What will MRSA do next? Duke researchers developed a computer-based algorithm to predict how bacteria might mutate to evade current antibiotics—and develop drugs that stay a step ahead.

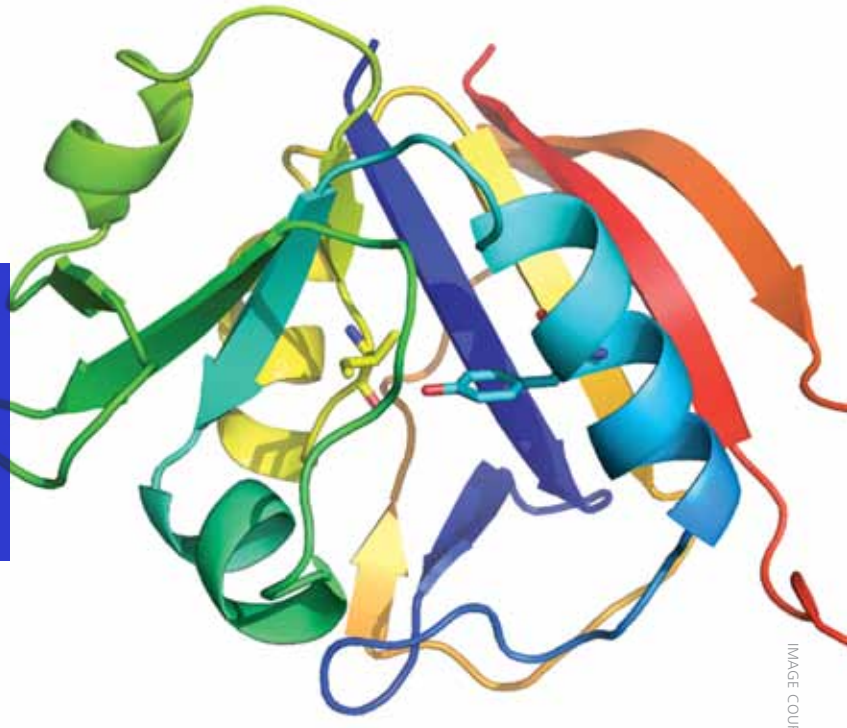

IMAGE COURTESY OF BRUCE DONALD

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—Ivelin Georgiev, PhD

Predicting MRSA's next move

COMPUTERS PREDICT snowfall accumulations during storms or where violent hurricanes will hit land. Now, Duke researchers are using computational prowess to develop smart drugs that can anticipate and defeat bacteria mutations.

Certain bacteria, such as MRSA (methicillin-resistant *Staphylococcus aureus*), are particularly dangerous because they can modify their structure quickly to sidestep any medications designed to prevent their ability to spread. But, according to Duke researchers, new predictive software that identifies and analyzes the myriad of ways bacteria can change could be a powerful weapon in fighting disease.

"It's very expensive and labor-intensive to go back to square one and redesign a drug when a bacterium gains resistance to a drug's existing structure," says Duke computer scientist and biochemist Bruce Donald, PhD. "The protein-design algorithms that predict mutations could be used in a drug-design strategy against any pathogen that mutates to gain resistance."

Duke investigators, along with collaborators from the University of Connecticut, tested the MRSA enzyme dihydrofolate reductase (DHFR), because several existing drugs already target it. It is responsible for turning folic acid into thymidine, one of the four building blocks of DNA, and is present in almost all living organisms. Researchers pushed DHFR through an algorithm to identify potential mutations that would resist drug therapies. The algorithm also has a "dead-end elimination" feature that sifts through all the outcomes that the bacterium uses to escape the drug.

Some bacteria, Donald says, outsmart antibiotics by changing the shape of their enzyme's active site. The computer program identifies all of the possible enzyme configurations a bacterium could use, much like chess moves, to evade drugs that bind to DHFR to slow or prohibit its function. "We're basically trying to do a pre-emptive strike, and this study is a step toward identifying antibiotics that can pre-emptively deal with possible resistance in nature," says Ivelin Georgiev, PhD, lead study author and one of Donald's former graduate students.

"My kids are now nine and 11," Donald says, "and when I ask about the antibiotics they took 10 years ago, I'm told these are not strong enough to treat the same illnesses." Identifying how these bacteria continue to function and multiply in the presence of drug therapies will, Donald hopes, help keep medicine a step ahead of illnesses.

Reference: Frey K, Georgiev I, Donald BR, Anderson A. Predicting resistance mutations using protein design algorithms. Proc. Natl. Acad. Sci. (PNAS) U S A. 2010;107(31):13707-12.