George Pólya Awards

Stanley R. Huddy and Michael A. Jones

"The calculus behind generic drug equivalence," *College Mathematics Journal*, 49:1, 2–9, 10.1080/07468342.2017.1391502.

This paper starts with a question of obvious real-world significance: how can we tell whether a generic drug is "equivalent" to its brand-name counterpart? It is not enough just to check that they contain the same amount of the same active ingredient, since factors such as pill coatings or inactive ingredients could affect the rates at which the drug is absorbed and eliminated by a patient's body. These rates cannot be measured directly, so they must somehow be inferred from measurements over time of the drug concentration in the patient's blood. How should the concentration curves of the two drugs be compared? This leads us to the intriguing mathematical problem presented in the article.

The US Food and Drug Administration (FDA) has set equivalence criteria which involve comparing three quantities: the time of the maximal concentration peak, the maximal concentration at that time, and the area under the concentration curve. But why did they select these three quantities in particular? It seems clear that some calculus will be involved in answering the question, and the authors lead us gracefully along this path. Starting with a commonly used pharmacokinetic model for the shape of the concentration curve, they eventually demonstrate that any two of the FDA's three measured quantities are sufficient to determine the desired absorption and elimination rates for this model; thus, the FDA criteria are mathematically sound. The journey takes us through several calculus topics, including integration, optimization, and, surprisingly, the Lambert W function. The latter provides a good opportunity for readers to think about the notion of implicitly defined functions with multiple branches, an important concept that calculus students may not realize goes beyond the familiar inverse trigonometric functions. Not every equation can be solved by mere algebra, and not every useful function has a nice closed-form expression or a button on your calculator!

The authors skillfully illustrate the interplay between applied and theoretical mathematics: understanding the properties of a mathematical model may involve different tools than were required to formulate the model in the first place. This well-written and engaging article could form the basis of a very nice project for students in a calculus or modeling course, providing an opportunity to apply and explore concepts from coursework while demonstrating that calculus is useful—and used—beyond the classroom.

Response

We are honored to be awarded the George Pólya award. We were motivated to investigate bioequivalence after hearing Jeremy Greene describe his book on the history of generic drugs when he was interviewed on National Public Radio's *Science Friday*. Fittingly, determining how calculus applied to bioequivalence, we followed, not consciously, Pólya's steps from his book *How to Solve It*, from understanding and honing the problem statement to using a picture to prove an inequality. Working on the project was also rewarding because, fifteen years ago, our relationship was that of student and teacher, and since then we have become colleagues and coauthors. We want to thank the anonymous referees and editor Brian Hopkins for their comments and suggestions that helped improve the presentation.

Biographical Sketches

Stanley R. Huddy is an assistant professor of mathematics at Fairleigh Dickinson University. He holds a PhD in dynamical systems from Clarkson University and his research interests include oscillator networks, game theory, and combinatorics. He was a National Science Foundation GK-12 Fellow and is a certified teacher of mathematics in the state of New Jersey. In his free time, he enjoys mountain biking, snowboarding, and playing the drums.

Michael A. Jones is an associate editor for the American Mathematical Society's *Mathematical Reviews* and is finishing his last year as editor of *Mathematics Magazine*. He was at Montclair State University (New Jersey) for 10 years where he recruited Stanley to work on a student research project. His PhD is in game theory from Northwestern University and his research interests often involve applications of mathematics to the social sciences. This year was his tenth time teaching The Mathematics of Decisions, Elections, and Games as part of the University of Michigan's Michigan Math and Science Scholars summer program for high school students. His free time is spent shuttling his kids to soccer, softball, and music lessons.