THE SCIENCES

Heart Rhythms Seem Circadian in Nature

By Sarah Graham on December 21, 2004

The chances of suffering heart problems are not equal throughout the day. Heart attacks occur more often around 10 o'clock in the morning than any other time, a peak that previously was attributed to daily behavior patterns getting underway. A report published online this week by the *Proceedings of the National Academy of Sciences* indicates that the heartbeats of healthy people, too, exhibit strong circadian rhythms, which could help explain the morning crest of adverse cardiac events.

Steven A. Shea of Harvard Medical School and his colleagues studied healthy individuals between the ages of 20 and 33 years old. The volunteers lived in individual suites for 10 days and had their regular daily patterns disrupted. They were monitored closely and asked to adhere to specific sleep and wake cycles while having their heartbeats monitored using electrocardiograms. The team discovered that a feature of the subjects' heartbeats known as the scaling exponent, which is a statistical classification of beats over time, displayed a significant 24-hour rhythm regardless of daily activities. What is more, the peak occurred between nine and 11 a.m.

According to the report, the findings suggest that "the underlying mechanism of cardiac regulation is strongly influenced by the endogenous circadian pacemaker." And because higher scaling exponents are associated with heart disease, the scientists posit that this fundamental pattern could influence vulnerable people, such as those suffering from congestive heart failure, and contribute to the pattern of early morning heart attacks observed in epidemiological studies.

ABOUT THE AUTHOR(S)

Sarah Graham

Home > About BWH > Newsroom > News > Awards > Awards, Honors & Grants

News

Overview

News
BWH In The News
Press Releases
Social Media
Awards, Honors & Grants
Seasonal Health Tips
Face Transplant
Hand Transplant
Total Artificial Heart

BWH Publications

For the Media

About BWH

Contact Communication & Public Affairs

Awards, Honors & Grants

View archived Awards, Honors & Grants

BWH is recognized as leader in both patient care and research, with expertise in virtually every specialty of medicine and surgery, and research spanning from basic, to clinical and translational. The BWH medical preeminence dates back to 1832, and today that rich history in clinical care is coupled with its national leadership in quality improvement and patient safety initiatives and its dedication to educating and training the next generation of health care professionals. Through investigation and discovery conducted at its Biomedical Research Institute (BRI), BWH is an international leader in research on human diseases, involving more than 900 physician-investigators and renowned biomedical scientists and faculty supported by more than $537 M in funding.

For the past 19 years, BWH has earned a place on the U.S. News & World Report's Honor Roll of America's Best Hospitals. The physicians, researchers and staff at BWH are recognized for excellence across specialties, while as an institution, the hospital also receives numerous accolades as care provider, employer, and more.

Awards & Honors - Feb 7, 2011

American Physical Society Fellow
Plamen Ch. Ivanov, PhD, DSc

Plamen Ch. Ivanov, PhD, DSc, of the Sleep Medicine Division at BWH, has been elected a Fellow of the American Physical Society (APS), the world's second largest organization of physicists with above 48,000 national and international members, publishing more than a dozen scientific journals, and organizing more than twenty science meetings each year. The APS Fellowship Program recognizes members who have made advances in physics through original research and publications, made significant innovative contributions in the application of physics to science and technology, or made significant contributions to the teaching of physics or service and participation in the activities of the Society. Each year, no more than one half of one percent of the Society membership is recognized by their peers for election to the status of Fellow in the American Physical Society.

According to the APS citation, Dr. Ivanov was elected a Fellow for his pioneering applications of statistical physics and nonlinear dynamics to physiology and biomedicine, and for uncovering fundamental scaling and multifractal properties, self-organized criticality, sleep- and circadian-related phase transitions in physiologic dynamics.

Skip to contents

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August 6, 2012

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Search

Browse the archive
Current issue

In This Issue:

Research Round Up

Phase Synchronization: A New Form of Cardio-Respiratory Coupling

Ronny P. Bartsch, PhD

An international research team from the USA, Germany and Canada led by Ronny P. Bartsch, PhD and Plamen Ch. Ivanov, PhD, DSc, both of the BWH Sleep Medicine Division, developed a method based on the concept of phase synchronization to identify and quantify a new form of coupling between the cardiac and the respiratory system.

Plamen Ch. Ivanov, PhD, DSc

The researchers found that the traditionally studied form of cardio-respiratory coupling, called respiratory sinus arrhythmia, defined as modulation of the average heart rate within the breathing cycle, does not fully represent the complex nature of cardio-respiratory interaction, and that this interaction is also characterized by stable phase synchronization between heartbeats and respiratory cycles.

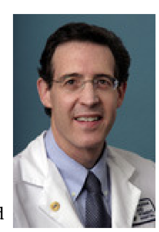
The team discovered that the degree of cardio-respiratory phase synchronization is influenced by neuroautonomic function and dramatically changes with transitions from one physiologic state to another. They observed a 400% change of cardio-respiratory phase synchronization across sleep stages, a factor of 10 higher than the corresponding change in respiratory sinus arrhythmia, and that key physiologic variables, related to regulatory mechanisms of the cardiac and respiratory systems, which influence respiratory sinus arrhythmia do not affect cardio-respiratory phase synchronization.

The researchers also are the first to demonstrate the physiologic relevance of phase synchronization as it relates to mechanisms of sleep regulation and healthy aging. Cardio-respiratory phase synchronization significantly decreased by nearly 50% with aging. The researchers note that the strength of synchronization gradually increased from REM sleep and wake, to light sleep and deep sleep, and that this sleep-stage stratification pattern is consistently present across subjects from all age groups between 20 and 95 years old, despite the general decrease of synchronization with aging.

Given that sleep regulation has a stronger impact on cardio-respiratory coupling compared to aging, such effects need to be taken into consideration when assessing cardiovascular risk.

The study was published in the June 26, 2012 issue of *Proceedings of the National Academy of Sciences*.

Natural Killer T Cells May Play Role in Controlling Hepatitis B



Richard S. Blumberg, MD

According to the United States Centers for Disease Control and Prevention, approximately 800,000 to 1.4 million people in the country have chronic hepatitis B virus (HBV) infection. Globally, the virus affects approximately 350 million people. A research team led by Richard S. Blumberg, MD, chief of the BWH Division of Gastroenterology, Hepatology and Endoscopy, is working toward better understanding how to curb infection. In their latest study, the team discovered that natural killer T cells may play a critical role in HBV control.

The researchers found that HBV-expressing hepatocytes generated endoplasmic reticulum-associated self-antigenic lipids. These lipids were sensed by natural killer T cells, thereby activating these cells. Absence of natural killer T cells or defects in the transfer process of these self-lipids, resulted in diminished HBV-specific immune responses and delayed viral control occurred.

"Previously, HBV was considered to be a 'stealth virus' which evades early components of the normal immune response," said Blumberg. "These studies demonstrate this is not the case and open up potential avenues for novel interventions directed at early viral control."

The study was published in the June 17, 2012 online issue of *Nature Medicine*.

Missing Pieces: Scientists Propose Cancer Gene Model


Stephen J. Elledge, PhD

A study led by Stephen J. Elledge, PhD, professor of Genetics, Department of Genetics, Harvard Medical School and BWH, results in a hypothesis that may help explain the driving force behind tumorigenesis (the formation of tumors) across many cancer types. The researchers studied genes located within hemizygous deletions in search for those with cancer-relevant properties. A hemizygous deletion is loss of DNA in only one of the two-paired chromosomes.

The researchers found that recurring deletions preferentially over-represented STOP genes and under-represented GO genes. STOP genes restrain cell proliferation and include many known tumor suppressors, while GO genes are enriched for essential genes.

From this observation, they proposed the Cancer Gene Island model showing that gene islands encompassing high densities of STOP genes and low densities of GO genes are hemizygously deleted.

"We think these findings suggest that many genes behave in a haploinsufficient manner to restrain tumorigenesis and that deletion of clusters of these genes act to spur proliferation without the need for a classical second hit in that region," said Elledge. "This gives us a new way to view tumor evolution."

The study was published in the May 24, 2012 online issue of *Science*.

Breathe Easy: Researchers Identify New Bronchodilator Response Gene


Blanca Himes, PhD

A new study from researchers in the BWH Channing Division of Network Medicine has found that the *SPATS2L* gene may be a regulator of bronchodilator response (BDR), an important asthma phenotype. BDR is a measurement of airway blockage reversibility taken by assessing the effect of short-acting $ß_2$-agonists (a common type of asthma medication) on lung function.

The researchers performed a genome-wide association study of BDR in 1,644 people with asthma from six clinical trials and attempted to validate the findings in two cohort studies with 1,051 participants with asthma.

After observing that variants near the *SPATS2L* gene were associated with BDR, the researchers knocked down *SPATS2L* mRNA in human airway smooth muscle cells. They found that $ß_2$-adrenergic receptor levels increased, leading to the conclusion that *SPATS2L* may be a BDR regulator.

"Our results may lead to a better understanding of asthma and $ß_2$-agonist treatment response." said Blanca Himes, PhD, BWH Channing Division of Network Medicine, and study first author.

The study was published online in *PLoS Genetics* on July 5, 2012.

To Dictate or Not to Dictate?


Jeffrey Linder, MD

According to a new study, doctors who dictated their patient notes appeared to have worse quality of care than those who used structured documentation.

The researchers evaluated 18,569 visits by 7,000 patients with coronary artery disease and diabetes to participating physicians in a regional healthcare delivery network in eastern Massachusetts.

Of these 234 doctors in the study, 20 (9 percent) dictated their notes, 68 (29 percent) used structured documentation, and146 (62 percent) typed free-text notes.

The main outcome measures were 15 coronary artery disease and diabetes measures assessed 30 days after primary care visits.

Compared to the other two documentation styles, quality of care was significantly worse on three outcome measures for dictators. These measures were antiplatelet medication, tobacco use documentation and diabetic eye exam.

Quality of care was better on three measures for doctors who used structured documentation. These measures were blood pressure documentation, body mass index documentation and diabetic foot exam. Doctors who used free-text notes had better quality of care in providing influenza vaccinations.

There was no measure associated with higher quality of care for doctors who dictated their notes.

"Doctors who dictate may not be paying as close attention to information and alerts in the electronic health record that are important for patient health," said Jeffrey Linder, MD, associate professor of medicine at BWH and Harvard Medical School, and lead study author.

The study is published online in the *Journal of the American Medical Informatics Association*.

"Browning" White Fat by Blocking Vitamin A Metabolism


Jorge Plutzky, MD

Jorge Plutzky, MD, director of The Vascular Disease Prevention Program at BWH and his team have discovered a way to turn the more dangerous white fat, which stores energy, into more beneficial brown fat, which releases energy. The findings raise the prospects of novel approaches to treat obesity and its complications.

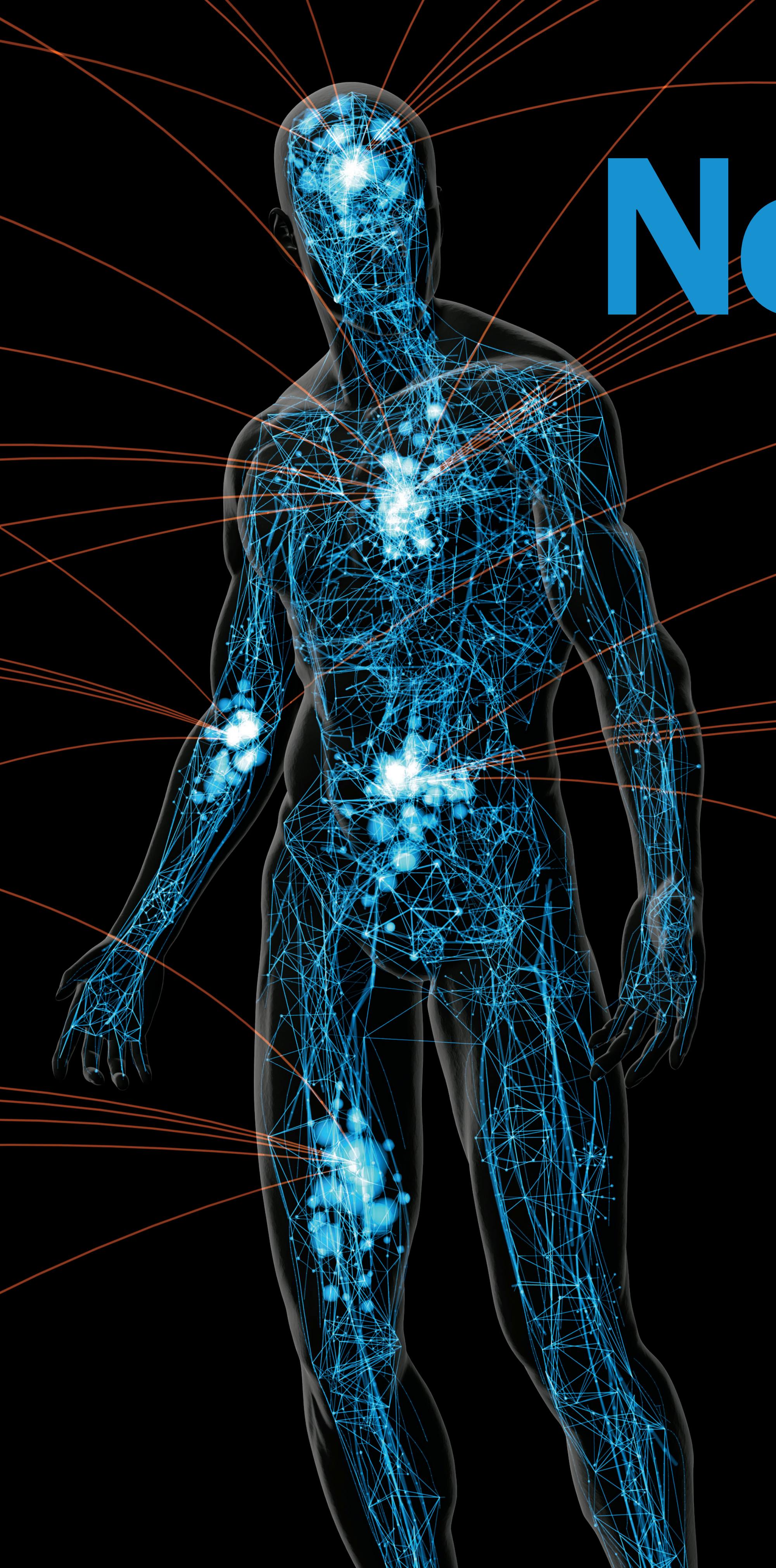
One of the functions of vitamin A metabolites, molecules known as retinoids, is to control fat cell development and function. A key step in retinoid metabolism occurs with help from an enzyme called retinaldehyde dehydrogenase 1, or *Aldh1a1*.

Plutzky and colleagues observed that in humans and mice, *Aldh1a1* was abundant in white fat cells, especially in the more dangerous visceral fat. Indeed, in humans, levels of Aldh1a1 correlated with visceral obesity and body mass.

By manipulating Aldh1a1, a key player in converting vitamin A-or retinol-into retinoic acid, Plutzky and colleagues found that white fat cells took on characteristics of brown fat.

One of the defining characteristics of brown fat is its ability to release energy as heat. Mice with either deficiency or inhibition of *Aldh1a1* become protected against exposure to cold. The researchers saw this classic indicator of brown fat and its ability to generate heat by oxidizing fat in their research.

The researchers, including first author and BWH post-doctoral fellow Florian Kiefer, MD, PhD, also found that knocking down expression of the Aldh1a1 gene by injecting antisense molecules into mice made fat by diet resulted in less visceral fat, less weight gain, lower glucose levels and protection against



When Netwo

Once studied solo, systems display surprising behavior when they interact

By Elizabeth Quill

Half a dozen times each night, your slumbering body performs a remarkable feat of coordination.

During the deepest throes of sleep, the body's support systems run on their own timetables. Nerve cells hum along in your brain, their chitchat generating slow waves that signal sleep's nether stages. Yet, like buses and trains with overlapping routes but unsynchronized schedules, this neural conversation has little to say to your heart, which pumps blood to its own rhythm through the body's arteries and veins. Air likewise skips into the nostrils and down the windpipe in seemingly random spits and spats. And muscle fluctuations that make the legs twitch come and go as if in a vacuum. Networks of muscles, of brain cells, of airways and lungs, of heart and vessels operate largely independently.

Every couple of hours, though, in as little as 30 seconds, the barriers break down. Suddenly, there's synchrony. All the disjointed activity of deep sleep starts to connect with its surroundings. Each network — run via the group effort of its own muscular, cellular and molecular players — joins the larger team.

This change, marking the transition from deep to light sleep, has only recently been understood in detail — thanks to a new look at when and how the body's myriad networks link up to form an übernetwork.

ARTWORK BY BRYAN CHRISTIE DESIGN

rksNetwork

"As I go from one state to another, immediately the links between the physiological systems change," says Plamen Ivanov, a biophysicist at Boston University. "It is quite surprising."

And it's not just in bodies. Similar syncing happens all the time in everyday life. Systems of all sorts constantly connect. Bus stops pop up near train stations, allowing commuters to hop from one transit network to another. New friends join your social circle, linking your network of friends to theirs. Telephones, banks, power plants all come online — and connect online.

A rich area of research has long been devoted to understanding how players — whether bodily organs, people, bus stops, companies or countries — connect and interact to create webs called networks. An advance in the late 1990s led to a boom in network science, enabling sophisticated analyses of how networks function and sometimes fail. But more recently investigators have awakened to the idea that it's not enough to know how isolated networks work; studying how networks interact with one another is just as important. Today, the frontier field is not network science, but the science of networks of networks.

"When we think about a single network in isolation, we are missing so much of the context," says Raissa D'Souza, a physicist and engineer at the University of California, Davis. "We are going to make predictions that don't match real systems."

Like their single-network counterparts, networks of networks show up everywhere. By waking up in the morning, going to work and using your brain, you are connecting networks. Same when you introduce a family member to a friend or send a message on Facebook that you also broadcast via Twitter. In fact, anytime you access the Internet, which is supported by the power grid, which gets its instructions via communications networks, you are relying on interdependent systems. And if your 401(k) lost value during the recent recession, you're feeling the effects of such systems gone awry.

Findings so far suggest that networks of networks pose risks of catastrophic danger that can exceed the risks in isolated systems. A seemingly benign disruption can generate rippling negative effects. Those effects can cost millions of dollars, or even billions, when stock markets crash, half of India loses power or an Icelandic volcano spews ash into the sky, shutting down air travel and overwhelming hotels and rental car companies. In other cases, failure within a network of networks can mean the difference between a minor disease outbreak or a pandemic, a foiled terrorist attack or one that kills thousands of people.

Understanding these life-and-death scenarios means abandoning some well-established ideas developed from single-network studies. Scientists now know that networks of networks don't always behave the way single networks do. In the wake of this insight, a revolution is under way. Researchers from various fields are rushing to figure out how networks link up and to identify the consequences of those connections.

Investigators including Ivanov are analyzing a deluge of data to understand how networks cooperate to make bodies function. Other researchers are probing the Earth around them to identify the links that keep the planet in balance. But it's not all rainbows and butterflies. Much of the recent focus has been on the potential dangers that come with connection. In one landmark study, researchers at Boston University and elsewhere have developed math for explaining the way networks of networks can suddenly break down. Studying the bad along with the good may lead to a sort of "how to" for designing integrated systems that not only perform well in normal times, but also keep working when things go wrong.

Cascades of failure

A series of CNN news clips posted on YouTube highlight the vulnerability of interdependent systems. In what Wolf Blitzer repeatedly reminds the viewer is only an "exercise," former U.S. government officials convene to respond to a simulated cyberattack. The War of the Worlds–esque report begins with a Russian computer infecting a smartphone with a virus. After jumping to other smartphones, the bug makes its way into U.S. computers. From there it crashes communication networks, which in turn take out power stations. The ensuing blackout shuts down transportation networks. Each failure leads to yet more failures as the effects of a single infection bounce back and forth between systems. Having no control over the Russian computer system and no authority to shut down smartphones, the U.S. government is powerless.

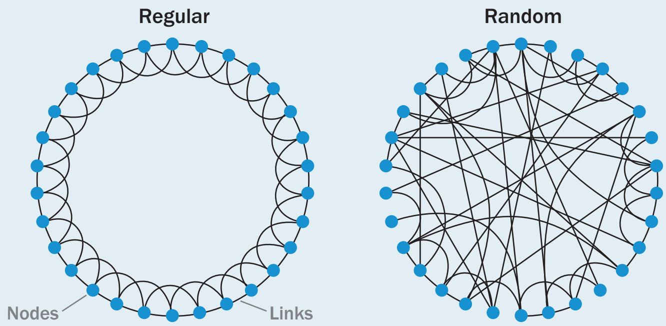
Shlomo Havlin of Bar-Ilan University in Israel sometimes shows portions of these clips during talks he gives on networks of networks. "If you have damage in one system, it can lead to damage in another system," Havlin says. But he points out that concerns about such rippling damages are not entirely new. Several reports — such as the CNN coverage — have highlighted worries about how fragile interdependent systems

Network milestones

A major breakthrough in the study of networks occurred when researchers discovered that a lot of real-world networks take a similar form. Dubbed "small-world," these single networks are characterized by clustering and shortcuts. Another refinement in thinking is now taking place as attention turns to interacting networks.

Single networks

A network consists of nodes (dots) connected by links (lines). Scientists characterize networks using properties such as size (number of nodes) and average degree (average number of links). In regular networks, each node has the same number of links. In random networks, the number of links per node is random. Small-world networks are a sort of intermediary and often more relevant to the real world.



might be. "What was not known was a systematic way to study this, a framework," Havlin says.

He first became interested in the problem when a program reviewer from the U.S. Defense Threat Reduction Agency visited the Boston University physics department in 2009. The agency was funding Havlin and H. Eugene Stanley, along with Boston colleagues Gerald Paul and Sergey Buldyrev, to work on questions plaguing single networks. The reviewer mentioned a new topic that interested the agency: How resilient are interacting networks when something goes amiss? Proposals were due in a couple of weeks. Despite the short time frame, the team, later joined by Bar-Ilan colleague Roni Parshani, decided to tackle the issue.

Overnight Havlin came up with a way of thinking about it. Single networks are typically represented by dots joined by lines. The dots, called nodes, are the players in the network. The lines, called edges or links, represent connections between those players. Havlin's insight was to connect some of the nodes in one network with nodes in another via a new type of line. His new lines, called dependency links, signal places where a node in one network relies on a node in the other to function — say, a computer that can't get by without its sole power source. These key dependencies could allow a failure to propagate between systems.

Once Havlin outlined a way of thinking about the problem, Buldyrev worked through the math. It wasn't simple. He had to use equations to explain each state of each network as the random removal of one node triggered the removal of other nodes. Buldyrev, whom Paul calls "a mathematical genius," cracked it. Answering the program reviewer's initial question took only about a week.

"One morning, I came in and Shlomo was — not quite dancing on the table — but he was very, very excited," Paul says.

In their analysis of connected networks, the researchers found a type of mathematical behavior that couldn't have been predicted from knowledge of single networks. When a node is removed from a single network, the failure tends to propagate gradually, the network coming apart bit by bit by bit. But removing nodes in a network of networks means the breakdown can occur abruptly. As nodes go offline, the system initially appears to be working properly. But all of a sudden, a threshold is reached. Lose one more node and — poof — the whole thing falls to pieces.

"Even if one more node fails, the network collapses completely," Havlin says. "It makes the network a much more risky place."

Stanley likens the single-network scenario to a drunken prisoner trying to escape with a pair of wire clippers. As the prisoner makes random cuts along a fence, a hole develops that gradually gets bigger and bigger. After a little while, maybe, the prisoner can stick an arm through, and with a few more snips, a head. Eventually enough snips may allow the prisoner's whole body to fit through. But in the case of networks of networks, the prisoner cuts just one or two wires and then appears to hit on a magical one that makes the whole fence disintegrate. The prisoner can walk to freedom.

"It's as if someone threw a switch," Stanley says. "But there is no switch."

After tweaking the math and running some simulations, the researchers submitted a paper to *Nature*. Since its publication, in 2010, more than 100 other papers have cited it.

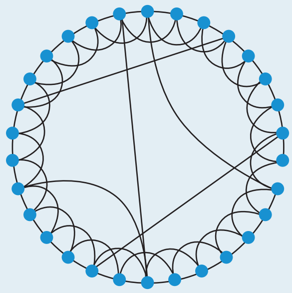
Other teams have also found unexpected behavior in networks of networks. In 2009, D'Souza and a colleague showed that connecting a large portion of nodes in a network of networks takes fewer links than would be required for a similar single network. Other scientists have revealed that imposing travel restrictions may not reduce the spread of an epidemic as much as would be expected because of the interconnected nature of human mobility networks. And in 2008, Italian researchers reported that a power station shutdown led to a failure in the Internet communication network, causing the breakdown of more power stations and triggering an electrical blackout affecting much of Italy. In its *Nature* paper, the Boston group used this disaster as a real-world example to model how failures can cascade back and forth between networks.

What set the *Nature* paper apart from the others was that it offered a simple mathematical model to explain real-world phenomena. That finding meshed with others to give network-of-networks science a theoretical foundation.

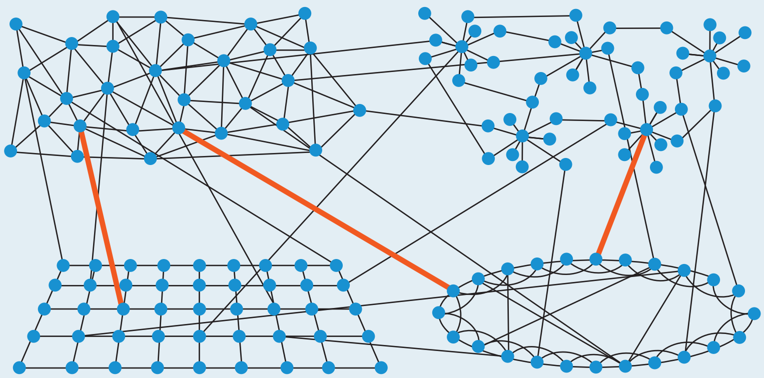
"They have really figured out the framework of how to think about it," says

T. DUBÉ

Small-world



Networks of networks
In practice, networks often link up. Though scientists don't yet know what form these übernetworks typically take, some of the same quantitative properties still apply. Links here come in at least two forms: connectivity (similar to links in single networks, shown in black) and dependency (interactions that can be the difference between life and death for a node, shown in orange).



Albert-László Barabási of Northeastern University in Boston, who made seminal contributions to studies of single networks. "They came along and said, let me show how you calculate this and what are the consequences of coupling these networks."

Since the discovery, the Boston cadre — along with a battalion of graduate students — has extended its framework to study the vulnerability of three or more interconnected systems. In another study, the researchers have found that terrorist-caused damage to an important power hub may differ from more arbitrary damage caused by, say, a rat chewing through an electrical wire.

Like a social scene in which all the popular kids hang out together, in some networks well-connected nodes are more likely to link up with other well-connected nodes. Stanley, grad student Di Zhou and colleagues have found that if one network in an interdependent system has this property, dubbed assortativity, then the whole system is more vulnerable to disturbance.

These early findings were unexpected based on studies of solo networks, leaving scientists wondering what other secrets networks of networks might hold. "There are many questions that appear immediately," Havlin says.

It's a small world

A similar burst of activity in network science occurred in 1998, after Cornell University's Steven Strogatz and then-colleague Duncan Watts published a groundbreaking paper, also in *Nature*. Titled "Collective dynamics of 'small-world' networks," it explained why the world seems so tiny.

At the time, "small-world phenomena" had already gained a degree of notoriety. In the 1960s, psychologist Stanley Milgram showed that a randomly selected person living in Nebraska could be connected via acquaintances to a target person in Massachusetts through just a few (typically six) other people. Students from Albright College in Reading, Pa., made the idea widely known in the mid-1990s when they invented a game known as Six Degrees of Kevin Bacon, based on the actor's appearances in so many movies. With the links defined as coappearances in any single film, Bacon could supposedly be connected to any other Hollywood celebrity in no more than six steps. In the network of actors, moving from the node of Kevin Bacon to the node of, say, Hilary Swank would pass you over fewer than six films. (In fact, it's hard to name an actor who is more than two or three degrees from Kevin Bacon. Try for yourself at www.oracleofbacon.org.)

Small-world, or Watts-Strogatz, networks exhibit two features: They are highly clustered, meaning the nodes clump together like cliques of middle school girls. And shortcuts connect those cliques, akin to a cheerleader who occasionally hangs out with a member of the nerdy group.

Much like the simple framework developed more recently by the Boston group, the Cornell duo's findings had implications for how a network behaves. "Systems synchronize much faster, epidemics spread much more rapidly," Strogatz says. "In the case of game theory — where you have people, companies, countries playing prisoner's dilemma — we were able to show that the small-world structure would make a difference in how that game evolved."

But what really launched the Watts-Strogatz revolution was the way features in their model matched multiple real-world networks. An electric power grid, actors connected to Kevin Bacon and the nerve cells in a worm were all in on a secret that scientists had only just uncovered.

"The legacy is the introduction of the idea of looking at the comparative anatomy of networks," Strogatz says. "What we were able to show was there were universal principles that applied to different networks that scientifically were completely unrelated but mathematically were following the same architectural principles."

Almost immediately, researchers from diverse disciplines abandoned existing projects and redirected their intellectual firepower to develop network math for proteins, planes, power stations and pathogens. Friends, film actors and financial players also got their fair share of attention. Over the last dozen years or so, this flood of effort has led to a better understanding of how nodes of all types come together to form networks and what happens when one gets plucked out.

But work so far has focused mostly on the comparative anatomy of single networks. Surprising behavior uncovered in networks of networks presents a new and still puzzling question: Do the übernetworks behind blackouts, stock market crashes, transportation gridlock and even sudden deteriorations in health — a particular worry of Stanley's — conceal a deeper shared anatomy?

Stanley believes they might. When he walks down the stairs, he has a habit of holding the railing. Breaking a hip, he says, could trigger a series of disconnections in his body's network of networks.

It's widely known that an elderly person who fractures a hip faces a greatly increased chance of dying within the next year, even if repair surgery is successful. What's not yet clear, though, is whether the cascading behavior outlined by the Boston team is behind this abrupt decline in health. An answer may emerge as scientists find out what networks of networks in the body, in finance and in nature have in common.

Plumbing networked networks

Of all the world's network-of-networks problems, climate change is one of the most challenging to untangle. How much global temperatures will increase over the next century depends on patterns of behavior in the air, the ocean, the land and among all the organisms living on the planet. Natural cycles are influenced by human-driven networks — the economics governing greenhouse gas emissions, the political drive behind energy alternatives and the social recognition of global warming as a problem in need of a solution.

In a recent study, physicist Jonathan Donges of Germany's Potsdam Institute for Climate Impact Research plotted hundreds of thousands of data points related to air pressure to study networks in just the atmosphere. By tracking how the data changed over time, he identified a series of horizontal networks that wrap around the Earth, layering on top of one another like Russian nesting dolls. The Arctic serves as the link, acting as a sort of atmospheric border patrol that controls mingling between the horizontal layers, he and colleagues reported last year in *European Physical Journal B*.

"The Arctic seems to be important in coupling atmospheric dynamics on the surface and in higher layers up in the atmosphere," Donges says.

If networks of air molecules sound complicated, consider the network of goings-on in your cells, where the nodes and their links come in different forms. Within each cell of your body there is a constant dance among DNA, RNA and proteins. DNA encodes networks of 20,000-plus genes; at any one time many are being decoded into complementary strands of messenger RNA, which form their own networks as they guide the production of proteins. Those proteins can do-si-do with other proteins, interacting within their own network in a very physical way, or can connect with other networks by pulling genes onto or off the dance floor.

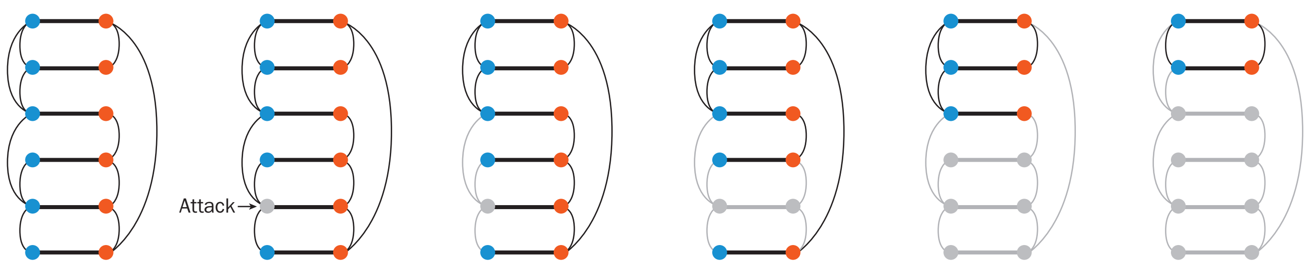
"You cannot look at these networks in isolation," says Tom Michoel of the University of Edinburgh's Roslin Institute. "Everything there is interconnected."

Michoel tries to understand networked networks by studying small-scale patterns that show up more often than expected in a particular system, and thus say something about its overall functioning. Consider a common workplace pattern, in which an intermediary can serve as a point of contact between a boss and an employee. Michoel found many examples of a similar pattern in yeast cells. One of two linked-up networks included interactions that regulated gene activity, in which a protein (the boss) chemically tags a gene that codes for another protein (the intermediary). The other contained more direct protein-protein interactions (between the intermediary and an employee).

By looking at how the small-scale patterns clustered and overlapped, Michoel discerned that one boss interacts with one intermediary but that each intermediary represents many employees, sort of like a union spokesperson acting on behalf of union members. Without the übernetwork analysis, there was no way to understand the distinct roles of bosses and intermediaries, Michoel says. Important large-scale interactions would have remained hidden.

Exposing unknown interactions is not the only issue. Strengths of the connections linking networks are also impor-

Back-and-forth failures When networks depend on other networks, such as a communications network that relies on a power grid, failure can cascade back and forth between the two. This behavior may explain sudden breakdowns in interacting systems. Thus, the effects of an attack on a single node can reduce an übernetwork (below) that starts with 12 operating nodes to just four. SOURCE: S.V. BULDYREV *ET AL/NATURE* 2010



Two networks (blue and orange) interact via dependency links (bold).

An attack on the blue network takes out a blue node.

Links connecting the attacked node to other blue nodes no longer function.

An orange node that had depended on the attacked node fails, along with all of its links.

Blue nodes detached from their network and dependent orange nodes exit.

Orange nodes detached from their network and dependent blue nodes exit.

T. DUBÉ

tant. The volume of buses traveling a route, for example, may ramp up during rush hour. Or in your social networks, you may see a coworker almost every day but a high school friend just once a year.

In his investigation of sleep cycles, Ivanov showed that changing how tightly two networks are coupled can affect physiology. Links don't have to be newly created or severed to matter.

A former student of Stanley's, Ivanov spent more than a decade collecting data on heart rate, breathing rate, muscle tone and eye movement to find out how the body's networks interact during the various stages of sleep. Much like Donges' approach with the atmosphere, Ivanov inferred links and the nature of those links by analyzing how measurable markers from each system parallel each other in time. His team found out how the networks hook and unhook, but also how those hookups vary.

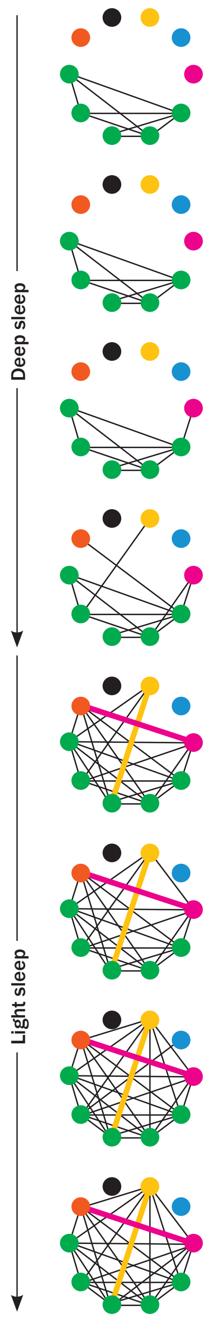
Ivanov believes his problem, as well as other network-of-networks puzzles that show up in the body, is a bit more challenging than the ideal scenario tackled by Stanley and Havlin's group.

"We could have failure even if a particular link between nodes doesn't disappear," Ivanov says. "We could still have all links present, but with different strengths, and the system can come to arrest."

Such considerations inject further complications into the emerging field, suggesting just how much more there is to be learned.

Physicist and computational scientist Alessandro Vespignani of Northeastern University, who studies epidemics and other spreading processes in networks, compares the current state of knowledge to what the Romans knew about Africa 2,000 years ago. The Romans had a pretty good map of the world, but they didn't journey deep into Africa. "There are lions, that was the only information," Vespignani says.

Right now, scientists have a map of the future of network science, and networks of networks offer an exciting new area, but people are only beginning to travel there. "We need to define new mathematical tools," Vespignani says. "We need to gather a lot of data. We need to do the exploratory work to really chart the territory."



Sleep shifts During the transition from deep to light sleep, networks in the body suddenly join up. Each small circle stands for a measurement of a bodily system, and the lines show which systems are acting in concert over a four-minute period. From an interacting networks perspective, deep sleep is quite distinct from light sleep, which more resembles waking.

- Eye activity
- Leg movements
- Chin muscle tone
- Respiratory activity
- Heart rate
- Brain activity at various frequencies

SOURCE: A. BASHAN *ET AL/NATURE COMMUNICATIONS* 2012

Linked resilience

D'Souza of UC Davis has made early strides in mapping a landscape different from the one where the Boston team planted its flag. When she and colleagues became interested in networks of networks, they focused on success rather than failure.

"We weren't looking in the realm of something so catastrophic that the node goes away forever," D'Souza says. "We are more interested in a dynamical thing that will keep the network still working."

In a recent study, her team looked at how two linked power grids might interact, say a grid that covers much of the eastern United States and another that services the West. She constructed links between the grids that are similar to the links between individual nodes within each grid: The nodes interact, but the survival of one doesn't depend entirely on the other. She calls them connectivity links.

Each node in each network was assigned a capacity, akin to the load a power plant can handle before it becomes overwhelmed by that demand. Links represent ways for a power plant to hand off its load. If a plant can't meet a given demand, it can pass some on to another linked power plant, which can pass it on to another and then another. As the researchers gradually add demand, like sand being added to a pile, they look for "avalanches" of load. Load will take off running across nodes the way that sand added to a pile will eventually start tumbling down the sides. Fittingly, network scientists call these avalanches "sandpile cascades."

In analyzing the mathematics of these cascades, D'Souza and her colleagues showed that having two networks can help take some of the burden off a single network, minimizing the threat of large avalanches. "A little bit of coupling was incredibly beneficial," D'Souza says. "The second network acted as a reservoir where the first could shed some load."

But add too many connections between the networks and larger avalanches become possible, the team reported in March in the *Proceedings of the National Academy of Sciences*.

Connected power grids are a good example of networks that cooperate, says D'Souza. Adding power lines to one network may boost the transmitting capabilities of the second. But such networks may also turn competitive, if, for example, an improvement in one puts the other at an energy-supplying disadvantage.

D'Souza's efforts have highlighted other flavors that networks of networks can come in, too. In your social web, you probably have overlapping networks, in which you simultaneously belong to a

T. DUBÉ

friend group and a family group. Or there may be networks in which the nodes are the same, but the links differ; think of banks that borrow money from each other in one network and invest in each other in another.

Then there are systems in which one network is actually built on top of another, the way hyperlinked Web pages sit atop electric, fiber-optic and wireless communication channels. These "overlay networks" also show up in the brain. Its physical architecture, the very anatomy of the brain, provides the structural network from which function — thought, memory, reason — emerges.

"Functional activity for me is more of a fleeting, fast-changing, difficult to characterize and for that reason much more ethereal construct in some ways," says Olaf Sporns of Indiana University. Sporns is a major player in the Human Connectome Project, which seeks to understand how all the nerve cells in the brain interact. "The structure of the brain, the anatomy is something that, if we have good enough instruments, we can measure," he says. "It is actual wiring."

Brain scientists agree that the functional network must somehow be rooted in the structural network. But exactly how one gives rise to the other isn't clear. What's more, the networks feed off each other, adding the element of evolution to an already hard-to-follow labyrinth of nodes and links. The architecture sculpts, constrains and molds the function, and the function leaves experiential traces on the structure over time.

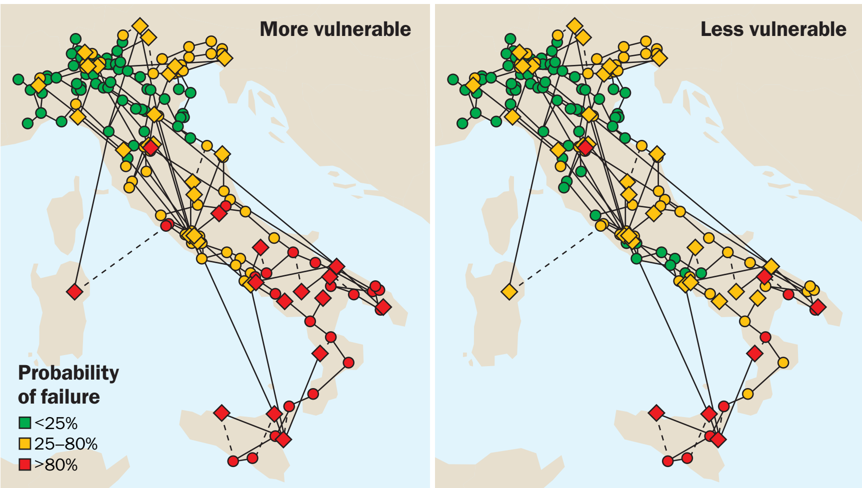
Sporns proposes that these dynamics represent a constant balancing act between the wiring cost in the anatomical network and the desire for efficient outcomes in the functional network. "This process of negotiating, and renegotiating trade-offs," Sporns and a colleague wrote in May in *Nature Reviews Neuroscience*, "continues over long (decades) and short (millisecond) timescales as brain networks evolve, grow and adapt to changing cognitive demands."

As the brain changes in time, so does the behavior of the body — influencing all the larger networks in which a person plays a part.

That can expand the puzzles facing scientists. Questions extend to how a network of networks reacts to what's happening within, and how people adapt to the system, says Vespignani. "If I know there is a blackout, I will do certain things. If I know there is an economic crisis, I will go to the bank and ask to get all my money back. If there is an epidemic, I will stay home."

Some scientists speculate that currently available theoretical approaches for übernetworks may be too simplistic to be useful. One economist went so far as to warn of the dangers of applying the Boston team's results too widely, assuming everything is a nail just because you have a hammer. Most researchers, though, offer a more measured take.

Saving nodes In a simulation of coupled networks in Italy (circles represent a power grid, diamonds a communications network), protecting just four nodes made a system less vulnerable. At left, all communications servers are coupled to the power grid; at right, four are decoupled. Colors show the probability that a node fails after 14 servers fail. SOURCE: C.M. SCHNEIDER *ET AL*/ARXIV.ORG 2011



MAP: GEOATLAS/GRAPHI-OGRE, ADAPTED BY T. DUBÉ

Toward better systems

While physicists and mathematicians strive for simplicity, engineers like Leonardo Dueñas-Osorio of Rice University favor a more data-driven simulation approach, enriching tools from network science with realities from physical systems.

"When you have a complex problem, abstractions of the analytical kind can help you narrow down where to focus," Dueñas-Osorio says. "Then you need to add refinement, make things more realistic."

Both approaches — theoretical and simulation-based — have some real-world payoff. With equations that are mathematically tractable, "you can do a lot of insightful derivations," he says. "Those are very valuable, but sometimes you only achieve those at the expense of simplifying the systems."

Dueñas-Osorio and others instead build network models that pin every node into its proper geographic location and give each one a different likelihood of failing, depending on factors such as its age or activity level. Many of these researchers get their data on the ground.

During a trip to Chile after a 2010 earthquake there, Dueñas-Osorio collected information about what transformers failed and what pipes broke. He talked to utility companies to track service interruptions. "This information allows us to get a sense of how strong the connections are between systems," he says.

Such data also reveal ways in which systems are suboptimal and could be improved. Some areas hard-hit by natural disasters don't have enough connections — with, for example, only one power plant supporting a pumping station.

Efforts by Havlin and colleagues have

yielded other tips for designing better systems. Selectively choosing which nodes in one network to keep independent from the second network can prevent "poof" moments. Looking back to the blackout in Italy, the researchers found that they could defend the system by decoupling just four communications servers. "Here, we have some hope to make a system more robust," Havlin says.

This promise is what piques the interest of governments and other agencies with money to fund deeper explorations of network-of-networks problems. It's probably what attracted the attention of the Defense Threat Reduction Agency in the first place. Others outside the United States are also onboard. The European Union is spending millions of euros on Multiplex, putting together an all-star network science team to create a solid theoretical foundation for interacting networks. And an Italian-funded project, called Crisis Lab, will receive 9 million euros over three years to evaluate risk in real-world crises, with a focus on interdependencies among power grids, telecommunications systems and other critical infrastructures.

Eventually, Dueñas-Osorio envisions that a set of guidelines will emerge not just for how to simulate and study networks of networks, but also for how to best link networks up to begin with. The United States, along with other countries, have rules for designing independent systems, he notes. There are minimum requirements for constructing buildings and bridges. But no one says how networks of networks should come together.

Ivanov hopes to develop a similar rulebook for the human body that shows actual designs. Many doctors' offices display diagrams of the body that outline the different systems — the circulatory system, the respiratory system, the musculoskeletal system. But no diagrams show how those systems interact with one another, and that knowledge might be just as crucial for fighting disease.

As more data come in, the goals of those working on human-built systems and natural systems may merge. More important than whether biological, social and technological systems exhibit similar mathematical properties may be whether they should. Can people design better systems by learning from the systems that exist in nature?

Sporns predicts the answer could be yes. "These systems naturally, just by virtue of being here, actually having survived, have been optimized to a certain extent," he says. "They are existing proof that you can have complex networks that are structurally buildable and realizable and sustainable, at the same time dynamically competent, resilient against perturbations and evolvable."

How to maximize sustainability, resilience and evolvability in networks of networks are questions that are still largely open. Geneticists seek answers in the genes, physiologists in the broader body and ecologists in the interactions that govern all living things. Connections forming among these growing webs of knowledge, as well as with engineers' models and theorists' frameworks, will provide much-needed fuel for a burgeoning intellectual endeavor.

If the efforts prevail, one day preventing blackouts, interrupting epidemics and handling a complicated commute may be as easy as waking up in the morning. ■

Explore more

- *Nature Physics* special issue, January 2012: www.nature.com/nphys/insight/complexity

Network catastrophes While researchers have not yet analyzed them in detail, some recent real-world incidents highlight what can happen if disaster strikes within a network of networks.

India blackout, 2012
Power grids collapsed in India earlier this year, leaving hundreds of millions of people without power. The outage triggered transportation failures as local and long-distance trains stopped running. Some sources speculate that the grid was overloaded because a weak monsoon had farmers using more electricity to pump water to fields.

Eyjafjallajökull eruption, 2010
Iceland's Eyjafjallajökull volcano erupted in 2010, spewing ash that shut down air travel throughout Europe. But travelers weren't the only ones affected: Manufacturers, medical suppliers and crop producers couldn't move their goods. The effects of the grounding rippled into the fuel, hotel and car rental industries.

Swine flu pandemic, 2009
When a swine flu outbreak hit Mexico in 2009, officials responded with travel bans and other control measures. But a drop in international air traffic to and from Mexico didn't prevent a pandemic. Viruses travel through a complex global mobility über-network that is made up of long-distance flights as well as local commutes, and interacts with social and economic networks.

FROM TOP: © AP, CORBIS; STOCKTREK IMAGES/RICHARD ROSCOE/GETTY IMAGES; ENEAS DE TROYA/FLICKR

e-Journal of Age Management Medicine | July 2012

Sleep Disorders and Neurodegenerative Diseases

Preetam Schramm, Ph.D.

The American Academy of Sleep Medicine held its annual SLEEP conference this year in Boston, MA. Of relevance to Age Management Medicine practitioners was the keynote topic, "Sleep disorders in neurodegenerative diseases: outcome, risk factor or both?" by Dr. Donald Bliwise, Professor of Neurology at Emory University School of Medicine in Atlanta, Georgia. His lecture highlighted sleep changes relating to brain dysfunction and abnormalities in Parkinson's Disease (PD) and Alzheimer's Disease (AD).

In this era of aging, Dr. Bliwise explained, PD not only involves decreases of the neurotransmitter dopamine in the limbic system but also involves loss of 1) cognition; 2) learning; and 3) motor control in the basal ganglia.[1] He added that early deposition of Lewy Bodies is seen in the thalamus' central medial nucleus, glossopharyngeal nerve, vagus nerve and the pedunculopontine nucleus that controls REM sleep. Sleep changes in PD show REM sleep without atonia (i.e. increased muscle tone) and increases in periodic limb movements in sleep. Involvement of the glossopharyngeal nerve in the disease progression could induce sleep apnea exacerbating a fragile physiological state. Limbic system control of autonomic nervous system cardiopulmonary functions maybe affected.

Greater than 50% of the population over 85 years of age meets the criteria for AD, he explained. Patients presenting with apolipoprotein E4 phenotype show a faster rate of cognitive decline and greater cerebrovascular amyloid plaques.[2] Polysomnography data shows decreased REM sleep, sleep efficiency, delta sleep and increased sleep fragmentation. Many patents redistribute their sleep around the 24 our clock so napping is common and indicates a circadian rhythm dysfunction related to decreases in the number of neurons in the suprachiasmatic nucleus.[4] Dopamine agonists like ropinirole 'screws up the circadian rhythm' and should be not be administered to AD patients.

Dr. Bliwise offered a provocative question: "Can sleep disorders [that have intermittent hypoxia, like sleep apnea] be a risk or mediating factor in the development of AD?" Chronic exposure to oxidative stress could predispose one to neurodegenerative disease. Animal studies show an up-regulation of dopamine receptor proteins by hypoxemia conditions that were consistent with depressed dopamine signaling.[5]

"Sleep is a protective factor," he accentuated. After six hours of sleep loss in young and old animals, a higher rate of brain cell death was found in the older age animals suggesting chronic sleep deprivation could increase amyloid plaque and play a role in the pathogenesis of Alzheimer's disease.[7]

New technology is available using cardiopulmonary coupling analysis to provide clinicians with an analogous perspective to traditional sleep assessment by quantifying sleep quality using the electrocardiogram. Sleep regulatory mechanisms that are captured in the electroencephalogram also describe sleep stage changes and show strong sleep stage stratification with cardiopulmonary coupling.[8]

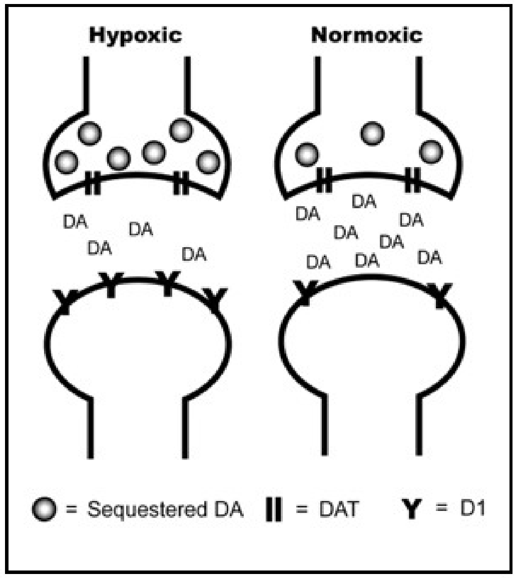


Figure 1. – Illustration of structural and functional observed differences of hypoxic and normoxic conditions in presynaptic and postsynaptic rat striatum leading to decreased dopamine release.[6]

Note: Dr. Bliwise emphasized that PD presents with more sleep disturbances than Alzheimer’s disease (AD) and sleep can differentiate between AD and Lewy Body disease.

Clinical pearl: Night time sleep disturbances present early in the disease process and REM sleep behavior disorder could be a premotor symptom of PD. Early recognition of sleep related symptoms could allow physicians to administer neuro-protective agents to forestall or avoid long-term disability.

Clinical trials suggest agents with neuro-protective effects include rasagiline, a monoamine oxidase inhibitor, CoQ10 and creatine.[3]

Take home message: Assessment and tracking of sleep quality in patients is important and could provide vital early warning signs about age-related diseases. Understanding the risks associated with poor or fragmented sleep allows for appropriate counseling and initiating of any potential neuroprotective therapies.

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Preetam Schramm, Ph.D., RPSGT, *has been in the sleep medicine and research field since 1998. From 1999 to 2001, he served as the Director at the Center for Sleep Physiology and Medicine, St. John's Cardiovascular Center and in the Department of Medicine, Harbor-UCLA Medical Center, Los Angeles, California. His clinical research knowledge consists of sleep physiology and pharmacological interventions in pulmonary and mental disorders. Dr. Schramm's basic science investigations emphasized neurophysiology, neuro-pharmacology and neuroendocrinology. He has contributed to numerous scientific publications and participated in many scientific investigations in the field of Sleep Medicine, Psychiatry Research, Neuroscience, Neuropharmacology and Neuroendocrinology. Recent works involve the use of cardiopulmonary coupling analysis, an alternative assessment of sleep quality. His focus is to phenotype patients with sleep disordered breathing and insomnia, predict treatment outcomes in sleep breathing disorders, identify complex sleep apnea, predict antidepressant and Mindfulness Based Cognitive Therapy response in adult depression.*

Return to July 2012 e-Journal

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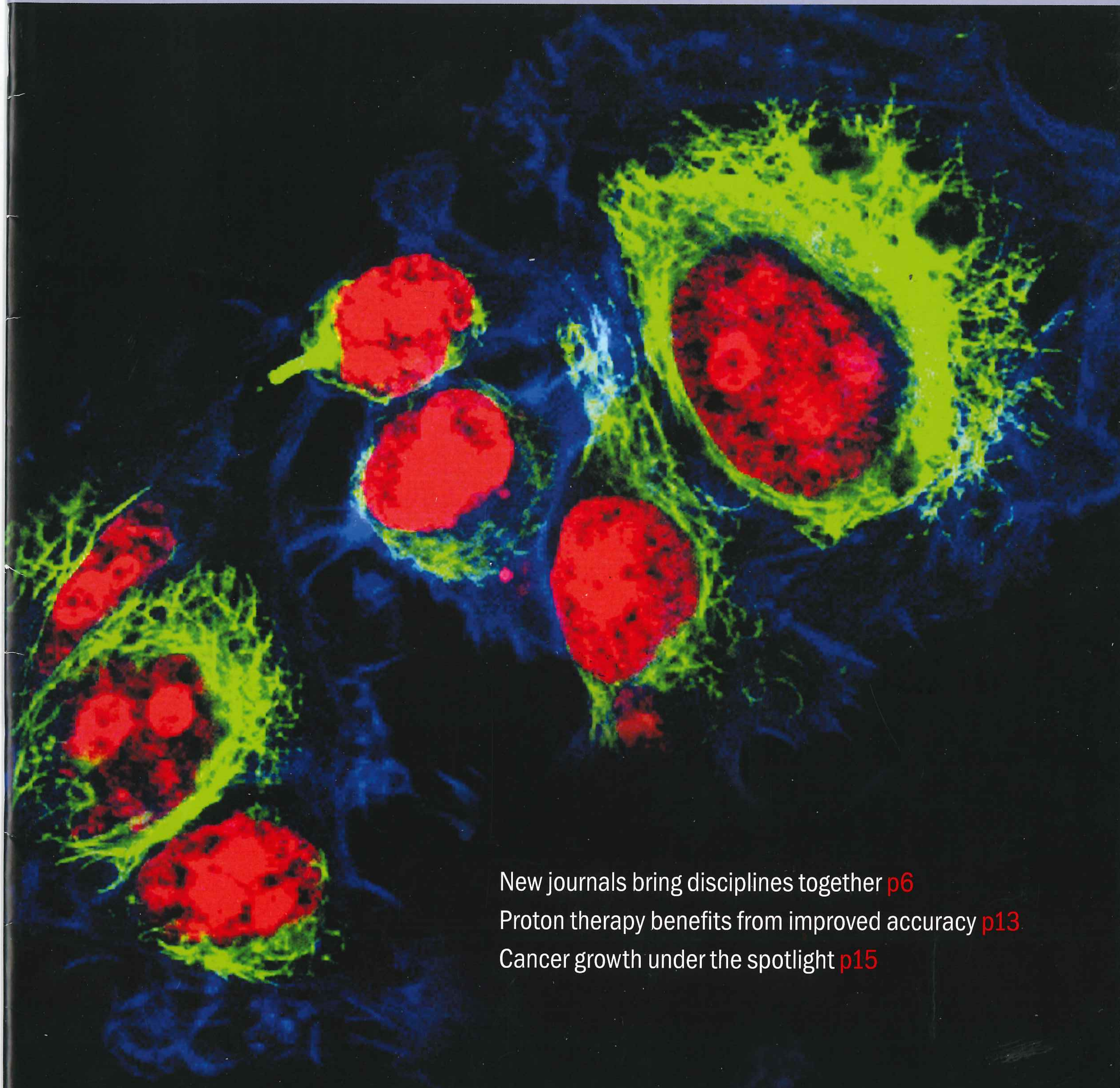
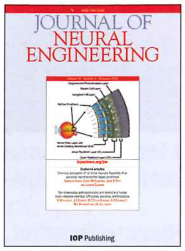
Taking research from the lab to the clinic



Research news

Robotic arm gets the thumbs up

A paralysed woman taking part in a pioneering research study has for the first time been able to pick up and manipulate a range of objects with a robotic arm. Jan Scheuermann, who has been paralyzed from the neck down since 2003, has been involved with the research programme at the University of Pittsburgh for the past two years, and in the latest advance – reported in detail in the *Journal of Neural Engineering* – the team has been able to increase the manoeuvrability of the robotic arm from seven to ten dimensions.



The extra dimensions come from four hand movements – finger abduction, a scoop, thumb extension and a pinch – that enable Scheuermann to pick up, grasp and move a range of objects much more precisely than with seven-dimensional control. As a result, Scheuermann has progressed from giving researchers "high fives" to the "thumbs up".

The arm is controlled through a brain-machine interface that links a computer with two grids of electrodes that at the start of the study were surgically implanted into Scheuermann's brain, specifically the regions that are responsible for right arm and hand movements. Each grid of electrodes have 96 tiny contact points that pick up pulses of electricity fired between the neurons in Scheuermann's brain, and then computer algorithms are able to decode these firing signals and identify the patterns associated with a particular arm movement.

To begin with, Scheuermann could make the robotic arm reach out to objects by simply thinking about the arm movement. In the latest work, the researchers used a virtual reality computer program to calibrate her control over the robotic arm, which they found was vital to allow reliable, real-time interaction with objects.

"10D control allowed Jan to interact with objects in different ways, just as people use their hands to pick up objects depending on their shapes and what they intend to do with them," said co-author Jennifer Collinger. "We hope to repeat this level of control with additional participants and to make the system more robust, so that people who might benefit from it will one day be able to use brain-machine interfaces in daily life."

Commenting on the latest results, Jan Scheuermann said: "This has been a fantastic, thrilling, wild ride, and I am so glad I've done this. This study has enriched my life, given me new friends and co-workers, and helped me contribute to research and taken my breath away."

J. Neural Eng. **12** 016011

New Journal of Physics

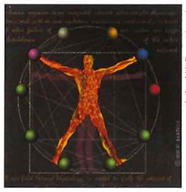
Complex networks probe secrets of the human body

Numerical techniques are increasingly being used to understand biological systems, sometimes giving rise to entirely new fields of study. One such example is network physiology and medicine, where concepts emerging from the theory of complex networks are providing fresh insights into the physiological structure of the human body and how it affects health and disease.

A recent focus issue in the *New Journal of Physics*, edited by Plamen Ch Ivanov of Boston University and Harvard Medical School in the US, explores how network physiology is being used to understand a number of different biological processes. These range from the genetic and sub-cellular level through to inter-cellular interactions and communications across integrated organ systems.

As examples, some of the articles in the issue describe how network theory can help to understand the spread of disease, improve the outcomes from deep-brain simulation, and identify links between brain activity and heart-rate variability in epileptic patients.

"The human organism is an integrated network where complex physiological systems, each with their own regulatory mechanisms, continuously interact, and where the failure of one system can trigger a breakdown of the entire network," explained Ivanov. "A new field, network physiology and medicine, is needed to probe the network of interactions among these diverse physiological systems."



Iris W Bartisch

Networks in the body
Ideas from complex network theory are being used to understand the interactions between different biological processes.

SOME ARTICLES IN THIS ISSUE

Identifying influential nodes in a wound healing-related network of biological processes using mean first-passage time
Tomasz Arodz and Danail Bonchev
New J. Phys. **17** 025002

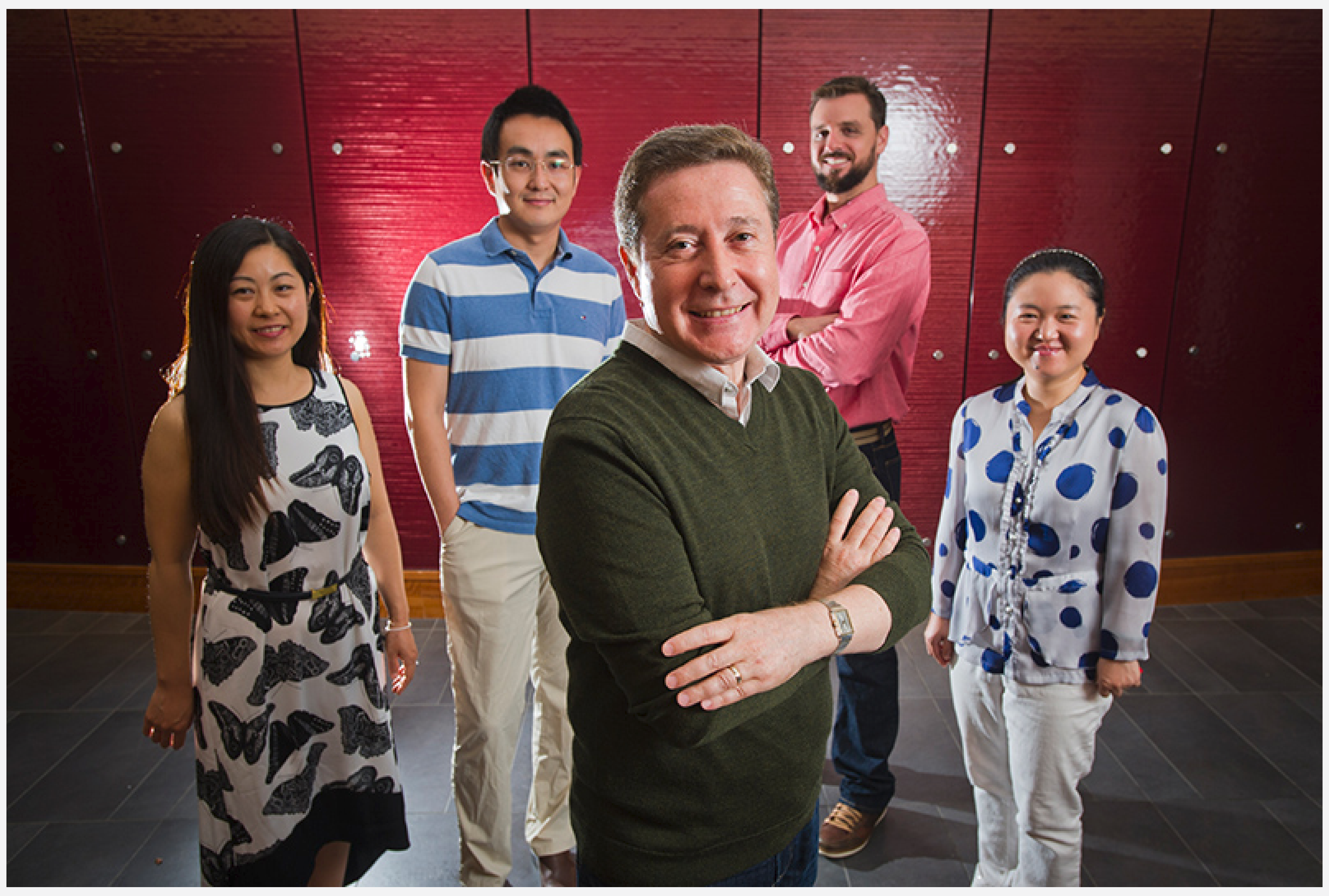
Novel fingerprinting method characterises the necessary and sufficient structural connectivity from deep brain stimulation electrodes for a successful outcome
Henrique M Fernandes *et al*
New J. Phys. **17** 015001

Information dynamics of brain–heart physiological networks during sleep
L Faes *et al*
New J. Phys. **16** 015005

PHYSICS

Mapping the Body's Internet

Physics researcher Plamen Ivanov and team study the body's communications network



Plamen Ivanov, a BU physics research professor, leads a team that draws on expertise in statistical and computational physics, neuroscience, physiology, applied mathematics, and biomedical engineering to reveal the connections between the body's systems. Ivanov and his collaborators were recently awarded a $1 million, four-year grant from the W. M. Keck Foundation to advance their work in the emerging field of network physiology. Ivanov (center) is pictured here with members of his team: Aijing Lin (from left), Kang Liu, Gustavo Zampier, and Xiaolin Huang. Photo by Cydney Scott

By Kate Becker

The patient seemed to be pulling through.

After the accident, he was rushed into surgery and, from there, into the intensive care unit, where he was recovering. But, days later, the dominoes started falling. One by one, his organs failed. The patient didn't survive. Later, trying to understand what went wrong, doctors ordered an autopsy. But the result was a puzzle: the organs weren't damaged. So why did they shut down?

This is a typical story of multiple organ dysfunction syndrome, better known as multiple organ failure. Although it's the leading cause of death in patients who make it through the first few hours after a trauma, its origins remain a mystery.

Plamen Ch. Ivanov (GRS'99), a research professor of physics in Boston University's College of Arts & Sciences, and his colleagues at BU's Laboratory for Network Physiology think the answer may lie not in the individual organs but in the biological communications network that keeps them working in sync. Now, with the support of a $1 million, four-year grant from the W. M. Keck Foundation, they are laying the groundwork for an emerging field—network physiology—to study these connections and generate a new human "atlas" that will reveal how organ systems interact in both sick and healthy patients.

Ivanov introduced the field to the scientific community with a 2012 paper in *Nature Communications*, and he delivered the opening lecture at a Harvard symposium on network medicine later that year. A special issue of the *New Journal of Physics* followed in 2013. "We were really opening a blank page," Ivanov says. With most federal funding reserved for advancing established fields, not launching new ones, the project could have stalled. But the Keck Foundation, established in 1954 by the founder of Superior Oil, the late W. M. Keck, provides funding specifically for pioneering work in science, engineering, and medical research that has the potential to lead to new paradigms, technologies, and discoveries that will save lives. They saw potential in the high-risk, high-reward work. "It allows us to really do something new as a field: develop the first analytic methods and theoretical framework to address the unique problems we encounter in network physiology," says Ivanov.

Biologists and doctors have typically studied organs in isolation. If you're having heart trouble, you go to the cardiologist; if your eyes are bothering you, you see an eye doctor. This "reductionist" approach "has been very useful scientifically in every field for the last two to three hundred years, but it has its limitations," especially in biomedicine, where it is impossible to isolate the systems that make up the whole, says Joseph Loscalzo, who studies the related field of network medicine, which aims to understand the relation between diseases and genetic mutations using graphs and networks. He is Hersey Professor of the Theory and Practice of Medicine at Harvard Medical School, chair of Harvard's Department of Medicine, and Physician-in-Chief at Brigham and Women's Hospital. Loscalzo and Ivanov discovered that they were both interested in developing novel network approaches to medicine and the human body when Ivanov joined Harvard Medical School's Sleep Medicine division.

Treating organs in isolation also can't explain medical crises that seem to happen in the space between individual organs, like multiple organ dysfunction, or altered states like coma.

Yet examining the linkages between the organs is a major challenge. For one thing, there's the problem of time: each organ seems to hear the ticking of a different clock. The eyes and brain exchange lightning-quick signals in a matter of milliseconds; the kidneys plod along through a 24-hour cycle; the heart beats every second or so. Communication between the organs takes multiple forms, too. Electrical signals combine with chemical messengers like hormones to form a sort of internal full-body internet. And, of course, we still don't have a complete understanding of how individual organs work.

But to figure out how the network functions, Ivanov and his colleagues have to start with even more basic questions, says Ronny Bartsch, formerly a BU research assistant professor of physics and now part of the faculty at Bar-Ilan University in Israel, who has worked with Ivanov since 2008. "What do we measure?" he asks. "Do we have the technology to measure it? And can we make sense of the measurements?" It isn't as simple as just collecting heart rate or EKG readings, points out Ivanov: the real challenge is getting useful information from these signals.

To address this challenge, Ivanov has assembled an interdisciplinary team of scientists at BU, including researchers with backgrounds in statistical and computational physics, neuroscience, physiology, applied mathematics, and biomedical engineering. The team also works with collaborators throughout Boston, including intensive care clinicians at Massachusetts General Hospital, sleep researchers at Brigham and Women's Hospital, and biomedical engineers at MD PnP, a maker of innovative biomedical devices. Ivanov is also an associate physiologist at Brigham and Women's Hospital and a lecturer on medicine in Harvard Medical School's Division of Sleep Medicine.

The ultimate result of their work, they hope, will be a new way of looking at the human body—what Ivanov calls a dynamic "atlas" animated with the living, changing connections between organs. Ivanov describes the atlas as a collection of "blueprint reference maps" that will ultimately show how the body's systems interact under all sorts of human conditions: healthy and sick, young and old, awake and asleep, stressed and relaxed. This atlas will be to the traditional, encyclopedia-style atlas of human anatomy what a live traffic report is to a paper road map, revealing not just the "infrastructure" of the body but the traffic that animates it.

"We want to understand how systems talk to each other," but to do that, the systems have to be under certain controlled conditions, says Kang Liu, a research scientist in the physics department who earned his PhD from BU in 2013. So Ivanov and his colleagues asked themselves: When is the body most isolated from all the noises, sights, smells, and activity of the world? Answer: During sleep. Sleep also presented a compelling scientific mystery: How do the body and brain manage to seamlessly transition from one sleep stage to another, over and over again, each night?

Ivanov had previously studied how variations in heart rate change during each stage of sleep. The next step would be to see not just how individual systems operate during sleep, but to map how the connections between brain and body change as a person passes into light sleep, deep sleep, and REM sleep. For full eight-hour sleep periods, Ivanov and his colleagues tracked subjects' brain activity, eye movement, breathing, heart rate, and leg and chin movement. Then they looked for correlations between activity in each part of the body.

During deep sleep, they found, most of the body's systems seemed to be disconnected. But new linkups suddenly switched on when each subject shifted into REM sleep. Even more connections flipped on for light sleep until, when subjects woke up, all the connections were suddenly illuminated. His team was astonished to find how quickly the communication network could be rearranged, Ivanov recalls. Though researchers had expected that the body's "network topology"—that is, the shape of a map that represents its connectivity—would change over hours or days, no one had anticipated that it might change in a matter of seconds. The results were published in *Nature Communications* in 2012.

Sleep, though, is just the first test case in a much broader research program. In 2015, with the support of the Keck grant, Ivanov's team will bring their work into a real-world laboratory where the stakes are, literally, life-and-death: the Medical Intensive Care Unit (MICU) at Massachusetts General Hospital (MGH), which takes a multidisciplinary approach to caring for severely ill patients. The goal: a new model of ICU monitoring in which the connections between a patient's body systems are being constantly mapped in real time, so that dangerous breakdowns, like the ones that might cause multiple organ dysfunction, can be anticipated and even prevented.

Today's monitoring devices aren't capable of taking in and integrating all this data from multiple systems, says Ivanov. That's where the device makers at MD PnP come in. Working with MGH's MICU physicians and members of the Network Physiology Lab, they will be designing new all-in-one monitors that record heart rate, respiration, and more.

Making sense of all that data, and discovering which dropped connections should raise alarms, will fall to data scientists like Aijing Lin, who is visiting the Network Physiology Lab from Beijing Jiaotong University in China, and Xiaolin Huang, a biomedical signals expert visiting from Nanjing University. With the right biomedical data in hand, they hope, it may even be possible to flip the "reactive" model of critical care on its head and prevent the events, like heart failure, that send patients to the ICU in the first place.

"It's very difficult to predict sudden cardiovascular events," says Huang. Doctors track patients' blood pressure and heart rate, but by the time blood pressure starts dropping, says Huang, it is too late to stop a heart attack. "Maybe we can see something in the coupling between systems that we cannot see in the individual systems," says Ivanov. That could help doctors predict imminent cardiac events before heart rate and blood pressure change.

Such developments are still years or even decades away, emphasizes Ivanov. "This Keck-funded pioneering research program is in a similar stage to what the Human Genome project was 25 years ago, when they started to develop first genomic maps," he says. Just as it has been a long road from the first human genome to meaningful medical applications, it will take time for network physiology to mature into new diagnostics and treatments. When it does, though, Ivanov hopes that it will reveal a fresh picture not just of illness, but of health, too. "Most biologists have a healthy skepticism about whether this approach will yield new insight. But the evidence that it will is growing," says Loscalzo.

"The human body is like an orchestra," says Ivanov. "Each instrument has its own sound and frequency. Each works on a different timescale, with different dynamics. If the musicians are all playing different tunes, it doesn't matter how skillfully they are performing—the result will be a cacophony. But when they all come together as an orchestra, the result is something beautiful."

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1ª Instituto verano internacional sobre"Network Physiology"

Durante los días 24 - 29 de julio de 2017 tendrá lugar en Como (Italia) un evento interactivo con profesores del ámbito de lamatemática aplicada a la neurociencia, psicología y medicina. ESte evento pretende crear un foro de discusión sobre las barreras actuales en este ámbito de la salud, los desafíos a los que enfrentarse y los futuros desarrollos en el campo emergente de la fisiología en red (Network physiology).

Puedes contribuir a estas jornadas subiendo una contribución aquí hasta **el 20 de abril de 2017.**

A continuación dejo más información del evento (inglés), así como los enlaces donde encontrar más información.

http://isinp.lakecomoschool.org/

Date:
24/07/2017 - 29/07/2017
Place:
Como, Italia

Calendar

- 03 May — SIAM Intenational Conference on Data Mining (SDM18)
- 28 May — BeDIGITAL by BIEMH: first event aimed at the industrial application of digital technologies.
- 28 May — 30 BIEMH, International Biennial of Machine Tools
- 04 Jun — EU Sustainable Energy Week
- 18 Jun — The 20th European Conference on Mathematics for Industry (ECMI2018)
- 19 Jun — IV Intelligent Buildings Congress
- 27 Jun — International Conference on Information Society and Smart Cities (ISC 2018)
- 30 Jun — Nanotexnology 2018

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