"臺灣學生未來針對跨領域基礎科學研究的方向”

Future Directions in Basic Research in Multi-disciplinary Science

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Academia Sinica

January 20. 2022

As a scientist, I have lived through an exciting era. Here are a few developments that have inspired me during my lifetime in the three disciplines of science: Physics, Chemistry, and Life Sciences.

Physics

- The development of quantum physics
- Einstein’s general theory of relativity
- Theory of elementary particles
- Discovery of the quarks
- Discovery of the black holes
- Evidence of the Universe’s expansion
- Detection of gravitational waves
- Discovery of superconductivity
- Invention of the transistor
- Invention of the laser

Chemistry

- The nature of the chemical bond
- Relating chemical thermodynamics to statistical physics
- Theory of reaction rates and prediction of chemical reactivity, including the role of catalysts
- Chemical synthesis of natural products and polymers
- Discovery of ferrocene
- Synthesis of Xenon hexafluoride and noble gas compounds
- Development of asymmetric synthesis and organocatalysis
- Understanding photosynthesis, biological N_2 fixation, CH_4 oxidation, O_2 reduction, and water splitting

Life sciences

- Watson-Crick structure of DNA
- The central dogma of molecular biology
- The deciphering of the human genome
- Genome splicing and editing
- Understanding the organization of the cell membrane
- Structure of proteins and their functions
- Bioenergetics: Chemi-osmotic hypothesis and ATP synthesis
- The molecular basis of prion diseases and the role of amyloidogenesis in neurodegeneration

All these accomplishments were the results of basic research driven by intellectual curiosity!

What is Basic Research?

“Basic research or fundamental research is the kind of intellectual exercise that helps expand existing knowledge. It is a type of investigation focused on improving the understanding of nature: the laws of nature, or a a particular phenomenon in nature. This type of research often involves the development of fundamental concepts or theories, but most scientists who do basic research examine data to find the unknown and fulfill a sense of curiosity. Usually, basic research involves the "how," "what" and "why" questions to explain experimental observations. Basic research looks at how processes or concepts work. Information obtained from basic research often creates a foundation for applied studies, which can culminate in new technologies. In this manner, applied research helps to provide solutions to existing problems and meet societal needs.”

Why is basic research important?

- **Without basic research, there will be no new discoveries, ideas and knowledge that will fuel the development of new technologies.**

- **Applied science helps to bring the science closer to the technologies needed for economical development of the country.**

There is basic research in the applied sciences as well!

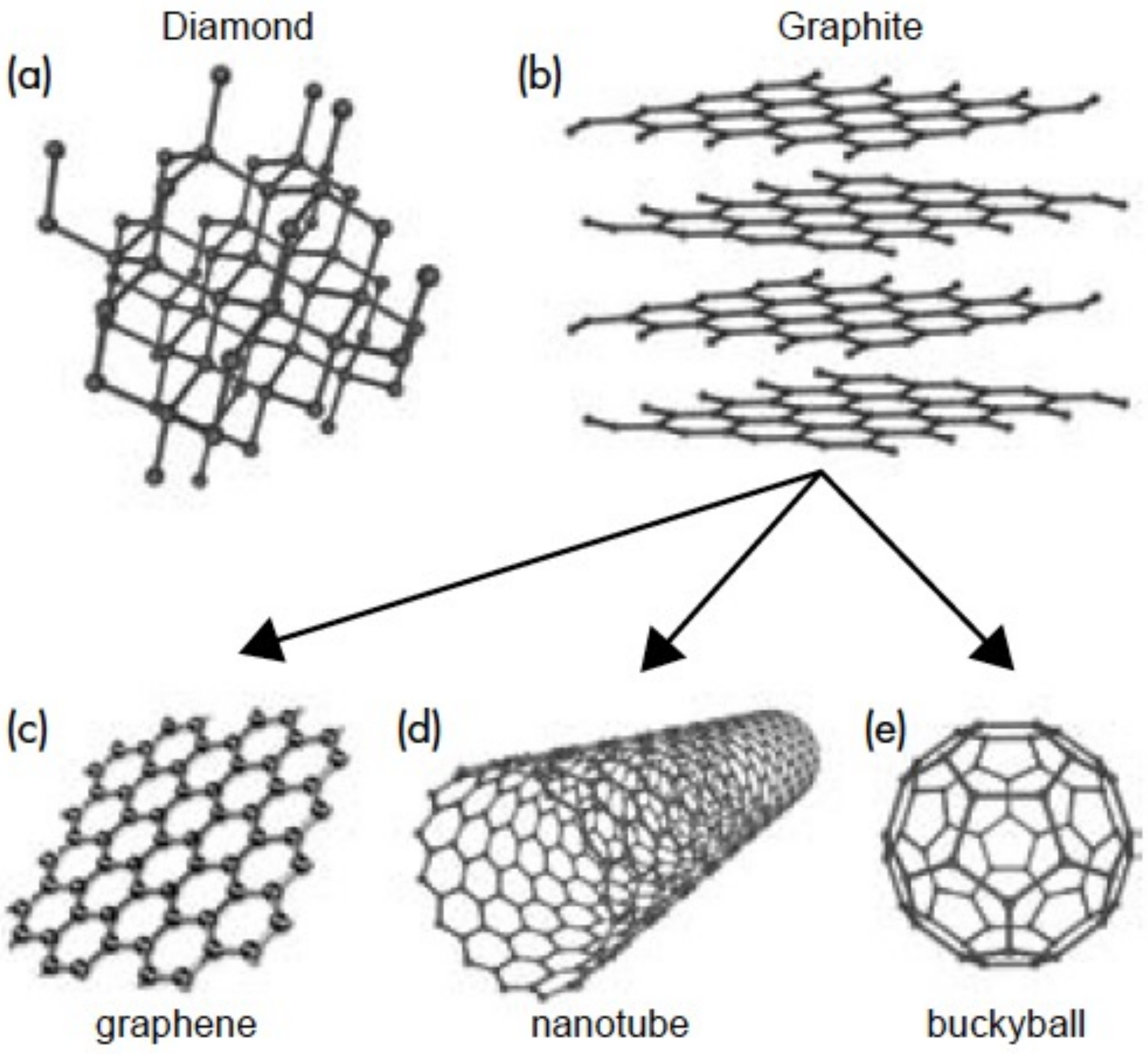
Often times, when performing applied research, one encounters situations wherein the concepts and fundamentals were not really well understood, or the understanding was incomplete or even incorrect, so the opportunity presents itself for the applied scientist to engage in basic or fundamental research! Happens more often that one thinks. Scientists typically analyze a problem under idealized situations. The boundary conditions could be quite different in practical applications and discoveries are made.

A few examples of science driven by intellectual curiosity and/or by potential applications.

Different forms of carbon

J. T. Robinson *et al*. NRL Review (2009) 89-96.

There are two major allotropes of carbon: (a) sp^3-bonded diamond and (b) sp^2-bonded graphite. The applied physicists discovered that the ihe sp^2-bonded allotrope is formable into three low-dimensional structures: (c) 2D sheets known as graphene; (d) !D nanotube, and (e) 0D buckyballs.



- **Buckminsterfullerene, C_{60}, was discovered at Rice University in 1985. Harry Kroto, Richard Smalley and Robert Curl, shared a Nobel Prize in chemistry for its discovery in 1996.**
- **Single-wall carbon nanotubes were discovered in 1993 by Donald S. Bethune of IBM and Sumio Iijima at NEC laboratories. The diameter of a single-wall carbon nanotube is around 0.4–2 nm.**
- **Single-layer graphene was unambiguously produced and identified in 2004 by Andre Geim and Konstantin Novoselov, who were awarded the 2010 Nobel Prize in physics.**

Basic research driven by potential industrial applications.

Grubbs catalysts for olefin metathasis

https://en.wikipedia.org/wiki/Grubbs_catalyst#Applicati
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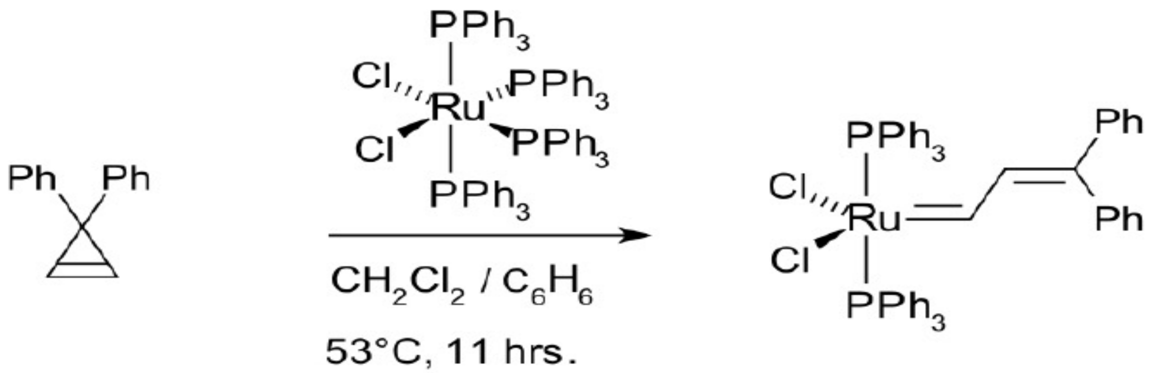
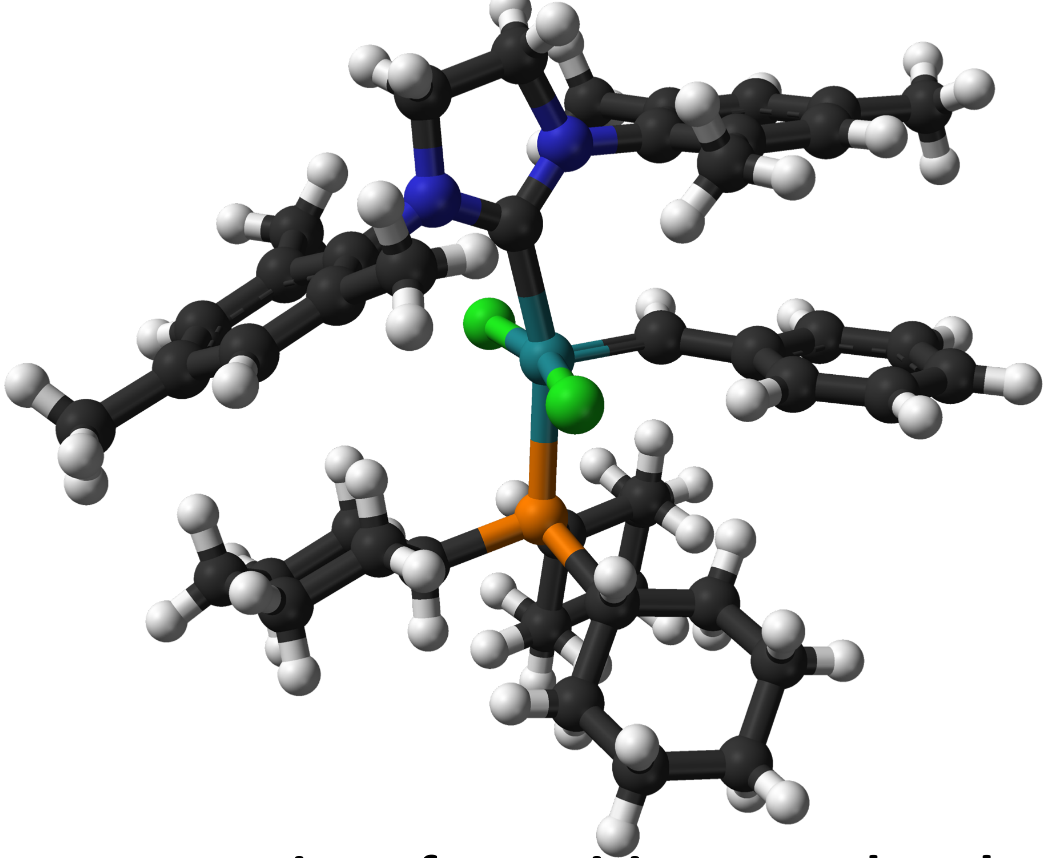
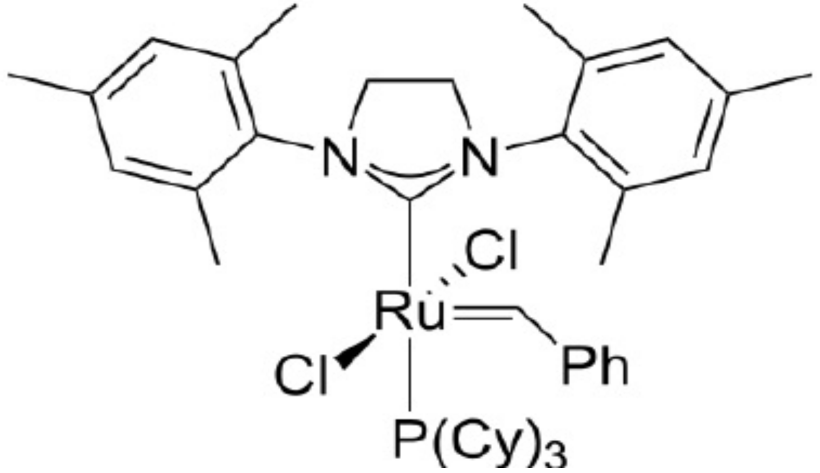




2nd generation Grubbs catalyst



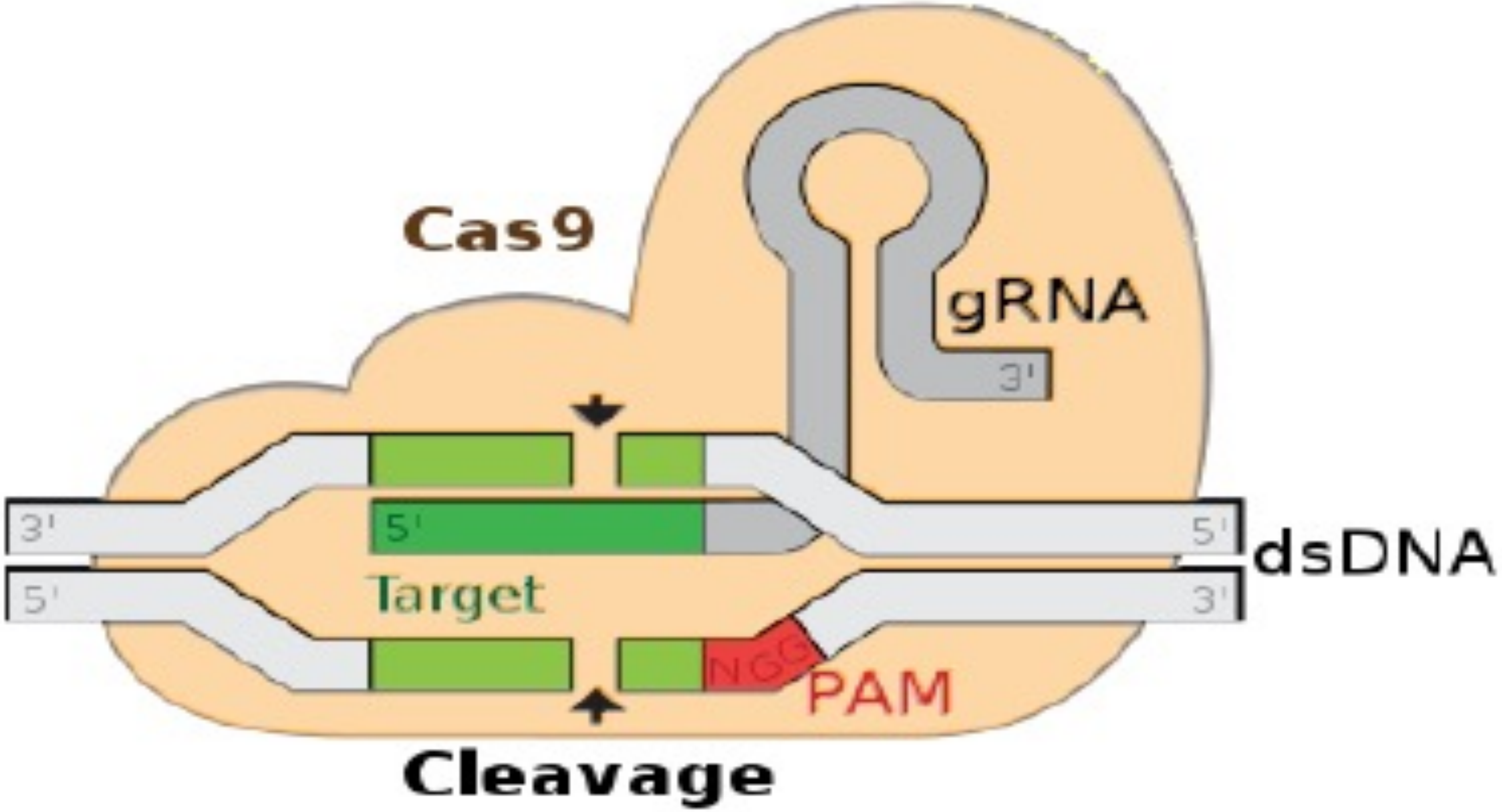
Grubbs catalysts are a series of transition metal carbene complexes used as catalysts for olefin metathesis. They can tolerate many functional groups in the alkene substrates, are air tolerant and compatible with a wide range of solvents. Robert Grubbs shared the 1992 Nobel Prize in Chemistry with Richard Schrock and Yves Chauvin in recognition of their contributions to the development of olefin metathesis.

So the boundaries between basic and applied sciences, or fundamental and applied research, are blurred, as they should be. This situation creeps up not only in the physical sciences but also the life sciences. So basic scientists do applied research; and applied scientists contribute to fundamental understanding of nature!

An example from the life sciences

Jennifer Doudna, a biochemist, solved the three-dimensional structure of the catalytic site of a ribozyme (a RNA enzyme). In 2012, she and her colleagues discovered the CRISPR-Cas9 genome editing technology that reduces the time and work needed to edit genomic DNA. This discovery is based on a protein named Cas9 in the *Streptococcus* bacterial "CRISPR" immune system that cooperates with guide RNA and works like scissors. The protein attacks the DNA of viruses and slices it up, preventing it from infecting the bacterium. This CRISPR-cas9 technology is now widely used for rapid editing of genome DNA in multicellular organisms for applications ranging from fundamental cell biology, plant, and animal research to treatments for diseases including sickle cell anemia, cystic fibrois, Huntington's disease, and HIV. For this major advance, Doudna shared the 2020 Nobel Prize in chemistry with her colleague Emmanuelle Charpentier.

The CRISPR-cas9 complex



https://en.wikipedia.org › wiki › Jennifer_Doudna

Science is organized into disciplines and sub-disciplines.

Physics

Cosmology
Astrophysics
High-energy physics
Theoretical physics
Statistical physics
Solid-state physics
Condensed matter physics
Liquid state physics
Nanoscience
Biological physics
……

Chemistry

Organic
Inorganic
Nuclear
Physical
Chemical physics
Analytical
Biochemistry
Biophysical chemistry
Bioinorganic chemistry
Materials
……

Biology

Microbial
Plants
Cellular & Organismic
Molecular biology
Biochemistry
Genomic science
Biomedical sciences
…….

Applied sciences

Engineering science
Materials
Information sciemce
Atmospheric sciemce
Earth science
Nanoscience and Nanotechnology
……

Scientists are social beings and like to be grouped for self-identity!

Boundaries between disciplines and sub-disciplines have become increasingly blurred in modern times.

- More people doing science.
- Greater scientific networking and communications.
- More borrowing of concepts and methods from one discipline to another.
- More cross-talk and cross fertilization.
- Advances in chemistry and physics, and advanced technologies, are fueling the development of the life sciences, materials sciences, earth science, atmospheric science.
- Research findings in biological sciences are generating new scientific issues and materials for study by the physical scientists.

Inter-disciplinary versus multi-disciplinary science (from NSF)

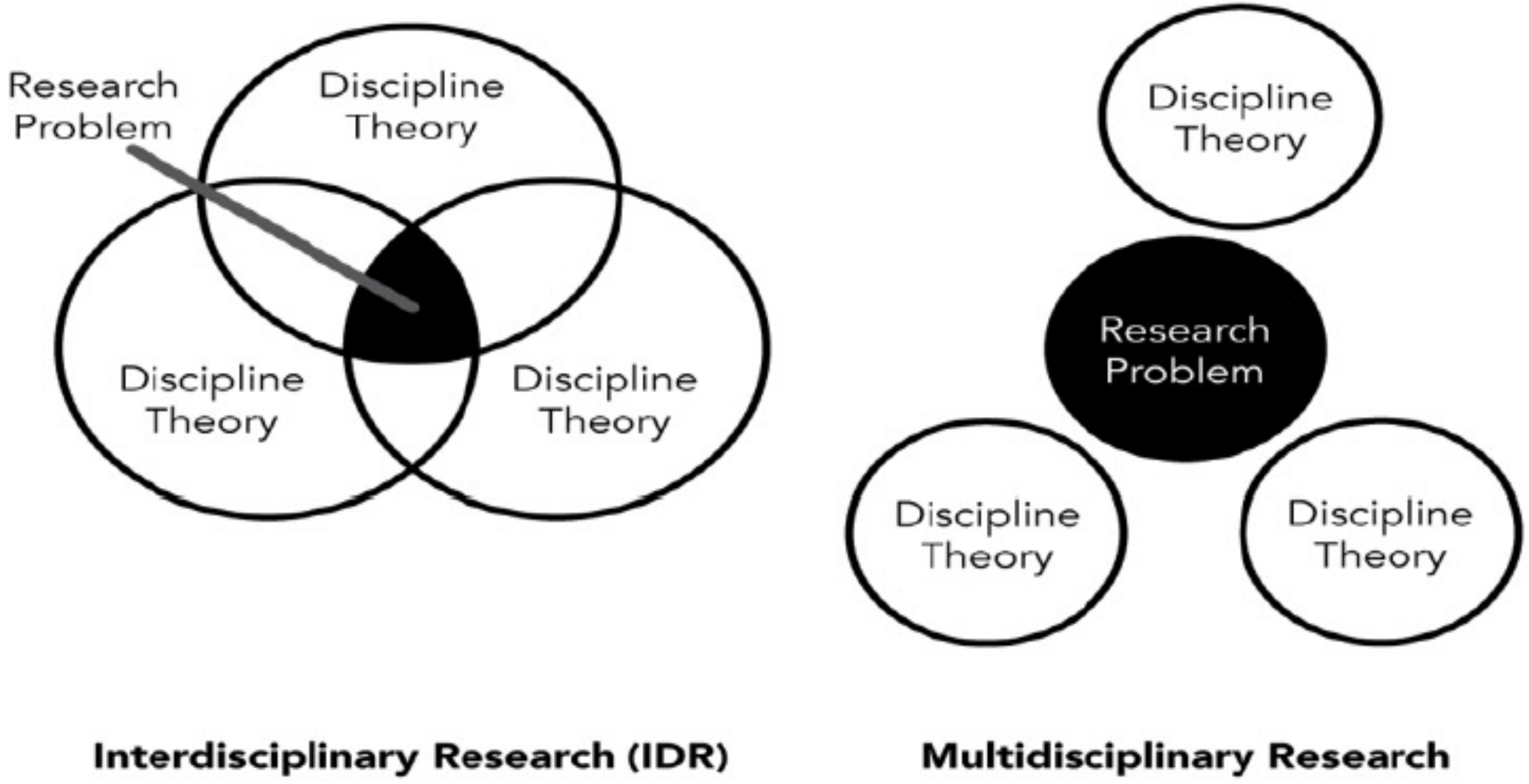
- "A multi-disciplinary approach involves drawing appropriately from multiple disciplines to redefine problems outside of normal boundaries and reach solutions based on a new understanding of complex situations."
- "Inter-disciplinary research is a mode of research by teams or individuals that integrates information, data, techniques, tools, perspectives, concepts, and/or theories from two or more disciplines or bodies of specialized knowledge to advance fundamental understanding or to solve problems whose solutions are beyond the scope of a single discipline or area of research practice."

Difference between multi-disciplinary and inter-disciplinary science

- So when a scientist takes knowledge and methods from multiple disciplines other than his/her own and works independently on an research problem, he/she is doing multi-disciplinary science.
- Inter-disciplinary research relies on shared knowledge from researchers working in different fields. When this happens, a fundamental shift can take place over time and a new inter-disciplinary field emerges.

An example: In research on functional and smart materials, typically chemists synthesize the materials and physicists characterize their properties. Eventually, they created a new field of materials science.

A comparison of multi-disciplinary and inter-disciplinary research



A. S. CohenMiller and P. E. Pate, *The Qualitative Report* **24**, 1211-1226 (2019).

Inter-disciplinary scientific fields

- Materials science
- Earth science
- Information science
- Atmospheric science
- Statistical science
- Energy science
- Applied science

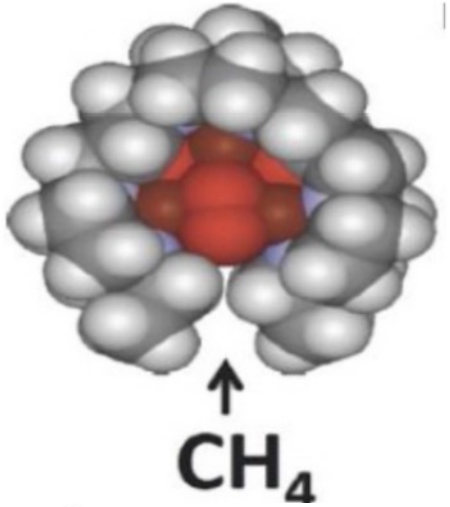
Sunney is a <u>multi-disciplinary</u> scientist!

Sunney's background

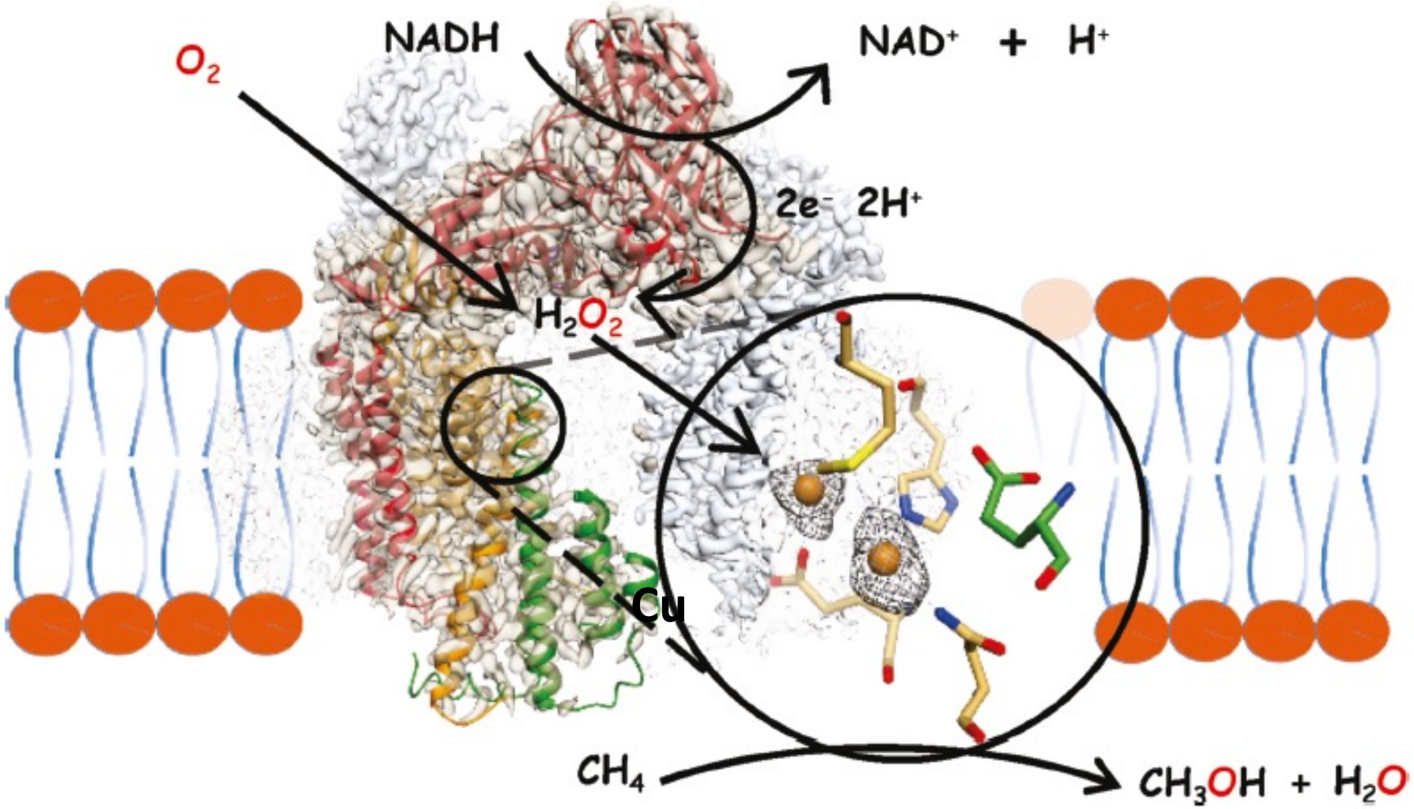
- **My training was in chemistry and molecular physics (B.S. chemical eng.; Ph.D. physical chemistry; Postdoc. Physics).**
- **At the very outset of my career, I elected to take advantage of my background to apply my training in physics and chemistry and solve problems in biology, despite that I knew no biology or biochemistry. (I never took a course in biochemistry, molecular biology, or one in the general life sciences).**
- **I have been a chemist, a physical chemist all these years, who applied the methods of both physics and chemistry to study biological molecules and systems. But the answers to the scientific questions that I have posed are of greater interests to biochemists, biophysicists than mainstream chemists, at least until recent years. So I am a multi-disciplinary scientist.**

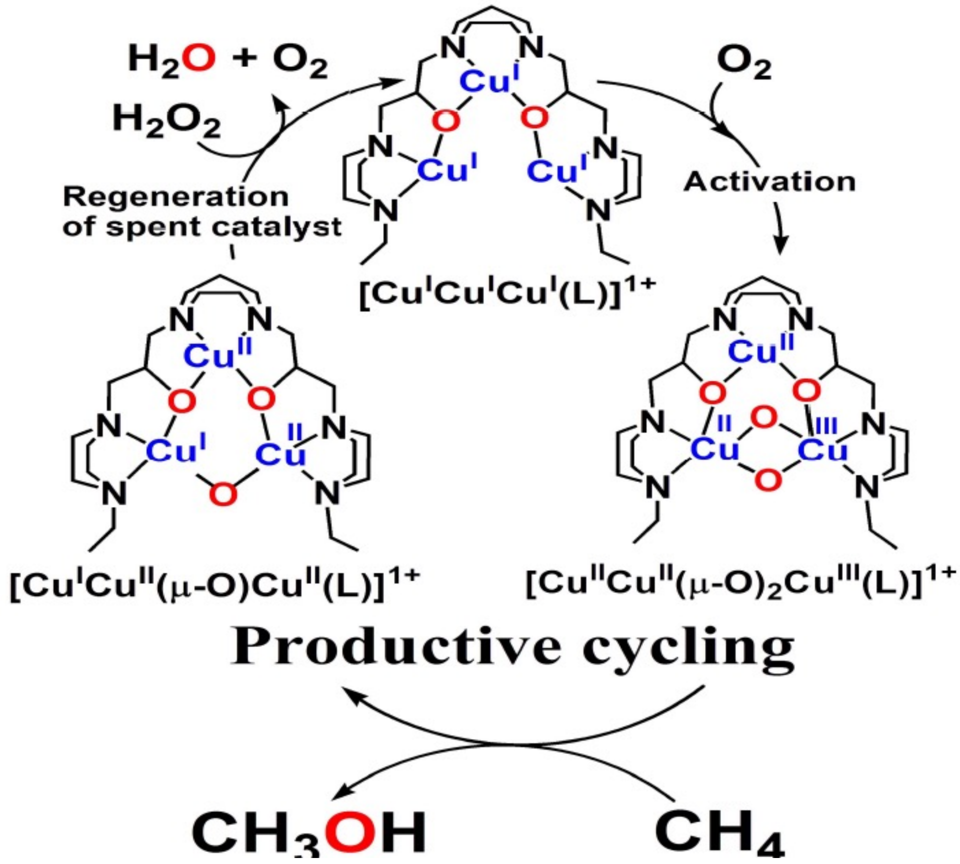
Sunney's recent research on methane oxidation

J. Am. Chem. Soc. **143**, 9922-9932 (2021)



Recently, Sunney and coworkers obtained the cyro-EM structure of the particulate methane monooxygenase, the methane oxidizer in methanotrophs, and confirmed that the active site is a tricopper cluster as predicted from spectroscopy in the 2000's. A tricopper catalyst capable of efficient and selction methane oxidation was reported in 2013.





<u>Different types of research in science</u>

Science, and then there is science!

To me, there are three different kinds of science as the business is being practiced today. First, there is what I called discovery science, or exploratory science. Exploratory science usually begins with asking a question about something nobody knows anything or much about. Like the question Christopher Columbus asked before he embarked on his journey west to discover America. He had a hunch. So with discovery science, you are stretching your imagination and probing the unknown. You are starting with a black box, without any clues about what is in the box This doesn’t mean nobody has never asked the question before. But nobody has found the answer yet. Or sometimes the nut was too hard to crack!

- **Discovery science, explorary science**

Science that has not been done before. To me, it is the most important kind of science. Research problem needs to be defined, questions need to be asked, and research strategy needs to be developed. Looking at a black box and groping in the dark. High risks and long term. In general, high intellectual content, but low productivity, at least at the beginning. Opportunities to open up new frontiers, new research areas. Usually low competition and not too much literature to worry about. Great for research training of students and postdocs, smart and motivated ones anyway. You train the student how to think, how to ask questions, how to define a research problem, how to come up with a research strategy, and execute the work with the highest possible intellectual standards.

- **<u>Main stream science</u>**

Fundamental research driven by recent scientific breakthroughs and fundamentally new ideas, hypotheses, new methods and techniques. As examples- basic research based on discoveries of fullerene, carbon nanotubes, graphene; new methods and techniques, such as atomic force microscopy, MALDI and ESI mass spectrometry, and high performance computing, artificial intelligence; cryo-EM. These advances are now part of main-stream science.

The collection of topics change over time. When I started my academic career, the issues were totally different: natural product synthesis, physical organic chemistry, chemical dynamics, surface science, molecular spectroscopy of various kinds, especially NMR, ultrafast spectroscopy, molecular beam scattering, electron scattering, quantum chemistry, etc. The scientific issues were mostly defined, and solutions were within reach. No intellectual breakthoughs or paradigm shifts expected.

- **<u>Mature science, improvements, further advances achieved by fine tuning</u>**

Issues largely defined. Understanding can still be fine-tuned or improved by additional experimentation and thinking. Frequently, the issues are revisited with new instrumentation and new methods. A lot of literature to follow. There is a lot of this kind of science that can still be performed, with occasional paradigm shifts and overturning of existing dogma. Scientific impact varies.

<u>Basic research: Future directions</u>

Where are the frontiers in basic science?

- I wish I know. If I knew, I wouldn't be here!
- The unknown is unknown to all of us. That's why discovery science is important!
- But I do know what constitutes important areas of basic science that are worth pursuing!

What comes to mind: a random sampling

- **Structure and properties of single atoms/molecules to nanoclusters**
- **Discovery of quantum materials**
- **Quantum computing**
- **Understanding collective phenomena**
- **Mechanisms of folding of large molecules, including self-assembly**
- **Novel materials**
- **Novel molecular systems (interacting molecules) from unusual and hostile environments**

- **Novel strategies for chemical synthesis**
- **Creating new catalysts to mediate important chemical reactions and to mitigate undesirable molecules selectively**
- **Understanding the effects of “impurities” and co-catalysts on heterogenous catalysis**
- **Learning more about how cells of life forms sustain life and understanding disease states**
- **Educating biological systems to make molecules not just for themselves: Designing biological systems to produce fuels, drugs, and fine chemicals (synthetic biology)**
- **Communication between cells and between life forms**

Physics: Physicists will continue to explore the the laws of nature.

- The large scale universe: observing the evolution (expansion) of the universe, formation of stars, galaxies, and black holes, death of stars, detection of gravitational waves, cosmochemistry, and relating these observations to theories on the origin of the universe, the big bang, the expanding universe, dark matter.
- The elementary structure of matter: elementary particles and their interactions, interconversion between energy and particles.

- **Properties of matter (quantum behavior, collective behavior, phases. and properties of materials.**
- **Computational physics.**
- **Quantum computing.**
- **Biological physics: physics of biological cells and cellular behavior.**
- **High-resolution biological imaging based on manipulation of light photons**
- **Medical imaging: Beyond computer-aided tomography (CAT) and magnetic resonance imaging (MRI)?**
- **Development of new physical methods and technologies for the detection, identification, and structural determination of biological molecules in three-dimensions.**

Chemistry: Chemists will continue to work on molecules.

- **Design and building of new molecules; development of synthetic methodologies.**
- **Isolation of molecules from microbes, plants, all living systems, and our environment: the ocean, atmosphere, the soil; and materials that we can retrieve from the ocean floors, as well as asteroids and other planets.**
- **Characterization of composition, three-dimensional structures of new molecules, their interactions with one another, their physical properties, chemical reactivity.**

- **Design of functional and smart molecules.**
- **Design of molecular machines.**
- **Design and study of molecular systems from single atoms to molecular clusters.**
- **Developing a better understanding of molecular catalysis.**
- **Rational Design of molecular catalysts for various chemical transformations, especially for important industrial processes.**
- **Development of efficient catalysts for energy production and interconversion, and mitigation of greenhouse gases.**

- **Exploiting synthetic biology for the production of fuels, metabolites, drugs, and fine chemicals.**
- **Theoretical predictions of design strategies, properties, and reactivity of molecules.**
- **Development of methods to study molecules at interfaces, surfaces, and behavior during phase transitions**
- **Molecular engineering to accomplish various functions: molecular recognition, chemical transformations.**
- **Studying reactions at shorter times.**
- **Detection and analysis of molecules In smaller quantities and lower concentrations.**

Biology: Life scientists will continue to work on the molecules that made up the genetic materials, and study how the information contained in genomes is transferred into the production of cellular molecules and processes that give the organism the capacity for cellular differentiation and development of phenotypes, growth, functional activity, cellular regeneration, reproduction, and continual change preceding cell death.

- **With the new paradigm of doing research in the life sciences, namely, genomics, proteomics, bioinformatics, the life sciences has become an integrated science. The same methods are used to do research in prokaroytes, single-cell eukaroytes, plants, fish.., and humans. The results obtained from one life form can be translated into making predictions about the others. For example, research on the earth worm, *C. elegans*, is often draw conclusions on higher organisms in the area of developmental biology. Similarly, research on the behavior of the fruit fly, *Drosophila melanogaster*, has been a model for making predictions on human behavior. The principles governing all life forms are the same. Only the life forms are different.**

- **Multiple opportunities for discoveries still exist for understanding in detail not only how different life forms exploits genes to store and express their genetic information, how the environment influences these processes (epigenetics), how this information is translated to make proteins, how the proteins are expressed to yield phenotypes, and how different life forms and species have developed molecular strategies to sustain life, including disease states, ageing, and death.**

- **Through evolution, nature has also discovered and even perfected simple chemistry to allow difficult chemical transformations to occur, with precision and speed that are difficult to achieve in the test tube, by appealing to large molecules that can build into their structures the capability to recognize reactants, bring them together and catalyze the chemistry between them to take place either directly or indirect ways, most of the time in simple ways, but occasionally with elegant new chemistry. Chemists can learn from the latter.**

- **Chemistry will continue to play a role in accelerating the progress in the life sciences. Biological cells are chemically heterogeneous. So new methods, ones that are more sensitive and faster, will continue to be developed for fishing out biological molecules from cells and cellular compartments for separation, isolation, identification and structural characterization.**
- **Dramatic progress has been made in genomic sequencing over the past twenty-five years, and we can expect further advances in the technologies to sequence genomes faster and with greater accuracy. Continued advances will be made in DNA and RNA sequencing; protein sequencing; structural analysis.**

- **The development of structural tools to obtain local and global structures of biological molecules, both purified and in the cellular milieu where they perform their functions, remains important, now that biology has become molecular. New methods for three-dimensional structural analysis will continue to be developed by the physicists and chemists. These tools will come and go, with more powerful methods replacing earlier ones within a decade at most.**

- **Witness the development of structural biology. For some decades since the mid 1990s, X-ray diffraction has been the main tool in this field. But crystals of the macromolecules have to be obtained; not all biological macromolecules crystallize. Then the data have to be collected, X-ray diffraction analyzed and interpreted in terms of the scattering electron densities. So the throughput of structural determination is slow. In the 1980s, it became possible to obtain the solution structure of a protein or nucleic acid in buffer under physiological conditions using solution NMR. By this method, the protein dynamics could also be determined to augment information on the locations of the atoms. But this method is limited to small water-soluble proteins of MW under 50 kD, but not for membrane proteins, which account for 25% of cellular proteins. The method is also slow and expensive, as isotopic labeling of selective amino acid acid residues was usually required to help the assignment of the spectrum.**

- **Less than a decade ago, high-resolution cryo-electron microscopy came on the horizon and is rapidly replacing X-ray and NMR as the structure tool of choice for macro-molecular structural determination, especially for membrane proteins and protein-protein complexes. My guess is that the cryo-EM technology will have a lifetime of some 10 years.**
- **Recently, X-ray free-electron lasers (XFELs) has opened the possibility of obtaining diffraction information from a single biological macromolecule within a femtosecond (10^{-15} sec). This method allows serial structural determination to give structural changes in real time. So it is possible that XFELs will replace or augment cryo-EM as the structural tools in structural biology.**
- **Research in biology requires access to large mega and giga data bases. So quantum computing may find its way in biological research.**

- **An emerging area of modern biology is on the horizon dealing with interactions of microorganisms within a host, e.g. the interactions of bacteria within the microbiota. Microbiota are the range of microorganisms that may be commensal, symbiotic, or pathogenic found in and on all multicellular organisms, including plants, guts of mammals, etc. For example, there is now convincing evidence that the microbiota in the human gut are involved in the control of the behavior and disease states of humans. Similar collections of microorganisms are also thought to play a role in the health of soil in various ecological niches.**

So biology is clearly a multi-disciplinary science.

A few conclusions

Benefits of basic research

- **Tantalizes the imagination of the human mind**
- **Tangible effects on the human spirit and society**

Scientific research is becoming increasingly <u>multi-disciplinary</u>!

<u>Modern science is now all multi-disciplinary. All basic and applied research is now multi-disciplinary and inter-disciplinary!</u>

- **The traditional disciplines of physics, chemistry, and biology have become out-moded.**
- **To do modern basic and applied research, we need to train young people to think multi-disciplinarily and to work multi-disciplinary and inter-disciplinarily.**

The subjects and methods used to study nature feed into one another from the different disciplines.

- The principles of chemistry are derived from the laws of physics.
- All molecules are molecules, regardless where they come from.
- They can all be characterized chemically and by methods developed and perfected by the physicists.
- Materials are just molecular systems, with unusual behavior between the molecules that form them. So they can be prepared and characterized by the same methods as for individual molecules.
- All the methods developed by physicists followed the laws of physics.
- All biology follows the principles of chemistry.

- Basic science and basic/aoplied research will be continually be driven by technology, especially in the life sciences and chemical sciences; well known to scientists who work in the fields of high energy physics and astrophysics.
- Technologies will continue to be invented and developed to assist basic scientists do their research better and faster.
- However, technologies last no more than a few years before they become displaced by improved or new technologies. Witness the development of genome sequencing, methods of structural, biological imaging, biological computing to study the structure of biomacromoles and their interactions with small molecules (drugs) and among themselves, protein folding, etc.

- **Emerging technologies: Robotics for chemical synthesis; artifiicial intelligence (AI) in the design of chemical synthesis; and AI in the prediction of protein folding and biological function. Robotics for genome sequencing? For structurql biology?**

Society is now in the 4th Industrial Revolution. Is this revolution affecting the development of basic science? What does the future bode for basic research in the sciences?

- The 1st Industrial Revolution took place from the mid-18th century to about 1830 (mostly in Britain) used water and steam power to mechanize production.
- The 2nd Industrial Revolution took place from mid-19th century until the early 20th century (in Britain, continental Europe, North America, and Japan) used electric power to create mass production.
- The 3rd Industrial Revolution, or Digital Revolution, began in the late 1900s and is characterized by the spread of automation and digitization through the use of electronics and computers, the invention of the Internet, and the discovery of nuclear energy. This period saw the emergence of computers and digital technology.

- **The 4th Industrial Revolution (4IR) is a fusion of advances in artificial intelligence (AI), robotics, digital platforms, Big Data, the Internet of Things (IoT), genetic engineering, quantum computing, and more.**
- **The 5th industrial revolution is dawning upon the world in unforeseeable ways as we increasingly rely on Industry 4.0 technologies. It is a new production model where the focus lies on the interaction between human and machine, namely, people working alongside robots and smart machines. It's about robots helping humans work better and faster by leveraging the collaboration between increasingly powerful and accurate machinery and the unique creative potential of the human being.**

As we adapt to the 4th Industrial revolution and getting ready for the 5th, it is perhaps time for scientists to instruct a machine or robot to do the science: do the experiment, analyze the data, interpret the results? A lot of the data handling and data analysis are already being taken over by the computer now. Is it time for the the computer or robot to design the study and do more and more of the thinking? At some point, will the robot be writing the paper, communicating it to the appropriate journal, having it reviewed and eventually edited for publication? A real nightmare for basic science and intellectual curiosity in my view!

Science and scientific research should be fun!

Thank you!