in Vitro

Volume I, Issue I

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In Vitro

Dear Readers,

Welcome to In Vitro, a bi-monthly publication that compiles topics related to Math/Science into a condensed and intriguing newsletter. We hope you enjoy our first issue!

Sincerely,
The In Vitro Team

2023

Nobel Prize:

The *mRNA* Revolution

By William Peng

The 2023 Nobel Prize in Physiology or Medicine was awarded jointly to Katalin Karikó and Drew Weissman for their groundbreaking work on mRNA vaccines, specifically for their discoveries concerning base modifications that enabled the development of effective mRNA vaccines against COVID-19.

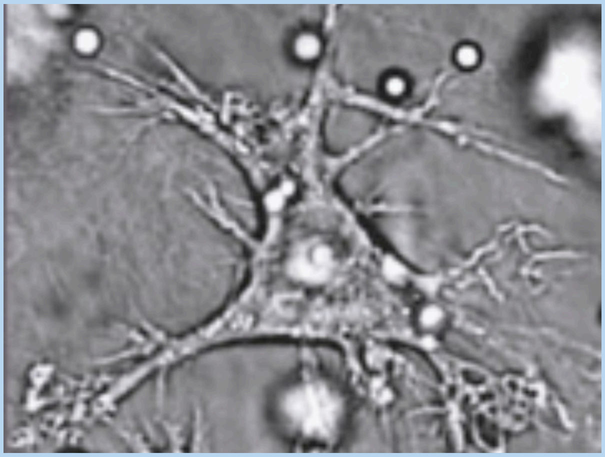
Karikó and Weissman's work has been instrumental in the rapid development of **mRNA vaccines**, a cornerstone in combating the COVID-19 pandemic. Their research fundamentally changed our understanding of how mRNA interacts with the immune system, thereby contributing to an unprecedented rate of vaccine development during one of the most challenging health crises in modern history.

Before their work, vaccines were primarily based on weakened / dead viruses or individual viral components (typically membrane proteins that antibodies can target). These traditional methods required large-scale cell culture, making rapid vaccine production difficult. However, Karikó and Weissman's discoveries have revolutionized this landscape. They focused on the molecular biology of mRNA and how it could be used for vaccine development, overcoming several challenges, such as mRNA instability and inflammatory reactions.

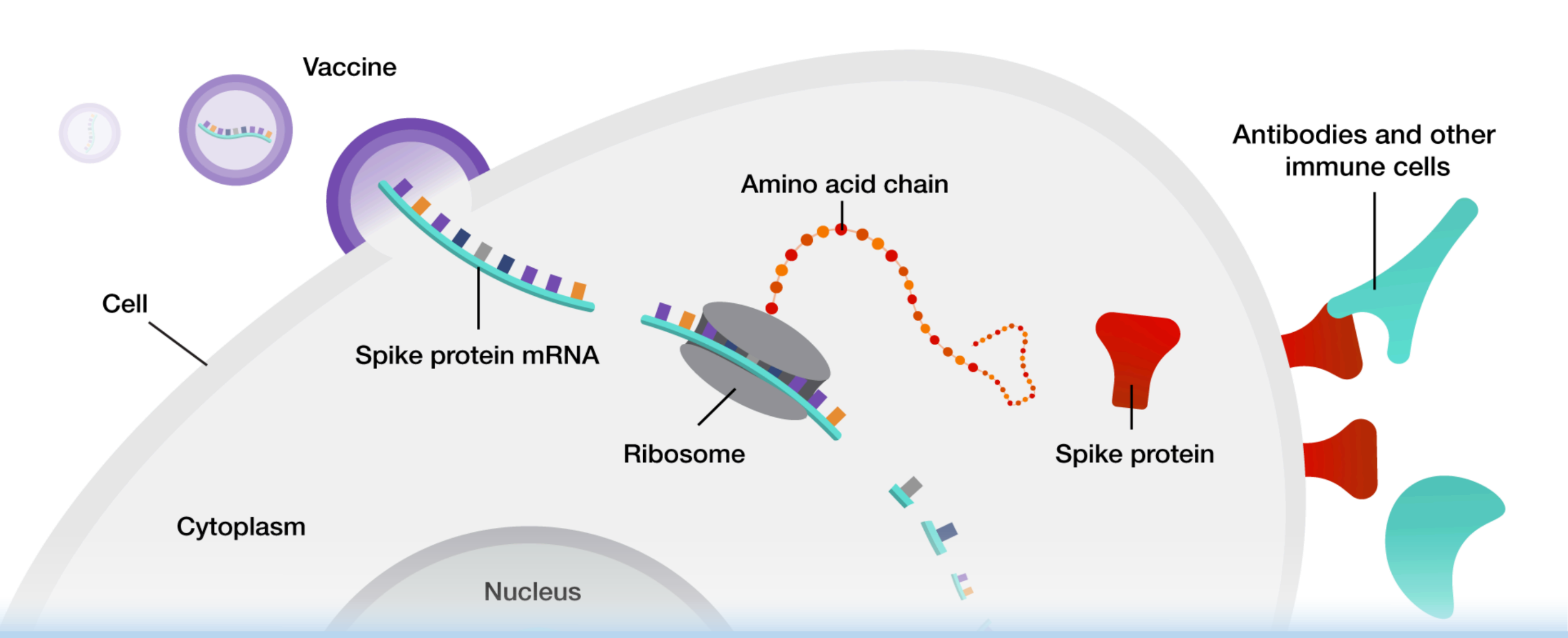
Karikó, a Hungarian biochemist, was devoted to developing methods to use mRNA for therapy. Despite difficulties securing research funding, she remained committed to her vision. Weissman, an immunologist, was interested in **dendritic cells**, which play a crucial role in immune responses. Their collaboration led to a focus on how different RNA types interact with the immune system.

What are Dendritic Cells?

Dendritic cells are responsible for initiating all antigen-specific immune responses. As such, they are some of the master regulators of the immune response. Think of it like a high-level coordinator in a complex organization. Dendritic cells determine which departments (immune cells) need to be activated for a specific task (such as fighting a particular pathogen).



A dendritic cell under the microscope.
Source: PLoS Pathogens



The **spike protein** (antigen) mRNA gets translated into a spike protein by a ribosome. Then, the spike proteins can simulate a viral infection, thus preparing antibodies and immune cells to respond accordingly.
Source: NIH Human Genome Research Institute

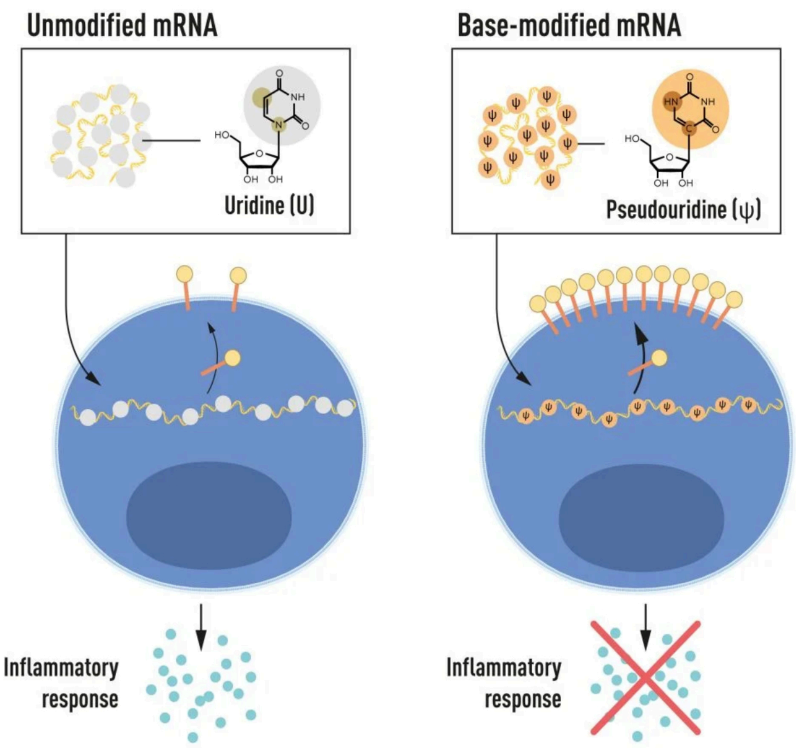
The duo noticed that dendritic cells recognized mRNA transcribed **in vitro** as foreign, leading to an immune response that destroys the mRNA, thus producing an unsuccessful vaccine. Interestingly, mRNA from mammalian cells did not produce this response. Karikó and Weissman knew that endogenous *(growing or originating from within an organism)* mRNA is frequently subjected to chemical modifications of its adenine, uracil, guanine, and cytosine **nitrogenous bases.** They thought that the absence of altered bases in in vitro transcribed RNA could be the reason for the resulting inflammatory response. Their subsequent research confirmed this, paving the way for the development of stable and effective mRNA vaccines.

Their work has had a profound impact, not just in the field of medicine but also in public health at large. The speed at which COVID-19 vaccines were developed and distributed is a testament to the significance of their discoveries. They have fundamentally altered our approach to vaccine development, making it possible to respond more swiftly to health crises in the future

Useful Words:

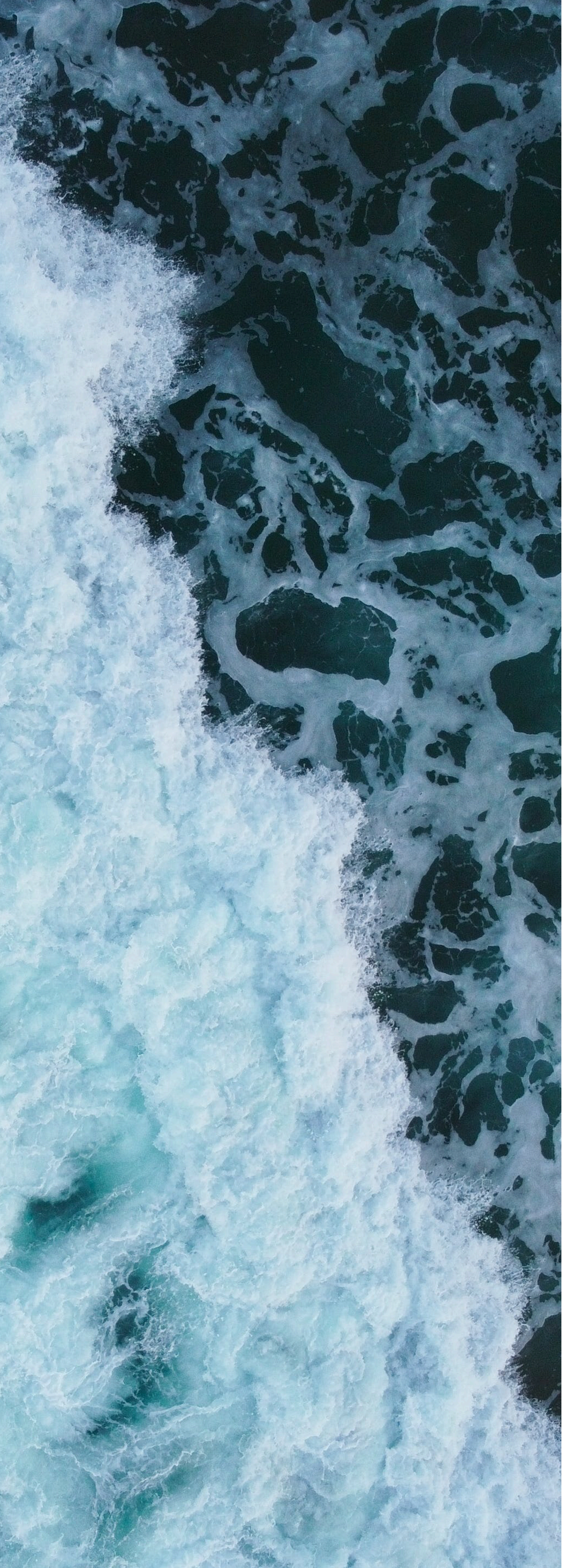
In Vitro: In a test tube, culture dish, or elsewhere outside a living organism.

Nitrogenous Bases: Part of all RNA and DNA, they consist of adenine, guanine, cytosine, thymine, and uracil. The specific sequence of bases are the DNA's genetic code



Unmodified vs Base-modified mRNA: As shown above, inflammatory response can be blocked in base-modified mRNA which increases protein production when mRNA is delivered to cells.
Source: NIH Human Genome Research Institute

The 2023 Nobel Prize in Physiology or Medicine honors Katalin Karikó and Drew Weissman for their transformative work on mRNA technology, which has had an immeasurable impact on global health, particularly in the fight against COVID-19. Their work exemplifies the Nobel Prize's mission to reward those whose discoveries have conferred the greatest benefit to humankind. ■



CHEM CORNER

Bonding Business

You may recall from basic biology or chemistry courses that bonds are what hold together atoms to create molecules. A widely used model for chemical bonding states that covalent bonds are formed when a pair of electrons are shared by two atoms and are attracted to the nuclei of both.

Valence bond theory describes a covalent bond as an overlap between two half-filled atomic orbitals that result in a pair of electrons that satisfy both orbitals. The most optimal overlap is the one that achieves the lowest amount of energy in a system. This leads us to this conclusion:

> **Bonding** *occurs* between two *atoms in* order to ***lower*** *their* ***overall energy.***

By Ian Shen

In order to go further, it is important that we define a few terms that are heavily used:

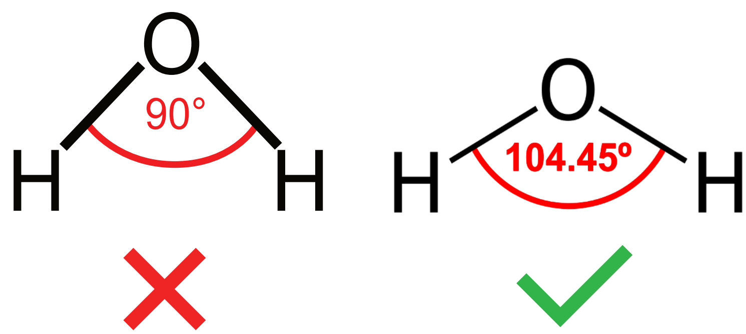
WAVE FUNCTION (Ψ): As particles become very small (for example, an electron), they tend to behave more like a wave. This observation leads to an important equation we call the "wave function," which describes the quantum state of the electrons. Solutions to the wave function are known as "orbitals"

ORBITAL: Atomic (and later molecular!) orbitals describe areas of high electron probability. Each orbital can hold two electrons.

VALENCE: The outermost orbital of an atom, used during covalent bonding.

Dihydrogen monoxide!

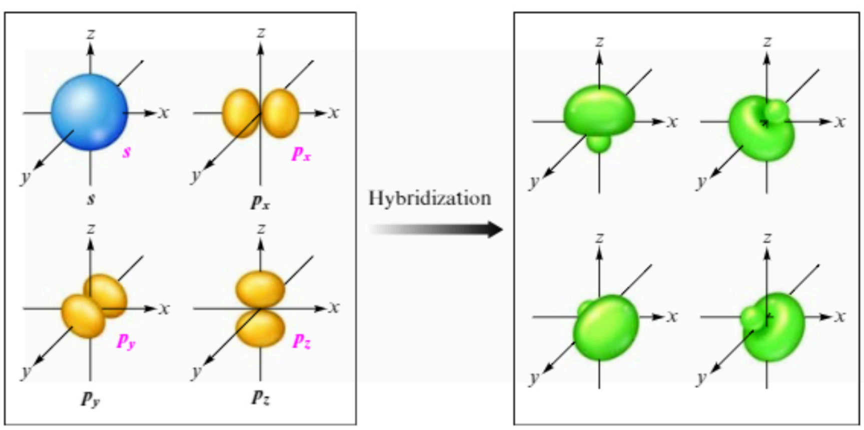
Further analysis of our current model reveals some holes. Looking at a water molecule (H2O), our current model says that the valence orbitals of the oxygen and hydrogen atoms would overlap to create a 90° bond angle. However, experimental evidence shows the bond angle of water is 104.45°. To account for this, the model must be changed.



"Expected vs. true water bonding angle"

Hybridization

To begin fixing our model, we first talk about hybridization:



Despite the scary-looking word, hybridization is actually a very elegant solution to the shortcomings of the previous model. When the wave functions of the bonding orbitals of both hydrogen and oxygen are combined, they produce new orbitals with different shapes and properties.

Important observations to keep in mind:

Hybrid orbitals only exist in covalently bonded atoms

The number of hybrid orbitals between two atoms is the same as the number of atomic orbitals of the separated atoms

Hybridized orbitals overlap to form sigma bonds

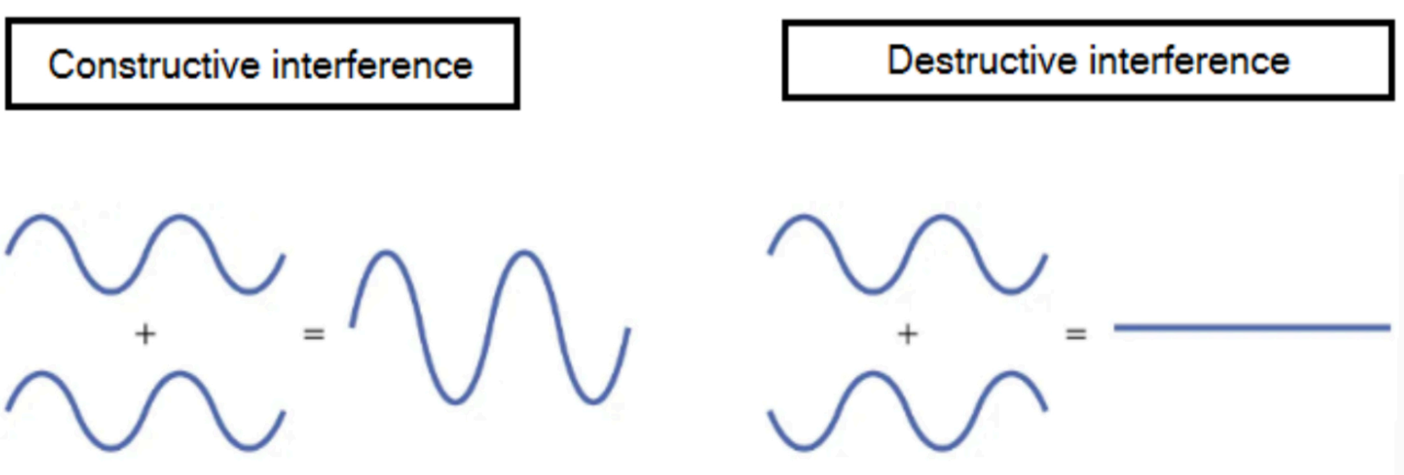
So far, we have defined a model for covalent bonding with orbitals and introduced corrections for when our model doesn't hold up. We're done, right? Nope! Upon further study, issues arise even with our current corrected model:

> Issues with the current model:
>
> 1. For molecules, the current model assumes electrons are localized to their atoms
> 2. The current model does not provide direct information about bonding energies

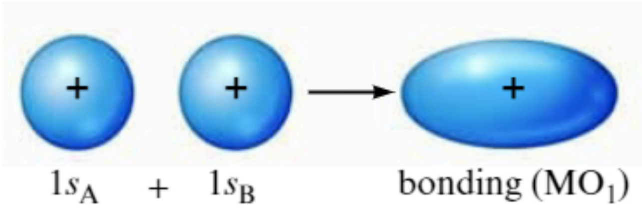
One of the most important corrections we must make to our current model is considering electrons to be delocalized throughout a molecule. This means with our current model, we assume that electrons are confined to an area in between two atoms when bonded. However, with our new model, we consider that the electrons are not necessarily localized– think resonance!

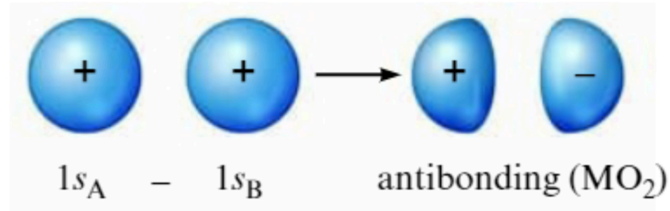
This new model is called molecular orbital theory. A molecular orbital is the region of space in which a valence electron in a molecule is most likely to be found. However, in order to know where these molecular orbitals came from, we must first return to the wave function.

> Constructive and destructive properties of waves:
>
> Recall that wave functions arise from the idea that small particles, such as electrons, behave more like waves than traditional particles. Waves, when combined, have constructive and destructive interference. In orbitals, the waves considered are 3D, so constructive interference would lead to regions with high electron probability while destructive interference would lead to regions of no electron density.



These wave interactions (constructive and destructive) have large implications for our new molecular orbital model. Take a simple molecule like H2. When the wave functions of the hydrogen molecule are solved, two molecular orbitals result:





When the wave function of the orbitals are added, (1sA+1sB) constructive interference creates a region of heightened electron probability between the nuclei– a bonding molecular orbital. Conversely, when wave functions are subtracted, destructive interference occurs. This leads to a region of no electron probability, referred to as an antibonding molecular orbital. Important points:

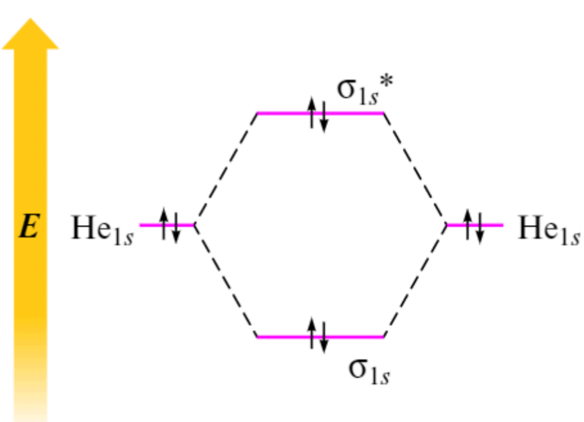
Before we look at some examples and applications of the new model, we first need to utilize one of the advantages of the MO model. Since MO diagrams directly tell you information about bond energies, we can use them to quantify bond strength.

Molecular Orbital one (MO1) and MO2 are referred to as sigma MOs (the same type of sigma bond as seen in valence bond theory)

MO1 is lower in energy than the atomic orbitals that it is made of. Electrons in this bonding MO are in between nuclei, minimizing the overall energy of the molecule and favoring bonding. MO2 is higher in energy than the atomic orbitals that it is made of, so electrons in this antibonding MO are mostly outside the space between nuclei, raising the overall energy of the molecule and favoring a separated state.

Applications of the Molecular Orbital Model

What makes noble gasses noble? In order to determine why noble gasses do not form bonds, we will consider a simple theoretical He_2 molecule. A complete molecular orbital diagram for He_2 is shown below:



As seen on the right and left of the graph, both helium atoms will use their 1s (valence) orbitals to bond. After placing the 4 electrons in the newly formed molecular orbitals, we find that both the bonding AND antibonding orbitals are filled. This suggests that a state where both helium atoms are bonded is not favored any more than a state in which they are separate. Both of these observations align with experimental evidence that helium gas exists as individual atoms instead of He_2 ■

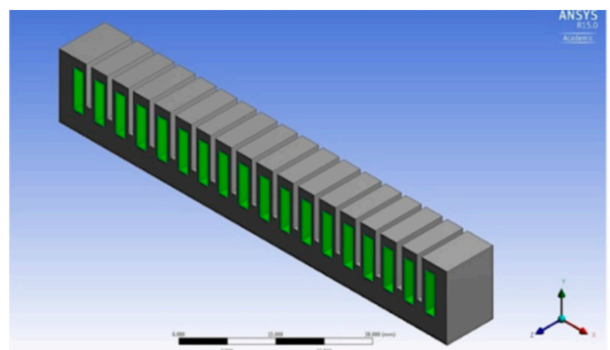
Senior Interviews

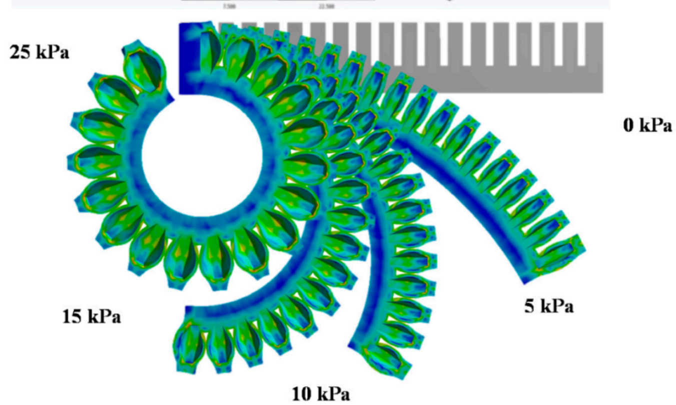
Abhai Anand

Introduction:
I'm Abhai Anand and I am interested in Biomedical Engineering

Give a brief summary of your research
Studying Soft Pneumatic Actuators (SPAs) and how the chambers can be manipulated for applications in glove rehabilitation devices.

What inspired you to do your research project?
I was always passionate about the medical field. When I came to ASFA and started learning about math/science, I became immediately passionate about combining my two favorite things together.





What's your favorite part of doing research?
Designing online using Solidworks.

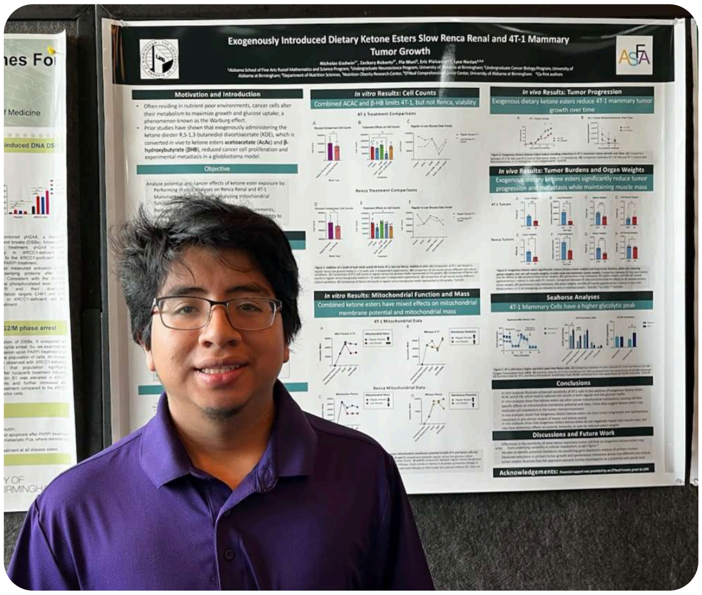
What have you learned during your research? Did you make mistakes, and how did you overcome them?
Lots of mistakes. Initially, I came to my mentor with very complicated research ideas. I wanted to do things that were not feasible, and my mentor told me about it. Even doing something that is quite feasible, I find the many fabrication errors (bubbles in the silicone structure) and problems I face to be quite difficult. Research is a slow and long process, and you will encounter many obstacles. However, overcoming each obstacle teaches you so much about how to do research.

What's some of your biggest advice for upcoming highschool researchers?
Research something that makes you happy or something that you are passionate about. Research is unpredictable and sometimes overwhelming. However, if you are truly happy with what you are doing, every day will fill you with joy and satisfaction.

I know life is quite difficult for the math/science department. Keep your heads up high, stay happy, and enjoy life for what it is.

Senior Interviews

Nicholas Godwin



Introduction:
Hi, my name is Nicholas Godwin and I am interested in the immunology field of study.

Give a brief summary of your research
My project was testing a substance called R,S-1,3-butanediol diacetoacetate (KDE) on different types of cancer cells. The substance works by changing how the cells get their energy, and when we gave this substance to mice with kidney and mammary tumor cell lines, it slowed down the growth of the tumors.

What inspired you to do your research project?
Immunology, specifically in the context of the cancer biology field, because it has many real-world applications.

What's your favorite part of doing research?
In-depth specialization of a particular field. Being able to perform literature reviews, learn all about a specialty (in this case, cancer biology and immunology), and apply it in a lab setting is a rewarding experience.

What have you learned during your research? Have you made any mistakes? How did you overcome them?
Through my senior research, I learned a lot of laboratory techniques. While there certainly is a learning curve, practice makes permanent.

What's some of your biggest advice for upcoming highschool researchers?
For Senior research, be sure to email mentors early. The earlier that you get a mentor, the sooner you can perform literature reviews and start planning. For research in general, keep a well-documented lab notebook (clean, well-dated, etc...)

Department Interviews

Ms. Chin

What do you love most about our department?
Student and faculty diversity; As a department, we stand out because of the research graduation requirement. Their research and skills learned lay the foundation for a student who wants to be a life-long learner.

How has M/S grown since you've been
- Graduation requirement (research) was adopted when I became chair of M/S
- Computer science offerings have increased and for the better
- Improved in college level math offerings like math modeling, etc.

What direction would you like to see this department go?
- To be as competitive as other reputable (STEM) programs in the nation
- Nurture and train more life-long learners
- Offer courses in entrepreneurship, debate, and leadership in more practical engineering courses/ research field experiences in science for each grade level.

Math / Science is a very intensive program, do you have any advice for struggling students based on what you've seen in the past?
Steps:
- Recognize you need help
- Ask for help - you must be comfertable to get help from adults and peers
- Listen to advice given by your teachers
- Act on the advice / suggestions for improvement
- Repeat these steps and continue to persevere to see the light at the end of the tunnel.

What is your favorite subject other than Math / Science?
Chemistry and physics.

How would students get on your good side?
By working hard, listening to all teachers advices, do not be a procrastinator, and have a positive attitude to want to be a better student

Upcoming Events

USABO Opens: February 1, 2024 (Biology)

AIME I: February 1, 2024 (Math)

AIME II: February 7, 2024 (Math)

F=ma: February 9, 2024 (Physics)

Science Olympiad: Feburary 10, 2024

Statewide Written: February 24, 2024 (Math)

National Chemistry Opens: March 1-24, 2024

AP Calculus Exam: May 13, 8:00AM

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