EXECUTIVE SUMMARY
Sometimes the key to understanding complex diseases lies as much in combing through the previously published literature as in the next laboratory experiment. But getting a handle on the disease when there are thousands of publications can be an overwhelming task. Dr. Gabor Juhasz discovered that Elsevier’s Pathway Studio could help him review the current literature and then plan their next laboratory experiments to build on previous observations.
Systems biology pioneer Gabor Juhász began his neural research career long before the term “systems biology” was coined.

In fact, as he says, it was “last century” when, as an electrophysiologist in the lab of Marcel Verzeano at the University of California, Irvine, he took his first steps toward thinking about a systems approach to understanding the brain.

“In 1976, people were very busy with the categorization of neurons on the basis of immunostaining and physiology,” he says. But Dr. Juhász thought something was wrong with their method of observing animals and recording single units as neurons fired. Observing that a single neuron fired differently in a cat when it was active than when it was asleep led him to develop the assumption that a single neuron can have several kinds of physiology – bursting, or stochastic firing, and so on so the characterization needs changing.

Later, working with the distinguished neuroscientist Robert Galambos at the University of California, San Diego, Juhász sought to understand how brain cells record information. They observed that all cells with their rigid pipes “look like computers with no memory,” but concluded that each individual cell contains a little piece of the memory he says, dismissing ideas about cell types and cell clustering in classical sense.

In the course of collecting data on sleep-related behaviors in cases of neurodegenerative diseases like epilepsy or psychiatric diseases, Juhász saw that a cell’s electrophysiology could perform as expected right up to its death with neurons firing normally until their end. “We believed that there is a physiological degeneration process, which makes roughly 5,000 neurons die each day,” he says. “This ratio is much higher and more specific when something is wrong inside the cell.”

His conclusion? The pathological changes happen inside the molecular machinery of the cell rather than in its membrane, electric performance, or neurotransmission. Therefore, “if we want to understand neurodegenerative diseases on the basis of physiology alone, our previous assumptions have been wrong.”

Juhász says he was initially stumped by trying to determine what takes place in the brain in the time between two epileptic seizures. “I know there is no consciousness during a seizure, but what happens (to the cells) between two seizures? Nothing unusual - the brain is normal. But when the subject is epileptic, something must be wrong; that’s why seizures reoccur,” he says.

So, to understand changes in the brain between two seizures, he turned from looking at electric activity to looking at molecules and neuropeptides. He discovered processes through which a neurotransmitter is automatically modulated during sleep, waking, and disease. That turned out to be “just the surface,” Juhász says. “Neurotransmitter releases are made by a little “machine” called a synapse that contains about a thousand of different proteins. The synapse very delicately adjusts the probability of a collision between the neurotransmitter and receptor.” It led the electrophysiologist down the path toward looking at proteins and their interactions rather than just electrical signals.

Today, as head of the Laboratory of Proteomics at Eötvös Loránd
University in Budapest, Dr. Juhász’s work contributes to the understanding of inter-neuron communication and the progression of neural diseases such as Alzheimer’s and various psychiatric disorders. Proteomics has been a game changer for his research, and Elsevier R&D solutions have been critical to his success, he says.

“Previously we worked for years to find significant changes. Now, when we evaluated 2D gels we found some 100 significant changes immediately,” he says. But the bounty came with a caveat: information overload. Understanding a few hundred different proteins involved in the pharmacological change in a rat brain could lead him to reading thousands of scientific papers, he says. For instance, for beta amyloid, a protein implicated in Alzheimer’s disease, “I found more than 10,000 published scientific papers.” Juhász jokes that he calculated that he could read perhaps one-third of them in all the hours left until his retirement – clearly not a viable option!

In fact, most genomic and proteomic research publications at the time provided readers with the experimental change they observed and then lists of previous papers that characterized the proteins they’d identified. “Who wants to read a paper in which you have a table of 200 different proteins and you list 10-50 publications for each protein and force the reader to do more research about what it means?” Juhász asks rhetorically.

He considered the situation hopeless until he discovered Elsevier’s Pathway Studio platform and persuaded a pharmaceutical company partner to pay for his lab’s initial license to use it. The semantic search engine, he says, was a breakthrough. “It made our data publishable.”

Today, Juhász’s lab uses Pathway Studio mainly for hypothesis making: His team puts data from its proteomics and single RNA transcript research into model networks to create physiologically-controlled models in which they uncover protein changes and develop hypotheses. “Change this protein and this protein in this disease and see how the mitochondria responds,” he says. “This is the way systems biology works in most laboratories now.” Those models guide the laboratory experiments, which generate data to refine the models, and so on.

Juhász calls it “a big change in thinking from the traditional approach of reading lots of papers in the library, to now be able to associate the work from many different papers and combine them together in new ways to uncover something new.” But, he notes, that older strategy was never efficient for psychiatry and neurodegenerative research because so few of those diseases are based on single gene mutations.

This protein-network/systems biology way of thinking is also an effective approach to drug development, Juhász says. “Similar to the start of the molecular biology era, people know this is the new track to follow. There have not been many big breakthroughs using systems biology approaches yet, but I’m sure they are coming.” At age 67, Juhász expects to still be working in the lab when they happen. “At 67 I’m still breeding Great Pyrenees dogs and climbing mountains. There’s still so many discoveries to make, I’m sure I’ll work until at least age 87.”