

TEST *flight*

Like pilots using a flight simulator to practice a perfect landing, University of Minnesota scientists use disease simulators to evaluate potential treatments

BY JUSTIN HARRIS

ILLUSTRATION BY KOTRYNA ZUKAUSKAITE



Life is complex, messy, and unpredictable. It can also be surprisingly straightforward.

Imagine a football flying through a goalpost, or a cat leaping onto a table, or a dancer twirling across a stage. Different though they appear, they're all following the same foundational laws of physics that explain, well, everything.

And sure, every movement has variables (like a kicker's leg strength, for example), but even those are beholden to those same basic principles.

Backed up by the laws of physics, and with enough observation, scientists can create mathematical models that explain, simulate, and predict the behavior of just about anything. Even things we can't see—like a dividing cancer cell or the marauding COVID-19 virus.

That's what David Odde, Ph.D., does. A biomedical engineer at the University of Minnesota, Odde brings a mathematical mindset to medicine. He and his team observe how different types of disease cells move, migrate, and grow in the body, and use that information to build models that predict how diseases will react in specific scenarios.

Think of it like a flight simulator, but on a microscopic level, Odde says. Instead of practicing landing a plane in different kinds of weather, Odde and his team run simulations that test how diseases like cancer will respond to different kinds of treatment.

And much like a flight simulator allows pilots to make mistakes without risk, mathematical models of disease allow researchers to rapidly try all kinds of treatments—including ones that fail—without putting a single person in harm's way. Once a successful treatment emerges from the models, the scientists behind it can be more confident that it's going to work.

That's the ultimate goal, says Odde, who holds the Medtronic Professorship for Engineering in Medicine. He thinks disease simulators have the potential to power up the potency of clinical trials, making their chances of success far better than they are today.

"We think it can change the trajectory of therapy development and outcomes for patients," Odde says.

A fierce foe

Odde was just a kid when he became enamored with the way things move. During a summer camp in Minneapolis, he used a microscope to watch microorganisms swimming in a pond water sample he had collected. He was fascinated.

The fascination sustained him through graduate school and led to a faculty position in chemical engineering, where he continued to study the ins and outs of cell movement. At that time, he had no plans to apply his knowledge directly to medicine. It wasn't until a happenstance conversation with a brain cancer physician that Odde realized his work could have a direct impact on treating disease.

"He said to me, 'I think your cell models could be relevant to cancer,'" Odde says. "I said 'Oh, yeah? Tell me more.'"

It was the start of a new career path. Odde began studying the way cells in a specific type of brain tumor called glioblastoma multiply and spread. He realized that not every glioblastoma was the same, and that differences in cell behavior could tell clinicians a lot about how their patients might fare.

Regardless of differences in tumor behavior, glioblastoma is nearly always fatal. Odde says that grim prognosis is part of the reason he has continued to study this specific disease.

"I know clinicians are frustrated," Odde says. "They want better for their patients. They're willing to consider new approaches. And I think that's why they've been open to me and my ideas. It's a devastating disease, but we have the potential to make a big impact."

The final word on ivermectin

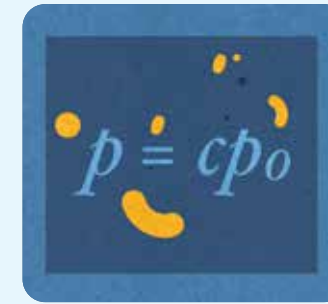
Results from COVID-OUT, a seven-site clinical trial led by Carolyn Bramante, M.D., M.P.H., an assistant professor at the U of M Medical School, found that the controversial drug ivermectin was not effective in treating COVID-19.

The study, fueled by support from the Parsemus and Rainwater foundations, was published in the *New England Journal of Medicine* in August and also showed that metformin, a common diabetes drug, prevented some of the most severe outcomes (ER visits,

hospitalizations, or death), while low-dose fluvoxamine, an antidepressant, was not effective.

The study provides some clarity around which drugs are successful in treating a virus that has killed more than 6 million people worldwide—and which ones aren't.

"We know that some new strains of the virus may evade immunity and vaccines may not always be available worldwide," Bramante says. "We felt we should study safe, available, and inexpensive outpatient treatment options as soon as possible."



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Solve for cancer

Odde ended up at the University of Minnesota, where he eventually crossed paths with David Largaespada, Ph.D., an accomplished brain tumor geneticist and holder of the Hedberg Family/Children's Cancer Research Fund Chair in Brain Tumor Research.

A professor of pediatrics at the U's Medical School and Masonic Cancer Center member, Largaespada creates animal models of glioblastomas that accurately reflect how the disease progresses in people. Information from the animal models is synthesized by Odde and his team, who are then able to create computer models that allow for risk-free experimentation, Largaespada says.

"We can ask, 'What happens if you change this parameter? What happens if you treat this with chemotherapy?' and then actually make predictions about how tumors will respond," he says. "Just like everything else in the universe, cancer follows physical laws that we can express with math. Eventually, we'll have a set of equations that describe cancer growth and, more importantly, its response to therapy."

Odde and Largaespada recently created state-of-the-art models of two of the three known subtypes of glioblastoma. The models highlight, for the first time, how cell growth and migration are different among the subtypes.

"We are now investigating how those differences could be exploited to create better therapies," Odde says.

Seven for seven

Odde was like many others in March 2020: He wanted to help in the fight against COVID-19.

He wondered if his mathematical modeling could help explain a virus that people then knew very little about. A reliable model of how COVID-19 spreads in the body could illuminate the virus' weaknesses, he thought.

After a few weeks of intense collaboration with biologists and virologists at the U, Odde and his team "hammered out what we thought was a reasonably good model based on the literature at the time."

The model locked in on the virus' protein production pathway as a potential weak point. From there, Christopher Tignanelli, M.D., an assistant professor in the Medical School's Department of Surgery, used a computer

tool known as natural language processing to search medical literature for examples of existing drugs that inhibit the pathway that controls protein production. Several options—out of thousands—emerged, including metformin, a relatively safe, inexpensive, and globally available drug.

Odde also used his model to predict how existing antiviral medications would fare against COVID. Since then, various clinical trials at sites across the country (including one at the U; see sidebar) have proven that his "reasonably good model" was more than that—it was perfect, going seven for seven in determining which drugs would work and which wouldn't.

"That combination of natural language processing and mathematical modeling was so successful," says Tignanelli. "Looking back on it, it was pretty impressive."

'Defeat cancer'

With the success of his COVID predictions demonstrating the clinical potential of simulators, Odde wants to expand their use beyond brain cancer. Odde, Largaespada, and their collaborators are launching a new Cancer Bioengineering Initiative at the U that will expand their work to other cancers. Their bold goal is to double the success rate of clinical trials over the next decade.

Today, only 5% of early-stage clinical trials for solid tumor cancers end in success. That means a vast amount of money, time, and, most importantly, patients' and families' hope is lost pursuing treatments that ultimately don't work, Odde says.

He believes computer simulators of disease could improve the trajectory of clinical trials by allowing researchers to try and fail before a person's life is ever on the line.

"Computer simulators have driven the technological transformation of our world—from aviation to pacemakers," Odde says. "Technology has advanced to the point where we can begin applying this practice to defeat cancer. And that is exactly what we intend to do."

 Make a gift to support Odde's research at z.umn.edu/simulators.