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Networks-Fractional Calculus Alliance versus COVID-19

By Luciano Abadias, Gissell Estrada-Rodriguez, and Ernesto Estrada

Since its onset in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an outbreak of pulmonary disease that soon morphed into the COVID-19 global pandemic. No specific drug currently exists to treat SARS-CoV-2, which makes the situation even more critical. Drug repurposing, a process through which scientists identify new uses for previously approved or investigational drugs, could offer a rapid means of drug discovery to fight SARS-CoV-2 and the associated COVID-19 disease [3, 6]. This method is advantageous because it begins with drugs that were previously found to be sufficiently safe in humans; most preclinical tests are complete and the necessary technology for production is available. Drug repurposing starts with hypothesis generation, wherein researchers identify the candidate molecule that targets a viral protein.

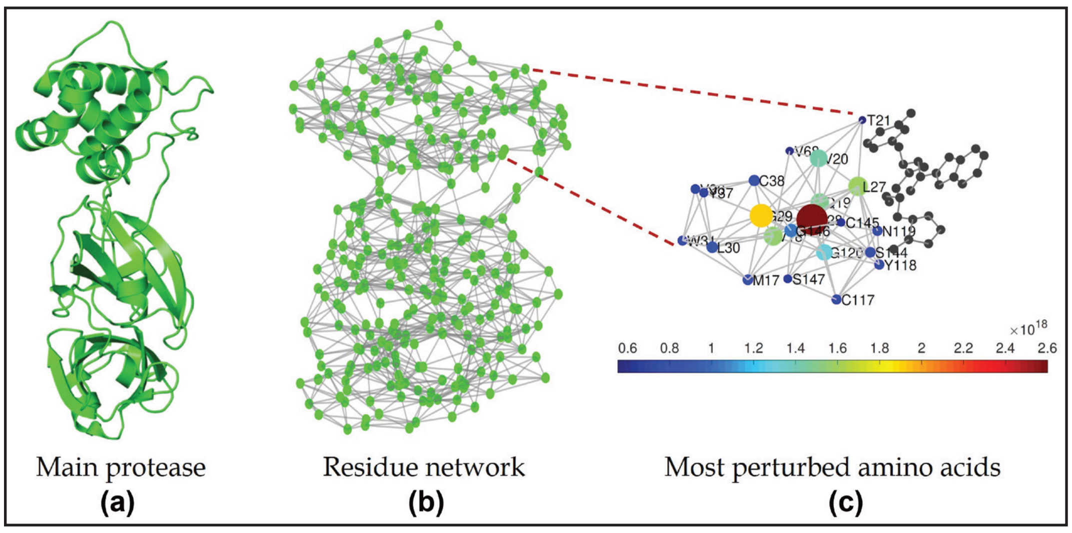

Figure 1. *Schematic illustration of the main findings reported in [4].* **1a.** *The SARS-CoV-2 main protease (M^{pro}).* **1b.** *The protein residue network of M^{pro}.* **1c.** *Contribution of amino acids (AAs) near the binding site of the matrix function $\mathcal{Z}$. Figure courtesy of Ernesto Estrada.*

SARS-CoV-2 M^{pro} as a Target

The life cycle of SARS-CoV-2 commences when the virus enters a human cell through receptor-mediated endocytosis [3]. Once inside the cell's interior, the virus releases its RNA and proteins in the cytoplasm. The viral messenger RNA is then translated into two viral replicase polyproteins, which are cleaved by two viral proteases—the papin-like protease and the main protease (M^{pro})—to create 16 non-structural proteins (NSP). The role of M^{pro} in NSP production is fundamental for virus proliferation in the human cell. It therefore constitutes an important target against SARS-CoV-2.

X-ray crystallography has resolved the three-dimensional (3D) structures of free SARS-CoV-2 M^{pro}, as well as M^{pro} that is complexed with some inhibitors. M^{pro} consists of two identical chains, each with 306 amino acids (AAs). A comparison of the SARS-CoV-2 M^{pro} with that of SARS-CoV (the virus that produced the 2002-2003 outbreak) revealed several similarities. They share 96 percent of their residue sequences, and superposition of their 3D structures revealed an almost perfect fit. But are they truly similar, or does the SARS-CoV-2 M^{pro} hide some "magic tricks" that make it more efficient in its damaging work?

SARS-CoV-2 M^{pro} as a Network

One can represent a protein as a network in the following way. Let the C_α atom of each residue be represented as a node on a graph, and let us fix a cutoff radius r_C, which represents an upper limit of separation between two residues in physical contact. Two nodes i and j are thus connected if $r_{ij} \leq r_C$. This graph is called a protein residue network [2]. Using this network representation, Estrada studied the 3D structures of the SARS-CoV and SARS-CoV-2 M^{pro} [4]. To compare both proteases, he utilized several network-theoretic descriptors: edge density, degree heterogeneity, clustering coefficients, modularity, average shortest path distance, and average betweenness centrality. His findings confirmed the previous observations that both proteases are very similar, with less than a two percent difference in the aforementioned descriptors. Other descriptors, such as communicability indices, experience up to a 20 percent

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Executive Director Jim Crowley Retires After 25 Years of SIAM Leadership

By Lina Sorg

After 25 years as SIAM's executive director, James (Jim) Crowley is retiring this September. Jim has been an active SIAM member since 1978 and has served as SIAM's second executive director since 1995. Under Jim's affable yet commanding leadership, SIAM has maintained strong fiscal health while remaining uniquely devoted to its membership community.

With Jim at the helm, SIAM's various programs and publications—including its international and digital presence—have experienced healthy and continued growth. When he first took office, SIAM had 8,684 members. That figure has risen to 14,346. SIAM has also launched seven new journals since 1995, including the recent *SIAM Journal on Mathematics of Data Science*, thus extending the total number of journals from 11 to 18. Since Jim's arrival, SIAM has published 455 books and added 11 new book series.

SIAM also founded its esteemed Fellows Program under Jim's domain. The program, which commenced in 2009, has recognized a total of 535 members as SIAM Fellows. Also of note is the exponential growth of SIAM Student Chapters—from nine to 195—in the last 20 years.

Jim came to SIAM after a 22-year career in the Air Force, where he retired as a Lieutenant Colonel. He held various positions during this time, including assistant chief scientist for Air Force Systems Command and directorate head of Mathematics and Information Sciences at the Air Force Office of Scientific Research. Jim also served as a tenured associate professor at the U.S. Air Force Academy and a program manager at the Defense Advanced Research Projects Agency.

Jim received his Ph.D. in mathematics from Brown University in 1982—under the direction of Harvey Thomas Banks—during his time with the Air Force. He also holds a bachelor's and master's degree in mathematics from the College of the Holy Cross and Virginia Polytechnic Institute and State University respectively. Jim's scientific interests are in control theory and large-scale computing. In addition to his involvement with SIAM, he is a Fellow of the American Mathematical Society and the American Association for the Advancement of Science.

In honor of Jim's retirement and the SIAM legacy he leaves behind, we have compiled several tributes from SIAM members in various leadership positions who have worked closely with him over the years. They share their memories, commendations, and well-wishes below.

Lisa Fauci (*Tulane University*): In any professional collaboration, there is nothing better than working with someone who is super smart, knowledgeable, responsive, and supportive; it's a bonus if that person has a subtle yet great sense of humor. You can therefore imagine that one of the highlights of my time as SIAM president has been working with Jim. I have learned so much from him about science policy, publications, conferences, and other pillars of professional societies. Mostly, though, I hope that I have picked up some of Jim's uncanny ability to listen carefully to other people's ideas and initiatives and provide critical input without an ounce of insult.

Jim's steadfast leadership and even-handedness was especially important this year when SIAM's conferences quickly became virtual and other SIAM business was conducted from kitchen tables and basements. While I had envisioned toasting to Jim's next chapter while we were face-to-face at the Second Joint SIAM/CAIMS Annual Meeting in Toronto, I will take a rain check on this and look forward to the time when Jim and the SIAM community can be together in person once again.

Tim Kelley (*North Carolina State University*): I first met Jim in 1994, right after he accepted the executive director

See **Jim Crowley** *on page 2*

Jim Crowley speaks at the SIAM Business Meeting during the 2016 SIAM Annual Meeting, which took place in Boston, Mass. SIAM photo.

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Jim Crowley

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position. Several weeks after taking the job, Jim helped me solve a few problems in getting my 1995 book, *Iterative Methods for Linear and Nonlinear Equations*, approved for publication. Since then I've worked with him as a SIAM officer, conference organizer, author, and conference attendee. He has been a consistent (and sometimes lonely) voice of sanity in all the SIAM work I've done. SIAM has become far more inclusive and open under Jim's leadership. Thanks, Jim!

Nicholas Higham (*University of Manchester*): Jim has been extremely visible in his leadership, not least through his many *SIAM News* articles, his attendance at SIAM conferences, and his representation of SIAM on various external bodies. But what most people don't know is how much Jim does behind the scenes. In addition to running a happy and efficient SIAM office, which has a remarkably low rate of staff turnover, Jim has been a fount of good advice for SIAM volunteers. He has provided support beyond the call of duty for SIAM officers and was always willing to help draft a document or attend a meeting in their place. I benefited hugely from Jim's support and guidance during my terms as vice president-at-large and president. He also cares deeply about the history of SIAM and knows more about it than anyone else.

Under Jim's leadership, SIAM has maintained a willingness to move quickly and exploit technological developments. SIAM was an early adopter of electronic publishing in the late 1990s, was quick to begin using social media in the late 2000s, and was one of the first societies to allow electronic voting in its elections.

One of the things I admire most about Jim is his ability to tactfully point out flaws in an idea that someone suggests without them taking the slightest offence. I'm still not sure how he does it.

Gilbert Strang (*Massachusetts Institute of Technology*): One type of leader (this does not describe my image of Jim) is full of untested ideas, urgent action, and "push." Those ideas turn into initiatives and the society is impelled to move, although general agreement may not have been reached. A forcing term has been introduced, something close to a point source. Another type of leader is more of a guide. There is space for others to have ideas. Instead of racing out front while the rest of the team tries to keep up, the leader and the society move together. Instead of a point source, there is constant support over a long time for the whole society. This is what Jim has given us.

Jim should be proud of the results of his leadership, which brought about new activity groups, new books and journals, new members, and an expanded vision of SIAM. I believe that other, larger groups of computer scientists and engineers respect our society for the quality of its work. On behalf of all the SIAM members who

From left to right: SIAM News editor-in-chief Hans Kaper (Georgetown University), Jim Crowley, and past president Pam Cook (University of Delaware) at the 2014 SIAM Annual Meeting, which was held in Chicago, Ill. SIAM photo.

have felt Jim's encouragement, support, and never-failing good will, I say thank you for 25 years of true leadership.

Margot Gerritsen (*Stanford University*): When I first joined the SIAM Council, I got a glimpse of what was happening behind the doors in the SIAM kitchen. Chef Jim seemed to effortlessly keep the office working by responding to new ideas from the many SIAM volunteers and frequently adding his own thoughts to the menu. He has been the strong and relatively hidden force of SIAM over the years, always working for the good of the society without seeking the limelight.

This became even more apparent as a member of the Board of Trustees, and now as chair of the Board. Jim has been fantastic: a wonderful leader to SIAM staff, a highly effective and responsible manager of SIAM affairs, a strong representative of SIAM in D.C., and a valuable liaison with peer organizations. He has also been a fabulous collaborator—always happy to provide insights and share experiences—and very responsive, often answering emails within the hour.

I cannot thank Jim enough for his dedication to SIAM and all of us. I'm so glad he will remain part of this community and look forward to raising a glass to him at a future SIAM meeting or conference. Cheers, Jim!

Margaret Wright (*New York University*): Jim and I first met at his interview for the position of SIAM's executive director. At the time, I was vice president-at-large and thus a member of the search committee. After Jim left the room, committee members looked at one other and said, "He's perfect!" And he was.

To reflect the "M" in SIAM, let me describe Jim's contributions with an equation: $\mathrm{SIAM} + \mathrm{jc} \gg \mathrm{SIAM}$. SIAM is a much better and stronger organization because of Jim. One can actually describe his years at SIAM in terms of his mathematical research area: control, a field that addresses the behavior of a complex system and attempts to guide it to a desired outcome. In many ways, this is precisely the job of an executive director.

Jim practices adaptive control via a leadership style that combines stability, creativity, thoughtfulness, and progress. A crucial ingredient is his unshakable integrity. It has not always been smooth sailing, but through it all Jim has maintained both a strong sense of SIAM's mission and a clear vision of the strategies and principles needed for SIAM to be effective in today's world.

Finally, I can't resist mentioning some lighthearted moments with Jim and Marty Golubitsky when we were planning SIAM's 50th Anniversary and 2002 Annual Meeting. In an initial discussion of special events for the meeting, Jim (perhaps rashly) said that Marty and I could have "carte blanche." We of course never wanted anything extravagant, but in later conversations Marty and I did not hesitate to utter the words "remember carte blanche," always followed by gales of laughter from the three of us.

Susan Palantino (*SIAM*): I have known Jim for almost 21 years as a remarkable leader and mentor. He has helped the society grow organically—increasing our imprint on applied math, computational science, and data science—and has successfully guided us through many changes and challenges, always motivated by SIAM's mission. Over the years, I have found that when I disagree with him, he is usually right. He seems to possess an almost innate understanding of the community's needs and desires with a remarkable veracity. His selfless, quiet yet convincing manner instills a sense of purpose in the staff and inspires them to make SIAM a place of excellence.

On behalf of both current and previous SIAM staff, I want to express our sincere gratitude to Jim for his leadership, openness, guidance, and intelligence, but most of all his ability to make everyone feel like they are a valuable contributor to SIAM. We will miss you!

Sam Gubins (*Annual Review Investment Corporation*): Reading the praise of Jim by my friends, my thought is "Enough already. Sure, Jim has been a great leader of SIAM for a quarter of a century, and I can add my own paean to my friend and colleague, but enough with the hero worship." Let's have a shout-out to the search committee of 1994, which wisely selected Jim to be our leader. SIAM has gone from strength to strength, as the committee clearly foresaw that Jim would be the ideal person to inspire the creativity of SIAM membership, leadership, and staff. So, thanks to both the search committee and to Jim, who may have lost the corner office but continues to serve SIAM as a loyal member. Bravo, search committee. Bravo, Jim.

We are incredibly grateful to Jim for his service and leadership, which have shaped SIAM into the robust society it is today, and wish him a happy and healthy retirement.

Lina Sorg is the managing editor of SIAM News.

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2020 SIAM Conference on Mathematics of Data Science: A Meeting Goes Virtual

By Gitta Kutyniok, Ali Pinar, and Joel A. Tropp

The 21st century has been called the "age of data science," since people now collect massive volumes of data on just about everything. This data facilitates new approaches to problems in science, technology, engineering, and society.

Mathematics is a necessary component to the development of principled and efficient methodologies for data analysis. For example, machine learning algorithms process data to make scientific discoveries; run critical infrastructure operations; and support vital decisions in a wide variety of fields, including healthcare, loan approval, and even parole. To deploy machine learning tools in high-consequence circumstances, researchers must formulate rigorous performance standards and design algorithms that meet these standards. Mathematics is the language they use to express the resulting guarantees.

Over the years, SIAM has taken a leading role in the advancement of data science. In 2019, the *SIAM Journal on the Mathematics of Data Science*[1] published its first issue. And this year saw the first installment of a new biennial conference series: the SIAM Conference on the Mathematics of Data Science (MDS).[2] A new activity group on data science (SIAG/DATA) has also been approved.

The goal of the MDS conference series is to convene an interdisciplinary community of researchers who are building rigorous foundations for data science and making principled applications to science, engineering, and beyond.

MDS20 was originally scheduled for May 2020 in Cincinnati, Ohio. The call for papers generated 156 minisymposium proposals, 148 contributed talks, and 39 contributed posters. As co-chairs for MDS20, we recruited seven founders of the field of mathematical data science to present plenary talks. Carola-Bibiane Schönlieb (University of Cambridge) and Ozan Öktem (KTH Royal Institute of Technology) organized a minitutorial on "Deep Learning for Inverse Problems and Partial Differential Equations." We anticipated over 1,000 attendees, which is unprecedented for the first installation of a SIAM conference.

However, as the threat of the ongoing COVID-19 pandemic became clear in early 2020, SIAM leadership chose to cancel the in-person meeting in the interest of safety. Instead, we reimagined MDS20 as an online event — the first virtual conference in SIAM's history.

After much last-minute planning, MDS20 took place online from May 4 through June 30, 2020. All seven plenary speakers graciously agreed to give virtual talks over the two-month period. Their talks covered a range of fundamental topics in data science:

1. Michael Jordan (University of California, Berkeley) discussed the decision-making side of machine learning and focused on computational, inferential, and economic perspectives.
2. Cynthia Dwork (Harvard University) introduced the concept of differential privacy, a mathematical approach that prevents identification of individuals' data.
3. Jennifer Chayes (Berkeley) spoke about modeling and inference for large, sparse graphs using the concept of a graphon (or graph limit).
4. Andrea Bertozzi (University of California, Los Angeles) presented methods for the analysis of graph data with tools from numerical partial differential equations, variational analysis, and imaging science.
5. David Donoho (Stanford University) surveyed recent literature on scaling up COVID-19 testing using pooled samples.[3]
6. Yann LeCun (Facebook and New York University) addressed the nexus between applied mathematics and deep learning, with a focus on open challenges.
7. Yurii Nesterov (University of Louvain) described higher-order optimization algorithms that are designed for large-scale machine learning applications.

Each plenary talk attracted between 200 and 500 live viewers. In addition, the minitutorial took place as a six-part virtual event in late May. Speakers included Weinan E (Princeton University), Eldad Haber[4] (University of British Columbia), Ozan Öktem (KTH Royal Institute of Technology), Christoph Reisinger (University of Oxford), Rebecca Willett (University of Chicago), and Lexing Ying (Stanford). Each tutorial

See **Meeting Goes Virtual** *on page 4*

[1] https://epubs.siam.org/journal/sjmdaq

[2] https://www.siam.org/conferences/cm/conference/mds20

[3] https://sinews.siam.org/Details-Page/the-mathematics-of-mass-testing-for-covid-19

[4] https://sinews.siam.org/Details-Page/deep-learning-for-covid-19-diagnosis

Obituary: James McKenna

By William A. Massey

James McKenna, an esteemed mathematician and SIAM Fellow, passed away on February 29, 2020. He was 90 years old. Jim, as he preferred to be called, was born in 1929. After displaying an interest in science at a young age, he earned his bachelor's degree from the Massachusetts Institute of Technology (MIT). Jim next became a Fulbright Fellow at the University of Edinburgh; this was followed by a four-year stint in the U.S. Air Force, during which he received his master's degree from MIT. He then pursued a Ph.D. in mathematics at Princeton University.

During his time at Princeton, Jim held a Bell Laboratories Fellowship. Upon earning his Ph.D., he joined Bell Telephone Laboratories as a member of technical staff in the Mathematics and Statistics Research Center. After multiple positions and nearly 30 years at Bell Labs, Jim became the executive director of the Systems Principles Research Department at Bellcore. Upon retiring from Bellcore, he spent 13 years as a Research Institute for Scientists Emeriti (RISE) Fellow at Drew University. Jim was recognized as a SIAM fellow in 2011 "for mathematical contributions to the underpinnings of telecommunications products and his support of SIAM." He was also a Fellow of the American Association for the Advancement of Science and the Institute of Electrical and Electronic Engineers.

My first encounter with Jim was in the spring of 1977. I was a senior mathematics major at Princeton University and had applied to a Bell Labs Cooperative Research Fellowship Program for Minorities (CRFP). Jim invited me to visit the Mathematical Sciences Research Center at Bell Labs during my CRFP interview.

Up until that point, I had been trained in commutative algebra and number theory. Jim introduced me to the world of applied mathematics; we hit it off well and he became my official CRFP mentor. During the summer of 1977, he gave me the opportunity to work at Bell Labs with one of his colleagues, John Morrison. By the end of that summer, I had completed my first research paper with John on a problem in queueing theory. This led to my first publication in the 1978 issue of the *Bell Labs Technical Journal*.

In the fall of 1977, I headed to graduate school at Stanford University's Department of Mathematics. Jim was always available for a phone conversation and even visited me several times to see how things were going on campus. While I was at Stanford, he facilitated two additional summer sessions for me at Bell Labs. Finally, in the spring of 1981, Jim offered me a position in his department—after completion of my Ph.D. in mathematics—as a permanent member of technical staff.

Jim's continuing and consistent commitment to diversity in mathematics was readily apparent during my time at Bell Labs. He also served as a mentor to Andrea Bertozzi (University of California, Los Angeles) as part of Bell Labs' Graduate Research Program for Women (GRPW). His actions inspired me to become the first CRFP mentee to mentor another CRFP student: Arlie Petters (Duke University). I once joked to Jim that this made him the first CRFP "grandmentor."

Jim's interests went well beyond applied mathematics and included travel, music, and history. He is survived by his wife Jane, son Matthew, and daughter Rebecca, as well as extended family and friends who will miss him greatly.

From left to right: William A. Massey (Princeton University) with "grandmentor" Jim McKenna and Jim's "grandmentee" Arlie O. Petters (Duke University) at the Mentoring for Success Symposium, which took place at the AT&T Learning Center in April 1998. Photo courtesy of William Massey.

In closing, I'd like to share a few comments from former researchers at Bell Labs' Mathematical Sciences Research Center who had the pleasure of working for Jim during the 1980s:

– *"Jim taught me an awful lot. I have always been extremely grateful to him for that and the many, many other things he gave to and did for me."*

– *"I remember Jim fondly. He was always a supportive manager — a prime example of the 'enlightened management' that made Bell Labs such an amazing place to work in those days."*

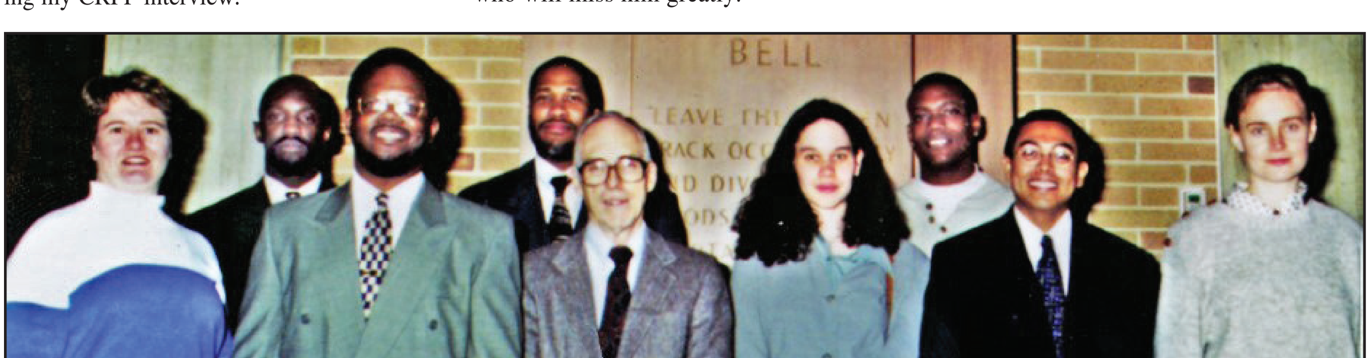
– *"What a great time we had in Jim's department. I always felt like he supported me 100 percent in doing just what I wanted at Bell Labs. As a department head, he worked very hard behind the scenes so that we who reported to him didn't have a care in the world and could concentrate on what we loved: our research."*

– *"When he and Andrea [Bertozzi] worked out some details of a multiple complex variables model, I recall that he was glad to let Andrea give the seminar alone. He was so happy in the work and in working with such an accomplished young colleague."*

– *"I remember Jim very well and with a great deal of respect and fondness. He was my department head when I first joined Bell Labs. I am sure I made many non-optimal decisions in that relatively early part of my career, but Jim was very open and caring and always gave good advice (which was not always taken!). I also remember very well the department parties that Jim and Jane regularly had at their house."*

– *"I frequently think of both [Jim and Jane] and of Jane's warm hospitality. During my first years fresh out of the university, the McKennas were like family to me."*

– *"What I remember most about Jim was his selfless appreciation of the people he interacted with. His delight at the insight of others was so pure and simple. What a wonderful man."*



Jim McKenna (center) with his mentees and "grandmentees" at the CRFP-GRPW 25th Anniversary Celebration, which was held at the headquarters of Lucent Technologies in January 1998. Photo courtesy of William Massey.

William A. Massey is the Edwin S. Wilsey Professor in the Department of Operations Research and Financial Engineering at Princeton University.

COVID-19

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difference between the two proteases. They are based on the following matrix function of the network's adjacency matrix A:

$$G := \sum_{k=0}^{\infty} \frac{A^k}{k!} = \exp(A), \qquad (1)$$

where $(A^k)_{ij}$ counts the number of walks of length k between two nodes i and j.

However, these indices heavily penalize relatively long walks, due to the fast-growing nature of $k!$ Therefore, the possibility of exploring the proteases' capacities to transmit effects through longer distances was an incognita. So Estrada examined a modification of communicability, which employs a double rather than single factorial [5]:

$$Z := \sum_{k=0}^{\infty} \frac{A^k}{k!!} = \frac{1}{2}\left[\sqrt{2\pi}\,\mathrm{erf}\left(\frac{A}{\sqrt{2}}\right) + 2I\right]\exp\left(\frac{A^2}{2}\right). \qquad (2)$$

The results from this new matrix function were astonishing. Namely, it indicated that the SARS-CoV-2 M^{pro} is 1900 percent more likely to transmit long-range effects than its SARS-CoV analogue. In addition, the AAs displayed increased sensitivity to perturbations around the new protease's binding site and near its catalytic site.

Estrada used these findings to analyze several structures of the SARS-CoV-2 protease, which was bounded to inhibitors. Remarkably, the strongest inhibitors of the SARS-CoV-2 M^{pro} are those that produce the least amount of change in its capacity to transmit perturbations across the protein, thus identifying a potential route for researchers' design of potent inhibitors for the SARS-CoV-2 M^{pro}. Figure 1 (on page 1) illustrates these results.

Networks-Fractional Calculus Alliance

A question still remained about the interactions of M^{pro} inhibitors: What is the mechanism through which one residue transmits its perturbations, such that it is "felt" at long distances in the protein? Although the communicability function $G = \exp(A)$ can be directly related to dynamical processes on the graph, the same is not true of the function Z. Thus, the question is actually as follows: Does a dynamical model exist on the network whose solution is related to Z?

The answer to this query stems from fractional calculus, a field that allows researchers to capture the sub- and superdiffusive behavior of many real-life processes. We developed the following fractional-order susceptible-infected (FSI) model to study the propagation of perturbations produced by protein inhibitors [1]:

$$\begin{cases} D_t^{\alpha}(-\log(1-x))(t) = \beta^{\alpha} A x(t), \\ x(0) = x_0. \end{cases}$$

Here, $x(t)$ is a vector quantity that depends on time t, which represents the probabilities that the corresponding residues will become perturbed at t. β is a positive constant that signifies the rate at which the perturbation is transmitted between AAs, and α is a number that belongs to the interval $(0,1)$, which provides the fractional order of derivation. We then employed the fractional Caputo derivative D_t^{α}. For example, $\alpha = 1$ yields the classical susceptible-infected (SI) model, which one can rewrite as $x'(t) = -(1-x(t))\beta A x(t)$.

We found an explicit upper bound $\hat{x}$ to the FSI model's exact solution, in terms of Mittag-Leffler functions of A. That is, $\hat{x} = f(\hat{y})$ where $f(\hat{y}) = 1 - e^{-\hat{y}}$ and

$$\hat{y}(t) = E_{\alpha,1}((\beta t)^{\alpha}\hat{A})\,g(x_0) + \sum_{k=0}^{\infty} \frac{(\beta t)^{\alpha(k+1)}\hat{A}^k A\, b(x_0)}{\Gamma(\alpha(k+1)+1)},$$

with $E_{\alpha,1}$ as the Mittag-Leffler function, $\hat{A} = A\,\mathrm{diag}(1-x_0)$, $b(x_0) = x_0 + (1-x_0)\log(1-x_0)$, and $g = f^{-1}$. The upper bound $\hat{x}$ represents the worst-case scenario on the propagation of perturbations across a protein residue network because $0 \le x_i(t) \le \hat{x}_i(t)$. Moreover, $\hat{x}$ converges asymptotically to the exact solution as time approaches infinity. When the perturbation is produced with equal probability at any residue of the protein, this upper bound is written as

$$\hat{y}(t) = \nu E_{\alpha,1}(\zeta A)\vec{1} - \phi\vec{1}, \qquad (3)$$

where ν and ϕ are constants for given fixed parameters and $\eta = (\beta t)^{\alpha}\,\mathrm{diag}(1-x_0)$.

We studied the average differences ΔE^{α} between all nondiagonal entries of $E_{\alpha,1}(\zeta A)$ when the protein is bounded to an inhibitor and when it is free for different values of α. For each α, we obtained the average length L of the paths between the pairs of nodes in the top ten ranking according to ΔE^{α}. We then counted the number N_{BS} of nodes in these rankings that belonged to the SARS-CoV-2 M^{pro}'s binding site. When $\alpha = 1$ (a normal SI model), the results indicated no clear trend between the calculated parameters and the potency of the inhibitors, as determined by $IC_{50}(\mu M)$. But when $\alpha = 0.5$, the most powerful inhibitor increases the transmissibility of perturbations through M^{pro} by 71 percent after its binding. The second most powerful inhibitor increases the transmissibility of perturbations by 13 percent. Interestingly, the weakest inhibitor actually lessens the transmissibility of perturbations across the protein (see Figure 2). In addition, the average length of the shortest paths and number of residues in the binding site follow the same trend as $IC_{50}(\mu M)$. Figure 3 offers an illustration of these perturbing paths for the least and most powerful inhibitors.

inhibitor	$\Delta E^{1/2}$	L	N_{BS}	$IC_{50}(\mu M)$
6M0K	70.7	9.1	7	0.04 ± 0.002
6LZE	13.4	8.1	6	0.053 ± 0.005
6Y2G	-4.0	5.8	3	0.67 ± 0.18

Figure 2. *Values of the average changes in transmissibility of perturbations $\Delta E^{1/2}$, average path lengths between the most perturbed amino acids (AAs) L, and number of residues in these paths that belong to the binding site of the main protease (M^{pro}) N_{BS} for the interaction between M^{pro} and three different inhibitors. $IC_{50}(\mu M)$ is the inhibitory concentration of the inhibitor. The least powerful inhibitor is 6Y2G and the most powerful is 6M0K.*

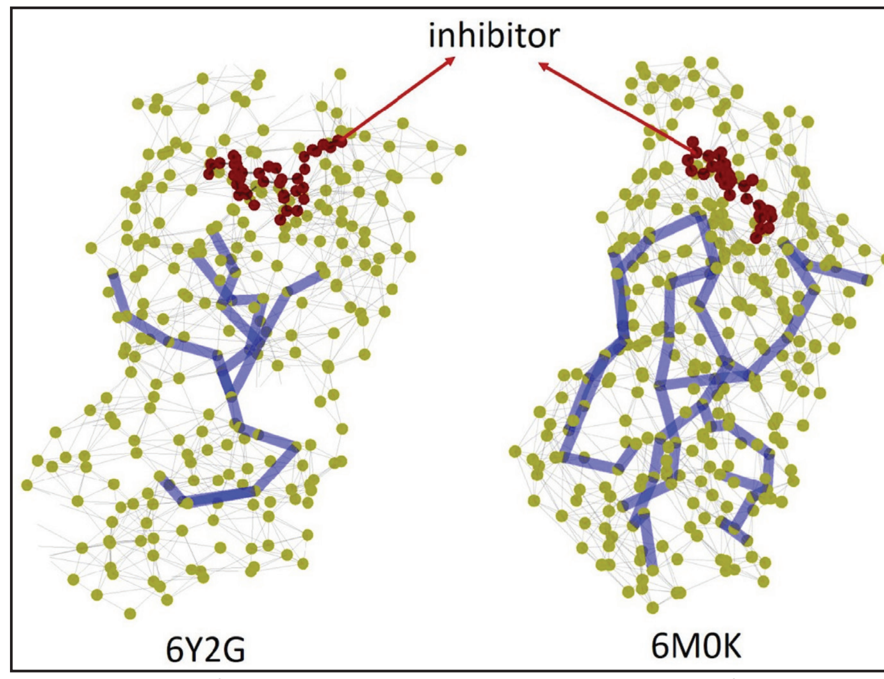

Figure 3. *Illustration of the shortest paths between the most perturbed pairs of amino acids (AAs) in the main protease (M^{pro}), bounded to two inhibitors of different potency. 6Y2G is the least powerful inhibitor and 6M0K is the most powerful inhibitor. Figure courtesy of Ernesto Estrada.*

The resulting Mittag-Leffler function of the network's adjacency matrix from the FSI model is

$$E_{1/2,1}(A) = \left[\mathrm{erf}(A) + I\right] \exp(A^2) = \sum_{k=0}^{\infty} \frac{A^k}{\Gamma(k/2+1)}, \qquad (4)$$

and the connection with the function Z stems from the fact that

$$k!! = 2^{(1+2k-\cos(k\pi))/4}\, \pi^{(\cos(k\pi)-1)/4}\,\Gamma(k/2+1). \qquad (5)$$

These efforts collectively illustrate the use of applied mathematics in helping to understand and combat COVID-19.

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Meeting Goes Virtual

Continued from page 3

talk drew roughly 200 synchronous views. Over the last several months, both the minitutorials and the invited talks have amassed thousands of additional views.

Organizers also held 63 minisymposia throughout the course of the conference. Altogether, these presentations have attracted thousands of synchronous and asynchronous participants. Many of the talks, including the invited lectures, are available on SIAM's YouTube channel.[5]

Unfortunately, some parts of the conference had to be postponed, including the career fair and a business meeting about SIAG/DATA. Other parts of the meeting, including the contributed talks, became untenable.

As MDS20 co-chairs, we can offer several positive conclusions from our experiences planning an online meeting. Virtual conferences reduce the costs and limitations (monetary, temporal, and carbon) associated with travel. Content is also more widely available—anyone with an internet connection can access the presentations at any time—which may increase participation from early-career scientists and researchers with limited resources or scheduling conflicts.

On the other hand, the logistics of online meetings still require further refinement. For example, it is impossible to accommodate every time zone. We also found that organizing and advertising the event was more challenging, especially because the meeting spanned two months. Subsequent virtual SIAM conferences—including the SIAM Conference on the Life Sciences, the Second Joint SIAM/CAIMS Annual Meeting, the SIAM Conference on Imaging Science, and the SIAM Conference on Mathematics of Planet Earth—have taken place over two- and three-week increments.

In addition, online conferences offer limited occasions for social engagement, which may be detrimental for scientists who wish to expand their research networks. The virtual format also reduces opportunities for serendipitous inspiration. We must not underestimate the importance of personal interaction in the sciences.

Despite the unexpected challenges, we were glad for the chance to offer MDS20 as an online event and maintain some of the meeting's integrity. We extend our thanks for the dedicated work of the organizing committee, which consisted of Barbara Engelhardt (Princeton), Mark Girolami (Cambridge), Ashish Goel (Stanford), Mason Porter (University of California, Los Angeles), Bernhard Schölkopf (Max Planck Institute for Intelligent Systems), Carola-Bibiane Schönlieb (Cambridge), René Vidal (Johns Hopkins University), Karen Willcox (University of Texas at Austin), Stephen Wright (University of Wisconsin-Madison), and Tong Zhang (Hong Kong University of Science and Technology). With the help of several collaborators, Porter put together a guide to managing an online minisymposium based on his experiences with MDS20.[6]

The SIAM staff also played an invaluable role in managing the physical conference and helping us pivot to the virtual platform. In particular, we would like to thank executive director Jim Crowley; Richard Moore, the director of Programs and Services; and Connie Young and Eva Donnelly of the conferences department.

Plans are already underway for the next MDS conference, which is scheduled to take place as an in-person event in the spring of 2022; the exact dates and location are yet to be determined. We hope to see you there!

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5 https://go.siam.org/m2u23p

6 https://dsweb.siam.org/The-Magazine/Article/how-to-move-a-siam-minisymposium-online-from-the-comfort-of-your-home

Data Assimilation in Medicine

By David Albers, Cecilia Diniz Behn, and George Hripcsak

Medicine is an ongoing forecasting process with sparse, inaccurate data. Practitioners rarely employ physiologic knowledge in actual medical practice because of limited data, imperfect models, and a disconnect between measurable variables and potential treatments. Nevertheless, the medical community is currently clamoring for effective employment of *precision medicine*, which involves providing the right treatment to the right patient; physiology can inspire the solution. We aim to apply current physiologic models—e.g., mechanistic ordinary differential equation (ODE) models of physiology—to medical data to produce useful forecasts. This approach requires fundamental changes to the way in which researchers merge models and data.

Consider the use of inference methods to estimate model states and parameters and evaluate the performance of predictions relative to actionable decisions. One can handle this coupling naturally via data assimilation (DA), a collection of deterministic and stochastic inference methods that estimate and forecast states and parameters of ODE-like models with individual patient data [7]. However, real patient data—which are often sparse and nonstationary—are particularly difficult to use, thus making both inference and model evaluation highly complex. Application to medicine is therefore not possible without model validation and verification that is anchored to clinical consequence. Mathematical innovations must address these realities, and the pursuit of methods that generate actionable knowledge within clinical-specified constraints provides an exciting and deep well of new problems.

One of the human endocrine system's many tasks is to maintain healthy glucose levels. When someone consumes carbohydrates (fat and protein have secondary effects), the carbohydrates are converted to sugar and absorbed by the gut; this causes glucose levels to rise. In response, the pancreas releases insulin, which facilitates glucose uptake for metabolism and makes blood glucose levels fall. As glucose concentrations return to baseline, the liver releases stored glucose to maintain the baseline concentrations. Glucose levels become elevated when the endocrine system is compromised, leading to acute and chronic harm that significantly reduces the quality and length of life.

Diabetes mellitus (DM) is a catch-all for many functionally different diseases that induce elevated glucose. It comprises type II diabetes (91 percent), type I diabetes (six percent), and other diseases (three percent). While DM is multifactorial, the primary defects include insulin resistance and insufficiency. In other contexts—e.g., the intensive care unit (ICU), where 80 to 90 percent of patients' endocrine systems cannot maintain healthy glucose levels—additional defects like stress hormones, kidney and liver damage, and gut absorption contribute to elevated glucose. Operationally, practitioners achieve glycemic management via trial and error; they utilize generic guidelines to direct administration of medications such as metformin and insulin, approach dosing conservatively, and iterate management until the patient is stable.

Computational approaches for quantitative glucose forecasting and control have largely focused on the artificial beta cell/pancreas project, a closed-loop insulin delivery system for patients with type I diabetes. The artificial pancreas represents a significant advance in the clinical practice of glucose management and is currently in clinical trials. Researchers have taken similar approaches without control for type II diabetes, but these methods remain underdeveloped [2].

An oral glucose tolerance test (OGTT) yields the most detailed characterization of the dynamical glucose-insulin interactions. During an OGTT, a fasting patient drinks a glucose solution with a predefined amount of glucose. Blood samples are taken at regular time intervals to assess the rise and fall in blood glucose concentrations (see Figure 1). Clinicians use thresholding approaches for blood glucose levels, which are evaluated at one or two-hour time points, to employ OGTTs for high-fidelity diagnoses. Because OGTTs are invasive, physicians use them in limited clinical circumstances — such as for diagnosis of gestational DM, occurrences surrounding bariatric surgery, and instances of cystic fibrosis-related diabetes. More common diagnostic measures include fasting and non-fasting glucose and hemoglobin A1C measurements, which require models and inference approaches that can cope with the lack of insulin data.

To gain additional insight into glucose-insulin dynamics, one can leverage the controlled conditions of an OGTT — as long as they are coupled with inference methods and models that are capable of differentiating mechanisms of metabolic dysregulation. For example, ODE models describe glucose-insulin dynamics and quantify insulin sensitivity based on the profiles of frequently-sampled glucose and insulin concentrations across the OGTT [5, 6]. These models mathematize hypothesized metabolic disruption in individuals and disease states. Inferring their parameters provides a potential pathway for researchers to pinpoint metabolic disruption in individuals and disease states, thereby informing therapeutic interventions, providing personalized treatments, and identifying factors that contribute to disease progression.

In practice, high-fidelity measurements that resemble controlled experiments such as OGTTs are uncommon. As a result, we must cope with sparse, nonstationary, and uncontrolled data. For example, ICU doctors never measure insulin; instead, they measure glucose approximately once an hour to ensure non-unique solutions for exact glycemic trajectories. In addition, they constantly apply interventions that induce non-stationarity and are meant to improve patient health. ICU data are also sparse in time (12 to 24 data points a day) and space (three measured input variables: glucose, nutrition, and medications), thus inducing severe inference and evaluation challenges. Maintaining glucose in the normal range improves patient outcomes, but errors can result in brain starvation, seizures, loss of consciousness, and even death. Doctors therefore attempt to keep blood glucose concentrations slightly high to minimize the probability of downward extremes.

The system that governs glucose-insulin dynamics in the ICU is a time-delayed, nonlinear scheme in which constant infusion of nutrition induces glucose oscillations and instability, including unexpected and dangerously low excursions. The mechanisms that drive glycemic instability in the ICU are poorly understood [9]. Recent work in shear-induced chaos may highlight mechanisms that can create this instability [8]. If one represents glucose-insulin dynamics as a phase space with natural shearing, an external forcing in the form of continuously administered nutrition can cause the space to fold; this phenomenon induces instability in a previously stable system. A series of hard external "kicks" like daily meals may retain a system's stability, but infrequent kicks—approximated by more or less continuous feeding—can cause the greatest risk. While more work is required to better understand the exact mechanisms of oscillation, the aforementioned approaches provide a language with which to study instability.

Given this variability, it is effort-intensive for medical personnel to manage glucose without the help of computational machinery; even with substantial effort, glycemic goals are difficult to maintain. Personalized endocrine parameter estimation can provide deeper understanding of patient states, and personalized glucose forecasting can maintain more normal glucose levels and produce better outcomes without risking low glucose. Such estimation requires inference machinery to manage the complexities of real-world data by leveraging the knowledge represented in models, data, and clinical expertise to provide accurate physiologic estimation and forecasts.

Figure 2 depicts an example of a personalized glucose forecast, which includes the DA model that synchronizes to the patient over the first 1.5 days, followed by continuous tracking over subsequent days. These forecasts yield a quantitative estimate that already represents an advance beyond current capabilities, but they also report the uncertainty surrounding that estimate. This allows us to make informed decisions about our management approaches.

The success of the forecast in Figure 2 should not overshadow the challenges that accompany robust forecasting for all patients. Advances in both models and inference machinery are imperative when facilitating model development and expanding model application in clinical practice. Physiological insights can help refine model structure to better represent the system. However, researchers should focus on developing models that impact decision-making and can be directly

See **Data Assimilation** *on page 8*

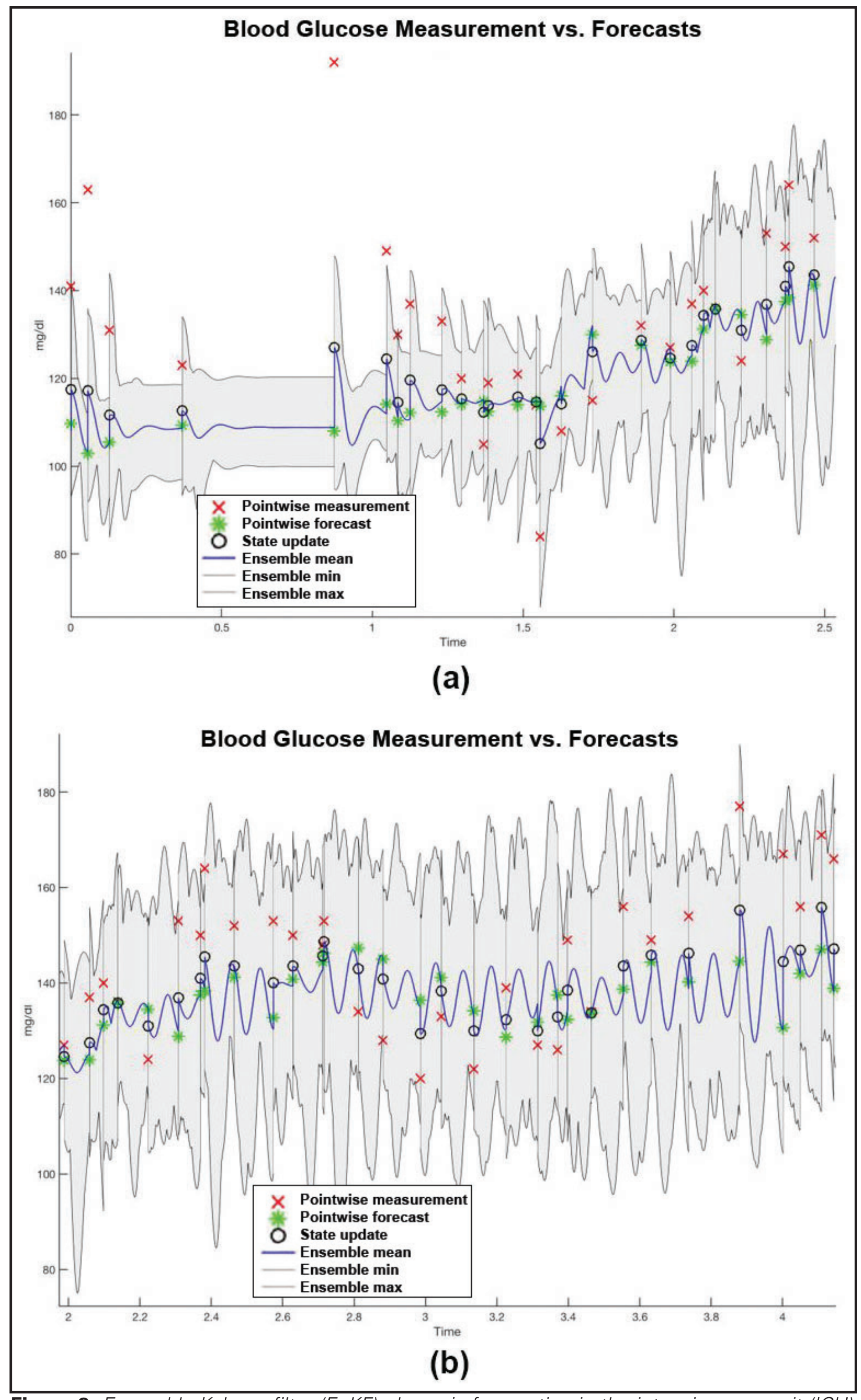

Figure 2. *Ensemble Kalman filter (EnKF) glycemic forecasting in the intensive care unit (ICU).* **2a.** *The path to convergence on admission to day 2.5.* **2b.** *Patient tracking between days 2 and 4. Most measurements lie within forecast expectations, but not all patients are well-estimated; the most unstable and complex patients with substantial interventions typically have the least accurate forecasts. Figure courtesy of David Albers and George Hripcsak.*

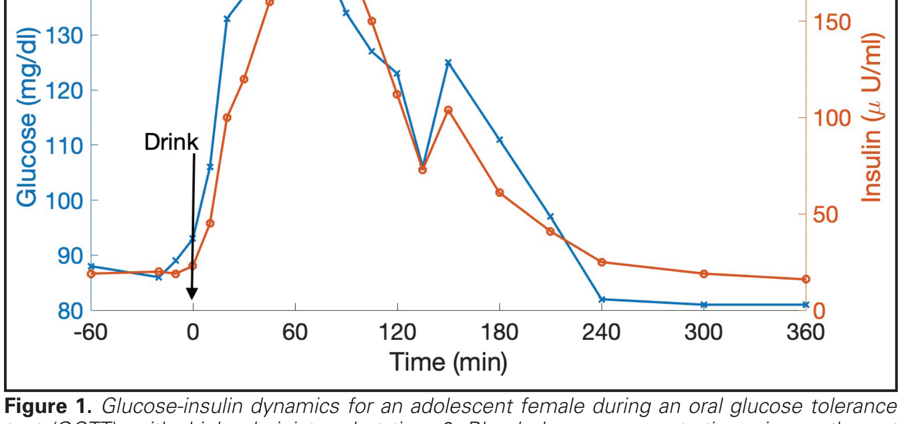

Figure 1. *Glucose-insulin dynamics for an adolescent female during an oral glucose tolerance test (OGTT), with drink administered at time 0. Blood glucose concentrations rise as the gut absorbs glucose from the drink and fall as glucose is taken up by the liver and peripheral tissues. The pancreas releases insulin in response to elevated glucose levels and facilitates glucose uptake. Insulin resistance in this individual requires a second phase of insulin release to return glucose to baseline. Data courtesy of Melanie Cree-Green, figure courtesy of Cecilia Diniz Behn.*

Questions of Responsibility: Modelling in the Age of COVID-19

By Maurice Chiodo and Dennis Müller

ETHICS IN MATHEMATICS

Throughout history, humanity has always battled pandemics with tools that are available in the time period. Today, these tools involve a combination of big data techniques and traditional epidemiological models. In the ongoing fight against COVID-19, many mathematicians work at the *third* level of ethical engagement: *taking a seat at the table of power* (we introduced *SIAM News* readers to the four levels of ethical engagement for mathematicians in 2018)[1] [3]. When conducting COVID-19-related research, mathematicians may find themselves in public service roles. They might engage in policy discussions, collaborate with politicians and other non-scientists, and use the predictive power of mathematics to shape substantial decisions. We aim to promote good practice for ethical mathematical modelling in these difficult times. We begin with some observations about mathematical modellers, then derive eight questions that all mathematicians should constantly ask themselves.

During a pandemic, circumstances demand rapid and immediate results. Consequently, researchers often publish or communicate preliminary findings before they are properly peer-reviewed. Like all scientists, mathematicians must strike a careful balance between quality and speed. Big data, analytics, and mathematical modelling have become the go-to options for many researchers in the age of quantitative decision-making. In particular, some may think that mathematical quantification *always* improves a situation. However, believing that "any model is better than no model" is potentially dangerous when the results influence life-or-death decision-making in areas ranging from high-level political offices to hospital frontlines.

Alternative methods of problem-solving do exist, and providing a false sense of security can skew other people's decision spaces. Scientists and mathematicians carry a burden of responsibility when they apply their tools and models to better understand a worldwide pandemic. Politicians like to be "led by science," but who is held responsible for the ensuing decisions? Is it the mathematicians, the politicians, or both? Generally, mathematicians are not politicians and politicians are not mathematicians. In order to work and communicate effectively as a team, each group might need to learn a bit about the other side. And if mathematicians are engaging with the political decision process, what exactly should they be doing?

Proper science communication is a crucial component of a mathematician's role, now more than ever. For example, the British government recently improperly explained its new alert level system to the general public as "COVID alert level = rate of infection + number of infections" [10]. This statement both confused people and lacked actual information, a combination that can seriously erode the public's trust in mathematics. When engaging in and supporting higher-level decision-making, mathematicians must find adequate ways to communicate their results and decisions to the public. Some researchers are acting with the utmost transparency, including a group of self-organized scientists called the Independent SAGE[2] that aims to provide transparent government advice during COVID-19.

Mathematical models, which range from predictions for reopening schools and universities to statistics pertaining to children's viral loads, can incur real-life costs. Therefore, clear and consistent advice is necessary for leaders to make proper decisions. For instance, a school principal cannot prepare his/her school for reopening when predictions—and thus government advice—are constantly changing or contradictory [9]. In all of their equations and theorems, mathematicians cannot forget the people at the frontline and those making the political decisions. They must ensure that their work is practical, useful, and does not overly constrain politicians' decision spaces. Otherwise, a lack of usability—combined with public distrust and an anti-science bias—could erode mathematics' authority [6].

The COVID-19 pandemic has also underlined mathematicians' increasing levels of political responsibility, which extend beyond their technical work. Private actions can undermine important mathematical and scientific research, even when the studies are sound. Such was the case when epidemiologist and mathematician Neil Ferguson resigned from his U.K. government advisory position after violating lockdown rules [1].

While assisting other mathematicians on COVID-19 modelling efforts, we observed that splitting large problems into smaller, manageable subproblems and subsequently compartmentalising teams consistently led to communication issues. Teams need members who are dedicated to ensuring seamless communication and avoiding structural problems in the models. Furthermore, identifying only one member to address ethical issues within a large team is insufficient, as there is simply too much ground to cover. Every mathematician must, to some extent, be aware of his/her own moral responsibilities.

Mathematicians never work in a political or ethical vacuum, and this is particularly true when their efforts impact a pandemic response. In these times, they cannot simply expect their work to "speak for itself." Instead, mathematicians must vocalise the importance and relevance of their research and ensure that they possess a solid understanding of their own ethical standards and the consequences of their work. For example, data scientist Rebekah Jones was reportedly fired from her job with Florida's Department of Health after refusing to manipulate COVID-19 data on a public-facing portal because she considered the requests unethical [7]. She has since begun publishing data on her private website.

Understanding, processing, and inferring meaning from complex data requires a broad perspective. An emphasis on the reproducibility of modelling results, which enables "outsiders" with different views to scrutinize the work in question, is also essential. When software engineers

See **Responsibility** *on page 7*

[1] https://sinews.siam.org/Details-Page/mathematicians-and-ethical-engagement

[2] https://www.independentsage.org/

Responsibility

Continued from page 6

identified sloppy code in a British COVID-19 model, journalists were quick to report on it. However, it is now evident that these results are actually reproducible [2].

But shouldn't mathematicians aim for more than just clean code? Computer scientists have long understood the value of commenting source code, but how common is it for mathematicians to properly comment and document their models? For critical results, mathematicians must document the *reasoning* that inspired their solution. Over the last decade, computer science and other disciplines have developed tools to better document data and models for artificial intelligence (AI) production systems. With slight adaptations, existing tools like Datasheets for Datasets [5] or Model Cards for Model Reporting [8] can help mathematicians make their models and decisions easier for the public to digest and scrutinise. These tools may also help ensure that researchers are not working with biased or incomplete datasets.

Good practice in AI development expects scientists to consider the origins of and biases in their datasets; document their models, data, and impact; consider feedback loops; and remain aware of their responsibilities to the public. These principles also apply in pandemic modelling. Mathematicians must not fall victim to limitations or biases in their datasets or thinking. As a rough guideline for others, we summarise our observations in eight questions that mathematicians who are working on COVID-19 models should keep in mind:

1. Am I using *authorised and morally obtained datasets*?
2. Do my co-workers, superiors, and I have *sufficient perspective*, and do we understand the *limitations and biases in our data and thinking*?
3. What *optimisation objectives and constraints* have I chosen, and what are their *real-life costs*?
4. Am I properly considering how to *comment and document my model* and *communicate the results* to those who need them?
5. Are my results *explainable and falsifiable*?
6. Do I have techniques to handle *feedback loops* and the *large-scale impact* of my work?
7. Am I aware of other *non-mathematical aspects* and the *political nature* of my work?
8. Do I have a *non-technical response strategy for when things go wrong*? Do I have *peers who support me with whom I can talk*?

Of course, these aspects are not entirely new. Emanuel Derman and Paul Wilmott laid out their "Financial Modelers' Manifesto" in the wake of the 2008 global financial crash [4]. But mathematicians should not overlook the tendency to forget basic principles in the heat of the moment. We designed these eight questions to promote good practices for ethical modelling. Good practices value everyone — colleagues and the model subjects alike. During these arduous times, mathematicians become part of bigger processes when they use their expertise to help policymakers and frontline workers make decisions. Contributing to the COVID-19 response is undeniably challenging; the stakes are high, the situation is unfamiliar, information is uncertain, and circumstances change quickly. Mathematicians must formulate their work responsibly and look beyond their LaTeX files to ensure that their work is adequately communicated and well-received among scientists, decision-makers, and the general populace.

For the past four years, the Cambridge University Ethics in Mathematics Project has been examining the ethical issues and social ramifications of all forms of mathematical research. Our work—which includes articles, two organised conferences, and a list of talks—is available online.[3] We hope that our insights and tools prove useful to mathematicians working on COVID-19, and welcome any contact or requests for collaboration, assistance, or advice. The mathematical community works better when it works together.

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[3] https://www.ethics.maths.cam.ac.uk/

It's All About the Story

Reflections of a Former Science Policy Fellowship Recipient

By Emily J. Evans

I learned many things during my time as a SIAM Science Policy Fellowship recipient, from decoding what felt like hundreds of acronyms to intuitively recognizing a representative or senator in the hall. But the most important thing I learned was how to tell a compelling story about the value of mathematics and science. Fellowship recipients and members of the SIAM Committee on Science Policy like to joke that Congress is most interested in anything that involves "health, wealth, or stealth." In reality, however, most members of Congress want compelling stories that they can share on the chamber floor when arguing for more funding. As a result, whenever we visited Capitol Hill we began with introductions and stories and closed our time with an "ask." In the interest of following this same pattern, I will discuss my time as a SIAM Science Policy Fellowship recipient and finish with a request.

When I first heard about the SIAM Science Policy Fellowship Program, I was very interested. Although I never wanted to be a politician, I have always been curious about the political process (and as my career developed, the funding process). I had hoped that the Fellowship Program would offer me an insider's perspective on these operations, and I was not disappointed. As part of my Fellowship, I received an intensive half-day training on budgets and appropriations, science advocacy, federal science policy, and outreach to other federal agencies. Although I was not surprised to hear that the appropriations process is perpetually behind, I was amazed by individual constituents' potential impact on the budget.

SIAM retains the services of Lewis-Burke Associates, which helps represent the society (and science policy in general) on Capitol Hill. Lewis-Burke took special care of the Fellowship recipients and ensured that we were prepared and knowledgeable during committee meetings. I was consistently impressed with their connections, understanding of the political process, and insight into exactly who votes for what (and why). As a case in point, a Lewis-Burke specialist once told me exactly how my two senators voted on a particular funding bill (they happened to be against party line), and why they voted that way.

As a Fellowship recipient, I also participated in SIAM's Committee on Science Policy meetings. At these meetings, officials from different government agencies routinely give presentations, explain their agencies' funding and research priorities, solicit feedback and suggestions, share their concerns, and request that attendees advocate for specific funding targets. Universally, they were interested in hearing about SIAM members' reactions to their goals, directions, and concerns. They were also interested in our stories, which allow them to advocate more effectively for math and science.

A highlight of the spring policy meeting is the visit to Capitol Hill. During these gatherings, committee members and Fellowship recipients meet with Congressional members and staffers in small groups, guided by Lewis-Burke representatives. The Hill visits were a high point for me for two reasons. First, I was able to spend a block of time with a few of the more senior committee members and learn about their research and experiences.

See **Science Policy** *on page 12*

Emily Evans (left) speaks with Senator Mike Lee (R-UT) and Miriam Quintal (right) of Lewis-Burke Associates during a constituent meet-and-greet, which took place in May 2018 in Washington, D.C. Photo courtesy of Senator Lee staff.

Data Assimilation

Continued from page 5

probed by external knowledge or clinically collected data. If a detailed physiological representation is not possible in the context of a deterministic model, an alternate approach could involve reducing model fidelity by creating a stochastic model that uses an estimated noise process to represent the poorly-understood or non-inferable physiology [4].

Integrating multiple methods—e.g., implementing a constraint methodology for ensemble Kalman filters (EnKF) [1] and applying machine-learning-based methods to select parameters—reduces identifiability problems and improves inference. For example, the Houlihan method [3] combines machine learning with simulated data to choose effective parameters for estimation, thus reducing the estimation space. One can further reduce this space by integrating clinical and physiologic knowledge into the DA via the introduction of constraints on the filters. Substantial room for innovation exists along this mixed-methodology path of DA and machine learning.

Requirements and limitations of the data and clinical application resulted in a novel method for constraining the EnKF. This method combines EnKF with quadratic programing and requires clinical contributions, physiological input, and mathematical skill. To influence the medical field, mathematical methods must accommodate the reality of sparse, nonstationary data while producing parameter inference and state forecasts that address a recognized need. We must integrate method identification, development, and evaluation—the machinery that facilitates the creation of new data-based knowledge—into an appropriate pipeline (see Figure 3). On the front end, this pipeline should include management of the data sources and translation from operational data into computable data (a complex process in healthcare). On the back end, it must account for translation of the newly created knowledge into a potentially useful form that maximizes end users' impact.

The ability to provide personalized diagnoses and forecasts will require hybrid approaches that exploit the physiology we do understand, effectively constraining the search space so that each patient's limited data can yield useful patient-specific results. These mathematical advances, which are necessary to realize precision medicine's potential, have the capacity to transform the delivery of medicine.

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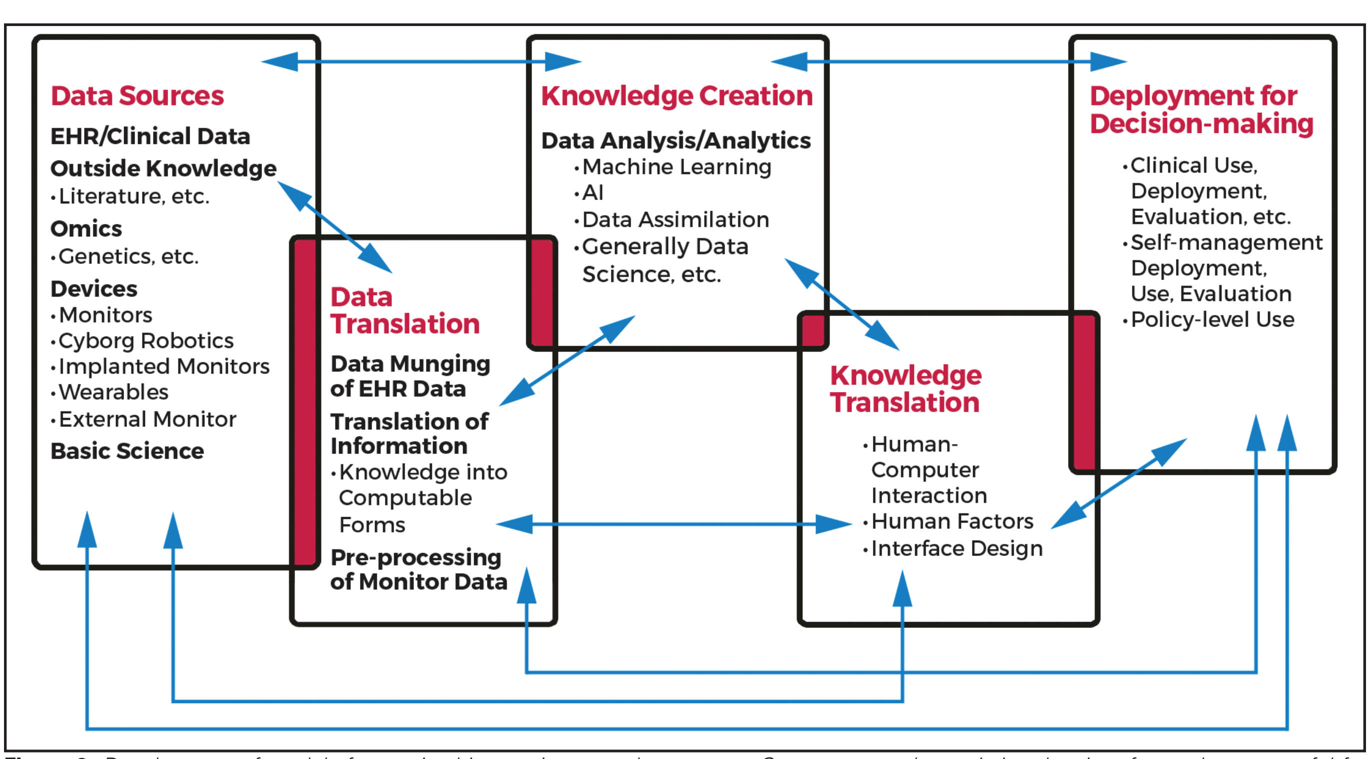


Figure 3. *Development of models for maximal impact is a complex process. One must translate existing data into forms that are useful for constraining the models and inferring model parameters; create new knowledge quickly and accurately based on available data; and transform complex model output into a form that benefits end users. Model development must also involve end users who can detail their explicit decision-making needs and workflow. Bi-directional interactions among these processes can guide the generation of new data, models, and inference approaches. Data courtesy of David Albers.*

David Albers is an informaticist and applied mathematician who develops mathematical machinery to model and understand clinically collected data. He is an associate professor in the Department of Pediatrics, Section of Informatics and Data Science; Department of Biomedical Engineering; and Department of Biostatistics and Informatics at the University of Colorado's Anschutz Medical Campus. Albers is also an adjunct assistant professor in the Department of Biomedical Informatics at Columbia University Medical Center. Cecilia Diniz Behn is an applied mathematician who focuses on nonlinear dynamics in biological systems. She is an associate professor in the Department of Applied Mathematics and Statistics at the Colorado School of Mines. She also holds an appointment as an adjoint assistant professor in the Department of Pediatrics at the University of Colorado School of Medicine. George Hripcsak is a professor of biomedical informatics and chair of the Department of Biomedical Informatics at Columbia University. He is a board-certified internist with degrees in medicine and biostatistics who focuses on nonlinear time series analysis of electronic health record data and causal inference.

Congratulations

to this Year's Major Prize Recipients

While we were not able to celebrate the 2020 prize recipients in person at the Second Joint SIAM/CAIMS Annual Meeting, which took place virtually this July, we extend our congratulations to those members of the SIAM community who were honored with prizes, awards, and special lectures.
Your contributions to the field of applied mathematics are very much appreciated.

John von Neumann Prize

Nick Trefethen *University of Oxford*
Rational Functions

I.E. Block Community Lecture

Erik Demaine *Massachusetts Institute of Technology*
Mathematics Meets Origami

SIAM Prize for Distinguished Service to the Profession

Tony F. Chan *King Abdullah University of Science and Technology (KAUST)*

AWM-SIAM Sonia Kovalevsky Lecture

Bonnie Berger *Massachusetts Institute of Technology*

Richard C. DiPrima Prize

Anna Seigal *University of Oxford*

W. T. and Idalia Reid Prize

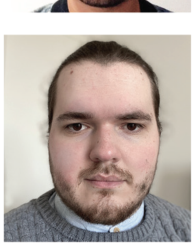
Roland Glowinski *University of Houston*
Investigating Numerically the Exact Boundary Controllability of the Wave Equation: A Historical Perspective

Theodore von Kármán Prize

Kaushik Bhattacharya *California Institute of Technology*
Mathematics, Mechanics and Materials: The Case Study of Liquid Crystal Elastomers

SIAM Student Paper Prize

Vasileios Kalantzis *IBM Research*
Beyond Automated Multilevel Substructuring: Domain Decomposition with Rational Filtering



SIAM Student Paper Prize

Jonas Latz *University of Cambridge*
On the Well-Posedness of Bayesian Inverse Problems

SIAM Student Paper Prize

Elizabeth Qian *Massachusetts Institute of Technology*
Multifidelity Monte Carlo Estimation of Variance and Sensitivity Indices

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All AN20 prize talks, as well as select additional presentations, are available on SIAM's YouTube channel at *https://go.siam.org/g1OjAs*

Exploring the Realities of a Mathematics Career in Industry

By Lina Sorg

Rapid growth and development in the fields of data science, machine learning, and artificial intelligence are shaping the nature of industry-based research. The continued evolution of these areas offers increased employment opportunities for applied mathematicians and computer scientists in business, industry, and government (BIG) settings. A virtual panel discussion at the Second Joint SIAM/CAIMS Annual Meeting,[1] which took place this July, explored the nuances and expectations of work beyond the realm of academia. Panelists consisted of Christiana Manzocco (Analythium.io and Alberta Enterprise Corporation), Nandi Leslie (Raytheon Technologies), Vakhtang Putkaradze (ATCO Ltd.), Sumanth Swaminathan (Vironix Health), and Stefan Wild (Argonne National Laboratory). They engaged in a lively conversation about their varied experiences in industry and offered advice for students and early-career mathematicians in search of BIG employment. The panel, chaired by Kevin Bongiovanni (Raytheon), was followed by an online mixer where attendees could network and engage with the speakers.

Students at both the undergraduate and graduate level often inquire about the coursework and skill sets that make them desirable employees. Putkaradze emphasized that there is no "correct" educational path. "What we're looking for in reality is an agile mind and someone who can learn new things easily," he said. "There's a push for people to learn machine learning and data science. But what we need to understand is that those are tools, not a magic wand for solving every problem." Students should possess a working knowledge of foundational subjects and a deeper, more thorough grasp of technical material—especially in their areas of expertise—that extends beyond the simple use of a formula to solve a problem.

CAREERS IN MATHEMATICAL SCIENCES

While many companies generally try to avoid constraining their hiring prospects based on specific tools, the panelists acknowledged that candidates should be able to quickly familiarize themselves with any necessary programs or languages. Swaminathan also suggested that substantial experience in a language other than MATLAB is valuable, while Wild recommended that all recent graduates be comfortable with version control and use it to maintain their CVs and personal websites.

During an interview, successful applicants demonstrate a clear understanding of the technical area in which they will potentially be working. "It's really critical to feel confident in the company you're going to interview with, and confident in your knowledge of what you're doing," Leslie said. "Really know your own portfolio and how you fit into the company." This level of preparation involves researching a company's vision and objectives beforehand, and catering interview preparation to each specific role.

The panelists agreed that mathematicians, engineers, and physicists are some of the best thinkers in the world, which helps them stand out in a competitive market. "The advantage of having an applied math background is that if you have a flexible and agile mind, you can learn quickly and know all kinds of things," Putkaradze said. "We focus on the depth of studies, but in industry your knowledge cannot be like a delta function and very narrow; it should be more like a pyramid."

Maintaining a wide variety of interests is also beneficial. Swaminathan spoke about his own interdisciplinary interests, which extend beyond the fields of science, technology, engineering, and mathematics (STEM). These passions inspired multiple skill sets that proved useful in the industry sector, though he did not exercise them much as a postdoctoral researcher. As a result, Swaminathan looks for candidates who demonstrate the aptitude for collateral thought and hires critical, hypothesis-oriented thinkers.

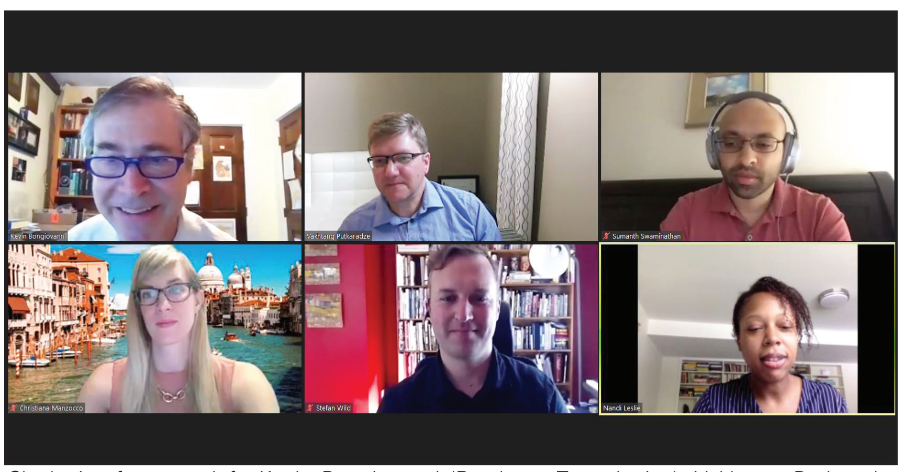
BIG organizations are especially partial to these types of well-rounded candidates because industry mathematicians often work within multidisciplinary teams. "We greatly value the ability to collaborate with diverse colleagues, in terms of background and technical expertise," Wild said. Manzocco, who has a background in management and consulting, echoed this sentiment. She added that collaboration between people with varied proficiencies is often necessary to obtain results. "Most corporations are still completely clueless about how to derive any value from their data," Manzocco said. "It's a big, dirty secret that no one wants to talk about." Because the data is often disorganized and spread between different functional teams and departments, employees with starkly different backgrounds—both inside and outside STEM fields—frequently work together to transform the data and extract business value.

As a strategic advisor at Analythium, Manzocco is involved in many simultaneous projects and spends her days talking to clients, recognizing their problems, and scoping their needs. After identifying and understanding an issue, she brings it back to her team and liaises with software programmers and developers to create a dashboard for the client. Strong communication and problem-solving abilities are thus particularly important in this type of interactive role.

Conversation then turned to the significance of mentorship, which frequently leads to networking prospects and rich

See **Career in Industry** *on page 11*

[1] https://www.siam.org/conferences/cm/conference/an20



Clockwise from top left: Kevin Bongiovanni (Raytheon Tecnologies), Vakhtang Putkaradze (ATCO Ltd.), Sumanth Swaminathan (Vironix Health), Nandi Leslie (Raytheon), Stefan Wild (Argonne National Laboratory), and Christiana Manzocco (Analythium.io and Alberta Enterprise Corporation) participate in a virtual panel discussion about mathematics careers in industry at the Second Joint SIAM/CAIMS Annual Meeting, which took place in July.

Career in Industry

Continued from page 10

collaborations. "I believe mentorship is critical at all stages of your career," Manzocco said. "As a professional, there's an opportunity for you to receive and give mentorship all along that continuum." She reminded attendees that there is always more to learn, regardless of one's experience level. The most effective steps when building a network include getting to know people, asking for and seeking out introductions, and learning about other individuals' work. Manzocco has never once applied for a role through a job board; all of her positions have resulted from networked connections.

Wild mentioned that now is a good time to make some contacts at the national laboratories since most labs currently have available positions. Leslie offered several possible leads for students and postdoctoral researchers. The National Research Council (NRC) and the National Academy of Sciences have openings for students at all levels, and the NRC Research Associateship Programs offer different tiers of funding and periods of performance, depending on one's education level and application strength. Oak Ridge Associated Universities also provides fellowships that place successful applicants at a laboratory where they can find advisors and mentors.

The technical and computational work at these labs—and elsewhere in industry—goes well beyond machine learning and data science. "There's lots of traditional math that you can use in different circumstances," Swaminathan said. "It's not a fully data-science-monopolized industry. In early industrial mathematics, I was doing a lot of work to solve traditional transport problems." Tackling these problems helped to expedite product development.

Leslie has also worked outside the machine learning domain. She has utilized game theory, stochastic processes, and probability theory in recent years, and indicated that industry mathematicians often apply optimization methods and other mathematical approaches that stem from operations research.

The speakers spent the last few moments of the panel discussing the realities of work-life balance, which depends on the nature of the organization in question and the structure of one's job. "My first few roles were really a grind," Manzocco said. "I put in a lot of time and long hours. But as I navigated my career, I was able to carve out positions that were a little better for me." She praised her employers for being fairly flexible with schedules. Swaminathan, who has spent the last five years in start-up culture, is also satisfied with the flexibility he has experienced. He works all the time, but that is solely by choice. "Some of this is on you, some of it is on the company," he said. In many cases, industry positions are much more accommodating than academic appointments.

Ultimately, the panelists encouraged attendees to continually expand their interests, actively seek out opportunities, take initiative, and prioritize experiences and interactions over the rigidity of learned coursework. "The courses you take are probably obsolete by the time you finish the final," Putkaradze said. "Don't take courses or degrees as something that will be the end of your education. They're just the beginning."

In an initiative to strengthen its programming for and ties to industry members, SIAM has planned a workshop to create a strategic five-year plan that will shape its relationship with business, industry, and government laboratories. The SIAM Industry Strategic Workshop is scheduled to take place virtually on October 8 and 12, 2020.

Lina Sorg is the managing editor of SIAM News.

Professional Opportunities and Announcements

Send copy for classified advertisements and announcements to ***marketing@siam.org****. For rates, deadlines, and ad specifications, visit* ***www.siam.org/advertising****.*

*Students (and others) in search of information about careers in the mathematical sciences can click on "Careers" at the SIAM website (****www.siam.org****) or proceed directly to* ***www.siam.org/careers****.*

Teaching Numerical Linear Algebra Online

By Robert van de Geijn and Maggie Myers

The COVID-19 pandemic's sudden arrival forced on-campus classes to go virtual practically overnight. At the time, we were in the midst of the first offering of a graduate-level online course on numerical linear algebra (NLA)—titled "Advanced Linear Algebra for Computing"—for the Master of Computer Science Online (MCSO) program[1] at the University of Texas at Austin. The MCSO program is partnered with edX,[2] a nonprofit that provides massive open online courses (MOOCs). For this course, we created a set of materials that we call "Advanced Linear Algebra: Foundations to Frontiers" (ALAFF);[3] we were also using ALAFF for an on-campus version of the same course and a MOOC on edX. Because we had specifically designed our materials for online learning—building on five years of experience developing three previous MOOCs—we were in better shape than many of our colleagues when all courses transitioned to an online-only format. Here we describe our efforts and their motivations.

One primary advantage of an online course is flexibility. An online format can target learners with different background experiences, learning styles and paces, and overall goals; building course material around this format thus greatly impacts the learning experience. Those who teach graduate-level NLA have likely encountered diverse audiences that include mathematicians, computer scientists, engineers, and domain scientists. NLA therefore benefits from the adaptability of online course material.

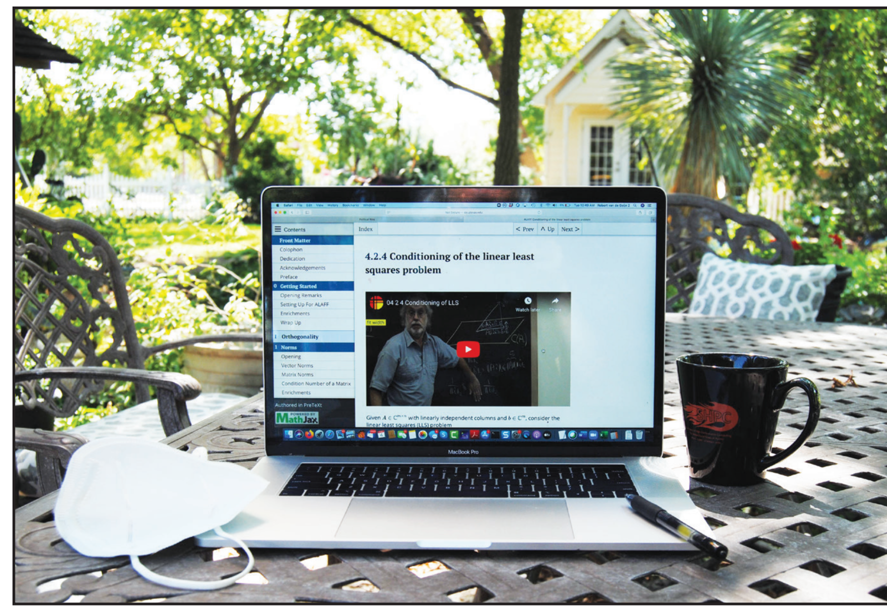
Like a traditional course, an effective online course incorporates lectures, readings, exercises, activities, discussions, and assessments. The benefit of an online format is that we can orchestrate these different components as easy-to-consume chunks that are interleaved to encourage "minds-on" engagement. Students can choose when, how, and in what order they access this content, depending on their learning styles and circumstances. For example, one learner may wish to watch all the videos and then move on to exercises. Another may dive straight into the exercises and consult the videos only when they need the instructor's perspective. This adaptable format puts students in control of their engagement with the material.

Professors can also use scaffolded exercises to guide participants' development of their own knowledge, understanding, skills, and fluency. Releasing new materials on a schedule and setting deadlines for completion encourages progress through the virtual course. Much like in-person classes, the goal of online instruction is to construct an active learning environment wherein an instructor, aided by the materials, guides the discovery of knowledge instead of simply feeding information to the learners.

When deciding how to flexibly provide a rich set of components, materials, and options without overwhelming the learner, the choice of authoring tool is key. We recently discovered the PreTeXt authoring tool,[4] which produces an electronic book as a set of webpages and optionally as a PDF. YouTube videos are embedded in the online version, the PDF includes hyperlinks to these videos, and a paper copy of the PDF provides access with QR codes. The look and feel of the PreTeXt webpages ensure that students are not inundated with too much information at once. A navigation bar provides an overview of the document's contents and organization, and users can remove clutter by exposing or hiding information on demand. For instance, proofs of theorems, hints, answers, and/or (multiple) full solutions for exercises are only exposed upon student request. Additional hyperlinks conveniently direct users to related topics. In other words, the document exploits the richness that webpages afford.

How did we translate this into a virtual NLA course? So as not to overwhelm students, we took the traditional topics of an NLA course and organized them into three parts: orthogonality, linear systems, and the algebraic eigenvalue problem. We introduced orthogonality first—including a treatment of norms, orthogonal spaces, the Singular Value Decomposition, and the solution of linear least squares problems—because it involves prerequisite knowledge for other courses that students often pursue in parallel with (or even before) NLA. Each part comprised four weeks and concluded with an assessment. Every week began with an "opener," which engaged learners in an activity that motivated the week's topic and established learning objectives that provided an *a priori* checklist of topics for mastery. A combination of videos, text, activities, and exercises guided students towards proficiency throughout the week, which ended with a summary of key insights. Prior to each summary, enrichments provided context and linked to recent advances in NLA, including our own research.

[1] https://www.cs.utexas.edu/graduate-program/masters-program/msonline
[2] https://www.edx.org/
[3] https://www.cs.utexas.edu/users/flame/laff/alaff/
[4] https://pretextbook.org/



In the time of COVID-19, masks, and social distancing, many universities are taking their classes online with flexible formats meant to encourage active learning for students. The University of Texas at Austin's graduate-level online course on numerical linear algebra—titled "Advanced Linear Algebra for Computing"—is one such example. Photo courtesy of Robert van de Geijn.

This format seemed to work well for participants. "This class really demonstrates how actually building a course around an online format can make a huge difference in the learning experience," one student said.

We have thus far described ALAFF, a freely available resource that takes the place of a traditional text and can be used independently as such. Students in our on-campus version of the NLA course during the spring of 2020 interacted in the classroom, during office hours, and on Piazza (an online question-and-answer platform) until the course went virtual due to COVID-19. We wanted to maintain a similar level of engagement with the 60+ students who had signed up for the online course. Our team accomplished this by communicating with students via a combination of the edX discussion forum, Canvas (a learning management platform), and Zoom (a popular video conference platform). As primary instructors, we personally answered questions on the discussion forums in a timely manner.

One student identified instructor feedback on assignments and exams, active professor communication and participation in discussions, and excellent organization of course material as the most effective aspects of the online experience. Another spoke highly of the interactive components. "I had concerns regarding the online platform of this program," the student said. "However, I am very impressed by how fast [instructors] respond to questions posted on the discussion board. The active interaction makes me feel like I am not studying alone and I'm not isolated."

We also built homework assignments and assessments that focused on active learning. These included take-home-style exams containing some programming assignments that involved back-and-forth communication with students. Exams and homework feedback were not part of the MOOC experience, which only incorporates self-assessments. One of our learners praised the exam style. "I thought that was the best final I've ever experienced," the student said. "I got hands-on experience implementing an algorithm to finally compute the Singular Value Decomposition, which we had been building towards all semester, and I learned about a cool factorization technique to compute eigenvectors even faster. Getting the chance to ask questions and actually learn from exam problems was a breath of fresh air."

The insights in this article stemmed from our experience creating and running other MOOCs, all of which are offered on edX. We began in 2013, when we were funded by the University of Texas System to create "Linear Algebra: Foundations to Frontiers" (LAFF):[5] a full-semester undergraduate introduction to linear algebra. "LAFF-On Programming for Correctness"[6] is a six-week course that shares our techniques for systematic discovery of families of algorithms for matrix operations, from which one can choose the best (e.g., highest-performing) in context. "LAFF-On Programming for High Performance"[7] is a four-week course that employs matrix-matrix multiplication to illustrate fundamental techniques for high performance on modern central processing units. These courses dovetail with ALAFF. A self-assessment (pretest) of preparedness for ALAFF points those who require a review of basic linear algebra to LAFF content. Some ALAFF enrichments address topics for which the other two MOOCs provide more in-depth study. Thus, our four MOOCs collectively offer a loosely coupled experience.

The ultimate takeaway of these courses is that effective and high-quality online education at the undergraduate and graduate level is certainly feasible. Institutions will likely see more courses of this nature in the coming semesters.

Acknowledgments: Development of the various MOOCs was supported in part by National Science Foundation awards ACI-1148125, ACI-1550493, CCF-1714091, and CSSI-2003921. Additional funding came from the University of Texas System, MathWorks, and a HornRaiser crowdfunding campaign.

Robert van de Geijn and Maggie Myers are faculty members at the University of Texas at Austin and are affiliated with the Department of Computer Science, the Department of Statistics and Data Sciences, and the Oden Institute for Computational Engineering and Sciences. Robert van de Geijn received his Ph.D. in applied mathematics from the University of Maryland and is a leading expert in the areas of high-performance computing, linear algebra libraries, and parallel processing. Maggie Myers holds a Ph.D. in mathematical statistics from the University of Maryland and has extensive experience developing educational materials for K-12, college, and graduate-level courses. Together they publish in the area of formal derivation of algorithms.

[5] http://ulaff.net/
[6] https://www.edx.org/course/laff-on-programming-for-correctness
[7] https://www.edx.org/course/laff-on-programming-for-high-performance

Science Policy

Continued from page 8

Second, I had the opportunity to talk about math and science with Capitol Hill staffers, whose eagerness to chat reinforced my belief that representatives in Washington, D.C., do want to hear from constituents.

As part of the Fellowship, recipients complete a project related to science policy. The projects were as varied as the recipients themselves and ranged from organizing special sessions, writing articles for SIAM, and generating white papers for various organizations. I chose to represent SIAM at the 24th Annual Coalition for National Science Funding (CNSF),[1] which was akin to a science fair for congressional staffers and members to learn about the impact of science funding. I presented a poster about a project at Brigham Young University—funded by the National Science Foundation—to improve undergraduate applied mathematics education. The event was another highlight of my time as a Fellowship recipient, as I had the opportunity to talk about SIAM's mission, applied mathematics education, and my own research with members of Congress and other people who are passionate about science policy in the U.S. Since I was in Washington, D.C., for the CNSF, the Lewis-Burke staffers took me to Capitol Hill where I spent a day advocating for science funding.

Now that my time as a Science Policy Fellowship recipient is over, I am thinking about how I will continue to advocate for science policy in the future. The answer is that I will keep telling stories. I have learned that our senators and representatives care a lot about their constituents' thoughts, and they cannot know what we think unless we tell them. Communication can be as simple as emailing their offices or as complex as inviting them to an event at your university. An important part of science advocacy is also making people aware of the immense benefits of science funding. This is where stories play a huge role. Stories about math and science successes help the average citizen relate to and understand what we do. And when they understand, they also advocate for science. My ask then is this: Will you find an opportunity to share your science success story this month?

Emily J. Evans is an assistant professor and director of the Applied and Computational Mathematics Emphasis program at Brigham Young University.

[1] https://sinews.siam.org/Details-Page/siam-participates-in-annual-cnsf-exhibition