frontiers | Frontiers for Young Minds

The Nobel collection, Volume 1

Edited by
Robert Knight and Idan Segev

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About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

About Frontiers for Young Minds

Frontiers for Young Minds believes that the best way to make cutting-edge science discoveries available to younger audiences is to enable young people and scientists to work together to create articles that are both accurate and exciting. That is why distinguished scientists are invited to write about their cutting-edge discoveries in a language that is accessible for young readers, and it is then up to the kids themselves – with the help of a science mentor – to provide feedback and explain to the authors how to best improve the articles before publication. As a result, Frontiers for Young Minds provides a collection of freely available scientific articles by distinguished scientists that are shaped for younger audiences by the input of their own young peers.

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The Nobel collection, Volume 1

Collection editors
Robert Knight
Idan Segev

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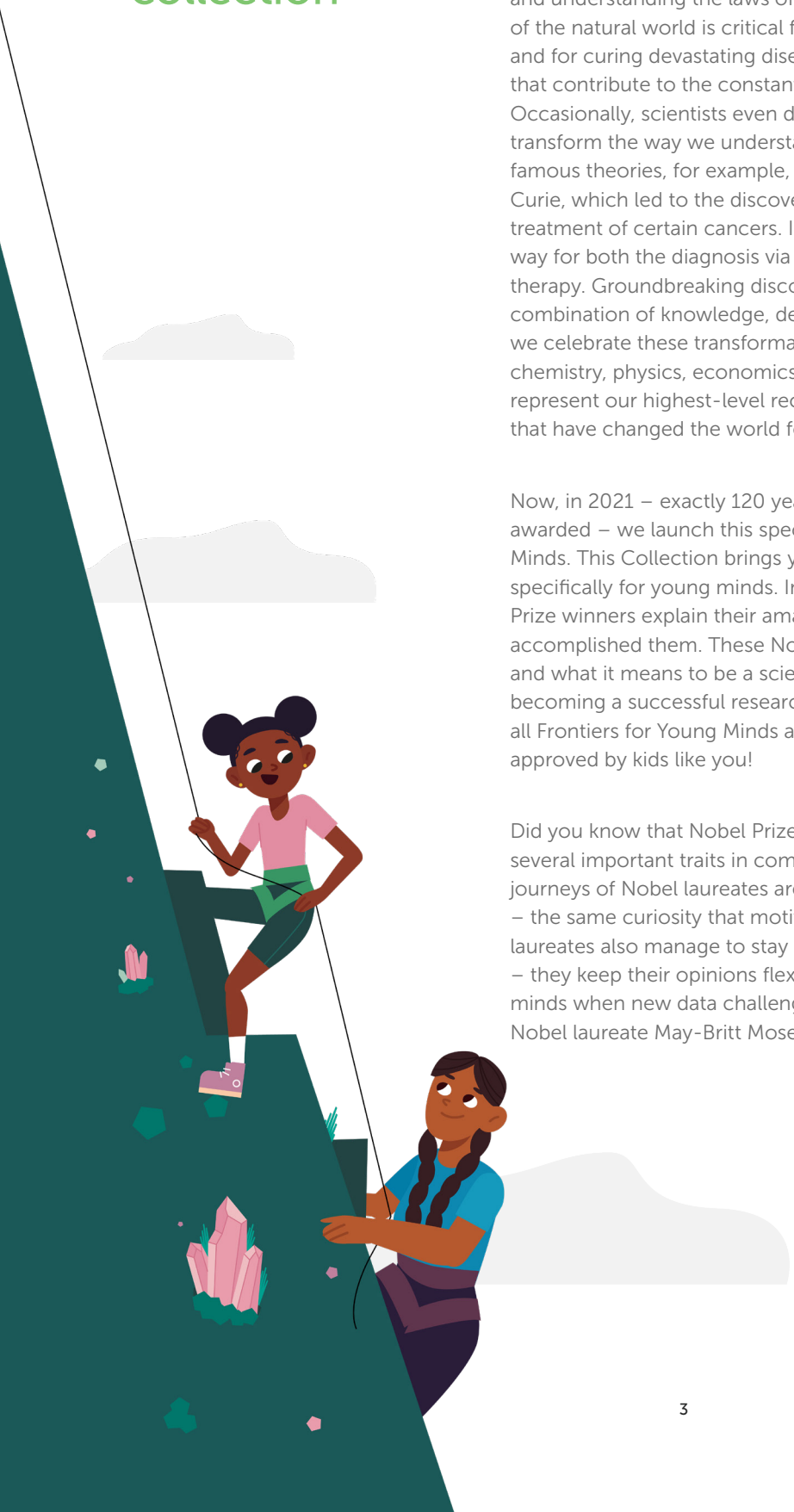
About this collection

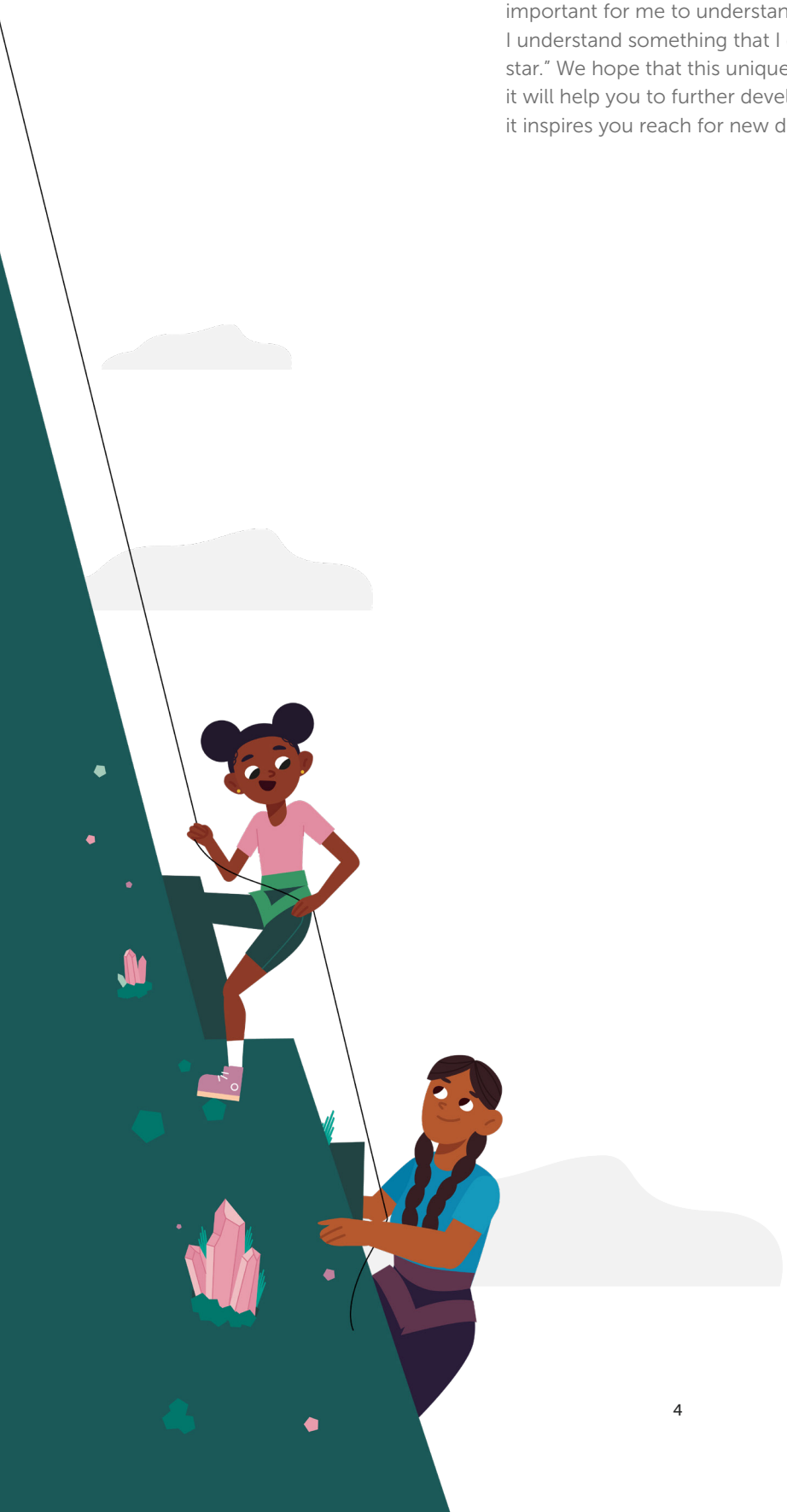


Humans are highly curious – we are eager to understand ourselves and the world around us, and we love the feeling of discovering something new. Some people choose to become scientists and devote their lives to exploring and understanding the laws of nature and life itself. A scientific understanding of the natural world is critical for developing new technologies and materials, and for curing devastating diseases. Every scientist makes discoveries that contribute to the constantly expanding body of human knowledge. Occasionally, scientists even discover entirely new phenomena that transform the way we understand the universe! Think of Albert Einstein's famous theories, for example, or the pioneering work of Marie Skłodowska Curie, which led to the discovery of new elements and advanced the treatment of certain cancers. Indeed, her discovery of radioactivity paved the way for both the diagnosis via X-rays, and treatment of cancer via radiation therapy. Groundbreaking discoveries such as these usually result from a combination of knowledge, dedication, brilliance, and good luck. Each year, we celebrate these transformative discoveries by awarding Nobel Prizes in chemistry, physics, economics, and physiology or medicine. These prizes represent our highest-level recognition of the scientific accomplishments that have changed the world for the better.

Now, in 2021 – exactly 120 years after the first Nobel Prize was awarded – we launch this special Nobel Collection in Frontiers for Young Minds. This Collection brings you articles by Nobel laureates, written specifically for young minds. In this first-of-its-kind collection, Nobel Prize winners explain their amazing discoveries and describe how they accomplished them. These Nobel laureates share their thoughts on research and what it means to be a scientist, and they even provide advice for becoming a successful researcher and living a happy, meaningful life. Like all Frontiers for Young Minds articles, these articles have been reviewed and approved by kids like you!

Did you know that Nobel Prize winners and Young Minds readers have several important traits in common? The first is curiosity. The scientific journeys of Nobel laureates are often fueled by an intense, child-like curiosity – the same curiosity that motivates you to read these articles. Many Nobel laureates also manage to stay as open-minded as Young Minds readers – they keep their opinions flexible and can be persuaded to change their minds when new data challenges their existing beliefs. In the words of 2014 Nobel laureate May-Britt Moser, "I believe that it is important to maintain

your curiosity about things, both now and as an adult, and find something that you have a passion for, that makes you enthusiastic and feel alive. For myself, I can say that I am very curious about things and that it is extremely important for me to understand things. It gives me so much pleasure when I understand something that I did not understand before - this is my leading star." We hope that this unique new Collection will be your leading star – that it will help you to further develop your own curiosity and openness, and that it inspires you reach for new discoveries in your own life!



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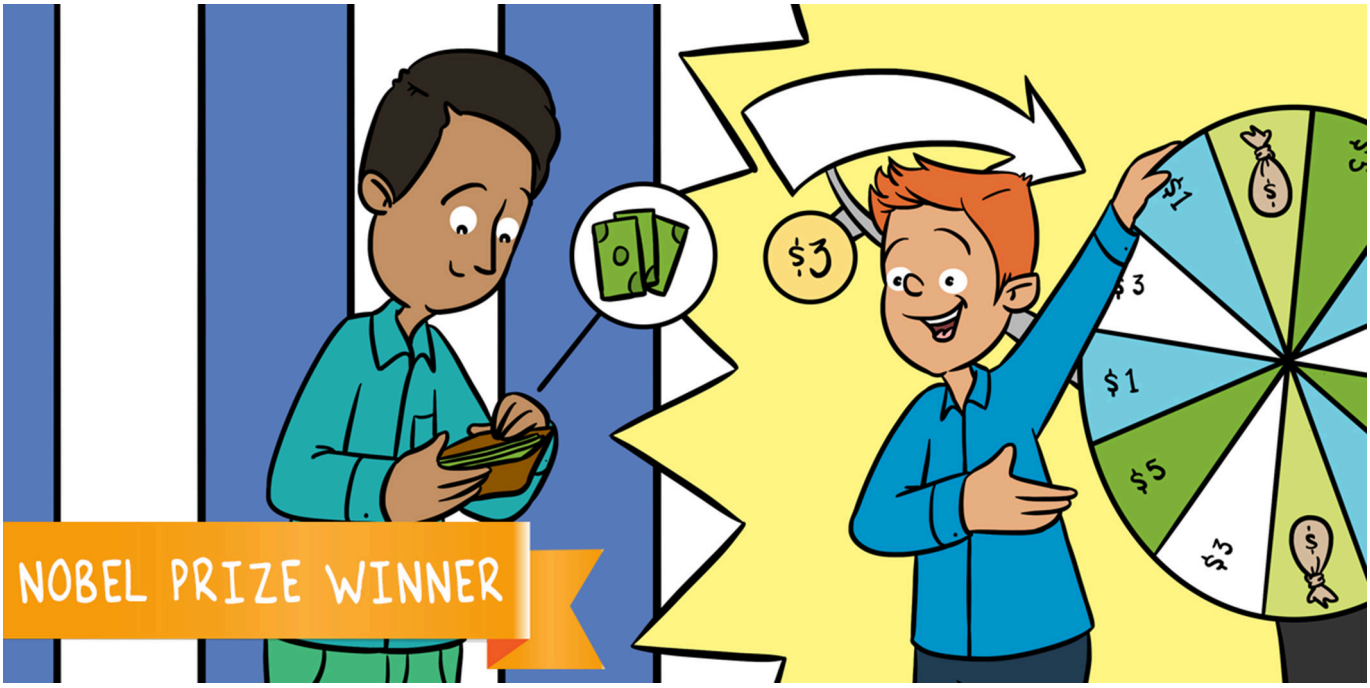

HUMAN RIDDLES IN BEHAVIORAL ECONOMICS

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YOUNG REVIEWERS

OHR TORAH STONE JERUSALEM, "AMIRIM" PROGRAM

AGES: 12–13

Human behavior is a diverse, complex, and highly interesting phenomenon. Despite the many differences that exist between any two people, we can find patterns that characterize typical behaviors in various situations, such as in a classroom or at a family dinner. The research field called behavioral economics studies human behavior in financial situations. In this article, I will present the main findings of the prospect theory, which I developed together with the late Amos Tversky. Prospect theory explains human choices in situations that involve gambling, and it answers questions such as whether people consider gains and losses equally and how a person's initial financial situation influences the value they give to gains and losses. At the end of the article, I will share important insights from my scientific career and explain why happiness has two faces.

Professor Daniel Kahneman won the Nobel Prize in Economic Sciences in 2002 for having integrated insights from psychological research into economic science, especially concerning human judgment and decision-making under uncertainty.

PROSPECT THEORY

Imagine that one of your friends suggests playing the following game: she will toss a coin and you need to guess whether it will land heads up or tails up. If the coin lands heads up you gain $3, and if it lands tails up you lose $3. In this situation, the amount you would gain or lose is the same, and there is a 50% chance of each happening, because the chances of heads and tails are equal. Would you choose to play this game? What if your friend changed the rules so that you would get $5 if the coin lands heads up but lose $3 if it lands tails up? In this situation the gain and loss are different, but there is still a 50% probability for each case (Figure 1).

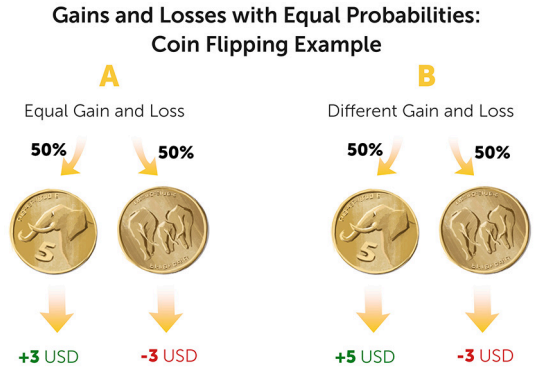

Figure 1

Coin toss with gains and losses. **(A)** A gamble with equal (50%) chance for a gain or a loss. Would you play this game if you would gain $3 (USD) if the coin lands on the elephant's head up and lose $3 if it lands elephant's tails up? **(B)** A gamble with a 50% chance for a gain or a loss, but with different gain and loss amounts. In this version, you would receive $5 if the coin lands heads up and lose $3. if it lands tails up. Would you choose to play this game?

Now imagine another situation where your friend suggests playing a different game: she will roll an ordinary six-sided dice. If she rolls any number from one to four, you will receive $3. But, if she rolls a five or a six, you will lose $3. In this situation, an equal amount would be gained or lost, but there are different probabilities: a 66% chance of winning (4 out of 6) and a 33% chance of losing (2 out of 6). Would you play this game (Figure 2)?

Figure 2

Dice throwing with equal gain and loss but different probabilities. In this game, if you roll a dice and get any number from one to four, you win $3 (USD, left side), but if you roll a five or a six, you lose $3 (right side). Would you want to play this game?

These are examples of simple gambling games with different situations of gain vs. loss. Now think about situations where there are *only* gains of various sizes—for example, if someone asks you to choose between getting a guaranteed $3 or having an 80% chance of receiving $6. Which option would you choose now? Or, if you were offered $3 now or $10 if you wait 2 weeks, which would you choose?

PROSPECT THEORY

A theory dealing with human behavior in situations of financial gambles. This theory is part of a branch in economics called behavioral economics.

BEHAVIORAL ECONOMICS

A branch of economics that explores the factors influencing people's choices in financial situations.

The **prospect theory** that I developed with my late friend, Amos Tversky, deals with the situations described above. Prospect theory is a theory of **behavioral economics**, which studies the choices that people make in uncertain situations, like when they are gambling [1–3]. Prospect theory aims to explain why and how people make their choices. In the next part of the article I will present two central findings of prospect theory, and explain their implications and how they are related to the situations you have seen above.

WHAT DO PEOPLE THINK OF WHEN THEY GAMBLE?

In the past, it was believed that when people think about the financial implications of gambling, they evaluate what their financial status will be if they win or if they lose. For example, a merchant that sends his goods (perfumes, for example) in a ship from Amsterdam to Saint Petersburg knows that there is a 5% probability that the ship will sink along its route and will not reach its destination. The merchant therefore thinks about two options. In the first, there is 95% probability that the ship will arrive safely to its destination. If this happens, he could sell the perfumes and make a predictable profit.

In the second option, there is a 5% probability that that the ship will sink, and the merchant will lose the money he spent on the perfumes. The merchant needs to decide whether to purchase insurance for the contents of the ship. Should he decide to invest an amount of money that will cover the cost of the perfumes if the ship sinks, or should he take the risk and not pay the insurance, hoping that the ship will arrive safely?

The famous scientist Daniel Bernoulli (1700–1782) studied this problem. Bernoulli theorized that people think about the future state of their assets. Namely, when people make an economic decision (gamble), they estimate what their financial situation will be if they win the bet, and what their financial situation will be if they lose. At this point, Amos Tversky and I entered the picture. We noticed that, when it comes to gambles that people make in everyday life (which usually do not involve gambling on a big merchandise that could get lost on the way as in the case of the ship described above), people think about *gains and losses* and not about the *overall* financial state they will be in after the gamble [2–4]. Recall the games we described above: when you choose whether to take the gamble, you probably thought about how much money you would *gain* if you won and how much money

VALUE FUNCTION

A function describing the connection between the subjective value that people attribute to gain or loss, and the objective value of the gain and loss.

you would *spend* if you lost. Chances are you did not think about the overall amount of money you would have in your private cash box in each of these cases. In other words, people focus on *changes* in their financial state resulting from the gamble. This insight is usually presented using a curve called the **value function** (Figure 3) [2]. These changes are measured relative to the person's financial status before the bet, which we call the "zero state," portrayed by the 0 at the origin of the axes in Figure 3.

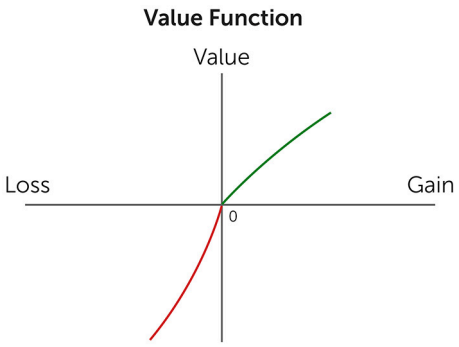

Figure 3

The value function. A major innovation of prospect theory is the shift from the emphasis on the final financial situation of the gambler, after the realization of the bet, to the emphasis on the gains (Gains) and losses (Losses) with respect to the initial financial status of the gambler before the bet, represented here by the origin of the axes ("0"). The gain or loss is measured relative to it, and is associated with a subjective value (Value) of the person making the bet. Each person decides for themselves how important profit (gain) is to them and how much loss "hurts" them. Prospect theory says that losses hurt more than does an equivalent amount of gain (the red curve is steeper than the green curve) (Adapted from [2]).

LOSS AVERSION

Now that we understand that it is the *changes* in a gambler's financial state that carry value, we can ask whether gains and losses have the same "weight" or importance to the gambler. Let us go back to the game in Figure 1. The first version of the game, in which there are equal chances for gain and loss and the gain and loss are equal, is a type of gamble that people do not like to take. People much prefer the gamble offered in the second version, in which the value of the gain is higher than the value of the loss and the chances for gain and loss are equal. In other words, people need the "compensation" of a potentially greater gain to allow for the risk of losing. The important conclusion is that people's attitudes toward gains and losses are *not* equal. People are averse to loss (meaning they dislike it) more than they are attracted to gain. We called this **loss aversion** [5].

LOSS AVERSION

A greater dislike of losses compared to the attraction of comparable gains. For example, people tend to avoid gambles in which the amount and probability of loss are equal to the amount and probability of gain.

Loss aversion is graphically displayed in Figure 3. Look at the green curve on the right side of the graph, representing the value people attribute to gains, and compare it to the red curve on the left, representing the value people attribute to losses. You can see that the gain curve rises more slowly, it is more moderate, than the loss curve, which is steeper. This means that, for the same actual value of gain and loss (like +$3 and −$3), people will experience the loss

as more negative than they will experience the gain as positive. Test this on yourself: would you be more excited from gaining $3 than you would be upset by losing $3? Most of you will say that it is more upsetting to lose $3 than it is exciting to gain $3. This human characteristic shows up in many cultures, and we believe it has an evolutionary basis (Challenge: could you think how this characteristic of increased aversion to loss serves humans from an evolutionary perspective?). It is interesting to note that, although *awareness* of loss aversion increased following our studies, loss aversion itself did not decrease. But our studies enabled us to understand people's behavior in financial situations, which earlier theories had failed to explain.

RECOMMENDATION FOR YOUNG MINDS—THE TWO FACES OF HAPPINESS

Finally, I would like to share with you some important insights from my research career that are not directly related to the world of economics. The first insight comes from behavioral psychology and arises from the question: "what makes people happy?" The other insight emerged from my own observations of myself as a scientist.

Happiness is a meaningful and elusive quality in every person's life. The road to happiness is highly individual and it depends on many factors. Nonetheless, you should be aware that there are two types of happiness—being happy *in* your life, and being happy *about* your life[1] (Figure 4) [6, 7]. Being happy *in* your life, also called experienced happiness, relates to the momentary experience in life: Is it pleasant to be myself? Do I feel good at the moment? This type of happiness is closely related to our moods. It turns out that, on average, people are the happiest when they spend time with people they love and who love them. In contrast, being happy *about* your life, also called life satisfaction, relates to general satisfaction from life: Is my life successful? Am I proud of my achievements? In other words, satisfaction results from looking back at your life and weighing it in terms of success and failure[2] .

My recommendation, therefore, is that you should think about two different aspects of happiness: how you would like to spend your time (being happy *in* life), and what your life goals are (being happy *about* life). These two aspects do not always go hand-in-hand at any specific moment. But if you pay attention to both, your chances of experiencing both increases. Another important thing for you to know is that, in additional studies, we found that the relationship between financial wealth and happiness is not as simple and clear as people tend to think [8]. So, to be happy, my recommendation is not to focus your attention too much on financial wealth. Instead, participate in

[1] For more information, see: Daniel Kahneman: Moving to California Will Not Make You Happy.

[2] For more information, see: The riddle of experience vs. memory | Daniel Kahneman.

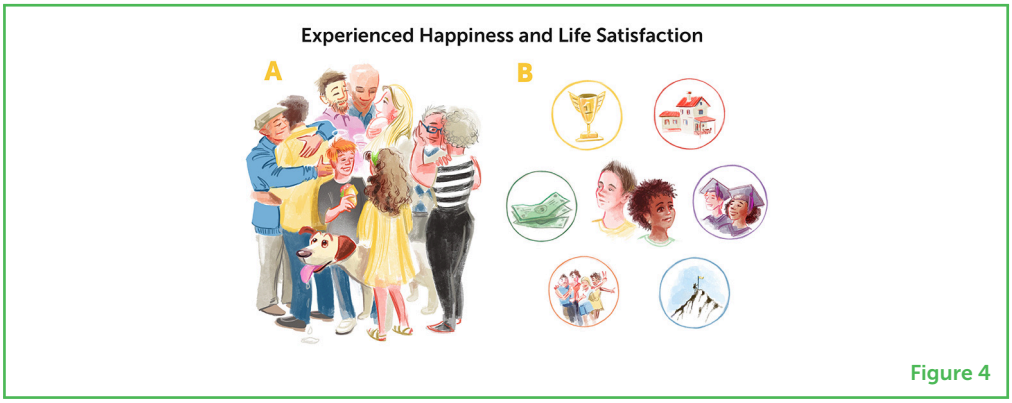

Figure 4

Figure 4

The two faces of happiness. Overall happiness is made up of two types of happiness—being happy *in* your life (experienced happiness) and being happy *about* your life (life satisfaction). **(A)** Being happy *in* your life relates to momentary enjoyment, which is usually caused by spending time with people you love. **(B)** Being happy *about* your life, i.e., satisfaction, is related to looking back at your life and feeling that your goals were accomplished. Wisdom lies in finding the way to fulfill both types of happiness, which does not always happen at the same time [6].

various enjoyable activities throughout your life and choose a variety of goals—not only financial ones.

THE SCIENTIST IS LIKE A KID WHO LIKES TO CHANGE HER MIND

To me, being a scientist is kind of like deciding to remain a child and maintaining a high level of curiosity. Of course, scientists do not fully understand the world around them, but they do make great efforts to *try* to understand it. As a scientist, I also like to change my mind. There are scientists who find it hard to change their opinions—they cling on to it and do not let go. For me, it is the opposite—only when I change my mind do I feel that I really learned something new. In this sense, working in science is an ongoing cycle. Again and again, there are moments of, "oh, how could I have been such a fool and not seen this earlier?" This experience of seeing things anew repeats over and over during life of a scientist. It continues throughout your life if you decide to become a scientist. It still happens to me at the age of 88 (my current age).

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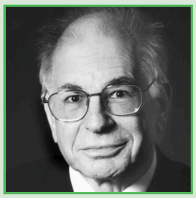
YOUNG REVIEWERS

OHR TORAH STONE JERUSALEM, "AMIRIM" PROGRAM, AGES: 12–13
Ohr Torah Stone Jerusalem, "Amirim" program, ages 12-13, 7th grade girls participating in the "Amirim" program for excellence. Ohr Torah Stone School

emphasizes the development of values, creativity and self-fulfillment for religious girls.

AUTHOR



DANIEL KAHNEMAN

Professor Daniel Kahneman won the Nobel Prize in Economics in 2002, although he says that he has never taken a course in economics! He is an Israeli-American cognitive psychologist who is a professor at Princeton University in New Jersey. He earned a bachelor's degree in psychology and mathematics at the Hebrew University, worked as a psychologist in the Israeli Defense Forces, and completed his doctoral studies at the University of California, Berkeley. Professor Kahneman returned to Israel as a member of the Department of Psychology at the Hebrew University of Jerusalem, where he began researching, with his colleague Amos Tversky, decision-making processes and subjective judgment in situations of uncertainty. Since 2000, he has been a member of the Federmann Center for the Study of Rationality at the Hebrew University. During this time, he began collaborating with economists and developing research in the field of behavioral economics. He has won many awards and honors. In 2013, US President Barack Obama awarded him the Presidential Medal of Freedom, the highest civilian award of the United States. His book *Thinking, Fast and Slow* is a worldwide bestseller, in which he explains the gap (and the reason for this gap) between the way we make decisions and the way we *think* we make them. Professor Kahneman has two children and three grandchildren. *kahneman@princeton.edu

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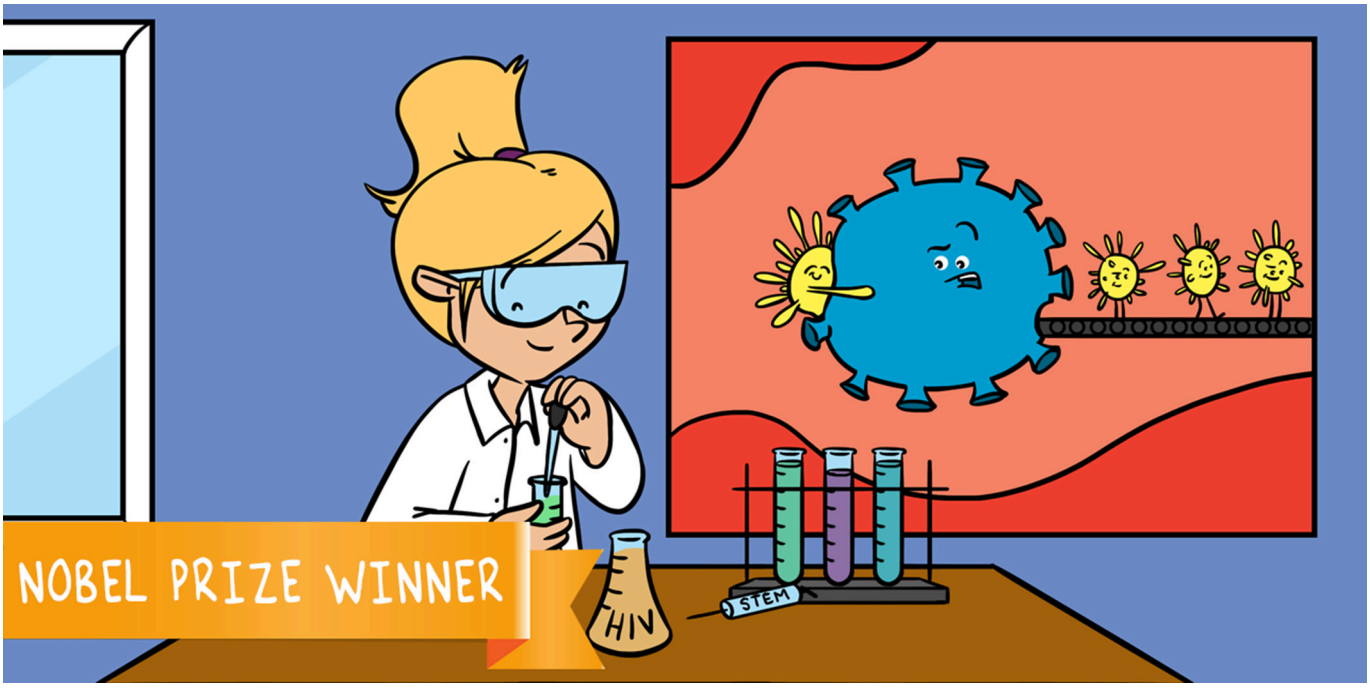

AIDS: FACTS, FICTION, AND FUTURE

Françoise Barré-Sinoussi *

Institut Pasteur, Paris, France

YOUNG REVIEWERS:

ELI
AGE: 14

ELISA
AGE: 12

NEVE
AGE: 14

AIDS (acquired immune deficiency syndrome) is the name used to describe a number of potentially life-threatening infections and illnesses that happen when the immune system has been severely damaged by the human immunodeficiency virus (HIV). HIV/AIDS is considered a pandemic, affecting almost 38 million people throughout the world in 2020 alone. There is no cure for this disease and no vaccine to prevent it. Although people can not be cured, they can live for years with appropriate treatment. In addition to the difficulty of living with a chronic and aggressive disease, people living with HIV/AIDS also suffer frequently from many forms of social stigma and discriminations. In this article, I will tell you about AIDS, the discovery of its viral cause, current available treatments, and future possibilities for decreasing the number of people living with HIV/AIDS. I hope that, by the end of this article, you will understand the global importance of dealing with HIV/AIDS—both scientifically and socially.

Professor Françoise Barré-Sinoussi won the Nobel Prize in Physiology or Medicine in 2008 (jointly with Luc

Montagnier) for the discovery of human immunodeficiency virus (HIV).

WHAT IS HIV/AIDS?

HIV (human immunodeficiency virus) is a virus that attacks the cells that help the body fight infection, making a person more vulnerable to other infections and diseases. It specifically targets a type of white blood cell called CD4 cells (Figure 1) [1]. CD4 cells are "helper" cells—they help the **immune system** by activating other immune cells when a foreign invader, like a virus, enters the body.

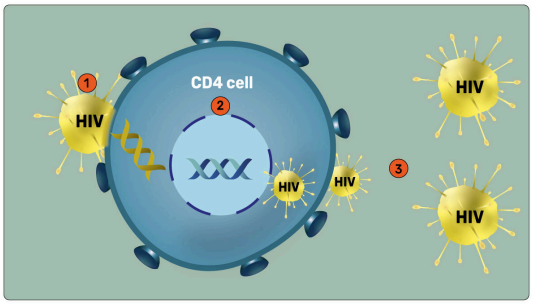

Figure 1

The human body cannot get rid of HIV by itself and no effective cure for HIV exists presently. Once someone has HIV, they have it for life. If it is left untreated, the body's immune system becomes so badly damaged that any infections, such as pneumonia, are much more dangerous and life-threatening [2].

The first cases of AIDS were reported in the early 1980s [2] and, soon after, it was declared a global **pandemic**. It is currently believed that the HIV infection in humans originated from contact with non-human primates (such as chimpanzees and gorillas) in Africa—this is referred to as cross-species transmission [3]. According to the World Health Organization[1], almost 80 million people have been infected with HIV since the beginning of the pandemic, and about 45% of them have died[2]. In 2020, 37.7 million people were living with HIV, 1.5 million people were newly infected with HIV, and 680,000 people died of illnesses related to HIV.

AIDS is found throughout the world, with about two-thirds (69%) of the cases in Africa, about 15.5% in Asia and the Pacific, about 6% in North America and in Central Europe, about 5.5% in Latin America, and about 4% in Eastern Europe and Central Asia (Figure 2).

IMMUNE SYSTEM

A system in the body that protects it from organisms that cause disease, such as bacteria and viruses.

Figure 1

Infection by HIV. (1) HIV attaches to a CD4 immune cell before entering it. (2) Viral genetic material (yellow spiral) combines with the DNA of the CD4 cell (blue), and takes over the reproduction system of the cell so that the virus makes additional copies of itself. (3) New HIV particles leave the CD4 cell and go into the blood to infect additional CD4 cells. In this way, HIV continues to multiply and spread throughout the body. Over time, CD4 cells are killed by HIV and the body's ability to recognize and fight various infections declines.

PANDEMIC

A pandemic is said to occur when a disease spreads over more than one continent and affects a very large number of people.

[1] For more information, see: https://www.who.int/data/gho/data/themes/hiv-aids#:~:text=Globally%2C_37.7_million_[30.2~,considerably_between_countries_and_regions.

[2] The global mortality rate for COVID-19 is estimated to be <6% [4]. This means that the mortality rates of HIV/AIDS is *seven times larger* than that of COVID-19.

Figure 2

Worldwide distribution of HIV in 2020. (Image adapted from: UNAIDS 2021 epidemiological estimates).

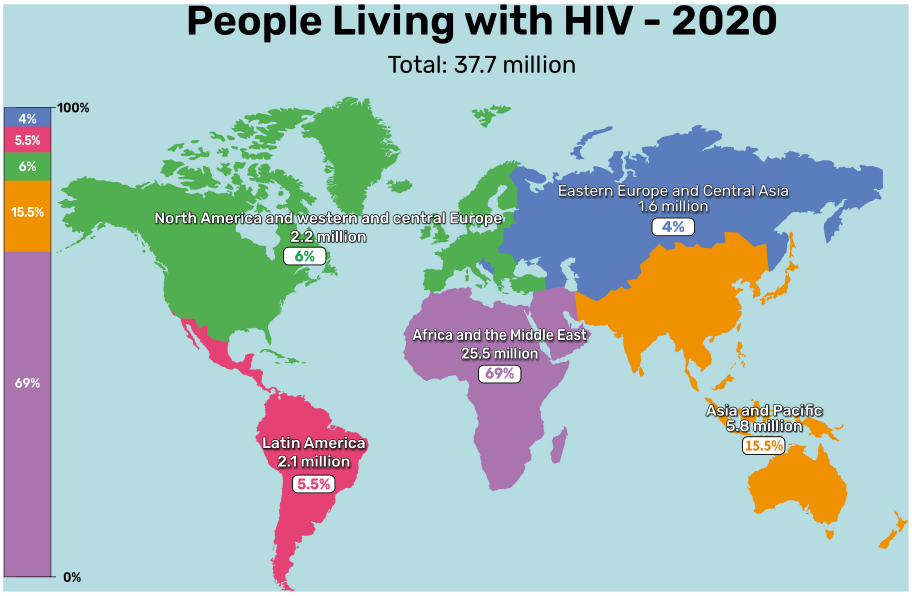

Figure 2

HOW IS HIV SPREAD AND WHAT ARE ITS SYMPTOMS?

There are three ways to become infected with HIV: unprotected sexual activity, direct contact with infected blood (for example, through blood transfusions), and transmission from infected mothers to their babies [5]. After HIV is contracted, there are three stages to the disease (Figure 3). The first stage is called acute HIV, which starts after the initial infection and lasts until the body makes an immune response and begins to produce HIV-specific antibodies. At this stage, HIV viruses are seen in the blood [6] and the virus reproduces rapidly, spreading throughout the body. Some people develop flu-like symptoms in the acute stage, such as fever, sore throat, muscle aches, diarrhea, rash, and fatigue. These symptoms usually appear about two to four weeks after the initial infection.

The second stage of an HIV infection is called chronic HIV. At this stage, the virus is still active, however, it is not producing any visible symptoms. Therefore, this stage is also called an asymptomatic (without symptoms) infection. If not treated, the asymptomatic stage can last for years before the third, symptomatic, stage of the disease develops. Although people can not be cured, they can live in the asymptomatic stage for years with appropriate treatment. If not treated, people living with HIV can pass on the virus even though they show no symptoms of the HIV infection. The final and most severe stage of HIV infection is called acquired immunodeficiency syndrome, or AIDS. People are diagnosed with AIDS when their numbers of CD4 cells drop to very low levels, or if they develop other infections that are related to AIDS, which are called **opportunistic infections**. Opportunistic infections take advantage of the weakened immune system and may eventually cause death if they are left untreated.

OPPORTUNISTIC INFECTIONS

These are infections that "take advantage" of the weakened immune system of people infected with HIV virus. These infections are usually the cause of mortality of people having AIDS.

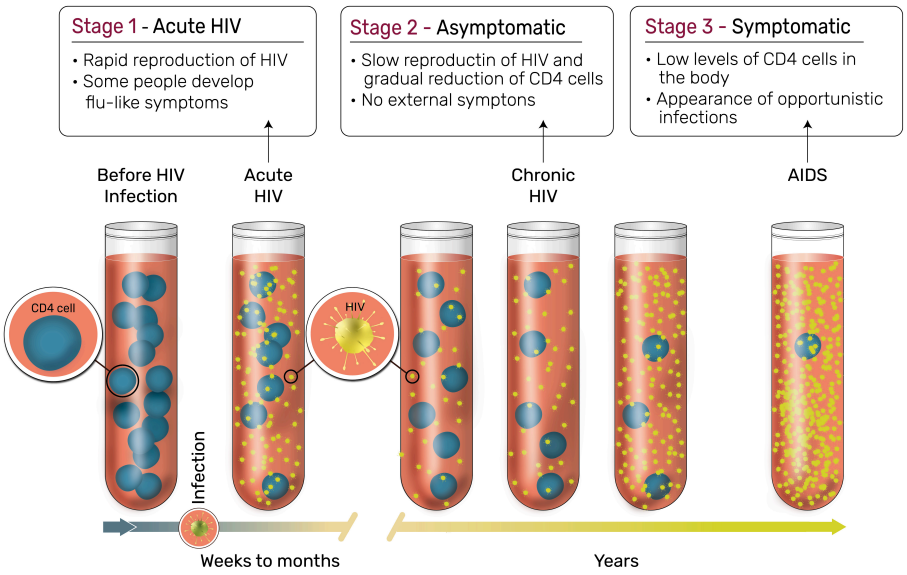

Figure 3

Stages of HIV infection. If we take blood from patients at the three stages of the disease, we find that in the first stage of the disease (Acute HIV), occurring in the first couple of weeks or months after the infection, the HIV virus spreads quickly. Some, but not all, patients develop flu-like symptoms in this stage. In the second stage (Asymptomatic), which could last for many years, the virus spreads slowly and patients show no symptoms. In the third and final stage (Symptomatic), patients are left with low levels of CD4 cells and show severe symptoms (Image adapted from: https://hivinfo.nih.gov/understanding-hiv/fact-sheets/stages-hiv-infection).

HIV/AIDS AND STIGMA

In the beginning of the 1980s, early studies found that AIDS was especially prevalent among people who used drugs people who received blood transfusions, and men who had sexual contact with men [3]. The stigma of having HIV/AIDS has become widespread and deeply rooted within societies all over the world. This means that people living with HIV are sometimes made to feel ashamed by the societies they live in, so they do not seek out the medical treatment they need. Negative attitudes and false beliefs about HIV and people living with HIV often lead to **discrimination** and can seriously impact the mental health and wellbeing of these individuals [7, 8].

DISCRIMINATION

Treating people unfairly due to their belonging to different groups or categories from the majority.

In addition to the negative psychological effects of the stigma faced by people living with HIV/AIDS, such stigma also reduces the effectiveness of prevention and treatment strategies [9] that could otherwise slow down the spread of the disease. For example, due to HIV/AIDS stigma and discrimination, people living with HIV are less likely to tell their sexual partners about their HIV status and are more likely to take part in unsafe sexual activity[3], both of which increase the chances of HIV transmission [9]. Additionally, some people living with HIV/AIDS hesitate to get treatments, since they are afraid of being stigmatized when others know that they are being treated [9]. Furthermore, stigma can lead to a lack of support networks for people living with HIV/AIDS [8]. For more information on young people and HIV, see this Frontiers for Young Minds article [10].

These are only a few of the many examples of how HIV/AIDS related stigma can negatively affect people living with HIV/AIDS—and all of society. I believe that it is very important to address stigma

[3] Research shows that psychological distress and lack of social support, which often result from HIV/AIDS stigma, increase engagement in sexual risk behavior. To learn more about it, see here.

by providing accurate information to people like you—the younger generation—who are the future of society. Diminishing stigma associated with HIV/AIDS, along with scientific and medical advances in HIV/AIDS prevention and treatments, can help us to achieve the goal of an AIDS-free generation [11].

THE DISCOVERY OF HIV

I will now outline the discovery of HIV, for which I received a Nobel Prize in Physiology or Medicine in 2008, with Luc Montagnier. In my Ph.D. studies, I worked on the relationship between cancer and a family of viruses called **retroviruses**. Retroviruses are particularly nasty viruses that cause serious illnesses. They have RNA as genetic material that must be transformed in DNA by a special enzyme of the virus, named reverse transcriptase. This transformation allows the integration of the genetic material of the retrovirus into the DNA of host cells that then reproduce viral RNA and viral proteins, resulting in the release of new retroviral particles capable to infect other healthy cells.

RETROVIRUS

A virus that produces a DNA copy from its RNA, and inserts it into the DNA of a host cell. This is the reverse of the usual genetic pattern, where RNA is produced from DNA; thus retro (backwards).

When AIDS appeared in 1981, most researchers were looking for viruses that could be responsible for it, but they were not having much luck. One group of doctors in France, who knew that we were experts in the study of retroviruses, came to our laboratory at the Institut Pasteur in Paris. They asked us a very simple question—did we think that a retrovirus, rather than a regular virus, could be responsible for AIDS?

Their own hypothesis was that the only known human retrovirus at that time, the human leukemia T-cell virus (HTLV), could be the cause of AIDS. However, we thought that this hypothesis was incorrect because HTLV is a virus that causes a type of blood cancer called leukemia, where cells become immortal, replicate themselves and spread quickly in the body. In contrast, physicians found in their clinical observations that AIDS patients lost their white blood cells—meaning that, unlike in leukemia, in HIV/AIDS the cells die and reproduce less than normal. Therefore, HTLV was unlikely the virus that caused AIDS.

REVERSE TRANSCRIPTASE

An enzyme used by retroviruses to generate DNA from RNA. Measurements of reverse transcriptase in cells are used to check whether cells are infected with a retrovirus.

We wondered whether we should look for a different retrovirus that could cause the disease, and this is how the story began. Knowing that HIV attacks the CD4 immune cells, we looked for a retrovirus virus in these cells. By then, I already knew how to detect retroviruses produced by cells, by looking for a **reverse transcriptase activity**, the retroviral enzyme used to generate DNA from viral RNA. If this enzyme is present in cell supernatants, it suggests that cells are producing retroviruses. In January 1983, after few days of culturing T cells from a lymph node biopsy of a patient with pre-AIDS syndrome, we eventually detected a reverse transcriptase activity in the culture. Later, on retroviral particles were observed by electron microscopy which

turned out to be a novel retrovirus later named HIV (which was called lymphadenopathy-associated virus, or LAV, at that time) [12].

This success story demonstrates why discussion and interaction between researchers and physicians is crucial. In our case, based on the physicians' observations, we could together identify an efficient strategy to search for the virus. Contact with physicians was important at all stages—from identifying the symptoms of the disease, its cause, its method of attack, and the development of the best possible prevention strategies and treatments.

TREATING HIV/AIDS—CURRENT AND FUTURE DIRECTIONS

ANTIRETROVIRAL THERAPY

A medical treatment for HIV, consisting of chemicals that limit the ability of HIV to reproduce.

Now, in 2022, there is still no cure for HIV/AIDS, and there is also no vaccine that prevents HIV infection. Therefore, people living with HIV are chronic carriers of the virus and they need to take medications every day of their lives. The medical treatment for HIV is called **antiretroviral therapy** (ART), which consists of a mix of chemicals that limits the ability of HIV to reproduce, therefore maintaining low amounts of the virus in the body[4]. When relatively small amounts of HIV are present in the body, the immune system can recover from the damage to CD4 cells that the virus causes. The lifespan of infected people on ART is similar to that of non-infected people, especially if they are treated early after infection. In addition, infected people on ART with no detectable virus do not transmit the virus to others. Indeed, ART can also be used as pre-exposure prophylaxis to efficiently prevent HIV infection in people at risk for HIV infection. Also, reducing the amount of HIV in the body reduces the risk of transmission of the virus to other people, when the virus is not detected in the blood it cannot be transmitted. Additionally, it prevents infected people from contracting other harmful infections that might lead to death.

[4] For more information about HIV treatment, see here: https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-treatment-basics

ART therapies have contributed to the significant decrease in AIDS-related deaths, though the numbers are still high. It is believed that these high numbers result mainly from delayed diagnosis of HIV infections (i.e., when the infection is diagnosed the immunological system is already severely damaged), limited access to the therapies (especially in developing countries), refusal of some HIV-infected subjects to receive ART therapies, and low adherence to these treatments (i.e., patients not following the medical advice) [13, 14]. Additionally, lifelong ART therapy has several limitations such as the possibility of developing drug resistance (meaning the therapy becomes less effective with time), side effects that can accumulate with time, and a high cost that places an impossible financial burden on patients with limited resources [15].

Apart from the ART therapies that are used worldwide, there are other new treatments that have great potential to become cures in the

future. One promising direction is called stem-cell transplant, in which **stem cells** are injected into the patient's body to help re-grow their immune cells[5]. I believe that we still need more scientific research to develop a reliable and widely applicable cure for HIV/AIDS, and to develop vaccines that will help prevent HIV infections [16]. It is important to note that, while concentrating our efforts on scientific solutions is important, we must also try to make wider changes [7]. By providing reliable information to individuals living with HIV/AIDS and educating all of society about the virus, we will succeed in reducing further its prevalence and mortality worldwide.

STEM CELLS

Immature cells that can become most other cell types, like muscle cells, brain cells, liver cells, etc.

[5] To learn more about stem-cell transplant, see here to learn about the procedure with HIV-infected patients and read here about a case of a patient who recovered from HIV infection by special stem-cell transplant.

RECOMMENDATION FOR YOUNG MINDS

It seems to me that, in today's world, people are too self-centered. My main recommendation for you, the younger generation, is to think about what is most important in life—is it yourselves, or is it helping others? In my opinion, the most important thing in life is to give to others, no matter what field you are in, and to help in whatever way possible. From my experience, if you give to others, you will receive back from others—and that will lead to a happy life. Otherwise, if your life is only for yourself, I believe you will never be entirely happy.

I would also like to share my perspective on challenges. What I have enjoyed most in my scientific career are the challenges that I have faced. Challenges always cause you to question yourself. In research, you can never be certain about the validity of the data you obtain, so you must try to verify your data and replicate it, making sure that you obtain the same results again and again. Additionally, if you obtain results that you were not expecting, you might need to change your research strategy, and sometimes also change your hypothesis. I think that science is like a game with yourself, where you repeatedly challenge yourself and change your ideas. If you choose the scientific path, I recommend that you learn to appreciate the unexpected, since it is a natural part of the process of scientific discovery. Additionally, for anyone who may be interested in the life sciences and clinical research, I would emphasize that it is very important to be in contact with both physicians and people affected by the disease, so that you remain in touch with real-world challenges, as well as with the research work in the laboratory. This was certainly a determining factor in my career working on HIV/AIDS.

Last, for all future women scientists, I will end on an optimistic note. When I started my career in the 1970s, it was much harder for women scientists than it is today. As a female student, I was told that I had no chance of getting a research position at the Institut Pasteur. Eventually, I *did* get a position at the National Institute of Health and Medical Research (INSERM) and worked at the Institut Pasteur for about 40 years, until I retired a few years ago. Today, there are about 50 women professors at the Institut Pasteur, compared to only about

5 when I joined. So, you can see that a lot of progress has been made in the last 50 years. Nonetheless, there is still much to do to further advance women in science. As female scientists, we should be particularly supportive of each other and work together toward the goal of complete equality in science. I believe we will keep seeing positive changes in that direction in the coming years.

ADDITIONAL MATERIALS

- Global HIV Statistics—World AIDS Day 2021 (UNAIDS).
- Why Is It Difficult for Young People With HIV to Share Their Diagnosis? Frontiers for Young Minds (frontiersin.org).
- How the Innate Immune System Fights for Your Health.
- Flu, Flu Vaccines, and Why We Need to Do Better.

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YOUNG REVIEWERS

ELI, AGE: 14

I am in 8th grade, and my favorite subject is science. I love going out in nature and camping with my family, playing rugby, and going to gym.

ELISA, AGE: 12

Elisa is a young girl with a curious mind. She is very passionate about science, especially related to health. She is interested in research and would like to start getting involved in conducting her own explorations in high school. She hopes that, with her critical thinking, her love for health discoveries and her drive, she will be able to contribute to science through journal review.

NEVE, AGE: 14

Hi, my name is Neve! I am currently in eighth grade, and my favorite subjects are history, english, and science. My passions include environmental science and politics. I love to read, play the guitar and be outdoors! In the future I hope to pursue a career in politics.

AUTHOR

FRANÇOISE BARRÉ-SINOUSSI

Prof. Françoise Barré-Sinoussi is a French virologist. She was born in 1947 in Paris and was drawn to science at an early age. After completing her high school studies, Barré-Sinoussi considered becoming a medical doctor, but eventually chose to study at the University of Sciences in Paris, thinking it would be a cheaper option that would not burden her parents financially, and also a faster option (she was wrong, but does not regret it). In 1966, she started her undergraduate degree at the University in Paris. She earned her Ph.D. in 1974 at the the Institut Pasteur, Paris, working on the relationship between retroviruses and cancers in mice. Prof. Barré-Sinoussi then continued for a postdoctoral work at the National Cancer Institute at the National Institutes of Health, United States. In 1975, she joined the Institut Pasteur as an INSERM (National Institute of Health and of Medical Research in France) researcher, where she continued studying the links between retroviruses and cancers. In 1983, 2 years after the first cases of AIDS were reported, Prof. Barré-Sinoussi and her team identified a retrovirus, later named HIV, that is the cause of AIDS. For that discovery, Prof. Barré-Sinoussi was awarded the Nobel Prize for Physiology or Medicine in 2008, together with Prof. Luc Montagnier. Prof. Barré-Sinoussi has co-authored over 300 scientific publications, has participated in over 400 international conferences, and has trained many young researchers. From 2012 to 2014, she served as the President of the International AIDS Society (IAS) and launched the IAS Toward an HIV Cure initiative. Prof. Barré-Sinoussi's career has also included work with resource-limited countries, such as Cambodia, Vietnam, Cameroon, and the Central African Republic. Her experiences working in developing nations were truly eye-opening and motivated her to continue to collaborate scientifically with countries through Africa and Asia. She constantly

works on establishing permanent links between basic research and clinical research, to achieve concrete improvements in the areas of prevention, clinical care, and treatment of HIV/AIDS. In 2009, she wrote an open letter to Pope Benedict XVI in protest over his statements that condoms are ineffective in the AIDS crisis. Presently, Prof. Barré-Sinoussi is Honorary President of the Pasteur Network and of the Virology Department at the Institut Pasteur, France. She is also a Member of the National Academy of Science in France and of the National Academy of Medicine in USA. She has been elevated to the rank of Grand Cross of the French Legion of Honor. *francoise.barre-sinoussi@pasteur.fr

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GRAVITATIONAL WAVES—A NEW WINDOW ON THE UNIVERSE

Barry Barish *

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YOUNG REVIEWER:

JIARUI

AGE: 13

Imagine you could choose a new set of eyes that would help you see things you have never been able to see before. Maybe you would choose Superman's X-ray vision, or maybe you would prefer to zoom into tiny things and see the wonders of the microscopic world. Science has recently gained a new set of eyes—a new way to look into the mysteries of the universe—using gravitational waves, which are waves produced by gravity itself. In this article, I will take you on a journey that begins with an explanation of gravity—from the classical perspective of Isaac Newton to the modern and more complex view of Albert Einstein. I will then explain how movements of massive objects create gravitational waves, which are ripples in space and time, and how they might be used to explain some mysteries of the universe, and even help us to understand the origins of our planet Earth.

Professor Barish won, jointly with Profs. Rainer Weiss and Kip Thorne, the Nobel Prize in Physics in 2017 for decisive contributions to the LIGO detector and the observation of gravitational waves.

GRAVITY—FROM NEWTON TO EINSTEIN

GRAVITY

A force that causes objects to move toward one another.

In 1687, the great English mathematician and physicist Sir Isaac Newton published his famous book, Principia [1], in which he presented his theory of **gravity**—the first "universal" theory in science. Newton's theory proved that the gravitational force between two objects is proportional to the product of their masses and inversely proportional to the square of how far apart they are. This sounds complicated, but it means that the more mass the objects have, and the closer they are to each other, the stronger the gravitational force they have on each other. While this is true, it turned out that Newton's wonderful theory has a few limitations.

First, have you ever wondered why, when an apple falls from a tree, it falls *down* and not *up*? When you jump, why do you come back down to Earth rather than flying upwards? Newton's theory does not actually answer these simple questions. It only tells us the *amount* of gravitational force the two objects exert on each other, like the force between the apple and the Earth or between you and the Earth. Newton's theory does not consider the *direction* of the force between objects (toward each other or away from each other) nor does it explain where gravity comes from in the first palace (Figure 1).

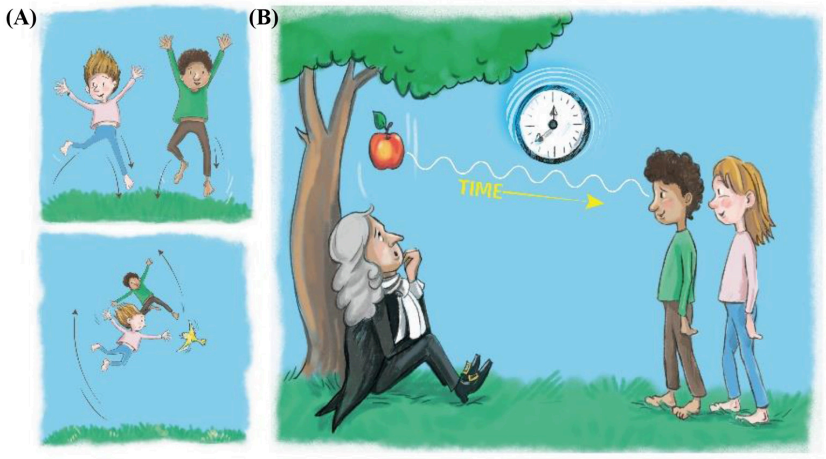

Figure 1

Figure 1

Isaac Newton's successful theory of gravity has several limitations. **(A)** Have you ever wondered why you fall back to Earth when you jump up, instead of flying into the sky? What attracts you back to Earth? Newton's theory could not answer this question. **(B)** When an apple falls from a tree, it takes time for an observer to know that it happened, because the information travels at the speed of light. Newton's theory assumes that the observer sees the apple falling instantaneously, at exactly the same moment that it falls. Both limitations were solved by Einstein's theory of gravity.

The second difficulty with Newton's theory is a little harder to grasp. Imagine that the Sun suddenly disappeared. If it disappeared right now, it would take about 8 min before we could see that it was no longer there, because it takes 8 min for light to reach us from the Sun. The same is true for everything else that happens in the universe—it takes time for the information to travel from the event to the observer. So, when an apple falls from a tree, it should take some time (even if only a tiny fraction of a second) for the observer to know what actually happened (Figure 1). Newton's theory does not take this time interval into account so, according to his theory, the observer sees the apple

falling at exactly the same moment that it actually falls. We know that this is not the case in reality; therefore, we can conclude that something is missing in Newton's theory.

How can we solve these two puzzles posed by Newton's theory? Luckily, more than 200 years after Newton, the beloved physicist Albert Einstein produced a solution. In 1915, Einstein published a new theory of gravity called the Theory of General Relativity [2]. Einstein's theory has a completely different way of looking at gravity, and it helps us to understand things that Newton's theory was unable to explain. This does not mean that Newton's theory was wrong or unhelpful—it just means that it was incomplete, and that the newer theory helps us understand things in a deeper way. Einstein's theory says that, around any massive object, space and time are affected and get distorted or curved, and this creates a pull toward that object.

Here is a simple way to understand Einstein's idea of gravity. Imagine placing a marble on a flat trampoline. The marble stays still and does not move (Figure 2A). However, if you put a large bowling ball at the center of the trampoline, which makes the trampoline curve, the marble will fall toward the center of the trampoline (Figure 2B). The presence of the heavy bowling ball distorted the space occupied by the trampoline in a way that made the marble move toward the bowling ball, as if attracted by it. That is basically what happens in Einstein's theory of general relativity. The presence of any mass distorts the space around it in a way that creates an attraction between masses. This picture of gravity answers the question that Newton could not answer: why (and how) does gravity create an attractive force, and why do you fall *toward* the Earth when you jump up? The second problem, which relates to time, was also solved by Einstein because his theory takes the speed of light into account. In the next section, we will see an interesting and important phenomenon called gravitational waves, which Einstein's theory of gravity predicts.

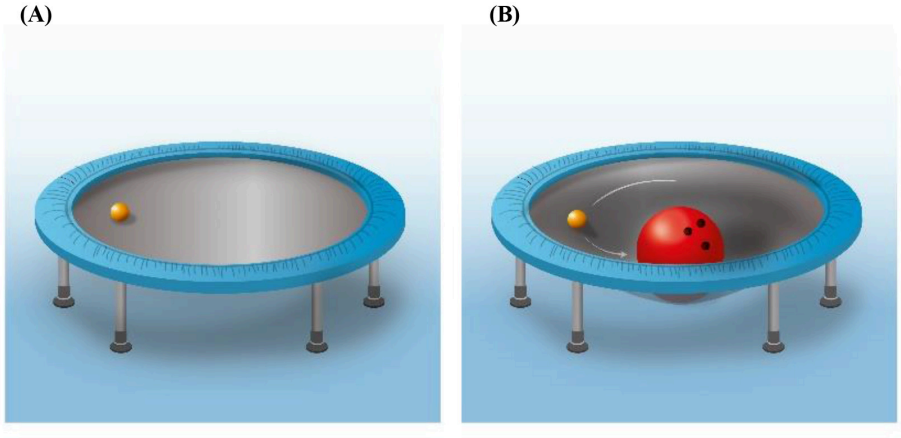

Figure 2

Figure 2

Gravity according to Albert Einstein. **(A)** When you put a marble on a flat trampoline, it stays in place. This represents the situation of space when there are no massive objects present. **(B)** When you put a heavy bowling ball in the middle of the trampoline, the trampoline becomes curved. If you now place the marble on the trampoline, it will move toward the center. This represents the gravity in Einstein's model, where a massive object (like a star) curves space and time, and therefore attracts another object (like an apple, or yourself) toward it.

WHAT ARE GRAVITATIONAL WAVES?

One of the predictions of Einstein's theory of general relativity is that gravity should have waves—**gravitational waves** [3, 4]. A simple way to think about gravitational waves is to imagine yourself by a still pond...then you throw a rock in the pond. The rock makes a splash and drops to the bottom of the pond. Although the rock is now resting at the bottom of the pond, you can still see the effect it had on the surface of the water, where waves are moving from the center outwards (Figure 3A). This is also the way to visualize what happens with gravitational waves. What makes a gravitational wave is not a rock falling into a pond, but rather the motion or collision of massive objects in space (Figure 3B).

GRAVITATIONAL WAVES

Disturbances in space and time that result from the motion of massive objects and spread as waves, at the speed of light.

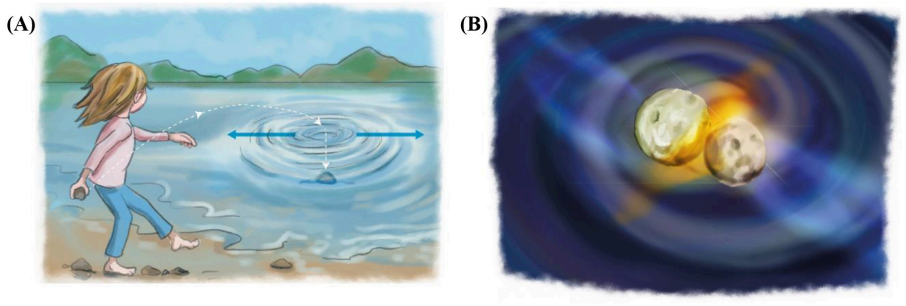

Figure 3

Gravitational waves. **(A)** When you throw a rock into a quiet pond, you can see ripples (waves) moving across the surface of the water, even when the rock is already standing still at the bottom of the pond. According to Einstein's theory of general relativity, this is similar to the way gravitational waves are formed when massive objects collide. **(B)** Gravitational waves are created when two massive objects collide with each other. The waves continue to travel through space, even after the collision has happened.

CHALLENGES AND SUCCESSES OF DETECTING GRAVITATIONAL WAVES

After Einstein's theory predicted the existence of gravitational waves, experimental physicists started trying to detect them. I myself have dedicated more than 20 years of my life developing methods to detect gravitational waves—and I am still doing so. It turns out that, when it comes to gravitational waves, we have both a big misfortune and a big fortune. The misfortune is that we cannot currently make gravitational waves in our laboratories because they are just too weak for us to detect with the techniques we have available. This is a misfortune because good experiments are ones where we understand all that is going on, and that is accomplished much more easily in the laboratory.

On the other hand, we were blessed with a great fortune—nature itself creates gravitational waves that are much stronger than any we could make in the laboratory. This means that some astronomical events that create gravitational waves—two of which I will mention below—can potentially be detected with our present, state-of-the-art detectors. Though these events must be the most violent and energetic astronomical events in the universe for us to detect them, they still occur frequently enough to study. The most violent

events in the universe are explosions and collisions of extremely heavy objects.

One excellent possible source of gravitational waves that we can detect is a type of explosion called a **supernova**. A supernova happens when a massive star gets old and collapses rapidly inward. The collapse creates a huge increase in temperature and pressure, which can enhance the **nuclear fusion**, when lighter nuclei in atoms are combined into heavier nuclei and release energy**.** This can trigger what is called a "runaway nuclear fusion,"[1] which causes the star to explode with enormous energy creating, according to Einstein's theory, strong gravitational waves.

When it comes to violent collisions in space, some of the most energetic are between massive objects such as black holes and neutron stars. **Black holes** are the most massive objects known in the universe, and they have such powerful gravitational attraction that they "swallow" anything that comes near them, even stars. Nothing can escape from inside black holes, not even light—hence their name. **Neutron stars** are the remains of supergiant stars that have collapsed and are extremely dense and consist mainly of neutral subatomic particle called neutrons.

In 2015, the first gravitational waves were discovered [5]. With my two colleagues, Rainer Weiss and Kip Thorne, I won the Nobel Prize in Physics for this discovery, just two years later, in 2017. Usually, it takes at least 20 years before scientists receive a Nobel Prize for their work, but the discovery of gravitational waves was of special significance, for reasons I will explain below. Since those first observations of gravitational waves from the collision of two black holes, we later detected other collisions that produced gravitational waves—one in 2017, between two neutron stars [6], and another in 2020, between a black hole and a neutron star [7].

MEASURING GRAVITATIONAL WAVES

When we measure gravitational waves, we actually measure the distortions (ripples) that they create in space and time. When these distortions arrive at our detectors, they are incredibly small—much smaller even than the size of a single **proton**. To measure such small signals, our detectors must have greater accuracy than 1/1,000 the size of a proton! As you can imagine, this is extremely hard to achieve, and it requires the use of a very special technique called **interferometry**. I will not describe it here in detail, but interferometry uses the interactions between laser beams to spot very small contractions and expansions

SUPERNOVA

When a massive star gets old, it runs out of fuel, cools down, and collapses inward. This produces an enormous amount of energy, triggering nuclear fusion that leads to a massive explosion.

[1] To learn more about runaway, see Thermal runaway.

NUCLEAR FUSION

A reaction in which the nuclei of atoms fuse to create heavier nuclei, which releases a great amount of energy to the surrounding environment. The warmth and light of the Sun result from nuclear fusion.

BLACK HOLES

The most massive objects known in the universe, where gravity is so strong that nothing, including light, can escape.

NEUTRON STARS

The remains of supergiant stars that collapse when they run out of fuel. They are typically only 10 km across and are extremely dense.

PROTON

A positively charged particle present in the nucleus of all atoms. Protons are less than a billionth of the width of a human hair.

INTERFEROMETRY

A measurement technique that uses laser beams to detect very small phenomena, such as gravitational waves in our case.

of space[2]. To make such sensitive measurements, we need to isolate our equipment so nothing can disturb our measurements—even a tiny movement could swamp the signal we are looking for. One source of disturbance is the movement of Earth itself, which shakes as it revolves on its axis (this shaking is too mild to be felt by humans, but it is detectable by sensitive instruments). This means that we need to float our measuring instrument so that it does not pick up the Earth's movements.

It has been extremely challenging to build instruments for measuring gravitational waves. The instrument we use is called LIGO, which stands for Laser Interferometer Gravitational-Wave Observatory. LIGO is a few kilometers long (Figure 4). Building and operating it cost more than 1 billion dollars. Much of my work still involves developing the technologies that enable us to achieve greater sensitivity in the detection of gravitational waves, without unwanted movements ruining our measurements. Many people ask me if it is frustrating to work on the same problem for more than 20 years. My answer is absolutely not! I have had a great deal of fun solving problems along the way, and it is a great privilege to do something that no one has ever done before.

[2] To learn more about interferometry and how it is used to detect gravitational waves, see: Interferometer facts for kids or Gravitational Waves Explained Using Stick Figures. For more in-depth exploration of gravitational waves, see this introductory book. For a more advanced book on general relativity and gravitational waves, see this book or this one.

Figure 4

The LIGO Gravitational Waves Detector (Livingston, Louisiana, United States). A bird's-eye view of one of the two gravitational wave detectors that detected the first-ever measured gravitational waves in 2015. Each LIGO detector consists of two arms, each 4 km (2.5 miles) long, made of 1.2-m-wide steel vacuum tubes arranged in an "L" shape, and covered by a 3-m wide, 3.7-m tall concrete shelter that protects the tubes from the environment. LIGO can detect gravitational waves coming from any direction, even from below (Photograph credit: Caltech/MIT/LIGO Lab).

GRAVITATIONAL WAVES: THE NEW WINDOW ON THE UNIVERSE

So, what is the importance of gravitational waves when trying to understand the universe? First, gravitational waves help us verify that Einstein's theory of general relativity is indeed correct. Even though Einstein's theory *seems* valid and very accurate, it is not the only theory that predicts gravitational waves. To confirm that Einstein's theory is

correct and can explain what gravity is and how it functions, we need to measure details of the gravitational waves that we detect.

Second, gravitational waves can help us learn new things about the universe. You can think of it as a new era in astronomy, much like the one that the famous astronomer Galileo Galilei initiated 400 years ago, when he made a telescope and looked at the sky with it. We can use gravitational waves to look at the universe in a completely different way than we could before—using a "gravitational telescope." Studying gravitational waves can help us better understand how cataclysmic (very powerful) astronomical events occur, such as collisions between black holes and neutron stars. This information could provide insights about events that occurred in the early stages of the universe's formation, and could also help us find answers to intriguing questions about our own planet, such as how heavy elements like gold and platinum arrived on Earth[3].

However, we are not yet very sophisticated in working with gravitational waves, so we usually combine the information that we get from measuring gravity with data that we already have from telescopes. This is enabling us to build a picture of cosmic events that goes well beyond what we could understand without the use of gravitational waves. In the future, as we get better at detecting gravitational waves, we hope to see cosmic phenomena by using *only* gravitational waves. These are very exciting times in cosmology, as our ability to detect gravitational waves opens a new window on cosmological events, which will help us to understand our universe better.

RECOMMENDATIONS FOR YOUNG MINDS

One of the lessons I have learned in life is that it is important to pay attention to your dreams and to try to fulfill them. Your dreams of the future tell you something about what you want in life—whether it is to be a physicist or an artist, or just to do something that is enjoyable, like travel or pursue a hobby that you love. You do not have to succeed in everything your dreams call you to do, but your dreams *are* telling you something about which routes to follow.

Another huge lesson that I have learned is that everything I do in my life is driven by one word: curiosity. Young people are naturally very curious, and you should treasure your curiosity and not let anything dim it—not your teachers, not your parents, nor anyone else. So, my advice is to pursue your curiosity, have fun, follow your dreams, and ignore everything that might limit your enthusiasm.

For those of you interested in science, science can be a lot of fun. There is nothing better in life than doing something good, having fun, and making a living. So, for me, science is a really good occupation.

[3] We know that heavier elements can be made from lighter elements by nuclear fusion in stars. But, as we studied the lifecycle of stars, we saw that the heaviest element created that way is iron (atomic number 26). After the stars burn and use up all their iron, they collapse and do not continue producing heavier elements. Therefore, there should be another mechanism to create the heavier elements. Currently, the most widespread hypothesis is that heavier elements are created in the collisions of neutron stars, which are detectable using gravitational waves (for more information, see this MIT News article). We hope that, in the next years, enough data will be collected using the LIGO and Virgo detectors to validate this hypothesis with higher certainty.

But you must remember that failure is a part of science and accept that not everything you do will succeed...and that failure can be a good thing. When you are at the forefront of science, doing something that has never been done before, it is frustrating at times. Each day, you will be in a situation where you do not really know whether you will make progress or perhaps even a new discovery, or whether you will do something that does not work at all. For individuals like me, this unknown contributes to the fun of doing science!

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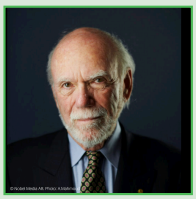
YOUNG REVIEWER

JIARUI, AGE: 13

My name is Jiarui, and I am a 7th grader at a middle school. I won national prizes in English speech competitions and state awards for coding. I like piano, and have gotten the Grade 8 Certificate of ABRSM with a distinction score. I am very interested in physics. I also like baking and cooking. I love dogs and have two poodles.

AUTHOR



BARRY BARISH

Prof. Barry Barish is a physics professor at the LIGO Laboratory at the California Institute of Technology (Caltech), United States. Prof. Barish did both his B.A. and Ph.D. in physics at the University of California, Berkeley, receiving his doctorate in 1962. In 1963, Prof. Barish arrived at Caltech, were he worked in the field of particle physics. Over the next 30 years, he worked with several particle accelerators, including the SLAC accelerator at Stanford University and the CESR accelerator at Cornell University. In 1994, he joined the LIGO (Laser Interferometer Gravitational-Wave Observatory) project at Caltech, dealing with the detection of gravitational waves. Prof. Barish has received many distinguished academic awards, including the Klopsteg Memorial Award (2002), the Enrico Fermi Prize (2016), the Henry Draper Medal (2017) and the Nobel Prize in Physics (2017). Prof. Barish is currently working on further improvements to the LIGO and Virgo detectors, toward higher detection resolutions of gravitational waves. Barry Barish is married to Samoan. They have two children, Stephanie and Kenneth, and three grandchildren, Milo, Thea, and Ariel. *barish@caltech.edu

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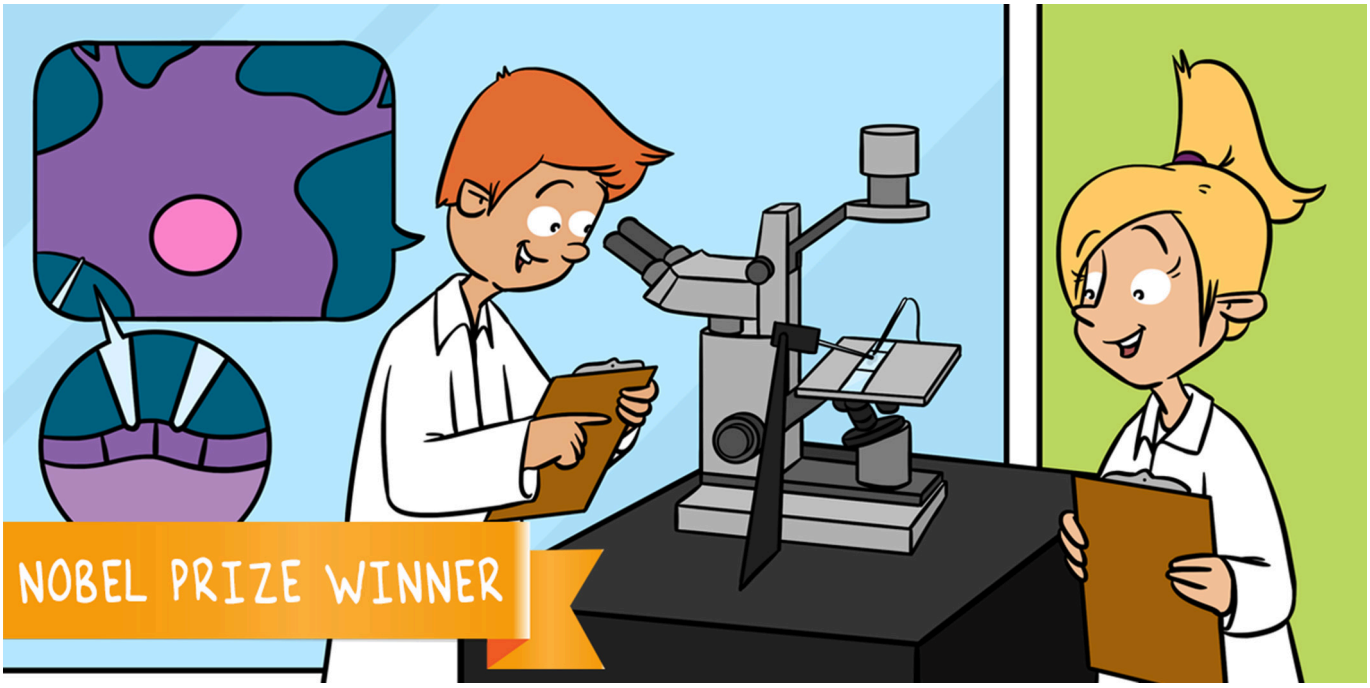

SPARKS IN THE BRAIN: THE STORY OF ION CHANNELS AND NERVE CELLS

Bert Sakmann *

Max Planck Institute for Neurobiology, Munich, Germany

YOUNG REVIEWERS:


ANGELIQUE
AGE: 15


CHASE
AGE: 14


DANIELA
AGE: 13


JAYDEN
AGE: 16


JEFFREY
AGE: 17

Understanding the communication between nerve cells in the brain is key to understanding how the brain works. Communication between nerve cells involves chemical messages sent from one cell that get translated into electrical activity in the receiving cell. This electrical activity is the core language of nerve cells and of the entire brain. How does a chemical message released in one cell results in electrical activity in another nerve cell, and how did we discovery this? Let us dive together into the electrifying world of nerve cell communication. I will tell you about our experiments, which enabled us to find the most basic component of electrical activity in the brain—ion channels. The discovery of ion channels paved the way to understanding the origin of electrical activity in the brain and other organs like the heart. This discovery provided new insights into the development of drugs for treating various electrical-related diseases, such as epilepsy and heart-rate disorders.

JONOVAN

AGE: 14

SHANIA

AGE: 16

Professor Bert Sakmann won the Nobel Prize in Physiology or Medicine in 1991, jointly with Erwin Neher, for their discoveries concerning the function of single ion channels in cells.

HOW DO CELLS COMMUNICATE WITH EACH OTHER?

Your body and every other living body is made of cells—the basic building blocks of life. Each cell is both an individual unit, with its own independent functions, and part of the whole multicellular organism (like the brain and the heart) which needs to operate in a coordinated way. Every cell is surrounded by a clear physical border, called the cell membrane, which separates the cellular contents from the outside (extracellular) environment and from other cells. The membrane allows each cell to have a defined interior environment and to perform its own specialized functions. But, since individual cells are part of a larger structure, most cells—and especially nerve cells—must communicate with other cells. How do cells communicate with each other if they are separated by the cell-membrane barrier? Well, there are several mechanisms that allow cells to communicate with each other. One of the most common ways, and the way we will focus on here, is that a cell sends a chemical messenger substance to the receiving cell [1]. By detecting this substance, the receiving cell "knows" that a signal was sent to it from another cell, and the receiving cell responds accordingly.

NERVE CELLS

The major cellular building-blocks of the brain. Nerve cells generate the electrical activity of the brain.

SYNAPSE

A contact point between two nerve cells, consisting of a small gap where chemical substance—the neurotransmitter—passes from the sending cell (the presynaptic cell) to a receiving cell (the post-synaptic cell).

NEUROTRANSMITTER

A chemical substance that is released from one nerve cell and received by another nerve cell, enabling communication between nerve cells.

COMMUNICATION BETWEEN NERVE CELLS

Nerve cells, the elementary building blocks of the brain, **"**speak" the language of electricity. At every given moment, each nerve cell shows a specific electrical activity, producing a set of brief electrical pulses called spikes. Together with other large networks of active nerve cells, a whole "electrical symphony" is generated in the brain. This electrical activity in large networks of nerve cells in our brain is correlated with every aspect of our behavior and experience; our actions, thoughts, feelings, and memories.

How do nerve cells communicate with each other to create such a coordinated "electrical symphony?" Communication between nerve cells is more complex than communication between other cell types, since it includes both chemical and electrical components. This communication happens at a specific contact location between the cells called the **synapse**, and is comprised of two basic steps. First, the sender cell secretes (emits) a chemical substance, called a **neurotransmitter** [1], into the extracellular space (a gap) between the sending and receiving cells. When the neurotransmitter arrives (*via*

DIFFUSION

A process of spontaneous movement through which particles move undirected from one place to another.

Figure 1

Messaging between nerve cells at the synapse. Communication between nerve cells happens at a specific contact location between the cells called the synapse. First, the transmitting (presynaptic) nerve cell (cell A) releases a chemical substance, called a neurotransmitter, into the small space between the cells. The neurotransmitter crosses this gap and binds to the receiving (post-synaptic) nerve cell (cell B). Consequently, ion channels open in the membrane of the post-synaptic cell through which ions start flowing, giving rise to an electrical signal called a spike (blue circle at right).

ION

A particle with either a positive or negative charge.

ELECTRICAL POTENTIAL

A difference in charge between two points, in our case between the two sides of the membrane. Ions with positive charge will flow from the more positive side to the less positive side.

diffusion) at the receiving cell, it binds there to specific receptors and, consequently, ions start to flow across the membrane of this cell. As a result, electrical activity is generated in the receiving cell (Figure 1).

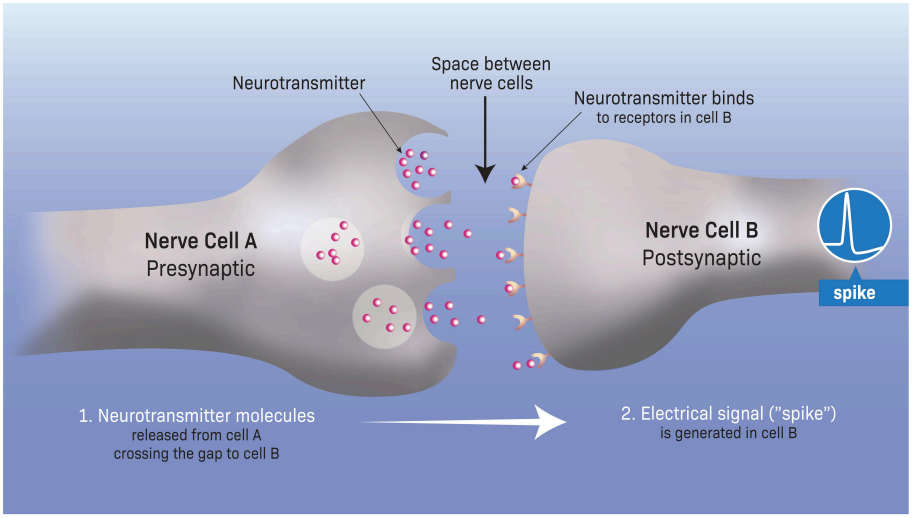

Figure 1

IONS AND MEMBRANE CHANNELS IN NERVE CELLS

Most of the electrical currents in the brain are generated by a small group of **ions**—four in particular. Three of these ions are positively charged (sodium—Na^+, potassium—K^+, and calcium—Ca^{++}) and one is negatively charged (chloride—Cl^-). These ions can enter or exit through the membranes of nerve cells. When they do, they change the **electrical potential** between the two sides of the cell's membrane. These rapid changes in the electrical potential across the nerve's membrane underlie the generation of the basic electrical "word" (or "bit") that nerve cells use; the electrical signals called spikes (Figure 1). You can think of a spike as a very short bolt of lightning—a brief (1 ms, which is 1/1,000 of a second) and tiny (one-tenth of a volt, or 100 millivolts) electrical pulse, that occurs in nerve cells when they are active.

How do these ions cross the membrane barrier of nerve cells to generate electrical activity? And how does the neurotransmitter released from one cell translate into electrical activity in the receiving cell? There must be some pathway for ions to cross the, otherwise insulating, membrane of the receiving cell. When I began to study this field, the mechanism by which ions move through nerve cell membranes was not clear.

Using a special experimental technique that I developed with my colleague, Prof. Erwin Neher [2], we found that ions *do* pass between

CHEMICAL GRADIENT

A difference in the concentration of a substance across locations. The substances, in our case ions in the two sides of the membrane, move "down" the gradient, from the side with higher concentration to the side with lower concentration.

ION CHANNEL

A small hole (pore) made of proteins in the cell's membrane which, when open, enables the passage of ions into and out of the cell.

Figure 2

Ion channels in the nerve membrane. Ion channels (purple) are pores (holes) made of proteins, which are located within the membranes of nerve cells. On the receiving (post-synaptic) cell (see Figure 1) these channels are typically closed (left) but they become open (right) in response to neurotransmitters released from the presynaptic cells. The opening of membrane ion channels enables the flow of ions (orange balls) across the membrane, and this serves as the basic mechanism for generating electrical activity in nerve cells.

the two sides of the membrane, according to their **chemical gradients**. We found that ions cross the membrane through small "holes" in the membrane, called pores. These pores are proteins that serve as channels connecting the outside and the inside of the cell. Since ions are the substances that pass through these pores, they are called **ion channels** (Figure 2). We found that ion channels open and close rapidly in response to neurotransmitters. The opening and closing of specific ion channels (for example, channels that are specific for Na^+ ions or K^+ ions) enables the flow of ions across the cell's membrane. This current flow, in turn, changes the electrical potential across the membrane. In response, the receiving cell generates the sparky spike—the basic electrical "word" in the brain.

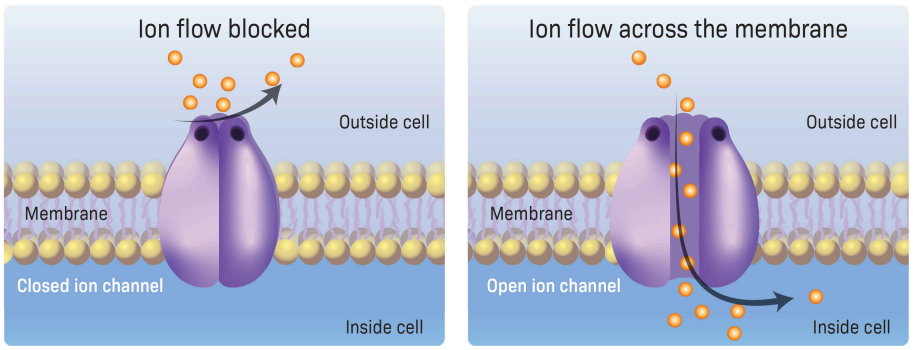

Figure 2

DISCOVERING ION CHANNELS: THE PATCH CLAMP TECHNIQUE

When Prof. Neher and I started studying ion flow in nerve cells, we considered two main ion-transport mechanisms that could be at work. The first mechanism involved a transport molecule. According to this idea, specific molecules in the membrane "catch" one ion at a time, pass it from the outside of the cell to the inside, and release it there. This mechanism was known to occur in other bodily processes, such as in energy production, in which nutrient molecules pass across the cell membrane *via* transport molecules.

The second possible mechanism that we considered, which was later confirmed by our experiments, was that ion channels exist in the membrane for specific ions. These channels may be either open or closed. When open, current can flow between the two sides of the membrane, connecting the external environment of the cell to its interior environment (Figure 2). To examine whether this mechanism is responsible for the transport of ions into and out of cells during the generation of spikes, we had to study the electrical activity resulting from ions crossing the membrane through individual ion channels. To do this, we had to isolate a very small area, or "patch," of the nerve cell's membrane, hoping to measure the electrical current

passing through a single ion channel that might exist in this small patch. If ion channels existed, then we would expect to measure a certain pattern of electrical activity corresponding to the opening and closing of the ion channel, which is different than the electrical pattern expected if transport molecules were used to move ions across the membrane.

To perform this kind of current measurement, we had to overcome two main challenges. First, we had to measure ions flowing across the membrane channel in the small patch of membrane without losing any of this current. This is difficult because, if the recording device is not tightly sealed to the membrane, ions that cross the membrane through the channel might escape sideways before entering the detection device. We therefore needed to make sure that the ions crossing the membrane were forced to flow thorough the detector.

The second challenge was to discriminate between two types of currents that flow through the nerve cell membrane. As it turns out, the membrane is always electrically active—a phenomenon that is called background noise. Background noise appears as constant electrical activity that is different from the electrical activity related to the flow of ions through the membrane in response to neurotransmitters. The background noise can be very large compared to the current that we wanted to measure from the opening of individual membrane channels. Therefore, we had to find a way to reduce the background noise so that it would not overpower (or "mask") the current flowing through single ion channels.

We solved both challenges by using a very thin glass tube called a pipette, with a tip around one micrometer (1/1,000 of a millimeter) in diameter (Figure 3A). The other end of the pipette has an amperemeter, which measures electrical current. The tip of the pipette is strongly pressed against a small patch of the cell's membrane and suction is applied, creating a very tight contact between the pipette tip and the membrane to ensure that no leakage of ions can occur. Recordings from such a small patch of membrane also reduced background noise and, therefore, improved the recording of the flow of ions through the ion channel.

CURRENT FLOW THROUGH THE ION CHANNEL

When no neurotransmitter was present, we found that no current passed through the channel and only minor background noise was observed (Figure 3B). When a neurotransmitter bounds to the membrane, the ion channel opened very rapidly, in a step-like manner, enabling the flow of a tiny current of a few picoamperes[1] across the membrane [2–4]. The unbinding of the neurotransmitter caused the channel to close again (Figure 3B). We found that the ion channel stayed open or closed for only milliseconds (a millisecond is 1/1,000

[1] Picoamperes (pA) are used to measure very tiny electrical currents—one pA is 10^{-12} amperes.

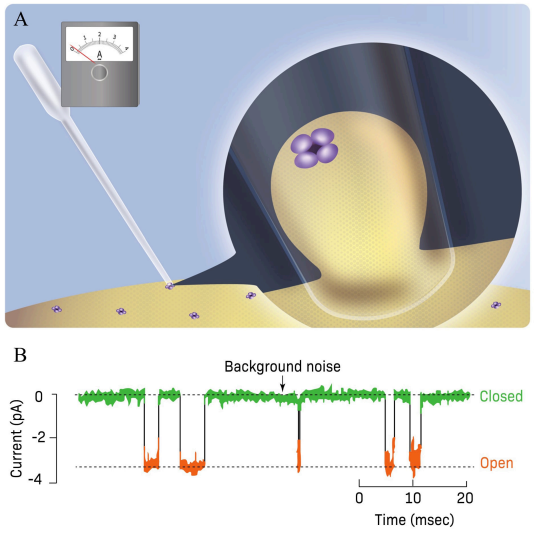

Figure 3

Figure 3

Current flow through membrane ion channels. **(A)** The patch clamp technique. The tip of a thin glass pipette is tightly sealed against a small patch of the cell membrane containing an ion channel (purple, see enlarged version at right). The pipette contains neurotransmitter that binds to the membrane and open an ion channel, which enables ions to flow across the membrane. The current flowing through the ion channel is measured by an amperemeter connected to the pipette. **(B)** Measurement of current flowing through a single ion channel in a small membrane patch. This ion channel opens and closes spontaneously in response to the binding (open) and unbinding (closed) of the neurotransmitter to the membrane receptor (Figure 1). When the ion channel is closed, a noisy background current is measured (green). When the ion channel opens, a rapid downwards, step-like, current is observed (orange) (Figure adapted from Neher and Sakmann [2]).

of a second) and that both the duration of the open state and the time interval between openings of the channel varied, due to the sporadic binding of neurotransmitter molecules. As you can see in Figure 3B, the amplitude of the current when it flowed through the open channel was quite constant.

After measuring the tiny current that flowed through the membrane patch and making some calculations, we estimated that around 10,000 ions crossed the small patch of membrane every millisecond. This told us that the opening of ion channels, rather than the transport of ions *via* transport molecules, is the mechanism enabling ions to across the cell's membrane! Transport molecules are too slow to transport ions across the membrane at such a high rate. This was an important discovery, as it confirmed the existence and function of ion channels as the basic mechanism producing the electrical activity, including the spike, in nerve cells. These ion channels are also responsible for the generation of electrical activity in other "excitable" tissues, such as peripheral muscles and the heart.

Furthermore, it was important to understand the functioning of membrane ion channels because many neurological disorders (as well as disorders of the heart and other body tissues) are due to ion-channel dysfunctions. Consequently, the new term "channelopathies[2]" was coined to describe the (very large) family of diseases caused by defects in the functioning of ion channels. Based on the discovery of membrane ion channels and their function, my colleague Prof. Erwin Neher and I were awarded in 1991 the Nobel Prize in Medicine or Physiology.

[2] See here on groups of diseases caused by the disfunction of ion channels https://en.wikipedia.org/wiki/Channelopathy.

RECOMMENDATIONS FOR YOUNG MINDS

I will start by telling you the most important thing I have learned from my scientific supervisor, Prof. Bernard Katz, who also received the Nobel Prize in Physiology or Medicine in 1970. He taught me that you need to be very critical about your results and always be ready for new findings that might invalidate your previous findings—as unpleasant as that might be. I try to pass this lesson on to my students and teach them to be critical of their results. Especially in biological tissues, there are many influences we cannot control and that must be taken into consideration. Therefore, when my students have a new finding, I advise them to keep it to themselves for a while and repeat their experiments to try to invalidate their results over and over again. They should only publish their results once they are completely convinced those results are correct.

From a more general view of life, in my opinion a good life is one in which you have something to think about that gives you the opportunity to follow your curiosity and possibly discover something new. In other peoples' perspectives, a good life could mean earning a lot of money or being recognized by others, and that is completely fine as well. I think that being a scientist is the best choice you can make, but only if you are curious about Nature. Do not try to be a scientist because you think it is a glamorous profession. If your insides do not burn with the urge to find things out, it is better to choose another profession—one that *does* make you burn with excitement and passion.

ADDITIONAL MATERIALS

- The Nobel Prize in Physiology or Medicine 1991.
- Patch Clamp Method.

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YOUNG REVIEWERS

ANGELIQUE, AGE: 15
My name is Angelique, I am a student in Mrs. Vidalon, 7th grade honors science class at Dodd middle school. My favorite thing to do is watch movies and shows that consist of money and murder. Those are also my favorite fields of study, finance, and criminology. I am incredible at math, I received mastery on the regents exam and I am consistent in getting awards for mathematics. I aspire to be an entrepreneur in the future, and Valedictorian in HS.

CHASE, AGE: 14
I am a student in Mr. Capaccioo's 8th grade honors science class at Dodd middle school.

DANIELA, AGE: 13
My name is Daniela and I am a student in Mrs. Vidalon's 7th grade honors science class at Dodd middle school. My favorite subject is math. I have three siblings, two sisters, and a brother. I love reading fantasy and adventure books.

JAYDEN, AGE: 16

My name is Jayden and I will be pursuing a career in computer science. Reading this article was a great experience as it was very interesting. I think that more kids should read these articles as they provide a great learning experience about topics most people would never see.

JEFFREY, AGE: 17

Hi, I am Jeffrey. I have one brother and one sister and a pet rabbit. My favorite subject is science and more specifically physics. I am currently a student in AP physics 1 and 2 with Dr. Capalbo.

JONOVAN, AGE: 14

My name is Jonovan and I am a student in Mr. Capaccio's eight grade Earth Science Honors class. I like science and math.

SHANIA, AGE: 16

I am a student in Mrs. Parigoris 10th grade honors science class at Freeport High School. I enjoy traveling and admiring new landscapes. My favorite show is Criminal Minds and my favorite musical artist is Abel Tesfaye, also known as "The Weeknd."

AUTHOR

BERT SAKMANN

Prof. Bert Sakmann is a professor at the Max Planck Institute for Neurobiology in Munich, Germany. Prof. Sakmann was first trained as a medical doctor at the Ludwig-Maximilian University in Munich. During his pre-clinical studies, he was exposed to the fields of biophysics and neurophysiology. As a result of his great emerging interest, he decided to move to the field of neuroscience and study fundamental scientific questions revolving around how electrical signals are generated and transmitted in the brain. In 1971, Prof. Sakmann moved to University College London, where he worked under the supervision of Prof. Bernard Katz (Nobel Prize 1970 in Physiology or Medicine, for his discoveries relating to the operation of neurotransmitters in nerve cells). In 1974, Prof. Sakmann joined the department of neurobiology at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, where he met his collaborator, Prof. Erwin Neher, with whom he developed the patch clamp technique that led to the discovery of single ion channels, and for which they won the Nobel Prize in Physiology and Medicine in 1991. Sakmann used part of his Nobel Prize money to establish the annual Bernhard Katz Lecture, in conjunction with the Humboldt Foundation, to promote collaboration between young Israeli and German scientists. In 1979, Prof. Sakmann became a research associate at the Max Planck Institute for Biophysical Chemistry. In 1988, he moved to Heidelberg as Director of the Max Planck Institute for Biomedical Research. In 2008, he moved to the Max Planck Institute of Neurobiology in Munich, where he established and headed the "Cortical Column *in silico*" group. From 2009 to 2011, he acted as the inaugurating director of the Max Planck Florida Institute;

he was a major force in establishing the Edmond and Lily Safra Center for Brain Sciences (ELSC) at the Hebrew University of Jerusalem, Israel. During his career, Prof. Sakmann was awarded several important prizes, including the Louisa Gross Horwitz Prize (1986), the Louis-Jeantet Prize for Medicine (1988), the Magnes Award of the Hebrew University (1982) and Harvey Prize of the Technion (1991), the Nobel Prize for Physiology or Medicine (1991), and Fellowship of the Royal Society award (1994). Prof. Sakmann is a proud father of three children and grandfather of five grandchildren. *bs@mpimf-heidelberg.mpg.de

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DISTANT PLANETS AND BIG PROMISES: HOW TO DETECT EXOPLANETS AND WHETHER THEY HAVE LIFE

Michel Mayor *

Department of Astronomy, University of Geneva, Geneva, Switzerland

YOUNG REVIEWERS:


ANUSHKA
AGE: 15


FAYDH MOHAMMED
AGE: 16


YUTONG
AGE: 11

One of the most interesting, exhilarating, and captivating questions that we can ask ourselves is: does life exist in other places in the universe? This question has sparked the imagination of many generations of science fiction authors, scientists, and intrigued citizens. In this article, I will tell you about the discovery of the first planet orbiting a sun-like star outside of our solar system (exoplanet), for which I was awarded a Nobel Prize in Physics in 2019. I will also tell you about the progress that was made since my discovery, and the current challenges we are facing when dealing with the question of discovering life elsewhere in the universe. How close are we to answering this long-standing question? Let us find out.

Professor Mayor won, jointly with Prof. Didier Queloz, the Nobel Prize in Physics in 2019 for the discovery of an exoplanet orbiting a sun-like star, and for his contributions to our understanding of the evolution of the universe and Earth's place in the cosmos.

Can you imagine the possibility of other life forms living somewhere out there in the universe? At first, this thought may seem a little farfetched or hard to fathom. But, as an astrophysicist, I can tell you that it is actually quite likely. Why? Because there are *so* many planets in the universe—an unimaginable number—and some could be good candidates to support the formation of life. Before we dive into the possibility of other life in the universe, we will first take a look at how we discover planets outside our solar system.

HOW TO DISCOVER DISTANT PLANETS

HABITABLE PLANET

A planet that has the conditions necessary to support life.

When we search for **habitable planets** that could host life as we know it, we look for planets that are similar to Earth. One of the necessary conditions is that these planets should orbit around a star, which radiates heat and light. The star would then provide suitable temperature and energy-production conditions necessary for the development of life, as the Earth receives from the Sun. But the presence of a bright star (like the Sun) near a dim planet (like the Earth) does not allow scientists to detect the planet directly because the light reflected from the planet is outshone by the light from the bright star. For example, the Sun is about a billion times brighter than the light reflected from any of the planets orbiting it. Therefore, we need to develop *indirect* methods to detect the presence of a planet. One of these methods involves detecting the changes that this planet causes on the velocity of the nearby star. To understand this method, we must become familiar with two concepts—spectral lines and the Doppler effect.

SPECTRAL LINES

SPECTRAL LINE

A line of light at a specific wavelength, which is either absorbed by or emitted from atoms.

As you might know, each atom has energy levels that correspond to the movement of electrons around its nucleus. When light passes through an atom, some of the light's wavelengths, corresponding to the energy levels of the atom, get absorbed by the atom. This means that, if we can detect the emitted light after it interacts with an atom, we get a specific "fingerprint" of that atom from the specific wavelengths we observe. The detected spectrum of light, which was previously continuous, is now composed of lines of reduced (dark) or intensified (bright) light at specific wavelengths. These lines are called **spectral lines**[1].

[1] To learn more about spectral lines, see here.

SPECTRAL LINES FROM DISTANT STARS

Each star has a specific combination of atoms in its surrounding atmosphere. So, when we detect the star's light after it passes through the star's atmosphere, we get its unique fingerprint of spectral lines, resulting from all the different atoms in the star's atmosphere. We can use small shifts in these spectral lines to infer the presence of a planet

orbiting around this star. These small shifts are due to a phenomenon called the Doppler effect.

THE DOPPLER EFFECT

Have you ever noticed that, when an ambulance with its siren on moves toward you, the siren's pitch changes—getting much higher, and more shrill, as it approaches and then dropping in pitch and becoming lower as it passes you? Actually, the sound coming out of the siren does not change. What does change is that, when the ambulance approaches you, each sound wave takes less time to reach you than the previous wave, which causes an increase in the frequency of the waves. This makes the siren sounds faster when it approaches you and slower when it moves away from you[2] (Figure 1). This shift in the observed frequency is called the **Doppler effect**.

[2] See demonstration here and explanation in Figure 1.

DOPPLER EFFECT

A physical effect in which the measured wavelength (frequency) of a wave changes as its source moves toward or away from the observer.

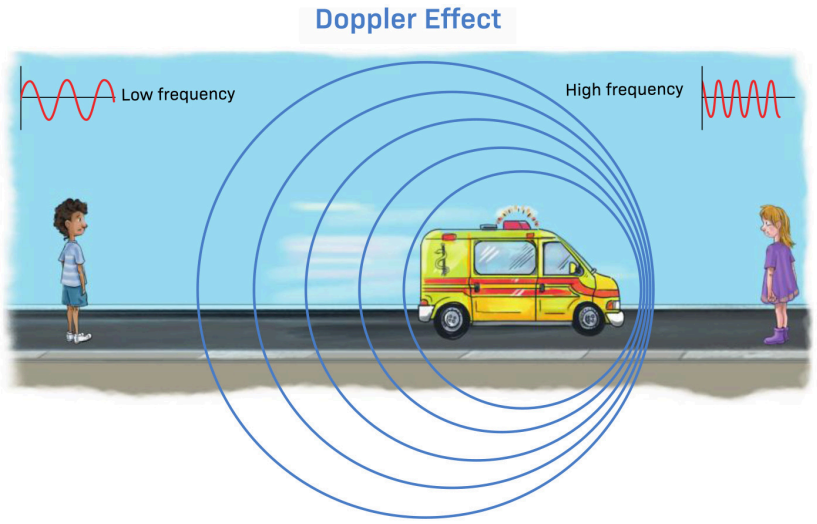

Figure 1

The Doppler effect. When an ambulance with a siren moves toward you (person on the right), the siren's sound reaches you more quickly (with a higher frequency) than when it moves away from you (person on the left, low frequency). This effect is due to the change in the frequency *from the point of view of the observer*. In reality, the frequency of the siren does not change.

The same is true for any type of wave, including light. So, when a shining object like a star moves toward us, its spectral line image will shift to shorter wavelengths and higher frequency (called blue shift), and when it moves away from us, the spectrum will shift toward longer wavelengths and lower frequency (called red shift). Now, when a planet orbits around a star, it influences the movement of the star due to the planet's gravity—the star moves along an elliptical path caused by the orbit of the planet, so at some points in time the star will move *toward* Earth and at other times it will move *away* from Earth. This change in the velocity of the star relative to Earth will cause a change in the star's spectral lines[3] . Overall, this means that we can indirectly infer the presence of an orbiting planet around the star by measuring the Doppler shift in the spectral lines of the star (Figure 2).

[3] See a video demonstration here.

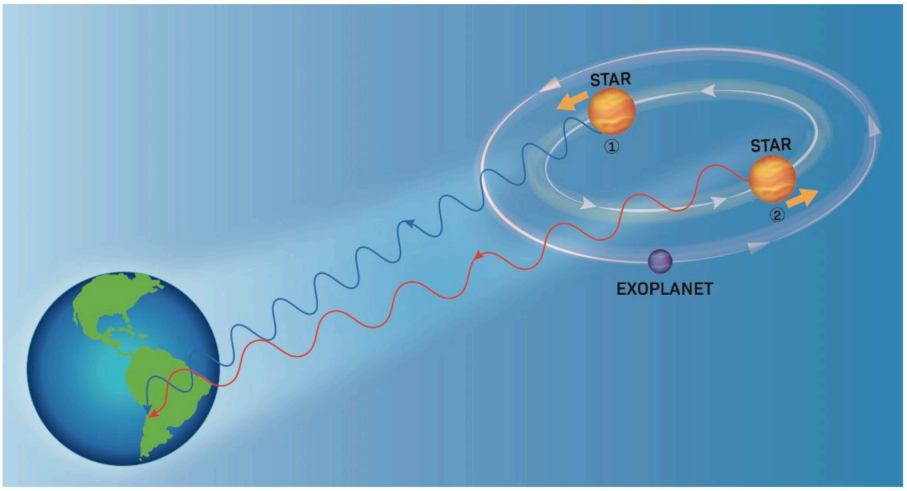

Figure 2

Detecting an exoplanet using the Doppler effect. An unseen exoplanet orbiting around a distant star causes the star to move along an elliptical path. The star will sometimes be moving toward Earth (1) and sometimes away from Earth (2). Due to the Doppler effect, we see shifts in the frequency of the spectral lines emitted by the star, which will be higher (blue) when the star is moving toward the Earth and lower (red) when moving away from it. This shift can be used to infer the presence of the exoplanet (Figure revised from ESO).

THE CROSS-CORRELATION TECHNIQUE

There is a big challenge in terms of using the Doppler effect to detect the presence of an unseen planet. The shifts in the star's velocity caused due to the exoplanet are in the range of only a few meters per second, or even less. In terms of Doppler shifts of a star's spectral lines, this small shift in the star's velocity means shifts of <1 billionth (1/1,000,000,000) of its emitted wavelength [1]. This is such a small fraction that it is impossible to precisely measure when using changes in only a single spectral line due to the Doppler effect.

So, what did we do to increase the precision of this measurement? We used another clever trick, called the **cross-correlation technique**, which was optimized in the 1980s and 1990s and played a big part in allowing us to detect planets outside our solar system.

CROSS-CORRELATION TECHNIQUE

A method that uses the Doppler effect on spectral lines from the light of a distant star to detect planets outside our solar system.

The key idea here is that, instead of measuring the shift in only one spectral line emitted from a star of interest, we measured the *collective* shift due to the Doppler effect on *all* the spectral lines emitted by the star. We did this by using a device called a CORAVEL **spectrometer** (Figure 3A) [1, 2]. The CORAVEL spectrometer contains a plate with a set of holes (Figure 3B), which are located exactly at the positions where we expect to have dark spectral lines in the light coming from a particular star. All the transmitted light emitted through these holes is sent to a single detector. When the dark spectral lines of the star are exactly in front of the holes in the plate, we detect a minimum of the transmitted light (Figure 3C, left). However, if we have a Doppler shift due to the exoplanet influencing the movement of the star, then the position of many thousands of spectral lines will shift simultaneously relative to the position of the holes on the plate, and the amount of light transmitted through the holes will increase (Figure 3C, right). After this Doppler shift, we need to move the plate so that the holes are again

SPECTROMETER

A device used to detect and analyze the spectrum of light, in our case light from stars and planets.

lined up with the black spectral lines, so that we again obtain minimum light in our detector.

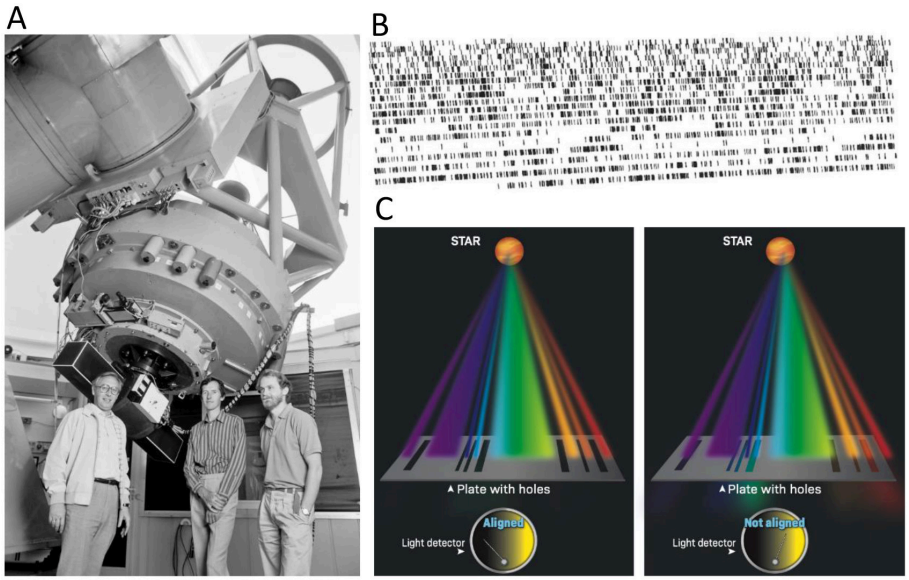

Figure 3

Therefore, when we measure the star's absorption spectral lines at two positions on its trajectory, and move the plate so that the minimum light is detected each time, we know how much the plate was moved between the first minimum (first position of the star) and the second minimum (second position of the star). This shift in the plate's position between two minima is the direct result of the Doppler shift of the spectral lines of the star, due to the presence of the exoplanet. By calculating the Doppler shift in the star's spectral lines, in combination with other measurement, we can learn about the characteristics of the detected exoplanet.

The cross-correlation technique enabled us to concentrate the Doppler information from all the individual spectral lines into one single quantity. We call this quantity the **Doppler velocity**, as it tells us the change in the velocity of the star due to the presence of the nearby orbiting planet. Using Doppler velocity, combined with some other measurements, we can infer not only the presence of the planet, but also learn about its mass, size, and the time it takes for the planet to complete one orbit around the star. This method enabled us to detect 51 Pegasi b—the first **exoplanet** that my colleague Didier Queloz and I discovered in 1995 [3]. With recent spectrographs, the stellar spectra is obtained in a somewhat different way. Instead of scanning the spectrum on a physical plate, the spectrum is recorded on special sensors called CCD detectors (like we have in digital cameras). Then, it is analysed by a computer, based on the same cross-correlation principle that we have seen above.

Figure 3

Cross-correlation measurement with the CORAVEL spectrometer. **(A)** Staff members standing in front of the CORAVEL spectrometer, located in the La Silla Observatory in Chile. **(B)** The original CORAVEL plate with its holes (black stripes) that we used to detect the Doppler shifts of many (dark) spectral lines arriving from 51 Pegasi, using the cross-correlation method. **(C)** The light coming from a star is concentrated by the CORAVEL telescope and projected onto a plate with holes. When the black lines are aligned with the holes in the plate, then the minimum amount of light reaches the light detector (left, "Aligned"). When the black lines are shifted due to the Doppler effect, as the result of the presence of a planet orbiting around this star, they are no longer aligned with the holes and a larger amount of light passes the plate and arrives at the detector (right, "Not aligned"). This shift in the location of the spectral lines, enables us to infer the presence of a planet orbiting around the star (Image credits: **(A)** ESO and **(B)** reference [1]).

DOPPLER VELOCITY

The change in the velocity of a star resulting from the presence of a close orbiting planet.

EXOPLANET

A planet that is located outside our solar system.

51 PEGASI B: THE DISCOVERY OF THE FIRST MEASURED EXOPLANET ORBITING AROUND A SUN-LIKE STAR

51 Pegasi b (Figure 4A) is a planet located about 50 light-years (about 4.7 hundred-thousand billion kilometers!) away from Earth, in the Pegasus constellation in the Milky Way[4] . Its temperature is hot, about 1,000 degrees Celsius. It orbits around a Sun-like star, called 51 Pegasi, and completes its orbit about every 4.2 days. 51 Pegasi b is composed mostly of gases, and is classified as a gas giant, like Jupiter. Because it orbits so close to its star, it is sometimes referred to as a "hot Jupiter." 51 Pegasi b is about 47% lighter in mass and 50% larger in size than Jupiter. The 51 Pegasi star is about 11% heavier and 23% larger than our Sun.

[4] See here.

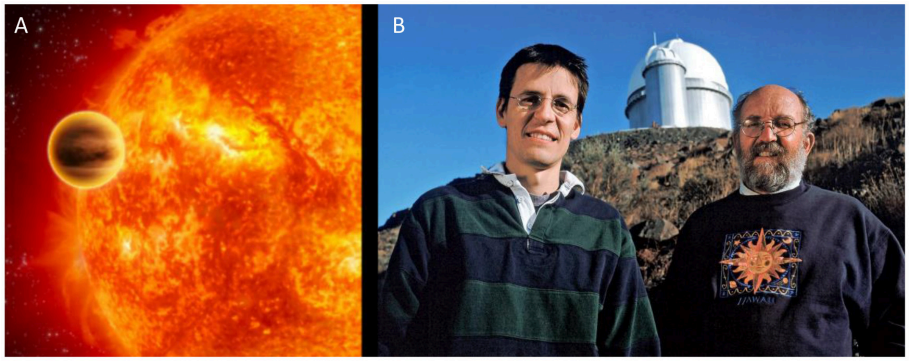

Figure 4

Figure 4

(A) An artistic representation of 51 Pegasi b exoplanet (small sphere) and the star it orbits, the 51 Pegasi star. Pegasi 51 b is a gaseous planet about 50 light years away from Earth. It is the first planet outside our solar system that was found orbiting around a Sun-like star. **(B)** My colleague, Didier Queloz (left) and me, standing in front of the 3.6-m HARPS telescope at La Silla observatory in Chile. Since 2003, the HARPS spectrograph, which implements the cross-correlation technique that we developed, is used to search for exoplanets [Image credits: NASA/JPL-Caltech **(A)** and L. Weinstein/Ciel et Espace Photos **(B)]**.

As mentioned above, 51 Pegasi b was the first exoplanet discovered orbiting around a star. While this star and exoplanet are themselves fascinating to study, their discovery also provided a breakthrough in the field of planet detection, in two significant ways. First, the discovery of 51 Pegasi b proved that planets orbiting stars exist in other places in the universe besides our solar system—something that was not definite before—and that these planets can be detected using the cross-correlation technique. Second, it proved a hypothesis called planetary migration, which is the idea that, over time, planets can migrate, or move, closer to the stars they orbit[5]. Giant planets that are very close to the stars they orbit are very attractive for astrophysicists because such planets can be discovered in a shorter time period using the cross-correlation technique. Prior to the discovery of 51 Pegasi b, scientists believed that the orbit period of a giant star could not be shorter than 10 years, which meant that it would take 10 years to detect one planet using the Doppler effect! But our discovery showed that the orbit period could be as short as a few days—a thousand times shorter than was expected! This means some exoplanets could be detected in just a few days.

[5] For more information about planetary migration, see here.

Both of these breakthroughs contributed significantly to the detection of additional star-orbiting exoplanets. Today, more than 5,000 such planets have been discovered! This is an important step toward finding possible life in the universe.

LIFE IN THE UNIVERSE

Our current definition of life as we know it includes three main characteristics: a living system should be able to protect itself from the environment, interact with the environment, and pass its information to the next generation. This passing of information is performed using long chains of atoms and molecules (called the genetic material, or the DNA), which are very fragile. DNA molecules require specific temperatures and the presence of water. This means that, if there is an exoplanet with life on it, it must fulfill these requirements[6]. Now, how likely is it to find such a planet? Well, since there are so very many planets in the universe, we are absolutely sure that many of them have the possibility for life to develop. But, as scientists, we are not satisfied with simply saying "yes, it is likely"—we want to prove it directly.

It might seem that the simplest way to discover life on other planets would be to send spacecrafts to them, to look around and take pictures. But this is impossible with our current technology and current understanding of physics, because it would take far too long for a spacecraft to get to these very far planets and it would require an unreasonable amount of energy[7] . This means that we need to use remote detection methods, which are indirect measurements and observations that would imply the probable existence of life on a certain planet. For example, we could analyze the chemical components in the atmospheres of exoplanets using spectral lines. Since we are very familiar with the spectral lines of the chemical components in Earth's atmosphere, such as oxygen (ozone), nitrogen, methane, and carbon dioxide, we can try to find similar patterns in the atmospheres of other planets[8] . This and other directions of research, though promising, are very complicated and require further development before they become useful. So, the big questions of whether and how can we detect life on exoplanets remain a marvelous challenge for the next generation of young scientists—like you!

RECOMMENDATIONS FOR YOUNG MINDS

To be a scientist, I believe that you need to have a lot of curiosity. Science is not a "normal" job, it is not only done to earn money. But if you are curious about any topic in science, I believe you will be happy as a scientist—it is that simple. I have never regretted choosing to be a scientist. For me, one of the pleasures of being a scientist is that you have the privilege of working with people from all over the

[6] If a planet *does* satisfy these requirements, it does not necessarily mean that there is life on it, only the *potential* for life. We could also dream about completely different life forms that could develop under conditions different from those we know, but we start with the simplest options based on current science.

[7] This also means that, even if we find a habitable planet outside our solar system, it will not be suitable for human immigration with our current understanding of physics. Therefore, we should make great efforts to protect Earth so that it stays habitable for humans for many generations to come.

[8] For more information about this method, you can read this paper [4].

world. It is nice to feel that you have friends in many places around the globe.

I also believe it is very important for scientists to be able to work well in teams. I have been leading several research groups for many years, and I noticed that even if only one person does not mix well with the team, the whole team can be negatively affected. As part of a team, you should be comfortable with your colleagues and love to go to work with them. So, make sure to match up with the right people, and enjoy your everyday interactions.

ADDITIONAL MATERIALS

- Michel Mayor, Nobel Prize in Physics 2019: Official interview (Nobel Prize).
- The 2019 Nobel Prize in Physics—The discovery of the first exoplanet (Nobel Prize).

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CONFLICT OF INTEREST: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

ANUSHKA, AGE: 15
My hobbies are reading and singing. Following a career in Astrophysics would be a dream come true. I have always been interested in space and Stephan Hawking. I love trying new things, meeting new people, and learning about different cultures.

FAYDH MOHAMMED, AGE: 16
My name is Faydh Mohammed. I like to play a lot of different sport and to learn interesting things. I am keen on technology and I like exploring new tech tools and gadgets. I am a somewhat artistic drawer too. I want to develop my mind and talents to pursue a fulfilling course for my senior years. I am very excited to be working with Frontiers for Young Minds!

YUTONG, AGE: 11
Hello, I am Yutong. I enjoy swimming, skiting and hiking. I love music and singing, I also play the piano. I hope that by reviewing these articles I could learn about new and interesting stuff!

AUTHOR

MICHEL MAYOR
Professor Michel Mayor is a Swiss astrophysicist, born in 1942 in Lausanne, Switzerland. At aged 11–16, he had an exceptional teacher of science, who greatly stimulated his interest in science. At school, he was an active member of the scouts: hiking, skiing, camping in high altitude mountains and every kind of outdoor activity. Prof. Mayor studied at the University of Lausanne, where he received his M.Sc. degree in 1966 for his study on the interactions of spins. He then moved to the Geneva Observatory (University of Geneva), where he completed his Ph.D. thesis in 1971 on density waves in spiral galaxies, and where he became a professor in 1988. He has also worked at the University of Cambridge, the European Southern Observatory in Chile, and the University of Hawaii. Prof. Mayor and his colleagues have developed

several techniques to precisely measure stellar velocities and refined Doppler-shift measurements of spectral lines by the cross-correlation technique, which eventually enabled the detection of exoplanets. In 1995, together with Prof. Didier Queloz, he discovered 51 Pegasi b—the first planet outside our solar system orbiting a Sun-like star in our home galaxy, the Milky Way. This discovery earned him the Nobel Prize in 2019. Among other prizes and awards, Prof. Mayor received the Albert Einstein Medal (2004), the Shaw Prize in Astronomy (2005), the Kyoto Prize (2015) and the Wolf Prize (2017). Prof. Mayor is currently a professor emeritus at the Department of Astronomy in the University of Geneva, and an active researcher in the Geneva Observatory. Prof. Mayor is married to Françoise and they have three children, Anne, Claire and Julien and five grandchildren. *michel.mayor@unige.ch

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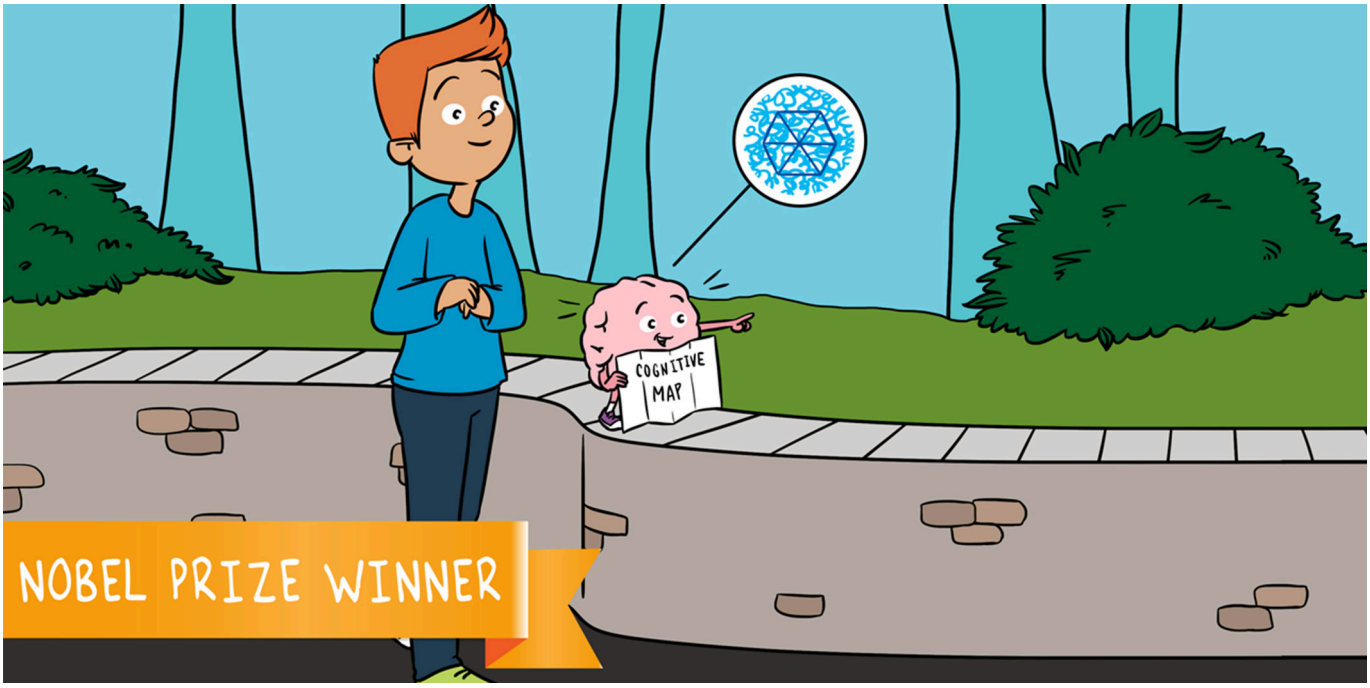

HOW DO WE FIND OUR WAY? GRID CELLS IN THE BRAIN

May-Britt Moser *

Centre for the Biology of Memory, Medical-Technical Research Centre, Norwegian University of Science and Technology, Trondheim, Norway

YOUNG REVIEWERS:

ORT DAFNA HIGH SCHOOL ISRAEL

AGES: 14-15

Navigation in the environment, getting from one place to another, is one of the most fundamental and vital skills in the animal kingdom, and for humans, too. To navigate successfully, an animal needs to create an internal "cognitive map" of the outside environment. This is performed by a specific system in the brain, containing several brain regions and various cell types, each with its unique role in navigation. In this article, I will outline some of the main components of this internal navigation system, focusing on the grid cells, an amazing and surprising group of nerve cells that we discovered, which create a coordinate system in the brain. I will end with a few general recommendations for you, based on my own life experiences.

Prof. May-Britt Moser won the Nobel Prize in Physiology or Medicine in 2014 for the discovery of cells that constitute a positioning system in the brain.

Interviewed and co-written by Noa Segev, graduate of the Grand Technion Energy Program, Technion, Israel Institute of Technology, Haifa, Israel.

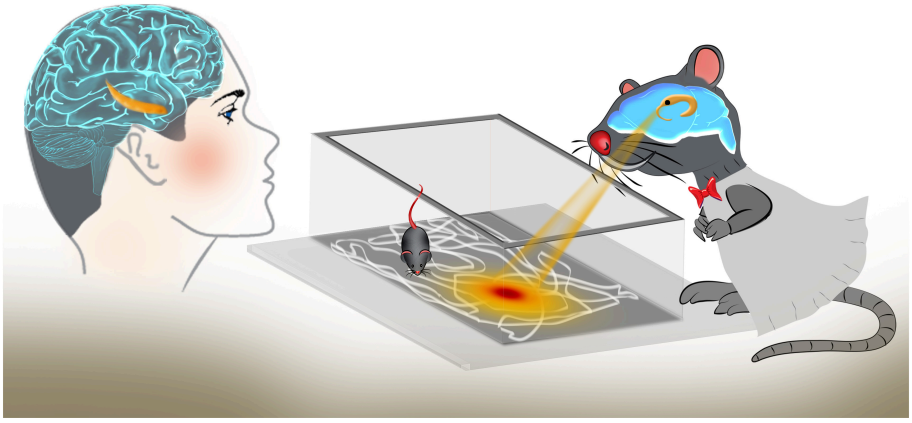

Figure 1

Figure 1

Place cells in the hippocampus participate in building an inner map of the environment. Place cells are found in the hippocampus of both mouse and human brains (light brown). White lines in the box show the running path of a rat in a laboratory environment. The red region shows the location where a specific place cell in the hippocampus (black dot on the rat's hippocampus) becomes strongly active. This is the location that this specific place cell represents. Different place cells are active when the rat is at different locations; together they build an inner, cognitive map of the environment (Adapted from here).

GRID CELLS

Nerve cells in a brain area called the entorhinal cortex, which create a "coordinate map" in the brain that enables navigation and metric (how far and in which direction) in the environment.

When you think about navigation, what is the first thing that comes to mind? Is it the well-known GPS system in your cellphone? An underwater journey of a submarine to its destination? Or perhaps a team assignment in the scouts, to find your way back to the camp at night? What if I told you that your brain has a built-in navigation system that is responsible for representing your location in the environment and for orienting you so that you can successfully get from one place to another? This mental representation of the environment is often called a cognitive map. While navigation in the environment appears seamless and automatic, the brain's navigation system is actually quite complex, composed of several brain regions and various cells types. This article will lead you through a journey of riddles about navigation, which will eventually bring you to a very special system of nerve cells in the brain called **grid cells**, a positioning system that we have discovered and for which we received a Nobel Prize in 2014.

STEP 1: WHERE ARE YOU NOW?

To start navigating in the environment, what is the first step that is required? You guessed it! You need to know where you are currently located. Can you think of a way that the brain figures out where you are located right now? I will give you a hint—it is different from the way the GPS in your cellphone determines your location. As you may know, GPS uses signals sent from at least four different satellites orbiting around the earth. Using mathematical calculations based on advanced physics, these satellite signals are used by your cellphone to determine your location with great accuracy[1]. But does the brain receive signals from an outside source to determine your location? The answer is no. So, what does your brain do to determine where you are? Try to think of at least two possible solutions to this riddle before moving on to the next paragraph.

[1] If you want to learn more about the GPS navigation system, click here.

PLACE CELLS

Nerve cells in a brain area called hippocampus, which tell the animal where it is located in space. Each place cell becomes active in one specific location in the environment. It differentiates between environments by not being active or being active in a very different place in the new environment from what would be expected in the other environment [1].

It turns out that, in the brain, there are nerve cells that represent your location, called **place cells**. In 1971, two researchers named John O'Keefe and John Dostrovsky were studying the electrical activity in rat brains [2]. When they looked at a brain region called the hippocampus, they saw that when the animal was at a specific place in its environment, certain nerve cells became active and started firing electrical signals at a high rate (Figure 1). Other place cells were activated when the rat was in different locations. In other words, if you are standing in a particular location in your room, there is a specific place cell in your hippocampus that is strongly active, and this cell tells you where you are. The electrical activity of these place cells is so precise that, if we simultaneously record the activity of 100 of them for a while, we can accurately predict the location of a rat within 5 cm! This is quite extraordinary, as these cells are deep in the brain, far from the senses; they do not have eyes or ears, or any other sense organ, so how do these place cells get their information about the environment?

STEP 2: HOW FAR DID YOU GO AND WHERE DID YOU ARRIVE AT?

SPEED CELLS

Nerve cells whose activity "reports" on the speed in which the animal moves by increasing their activity when the animal moves faster. These cells are located in the entorhinal cortex and are used by the animal to calculate the distance it passes in the course of its movement.

ENTORHINAL CORTEX

An area located deep in the brain, near the hippocampus, slightly beneath the ear level. This area is an important part of the navigation system (the "cognitive map") of the brain, and it contains, among others, the grid cells, head direction cells and speed cells.

Let us say that you figured out that you are standing in a specific place, using a specific place cell. You then walked for a while and determined your new location, using another place cell. But how do you know the distance between these two locations? In other words, how do you know the relative location of the two places? First, try to think of what you need to know to calculate the distance between two points. If I told you that I was walking for 2 min, what would you ask me to determine how far I walked? That is right, you would need to know my walking speed. The brain solves this problem with the help of **speed cells** [3], which tell you the speed at which you are moving. These cells are not located in the hippocampus, but rather in a different, deep brain region called the **entorhinal cortex**.

If you knew my starting location, my walking speed, and how long I walked for, could you tell where am I now? Or is additional information needed? For example, if you knew that the starting point and the destination point are 100 m apart, could you tell where I am on the circle around my starting point, which has a radius of 100 m? (Figure 2). The answer is no. The additional information you need is direction. The brain also has **head direction cells**, which are found in several brain areas [4]. When these cells are active, they inform the animal of what direction it is moving. Knowing your initial location, your walking speed and time, and the direction of your walk, you can know exactly where you are now relative to where you started (Figure 2).

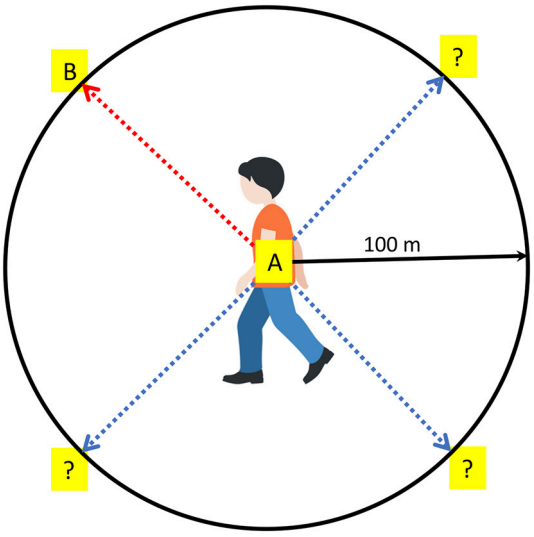

Figure 2

To navigate successfully in the environment, you need to know your starting position **(A)**, target location **(B)**, walking direction, and speed. Knowing that you started walking from a given location (using place cells) and walked for 2 min at a speed of 50 m per minute (using speed cells), you know that you traveled a total of 100 m. But can you determine where exactly you are on the circle with a radius of 100 m around you? No! (blue dashed lines). For this, you need head direction cells, which provide the direction you are heading (red dashed line).

STEP 3: ARE THERE OTHER WAYS TO FIND YOUR LOCATION AND GET FROM A TO B? GRID CELLS

Here is a difficult (but rewarding) riddle. To navigate from location A to location B, we saw that it is enough to know the initial place, the speed, the time, and the direction of movement. However, to the surprise of many brain researchers, the brain uses an additional and amazing trick to solve the problem of navigation. I will give you a hint: it is related to a coordinate system on a map. This brain system is called the grid cell system.

The grid cell system is located in the middle of the brain, a bit below the ear level, in a deep brain area called the entorhinal cortex (Figure 3, purple area), which is located close to the hippocampus. Unlike hippocampal place cells that become active when the animal passes through one specific location, a grid cell becomes active at many locations in the environment (Figure 3). Most surprising was the finding that these locations form a symmetric and extremely accurate crystal-like pattern, characterized by equilateral triangles connecting the centers of nearby locations. These locations, called coordinates, form a hexagonal (six-sided polygon) grid and, therefore, we decided to name these cells grid cells[2]. It is important to emphasize that the coordinate patterns of grid cells are generated within the brain, they do not exist in the outside world.

Each grid cell forms a unique pattern of coordinates, which is shifted with respect to the coordinates formed by other nearby grid cells. In this way, the whole environment is "filled" with grid patterns (Figure 4A). Using only one grid cell you cannot know where the animal is, because each grid cell is active in multiple locations, forming a grid. But, because of the shift in location between different grid cells, and because of the varying scales of the grids (Figure 4C), it is possible

[2] Watch this video to see https://www.youtube.com/watch?v=i9GiLBXWAHI.

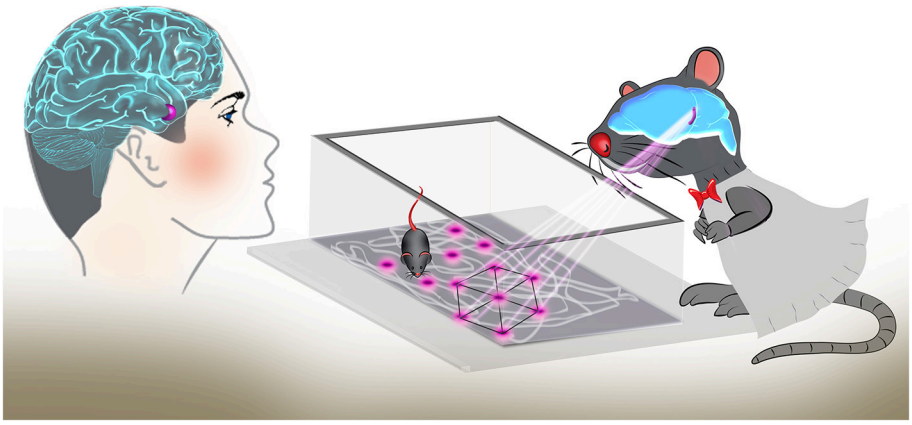

Figure 3

Grid cells in the entorhinal cortex are activated at multiple locations, forming a symmetrical coordinate system in the brain. Grid cells are located in a brain region called the entorhinal cortex (purple). White lines in the box show the running path of a rat in an environment. The same grid cell becomes electrically active at multiple locations along the rat's path (purple circles). The locations where the grid cell fires are arranged in a highly symmetrical hexagonal grid.

[3] You can watch these overlapping grid cell patterns and how it provides the location of the animal in this video.

to define the animal's current location with great accuracy, using the overlapping grids of several cells[3]. These grid patterns serve as an internal map of coordinates in the brain and can also be used for measuring the distance between different points in space, a critical requirement for navigation (Figure 4B).

MORE SURPRISES ABOUT GRID CELLS

We found that the grid structure of the grid cells persists even when an animal walks in the dark [5]. We found that, to anchor the grid to the specific environment the animal is in (is it a large or a small room?), the animal uses sensory information, specifically visual information, such as cues on the walls and the location of the walls in the room. The grid patterns rotate when cues on the walls are rotated, and grids may expand or contract when one of the walls is moved to make the room larger or smaller. Interestingly, grid cells in different depths along the entorhinal cortex represent the same environment at different scales [5]. Grid cells located at the dorsal (upper) part of the entorhinal cortex fire at close physical locations of ~25 cm apart (Figure 4C, top right)—representing the environment with a fine ruler, whereas deeper (ventral) grid cells form a coarse ruler, as they fire at more distant locations of up to 3 m apart (Figure 4C). Grid cells with varying scales all keep a similar symmetrical grid pattern.

Let me tell you yet another surprise about grid cells. Apparently, it is not only the brain that uses grid cells for successful and efficient navigation. In a fascinating study recently performed at an artificial intelligence company called DeepMind in London, U.K., researchers gave information about head direction and speed to a learning machine. The machine was supposed to learn to navigate in a new and challenging environment. After learning, the machine outperformed humans in navigating. Surprisingly, the machine spontaneously created artificial units with grid patterns, very similar to those of the grid cells in the brain [6]. What does this tell us? Even if the grid cell

HEAD DIRECTION CELLS

Nerve cells found in several brain areas that inform the animal in which direction it is heading. Each head direction cell fires only when the animal's head is facing in a specific direction in space (e.g., north-west, but it is a private/subjective map and does not follow magnetic poles). Thus, a cell which is active when the head is pointing north in one environment might fire to south in the other environment. And cells follow each other: if one cell is shifted 180° in one environment all other cells would do the same.

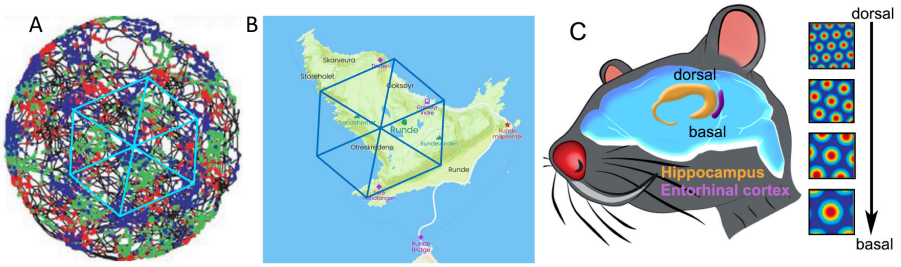

Figure 4

Figure 4

Grid cells coordinates map the environment. **(A)** Grid structure of three nearby grid cells (green, blue, and red), recorded simultaneously when a rat was running in a circular environment. The grid structure for the blue cell is highlighted by the light blue hexagon. The three cells have the same grid spacing and orientation but are shifted in space. **(B)** The grid structure could serve as a coordinate system for a cognitive map of the environment. **(C)** Grid cells located at the dorsal (upper) part of the entorhinal cortex (purple) represent the environment in fine scale (dense grid at top right), whereas ventral (deeper) grid cells form a coarse ruler (sparse grid at bottom right).

pattern is something that "just happened" during evolution, it must be extremely useful for navigation. We know that the brain is very efficient, and if there is a phenomenon (like grid cells) that is created almost by accident, it could become beneficial for the functioning of the animal. Think of it this way: imagine you receive a tool, such as a screwdriver, and you do not know what it is used for. As time passes, you will probably try to use the screwdriver in different circumstances, and eventually you will find ways that it is useful, right? The same holds true with the brain: it explores ways to use all the tools that it has, and finds ways that those tools are beneficial for the animal's survival.

Together, grid cells produce internal coordinate maps that allow an animal to navigate from one location to another. The grid cells work in unison with place cells and with other cell types, such as head direction cells and speed cells. This navigation system also integrates information from the senses, to calibrate the internal maps with the environment. This whole navigation system in the brain allows us to perform complex navigation tasks in a smooth and seamless manner. While we have learned a lot about this fascinating brain system, many aspects of it are yet unknown. For example: How does paying attention to cues in the environment or in memory affect the navigation system? How is the volume of an animal's body taken into account when the animal navigates? And what happens to the navigation system in a sick brain, such as in Alzheimer's disease, where cells in the entorhinal cortex die and the ability to navigate is lost? Another exciting question is how distance and direction between an animal and external objects are coded in the entorhinal cortex, and whether the cells also code for moving items like a ball in a soccer match [6]. These are challenging and important questions that could be part of a fascinating scientific journey for those of you who would like to become brain scientists.

RECOMMENDATIONS FOR YOUNG MINDS

As children and teenagers, you should remember that it is very difficult to understand what life will look like when you become an adult. I believe that it is important to maintain your curiosity about things, both now and as an adult, and to find something that you have a passion for,

something that makes you feel enthusiastic and lively. I think that it is all about passion—your passion could be for math or physics, dance, writing, or anything else. You should always follow this internal drive and build your life around your strengths and your passion. Then your life will be much better than it would otherwise.

Many people will tell you which career you should have and why; because then you can get money or you earn a reputation, or you can get a Nobel Prize... but do not take this path. Go through the path that you feel is right for you. It might be anything that enriches you, that you like, that you can master. For myself, I can say that I am very curious about things and that it is extremely important for me to understand things. It gives me so much pleasure when I understand something that I did not understand before—this is my leading star.

Lastly, as a woman who won the Nobel Prize, it is important for me to emphasize that when you find your passion, it should not matter whether you are a man or a woman. I always thought of myself as a person, and when I became a scientist—as a scientist. I did not think so much about the fact that I am a woman. I think of myself as a scientist who was very lucky and who worked very hard and have fantastic collaborators. This, eventually, led me to win a Nobel Prize. But, even though being a man or a woman is irrelevant when it comes to passion, we should all be aware that there are specific environments where people do try to push females aside. In these environments we all—both males and females—should strongly support females or other minorities.

ACKNOWLEDGMENTS

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YOUNG REVIEWERS

ORT DAFNA HIGH SCHOOL ISRAEL, AGES: 14-15
The students in this class study in a special program that focuses on physics, biology, mathematics, and computers sciences.

AUTHOR

MAY-BRITT MOSER
I am a professor of neuroscience, the director of the Center for Neural Computation, and co-director at the Kavli Institute of Systems Neuroscience at the Norwegian University of Science and Technology in Trondheim. I received the Nobel Prize in Physiology or Medicine in 2014, together with my long-term colleagues Edvard Moser and John O'Keefe. I was born in a small town called Fosnavåg in Norway. I attended the University of Oslo, where I studied mathematics, physics, and chemistry. I was awarded a degree in psychology in 1990 and a Ph.D. in neurophysiology in 1995, supervised by Per Andersen. Edvard Moser's and my two daughters were born in 1991 and 1995. Both during my Ph.D. and until I returned to Norway in autumn of 1996, when both Edvard and I were appointed as associate professors in biological psychology at the Department of Psychology at the Norwegian University of Science and Technology (NTNU) in Trondheim, we worked in Richard Morris' lab at the Centre for Neuroscience, University of

Edinburgh. In the summer of 1996, I was a visiting post-doctoral fellow at the laboratory of John O'Keefe at the University College, London, for 1 month. In 2000, I was promoted to a position of full professor of neuroscience, and at that time we moved to the medical faculty at NTNU. I am a member of the Royal Norwegian Society of Sciences and Letters, Norwegian Academy of Science and Letters, and the Norwegian Academy of Technological Sciences; an elected foreign associate of the National Academy of Sciences (USA), international member of the National Academy of Medicine (USA), and elected international member of the American Philosophical Society (USA). I have received numerous honors and prizes, including the Liliane Bettencourt pour les Sciences du Vivant in 2006, elected member of the European Molecular Biology Organization (EMBO) in 2012, 26th Louis-Jeantet Prize for Medicine (Louis-Jeantet Foundation) in 2011, the Andre Jahre Award in 2011, 13th Perl/UNC Neuroscience Prize (University of North Carolina) in 2013, Best Female Leader Award from Trondheim Business Society (Madame Beyer Award) in 2013, 47th Louisa Gross Horwitz Prize for Biology or Biochemistry (Columbia University) in 2013, 59th Karl Spencer Lashley Award (American Philosophical Society) in 2014, 30th Koerber European Science Prize (Koerber Foundation) in 2014, 102nd annual Fridtjof Nansen Award of Outstanding Research in Science and Medicine in 2013, Norwegian Academy of Science, Elected as a Fellow of the Association for Psychological Science for sustained and outstanding distinguished contributions to psychological science in 2018, and the Grand Cross of the Royal Norwegian Order of St. Olav (H.M. Harald of Norway)—the highest Royal Norwegian Order in 2018, and Gunerius gold medal 28th of February, awarded by the Royal Norwegian Academy for Sciences and Letters. *may-britt.moser@ntnu.no

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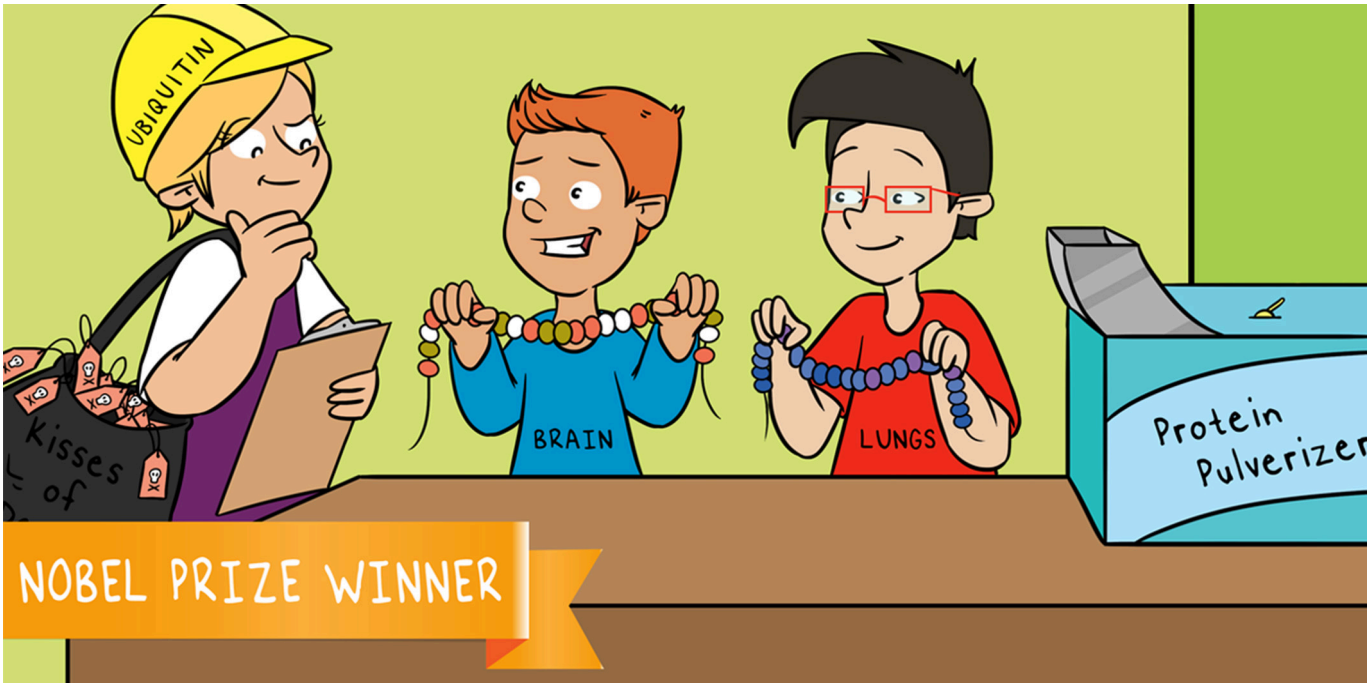

TARGETED DEGRADATION OF PROTEINS — THE UBIQUITIN SYSTEM

Aaron Ciechanover*

The Rappaport-Technion Integrated Cancer Center (R-TICC), The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel

YOUNG REVIEWERS

HEBREW UNIVERSITY SECONDARY SCHOOL

AGE: 14

Proteins are the engines of all forms of life, for humans and for all the plant and animal kingdoms. Proteins are used both to build organs (such as bones, muscles, and skin) and to perform bodily functions. These functions range from digestion (processing food and converting it into energy), to enabling movement and sensation (sight and hearing), to protecting the body from foreign invaders with our antibodies, which are also proteins. What are proteins? They can be compared to words in a language that contains letters. In the Hebrew alphabet, there are 26 letters out of which countless words can be composed. But when we write, we use just a fraction of these infinite options, with the average number of letters in a word ranging between 3 and 8. The biological "protein alphabet" is comprised of 20 "letters" called amino acids, which are the building blocks of the proteins that make up the body. Proteins are chains of amino acid, linked together in a specific order governed by the DNA. Unlike the words of a spoken language, the average protein consists of hundreds of amino acids. The extensive length of proteins and the

chemical composition of the amino acids make proteins sensitive to many factors, such as high temperatures, radiation, and chemicals. All these factors damage proteins and alter their fragile structures, negatively affecting how they function. When proteins are damaged or when they finish performing their functions and are no longer needed, the body breaks them down. With my doctoral adviser, Prof. Avram Hershko, and our research collaborator, Prof. Irwin Rose from the Fox Chase Cancer Center in Philadelphia, we discovered the mechanism responsible for targeted degradation of proteins in cells. This degradation can recognize damaged proteins or proteins that are not needed anymore, while leaving intact the "healthy," functional ones. This mechanism is called the ubiquitin system after its principal protein, ubiquitin, which was the first protein we discovered in the system. Ubiquitin's role is to tag undesirable proteins so that the cell's "grinder" can recognize them and break them down, enabling the cell to function normally. In this article, we will explain the story of proteins and the ubiquitin system that we discovered in a study that earned us, among other prizes, the Nobel Prize in Chemistry in 2004.

Professor Ciechanover won the Nobel Prize in Chemistry in 2004 for the discovery of the ubiquitin system, which is responsible for protein degradation in the body's cells.

Interviewed and co-written by Noa Segev, graduate of the Grand Technion Energy Program, Technion, Israel Institute of Technology, Haifa, Israel.

PROTEINS: WHAT ARE THEY AND WHAT FUNCTIONS DO THEY PERFORM IN THE BODY?

Twisting Chains of Beads

Proteins are essential biological molecules that are made from building blocks called amino acids. There are 20 different amino acids that comprise all the proteins in our bodies (and in all other plants and animals). Think of amino acids as beads that connect to each other to form a chain. This chain is the most basic structure of a protein, and it is called the primary structure (Figure 1A). When this chain begins to twist and turn, more complex structures are created (Figure 1B). The most common are a spiral called an alpha (α) helix, or a pane-like structure called a beta (β) sheet. The tertiary structure (Figure 1C) is a three-dimensional structure formed by the folded secondary structures, and it creates a protein that can perform a variety of functions in the cell. The fourth and final structure is called the quaternary structure (Figure 1D), and it is formed from at least two proteins that interact with each other.

PROTEIN

An organic molecule present in all organisms, including viruses. A protein is a chain that can be composed of 20 different building blocks called amino acids. This chain has a primary structure (the amino acid sequence), a secondary structure (the arrangement of the acids in helices and sheets), a tertiary structure (the three dimensional arrangement of the structure), and a quaternary structure (the structure of the different subunits in a complex). Proteins are central components in many processes in the body, such as: food digestion, energy production, structure (bones), movement (muscles), cell division, sensory (such as sight), and defense from foreign invaders (antibodies). Proteins are very sensitive to environmental conditions like temperature and oxygen, and are constantly being damaged, which is why they are in a constant turnover of formation and degradation.

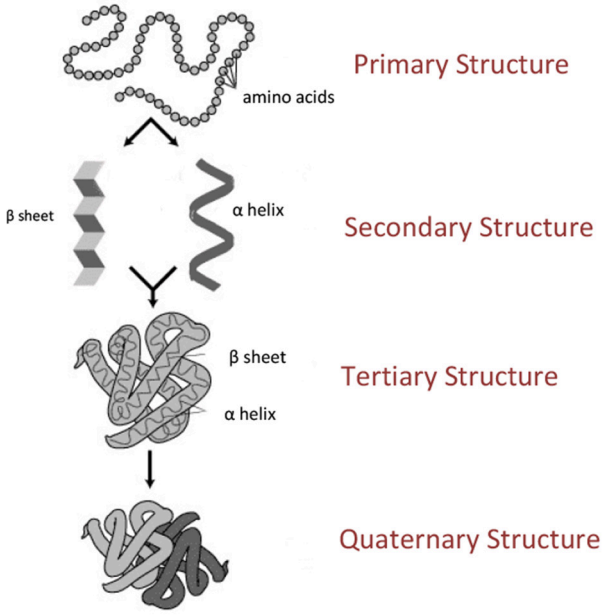

Figure 1

The structure of a protein. Proteins are made from 20 "beads" called amino acids. When the amino acids join to each other, they create a chain called the primary structure (A). The primary structure can twist and turn and take on more complex forms, called secondary, tertiary, and quaternary structures (B–D, respectively). The secondary structure comes in two main forms—the alpha helix and the beta sheet (B). The tertiary structure arises from the folding of the secondary structure (C). The quaternary structure, which is formed only in certain proteins, is made up of at least two proteins that interact with each other (D) (Image credit: Wikipedia).

It is important to mention that when we consume proteins through foods, like eggs, cheese, or meat, it is not possible to absorb them in their chain form, since in this state they are like foreign substances that invade the body, and they may trigger an immune response. Instead, the digestive system breaks down the proteins from their complex, chain form into their amino acids, and these are absorbed by the body. The body can use these absorbed amino acids to create any new proteins that it needs.

The Protein Symphony Within Us

There are about 25,000 different proteins in the human body, with millions of copies in each of the body's cells. Some proteins, which are essential for basic functions, such as energy production, are found in every single cell, while others are only found in specific tissues, like light receptors in the eye. These proteins play together in a wondrous symphony, the symphony of life. The beauty of this orchestra is that proteins do not even need a conductor; each protein knows exactly what it must do at any given moment. Most of these functions are automatic: the beating heart, the exchange of gases in the lungs, filtration in the kidneys, digestion in the digestive tract, even posture and walking. We actively think about only a small fraction of the things we do, like thinking, talking, and writing.

Proteins carry out a variety of diverse functions in the body (Figure 2); here are a few examples. To move, the body must use muscles. But what makes our muscles move? Two proteins called actin and myosin, which are found in our muscle cells. You can think of actin and myosin as cogwheels that lock into and move against each other. Myosin's "head" can move toward actin, and once it binds to the actin

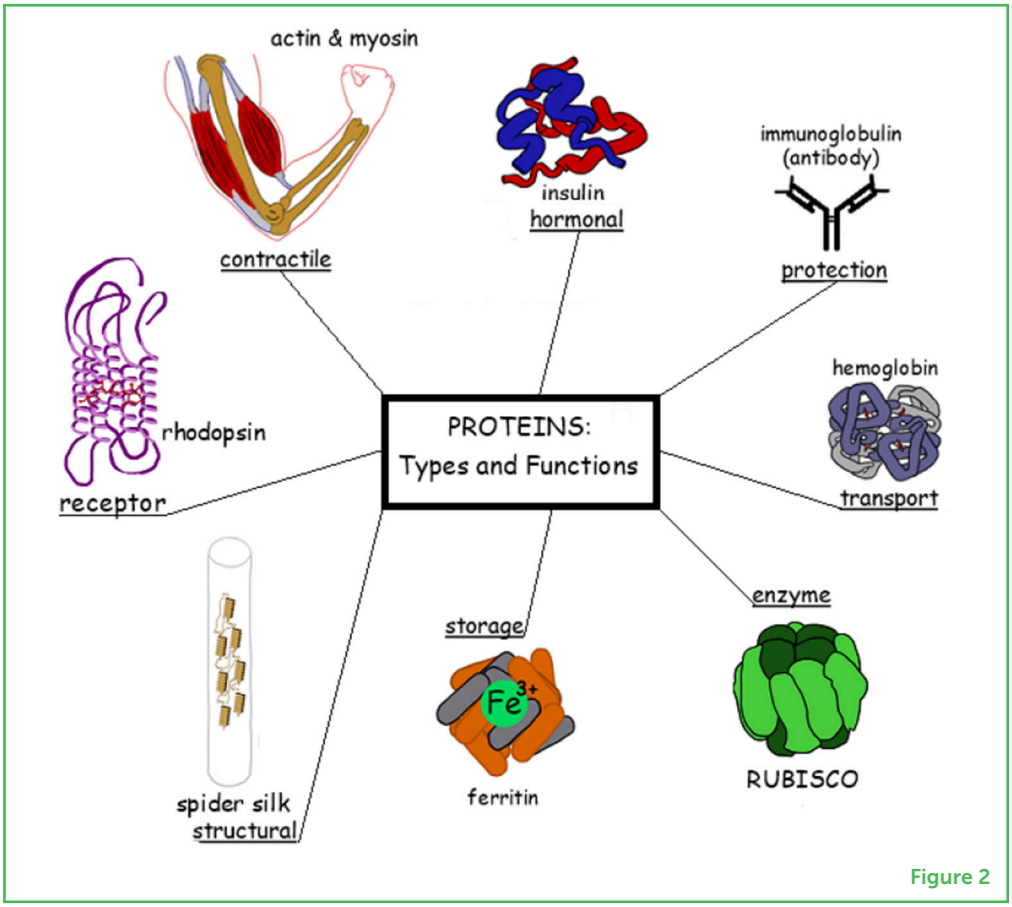

Figure 2

Figure 2

Examples of functions of proteins in the body. Clockwise from the left: a light receptor in the eye called rhodopsin enables sight in low-light conditions; in muscle cells, actin and myosin enable muscles to contract; a hormone called insulin, secreted by the pancreas, regulates the sugar levels in the blood; immune system proteins called an antibodies help neutralize foreign invaders; hemoglobin in red blood cells carries oxygen to the cells; rubisco plays a role in the conversion of sunlight into energy in the form of sugars in plants and other organisms; ferritin binds iron in cells so that it can be stored (a ferritin deficiency may lead to anemia); spider webs are made out of structural proteins that are secreted by the spider.

filament it pulls it, while simultaneously pulling another adjacent actin filament toward it. The pulling of two actin filaments toward each other (occurring simultaneously by many myosin heads in a muscle) is what causes muscles to contract (a demonstration of the action of myosin and actin can be seen in this clip).

Let us look at a different example, breathing. Do you know why we breathe? To create energy. We absorb oxygen from the air into our tissues so that we can make energy for our cells to use. In the process of making this energy, CO_2 gas is formed as a waste product and must be expelled from the body by the lungs. Both the transfer of oxygen from the lungs to the cells (during inhalation) and the transfer of CO_2 from the cells to the lungs (during exhalation) are mediated by a protein called hemoglobin. Hemoglobin is found in red blood cells and gives blood its red color and that can be found in red blood cells; see Figure 2, right).

If we look at the body's **immune system**, which protects us from diseases and infections, we will also find proteins, in this case called **antibodies**. Antibody proteins attach themselves to invading viruses or bacteria and cause the invader to be neutralized and destroyed (Figure 2, top right corner). One way to create antibodies is by administering a vaccine against diseases, such as flu, polio, or measles. Vaccines can

IMMUNE SYSTEM

The body's defense system against harmful invaders like viruses and bacteria.

ANTIBODY

A protein in the immune system, whose function is to help neutralize harmful invaders.

Figure 3

Figure 3

Proteins found in foods are damaged at room temperature and higher. Milk and meat spoil very quickly out of the refrigerator, for the same reasons that you cannot "uncook" a hardboiled egg. At room temperature and higher, proteins lose their organized structure, which gives them their proper function, and they become "disorganized." This process of altering a protein's structure is called denaturation, and it may occur due to heat, or exposure to oxygen or radiation (Image credit: istockphoto.com/fcafotodigital).

consist of a dead or weakened virus that cannot cause the disease, but can still trigger the immune system to create antibodies against it. After vaccination, if viruses or bacteria of the same type invade the body, the body will be ready to take them on and destroy them, using the antibodies that were formed against the vaccine. This is especially important today, since we hope that antibodies will protect us from SARS-CoV-2, the coronavirus that causes COVID-19, whether they are formed after we get sick (heaven forbid) or after we are vaccinated. Further examples of protein functions can be found in Figure 2.

Sensitive Proteins: Why Cannot a Cooked Egg Be Returned to Its Liquid State?

As described, the body has many types of proteins that perform a variety of important functions. The trouble is that proteins are extremely sensitive and are easily damaged. For example, if you leave milk or fresh meat out of the refrigerator, they will spoil very quickly (Figure 3). Similarly, when an egg is cooked, the heat transforms the proteins from a liquid state to a solid one and it is impossible to return the egg back to its original state, no matter what you do. The same goes for a fried egg. Even if you were to piece the broken shell back together, put everything back into the shell, and cool it in the refrigerator, the egg would not return to its original, liquid state.

Why does this happen? Because proteins in foods get ruined at room temperature and higher, such as temperatures used in cooking. Proteins, as we have explained, fold into complex structures, such as spherical coils. When proteins are heated, the relatively weak chemical bonds that hold their three-dimensional structures together become weaker, causing the proteins to lose their shape and become "disorganized." Think of a ball of yarn that has been unwound then tangled. This disorganization makes proteins lose their functions. This process is called **denaturation**. Denaturation can also be caused by radiation from radioactive materials or ultra-violet radiation from the sun. Another cause of protein denaturation is chemical changes to the amino acids, like those caused by the oxygen in the air. The damage

PROTEIN DENATURATION

A process in which the three-dimensional structure of a protein is altered as a result of high temperature, for example. Denaturation damages the proper function of the protein.

to protein structure from denaturing factors causes the protein to stop functioning as it should.

In addition to damaged proteins, there are many proteins whose function is needed only during specific times, like during cell division. This is one of the steps in the lifecycle of the cell, and it occurs, when all is well, at a specific point every so often. As a result of the division two cells are formed. Also, when one cell dies the remaining cell will divide again to make up for the one that was lost. This division is mediated by certain proteins ("division accelerators"), and once division has occurred they are no longer needed. They are degraded and in their place "division inhibitors" are created and so forth. If, for instance, these division accelerators were to remain in the cell, the cell will continue to divide many times in an uncontrolled manner, which can lead to diseases, such as cancer.

For all the above reasons, the proteins in the human body can be damaged as well. The body's high temperature (roughly 37°C), exposure to the oxygen in the air, radiation and chemicals are all causes of harm to the proteins that make up our body.

An important point to mention is that life at 37°C is necessary to optimize all the chemical reactions whose purpose is one- maintaining life. No one can deny the need for oxygen, either. Thus, perhaps paradoxically, the two most important factors for maintaining life were discovered to be harmful to the structure of proteins. Therefore, evolution made sure to develop mechanisms for fixing and quality checking to deal with this damage, neutralize it and enable life. These mechanisms are an intrinsic part of life itself. This is not like a traffic accident and then repairing the subsequent damage, since accidents may or may not occur. Rather, these are coupled processes, the price we pay for the pleasure of being alive, which I would term destruction for the sake of construction. The body has many mechanisms for quality control that protect all its elements including the genetic material, the DNA, from damage. There are even a number of different mechanisms for protecting each element, a sort of safety net, evidence of how important this protection from the environment is. We will discuss here just one of these systems, the one that degrades damaged or unneeded proteins, to avoid the damage caused by their accumulation.

How Does the Body Deal With Damaged Proteins or Those That Completed Their Function and Are Not Needed Anymore?

If so, how does the body deal with damaged proteins and those whose function has come to an end and are no longer needed, and whose continued function and\or accumulation may cause harm? It breaks them down into their most basic elements—the amino acids. The rate of degradation is astounding: about 6–7% of the proteins in the body are degraded every single day and are very accurately replaced by new

ones created in their wake (by the DNA and RNA systems that exist in every cell in our body). This means that in the short time of a month or two all the proteins in our body—beside a small number of unusually stable ones—are replaced. Note that this is an average number. There are some proteins that have very short lives and are replaced a few times an hour, and there are others, like hemoglobin, that are long-lived and are replaced only once every few months. A fascinating question that arises is, if all the proteins in your body are different from those of 2 months ago, are you still the same person that you were before? How are memories, talents, and emotions, the "software" that makes us human, maintained, while our entire "hardware" is replaced? Another question is, if we are constantly regenerating, why do we age? These captivating questions are still unanswered. What we do know is how the cellular system responsible for the specific degradation of damaged or unneeded proteins functions. This system is called the **ubiquitin** system [1].

UBIQUITIN

A protein that tags other proteins for degradation.

It is worth mentioning here that there are some diseases, some of which are severe, that are linked to the malfunctioning of the protein degradation systems in the body. In Alzheimer's disease, for example, certain proteins that should degrade but fail to do so, accumulate in the brain, which ultimately leads to brain shrinkage and the loss of cognitive functions, memory among them. A similar situation occurs in Parkinson's disease. Malignancies too can sometimes be caused by mutations in genes, the code for functional regulatory proteins. These mutations transform them into oncogenes, genes that cause cancer (oncos-swelling in Greek). Understanding the mechanisms for protein degradation in the body may therefore enable us to develop drugs and to treat conditions like Alzheimer's disease by restoring the proper function of the protein degradation system. It is also possible to deliberately damage the protein degradation system in cells to treat some diseases. An example of such a disease is multiple myeloma. This condition is caused by the uncontrolled cell division of the cells in the bone marrow that create antibodies. This accelerated division leads to damage to bone structure, causing breaks, and also to suppression of the division of other cells in bone marrow, such as white and red blood cells. This can cause breathing difficulties because of the reduced ability of the blood to bind oxygen, and to infections due to the lack of white blood cells to fight them. By interfering with the protein degradation systems in these cells and purposefully preventing the degradation of antibodies, proteins can build up and kill the cells that produce them, thus slowing down the disease. In a later section we will refer in more detail to the multiple myeloma disease and its medicinal treatment.

A SYSTEM FOR PROTEIN DEGRADATION

Ubiquitin: The "Kiss of Death" for Proteins

As we previously mentioned, there are several reasons for the degradation of proteins in the body. The first reason is for quality

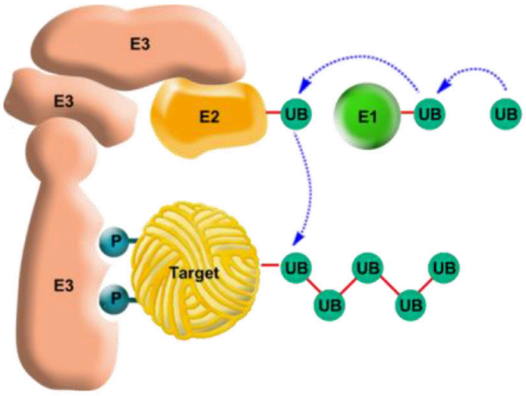

Figure 4

Figure 4

The ubiquitin system for tagging proteins for degradation. The ubiquitin system is a complex system whose purpose is to tag proteins meant for degradation ("Target" protein in the center). The system is comprised of three different types of proteins: two carrier proteins, E1 and E2 (above, in green and orange, respectively) whose job is to activate and later carry the ubiquitin protein, and its ligase (E3, left, in pink) whose job is to hold the target protein while ubiquitin binds with the latter. Once the ubiquitin has been activated by E1 it is transferred to E2 and binds to the target protein that is "harnessed" to E3 (sometimes it can be transferred first to E3 and only then to the target protein). At first a single ubiquitin molecule is attached to the target protein, and later more ubiquitin molecules bind to it and to each other, head to tail, to create a polyubiquitin chain (UB, dark green top right). This tagging of the target protein by the polyubiquitin chain is what signals to the cell that it must now recruit the "grinder" to degrade the protein. This "kiss of death"—the polyubiquitin chain—can be equated to those that are sentenced to death in the United States and that are dressed in a different uniform, to mark them in advance.

control, in other words degrading abnormal proteins, such as those that were harmed by the denaturation that was mentioned above. Another reason is for process regulation, in other words accelerating or inhibiting processes that are protein-dependent, such as cell division. A third reason is for the proper differentiation of tissues. As a part of embryo development, cells need to differentiate in order to build the different tissues and organs of the body: brain cells, pancreatic cells, muscle cells, and so on. Each tissue is constructed from proteins needed for its function only, and not from the sum of all proteins in the body. Thus, as part of the cell differentiation process it is necessary to degrade proteins, which allows for the correct differentiation of cells and proteins into the appropriate tissue.

How can the body distinguish between dysfunctional or unnecessary proteins and functional proteins whose continued presence is necessary? And once the proteins that need to be degraded are recognized, how are they actually broken down? It turns out that all the proteins meant for degradation are recognized by the cell and undergo a tagging that we call the "kiss of death." How are they tagged? One speculation is that the tagging system might be able to identify the parts of the protein that are exposed if the protein denatures—parts that are not normally exposed. Another possibility is that, as a protein begins to denature, further changes happen to it, such as the addition of a phosphate molecule, and it is this addition that attracts the "kiss of death." This "kiss" is carried out by a protein called ubiquitin. During the first step, the protein that needs to be tagged, the one meant for degradation (Target protein in Figure 4, yellow) associates itself with one of a thousand proteins that are called ubiquitin ligases (since they ligate, or join, ubiquitin to the target protein) and that are called E3 (Figure 4, pink). This binding between the target and ubiquitin ligase is very specific, like a lock and a key. This connection between the "victim" and the ligases fixes the protein in its place, like a car mount for a cellphone, so that it will be "comfortable" for ubiquitin to bind to it.

Figure 4

Yet, just as those prisoners have the right of appeal, also in nature there is a possibility of saving the target protein: if the protein has regained its natural form, folded correctly and is prepared to function once again then ubiquitin remover proteins can separate the chain from the former target and disassemble it to single ubiquitin molecules for reuse in the cell where they will attach to other proteins needed for degradation, similar to the process of pardoning those sentenced to death (see also Figure 5).

PROTEIN ACTIVATION

Moving the protein from a state in which it cannot carry out a certain function (this state is called "dormant") to a state in which it is capable of carrying out that certain function (it can now be called "active").

ENZYME

A protein whose function is to speed up chemical reactions by lowering the amount of energy necessary for the reaction.

Before ubiquitin binds to the target protein and "kisses" it, it must go through two stages of **activation**. This activation can be thought of as activating an app on a cellphone—the app is always installed, but until you open it, it is not active (and there is no reason for it to be constantly active. The activation of ubiquitin is accomplished by E1—a single protein known also as an **enzyme** that activates ubiquitin (Figure 4, top right). Once activated, the ubiquitin is carried by one of the fifty E2 proteins to the bound target protein. The activated ubiquitin attaches itself to the target protein (Figure 4, bottom) and then additional ubiquitin proteins connect to it, to form the polyubiquitin chain that constitutes the "kiss of death" that signals the cell to degrade the target protein.

Once the target protein is tagged with a polyubiquitin chain, this chain binds an enzyme (which is also a type of protein) called the proteasome (Figure 5), whose purpose is to degrade the protein. The proteasome can be thought of as a "grinder" that grinds up the protein and disintegrates it into its basic components—the amino acids. At first, the polyubiquitin chain serves as glue to adhere the target protein fated for degradation to the "blender" (Figure 5, right). Next, the target protein is unfolded by other enzymes into a long chain (Figure 5, center), and fed into the proteasome. While passing through the proteasome it is degraded into its basic components (Figure 5, left) which the cell can recycle and use to build new proteins.

We have seen that, for a protein to be degraded in the cell by the ubiquitin system, there are two main stages: (A) The creation of the polyubiquitin chain that is attached to the target protein; and (B) The recruitment of the proteasome followed by the degradation of the target protein and recycling of its components, the amino acids, to build new proteins. The ubiquitin molecules are also recycled, so they can tag other proteins for degradation. The wonderful thing about this system is that each protein destined for degradation is like a needle in a haystack; it is one among millions of other proteins that are needed and that the body must not break down. The beauty of this system is that it can recognize this needle in a haystack, using ubiquitin as a tag, and perform targeted degradation only of the damaged/unneeded proteins.

This targeted mode of action is unique to the ubiquitin system in relation to other biological processes that degrade proteins and that do so indiscriminately. These systems, like the lysosome and autophagy, "swallow" everything around them and degrade all the swallowed protein without discrimination. This too serves a purpose, such as providing building blocks and energy during starvation. In such a time of stress, it does not matter which proteins are degraded. The body needs building blocks and energy, and any protein can serve this purpose. The function of the ubiquitin system is different; it can identify and guide the degradation only of proteins that must be degraded, and not the other proteins that are critical for most of our functions. As the

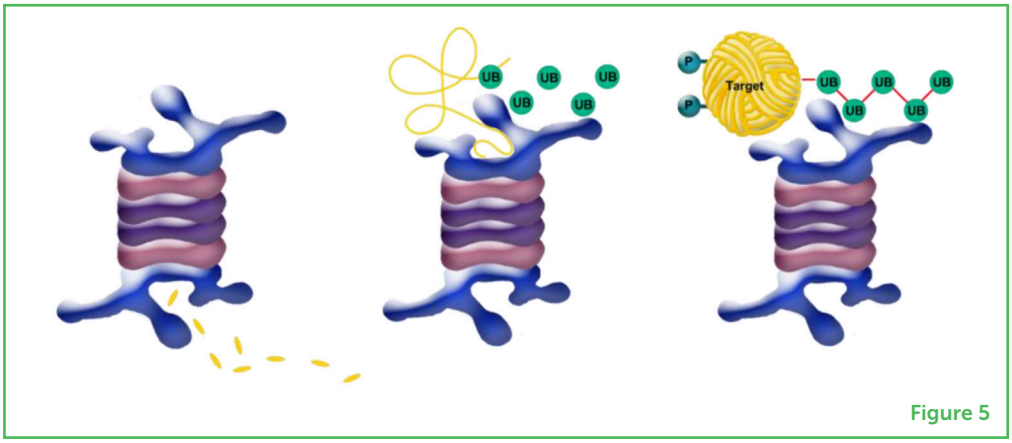

Figure 5

Figure 5

Degradation of ubiquitin-tagged target protein. The target protein is degraded by the "blender" or "garburator," a protein complex called the proteasome (blue body). **(Right)** The target protein ("Target," yellow), fated for degradation and tagged by the chain of activated ubiquitin proteins (UB, see Figure 4, above), is attached via this chain to the proteasome. **(Middle)** Other enzymes unfold the target protein (yellow open coil, above) and feed it into the proteasome, while ubiquitin remover proteins release the ubiquitin which is recycled. **(Left)** The proteasome complex degrades the unfolded target protein into its fundamental units- small chains of amino acids (called peptides) that are later broken down into single amino acids (yellow fragments, below).

wisest of men, the author of Ecclesiastes, said, "To everything there is a season, and a time to every purpose under heaven: A time to be born, and a time to die; a time to plant, and a time to pluck up that which is planted; a time to kill, and a time to heal; a time to break down, and a time to build up; a time to weep, and a time to laugh; a time to mourn, and a time to dance."

Drugs Based on the Ubiquitin System

Once we understood how the ubiquitin system works, the fact that its disruption can lead to disease, and the fact that this system can be regulated, it was time to develop medical applications based on the ubiquitin system. As we have seen, proteins carry out many important functions in the human body, and their normal functions are dependent on the proper functioning of the ubiquitin system. Yet there are cases where the ubiquitin system malfunctions, like when it is overloaded (when too many proteins need to be degraded at once) or when the function of one of its elements is disrupted, such as is caused by a mutation in one of the E2 (one of the ubiquitin carrier proteins) or E3 enzymes (one of the ubiquitin ligase proteins, see Figure 4). When the ubiquitin system is not operating properly, proteins may be degraded either too much or not enough, and then a disease may develop. Cancer is an important example. The cells in our bodies have different rates of division. Some of them divide once every few days (the epithelial cells that coat the digestive system or bone marrow cells, which are the blood "factory"). Others, such as brain, muscle, and fat cells, do not divide at all. Still others divide very slowly, including bone and cartilage cells. In cancer, the cells of the affected tissue divide rapidly and uncontrollably and form a tumor. One of the causes of cancer is the malfunction of the ubiquitin system. This can happen when the body degrades too many proteins that repress cell division, or when it fails to degrade proteins that encourage cell division. In these instances, cells may increase their rate of division uncontrollably and become cancerous. It is not necessarily a result of a failure in the ubiquitin system. Cancer is "sneaky" and can create proteins "on purpose" which encourage cell division that the ubiquitin system is not

familiar with and cannot recognize them as proteins that need to be degraded. It is these proteins that initiate the cancerous process.

Today, there are two families of drugs in use to treat cancers of the blood, especially cancer of the lymphocytes, the cells that produce antibodies (multiple myeloma). One family of drugs is called proteasome inhibitors. They inhibit the degradation of the antibodies that are formed in the cancer cells and should be broken down; this buildup and retention causes cell stress that kills the cancerous cell. It is interesting to note that this mode of action is different than that of most anti-cancer treatments, like chemotherapy, and this difference means that proteasome inhibitors can be given along with chemotherapy drugs, to make chemotherapy more effective. Drugs in the second family contain a molecule that connects "by force" the cancer-causing proteins to the ubiquitin ligase, which otherwise would not have bound them. These are "double-headed" proteins, in which one head binds to the cancer-causing protein and the other to the ubiquitin ligase. Ubiquitin ligase then attaches ubiquitin to the cancer-causing protein, which results in its degradation by the proteasome. These two types of drugs have dramatically increased the odds of recovery from multiple myeloma. Previously, this disease killed people painfully within 2 years of diagnosis. Now, multiple myeloma is curable in some patients, while others survive longer, with improved quality of life. Therefore, our understanding of the ubiquitin system has contributed, and continues to contribute, to the development of life-saving drugs.

Here is a personal story that touches on the saving of a life and also to my career, that changed direction from medicine to research. When we arrived in Sweden to receive the Nobel Prize in December of 2004, the Israeli ambassador threw us a party, along with the leaders of the local Jewish community. This party celebrated both the Nobel Prize and the holiday of Chanukah, which took place at the same time. The ambassador prepared a "gift" for us. This gift was not a box wrapped with paper and a colorful bow, but a Swedish man. Up until a few weeks before then, this man had been on his deathbed in a hospital in Stockholm, suffering from multiple myeloma. His last resort was a drug that was still experimental, a proteasome inhibitor called Velcade® that had been developed in the United States based on the function of the ubiquitin system we had discovered. In Figure 6, you can see an example of the state of the bone marrow (tissue that is the "factory" that makes all the blood cells and that can be found mostly in the core of vertebrae and long bones of the body, the thigh, and arm bones) of a patient before and after treatment with Velcade®.

A few days after receiving the drug intravenously, the patient was able to get up and return to living a normal life. That moment, in which a person approached us, passionately embraced us with tears in his eyes, and thanked us for saving his life (albeit indirectly) was a very emotional moment for me, a moment of coming full-circle. Although

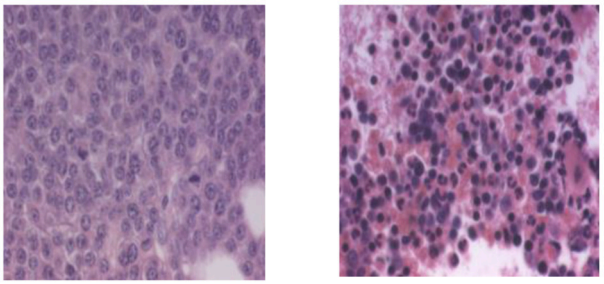

Figure 6

Figure 6

Bone marrow from a multiple myeloma patient before and after Velcade®. In multiple myeloma malignancy, plasma cells that normally generate antibodies undergo a transformation and begin to multiply uncontrollably in the bone marrow, the "factory" that creates all the types of blood cells. **(Left)** The bone marrow of a patient prior to treatment with Velcade®, which is a drug that inhibits the proteasome. The marrow is flooded with plasma cells that have multiplied uncontrollably. It contains 41% cancerous plasma cells. **(Right)** Bone marrow from the same patient after treatment with Velcade®. It now contains only 1% cancerous plasma cells. This photo was given to Prof. Ciechanover courtesy of Millennium Pharnaceuticals.

I did not continue my original career path as a doctor, I still ended up affecting lives through my research, perhaps more profoundly than I would have had I continued to practice medicine.

RECOMMENDATIONS FOR YOUNG READERS

If you are uncertain about what you want to be when you grow up, I would recommend you do this: pursue what you feel that you are very good at and that you love doing. Often, these things go together: if you really love doing something, and it is your biggest hobby, then you will also be good at it. You will devote yourself to it and study it, and you will learn how to deal with the obstacles along the way. If you truly love something, you will realize that there are no failures but rather lessons to be learned, and progress toward the success that will surely come.

When people ask me about the secret of my success, I say that I was wise to identify that maybe I was not good enough at my first occupation (medicine), but mostly that I did not love it enough. I realized that I needed to move to another occupation. I knew that I was not good at mathematics, so I did not even attempt a career that required significant knowledge in that field. I actually liked medicine, but once I was deep in it I realized that over the years in this profession (which is a fascinating one), I would repeat myself over and over again, diagnose and treat the same diseases. Although it was important and interesting, I thought I was more suited for innovation. I chose research and knew right away that this is my hobby; it is what I love to do. I also knew to choose a young and inexperienced supervisor who made a great name for himself, Avram Hershko, with whom I came a long way (and together we were awarded the Nobel Prize). He had only just completed his post-doctoral fellowship, and I purposefully chose him because he offered me an adventurous path into the unknown. He had a hypothesis that was a starting point in a different direction than the conventional one. Of course, we needed luck, too. When I am asked, "why did you decide to work on ubiquitin?" I answer that I did not, but rather I decided to work on the biological problem of how proteins are degraded. Working on this biological question

using biochemical techniques is what revealed ubiquitin to us. Later, techniques for sequencing the human genome revealed the full extent of the ubiquitin system and its important function in regulating many bodily processes. Eventually, the importance of the ubiquitin mechanism in the development of life-saving drugs was discovered, but even now we are only at the beginning of the road.

I have been in this field for almost five decades, but every day is like the first day for me. I am surrounded by young and creative people who enrich me with their innovative ideas, and I contribute to them from my experience. The meeting between innovation and experience is fascinating and develops new ideas that are often correct. For me, the love of the profession is no different from any other love: loving one's parents, close friends, or one's partner. So, my wish is that you find that professional love, and that it brings you success. This love need not be in science, it can be in any field: art, music, engineering, medicine, law, or architecture. What is important is that you feel that what you are doing fits you like a glove. This will ensure your success and your contribution to others, and will keep you interested and curious for many years to come.

To those of you who do choose science as a career, I have further advice: tell a story. If you want to have an impact, you need to be consistent and construct a story. As soon as you have found an interesting beginning to a potential story, persist, develop it, and do not constantly jump around from subject to subject. It is like being every day someplace else—people would not recognize you and would not be able to identify your special story. Prof. Hershko and I are each identified as "Mr. Ubiquitin." Ubiquitin is our story, and that is what enabled us to open up a whole new field of research, to pave new trails in science, and to generate knowledge that ultimately led to saving lives. If I had abandoned the story after publishing the first paper, these things would never have been possible. Remember to be patient, and remember that our goal in science is not to become professors and especially not to receive awards; these will follow if you succeed. Our goal as scientists is to uncover the secrets of nature and maybe also to use them for the benefit of mankind. The true test of science comes when someone repeats your experiment in Buenos Aires, New York, or Paris without you even knowing it, and then someone else does a follow-up experiment, and then a follow-up to that, and gradually a whole new story of innovation is revealed. Today, there are many thousands of people worldwide who are working with a system that was first discovered in the early 1980s, in a small lab in the Technion in Haifa. Big drug companies manufacture life-saving drugs, many millions of people have benefited, and more will continue to benefit when their lives are saved, and their quality of life is improved. That is the most enjoyable reward that anyone can dream of.

Additional Material

1. דפנה מנדלר - מאורע היסטורי במדינת ישראל – פרס נובל בכימיה

2. חלבונים ומפרקים - חדווה גונן ואהרן צ'חנובר בכתב העת גליליאו

3. The Nobel Prize in Chemistry 2004—Aaron Ciechanover

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I would like to thank Noa Segev, a graduate of the Nancy and Stephen Grand Technion Energy program (GTEP), Israel for the interview that was the basis for this article, and jointly writing it. Thanks also to Prof. Michael Brandies for the help in answering the questions of the young reviewers.

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CONFLICT OF INTEREST: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

HEBREW UNIVERSITY SECONDARY SCHOOL, AGE: 14

We are a group of students in eighth grade at the Hebrew University High School in Jerusalem, we study in the biology honors program, meaning we chose to study biology in depth and breadth. This year (2019–2020) we are learning about the cell, its components and the processes that occur in it.

AUTHOR

AARON CIECHANOVER

Professor in the Technion Integrated Cancer Center in the Faculty of Medicine, recipient of the Nobel Prize in chemistry in 2004 for the discovery of the ubiquitin system for protein degradation in the cell. Professor Ciechanover is a doctor by training, a graduate of the Hadassah medical school and of Hebrew University of Jerusalem (1972) as part of the academic army service (atuda). After graduating, he served in the Israel Defense Forces as a combat doctor, then he joined the department of biochemistry in the faculty of medicine in the Technion, where he conducted his Ph.D. research under the supervision of Professor Avram Hershko. His research from 1976 to 1981 was an attempt to understand how cellular proteins are degraded in a specific manner; in other words, how the cell gets rid of only the proteins that need to be destroyed at that point in time, like those that have been damaged. This research resulted in the award of the 2004 Nobel Prize in Chemistry to Professor Ciechanover, along with Professor Hershko from the Technion and Professor Irwin Rose from the Fox Chase Cancer Center in Philadelphia, USA. In the same year, Professor Ciechanover was also chosen to be a member of the Israel Academy of Sciences and Humanities in the field of biochemistry. Before receiving the Nobel Prize, Professor Ciechanover was awarded other important prizes, such as the Albert Lasker Award for Basic Medical Research (2000), the Michael Landau Prize for Life Sciences (2001), the EMET prize (2002), and the Israel Prize in biology (2003). Professor Ciechanover is a member of many academies of science, among which are the Israel Academy of Sciences and Humanities, and the National Academies of Sciences, Engineering, and Medicine (United States). Professor Ciechanover lives in Haifa, Israel. He is married to Dr. Menucha Ciechanover and father of Itzchak (Tzachi).
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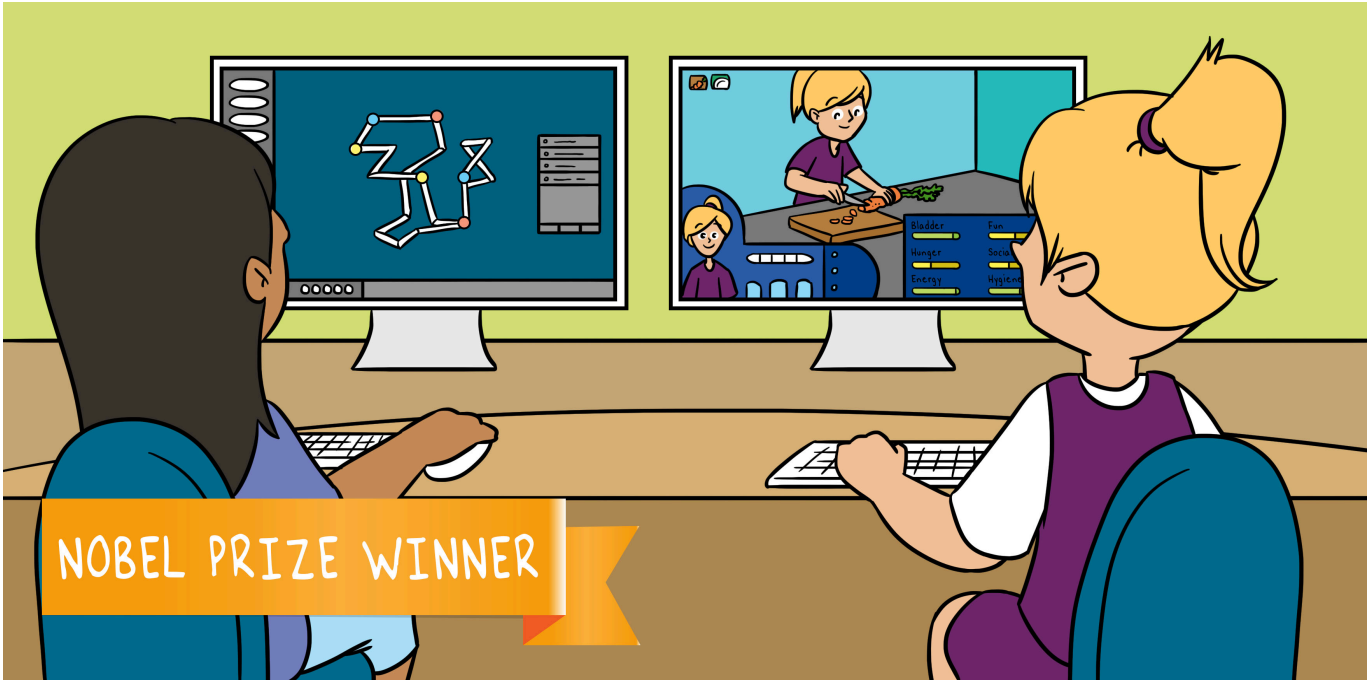

COMPUTER SIMULATIONS IN SERVICE OF BIOLOGY

Michael Levitt *

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YOUNG REVIEWERS

NATAN ALTERMAN ORT JUNIOR HIGH SCHOOL, ISRAEL

AGES: 13-15

Computer simulation is an important research tool in today's scientific world. Computers allow us to perform computations that mimic the behavior of complex (biological) systems in ways that we could not otherwise achieve. You could think of these simulations as a computer game, in which a virtual world is created that works according to certain (e.g., physical) rules. While we play the game, we learn the rules governing this virtual world and its environment, and also the way that we affect this world as players. In this article, I will explain how we use computer simulations in the world of structural biology to study the structure and function of molecules. I will also describe how I think that we could use insights from the world of biology and computer simulations to advance the society that we live in.

Professor Levitt won the Nobel prize in Chemistry in 2013 for the development of multiscale models for complex chemical systems.

Interviewed and co-written by Noa Segev, graduate of the Grand Technion Energy Program, Technion, Israel Institute of Technology, Haifa, Israel.

Figure 1

An example of a computer simulation as implemented in computer games. The figure is taken from the online game "Fortnite." The challenge is to throw the ball so that it hits the objects in the room 15 times before it falls to the ground. This game is actually a simulation of physical laws. To realistically present the motion of the ball in the game visually, the computer needs to compute the physical path of the ball based on physical equations—Newton's equations of motion. In other words, the computer simulates physical laws and presents the result on the screen. By adopting the same principle, the computer can simulate different processes in nature, such as weather or biological processes, to help us better understand them (Source: Forbes).

COMPUTER SIMULATION

A tool for performing scientific studies based on computations using a computer. You can think of computer simulations like computer games that help scientists to learn and better understand the phenomena they investigate.

WHAT IS A COMPUTER SIMULATION?

A simple way to understand a **computer simulation** is to think about computer games. Think, for example, about an adventure game, in which your character walks around an environment performing various actions. For the game to look realistic, the computer must build a virtual world that behaves like the real world. For example, if you throw a ball during the game, the computer must use the appropriate physical equation (Newton's equation of motion, in this case) in order to compute the motion of the ball and create a realistic simulation of the physical path of the ball during its motion (Figure 1). By the same principle, the computer can simulate other real-life processes, assuming we know the physical laws that govern them. In other words, not only the laws governing the motion of objects could be simulated, as we saw in the above example, but also more complex processes, such as the weather, chemical reactions, and also a variety of biological processes, such as the folding of **proteins**, which we will discuss below.

WHAT CAN WE LEARN FROM COMPUTER SIMULATIONS?

Let us think about an adventure game, like Assassin's Creed. Assuming that your mission takes place in Florence, Italy, you walk around this city using a computer simulation of the streets of Florence. While walking, you see various houses and historical sites, such as the beautiful cathedral called the Duomo. After many hours playing this game, you will know a great deal about the geography of Florence. With this knowledge, you could walk around the real city of Florence, feel familiar with it, and identify different places and sites that you

PROTEINS

Big biological molecules that perform all the functions of life—build the body, take part in chemical reactions, digest food, etc. You can think of proteins as necklaces, composed of different types of beads, that fold into unique 3D shapes, so that each protein has its own unique folded shape.

encountered in the computer game. This means that the game provided you with real knowledge of the city itself, even though you had never actually visited the city. Such learning through computer simulations is a safe process—you are not afraid to get hurt while playing the game, so you can let yourselves perform actions in the game that you would not dare to perform in real life. Depending on the game, sometimes there are even actions that cannot be performed in real life but can be done in the computer game (like you having the power to fly or meeting imaginary creatures).

This principle of acquiring knowledge through computer simulations is also used in the scientific world: we build a model of a physical or a chemical process that we are studying and then simulate it using a computer. The model is based on mathematical equations describing the process (as in Figure 1, where the model utilizes the equations that describe Newton's laws and govern the physical behavior of a ball). The computer allows us to view how the process unfolds with time, so we can examine whether the results of the simulation fit the real-world process. If the results fit, then we conclude that the model is good and could be used to better understand the phenomenon that we are investigating. If the computer results do not fit the real-world results, then we conclude that the model needs to be revised. Modifying the model can help us to identify errors in our understanding of the process we are studying. Since a simulation is not dangerous, we might try all sorts of models and possibilities that might even be impossible to explore in real life situations. Sometimes there are surprises during such computer simulations, and we might find that a "wild" model that we have examined actually best describes the phenomenon under investigation. Computer models give us the freedom to be creative and find explanations of reality that are otherwise hard to find.

JUST RIGHT

When using computer simulations in science, one of the most important principles is one that I call "just right." According to this principle, we need to build a model that is not too simple and not too complicated. If the model is too simple, it will not describe the phenomenon we want to investigate in sufficient detail. In contrast, if the model is too complicated, we will not be able to use it to get information that will contribute to our understanding. I think that every researcher should understand what they are doing at a simple and basic level, so that they can explain their research to others. If someone says that they have discovered something great but it is too complicated to explain, I get filled with doubts and I am not convinced that they really understand what they are studying. Therefore, I always search for the simplest model that is good enough (as you will see in Figure 2 below about the folding of proteins). I believe that this is a very general idea for life—each explanation has its own "just right" level. Therefore, I advise you to always look for the simplest explanation that clarifies what you are trying to understand—not more and not less.

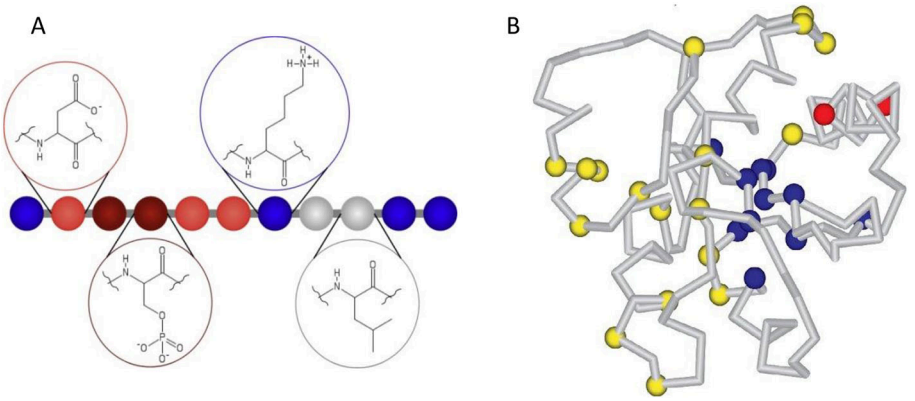

Figure 2

Figure 2

The folding of proteins. **(A)** A simple model for simulating a protein using a computer. The protein is described as a necklace composed of beads with different features. Each color describes a different type of bead, and each bead describes a collection of atoms and their interactions (as you can see in the circles above or below the beads) (Adopted from Cragnell et al. [2]). **(B)** A simple model of a protein as a necklace of beads that also includes the mathematical equations describing the interactions between beads of specific colors. This model is sufficient to describe the folding of proteins into stable 3D shapes (Adopted from Researchgate).

STRUCTURAL BIOLOGY

A research field that studies the structure of large molecules (macromolecules) built from collections of smaller molecules. Researchers try to understand the principles by which molecules fold to create a certain 3D structure.

COMPUTER SIMULATIONS IN STRUCTURAL BIOLOGY

I will now show you how we used computer simulations and the "just right" principle to understand a very important phenomenon in biology—the folding of proteins. Research into the structure of proteins is part of a field called **structural biology**. Let us think about how living organisms function. Inside the body, there are many string-like structures called proteins. These proteins fold up to create three-dimensional shapes. Each protein has its own unique shape, which is identical inside every living body. The amazing thing is that these 3D-shaped proteins perform all the functions of life—building the body, undergoing chemical reactions, moving the muscles, and digesting food. Therefore, understanding the process of folding that determines the final shape of a protein is extremely important.

Proteins are large molecules made from thousands of atoms with many interactions between them. If we want to run a computer simulation to deal with all these atoms and their interactions inside a protein, it becomes far too complicated. In the early 1970's I worked on this problem with Arieh Warshel, and in 1975, we published our findings in an important scientific journal [1]. We found that we could build a simple model of a protein presented as a necklace composed of different types of beads, in which each type of bead has somewhat different features than those of other beads (Figure 2A). Each bead represents a collection of (say 10) atoms and their interactions. Specific beads (say red beads) are attracted to other specific beads (say blue beads). This simple model managed to provide an adequate and useful explanation for the folding of proteins (Figure 2B) and it has been accepted as a model for many other molecular computations [2]. These simulations allow us to understand, and even predict, the three-dimensional structure of different proteins and to better understand their biological activity. We can also use the computer to design molecules that can be used as drugs.

COMPUTER SIMULATIONS BEYOND BIOLOGY—VISION FOR THE FUTURE

Diversity, Diversity, Diversity

Biological systems face a unique challenge: they need to be prepared to deal with unexpected situations that might occur sometime in the future. How can any system be prepared for scenarios that have never been experienced before? The answer is simple: through diversity. Nature attempts to create a large range of variations within a system so that the system can adapt and modify its processes to deal with unforeseen challenges.

In animals, for example, each offspring receives a random half of the genetic information (DNA) of each of its parents, so each offspring is unique and enhances the diversity of the species. In this way, for a whole group of animals, the readiness to respond to possible future scenarios increases, and this increases the collective resilience of the species to unexpected situations.

I think that this diversity principle that biology teaches us is also applicable in many other aspects in life. For example, a strong society is a diverse society, in which different people, of different social backgrounds, sexes and educations, should learn to live together and understand and accept one another. Indeed, at school, or at home, we always have to find ways to negotiate with the people around us. Sometimes we have to deal with difficult and complex social situations, and of course some of us are better than others at resolving the conflicts we encounter. Furthermore, our life itself is diverse, with ups and downs and unexpected situations. The key for a better future and a stable society relies on our capabilities to handle life's diversities successfully. Dealing with a diverse range of social and personal situations requires a well-developed **emotional intelligence**. I believe that we can use computer simulations to help us improve our emotional intelligence.

EMOTIONAL INTELLIGENCE

The ability to identify emotions in yourself and others, understand them, and use them to interact better with different people.

Computer Simulations for the Development of Emotional Intelligence

A computer simulation to improve emotional intelligence could be in the form of an interactive game that simulates a difficult social situation and allows you to pursue different strategies for resolving the problem (Figure 3). For example, someone insults you in class. How should you react to ensure that you do not totally destroy any possibility of working cooperatively with that person? Using a computer simulation, you could see the outcomes of a diverse range of different actions that you might take. This type of activity, done both individually and as part of the educational system, could play an important role in enhancing the development of emotional intelligence.

Figure 3

Figure 3

Computer simulation for developing emotional intelligence. Computer simulations may be able to teach us about complex situations in life. Imagine a game like the one shown, which allows you to experience a complex social situation and to try different ways of reacting and responding to the situation. Such a game could prepare you to better deal with real-life situations and with the diverse responses of different people: it could help you develop a more sophisticated emotional intelligence (Adopted from Rockpapershotgun).

RECOMMENDATIONS FOR YOUNG MINDS

I want to share with you some insights that I gained from my scientific career and from life in general. First, it is important to do what you love. Do not do what your parents want you to do or what society tells you to do; try doing what you genuinely love doing. There is no better life than a life in which you do what you really love doing. Second, do not give up. Believe in yourself and do not get too excited by success or failure. Remember that every bad thing has something good in it, and every good thing has something bad in it, and we learn from both. Keep believing in yourself and eventually others will also believe in you. Third, try to be original. Each of us is special and unique. Try expressing your uniqueness and not just copy others. Fourth, be ready to make mistakes. I always say that a good scientist is someone who makes mistakes 90% of the time, and a really good scientist makes mistakes 99% of the time. Why? Because if you are excellent in your field, you deal with the most difficult problems. If you are not prepared to make mistakes, you will never deal with the more challenging things. Fifth, be a kind person—be generous and warm—these are important qualities to nurture.

The last thing I would like to recommend to you is related to planning. I think that in life, while you do need to be able to plan ahead, too much planning can lead to disappointment. Life never goes exactly the way we planned and surprising things often happen that are not part of the plan. If you are too busy with your original plan, you will not even notice new opportunities. The ideal is a delicate balance between following plans and being ready to respond to the surprises that life brings.

ADDITIONAL MATERIALS

Michael Levitt—Nobel Lecture.

Michael Levitt Explains His Work To Young Students—Youtube.

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NATAN ALTERMAN ORT JUNIOR HIGH SCHOOL, ISRAEL, AGES: 13–15
Technological Scientific classes in "Beit Chinuch" are classes containing excellent students in the fields of science and technology. The students are curious about everything relating to science, always questioning the world around them in order to understand it better.

AUTHOR

MICHAEL LEVITT
Michael Levitt is a professor of structural biology at Stanford University, Stanford, California. He received a Nobel Prize in chemistry in 2013, together with Martin

Karplus and Arieh Warshel. Michael Levitt was born in Pretoria, South Africa. The family moved to England when he was 15. He attended King's College London, graduating with a first-class honor degree in physics. With his Israeli wife Rina, he then moved to Cambridge, where their three children were born. Levitt earned his Ph.D. in computational biology at Gonville and Caius College, Cambridge, and was based at the Laboratory of Molecular Biology from 1968 to 1972, where he developed a computer program for studying the conformations of molecules. From 1980 to 1987, he was a professor of chemical physics at the Weizmann Institute of Science, Rehovot, Israel. Levitt belongs to several scientific societies and has served on the scientific advisory boards of many companies. Recently, Levitt and colleagues developed a mathematical approach to successfully analyze and predict COVID-19 outbreaks. *michael.levitt@stanford.edu

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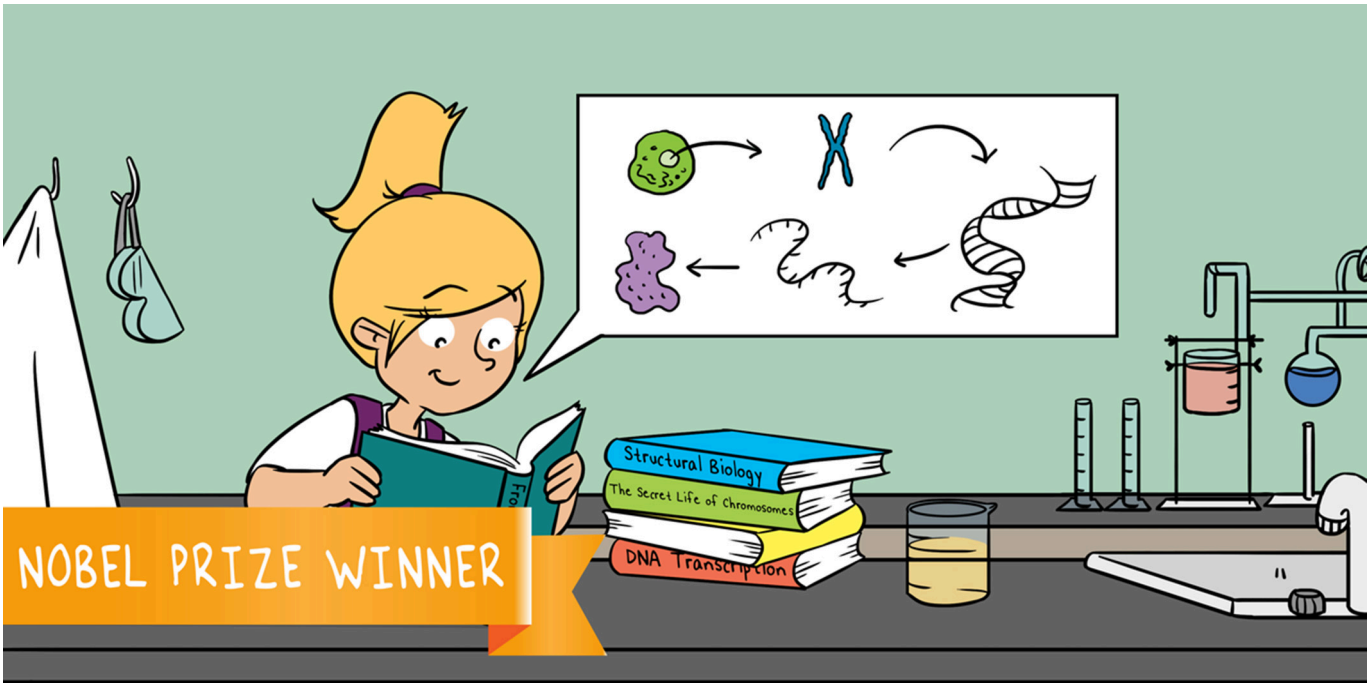

THE TRANSCRIPTION OF LIFE: FROM DNA TO RNA

Roger D. Kornberg *

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AGES: 13–15

In the last 50 years, I have dedicated my career to studying fundamental questions in biology. These questions address some of the most basic processes of life, such as "How do cells carrying the same genetic information differentiate into some 200 cell types in the human body?" and "How do cells remodel in response to environmental information?" In this article I will take you on a journey through some of my research into these questions. I will describe my main findings about DNA and its transcription to mRNA through a complex machinery called RNA polymerase II. mRNA is eventually translated into proteins that play a variety of major roles within the organism, including building cells, responding to environmental signals, accelerating chemical reactions, and transmitting signals between distant tissues. Last, I will share with you some fascinating open questions that we are now working on and close with a few tips for you—the scientists of the future.

Professor Kornberg won the Nobel Prize in Chemistry in 2006 for the study of the molecular basis of eukaryotic transcription.

Interviewed and co-written by Noa Segev, graduate of the Grand Technion Energy Program, Technion, Israel Institute of Technology, Haifa, Israel.

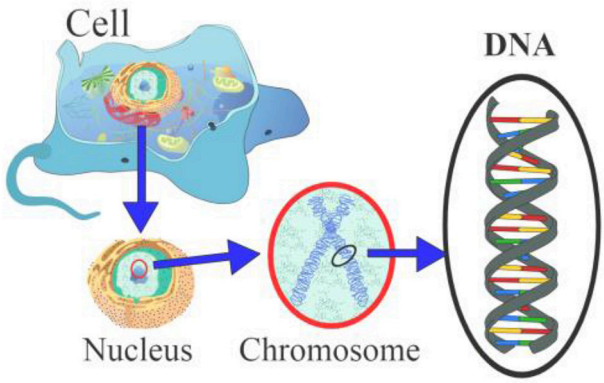

Figure 1

The cell's membrane and the nucleus containing the DNA. The cell is the basic unit of life. The nucleus, which is the information center of the cell, contains chromosomes. Each chromosome is an "X"-shaped structure (red circle) that holds a portion of the DNA [Image source: Wikipedia (https://en.wikipedia.org/wiki/Chromosome)].

MY WAY TO RNA

My father was a biochemist and was awarded a Nobel prize in 1959 for his work on **deoxyribonucleic acid (DNA)** replication. He shared his immense enthusiasm for his research with anyone who would listen, and I absorbed his love for science. In college I studied mathematics, physics, and chemistry, and for my Ph.D. I did research on the dynamics of membranes (Figure 1, left). Membranes play the most fundamental role in life, because this envelope surrounding the living cell is what defines the existence of a cell—the basic unit of every living thing.

Toward the end of my work on membranes, I knew that I wanted to continue working on the physics and chemistry that relate to the life sciences. At that time, the field of structural biology, which is the study of cell components and processes, was rapidly growing. New technologies enabled the structures of simple **proteins** to be solved. I then became aware of the interesting problem of **chromosome** structure (see Figure 1). The chromosome is the structure in which our genetic material, the DNA, resides in all cells. Chromosome structure was intriguing for structural biologists because of DNA's fundamental importance and its seemingly simple structure. We already knew that the chromosomes are made up of DNA and an equal mass of four very small proteins. All we needed to figure out was how the DNA and the four proteins were arranged together to form the structure of the chromosome.

Well, it turned out that this problem was not at all simple. Eventually, I solved it by identifying the few relevant research papers among the many hundreds of them written on chromosome structure. These papers led me to the solution. I performed relevant experiments and put the pieces of the puzzle together and elucidated the structure of the chromosome. This structure was later proven to be correct by a technique called X-ray crystallography.

DEOXYRIBONUCLEIC ACID (DNA)

The material that carries genetic information in living organisms. DNA is built from two strands in the form of a double helix and it is located inside the cell's nucleus.

PROTEINS

Large molecules, found in all living cells, which play many important roles in organisms.

CHROMOSOME

The basic structure into which the DNA is arranged inside the cell's nucleus.

After solving the structure of the chromosome, the next natural step was to investigate the implications of this structure for biology, for life itself. How does DNA, organized in this way inside the chromosome, engage in the expression of genetic information? Gene expression begins with a process called **transcription**, in which a **messenger RNA** (mRNA) molecule is formed from the DNA. The mRNA molecule is similar to the DNA molecule, but it has a different structure and function. Unlike the two strands from which DNA is made (Figure 1, right), the mRNA molecule is made of a single shorter strand, which is a copy of a particular segment of the DNA sequence. The mRNA serves as an intermediate, linking the genetic information coded in the DNA to the proteins that are eventually synthesized based on this information. To investigate the role of the chromosome in gene expression, I began by studying one of the three **enzymes** that participate in transcription. This enzyme is called RNA polymerase II [1].

TRANSCRIPTION

The first step in gene expression, in which a segment of the DNA is copied into an mRNA molecule.

MESSENGER RNA (mRNA)

A type of RNA that is involved in building proteins based on the information stored in the DNA.

ENZYMES

Large molecule that accelerate chemical reactions that take place in the body or inside the cell.

FROM DNA TO RNA—THE RNA POLYMERASE II TRANSCRIPTION MACHINERY

The function of the RNA polymerase II transcription machinery is to create mRNA. As I mentioned above, mRNA serves as a link between the DNA code and the proteins that are produced from this code. The RNA polymerase II transcription machinery consists of almost 60 different proteins! I will describe the three main components [2]: the RNA polymerase II enzyme, a set of proteins called **general transcription factors**, and a complex of proteins called **Mediator**.

GENERAL TRANSCRIPTION FACTORS (GTFs)

A group of proteins that assist the initiation of DNA transcription to mRNA.

MEDIATOR

A multi-protein complex that processes information about gene regulation and transmits that information to the GTFs and RNA polymerase II.

RNA Polymerase II Enzyme—Structure and Function

The RNA polymerase II enzyme (Figure 2A) is the structure within which the transcription process takes place. This means that DNA enters this enzyme from one direction and an mRNA product exits from another direction. Much of our work revolved around solving the complex structure of this enzyme. After solving the structure of the enzyme on its own, we also managed to solve its structure with both the DNA and the RNA present in it during the transcription process (Figure 2B).

RNA polymerase II is made up from 12 different proteins, represented by the different colors in Figure 2A, and built from almost 30,000 atoms. RNA polymerase II has a central channel that leads to a magnesium ion. The central channel is the place where transcription happens. A double-strand DNA enters the central channel and the two DNA strands split apart (Figure 2B). One strand bends, near the magnesium ion at the center of the enzyme. At this location, called the active center, the mRNA is synthesized, following the instructions of the bent section of the DNA strand. Finally, the hybrid DNA-mRNA structure exits the enzyme at an angle of about 90° relative to the DNA entering the enzyme.

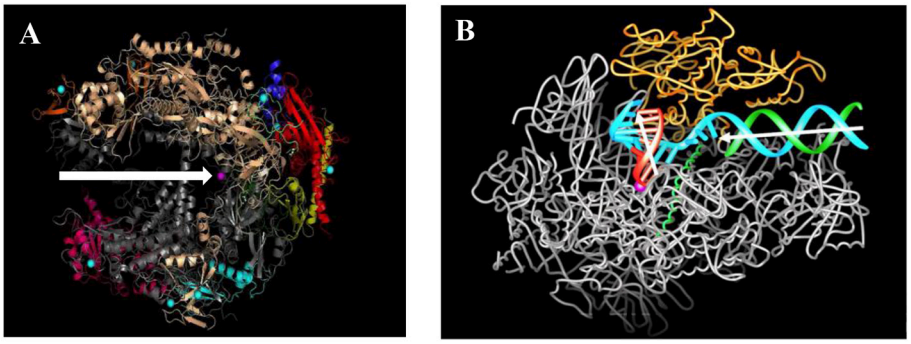

Figure 2

Figure 2

The structure of the RNA polymerase II enzyme before and during transcription. **(A)** RNA polymerase II is made of 12 subunits (indicated in different colors) and some tens of thousands of atoms. It has a central channel (white arrow) leading to a magnesium ion (pink dot). The zone where the magnesium ion is located is called the active center, since this is the region where the mRNA is synthesized from the DNA. **(B)** A double strand of DNA (blue and green strands) enters through the central channel of the RNA polymerase II enzyme (horizontal white arrow) and splits up toward the middle of the enzyme. The strand that controls the synthesis of the mRNA (blue) is flipped 90° upwards near the active center (upward-pointing white arrow) and a short mRNA strand is synthesized from it (short red strand at middle). This DNA-mRNA hybrid complex exits the enzyme in a direction perpendicular to the direction from which the DNA originally entered (Image credit: Prof. Roger Kornberg).

GENE

A segment of DNA that contains information for building a protein.

General Transcription Factors (GTFs)—Key Components in Gene Expression

The most important step in the process of transcription is the start of the process, called initiation. When DNA is transcribed into mRNA, it is not transcribed in its entirety. Only a specific part of it is transcribed for a specific purpose. This part of the DNA is called a **gene**. Each gene contains information about the production of specific proteins in our body. For the recognition of a specific gene and for deciding whether to transcribe it, the RNA polymerase II makes use of five additional molecules. These are proteins called **general transcription factors** (GTFs) and they come in contact with the RNA polymerase II enzyme during the transcription process (gray spheres at the bottom of Figure 3). Broadly speaking, you can think of these GTFs as components in the transcription machinery that help turn specific genes "on" or "off."

As we previously saw in Figure 2B, when the DNA moves inside the RNA polymerase II, it needs to bend to be transcribed into mRNA. However, DNA in its regular form is very stiff and not easily bent. In order to bend, it needs to be split into the individual strands, whereupon it becomes completely flexible and can bend freely. This is where the GTFs come into play: after the GTFs find the beginning of the gene in the DNA molecule, they then open the DNA and bend it near the active site of the transcription in RNA polymerase II. In this way, the GTFs begin the process of transcription.

Mediator—The "Middleman" for Gene Regulation

In the process of DNA transcription, very important decisions must be made: which gene to transcribe, in what place of the body and when to do it. This group of decisions and actions is called gene expression regulation and it is critical for the proper functioning of our body. The Mediator is a group of proteins that we discovered in 1990 [3] and it is an important part of the gene regulation mechanism: it processes all the regulatory information and delivers it to the RNA polymerase to control the decision of whether to transcribe a certain gene.

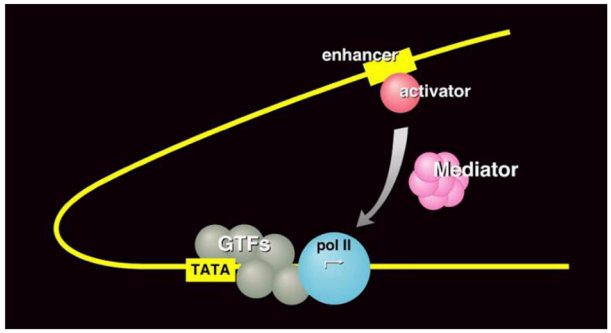

Figure 3

Figure 3

RNA polymerase II transcription machinery. Bottom: General transcription factors (GTFs, gray) interact with RNA polymerase II enzyme (pol II, blue) to start DNA transcription inside the enzyme. The Mediator (pink) serves as a connecting link that delivers gene regulatory information from inside or outside the cell to the pol II enzyme. In this case, the Mediator delivers information from an activator protein (red) about the activation of a specific gene for transcription (Image credit: Prof. Roger Kornberg).

Figure 3 shows schematically the function of the Mediator in the transcription process: the mediator (in pink) links between a protein called an activator (in red), which influences the "turning on" of a gene for transcription, and the RNA polymerase II enzyme (in blue). In other words, the Mediator serves as the "middle man" that delivers to the RNA polymerase enzyme regulatory information about gene expression.

OPEN QUESTIONS FOR THE FUTURE

I want to pique your curiosity by briefly mentioning two unsolved problems that relate to what I have told you in this article. These topics are at the cutting edge of research in biochemistry today and we are currently working on both of them in my lab.

The first problem relates to the structure of the chromosome. At a certain stage in the division of a cell, the DNA contracts in length by a factor of about 10,000 so that the DNA, which previously occupied the whole nucleus of the cell, is condensed into the shapes of the chromosomes. What we know for sure about the structure of the chromosome can only explain the shortening of the DNA length by a factor of 5, but not by a factor of 10,000. So, the open question is: how does the DNA in the chromosome condense by an additional factor of 2,000?

The second problem relates to the Mediator and the regulation of gene expression. As you saw in Figure 3, the Mediator delivers regulatory information to the RNA polymerase II enzyme. But how is the regulatory information processed by the Mediator? How exactly is this information transmitted to the polymerase? How does the Mediator assist in the unfolding of the DNA to allow it to be transcribed? We have some ideas about what might happen and how, but these are still open problems that we are trying to solve.

TIPS FOR YOUNG MINDS

In many ways, the questions I mentioned above are the same fundamental questions with which I started my academic endeavors. As you probably know, many scientific questions are complex and require many years of hard work to be fully addressed. Science is challenging, it requires hard work, and can be difficult and frustrating at times. But for me the occasional rewards are completely worth the struggle. If you love science and want to pursue a career as a scientist, my first advice to you is to take pleasure in the activity itself and enjoy the small, everyday activities of science. In my case, for example, these activities are experimental—mixing and dissolving different materials and making the solutions for my experiments. I personally enjoy each of these small steps and I love spending time in the laboratory.

Another important thing is to learn how to experience failure as something stimulating, something challenging—as an invitation to try again with the same high expectation of success as the last time. Every once in a while, something new and surprising happens during research. However, good scientists do not believe it straight away. First, you must make sure that it was not a mistake, so you need to think of ways to prove that you are wrong. A really good scientist thinks of extremely sophisticated ways to prove that they are wrong. When they fail to prove that they are wrong, even by ingenious experiments, then they have discovered something. These are unique and unforgettable moments in a scientist's career and they greatly outweigh the hard work that was invested in the process.

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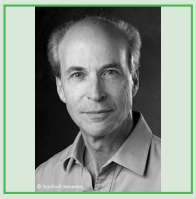

ROGER D. KORNBERG

Prof. Roger D. Kornberg, is professor of Medicine in the Department of Structural Biology at Stanford University, California U.S.A. Previously, he was a professor at Harvard Medical School. He received a Nobel Prize in chemistry in 2006 for his studies of the molecular basis of eukaryotic transcription, the process by which DNA is copied to RNA. Over the years, Prof. Kornberg has been awarded many important prizes. Kornberg received his B.S. in chemistry from Harvard University in 1967 and his Ph.D. in chemistry from Stanford University in 1972. He has served as a director of OphthaliX Inc. Since 2012 and he also serves as the Chief Scientist of Cocrystal Pharma, Inc. Prof. Kornberg is married to Prof. Yahli Lorch and they have three children, Guy, Maya, and Gil. *kornberg@stanford.edu

CHEMISTRY AND MATERIALS
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QUASI-CRYSTAL, NOT QUASI-SCIENTIST

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YOUNG REVIEWERS:

8TH GRADE "NACHSHON" CLASS, "MAKIF AMIT SCHOOL, ISRAEL"

AGES: 12–13

Materials science investigates the structure and properties of different materials. One of these materials is the crystal. Crystals are solid materials with building blocks (atoms, ions, or molecules) that are arranged in a highly organized manner. Salt, quartz, and diamonds are examples of crystals. In ordinary crystals, these building blocks are organized in a repeating pattern in all directions. In contrast, in special crystals called quasi-crystals, the building blocks are organized in a non-repeating manner. The discovery of quasi-crystals created a revolution in the science of crystallography and changed our most basic definition of a crystal. Since their discovery, many hundreds of quasi-crystals have been found. Some of these quasi-crystals have unique physical properties and are useful for a variety of different applications.

Professor Shechtman won the Nobel Prize in Chemistry in 2011 for the discovery of Quasi-Crystals.

Interviewed and co-written by Noa Segev, graduate of the Grand Technion Energy Program, Technion, Israel Institute of Technology, Haifa, Israel.

HOW I BECAME A MATERIALS SCIENTIST

When I was 7 years old, my grandfather bought me an extraordinary present—a magnifying glass! It made me very happy and I started walking around the city of Ramat Gan (in Israel) with this magnifying glass. I looked at everything I could find—flowers, bugs, sand, and many other small things. During this process I fell in love with the world of small things. A few years later, when I was in the fifth grade, a microscope was delivered to our school. Week after week, I asked my teacher to bring the microscope to our class. Eventually he did, and he invited me to be the first to look through it. We looked at a leaf, and I could see the motion of the chlorophyll, a small molecule inside the leaf responsible for its green color. Since then I could not leave the microscope. Years later, during my studies at the Technion (Israel Institute of Technology), an exceptionally strong microscope arrived at our facility, called a **transmission electron microscope (TEM)**. I fell in love with this microscope because it allowed me to realize my scientific curiosity for the world of small things. I soon specialized in operating this microscope, and by using it I discovered a new type of material which, many years later, earned me a Nobel prize.

THE DISCOVERY OF QUASI-CRYSTALS

In 1981, I went to the United States to study aluminum-based materials for use in airplanes. Initially, I worked on an **alloy** of aluminum and iron and discovered a new **phase**—a special arrangement of the atoms in this alloy. I wanted to study this arrangement, but it was unstable. So instead, I prepared various alloys with aluminum and manganese, which were stable. I started preparing alloys of aluminum-manganese in different concentrations. Some of these alloys were useful for aviation applications and some were not, but I still prepared them because of my scientific curiosity. I studied all of these aluminum-manganese alloys using the TEM. I call the TEM "the king of microscopes," since it is a very powerful tool with amazing capabilities. TEM allows us to see the way the atoms are arranged in different materials.

On Thursday, April 8th 1982, I studied one of my alloys using the TEM and I saw a very special pattern on the screen. We call the pattern made when electrons interact with a solid obstacle, like a **crystal**, a **diffraction** pattern (Figure 1, left). I immediately recognized that there was something unusual in the diffraction pattern, and thus in the structure of this material, which we now call "**quasi-crystal**," and so I wrote, "10-fold???" in my laboratory notebook (Figure 1, right, line 6 in brackets). I will now explain what was so special about this pattern, the meaning of the remark in my notebook, and why it revolutionized the world of **crystallography**.

TRANSMISSION ELECTRON MICROSCOPE (TEM)

A microscope that uses a beam of electrons to penetrate the material being examined. The electrons produce a diffraction pattern that shows the atomic structure of the material.

ALLOY

A material made from at least two elements, in which one or more is a metal.

PHASE (CRYSTAL)

A certain state of a material. Many times we speak about phases in the context of the state of the material—gas, liquid, solid, or plasma, but here we mean a specific arrangement in space of the atoms constituting the material.

CRYSTAL

A solid material with building blocks (atoms, ions, or molecules) that are arranged in space in an ordered manner.

DIFFRACTION

A phenomenon in which light or electrons are scattered when they interact with an obstacle, such as a crystal or other solid material.

QUASI-CRYSTALS

Crystals with building blocks that are arranged in space in a non-periodic manner, meaning they are not duplicated in all directions in a repeating pattern.

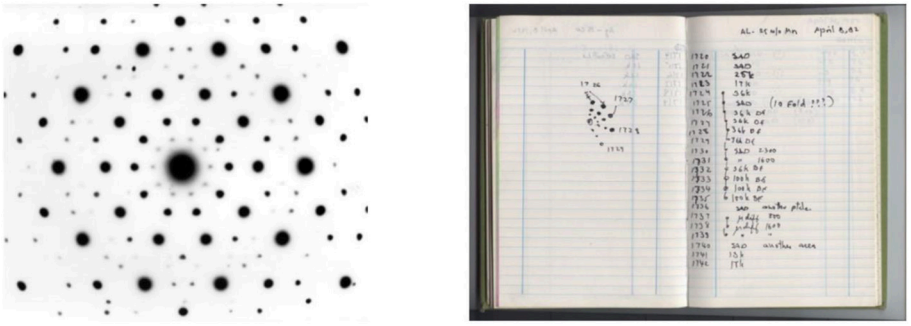

Figure 1

Figure 1

The discovery of the first quasi-crystal. **(Left)** Diffraction pattern of the aluminum-manganese quasi-crystal that I discovered in 1982. The scattered pattern of the dots shows us the arrangement of the atoms from which this material is built. **(Right)** My laboratory notebook, documenting my surprise over this discovery (scan 1725, line 6). Credit: Dan Shechtman.

CRYSTALLOGRAPHY

A scientific field that investigates the spatial arrangement of atoms in solids, among which are crystals.

ORDER

An organized pattern that is not random.

PERIODICITY

A repeating pattern that is duplicated again and again (in time or space).

ROTATIONAL SYMMETRY

A pattern repeating itself by rotations around a central axis.

CRYSTALS—BEFORE AND AFTER THE DISCOVERY

The science of crystallography (the study of crystals) started in 1912, with a German physicist named Max von Laue. Von Laue was the first to send X-rays through a crystal, and he saw that the atoms formed an **ordered** diffraction pattern. In the same year, two father-and-son English physicists, the Braggs, developed a mathematical equation describing the experimental phenomenon that von Laue observed. That is how crystallography emerged as a new scientific field. After the birth of crystallography, many thousands of crystals were studied and they all exhibited two common properties: they were ordered (not random) and **periodic** (exhibiting a repeating pattern) (Figure 2). Because of all these observations, the definition of a crystal became "a solid material in which the atoms are arranged in a fixed, repeating structure." Well-known examples of crystals are salt grains, quartz stones, and diamonds, but most metals, such as copper, aluminum, and iron, are also crystals. Classical crystals also have a property called **rotational symmetry**. Due to mathematical rules describing the internal arrangement of crystals it was found that crystals can have rotational symmetries from different types, called "orders" (i.e., order 1, 2, 3, 4, or 6; see Figure 2, center, for a demonstration of a rotational symmetry of order 4) and not of other orders (e.g., order 5 or 10).

Seventy years after the birth of crystallography, I found a crystal that is ordered but is not periodic. In order to better understand what this means, look at the left side of Figure 3. You can see widening circles of dots (blue, yellow, and red) around the big central dot. Each circle is composed of 10 dots, resembling a flower with 5 pairs of opposite leaves (point 1 is the partner of point 6, point 2 is the partner of point 7, etc.). If you measure the distance from the center to the first circle, you will see that it is not half the distance between the center and second circle (blue and yellow lines in Figure 3 on the right). Also, the distance between the center and the first circle is not one-third the distance between the center and the third circle (blue and red lines in Figure 3 on the right). This means that we cannot take one circle and duplicate it in equal distances from the center and get the crystal that I saw, which means that the crystal is non-periodic. But we can

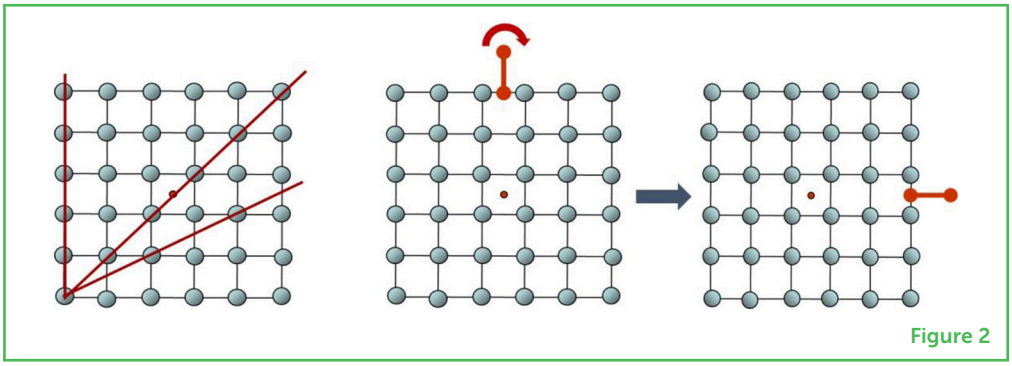

Figure 2

Figure 2

Order, periodicity, and rotational symmetry. **(Left)** A simple, ordered, periodic crystal. The dots, representing the crystal's atoms, are arranged in an ordered, non-random manner. The crystal is also periodic, meaning that, if you choose one direction (red lines) and proceed from one dot to the next, the distance between every two dots on the line is identical. You can also see periodicity if you choose a square containing four atoms and duplicate it in all directions, because you will get exactly the same structure. **(Center)** A structure with 4-fold rotational symmetry. Imagine yourself holding the red handle and turning the structure in 90° clockwise. Now the handle is to the right (as seen in the square on the **right**). Without the red handle, the whole structure looks exactly the same before and after the rotation. In this crystal, the structure repeats itself in every 90° rotation. This is called 4-fold symmetry because, for every four such rotations, we complete a 360° turn and all the dots return to their original locations. Credit: Dan Shechtman.

use mathematics to describe the distances between the center and the widening circles, which means that the crystal structure is not random, but is ordered (Here is a puzzle: can you find the connection between my crystal and the famous Mona Lisa painting? The answer is at the end of this article).

Notice how the dots in Figure 3 (left) are arranged with identical distances from each other on the circle. Since there are 10 equally spaced dots in the circle, if you put an axis at the center of the circle and turned it in 36° (360°/10 = 36°) in either direction, you would get the exact same picture as before the turn. We call this 10-fold rotational symmetry. Since 10- or 5-fold rotational symmetry do not occur in periodic crystals (for more information, see this link), this crystal was clearly not periodic. This is why I wrote, "10-fold???" in my notebook, as an abbreviation of "10-fold rotational symmetry." I added the three question marks because I knew that a crystal with 10-fold symmetry had not been seen before.

To summarize, I found a crystal which contradicted the classical definition of a crystal and was considered "forbidden" by the physical laws of that time. This situation meant that there were two options: either there was another explanation to the phenomenon that I witnessed, which did not contradict the existing definitions, or the existing definitions needed to be updated to include the crystal that I discovered. In the next section I will describe how the scientific community became convinced that a new definition for a crystal was required.

THE DISCOVERY OF QUASI-CRYSTALS WAS CRITICIZED BEFORE IT WAS ACCEPTED

Two years after the discovery, I published two papers on this topic with my colleagues [1, 2]. Thousands of researchers around the world joined us and started studying quasi-crystals (now there are more than 10,000 published papers about quasi-crystals). But a strong opposition also arose, led by the great American scientist Linus Pauling, who won the Nobel prize twice. Pauling attacked me personally and even

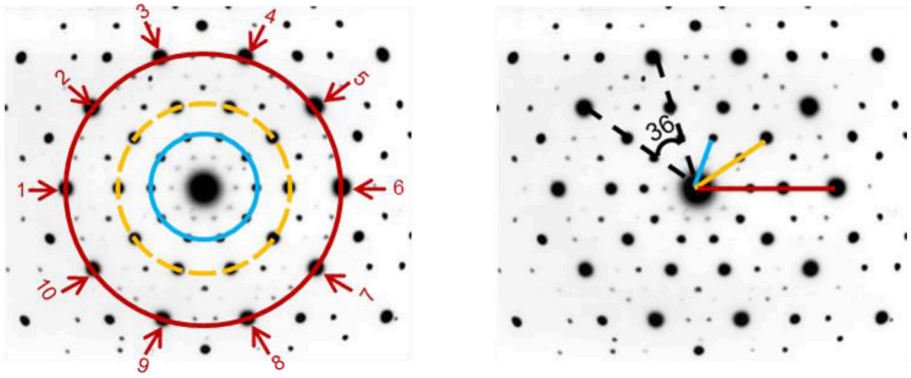

Figure 3

Figure 3

Diffraction pattern of a quasi-crystal. **(Left)** The diffraction pattern appears as widening circles (blue, yellow, and red), each of which is composed of 10 dots arranged in pairs that are across from each other (dot 1 is a partner of dot 6, for example). **(Right)** The angle between any two nearby dots on the same circle is 36° (dashed black lines), meaning that one rotation of 36° from the center makes the pattern look the same as before it was rotated. Ten such rotations will bring all the dots to their original locations; so this pattern is called 10-fold rotational symmetry. You can also see that the distance between the center and the first circle (blue line) is not half the distance between the center and the second circle (yellow line), and it is not one-third the distance between the center and third circle (red line). This means that this pattern is not periodic.

said, "there are no quasi-crystals, there are quasi-scientists." Pauling and his supporters claimed that what I saw in the microscope was a phenomenon called twins (Figure 4). This is a phenomenon of crystals in which two crystals are coupled to each other. Each crystal is ordered and periodic, and because of the couples, the crystal appears to have a 5-fold symmetry.

I checked right away to see if there were twins in my crystals, but I did not find any twins and I was certain of my original result. I knew that I had identified a new phenomenon and discovered a new material. Pauling's opposition to my findings proceeded for 10 years! After Pauling's death in 1994, most of the opposition to my scientific discovery faded away and the door opened to its full acceptance. The recognition of my discovery resulted in a new definition for a crystal, and it also inevitably shed new light on the science of crystallography. Of the hundreds of quasi-crystals discovered after my own discovery, some of them exhibit useful properties, such as resistance to deterioration, and interesting electrical properties that change as a function of temperature. A few products using quasi-crystals have been produced, such as Sitram's non-stick coating for pans, and Sandvik's strengthened stainless steel.

RECOMMENDATIONS FOR YOUNG SCIENTISTS

If you want to become a scientist, you need to develop two qualities. First, you need to be people of the big world of science. You need to have a broad knowledge of different fields, such as mathematics, physics, chemistry, biology, computers and you also need to know what has already been discovered, and what is "allowed" or "prohibited" according to current theories. In the case of my discovery, I knew that 5-fold symmetry was "prohibited" by the then-accepted definition of crystals and was observed only in twin crystals up until then.

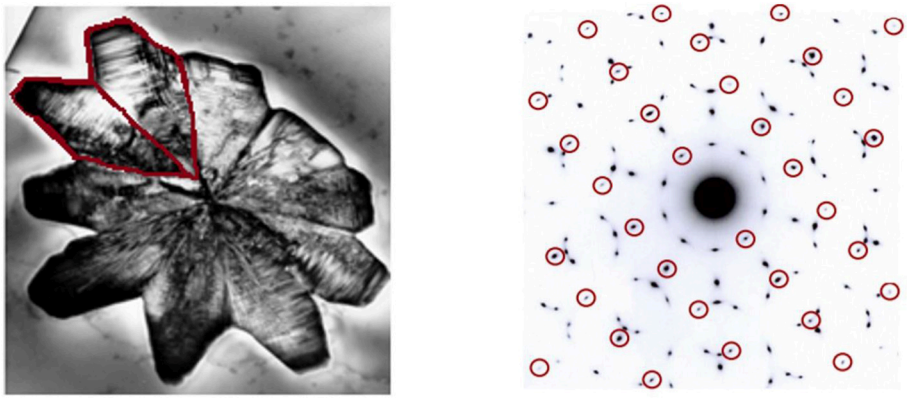

Figure 4

Figure 4

Twin crystals exhibiting a 5-fold symmetry. **(Left)** An aluminum-iron crystal made from five twin crystal couples. Every "leaf" is an ordered, periodic crystal and every two coupled crystals (like the ones marked in red) are called twins and are mirror images of one another. **(Right)** A diffraction pattern of a twin crystal. You can see that the resulting pattern is similar to that of the quasi-crystal (Figure 1). This image is the sum of the diffraction patterns of each individual crystal. The red circles in the figure mark the diffraction pattern of one crystal out of the 10 adjacent crystals. You can see that the pattern is ordered and periodic, so it satisfies the classical definition of a crystal.

But knowing the existing theories is not enough to make you a successful scientist. You also need to develop an expertise. Find something that you enjoy doing, something that you are good at and that interests you—and become an expert in it. I developed expertise with the TEM and, at the time, there were only a few people who knew how to operate it as well as I did. This was my advantage and what allowed me to remain confident in my results, even in the face of Pauling's harsh criticism.

In conclusion, remember that life presents us with many opportunities and we need to know how to utilize them. Also, remember that life is built from a variety of rich elements. When I am asked about the happiest moments of my life, I reply that these times were the births of my wife and my four children and 12 grandchildren. I hope that you will also experience the wonder of creating life and understanding the world, and I wish you the best of luck in your journey.

ANSWER TO THE RIDDLE FROM "WHAT IS A CRYSTAL"

In the crystal that I found, the ratio between the diameters of the widening circles (Figure 3, right) is the golden ratio—an irrational number with a value equal to about 1.618. The same golden ratio is found in the face of Mona Lisa—the most famous painting by Leonardo da Vinci. The golden ratio produces a pleasing experience of beauty for the observer. Can you notice the beauty in the diffraction pattern that I discovered?

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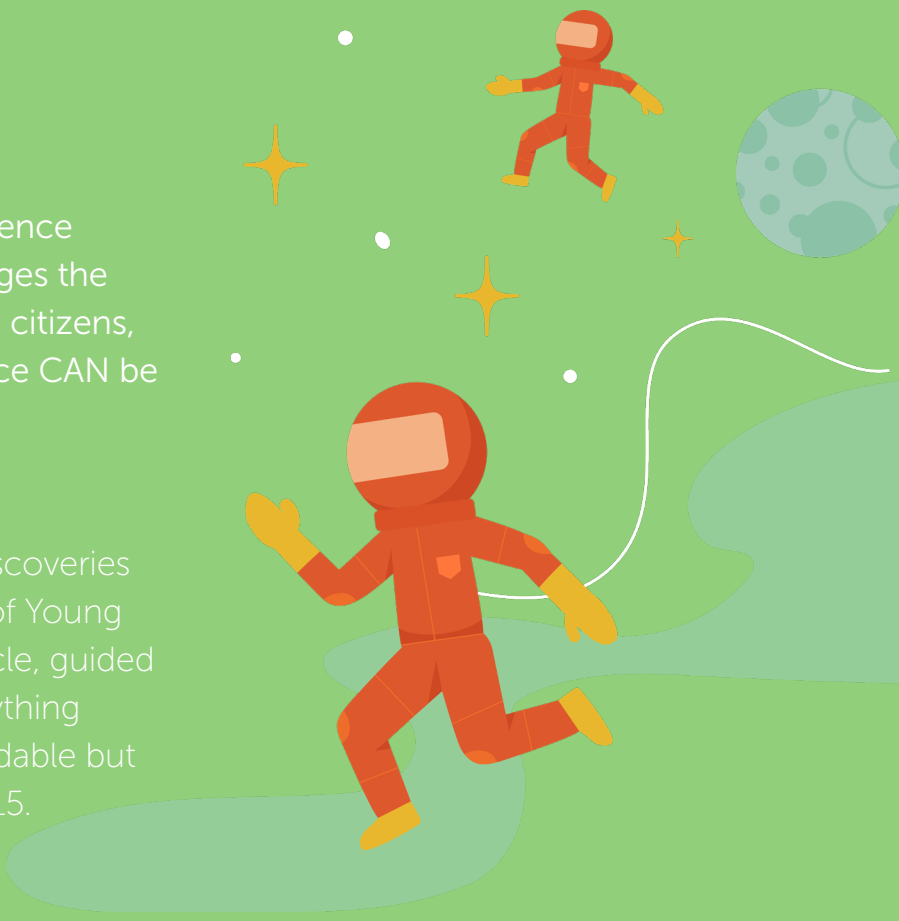

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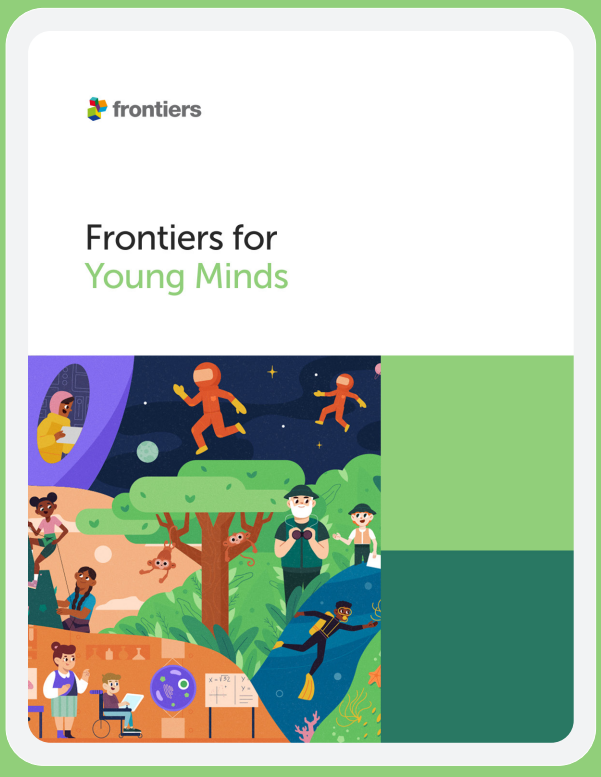

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