipped with semiconductors manufactured by EUV lithography are finally available in the market. The notebooks released by Apple (US) in November 2020 (MacBook Air, MacBook Pro, and Mac mini) contain the M1 processor, designed by Apple and manufactured by TSMC (Taiwan) using EUV lithography technology. Like the current generation of EUV lithography, it is likely that next-generation EUV lithography will initially be applied to devices such as smartphones, laptops, wearable devices, and game consoles, and will penetrate the market by satisfying the demand for new functional add-ons that require high-speed processing, such as 5G support and healthcare monitoring. Judging from the rate of performance improvement that TSMC has announced, they are expected to aim for about 20% improvement in processing speed in the event next generation EUV lithography replaces current generation EUV lithography in all the critical parts of each circuit.

Servers

Existing servers are also expected to adopt processors and DRAMs that have been miniaturized by applying EUV lithography due to the increasing demand for lower power consumption arising from decarbonization, circular economy, and other trends. In addition to this, the emergence of new needs such as automated driving, smart cities, and telemedicine will require more servers to analyze and utilize the massive amount of data generated, and the demand for processors and DRAM to be placed in these servers is also expected to increase.

If all the important parts in current generation processes are replaced with next generation processes in the same way as mobile devices, it is expected that power consumption will be reduced by about 40%.

Future Prospects

Continued miniaturization

On top of existing smartphone and server demand, the emergence of new applications such as automated driving, smart cities, and telemedicine as well drives the demand for miniaturization of semiconductors limitlessly. With the successful application of EUV lithography in mass production, next generation EUV lithography offers a roadmap for miniaturization to the 3 nm generation and technically to the 2 nm generation. However, at the transition from the current generation to the next generation, it will be necessary to respond to many changes in each elemental technology as summarized in Figure 8, including manufacturing equipment, materials, and manufacturing technology, and fierce competition is to continue in development.

Figure 8: Possible changes required in elemental technologies to progress from current-generation to next-generation EUV lithography

Elemental technology	Changes expected in the progress from the current generation to the next
Lithography equipment	The optics and equipment will become even larger and more expensive to increase the numerical aperture from 0.33 to 0.55.
Mask	Both mask blanks and electron beam printing require even higher precision and durability.
Photoresist	The transition from existing resin-based resists to metal-based and nanoparticle-based resists may begin from the 2 nm generation.
Developing solution	Not only the solution itself, but also filter performance requirements to remove foreign matter may become more stringent. If the photoresist system changes, the solution will also need to be changed. Etching gas could also be used.
Circuit	The points where cobalt is applied are expected to increase in areas where copper and barrier layers are combined.
Insulating layer	In DRAM, there is a possibility that insulators other than silicon oxide (such as high-k insulators) will be applied in more places.
CMP Slurry	In addition to designing polishing performance to meet the needs of miniaturization, it is expected that requirements for post-polishing removability will become more stringent in order to reduce foreign matter. As with the photoresist, the requirements for filter performance may also become more stringent.
Inspection equipment	In addition to higher inspection performance to meet the needs of miniaturization, it is expected that functions to predict abnormalities using AI etc. and functions to take on-the-spot action such as foreign object removal and repair when an abnormality is detected will increase in importance in the inspections in lithography equipment.
Manufacturing technology	For foundries in particular, the champion will be determined by how quickly they can obtain and use prototypes of next-generation EUV lithography equipment. Accurate decisions on both investment and technological development are required.

Source: Compiled by MGSSI

On the other hand, since the theoretical limit for miniaturization beyond the next generation of EUV lithography is considered to be 0.3 nm – the interatomic distance between atoms, which are the smallest material that can be used for lithography – research and development is in full swing for mass production of technology to increase integration per unit wafer area by implementing 3D stacking of logic. Since 3D integration requires a different control technology than the process on a flat surface, some companies that are struggling to develop EUV lithography, including Intel (US), are hoping that 3D stacking by ArF lithography will turn the tide. However, as the mass production of EUV lithography is getting on track, 3D integration by EUV lithography will probably have a head start over that by ArF lithography when comparing them.

Study of patent application trends regarding EUV lithography

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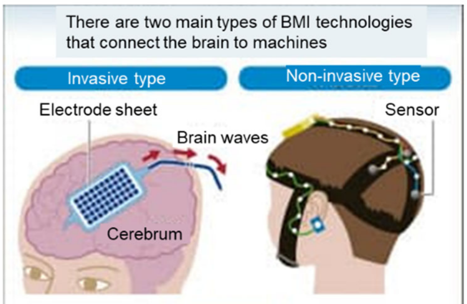
Invasive Brain Machine Interfaces (BMI)
— The future of connecting the brain and digital data —

Akira Yoshimoto, Consumer Innovation Dept., Technology & Innovation Studies Div.

What is Invasive BMI?

A BMI is an interface that inputs and/or outputs brain information to sensors and actuators and other devices; communication networks; and cloud servers (cumulatively referred to as "digital" in this paper for convenience). It is a technology that enables the input and output of brain information without the use of text or voice. BMI can be broadly classified into invasive, which involves surgical procedures, and non-invasive, which involves attaching sensors to the outside of the human body. The invasive type, which is the subject of this paper, directly exchanges electrical and other information with the brain, and is expected to be able to do so with high precision and dimensionality (Figure 1).

Figure 1: Difference between invasive and non-invasive BMI



Measures signals of brain activity by attaching electrodes directly to the brain	**Character -istics**	Measures brain activity by sensors attached to the scalp
Highly accurate measurement of brain waves, etc.	**Merits**	No need to harm the body and less physical burden on the user
Difficult to use easily due to the need for surgical procedure	**Demerits**	A limited signal is obtained, and even blinking or sweating can cause noise in the signal

Note: Figure based on data from the National Institute of Advanced Industrial Science and Technology (AIST) and other sources

Source: The Nikkei
https://www.nikkei.com/article/DGXLZO16842470V20C17A5TJN000

Although this field has been studied for many years under the umbrella of brain science, there are three reasons why it now deserves attention. The first is that private companies such as Neuralink, founded by Elon Musk, who leads Tesla, and other people, are beginning to enter the market to implement the technology with combinations of general-purpose devices. Secondly, as a byproduct of the development of deep learning, it has become widespread to mimic the circuits of the human brain in the digital world, and as a result, the "common format" of information exchange between the digital world and the human brain is now complete. Finally, as the importance of data is being recognized by society, there is an increased need to recognize the possibility of obtaining information that is more closely related to human thoughts and preferences in the not-too-distant future.

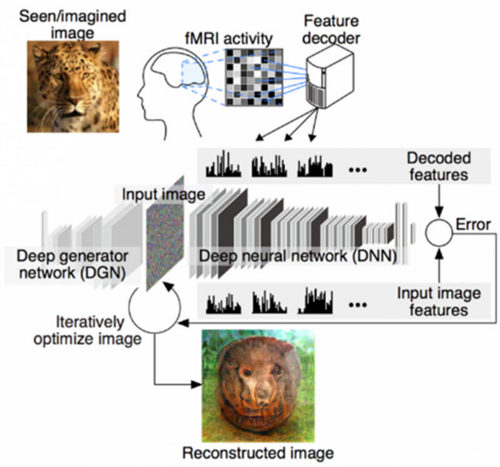
Consciousness to digital; digital to consciousness

The information in the brain includes not only the information by which to move ones' own body, but also information to convey to other people. When information is sent by voice, language, or gesture and received through sight, hearing or other of the five senses, it is often difficult to communicate correctly due to differences in interpretation or noise resulting from the indirect exchange of brain information. BMI offers the possibility of being able to resolve these problems, which will enable communication through thought.

In a study reported in the Proceedings of the National Academy of Sciences of the United States of America (PNAS)[16] in 2013, monkeys were made to learn in advance to shift their gaze when their finger was touched, and when the signal "finger touched" was sent from an electrode implanted in the brain, they shifted their gaze in the same way even though they were not actually touched. This is an example of information transfer directly to the brain. By extending this technology, it will be possible not only to transmit information directly from brain-to-brain without any discrepancy or noise, but also to communicate between humans and digital devices.

In addition, the Kamitani Laboratory at Kyoto University has reported the results of restoring images seen by subjects from brain activity obtained by non-invasive BMI (Figure 2). What is noteworthy here is the use of deep learning, which mimics human brain functions, to digitally reproduce the process of recognizing input image information, albeit in a rough manner. This means that the digital side is becoming ready to accept the information of the human brain through deep learning research.

Figure 2: Mechanism for applying deep learning to restoring information obtained visually from brain waves



Source: Deep image reconstruction from human brain activity
Guohua Shen, Tomoyasu Horikawa, Kei Majima, Yukiyasu Kamitani
https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1006633

The ability to reproduce consciousness digitally means that consciousness degraded due to memory loss, dementia, or trauma-induced brain damage can be supplemented by external digital technology. Furthermore, this consciousness does not have to belong to the person. In other words, it will be possible to acquire consciousness that has been created digitally or by others, i.e., thoughts and cognitive abilities that the person does not possess, like an app on a smartphone.

Useful Fields of Application

Artificial limbs and human augmentation

Prosthetic engineering is the art of replacing a part of the human body missing due to congenital or other reason with an

16 Active tactile exploration using a brain-machine-brain interface Joseph E O'Doherty 1, Mikhail A Lebedev, Peter J Ifft, Katie Z Zhuang, Solaiman Shokur, Hannes Bleuler, Miguel A L Nicolelis https://pubmed.ncbi.nlm.nih.gov/21976021/

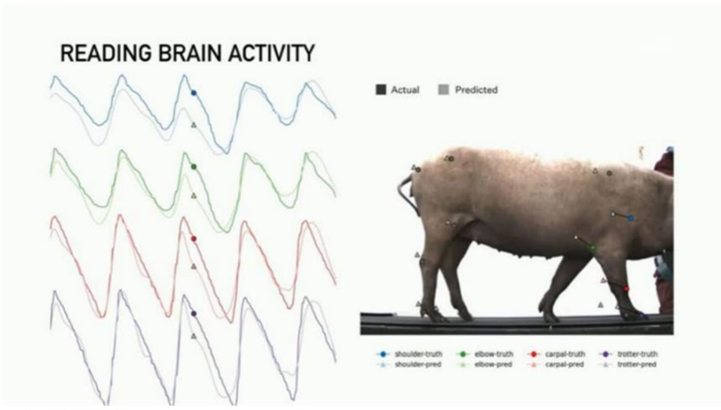
apparatus, such as a prosthetic hand or leg. In order to make them move in the same way as the user's own body, it is necessary to detect and transmit the command signals issued by the brain, which is why there are high expectations for BMI. Already in 2012, a case was reported in which a patient whose limbs were paralyzed due to a stroke was able to move a robotic prosthetic hand and drink coffee based on information from electrodes implanted in the brain (Figure 3).

In research results published by Neuralink in 2020, it was reported that leg movements predicted from information obtained by implanting electrodes in the brains of pigs were almost identical to their actual movements. In other words, technology is being established that can obtain accurate limb movement command information from the brain (Figure 4).

Figure 3: Using a robotic prosthetic hand to drink coffee based on information from electrodes inserted into the brain

Source: Nature
https://www.nature.com/news/mind-controlled-robot-arms-show-promise-1.10652

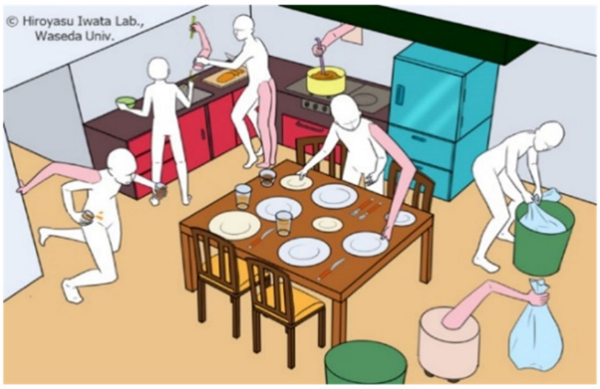
Figure 4: Accurate leg movement commands obtained from BMI implanted in pig brains



Source: Neuralink
https://www.youtube.com/watch?v=DVvmgjBL74w&feature=emb_logo

This kind of technology could be used for human augmentation, for example, attaching a robotic arm or other device to one's body, a wall, etc. that one can manipulate at will, just like one's own limbs. This has the potential to create new convenience, lifestyles, and hobbies (Figure 5).

Figure 5: Human augmentation by freely movable arms and legs attached to one's own body, moving objects, walls, etc.



Source: Iwata Laboratory, Waseda University

Medical field: treatment of depression, anxiety, and other mental disorders

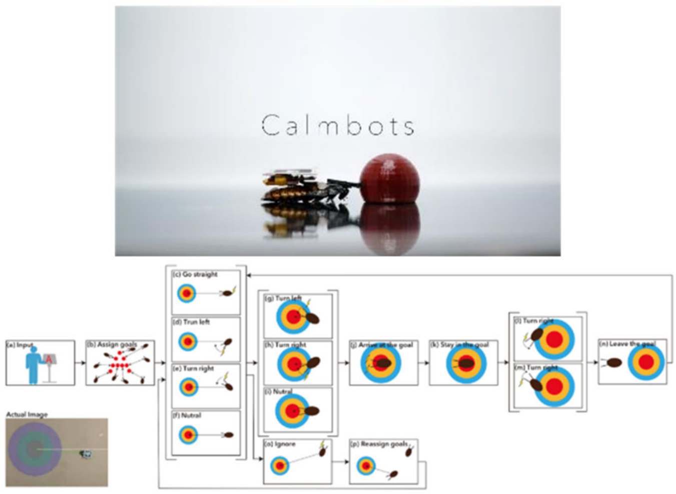
The fact that the brain can be fed information from the digital side means that, for example, the symptoms of mental illnesses such as depression can be improved by sending the patient information that has been prepared in advance.

Neuralink states, "if you can correct these signals (sent by neurons to your brain), you can solve everything from memory loss to hearing loss, blindness, paralysis, depression, insomnia, extreme pain, seizures, anxiety, addiction, strokes, brain damage. These can all be solved with an implantable Neuralink.” Mitsuo Kawato, a fellow at the Advanced Telecommunications Research Institute International (ATR), is monitoring the brain activity of patients with post-traumatic stress disorder, depression, and autism to understand the differences between them and healthy subjects, suggesting the possibility of diagnosis and treatment through training.

Animal and insect IoT

The application of invasive BMI is not limited to humans. The University of Tsukuba has reported the results of an experiment in which electrodes were inserted into the antennae and cercus of Madagascar cockroaches to control them by electrical stimulation (Figure 6). They were able to make them push and carry objects, and write with a brush. Applying this technology will make it possible to freely manipulate animals and insects and acquire information obtained by them, enabling them to function as an IoT. In this way, digital may be combined with the information held by animals to form a network that collects a variety of information from various locations at low cost.

Figure 6: Experiments with Calmbots (controlling cockroaches) at University of Tsukuba



Source: ITmedia
https://www.itmedia.co.jp/news/articles/2012/01/news098.html

Future Outlook: Technical and Ethical Issues

The cutting edge of social implementation of invasive BMI — democratization of invasive BMI pioneered by Neuralink —

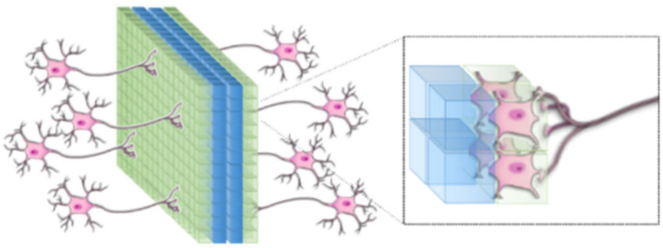
Brain science itself has been studied for a long time, but what has been lacking so far is the field of applied technology, that is, the implementation and dissemination of such technology in society. The aforementioned company, Neuralink, is strongly promoting this aspect. Its BMI, Link, has been approved by the U.S. Food and Drug Administration (FDA) on the Breakthrough Devices Program, and is awaiting approval to be tested on human subjects while steadily verifying safety. One of the technologies supporting the company is surgical robots. It takes a skilled doctor about 10 minutes to precisely insert each BMI electrode into the designated areas of the brain. Neuralink's V2 robot (Figure 7) can replace this elaborate and generalize it like LASIK surgery, according to Elon Musk. Social implementation will only proceed when the technology to apply it in a legally-compliant manner is in place, combined with a cost of about USD 1,000, which would enable diffusion. There is little doubt at this point that Elon Musk, who is backing these efforts with a huge amount of money, will be the driving force behind the awareness, education, and popularization of invasive BMI.

Figure 7: Neuralink's V2 surgical robot that implants a BMI in the brain

Source: Neuralink
https://www.youtube.com/watch?v=DVvmgjBL74w&feature=emb_logo

In addition, it is expected that the company's efforts to lobby for legislation and lay the groundwork for the technology will greatly advance the research activities of other companies. The Japanese firm MinD in a Device is one such company. MinD in a Device is working on a new type of BMI that uses CMOS sensor technology to place two-dimensional, high-density, double-sided arrays of electrodes across the corpus callosum, the area where information is exchanged between the left and right hemispheres to link them together (Figure 8). By embedding cultured neurons in the coating layer of the sensor to create an organic-inorganic interface, they aim to achieve long-term stable reading and writing of information, and by measuring and electrically stimulating the axons of the neurons, they hope to eliminate the discrepancy[17] between reading and writing of neurons of existing invasive BMIs, thus realizing true high-density BMI for the first time. If the legal framework is put in place through the efforts of Neuralink and the like, the company has the potential to make great strides in this field using its brain science and AI technologies.

Figure 8: MinD in a Device's nerve bundle cross-sectional measuring BMI



Source: Courtesy of MinD in a Device

Ethical issues

On the other hand, as well as legal issues, ethical issues are of key importance. Industry has a history of pioneering procedures that were difficult to perform in line with earlier values, while considering the balance between safety, convenience, and the benefits, such as Jenner's smallpox vaccination using cowpox long ago, and more recently, LASIK surgery to restore eyesight, and implantable devices with chips implanted in the hands that can be used for national railway passes, etc., which are being put to practical use in Sweden. Such matters eventually have to be resolved according to the common understanding of medical research, such as the Declaration of Helsinki, and the debate on whether or not to test on primates and other animals. Based on the above, it is expected that the application of invasive

[17] Dr. Clay Reid of Harvard University pointed this out in a paper (Histed et al., Neuron 2009).

BMI to the human body will start with a prosthetic engineering approach to compensate for functions missing due to accidents or congenital factors, rather than with healthy people, and Neuralink has made a statement to this effect.

However, BMI has the potential to read human consciousness, such as preferences and thoughts and write it down from outside. This will raise a number of issues, including violation of privacy, use in ideological education, and misuse of drug-like substances within the brain. In order to handle this technology correctly, it will be necessary to establish operational rules for the protection of privacy and utilization of personal information that are stricter and more global than ever before, and to have a system in which all these activities are judged in a diverse, ethical, and detailed manner.

If these issues are solved, for example, BMI can be used as an interface for smartphones and AR goggles to improve convenience; in the treatment of mental disorders; and in prosthetic engineering to solve various social problems such as aging and barrier-free access. In addition, the technology also offers the potential for new sports and musical instruments using third and fourth prosthetic arms that can be manipulated at will. Furthermore, if we can download consciousness into the brain, the concept of school and examinations will change dramatically. In this way, BMI may bring about immeasurable social change, such as satisfying the desire for self-actualization and radically changing the values of society. It will be important to think about how we will be affected when such a BMI society arrives and the impact we should have on it, while focusing on the fact that this is no longer science fiction and social implementation is already underway.

Study of patent application trends regarding BMI (Brain Machine Interfaces)

Study of Patent Application Trends Regarding *Technologies to Watch in 2021*

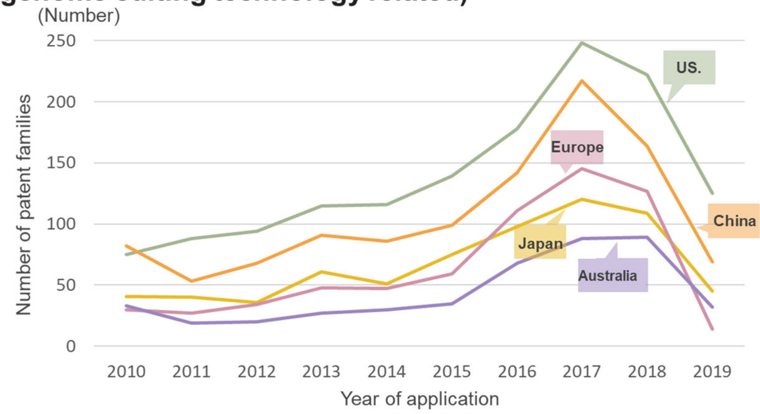
Yui Matsuura, Intellectual Property Dept., Technology & Innovation Studies Div.

This section reports from various perspectives on patent application trends for each technology for the four themes discussed in *Technologies to Watch in 2021*: prime editing, super clocks, EUV Lithography, and Brain Machine Interfaces (BMI).

Patent Application Trends Regarding Prime Editing (Genome Editing Technology)

Because the number of patent applications for prime editing is still small, we will look at the trends in patent applications for genome editing technologies, including prime editing. The number of patent applications related to genome editing technology in recent years (2010-2019) by country/region (Figure 1) was 1,400 in the US, 1,071 in China, 676 in Japan, 642 in Europe, and 441 in Australia. These patent applications have been issued in various countries and regions, mainly based on 959 applications first filed in China, 629 applications first filed in the United States, 50 applications first filed in Japan, and 44 applications first filed in Europe. Note that the number of applications in 2018 and 2019 appears to be decreasing due to the existence of unpublished applications.

Figure 1: Number of patent applications by country (genome editing technology related)



Source: Compiled by MGSSI, based on data from Questel's global patent search database Orbit Intelligence

A PCT international application has already been filed for prime editing by Professor Liu and colleagues at the Broad Institute (WO 2020/191153). A single PCT application has the same effect as filing simultaneously in all PCT member countries[18]. However, it is not possible to obtain a patent right by filing a PCT application alone, and it is necessary to select the countries in which one wishes to obtain a patent right after filing the application. As the application is not yet finalized in the countries, it is worth noting in which countries application will be filed.

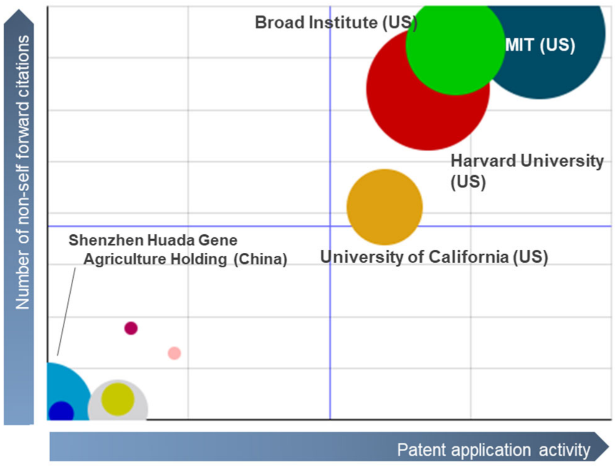
The top five applicants (in terms of number) for patents in genome editing technology are, in order, MIT (US), Harvard University

[18] 153 countries as of January 2021.

(US), Broad Institute (US), Shenzhen Huada Gene Agriculture Holding (China), and University of California (US).

Figure 2 shows the patent application activity of the top applicants (horizontal axis), the number of non-self forward citations (vertical axis), and the number of patent applications (bubble size). The number of non-self forward citations is a value that indicates whether a patent is cited in the examination of subsequent patents, etc. The more a patent is cited by subsequent patents, the more influential and important the patent is considered to be, and the higher the value and quality of the patent[19]. It can be seen that the three institutions MIT, Harvard University, and the Broad Institute are actively applying for patents and are highly influential. On the other hand, Shenzhen Huada Gene Agriculture Holding, which ranked fourth in terms of the number of applications, has not continued to file applications to date because its activity is zero, indicating that its influence is low in relation to the number of applications.

Figure 2: Top applicants and the influence of their patents (genome editing technology related)



Source: Compiled by MGSSI, based on data from Orbit Intelligence

Trends in basic patents on genome editing technology

A basic patent refers to a patent that covers the basic technology of a new concept and must be used to implement that technology. It is very powerful in that it cannot be avoided, and having a basic patent can be very advantageous for business.

Concerning the basic patent for CRISPR-Cas9, it has been disputed as to who invented it first. The main players are the Broad Institute (priority date: December 12, 2012), which was the first to be granted a basic patent in the US, and the University of California (priority date: May 25, 2012), which was granted patentability later. The basic patent for CRISPR-Cas9 continues to be a complicated case, as the battle, which has attracted worldwide attention, includes outsiders such as the Vilnius University in Lithuania (priority date: March 20, 2012), which filed earlier than both of them.

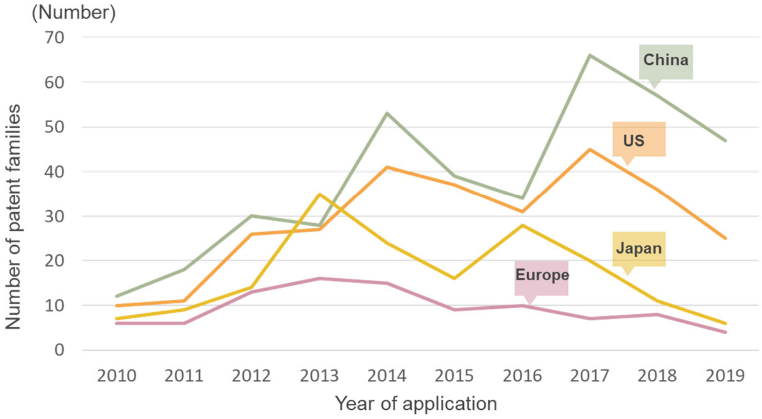
The reason why academic institutions such as the Broad Institute and the University of California obtain basic patents is to license them to a number of companies and use the revenue to further research genome editing technology. Their position is that they do not intend to monopolize research and that they will not restrict use in non-commercial research.

[19]For example, see the following reference. Yasukawa, S. (2017) Patent Vol. 70 No. 4 73-87

Patent Application Trends Regarding Super Clocks

The number of patent applications related to super clocks is on the rise (Figure 3), and the ratio of applications by country/region from 2009 to 2018 was 35% in China, 26% in the US, 15% in Japan, and 9% in Europe. Note that the number of applications in 2018 and 2019 appears to be decreasing due to the existence of unpublished applications.

Figure 3: Number of patent applications by country (super clock related)



Source: Compiled by MGSSI, based on data from Questel's global patent search database Orbit Intelligence

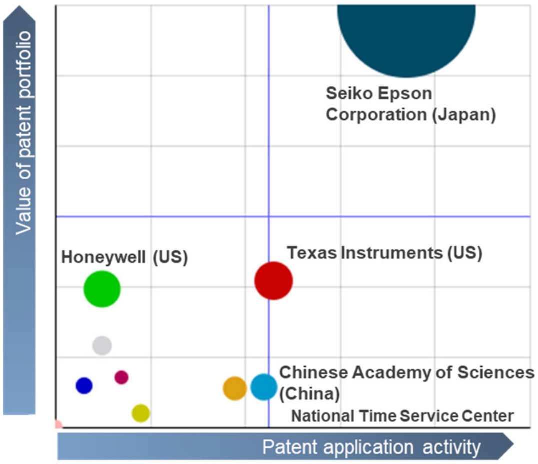
While Japanese applicants file 80% of their applications in the US, China, Europe, etc., US applicants file 50% of their applications in foreign countries, and Chinese applicants file only 5% of their applications overseas. The coverage of applications from China is mostly within China itself, and the large number of applications is not considered to be a threat to business outside of China.

The top applicants (in terms of number) for patents related to super clocks are, in order, Seiko Epson (Japan), Texas Instruments (US), Honeywell (US), and the Chinese Academy of Sciences (China), with Chinese universities and research institutes following from there on. China has many patents originating from universities, and the reason for this is that universities and other institutions are encouraged to invent and apply for patents. China has a top-down system of industry-academia collaboration focused on national policy goals, and universities and other institutions can be considered to be conducting research and development of super clocks under government-led policies.

Figure 4 shows the patent application activity of the top applicants (horizontal axis), the value of their patent portfolio[20] (vertical axis), and the number of patent applications (bubble size). Top-ranking Seiko Epson is far ahead of the competition and could become the IP leader in this field.

[20]An index calculated by taking into account the number of forward citations, years remaining, and country of application.

Figure 4: Top applicants and their patent portfolio value (super clock related)



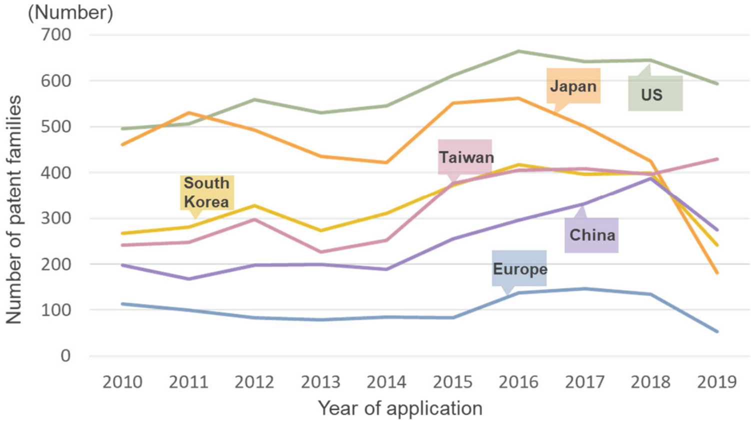
Source: Compiled by MGSSI, based on data from Orbit Intelligence

Professor Hidetoshi Katori of the University of Tokyo is also an inventor and has filed patent applications, although he is not included in the ranking. The latest application he has published is Radiation Shield and an Optical Lattice Clock Using It (JP2019-129166A) [in Japanese].

Patent Application Trends Regarding EUV Lithography

The number of patent applications related to EUV lithography in recent years (2010-2019) by country/region (Figure 5) was 5,795 in the US, 4,562 in Japan, 3,287 in South Korea, 3,280 in Taiwan, 2,497 in China, and 1,014 in Europe. Where the US and Japan were leading, South Korea, Taiwan, and China appear to be catching up. Note that the number of applications in 2018 and 2019 appears to be decreasing due to the existence of unpublished applications.

Figure 5: Number of patent applications by country (EUV lithography related)



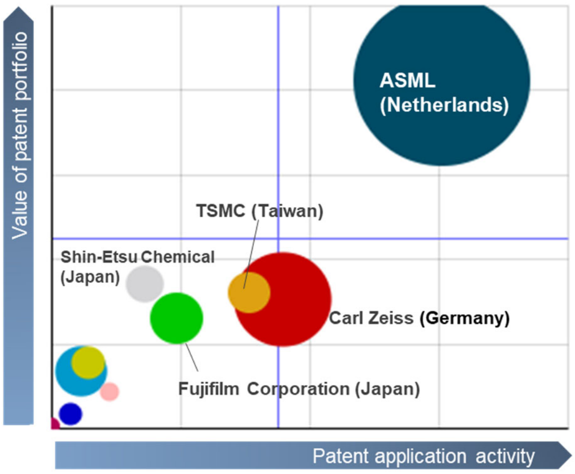
Source: Compiled by MGSSI, based on data from Questel's global patent search database Orbit Intelligence

The number of applications includes both applications filed by domestic applicants and those filed by foreign applicants. For example, the number of applications filed in Japan includes applications from Japan, the US, Germany, Europe, Korea, and other countries. The decline in the number of applications filed in Japan is due to a decrease in the number of applications filed by domestic applicants and a decrease in the number of applications filed by US applicants.

The top five applicants (in terms of number) for patents related to EUV lithography are, in order, ASML (Netherlands), Carl Zeiss (Germany), TSMC (Taiwan), Fujifilm (Japan), and Shin-Etsu Chemical (Japan). ASML and Carl Zeiss have many applications related to lithography equipment technology, TSMC has many related to process technology, and Fujifilm and Shin-Etsu Chemical have many related to photoresist.

Figure 6 shows the patent application activity of the top applicants (horizontal axis), the value of their patent portfolio[21] (vertical axis), and the number of patent applications (bubble size). The dominant position is held by ASML. As the only equipment manufacturer that can supply EUV lithography equipment, ASML may also be the only one with a patent strategy.

Figure 6: Top applicants and their patent portfolio value (EUV lithography related)



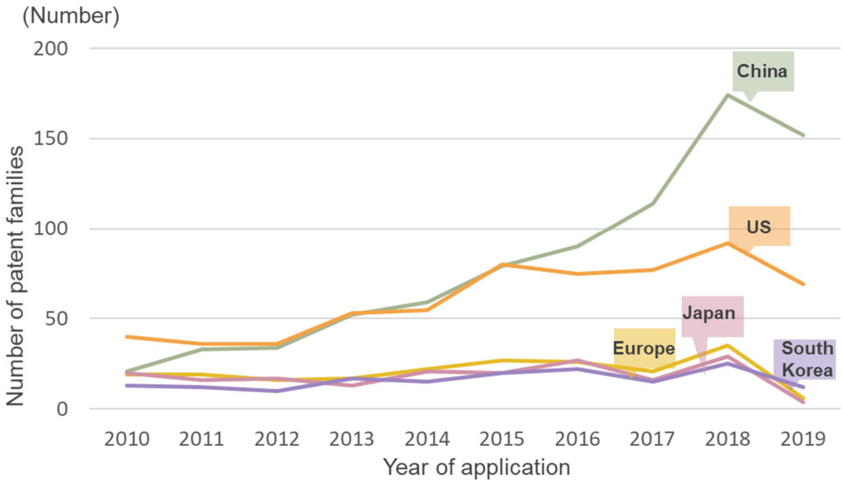
Source: Compiled by MGSSI, based on data from Orbit Intelligence

Patent Application Trends Regarding BMI

The number of patent applications related to BMI in recent years (2010-2019) by country/region (Figure 7) was 808 in China, 613 in the US, 208 in Europe, 183 in Japan, and 161 in South Korea. Note that the search was conducted using the keywords "BRAIN MACHINE INTERFACE" or "BRAIN COMPUTER INTERFACE" and did not distinguish between invasive and non-invasive types. The number of applications in 2019 appears to be decreasing due to the existence of unpublished applications.

[21] An index calculated by taking into account the number of forward citations, years remaining, and country of application.

Figure 7: Trends in patent applications by country (BMI-related)



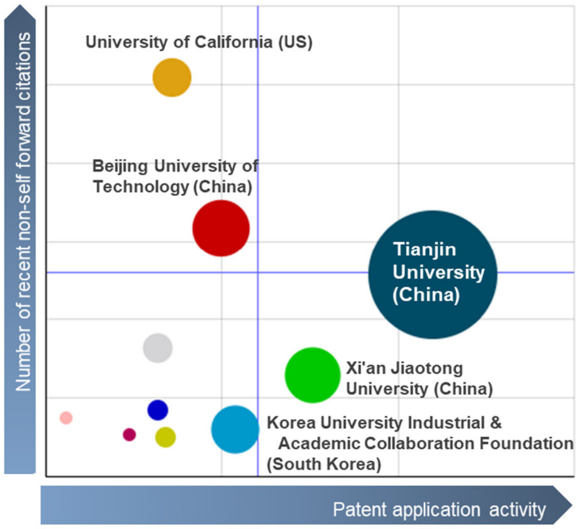
Source: Compiled by MGSSI, based on data from Questel's global patent search database Orbit Intelligence

From 2012 to around 2015, the number of applications filed in the US and China was almost the same, but from 2016 onward, the gap became larger. Europe, Japan, and South Korea rank joint third after China and the US in terms of the number of applications filed, but the number of their applications has remained flat, and the gap with China and the US has not narrowed.

The top five applicants (in terms of number) for patents related to BMI are, in order, Tianjin University (China), Beijing University of Technology (China), Xi'an Jiaotong University (China), Korea University Industrial & Academic Collaboration Foundation (South Korea), University of California (US). Universities and research institutions follow from thereon. The highest ranked company is Panasonic (Japan), which ranks 12th.

Figure 8 shows the patent application activity of the top applicants (horizontal axis), the number of most recent non-self forward citations (vertical axis), and the number of patent applications (bubble size). The number of non-self forward citations is a value that indicates whether a patent is cited in the examination of subsequent patents, etc. The more a patent is cited by subsequent patents, the more influential and important the patent is considered to be, and the higher the value and quality of the patent. Tianjin University is actively filing for patents and has a large number of patent applications, but it loses in patent influence to the University of California, which has about one-third the number of patent applications.

Figure 8: Top applicants and the influence of their patents (BMI-related)



Source: Compiled by MGSSI, based on data from Orbit Intelligence

Summary of Technologies Highlighted in 2020

(Human Augmentation, Implantable Devices, Photon Technology)

The following briefly summarizes the subsequent developments in human augmentation, implantable devices, and photon technology, which were discussed in *Technologies to Watch in 2020* published in January last year.

Human Augmentation

The 2020 report stated that human augmentation is a technology that uses AI, sensing, and actuation technologies to augment human capabilities, and will be used in prosthetic engineering and telexistence.

COVID-19 had a large impact in 2020, as people were greatly restricted in their mobility, which greatly facilitated remote communication such as web conferencing, telecommuting, and telemedicine. This means that the groundwork for telexistence is being laid. In addition, many teleoperated avatar robots produced by, for example, avatar-in, Ory Laboratories, and Mira Robotics in Japan, have been implemented in society since non-contact communication was recommended due to the spread of COVID-19. In addition, the launch of commercial 5G communication services in Japan and many other developed countries is likely to be a tailwind for the future roll-out of telexistence.

In the field of prosthetic engineering, CYBATHLON 2020 was scheduled to be held in Zurich, Switzerland in May, but due to COVID-19 disaster, 55 teams from 21 countries competed at different sites, and the results were broadcast online in November. In Japan, competitions in the powered wheelchair and powered leg prosthesis (Tokyo venue only) categories were held at venues in Tokyo and Kansai, with Keio University's Fortississimo taking third place and Wakayama University's RT-Movers taking fourth place in the wheelchair category. In contrast to the Paralympics, the CYBATHLON is a competition in which engineers and people with disabilities solve problems by focusing on movements necessary for daily life, and recognition of such activities will bring us closer to a true barrier-free society. (Akira Yoshimoto, Consumer Innovation Dept.)

Implantable Devices

Implantable devices have emerged as ICT devices have become smaller and wireless communication technology has evolved. Although so far application has been mainly for serious diseases, the 2020 report mentioned the possibility of expansion to the field of preventive medicine, especially for patients at high risk of heart failure.

In 2020, COVID-19 spread and mortality of COVID-19 in patients with a history of cardiovascular disease was four times higher than in patients without comorbidities[22]. The importance of home care for patients with heart failure utilizing implantable devices was further increased due to the need to reduce the risk of exposure to COVID-19. In February, a 970-patient clinical trial (PROACTIVE-HF trial) was initiated at 38 sites, including Tufts Medical Center in the US, to

[22] Fan Yang et al, Analysis of 92 deceased patients with COVID-19, J Med Virol. 2020 Nov;92(11):2511-2515.

optimize home care using the implantable device Cordella Pulmonary Artery Pressure Sensor System (Endotronix), and a clinical trial (SIRONA 2 trial) is also being conducted in Europe. The implantable device can be used to collect pulmonary artery pressure data from people at high risk of heart failure in less than five minutes and share it remotely with care providers, enabling preventive early intervention by matching it with comprehensive medical data over time. Clinical trials currently being conducted in the US received Category B Investigational Device Exemption (IDE) trial approval from the Centers for Medicare & Medicaid Services (the U.S. Department of Health and Human Services' public insurance program administration center) in 2019, with the costs of the trial covered by public health care funding. Implantable devices are steadily making their way toward social implementation in the field of preventive medicine. (Mika Kinoshita, Consumer Innovation Dept.)

Photon Technology

Photon technology is a basic technology using light — that is, electromagnetic waves classified into ultraviolet light, visible light, and infrared light — for various applications by making use of both the wave and particle properties inherent in light. The 2020 report described the development trends of optical tweezers, photoimmunotherapy, and optical lattice clocks.

With regards to trends in optical technology, research and development of optical devices, optical measurement and analysis equipment, and optical information processing equipment, which use the typically analogue "light," continued to produce steady results in 2020. Among them, the quantum Internet has attracted much attention as mentioned in last year's report, and remarkable results have been produced in this field.

The country with the most notable achievements in the field of quantum Internet in 2020 is China. In January 2020, Micius (Quantum Experiments at Space Scale) satellite and the Beijing–Shanghai Quantum Secure Communication Backbone were connected to form a link between space and the ground. Then in June, the same Micius was used for successful quantum cryptography satellite communication over a long distance in excess of 1,000 km.

In the US, on July 23, 2020, the Department of Energy announced a strategy for the development of the quantum Internet[23], and the EU established the Quantum Technologies Flagship in which it will invest € 1 billion (about JPY 125 billion). Japan and Canada are moving forward with plans to create a quantum ICT environment based entirely on photons, combining the quantum Internet, which is the culmination of photon technology, with photonic quantum computers. Trends in the development of quantum Internet, which is expected to become increasingly advanced, and other forms of photon technology will continue to warrant close observation in 2021 and beyond. (Yutaka Abe, Technology Foresight Center)

[23] https://www.energy.gov/articles/us-department-energy-unveils-blueprint-quantum-internet-launch-future-quantum-internet