Professor Daniel Fologea, an associate professor at Boise State University, studies the way cells interact with their environment by selective transportation of ions and molecules through the cell membrane. His research group examines these interactions in order to understand how diseases occur, and how to use them for biosensing, early diagnosis, and to cure diseases like cancer.

**WHAT IS LYSENIN?**
Lysenin is the name of a pore-forming toxin that can be found in fluids from the main body of an earthworm called redworm or *Eisenia fetida*. The worm, typically found in Europe, lives on decaying organic material and can be used for composting household and industrial waste – like sheep manure, coffee pulp, and even wood chips. Despite its origins, this protein inside the earthworm might be the key to the better diagnosis and treatment of deadly diseases, according to Prof Fologea’s research.

Lysenin destroys cells through cytolysis, a process by which a cell bursts due to excess water flowing into the cytosol (the fluid within the cell). Once lysenin is inserted into the membrane, it forms stable nanosized channels, or pores, through the hydrophobic, or water-repelling, cell wall. Prof Fologea and his colleagues use these channels to their advantage, by recreating the way the protein forms the pores in the cell wall.

**LYSENIN: CHANNEL, SENSOR, OR MEMORY ELEMENT?**
In earlier works published in 2010 and 2011, Prof Fologea and his team focused on understanding the biophysical properties of lysenin channels by reconstituting them in artificial membrane systems and investigating their response to physical and chemical stimuli. Their findings have shown a pore-forming toxin that deviates considerably from its previously assumed killer role. Unlike any other pore-forming toxins, lysenin channels are highly regulated by transmembrane voltage, multivalent metal ions, and temperature. His research group proposed using these channels as cheap and reliable sensors for detecting toxic metals in water by monitoring the changes in the electric currents through channels in the presence of tiny amounts of metal cations (positively charged ions).

When Prof Fologea’s team investigated the response of lysenin channels to variable external voltages they recorded a striking feature: lysenin channels responded to the applied voltages in a history-dependent manner. In simple terms, lysenin channels are molecules with memory, capable of “remembering” the last state they were in. This work demonstrated beyond any doubt that memory in biological systems is not necessarily a function of evolved organs like the brain, but may be achieved at single molecule levels.

Lysenin, a protein found inside earthworms, might be the key to early diagnosis and treatment of deadly diseases such as cancer.
current is affected by any tiny changes caused by molecules passing through the channel. The team can monitor the current, and watch for these tiny changes, enabling the detection of even a single molecule as it passes through the channel in the membrane. In one of the latest studies Prof Fologea and his team published in 2017, they found that lysenin channels can act as nanosensors, by allowing the hormone angiotensin II to pass through channels when an electric field is applied. Angiotensin II is a peptide that causes vasoconstriction, thereby tightening of blood vessels, and a consequent increase in blood pressure. In contrast to other pore-forming proteins that may be used for similar studies, lysenin has the advantage of a large pore, therefore allowing analysis of bigger molecules. This work is expected to advance our ability to characterise and even sequence important biomolecules such as DNA and proteins. In addition, by endowing the channel with the recognition elements capable of recognising and binding disease-specific biomarkers in complex biological fluids, this technique enables early diagnosis of cancer and other diseases.

**LYSENIN AS A CONTROLLED NANO-VALVE FOR DRUG DELIVERY**

‘The remarkable biophysical properties of lysenin channels present a tremendous potential for multiple scientific, technological, and biomedical applications,’ says Prof Fologea. The large pore size may accommodate the passage of large molecules, and the ability to open and close the pores at will is a feature uncommon among pore-forming toxins. To exploit these capabilities, one of the group’s goals is to transport drugs to diseased sites through lipid-made nano-sized carriers mimicking a spherical membrane, and release them by controlling the opening and closing of the lysenin channels inserted into it. Similarly, the channels can be reconstituted directly into live cell membranes and used to transport foreign molecules into and out of the cells. Not only drugs, but genes could also be introduced into cells to manipulate their functionality or correct other deficient genes. Prof Fologea’s group demonstrated that whether or not a molecule can pass through the channels can be controlled by external electric fields, multivalent cations, pH, temperature, and even adenosine triphosphate (ATP), which transports chemical energy within cells. Current delivery systems deliver drugs at the same dose to all tissue as a result of limited targeting capability. X-rays can be used to trigger the release of anti-cancer drugs only at the diseased site, which can be easily targeted with focused X-ray radiation. Such achievement would enable concomitant highly localised radio and chemotherapy while significantly reducing the remote affects associated with systemic chemotherapy.

**LYSENIN RESEARCH PROVIDES OPPORTUNITIES FOR MULTIDISCIPLINARY MENTORING AND LEARNING**

While Prof Fologea and his colleagues are making great strides towards developing cures for diseases like cancer, he also recognises the importance of mentoring future generations of scientists. With this in mind, Prof Fologea dedicates a great amount of his time to mentoring students in the Biomolecular Sciences Graduate Program at Boise State University. His affiliation with the Biomolecular Sciences Graduate Program at Boise State University provides unique opportunities for fruitful collaborations with faculty from Biology, Chemistry, Physics, and Engineering.

You studied physics and biophysics, why did you choose to go into research about cell membranes? What is the main challenge or limitation in your research? What inspired you to pursue your research in this area? What kind of interdisciplinary backgrounds do your students, whether they are undergraduates, PhD students or post-docs, have? How is your experience in both physics and biology a must? Biophysics is interdisciplinary by definition, therefore advanced knowledge from Physics and Biology is a must for advancing the field. However, this is not a requirement for undergraduate students interested in starting their research career in my lab. Nonetheless, all the undergraduate students who have worked in my lab ended up taking relevant classes outside their home department, which demonstrates a strong motivation for gaining multidisciplinary knowledge and skills. With regards to graduates, they are required to demonstrate excellent knowledge of Biology, Chemistry, Physics, and Math as a condition for admission into our graduate program.

To what extent do you have to develop new experimental tools and equipment to go alongside your research? Sometimes we are unable to purchase what is required for our investigations because what is available does not satisfy our needs. Many of our small tools and devices are homemade, and the students bring great contributions to such developments. I can say that many devices, tools, and software packages developed by our students are outperforming their commercially available counterparts with respect to fulfilling our needs. What is the ultimate goal for your research, in your own personal opinion? If the results of my research will improve someone else’s life, I shall consider my research goal achieved.

Through his mentoring activities, Prof Fologea’s work will continue to greatly impact the field long after he stops undertaking his own research.