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The Paradox of Malaria: Protection Against Antibiotic Resistance in High-Transmission Areas

By Lakshmi Chandrasekaran

In the early 17th century, two French scientists successfully extracted quinine—a potent medication that is highly effective against malaria [2]—from the bark of the cinchona tree. Since then, physicians and researchers have raced to treat and prevent the disease. Chloroquine, a synthetic alternative of quinine that was produced to counter the drug's scarcity during World War II, quickly became the medication of choice to combat malaria. Despite the prevalence of effective remedies, sub-Saharan Africa remains a malarial hotbed. The malaria parasite's ongoing evolution towards drug resistance is a primary challenge in the fight against the epidemic.

The story of choloroquine resistance is particularly illuminating. Resistance to this drug first developed along the Thai-Cambodian border in the late 1950s [3], but malaria did not appear in Africa until 1978. Over a decade later, choloroquine resistance spread rapidly across the African continent with devastating consequences.

"The same happened with sulfadoxine-pyrimethamine, the next popular treatment for malaria," Silvie Huijben, malaria expert and assistant professor at Arizona State University, said. "Now history appears to repeat itself for the current artemisinin-based drugs." Resistance to these drugs has emerged and spread in Southeast Asia, and it is only a matter of time before it reaches Africa.

Why does a high-transmission setting like Africa experience delayed evolution of drug resistance? Mary Bushman of Emory University investigates this question using a set of mathematical models to track the dynamics of a population of humans, mosquitoes, and the parasites that circulate among them [1]. "We used a 'nested' model to simulate the infection dynamics within each individual host, and a stochastic transmission framework to allow transmission of parasites from humans to mosquitoes and vice versa," Bushman said. A *within-host* model governs the population dynamics of the parasites once they are transmitted from a mosquito to a human.

Within-host and Between-host Dynamics

Parasites in the form of merozoites (an extracellular stage capable of initiating a new developmental cycle) infect red blood cells (RBCs) and grow within them, destroying the cells in the process. The RBC (X) dynamics are modeled as

$$\frac{dX}{dt} = B - \alpha_X X - \beta X(S_1 + S_2), \quad (1)$$

where B is the production rate of new RBCs, α_X is the death rate of uninfected RBCs, and β represents the rate of RBC infection by free merozoites.

The model explores the evolution of drug resistance by detailing the dynamics of RBCs infected with both drug-sensitive (S1) and drug-resistant (S2) parasites. The population of RBCs infected with either form of the parasite is denoted as Y1 or Y2. "Allowing the model to capture sensitive and resistant parasite dynamics in the same host yields realistic interactions that affect transmission as well as processes

See **Malaria** *on page 2*

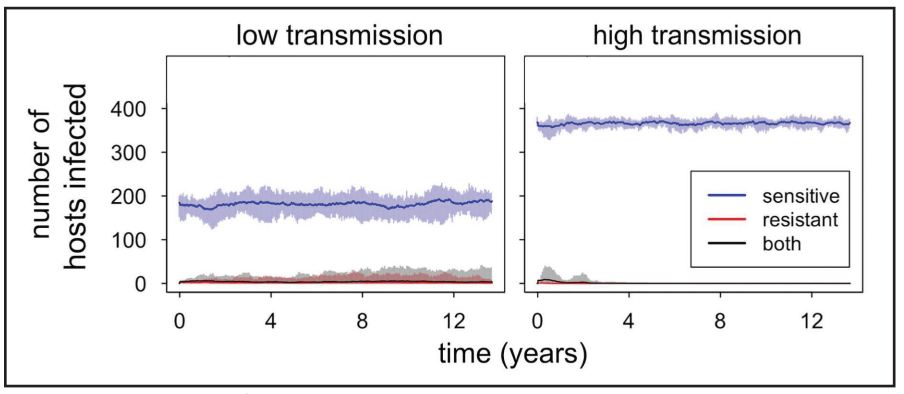

Figure 1. *Introduction of drug-resistant parasites in low-transmission and high-transmission settings (left and right panels respectively) with no antimalarial drug use. Each panel summarizes 10 independent simulations with identical parameters and starting conditions; solid lines indicate mean values and shaded areas depict the range of observed values. The blue, red, and black coloring represents the number of hosts infected with drug-sensitive, drug-resistant, or both types of parasites (mixed infections). Figure courtesy of Mary Bushman.*

New Mathematics for Next-Generation Stent Design

By Sunčica Čanić

Stents are mesh-like tubes that interventional cardiologists use to prop open diseased arteries and restore normal blood flow (see Figure 1a). They were first introduced in the late 1980s to help reduce the rate of restenosis—re-narrowing of coronary arteries—commonly associated with angioplasty procedures employed to treat coronary artery disease. First-generation stents were bare metal stents (BMSs). BMSs are still in use with various improvements, including better construction materials and enhanced topological and geometric features. While BMSs do reduce restenosis rates following coronary angioplasty, they can cause severe intravascular problems—such as damaged endothelium and medial layer stretch leading to smooth muscle cell injury—that often result in complications like in-stent restenosis associated with smooth muscle cell proliferation into the arterial lumen. To further improve restenosis rates, next-generation stents were born in the late 1990s with the introduction of drug-eluting stents (DESs). DESs are coated with a polymer that incorporates an anti-proliferative drug. However, emerging reports in 2006 linked DESs with an increased risk of late-stage stent thrombosis arising from an inflammatory reaction to the polymer-based coating.

While DESs are currently state of the art in stent development, new designs are emerging that would circumvent the use of polymers. For example, Tejal Desai (University of California, San Francisco), is working on *nanoengineered stents* based on drug-free nanotechnology. The surface of such stents is nanoengineered in a way that promotes accelerated restoration of functional endothelium and provides a drug-free approach to keeping stents patent long term [8].

Mathematical modeling and numerical simulations are indispensable tools in guiding optimal stent design [10]. The past two decades have yielded extensive studies on the mechanical properties of stents, biodegradable stents and coating, optimal strategies in anti-inflammatory drug delivery, and stent impact on local and global blood flow and vascular walls. See the works of Paolo Zunino, Francesco Migliavacca, Joao S. Soares, Kumbakonam Rajagopal, Wei Wu, Dario Gastaldi, James E. Moore, Lucas H. Timmins, Alison Marsden, Sean McGinty, Christopher McCormick, Dimitrios Kiousis, Christian Gasser, and Gerhard A. Holzapfel, to name a few.

As models became more sophisticated, deeper mathematical questions had to be addressed to continue advancing the field. This spurred the development of new mathematics in the area of fluid-structure interaction (FSI) involving elastic, viscoelastic, poroelastic, and mesh-like structures to capture the interaction between time-dependent blood flow and stented vascular tissue.

Our group has been working on modeling, mathematical analysis, and computations of FSI between blood flow and vascular walls treated with stents. While the creation of computational methods for biological FSI has been an active research area for the past 40 years (see, for example, the works of Charles Peskin, Jean-Frédéric Gerbeau, Boyce E. Griffith et al., Alfio Quarteroni et al., Thomas J.R. Hughes et al., Yuri Bazilevs et al., and Shawn C. Shadden et al.,) the *mathematical analysis* of solutions for this class of problems is still under development.

The problem consists of coupling the Navier-Stokes equations for an incompressible, viscous fluid that model blood flow to a system of partial differential equations (PDEs) modeling the elastodynamics of an elastic structure. Equations of linearly and nonlinearly elastic membranes or shells

See **Stent Design** *on page 3*

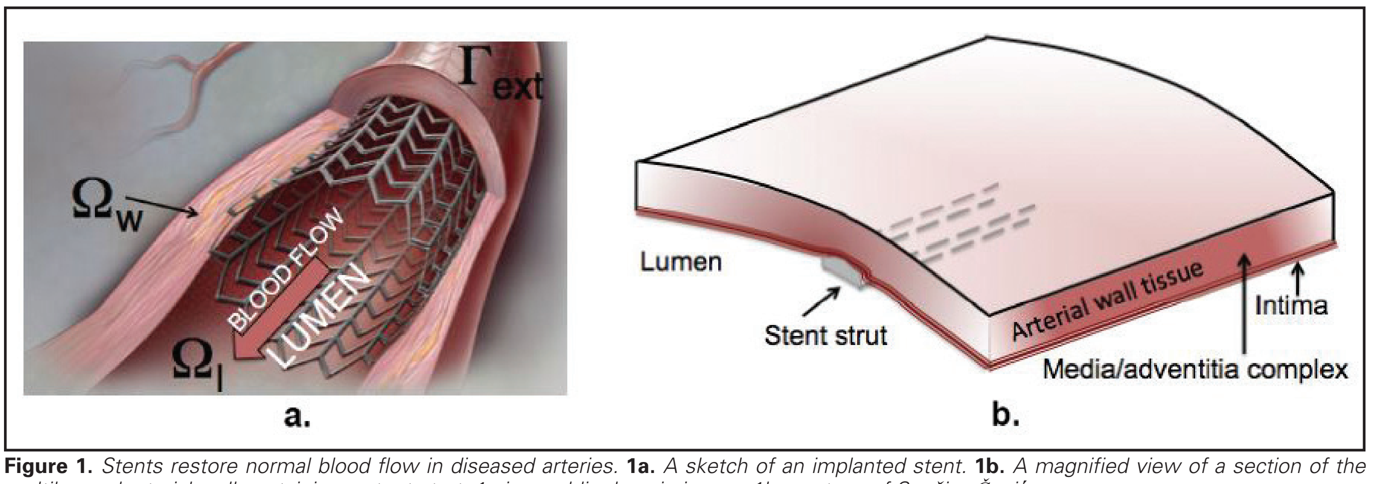

Figure 1. *Stents restore normal blood flow in diseased arteries.* **1a.** *A sketch of an implanted stent.* **1b.** *A magnified view of a section of the multilayered arterial wall containing a stent strut. 1a is a public domain image, 1b courtesy of Sunčica Čanić.*

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Malaria

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occurring at the epidemiological level," Bushman said.

In the following equations, subscripts i and j denote the type-specific variables and parameters, i.e., $(i,j)=(1,2)$ or $(2,1)$. An infected RBC of type i is modeled as

$$\frac{dY_i}{dt}=\beta XS_i-\frac{1}{1-e_i}\alpha_Y Y_i-\gamma Y_i \\ -\delta_Z ZY_i-\delta_I(I_i+\omega_j I_j)Y_i. \quad (2)$$

The rate of merozoite (S_i)-infected RBCs is countered by the death rate (α_Y) of infected RBCs and is further facilitated by the drug treatment ($e_i=0$ in the absence of antimalarial drugs and $e_i=\varepsilon_i$ when the drug is present; ε_i represents the drug's efficacy against type i). To account for the role of the body's defense mechanism, Bushman models parasite-immune system interactions with elimination by both innate (Z) and adaptive immunity (I_i, I_j).

Innate immunity acts in a strain-independent manner that is critical to controlling parasitic growth during the acute phase of infection. On the other hand, adaptive (acquired) immunity is parasite-specific and required for infection clearance. Parasites trigger both immune responses, which decay in their absence. However, innate immunity turns on and off at a much higher rate than adaptive immunity, which takes longer to develop and decay.

Antigenic variation—a strategy that parasites have developed to "beat" acquired immunity—further complicates adaptive immunity dynamics by preventing the body's adaptive immune response from recognizing parasites; this helps the latter survive. "We were the first group to model immunity in a quasi-mechanistic way that displays the right dynamics while still being tractable," Bushman noted. "Past models that included immunity sort of ignored the within-host dynamics and assumed that one returns from infected to uninfected or recovered states independently of whatever is happening within the host." But that does not occur biologically for any pathogen.

The infected RBCs produce more merozoites that can in turn infect new RBCs. The dynamics of free merozoites (S) of type i are modeled as a combination of fitness costs (φ_i) associated with drug resistance, natural merozoite death (death rate α_S), and killing by innate (Z) and adaptive immunity (I_i, I_j):

$$\frac{dS_i}{dt}=R\alpha_Y(1-\varphi_i)Y_i-\alpha_S S_i \\ -\beta XS_i-\delta_Z ZS_i-\delta_I(I_i+w_j I_j)S_i. \quad (3)$$

To continue the next phase of the parasite's life cycle in the mosquito, some infected RBCs give rise to gametocytes (cells that divide to form gametes capable of sexual reproduction) rather than merozoites. Since these are produced in very low amounts, they are unlikely to elicit an adaptive immune response.

The following equation describes gametocyte dynamics:

$$\frac{dG_i}{dt}=\gamma Y_i-\alpha_G G_i-\delta_Z ZG_i, \quad (4)$$

with γ signifying birth rate. The remaining terms collectively represent gametocyte elimination, with α_G (denoting natural death rate) and the last term representing killing by innate immunity.

The between-host model describes the feedback loop of human-to-mosquito interaction, which is modeled via stochastic principles, i.e., each human host is bitten by an assigned number of mosquitoes in a given day, drawn from a Poisson distribution with a specific mean.

Evolution of Drug-resistant Parasites in the Presence of Anti-malarial Drugs

Bushman and her colleagues first tested the model's behavior in the absence of anti-malarial drugs. "We wanted to determine what would happen if you have a population of completely drug-sensitive parasites and just throw a handful of drug-resistant infections in there without any drugs," she said. As Figure 1 (on page 1) indicates, the resistant parasites—identified by the red curve—persisted in low-frequency, low-transmission settings for several years. In contrast, the resistant strains died down pretty quickly in high-transmission scenarios.

What happens when the drug is introduced? As in the previous case, Figure 2 demonstrates that the drug-resistant strain persists in the low-transmission setting. However, the resistant strain does not die out in the high-transmission situation, but rather establishes itself over time and actually spreads faster than in low-transmission circumstances. How does this happen?

Bushman reasons that a high-transmission setting presents a challenging environment for the resistant parasite's survival, as most hosts harbor the drug-sensitive parasite; the resistant one thus falls victim to within-host competition. This complicates a resistant strain's effort to establish itself in a high-transmission setting.

Bushman compares the high and low transmission settings to an overcrowded versus sparse garden. "If you plant some seeds or resistant strains in a crowded garden already teeming with different kinds of plants, most of the new seeds won't take root due to lack of space," she said. "But if the garden is sensitive to a herbicide and you throw in a herbicide-resistant flower, the latter would fill up the entire garden as the herbicide would have killed everything else." This analogy explains why a resistant parasite spreads quickly after overcoming the initial barrier and establishing itself. Drug treatments in high-transmission areas paradoxically lead to the establishment and spread of drug resistance.

These findings emphasize the fundamental differences regarding the evolution of drug resistance in various settings. Bushman's model explains both the delayed appearance of chloroquine resistance in Africa *and* its rapid spread upon emergence. "It has not previously been recognized that the high prevalence of infection might, in itself, provide a sort of protection against the evolution of drug resistance," she observed.

The results from Bushman's study will be instructive for policymakers and healthcare professionals who are planning or implementing malaria control measures, particularly in high-transmission settings. "One of the most important deductions from this work is that intense malaria control and eradication activities aimed at reducing transmission could lead to a higher risk of antimalarial resistance evolution in sub-Saharan Africa," Huijben said.

Bushman concluded with her own caveat to this sentiment. "[This is not to say that] we shouldn't aim to reduce malaria burden," she said. "But we should be mindful of the opportunity such reductions provide for drug resistances to emerge, and plan accordingly."

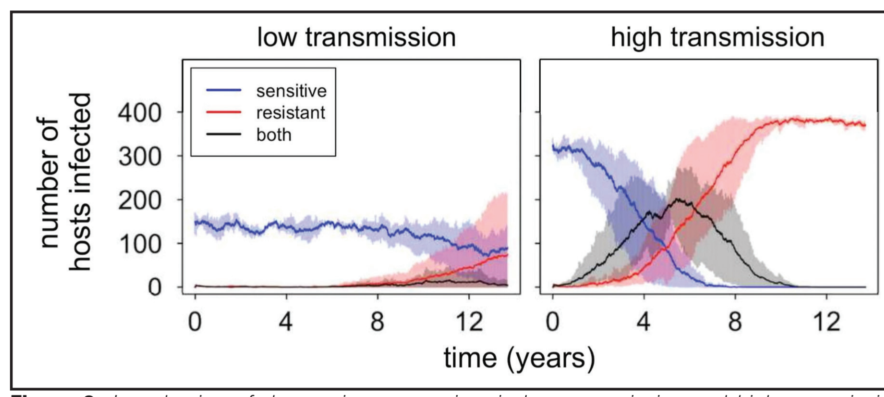

Figure 2. *Introduction of drug-resistant parasites in low-transmission and high-transmission settings (left and right panels respectively) with ongoing antimalarial drug use. Each panel summarizes three independent simulations with identical parameters and starting conditions; solid lines indicate mean values and shaded areas depict the range of observed values. The blue, red, and black coloring represents the number of hosts infected with drug-sensitive, drug-resistant, or both types of parasites (mixed infections). Figure courtesy of Mary Bushman.*

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Lakshmi Chandrasekaran received her Ph.D. in mathematical sciences from the New Jersey Institute of Technology. She earned her masters in science journalism from Northwestern University and is a freelance science writer whose work has appeared in several outlets. She can be reached on Twitter at @science_eye.

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Stent Design

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have been used to model the thin intimal layer, while equations of finite elasticity assuming linear or certain nonlinear hyperelastic models have been used to model the thick media/adventitia layer.

Researchers have proposed several approaches for modeling stents, mostly based on three-dimensional (3D) approximations. However, such approximations are computationally expensive because stent components (stent struts) are slender bodies (see Figure 2). In 2010, we developed a reduced, *one-dimensional (1D) stent net* model in collaboration with Josip Tabača [9]. Our model uses a network of Antman-Cosserat 1D curved rods [4], which approximates the full 3D model with high accuracy and provides significant computational savings. *The resulting stent net model is a system of 1D hyperbolic balance laws defined on a graph domain* [5]. Coupling this model to arterial walls and fluid flow is very challenging from a mathematical standpoint since it involves coupling PDEs of different dimensions [5]. Analysis of these problems is currently an active research area (see the works of Tabača, Zunino, Kent-Andre Mardal, Jan M. Nordbotten, and Marie E. Rognes).

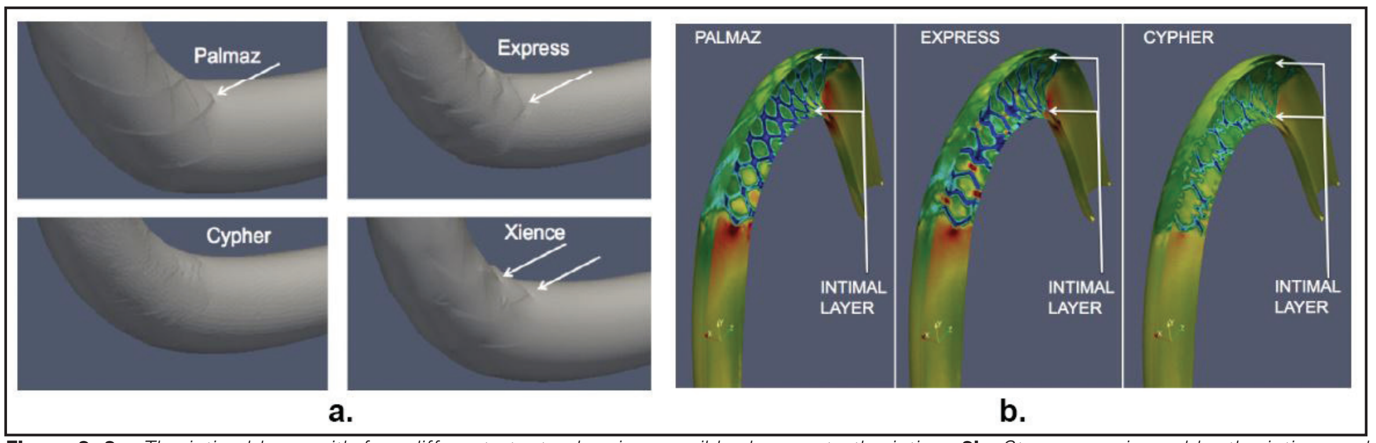

Figure 3. 3a. *The intimal layer with four different stents showing possible damage to the intima.* **3b.** *Stress experienced by the intima; red designates excessive elastic deformation and blue represents resistance to deformation. The colors indicate deviation from normal stress values (green). Cypher-like stents have the best performance. Figure courtesy of Sunčica Čanić research group.*

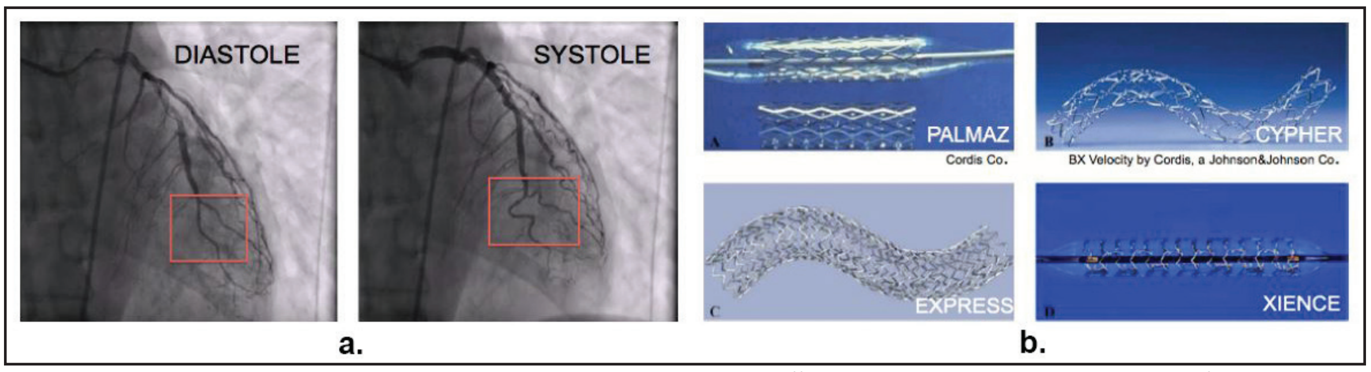

Figure 2. 2a. *A patient's angiogram showing a curved coronary artery.* **2b.** *Four different stents analyzed in [3]. 2a courtesy of David Paniagua, 2b courtesy of Boston Scientific and Abbott Vascular.*

In collaboration with medical specialists David Paniagua and David Fish of the Texas Heart Institute, we used our model to suggest optimal design of a stent for transcatheter aortic valve replacement (U.S. patent US9125739 B2) that is currently utilized in medical interventions involving Colibri Heart Valve.

The coupled FSI problem is difficult to study. In addition to nonlinearity in the fluid equations (and possibly the structure models), coupling across the deformed fluid-structure interface gives rise to a strong geometric nonlinearity. This is because fluid and structure have comparable densities in biological problems, and their interaction results in significant energy exchange. The structure's motion is substantially affected by the fluid mass it displaces as it moves, since both fluid and structure are "equally heavy." This is known as the added mass effect. Energy imbalance and stability issues arise when the added mass effect is not factored into the design of numerical schemes and in the mathematical analysis of the problem, as it keeps the frequency of structure oscillations under control.

Mathematical analysis of solutions to the coupled fluid-stent-artery interaction problem has practical relevance. It provides detailed understanding of how the energy of the problem depends on the parameters in the problem, it gives insight into possible singularities that may be associated with tissue damage (see Figure 3a), and it offers information about wave reflections due to the presence of stents, which have been known to increase the overall blood pressure and workload on the heart. Moreover, constructive existence proofs can motivate the design of a computational scheme for solving the underlying FSI problem. In a series of manuscripts with Boris Muha over the last five years, we have developed constructive existence proofs to study a class of nonlinear, moving boundary problems involving blood flow and various structures used in modeling vascular walls with and without a stent [1, 6]. The proofs are based on semi-discretization of the coupled problem in time and use of an operator splitting strategy to separate the fluid (parabolic) and structure (hyperbolic) subproblems. This approach defines a sequence of approximate solutions whose subsequences converge to a weak solution of the coupled problem as the time-discretization step goes to zero. As the problem is nonlinear, a compactness argument must be used to allow passing to the limit in nonlinear terms. However, classical compactness results cannot be directly applied since approximate problems are defined on different (fluid) domains that move in time. This led us to develop a generalization of the Aubin-Lions-Simon compactness lemma for problems on moving domains [7]. Our result explained that the reason the semi-discretized approximations converge to a weak solution is the regularization by fluid viscosity, which is transferred to the vascular wall via the no-slip condition. Namely, the oscillations in the structure (vascular wall) "feel" the fluid viscous damping through an operator similar to the square root of the negative Laplacian—obtained via the Dirichlet-Neumann operator—which acts on the structure velocity and keeps the amplitude of structure oscillations under control.

The algorithm developed in the constructive existence proof served as a foundation for a class of partitioned, loosely-coupled numerical schemes (devised with Martina Bukač and Roland Glowinski [2]). We successfully used these schemes to study various questions related to the performance of stents inserted in curved coronary arteries and moving with the heart's contractions. Our numerical simulations with Yifan Wang [3] revealed that the Cypher-like stent outperforms the Palmaz-like, Xience-like, and Express-like stents based on injury to the intimal layer and tissue distortion in the media layer measured by von Mises stress (see Figure 3). Additionally, we found that open-cell design—with every other horizontal stent strut missing—and stents with sinusoidal horizontal struts have significantly less overall bending rigidity while maintaining the radial stiffness necessary to keep arteries open. These traits are preferred for curved coronary arteries.

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Sunčica Čanić is a professor in the Department of Mathematics at the University of California, Berkeley. She has been recognized for her contributions to the modeling and analysis of partial differential equations motivated by applications in the life sciences.

Mid-Career Panel at CSE19 Guides Attendees through Academic and Industrial Crossroads

By Lina Sorg

CAREERS IN MATHEMATICAL SCIENCES

A professional's career path follows various stages throughout the course of employment, each of which presents novel challenges and opportunities for further growth. Although occupation-related guidance often emphasizes early-career decision-making, a mathematician's mid-career is an equally exciting time wrought with choices that define future direction and shape community involvement. During an inaugural panel discussion at the 2019 SIAM Conference on Computational Science and Engineering (CSE19), which took place earlier this year in Spokane, Wash., Misha E. Kilmer (Tufts University), Sven Leyffer (Argonne National Laboratory), and Lois Curfman McInnes (Argonne National Laboratory) spoke candidly about personal and professional difficulties and successes that emerge at the midpoint of one's career.

"Moving to your mid-career is an exciting time because you can define your research agenda and set and solve your own puzzles," Leyffer said. Upon joining Argonne's Mathematics and Computer Science Division in 2002, he began working on problems with mentees and postdoctoral students. This both yielded new perspective and emphasized the value and necessity of teamwork. "You need people to work for you," Leyffer continued, adding that he is currently writing a nonlinear optimization solver with a postdoctoral researcher simply because he did not have time to tackle it alone.

As one advances on his/her career trajectory, time management becomes increasingly crucial. Offers for volunteer work, involvement in conference committees, and editorial positions increase exponentially at the mid-career level and can quickly become overwhelming, especially when balanced with mentoring obligations. All three panelists encouraged attendees to reevaluate and define their time management tactics, and stressed the importance of saying "no" to unrealistic requests or service-related ventures that might ultimately affect one's career goals — say, for example, full professorship in academia. Kilmer once refused a flattering offer to sit on a prestigious journal board because she was struggling to juggle her existing tasks. Leyffer also declined a position on a new journal because he knew he would not do it justice.

Pressures within one's immediate institution are often just as demanding. Kilmer admitted that she was lucky to walk right into an assistant professorship at Tufts, given her minimal teaching experience at the time. After being promoted directly to full professor, she agreed to temporarily serve as chair of the Department of Mathematics during a colleague's year-long leave of absence — and unexpectedly held the post for six years. The appointment came with additional responsibilities and persistent recruitment by headhunters seeking to fill open dean positions at numerous other schools, which was not in line with her goals. As her stint as chair comes to a close, Kilmer is looking forward to taking a break from administration and focusing on other projects. "One of the things I really missed was teaching more, mentoring more, and spending more time with students," she said. "It really fragmented my time."

Of course, some level of increased commitment is necessary for professional growth, and transition to the mid-career level yields opportunities for balanced participation in new activities, collaborations, and societies. Such actions could include serving on a SIAM committee or volunteering with an activity group, and McInnes recalled the thrill of organizing her first minisymposium at a SIAM conference. "CSE is inherently very collaborative," she said. "You have to figure out what brings you passion and enjoyment." For example, McInnes found that she really enjoys collaborative projects. While she has been with Argonne since she was a postdoctoral student, her role has expanded to include ample collaboration across teams and organizations as well as escalating leadership roles in projects, institutes, and the broader community. Yet every duty comes with a tradeoff; in focusing on project-oriented tasks, McInnes has deliberately minimized her involvement in technical assignments.

Kilmer noted that the mid-career stage correlates well with transition to a new institution. "The period before you become senior is a good time to think about doing something like that," she said. However, she clarified that switching institutes is not an inconsequential decision, and conceded that an offer would have to be compelling for her to think seriously about moving — especially because a move would also uproot her husband, two children, and dog. "The grass is always greener on the other side," Kilmer said. "You need to think about what you want to accomplish in the next five to 10 years, and whether a new position would get you there faster than where you are."

There are certainly other incentives to move. While Leyffer thoroughly enjoys working at a national laboratory, he misses teaching and looks for supplemental teaching opportunities to fill that void. "I really love teaching," he said. "I teach summer schools whenever I can. Interacting with students—not just telling people what to do but learning how to explain things well—is so rewarding." He would thus consider switching institutions for a promising teaching opportunity. "For me, moving is something I would do if I feel that there's something I could really be excited about," he added.

Multiple panel attendees voiced concerns about maintaining work-life balance beyond the early-career level. McInnes confessed that she sometimes struggles with balancing professional and familial commitments. "At different points in life I've had a better or worse handling on this balance," she said, revealing that she has turned down auspicious work travel prospects in favor of time with her two daughters. Leyffer suggested that researchers take no more than one trip per month to maintain a semblance of stability in their lives. And Kilmer never schedules early meetings; she has a lengthy commute to work but does not want to put her kids in early-morning daycare.

Sometimes balance means sacrifice. When an audience member questioned whether the panelists regretted passing up any specific endeavors, they concurred that any sense of disappointment or second-

See **Mid-Career Panel** *on page 5*

Making Progress towards Gender Parity and Increased Diversity

By Ute Eberle, Falk Hante, Frauke Liers, and Michael Stingl

The fact that *something* must be done to narrow the gender gap and achieve more diversity in male-dominated disciplines (like mathematics) is undisputed. For example, women in the U.S. hold only 14 percent of full-time tenured positions in academic doctoral math departments [1].

The question of *how* to achieve gender parity poses more of a challenge. Many previous attempts—like special awards for women—are decried as tokenism; while they may benefit the individual, they seem unlikely to induce sustained and systemic change. Given this mindset, our research team decided to take a slightly different approach — with promising results.

Our project—the German Collaborative Research Center (CRC) 154[1]—develops mathematical solutions in the fields of modeling, simulation, and optimization, using gas networks as an example. Multiple companies in the newly-deregulated European market must cooperate to adapt gas supply and transport to ever-changing demand. Adjusting gas flow in the network of pipelines to safely and quickly deliver energy requires complex optimization- and simulation-based tasks with thousands of variables, including pressure changes, valve operations, compressor workload, and hub management. All of this must be completed in a dynamic and robust fashion while accounting for both market forces and uncertainties.

Within the CRC, teams at four universities—Friedrich-Alexander-Universität Erlangen-Nürnberg (home of CRC spokesperson Alexander Martin), the Technische Universität Berlin, the Humboldt-Universität zu Berlin, and the Technische Universität Darmstadt—in three German cities are cooperating to develop the necessary mathematical theory and algorithms. As is typical in such situations, nearly all of the project's first hires were male. While this may have been coincidental and illustrative of small-number statistics, it also reflects a bigger issue. In Germany, mathematics and the natural sciences are now attracting equal numbers of male and female undergraduate students, and many women go on to finish graduate school. However, the numbers plummet when it comes to careers in academia. Only one in five tenured professors in the sciences is a woman [2]. It is widely acknowledged that the uncertainty of succeeding in an academic career contributes to this disparity, particularly since tenure is typically acquired relatively late in the German system.

CRC 154 is funded by the German Research Foundation with the understanding that part of the budget will go towards promoting gender equality and diversity. From the beginning, we considered this as much an opportunity as a challenge and focused on developing tailored strategies to make progress throughout the project's duration. We established gender teams, each with a female and male principal investigator at all three project sites who played critical roles in determining measures to advance gender parity.

Raising awareness became a special focus, as many people do not grasp the challenges that male and female researchers face to grow beyond traditional gender roles. To address this difficulty, we incorporated *obligatory* workshops into research meetings. One of these workshops explored the different communication styles of men and women and offered solutions on how to avoid (and resolve) conflicts that arise from this discrepancy. Although the mandatory nature of these workshops elicited some groans, we feel that the effort helped to at least increase people's awareness of the problem.

We also participated in high school programs that encourage young women to consider science-based careers. We established a summer school for female students in the fields of mathematics and informatics that promoted interdisciplinary networking and introduced them to project-specific modeling methods. An existing budget, which includes research grants for up to one year for prospective doctoral candidates,[2] helps women pursue scientific collaborations abroad and improve career-enhancing soft skills in management and leadership. Additionally, we recently implemented steps to ensure that job postings are gender inclusive and promote diversity.

Another set of measures aims to make family and work life more compatible. These include practical steps, such as guaranteed access to local childcare facilities and "mobile parent-kid-stations"—wheeled cupboards equipped with toys, diaper changing supplies, and everything else a parent might need to keep a small child happy for a few hours at the workplace in case of a childcare emergency—at every project site. We also recorded a selection of conference presentations for project members unable to attend sessions in person.

Financial support is available for project members who need to hire babysitters during out-of-town meetings or at times when regular childcare facilities might be inaccessible. For example, one colleague participated in a weekly project-related teleconference on late Friday afternoons when the local daycare was closed. CRC 154 provided a budget that helped offset the cost of babysitting services during those times.

Our overall goal is to achieve an equal representation of female and male researchers at all levels. We often find that the names of male researchers are first to spring to mind when putting together a high-caliber board or workshop program. It may take more time and sometimes require creativity to identify outstanding female candidates, but of course it can be done.

This premise is borne out by our own project. The aforementioned measures—as well as some very active headhunting in the recruitment stages—are making a noticeable difference. During the project's initial four-year phase, we increased the ratio of female team members to 24 percent within the group of doctoral candidates and 33 percent at the postdoctoral level. The number of female professors involved in CRC 154 has risen from 17 to 21 percent in the beginning states of the project's second phase. These statistics compare favorably with the German national average in mathematics.

Participants of a mathematics and informatics summer school for female students established by the German Collaborative Research Center. The school promoted interdisciplinary networking and introduced students to project-specific modeling methods. Photo courtesy of Petra Metz.

The biggest lesson we have learned from our experience thus far is that it is essential to grant teams some autonomy and flexibility when it comes to effectively boosting gender equality and diversity. For example, most institutional budgets simply do not include provisions to allocate travel money for family members who might accompany young researchers to out-of-town conferences and provide reliable childcare. But this is the kind of financial investment that can make a very big difference in either allowing a junior scientist to fully participate and build a career in her chosen area, or forcing her to abandon the field.

CRC 154 is scheduled to run for another three to seven years. By the end of that time we hope to have made continued and long-lasting strides towards our goal of full gender parity.

Acknowledgments: We are very grateful to members of German Collaborative Research Center (CRC) 154's former and current gender team for their fruitful joint work and many inspiring discussions on establishing gender equity in the CRC and beyond. Many thanks go to Pia Domschke, Herbert Egger, Veronika Grimm, René Henrion, Max Klimm, Alexandra Schwartz, and Caren Tischendorf for their invested time, energy, and thoughts.

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Ute Eberle is a German freelance writer focusing on science, medicine, socio-political topics, and travel. She currently resides in Baltimore, Maryland. Falk Hante, Frauke Liers, and Michael Stingl are affiliated with the Department of Mathematics at Friedrich-Alexander-Universität Erlangen-Nürnberg, principle investigators in CRC 154, and members of former or current gender teams within this project.

[1] https://www.trr154.fau.de

[2] https://trr154.fau.de/index.php/en/scholarships

Mid-Career Panel

Continued from page 4

guessing nearly always fades with time. "I try to think that opportunities keep coming around," Leyffer said. "If you turn down an opportunity to be an editor on a journal, that's OK because somebody will ask you again later. And if they don't, that's OK too." Kilmer echoed this sentiment and stated that while she's excited to relinquish her position as chair, she certainly does not regret accepting the post.

Panelists underscored the importance of maintaining strong networks with friends from conferences and other circles for support and consultation. Kilmer values the friendships she established at the junior level with colleagues who act as her current sounding boards. "I would encourage you to keep building your network as you go forward," she said. "Take advantage of people who are willing to give free and hopefully-useful nuggets of wisdom." She added that she has never lacked mentorship in the Department of Mathematics at Tufts, regularly consults her predecessors, and has fellow coworkers review sensitive emails before she sends them.

McInnes specifically acknowledged the guidance of both peers and senior colleagues who have recommended her for multiple opportunities over the years. As a result, she makes it a point to pay that kindness forward. Kilmer reiterated this mindset and reminded researchers moving towards senior positions to seek out opportunities to promote junior colleagues.

Ultimately, the panelists encouraged attendees to regularly assess both their short- and long-term goals and aspirations, as the mid-career level is a good point at which to make significant professional changes and take on added responsibilities. "The challenge I try to seek for myself at each phase of my career is to think deeply about what matters to me," McInnes said. "I believe that it's essential to periodically reevaluate your own goals. Each of us has many more opportunities coming our way than time in a day. I'm not saying I always succeed with this, but I try."

Lina Sorg is the associate editor of SIAM News.

A mid-career panel discussion at the 2019 SIAM Conference on Computational Science and Engineering, which took place earlier this year in Spokane, Wash., addressed pressures and opportunities that manifest at the midpoint of one's career. From left: panel moderator Katherine J. Evans (Oak Ridge National Laboratory), Lois Curfman McInnes (Argonne National Laboratory), Misha E. Kilmer (Tufts University), and Sven Leyffer (Argonne National Laboratory). SIAM photo.

Getting Focused

A glass cylinder—essentially a thick, flat lens—is neither focusing nor defocusing in the sense that entering parallel beams remain parallel as they pass through, width unchanged.[1]

Let us now cut this slab and open the gaps a bit to obtain a series of lenses (see Figure 1). The alternating focusing and defocusing effects should presumably cancel out, just as they did before we spread the lenses apart. Interestingly, this presumption is wrong; instead, *the gaps turn the neutral slab into a focusing device*. For some mysterious reason, focusing always "wins" over defocusing.

Why Does Focusing Win: a Variational Explanation

It suffices to show that the lens is "optically thicker" between points A and B than between A_1 and B_1, just as a magnifying glass is thicker in the middle than near the edge:

$$T_{A_1B_1} < T_{AB}, \qquad (1)$$

where T is the light's travel time between two points.

To justify (1), it suffices to produce a path between A_1 and B_1 that would take less time than path AB (this path need not be the actual path of light). Figure 1 depicts such a path. Starting with straight line A_1B_1—whose optical length is the same as that of AB—we move the segments passing through the lenses towards the thinner direction of each lens, thus shortening the path's "expensive" part in which the light travels more slowly (we assume that the light travels much slower in the glass). Provided this displacement is not too far, the time savings in the glass will exceed the time gain in the air and the new path will indeed be shorter. In fact, the light's true path will zigzag roughly as shown (with an additional gentle bend away from the axis), according to Snell's law.

MATHEMATICAL CURIOSITIES
By Mark Levi

[1] In contrast, any optical device that narrows parallel beams is automatically a telescope; it magnifies objects regardless of its internal workings. This is a consequence of the symplectic nature of geometrical optics. More details are available in [1].

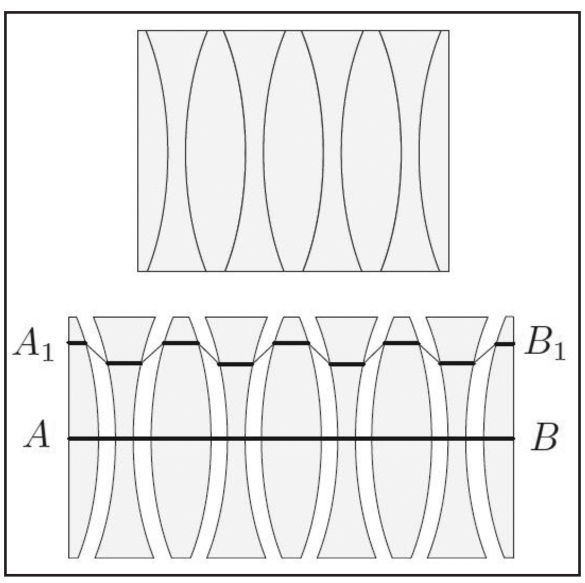

Figure 1. *Separation causes focusing. The optical length of the path A_1B_1 (not a true ray) is shorter than that of AB.*

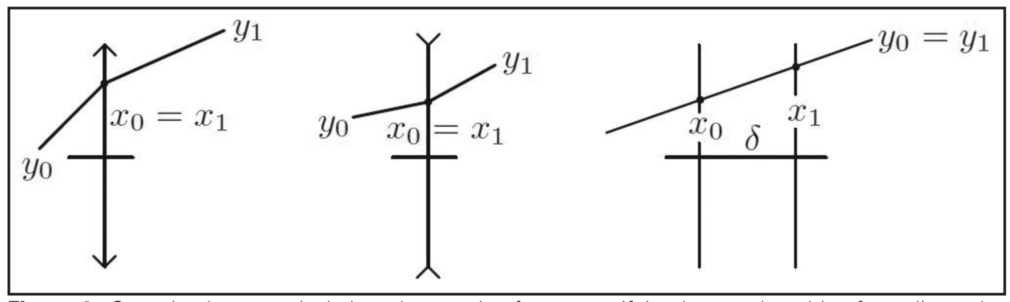

Figure 2. *Gaussian lens: vertical shear is negative for a magnifying lens and positive for a dispersing one. A gap of width δ represents the horizontal shear of strength δ.*

An Alternative Explanation

Unlike in the previous discussion, we now assume that the lenses are negligibly thin and the break in the ray's slope is linearly proportional to the distance from the optical axis to the point of passage through the lens. In other words, our lenses are Gaussian. When superimposed, the two such lenses cancel out exactly as if they were not there at all. To see why focusing wins upon separation, we convert the problem into a question about matrices.

A ray that enters or exits the lens is described by the pair (x, y), where x is the distance from the point of crossing the lens to the axis and y is the ray's slope (see Figure 2). By the definition of the Gaussian lens, its "transition map"—i.e., assignment of the exit data to the entrance data—is

$$\begin{cases} x_1 = x_0 \\ y_1 = y_0 \pm s x_0 \end{cases} \quad \text{or} \quad z_1 = \begin{pmatrix} 1 & 0 \\ \pm s & 1 \end{pmatrix} z_0 = V_{\pm} z_0. \qquad (2)$$

The sign $\pm$ corresponds to defocusing/focusing lenses and the coefficient s has a nice physical meaning: it is the reciprocal of the lens' focal length[2] f, $s = 1/f$. Indeed, an incoming ray parallel to the axis (see Figure 3) refracts and passes through the focus (by definition of the latter). On the other hand, $f = x_1 / y_1$ ("run=rise/slope"); but setting $y_0 = 0$ in (2) yields $x_1 / y_1 = 1/s$, so that $f = 1/s$ as claimed. The transition map $(x_0, y_0) \mapsto (x_1, y_1)$ is given for the gap of width δ—according to Figure 2—by

$$\begin{cases} x_1 = x_0 + \delta y_0 \\ y_1 = y_0 \end{cases} \quad \text{or} \quad z_1 = \begin{pmatrix} 1 & \delta \\ 0 & 1 \end{pmatrix} z_0 = H z_0. \qquad (3)$$

In summary, *a Gaussian lens with focal length f corresponds to the vertical shear of strength $s = 1/f$* with the shear's sign dependent on the lens' status as defocusing or focusing. The empty gap of width δ corresponds with the horizontal shear of strength δ.

[2] Normally f is taken to be negative for defocusing lenses, but we do not do this here.

Let us now consider the sequence "Focusing→Gap→Defocusing→Gap." This combination of lenses corresponds to the product (read from left to right)

$$M = HV_+HV_-,$$

assigning the outgoing data to the incoming data. Multiplication shows that

$$\operatorname{tr} M = 2 - (s\delta)^2 < 2. \qquad (4)$$

If we also assume that $\delta < 2f$—the gap is less than twice the focal lengths—then $|\operatorname{tr} M| < 2$. Together with $\det M = 1$, this implies that M is an elliptic rotation; and *this* implies that the combination of lenses F-G-D-G is a focusing device.

It is interesting that we arrived at essentially the same result via two arguments that are so different from one another: the variational one in Figure 1 and the matrix argument. This shows that the purely algebraic result (4) on matrix multiplication is not actually purely algebraic and instead has an alternative variational explanation.

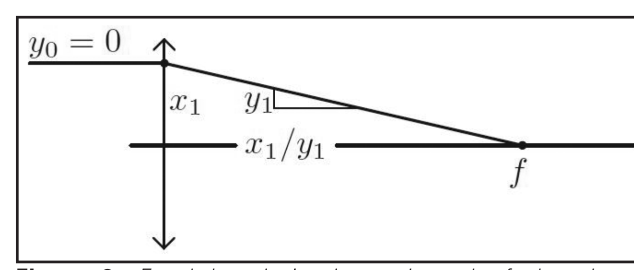

Figure 3. *Focal length is the reciprocal of the shear's strength: $f = 1/s$.*

As an aside, a series of lenses gives rise to the product of matrices. A nice undergraduate project would be to build an optical "matrix multiplier" (for 2×2 matrices of determinant one).

The figures in this article were provided by the author.

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Mark Levi (levi@math.psu.edu) is a professor of mathematics at the Pennsylvania State University.

2019 AWM-SIAM Sonia Kovalevsky Lecture

Catherine Sulem of the University of Toronto is the 2019 recipient of the AWM-SIAM Sonia Kovalevsky Lecture prize. She received her Doctorat d'Etat from the Université Paris-Nord in 1983 and held a French National Center for Scientific Research position at the Ecole normale supérieure in Paris before joining Toronto's faculty in 1990.


Catherine Sulem of the University of Toronto.

Sulem works in nonlinear partial differential equations arising in wave propagation and received the Canadian Mathematical Society's (CMS) Krieger-Nelson Prize in 1998. She was elected as a Fellow of the Royal Society of Canada in 2015, as well as an Inaugural Fellow of the American Mathematical Society and the CMS in 2013 and 2018 respectively.

"The Sonia Kovalevsky Lectureship is of special significance to me," Sulem said. "The Cauchy-Kovalevskaya theorem was among the first and deepest theorems I studied when I entered the field of partial differential equations (PDEs) as a graduate student, and I have used it extensively in my work."

She continued to describe the research that won her the prize. "I work on nonlinear PDEs that model wave propagation arising in physical contexts such as fluid dynamics, nonlinear optics, and plasma physics," Sulem said. "The main PDEs involved are the nonlinear Schrödinger equation and related systems and the water wave equations, which describe the motion of the free surface of a body of fluid under the influence of gravity and surface tension."

The joint AWM-SIAM prize was established in 2002 to honor Sonia Kovalevsky and her work on the theory of differential equations. It is awarded to a female researcher in the scientific or engineering community whose work highlights the achievements of women in applied and computational mathematics.

Sulem will present her prize lecture at the 9th International Congress on Industrial and Applied Mathematics (ICIAM 2019), to be held in Valencia, Spain, from July 15th-19th.

AWM-SIAM Sonia Kovalevsky Lecture: The Dynamics of Ocean Waves, *Wednesday, July 17, 2019*

Many aspects of mathematical analysis were originally motivated by the study of fluid dynamics; this is especially true of waves and currents in bodies of water. Sulem will discuss how mathematical analysis—combined with asymptotic theory and accurate numerical simulations—contributes to a better understanding of ocean wave dynamics at the ocean's surface and in its interior for both regular and extreme events.

Exploring the Rich Lore of the Pendulum

The Pendulum Paradigm: Variations on a Theme and the Measure of Heaven and Earth. *By Martin Beech. Brown Walker Press, Boca Raton, FL, February 2014. 290 pages, $25.95.*

"In [the Pisa Baptistry] hangs the lamp whose measured swing suggested to Galileo the pendulum. It looked an insignificant thing to have conferred upon the world of science and mechanics such a mighty extension of their dominions as it has. Pondering, in its suggestive presence, I seemed to see a crazy universe of swinging disks, the toiling children of this sedate parent. He appeared to have an intelligent expression about him of knowing that he was not a lamp at all; that he was a Pendulum; a pendulum disguised, for prodigious and inscrutable purposes of his own deep devising, and not a common pendulum either, but the old original patriarchal Pendulum — the Abraham Pendulum of the world."

– Mark Twain, *The Innocents Abroad*

BOOK REVIEW
By Ernest Davis

The pendulum—a bob connected to a fixed frame by a cord—is one of the simplest tools of experimental physics. Many of us likely recall working through the simple analysis in an early physics class and deriving the equation

$$l\ddot{\theta}+g\sin(\theta)=0.$$

Under the small angle approximation $\sin(\theta)\approx\theta$, we can find the solution $\theta(t)=C\sin(\omega t+\delta)$ with $\omega=\sqrt{g/l}$. With that, we are done with the pendulum; what more is left to say?

A lot more, actually, as Canadian astronomer Martin Beech demonstrates in his fascinating book, *The Pendulum Paradigm*. The lore of pendulums is deep, their history rich, their applications in science and technology multifarious, and their design and analysis surprisingly complex.

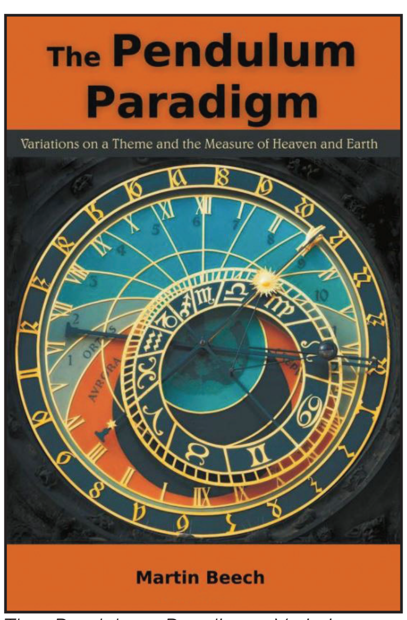
Firstly, the straightforward reasoning that yields the aforementioned simple differential equation hides a multitude of sins. Dissipative forces spoil the equation's elegant purity with additional terms of more arbitrary mathematical form. The length l—from the pivot point to the center of mass—may be difficult to measure with precision. The cord length will likely vary with time on account of its elasticity or due to thermal expansion or contraction. And the position of the bob's center of mass might change; for instance, a wooden bob may absorb humidity.

The acceleration of gravity g can depend on one's height or geographical location. As Pierre Bouguer discovered in 1735, gravity might not even pull straight downward; camped at the base of Mount Chimborazo in Ecuador, he realized that all of the stars were several arc seconds away from their expected location relative to his plumb line. Although the frame that supports a pendulum is supposed to remain still, a seismograph—in its simplest form, just a pen attached to a pendulum over a scroll of paper—indicates that this assumption does not always hold. And as Léon Foucault's pendulum dramatically demonstrates, the observer is also not standing still; he and the pendulum are both rotating around Earth.

As a result, the complications associated with designing and using pendulums tend to be twofold. On the one hand, engineers may design mechanisms to counteract these distracting issues. For example, an escarpment restores energy lost to friction. Henry Kater's pendulum makes the distance between two knife edges—which one can accurately measure—the critical length. George Graham's mercury compensation pendulum and John Harrison's gridiron pendulum both ingeniously keep the pendulum at a fixed length regardless of temperature.

On the other hand, one can use the perturbed responses of the pendulum to detect and measure the sources of perturbation. A seismograph measures small Earth movements from far-off earthquakes. Foucault's pendulum demonstrates Earth's rotation. Henry Cavendish's experiment—essentially a horizontal pendulum—calculates the gravitational constant (or, in Cavendish's terms, Earth's weight). Deviations in plumb lines can detect underground oil reserves. Of course, effectively accomplishing these tasks often involves solving the first problem as well, since one must isolate the perturbations of interest.

The associated mathematics—summed up by the book's subtitle—consist mostly of variations on a single theme, namely the preceding second-order differential equation. By my count, *The Pendulum Paradigm* includes 21 variants of this equation, with assorted corrections for different circumstances. Of course, only a handful of these have an analytic solution.



The Pendulum Paradigm: Variations on a Theme and the Measure of Heaven and Earth. By Martin Beech. Courtesy of Brown Walker Press.

Taking the pendulum as the point of departure, Beech's account explores a wide range of topics in the history of horology, gravitational physics, planetary science, and astronomy, mostly (though not entirely) confined to the 18th and 19th centuries. Readers learn about clock design, from the mechanical clock of Richard of Wallingford (c. 1330) to the Wishing Fish Clock built by artist Kit Williams; Pierre Louis Maupertuis's 1736 expedition to Lapland to adjudicate between Isaac Newton's theory that Earth is oblate and Jacques Cassini's theory that it is prolate; irregularities in Earth's gravitational field and shifts in its rotational axis; the ergodic and chaotic behaviors of pendulum systems with multiple degrees of freedom; and much more. The book is richly illustrated with diagrams and photographs.

There is plenty of content in *The Pendulum Paradigm* to engage a casual reader with an interest in science and its history, but Beech also provides careful descriptions and analyses of each issue he discusses. These explanations do require some work from readers if they hope to fully appreciate his examinations. I cannot claim that I always followed my own advice, but the few times that I carefully worked through Beech's arguments proved extremely worthwhile. In particular, it took me four readings and some concentrated thought to grasp the explanation of why the rotation period of Foucault's pendulum amounts to one day divided by the sine of the latitude. But in the end I was able to truly understand it. That in itself was worth the price of the book.

Ernest Davis is a professor of computer science at New York University's Courant Institute of Mathematical Sciences. His book—Rebooting AI: Building Artificial Intelligence We Can Trust—with psychologist Gary Marcus will appear this fall.

Geometric Design: New Trends and Challenges

By Rida T. Farouki and Kai Hormann

Geometrical models play a critical role in diverse fields such as engineering design and analysis, manufacturing automation, computer graphics and animation, architectural and environmental planning, computational fabrication, and medicine and biomedical technology. The field of computer aided geometric design (CAGD) arose in the 1960s from a desire to supplant two-dimensional drawings and three-dimensional (3D) sculpted models—which had previously sufficed to specify complex shapes—with precise digital representations based on novel mathematical formulations.

Explosive growth in the speed and memory of digital computers has fueled substantial progress regarding basic mathematics, efficient algorithms, and adoption of CAGD methods in the aforementioned applications through both commercial software packages and open source algorithm libraries. Nevertheless, fundamental mathematical challenges inhibit further progress in CAGD.

The SIAM Activity Group on Geometric Design[1] was founded in 1989 to tackle these challenges. It provides an interactive environment that brings together researchers and practitioners from academia and industry at the biennial SIAM Conference on Computational Geometric Design.

In CAGD, a very high premium is placed on the accuracy and robustness of geometrical models, as they are typically employed as input to subsequent applications (finite element analysis, surgical planning, manufacturing processes, etc.), and model inaccuracies or inconsistencies generally incur failure of the applications. As in other fields of applied mathematics, the range of mathematical problems of practical interest that admit exact solutions is quite limited in scope, necessitating the use of approximate and computational solutions.

There have been two independent evolutionary threads in the specification of geometrical models, motivated primarily by distinct application domains. Engineering design places great emphasis on the use of analytic or piecewise-analytic (spline) geometries, which satisfy demanding functional requirements like surface smoothness and precision tolerances of mating parts. On the other hand, mesh models (i.e., surfaces tessellated by triangular facets) are preferred in representing natural or "amorphous" shapes, such as computer-animated figures or human organ models employed in surgical or radiation therapy. The mesh model approach offers great robustness and topological flexibility but often at the expense of huge file sizes, and in most instances does not satisfy critical engineering precision requirements (e.g., for aerodynamic surfaces).

Accurate and efficient porting of geometrical models to applications remains a key challenge in their optimal utilization. Over the past decade, the field of isogeometric analysis (IgA) has generated considerable interest and activity. One of the original goals of IgA was to directly exploit 3D geometrical models in finite element analyses of stress, fluid flow, heat transfer, etc., rather than immediately replacing them with 3D mesh approximations. Due to the complexities associated with "trimmed" surfaces—parametric surfaces with complicated parameter domains defined by their intersections with other surfaces—the focus has instead drifted to adoption of the Bézier/B-spline bases employed in geometric modeling as "shape functions" for finite element analyses.

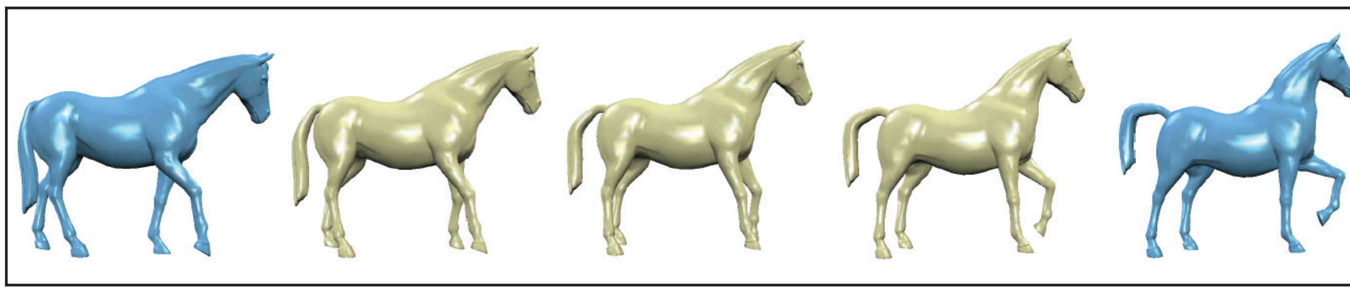


Figure 2. *Example of a nonlinear and physically realistic interpolation (yellow) between two given meshes (blue). Figure courtesy of [1].*

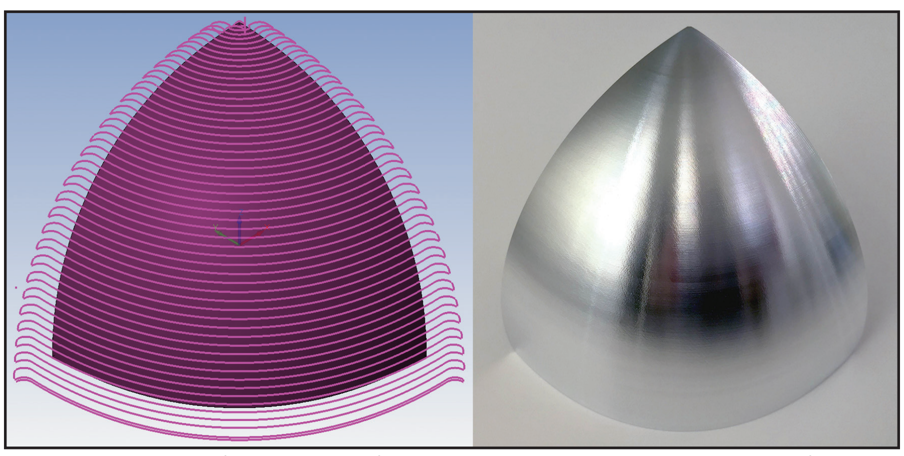


Figure 1. *Depiction of the toolpaths for computer numerical control machining of a swept surface (left), and the swept surface machined in aluminum directly from its exact procedural definition (right). Figure courtesy of [2].*

Similar limitations prevail in manufacturing. In computer numerical control (CNC) machining, the precise part model is typically replaced by voluminous piecewise-linear/circular (G code) toolpaths that limit the accuracy, speed, and smoothness of the tool relative to the workpiece (see Figure 1). Likewise, in 3D printing, the precise part model is first replaced by a surface tessellation known as an STL file (the acronym is derived from stereolithography, the original 3D printing process). The printer must slice the STL model into hundreds or thousands of parallel planes and generate area-covering paths for each slice. G-code part programs and STL files are universally applicable but can incur huge data volumes and loss of accuracy, efficiency, and reliability. Although originally intended as stop-gap measures to facilitate CNC machining and 3D printing technology, they have become entrenched "industry standards" that are extremely difficult to dislodge.

Geometrical 3D models are also of paramount importance in physical simulations, since the physical behavior of an object is intimately tied to its geometry. Although discrete differential geometry helps to elegantly discretize physical effects, it is hard for computational tools to take problem- and material-specific constraints into account and correctly handle the highly nonlinear and global deformations that models experience during simulation (see Figure 2). While engineering applications emphasize physical accuracy, the key aspect in computer graphics is speed. During his keynote presentation[2] at the 2017 SIAM Conference on Industrial and Applied Geometry in Pittsburgh, Pa., Tony DeRose of Pixar Animation Studios entertained attendees by sharing secrets of Pixar's solution to this problem.

Such problems, especially at the interface of geometrical models and their intended applications, continue to make CAGD research an active and fruitful endeavor. The development of novel mathematical representations and algorithms—rather than just increased computing power—will be imperative to addressing these challenging issues.

The upcoming SIAM Conference on Computational Geometric Design (GD19)[3] is part of the International Geometry Summit, which will feature four geometry-related conferences from June 17th-21st in Vancouver, Canada. This summit is a prime opportunity to interact with the CAGD community and learn about recent advances in the field. In particular, GD19 will feature exciting keynote presentations by Jessica Zhang (Carnegie Mellon University) on incorporating isogeometric analysis into existing software, such as Abaqus and LS-DYNA; Michael Bronstein (Università della Svizzera italiana (USI), Imperial College London, and Intel Perceptual Computing, Israel) on debunking "folklore" of spectral geometry regarding the behavior of manifold Laplacian eigenvalues and eigenfunctions; and Shahram Izadi (perceptiveIO) on the latest advances in virtual and augmented reality.

[1] https://www.siam.org/Membership/Activity-Groups/Detail/geometric-design

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Rida T. Farouki worked in the research divisions of General Electric and IBM for a decade before returning to academia, and is currently a professor of mechanical and aerospace engineering at the University of California, Davis. He is current chair of the SIAM Activity Group on Geometric Design (SIAG/GD) and co-editor-in-chief of Computer Aided Geometric Design (an Elsevier journal). Kai Hormann is a full professor in the Faculty of Informatics at the Università della Svizzera italiana (USI) Lugano and former chair of SIAG/GD. His research interests are focused on the mathematical foundations of geometry-processing algorithms and their applications in computer graphics and related fields. In particular, he is working on generalized barycentric coordinates, subdivision of curves and surfaces, barycentric rational interpolation, and dynamic geometry processing.