College of Letters & Science

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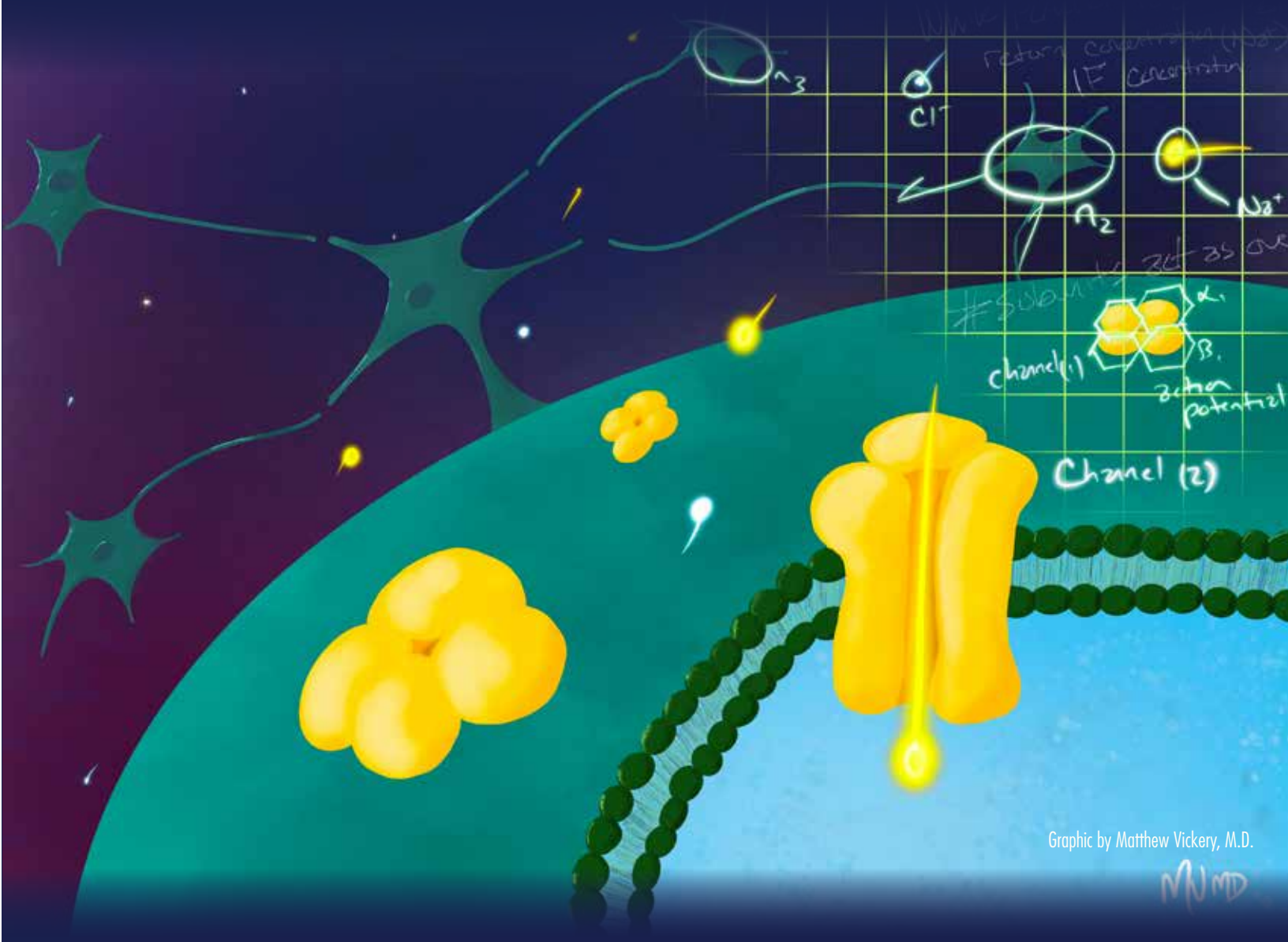
An ion channel's model behavior



Graphic by Matthew Vickery, M.D.

Mathematics professor wins NSF grant to build computer models of mysterious biological processes - Pg. 6

Channeling model behavior: Mathematics prof wins NSF grant

Electrically charged ions like sodium, potassium, and calcium are essential for the body's cells to perform their functions. But, cells are surrounded by an impermeable barrier made of lipids, or fats. There are channels in the cell wall that ions may pass through to cross that barrier and make their way inside the cell.

In the cell there is an organelle called a mitochondrion. If you think back to high school biology class, you may remember that mitochondria are the "power houses" of the cell. Mitochondria produce a molecule known as ATP, which provides the body energy for functions like muscle contraction, cellular signaling, and protein synthesis.

To do that, mitochondria need ions, and to get inside the mitochondria, the ions must pass through another ion channel. Known as VDAC (voltage-dependent anion channel), this channel is much different than regular ion channels in the cell membrane. A regular ion channel is specific to one kind of ion. In other words, only a sodium ion can pass through a sodium ion channel, and only a potassium ion can pass through a potassium ion channel. But the VDAC allows multiple ionic species to pass through – and even small molecules like ATP.

"You also have to consider multiple ionic species that have different ionic sizes. How are you going to simulate these particles across the channel?" mused Dexuan Xie, a professor of mathematical sciences at UWM.

That's the question that Professor Xie and his collaborator, Professor Ranjan Dash from the Medical College of Wisconsin, will answer with the help of a new, $600,000 grant from the National Science Foundation (NSF) awarded on July 13, 2022.

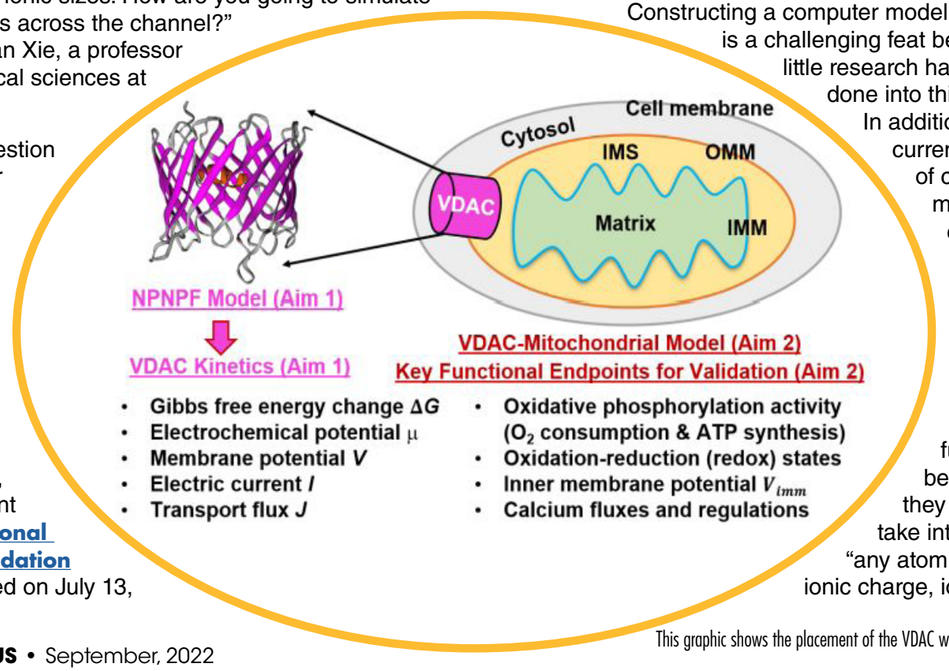
The grant is titled, "DMS/NIGMS 1: Collaborative Research: Advanced Ion Channel Modeling and Computational Tools with Application to Voltage-Dependent Anion Channel and Mitochondrial Model Development." Xie is collaborating with Dash to build computer models that will simulate how ions move through the VDAC and how the properties of those ions impact the function of the mitochondria.

Solving this problem could result in solving a host of other problems. According to Xie and Dash's grant proposal, "mitochondrial dysfunction … plays a critical role in the pathogenesis of numerous human maladies, including cardiac ischemia-reperfusion injury, heart disease, hypertension, diabetes, cancer, aging, and neurodegenerative diseases. Therefore, alleviating mitochondrial dysfunction through targeted interventions would curb the progression of these diseases and attenuate their severities."

In other words, understanding how VDACs impact the mitochondria may help researchers discover treatments or even cures for diabetes, heart disease, cancer, and many other illnesses.

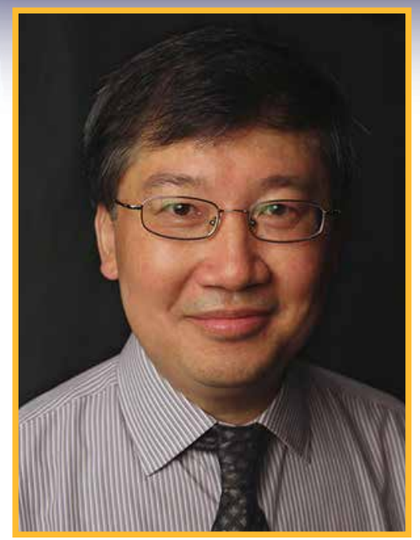
Building a model

Constructing a computer model of a VDAC is a challenging feat because very little research has been done into this area. In addition, the current methods of computer modeling ion channels won't give an accurate picture of how a VDAC might function because they do not take into account "any atomic charge, ionic charge, ion size, or membrane protein molecular structure," according to Xie and Dash's grant proposal.



This graphic shows the placement of the VDAC within a cell. Dexuan Xie has an NSF grant to build a computer model of how a VDAC works. Graphic courtesy of Dexuan Xie.

That's a problem because computer modeling relies on mathematical calculations for accuracy. Using the simulation data derived from specific equations, the computer can generate images of how a VDAC functions – impressive given that these functions are carried out on an atomic level.



Dexuan Xie

Over the past five years, Xie has developed increasingly efficient modeling methods to generate models of cellular ion channels. His work has been based on what is called either a Poisson-Nernst-Planck equation or a Poisson-Boltzmann equation, so named for the types of equations used to produce the data the computer needs to generate a vivid image of ion transport across a membrane via an ion channel.

That works well in regular channels because ion channels have few variables. "These channels have a select function and only allow one kind of ionic species through and block others," Xie explained. He was actually halfway through a five-year, $42,000 grant awarded by the Simons Foundation to build ion channel models when he was awarded the NSF grant. He will continuously carry out this project in the coming three years under the support of a gift grant (a total of $8,400 per year) that he received from the Simons Foundation on Sept. 1.

But modeling VDACs involves many more variables because a VDAC allows multiple types of ionic species and small molecules like ATP through the channel. So, Xie decided, he will have to develop more equations to account for those extra variables. The result will be a "nonlocal Poisson-Nernst-Planck-Fermi" model, or NPNPF for short.

What does NPNPF mean?

- **Poisson Equation:** This equation calculates the potential field caused by electrical charges – important, as ions from a solution and atoms from a protein molecule are electrically charged particles.

  "That's a fundamental equation when you consider any electrostatic potential modeling," Xie said. "The Poisson-Boltzmann equation calculates the distribution of the ions in an equilibrium state," Because the ions are moving, they are unequal. That's widely described as the transporting movements of the ions, and they cause the electrical current. A Nernst-Planck equation is a powerful tool to model a non-equilibrium state of ions."

- **Nernst-Planck Equation:** This equation is used to describe how charged ions move within water. It addresses the concentration of ions in water outside of an ion channel subject to an electric field.

  However, the Poisson-Boltzmann equation assumes that the water molecules outside of an ion channel are uniform.

  "But under an electrical field, water molecule distribution will be changed," Xie noted. Because an electrical field is not uniform, some areas are stronger and some areas are weaker. ou cannot use one constant to describe this dielectric property. That's why the equation must be…

- **Nonlocal:** "It means each water molecule is correlated to all other water molecules. That's nonlocal. Local means that you're only related to yourself. Nonlocal means that each one is related to others," Xie said.

- **Fermi:** "Fermi is another kind of equation. (It) allows us to treat ionic size problems," Xie said. That will address the different sizes in sodium ions versus potassium ions versus ATP versus the other molecules that can be transported across a VDAC.

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Ion channel modeling

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"When you combine that all together, we are going to develop new kinds of channel models that I consider nonlocal electric forces," Xie said.

"The more equations, the higher the resolution of the computer model, and the more accurate the model will be," he added.

Applications beyond mitochondria

This grant represents the **fourth major NSF grant** Xie has been awarded during his tenure at UWM. His work tends to build; with each passing project, Xie discovers new ways to make computer modeling more efficient and more accurate.

Like his other work, Xie anticipates that this grant project will lend itself to other useful applications. After all, he noted, "all of these techniques or numerical algorithms can be adapted to other situations. The models, the equations were the same; we just changed the meaning of the functions."

For example, Xie and Dash anticipate that their work might have applications for scientists studying the transport of electrons in semiconductors and ion transports in lithium ion batteries and fuel cells.

Or there might be applications in creating anti-viral drugs for diseases like COVID-19. Xie and Dash are hopeful that their work in electrostatics might shine light on exactly how the virus enters a cell, in hopes that they can identify parts of the virus that might be a good candidate to be targeted by new medicines.

The NSF grant is funded through 2025.

By Sarah Vickery, College of Letters & Science

Geosciences student is a beach ambassador

Beach ambassadors Mikayla Walker and Gavin Schmidt at the lakefront, getting ready to start their day at the beach. (UWM Photo/Elora Hennessey)

Three UWM students have an office with one of the best views in Milwaukee.

As beach ambassadors, Mikayla Walker, Gavin Schmidt and Chris Giddens patrol Bradford and McKinley beaches along Lake Michigan from Thursday through Sunday afternoons.

The beach ambassadors, wearing matching blue T-shirts, educate visitors about potential dangers and encourage them to enjoy the lake while being aware of its hazards.

The program is a response to the four drownings on McKinley Beach in 2020 and 56 overall in Lake Michigan that year. A shortage of lifeguards has made the situation worse.

The beach ambassadors aren't lifeguards, but try to keep people safe by offering information and advice about water conditions and safety. For example, many beach visitors aren't aware that when red flags are flying, it's not safe to go into the water because of dangerous currents and high waves.

The beach ambassador program was organized in 2021 as a pilot program by Milwaukee Riverkeeper, Milwaukee Water Commons, Milwaukee Community Sailing Center, Coastline Services LLC and the University of Wisconsin Sea Grant Institute. That pilot effort was renewed this summer.

Walker, a senior in geology, saw a department email about the program and thought it was a good fit with her interests. She'd previously done undergraduate research studying fossils deposited along the lakeshore in a park near Cudahy.

"We want people to have fun, but stay safe," Walker said. She feels a special responsibility to reach out people of color who may not have had early opportunities for swimming lessons or safety courses. She noted that all four drowning victims at the beach last year were Black. "As a person of color, I feel it's particularly important to reach out to them whenever possible."

By Kathy Quirk, University Relations

UWM microcredentials offer specific skills in nonprofit management 'a la carte'

When it comes to continuing education in the field of nonprofit management, the No. 1 skill training that professionals are looking for is fundraising.

That may seem odd, since the need is largely coming from people already employed in the field, said Bryce Lord. But many people working in nonprofits need to learn a specific skill to fill a knowledge gap.

"People in the nonprofit field may come to it from all walks of the workforce," said Lord, associate director of UWM's Helen Bader Institute for Nonprofit Management. "They may have a degree in something different, like an MBA or a bachelor's in an unrelated field."

Eight important skill areas

Beginning this fall, UWM will be offering microcredentials in eight sought-after skill areas of nonprofit management. To earn a microcredential in Nonprofit Management, students take a cluster of three courses focused on a specific topic. This cluster can be completed in a year to a year and a half. Completion comes with a badge that can be used on a resume or LinkedIn account as evidence of competency.

"This is a way for people to get training in a much more concentrated form without having to make a larger investment, in a longer time frame," Lord said. "The microcredentials are creating an 'a la carte' system for learners."

The inspiration for microcredentialing grew out of a demand by students and employers for shorter, more competency-based learning experiences, said Phyllis King, UWM associate vice chancellor for academic affairs.

These microcredentials are designed for working people who have not attended college, current college students and those who have completed a degree. For those without a degree, the credits earned from completing a microcredential could count toward a formal degree later, dependent upon the specific program requirements.

"The use of microcredentials could translate into better jobs, higher starting salaries and faster promotion by making a learner's qualifications clear and transparent to employers," King said.

Marketing, innovation, technology

Besides fundraising, UWM will offer microcredentials in seven other nonprofit-specific skill areas: nonprofit governance, nonprofit advocacy, nonprofit financial management and accountability, nonprofit marketing, nonprofit innovation, nonprofit technology and nonprofit administration.

Bryce Lord, associate director of the Helen Bader Institute for Nonprofit Management, says that microcredentials are quick route to specializing in a specific skill. (UWM Photo/Elora Hennessey)

For this pilot program, students with a bachelor's degree **can apply as non-degree students** without committing to a full graduate degree. No letters of recommendation or GRE scores are needed to enroll in this master's-level microcredentialing program.

New undergraduates **can also be admitted as "non-degree/guest students"** to enroll in the microcredential courses.

Can apply toward a degree

The nonprofit microcredential carries nine college credit hours that can be used toward a master's degree in nonprofit management or a 15-credit certificate in the discipline, Lord said. Students enrolled in either program could structure their coursework so that they simultaneously complete a microcredential badge with their degree or certificate.

UWM will be creating microcredentials in other academic departments, with a goal of offering 20 to 30 microcredentials in various disciplines within the next two years, King said.

According to UWM surveys, undergraduate students were most interested in microcredentials in information technology, health, business and social work, she added. Graduate students had similar responses, but with the addition of leadership and diversity.

By Laura Otto, University Relations