Medical Xpress

Using mathematical theory and software tools, team studies why a variable heart rate is a sign of health and fitness

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Although the heart beats out a very familiar "lub-dub" pattern that speeds up or slows down as our activity increases or decreases, the pattern itself isn't as regular as you might think. In fact, the amount of time between heartbeats can vary even at a "constant" heart rate—and that variability, doctors have found, is a good thing.

Reduced heart rate variability (HRV) has been found to be predictive of a number of illnesses, such as congestive heart failure and inflammation. For athletes, a drop in HRV has also been linked to fatigue and overtraining. However, the underlying physiological mechanisms that control HRV—and exactly why this variation is important for good health—are still a bit of a mystery.

By combining heart rate data from real athletes with a branch of mathematics called control theory, a collaborative team of physicians and Caltech researchers from the Division of Engineering and Applied Sciences have now devised a way to better understand the relationship between HRV and health—a step that could soon inform better monitoring technologies for athletes and medical professionals.

The work was published in the August 19 print issue of the *Proceedings of the National Academy of Sciences*.

To run smoothly, complex systems, such as computer networks, cars, and even the human body, rely upon give-and-take connections and relationships among a large number of variables; if one variable must remain stable to maintain a healthy system, another variable must be able to flex to maintain that stability. Because it would be too difficult to map each individual variable, the mathematics and software tools used in control theory allow engineers to summarize the ups and downs in a system and pinpoint the source of a possible problem.

Researchers who study control theory are increasingly discovering that these concepts can also be extremely useful in studies of the human body. In order for a body to work optimally, it must operate in an environment of stability called homeostasis. When the body experiences stress—for example, from exercise or extreme temperatures—it can maintain a stable blood pressure and constant body temperature in part by dialing the heart rate up or down. And HRV plays an important role in maintaining this balance, says study author John Doyle, the Jean-Lou Chameau Professor of Control and Dynamical Systems, Electrical Engineering, and Bioengineering.

"A familiar related problem is in driving," Doyle says. "To get to a destination despite varying weather and traffic conditions, any driver—even a robotic one—will change factors such as acceleration, braking, steering, and wipers. If these factors suddenly became frozen and unchangeable while the car was still moving, it would be a nearly certain predictor that a crash was imminent. Similarly, loss of heart rate variability predicts some kind of malfunction or 'crash,' often before there are any other indications," he says.

To study how HRV helps maintain this version of "cruise control" in the human body, Doyle and his colleagues measured the heart rate, respiration rate, oxygen consumption, and carbon dioxide generation of five healthy young athletes as they completed experimental exercise routines on stationary bicycles.

By combining the data from these experiments with standard models of the physiological control mechanisms in the human body, the researchers were able to determine the essential tradeoffs that are necessary for athletes to produce enough power to maintain an exercise workload while also maintaining the internal homeostasis of their vital signs.

"For example, the heart, lungs, and circulation must deliver sufficient oxygenated blood to the muscles and other organs while not raising blood pressure so much as to damage the brain," Doyle says. "This is done in concert with control of blood vessel dilation in the muscles and brain, and control of breathing. As the physical demands of the exercise change, the muscles must produce fluctuating power outputs, and the heart, blood vessels, and lungs must then respond to keep blood pressure and oxygenation within narrow ranges."

Once these trade-offs were defined, the researchers then used control theory to analyze the exercise data and found that a healthy heart must maintain certain patterns of variability during exercise to keep this complicated system in balance. Loss of this variability is a precursor of fatigue, the stress induced by exercise. Today, some HRV monitors in the clinic can let a doctor know when variability is high or low, but they provide little in the way of an actionable diagnosis.

Because monitors in hospitals can already provide HRV levels and dozens of other signals and readings, the integration of such mathematical analyses of control theory into HRV monitors could, in the future, provide a way to link a drop in HRV to a more specific and treatable diagnosis. In fact, one of Doyle's students has used an HRV application of control theory to better interpret traditional EKG signals.

Control theory could also be incorporated into the HRV monitors used by athletes to prevent fatigue and injury from overtraining, he says.

"Physicians who work in very data-intensive settings like the operating room or ICU are in urgent need of ways to rapidly and acutely interpret the data deluge," says Marie Csete, MD (PhD, '00), chief scientific officer at the Huntington Medical Research Institutes and a coauthor on the paper. "We hope this work is a first step in a larger research program that helps physicians make better use of data to care for patients."

This study is not the first to apply control theory in medicine. Control theory has already informed the design of a wearable artificial pancreas for type 1 diabetic patients and an automated prototype device that controls the administration of anesthetics during surgery. Nor will it be the last, says Doyle, whose sights are next set on using control theory to understand the progression of cancer.

"We have a new approach, similarly based on control of networks, that organizes and integrates a bunch of new ideas floating around about the role of healthy stroma—non-tumor cells present in tumors—in promoting cancer progression," he says.

"Based on discussions with Dr. Peter Lee at City of Hope [a cancer research and treatment center], we now understand that the non-tumor cells interact with the immune system and with chemotherapeutic drugs to modulate disease progression," Doyle says. "And I'm hoping there's a similar story there, where thinking rigorously about the tradeoffs in development, regeneration, inflammation, wound healing, and cancer will lead to new insights and ultimately new therapies."

More information: Robust efficiency and actuator saturation explain healthy heart rate control and variability, dx.doi.org/10.1073/pnas.1401883111

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