Is Mathematics Invading Human Cells? Impressions from a Collaboration with Diabetes Doctors

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Viewpoint

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The Viewpoint *column offers readers of* The Mathematical Intelligencer *the opportunity to write about any issue of interest to the international mathematical community. Disagreement and controversy are welcome. The views and opinions expressed here, however, are exclusively those of the author, and the publisher and editors-in-chief do not endorse them or accept responsibility for them.* Viewpoint *should be submitted to the editor-in-chief, Marjorie Senechal.*

Jointly with another mathematician, a biophysicist, and two diabetes doctors, I released a textbook, *BetaSys – Systems Biology of Regulated Exocytosis in Pancreatic β-Cells*,[1] in which a broad international team summarizes the state of our current understanding of the cell-physiological events accompanying both successful and impaired insulin secretion. In this *Viewpoint*, I describe some of my experiences as a mathematician cooperating with diabetes specialists, and the wider questions that those experiences raise.

Advanced Equipment and Basic Ignorance

Along with space exploration and military and civilian nuclear power design, medical devices belong to the mathematically most sophisticated areas of modern technology. Many mathematicians have or could have contributed to magnetic spin resonance imaging (MRI), and there is hardly a single mathematician who masters the entire math involved in that technology. The same goes for electron tomography, multibeam confocal laser microscopy, and many other advanced devices. Medicine has become a mathematical discipline. The ominous military–industrial complex has metastasized; an eminently mathematical sickness-and-health industry has grown up alongside it.

But mathematics is encapsulated in the apparatus. Whether it is about a specific diagnosis or treatment, most patients, at least those who are mathematical physicists, will be surprised at how little medical science really seems to know and understand about particular diseases. It is quite normal that a doctor must simply experiment – or just stick to an established symptom diagnosis and symptom treatment. Without a detailed identification of the real causes of the individual patient's ailment, often a successful treatment, defined as a cure, is unattainable.

Physics can also be complicated and in many cases without established answers. But in physics there is after all only a very short list of "First Principles" that one must stick to. There we have relatively well-defined interfaces between established knowledge, reasoned or vague presumption, and ignorance. And in most cases, our ignorance in physics can be condensed in some mathematical equations (which we may not immediately fully understand). This is not so in medicine.

Challenges (for Mathematicians) in Cell Research

The Strong Medical Pull

From pure mathematical research, we know the feeling of being pulled forward by an overarching issue: the

[1] Booß-Bavnbek, B.; Klösgen, B.; Larsen, J.; Pociot, F.; Renström, E. (eds.), *BetaSys – Systems Biology of Regulated Exocytosis in Pancreatic β-Cells*, series: Systems Biology, Springer, Berlin-Heidelberg-New York, 2011, XVIII, 558 pages, 104 illustr., 53 in color. With online videos and updates. ISBN 978-1-4419-6955-2.
[1] Comprehensive review in *Diabetologia*, DOI 10.1007/s00125-011-2269-3. In the following this monograph will be cited as [1]

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relationship between local and global properties, between the smooth and the continuous, between analytic and algebraic methods, the Four-Color Problem, the Poincaré Conjecture, the Riemann Hypothesis, the Clay Millennium Problems. Of course, we would never admit such personal ambitions in public. But to me there is no doubt about the role that major well-stated problems play and have played in the design of the career paths of many mathematicians, at least indirectly and in daydreams: with many doubts and a persistent feeling of self-deception and of fighting against mountains – or windmills.

Working as a mathematician with diabetes doctors is different. A bristling cascade of medical issues pulls the research forward: For nearly 90 years we have known that lack of secretion of the hormone insulin is one of the many serious issues in both diabetes type 1 (juvenile) and type 2 (obesity and age driven). For a large group of these patients, insulin *is* actually produced in their pancreatic β-cells (Fig. 1), and it is stored in thousands of minibags, vesicles, in the cell's interior (Fig. 2). But the cells do not respond correctly to external stimuli with the actual secretion, called regulated exocytosis. That manifests itself in elevated blood sugar, which for 4000 years has been tested and measured by urine samples.[2] We call it a symptom diagnosis, because the diagnosis says nothing about the wide range of causes that may underlie the lack of uptake of glucose in the muscles.

Previously, failure of insulin secretion automatically led to weakening of the muscles, inflammation of the extremities, loss of vision, and the body's final decay. Since the discovery of insulin, this tragic development can be countered by an artificial supply of insulin by injection several times a day. We call it a *symptom treatment*, because it is not even an attempt

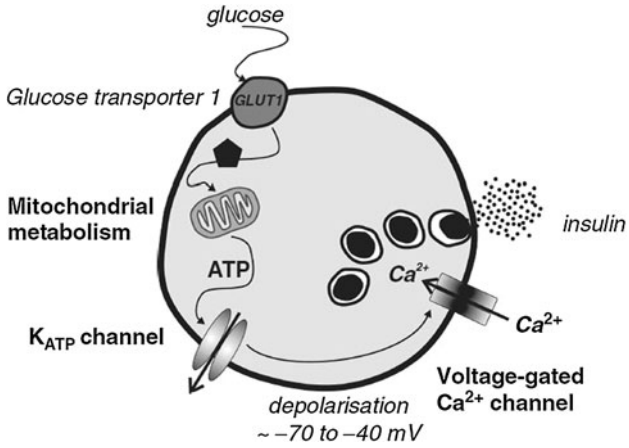

Figure 1. Cartoon of a pancreatic β-cell with glucose-triggered insulin secretion. After Renström (2011) in ref. [1] in footnote 1, p. 37, reproduced with permission. Original figure © Springer-Verlag.

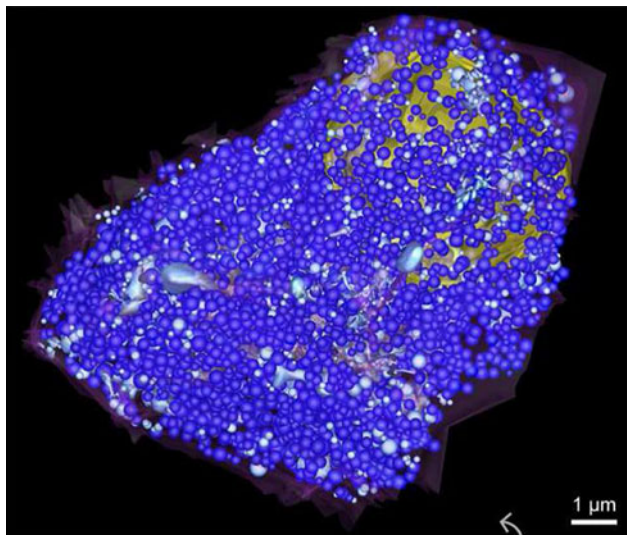

Figure 2. Electron tomographic image of pancreatic β-cell. Details of cellular anatomy marked by false-colour coding. Note insulin-containing granules entered in blue and nucleus in yellow (courtesy B. Marsh).

to cure the patient or to make an effort to restore the body's own insulin secretion. Some claim that the relative success of the overall symptom diagnosis and symptomatic treatment of diabetes has blocked patient-centered, individualized diagnosis and treatment.

In any case, in collaborating with diabetes doctors, a mathematician is continually pulled forward by well-defined medical problems. In this case, the problem is to detect the functioning and system behavior of the regulated exocytosis in healthy β-cells and to identify everything that can stand in the way in the case of weakened β-cells. Doctors hope that mathematicians will help find a way to an earlier and more specific diagnosis, or even a cure or

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[2]The earliest preserved report (in Bendex Ebbell's Copenhagen interpretation of 1937) is from the Egypt *Ebers Papyrus* of 1536 BCE, instruction 197, column 39, line 7, reproduced in all its ambiguity on http://biology.bard.edu/ferguson/course/bio407/Carpenter_et_al_(1998).pdf.

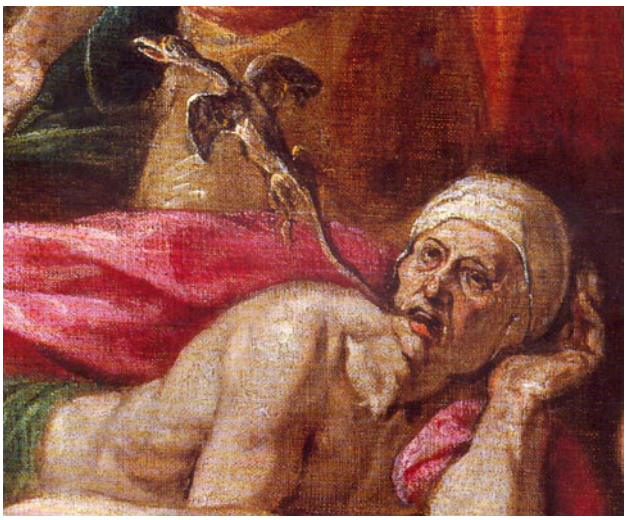

Figure 3. Crispin Van den Broeck (detail, 1577), with permission of the Royal Collection, London, chosen as the logo for the interdisciplinary exocytosis modeling initiative "Getting information out before therapy in: Towards curing diabetes by systems biology of regulated exocytosis in pancreatic β-cells".

alleviation of the specific failure. A few years ago, when I brought together an international team of medical doctors (from hospitals and industry), biologists, biophysicists, powder chemists, electrical engineers, computer scientists together with mathematicians, we were frustrated about the huge gap between the ubiquity of standardized symptom diagnosis and symptom treatment on the one side and how little we knew about functioning and malfunctioning of regulated exocytosis. Therefore, we chose the motto "Getting information out before therapy in" with a corresponding logo (Fig. 3). Instead of short-term orientation toward immediately applicable and rapidly publishable results, we oriented toward good old fundamental research.

The Technological Push

This we know from mathematics: Readily available electronic journals, large user-friendly databases of mathematical preprints and reviews, efficient numerical software packages, and desktop LaTeX editing put us under pressure as mathematicians. But all this is nothing compared to the immense technological pressure that cell research is subject to: with each new generation of equipment, oceans of new data inundate us on quite different length scales. Rapidly expanding technology-driven innovations deal with individual genes in the DNA, with proteins and with electrical cell membrane processes. But also the structure and function of a β-cell as a whole can be described in momentary images (by electron tomography) or dynamic sequences (by tracking of properly primed nanoparticles in living cells – a developing technology; see Fig. 4).

Heavy Preponderance of Ad-Hoc Perceptions

There is no shortage of heroic attempts by some scientists to bring order and overview into this wild jungle of real data. Most approaches, however, restrict themselves to ad-hoc fiddled perceptions of unconfined creativity, à la: "it should probably be the cell nucleus that controls the process," or "there is a certain rate, which determines the transition between one stage and the next," or "a correlation between the one process and another process is unquestionable." Explanations hold until overtaken by new data and will then be "adjusted." They will never be falsified, because they are freestanding and variable and not, as in physics, tied to first principles and the geometric properties of the 3-dimensional space. The only quality criterion is whether a model *looks like* the known observations or can be tuned to coincide with them. It is a free kingdom of modeling, admitting fancied ghosts to explain actual observations, but a nightmare when looking for durable descriptions and durable explanations that will not be outdated by any new observation and that are prone to have their limits of validity checked theoretically. For my own work, however, I found such approaches very stimulating. In his groundbreaking and beautiful work, the mathematician Arthur Sherman (NIH, Bethesda, Maryland) uses dynamical system techniques to study the striking two phases character of secretion that is experimentally established: Upon stimulation, the insulin release of a healthy cell begins with a short peak of about five minutes length, followed by a more steady and substantial release with a duration of about 25 minutes. In stressed or tired cells the absence of the first peak is an early indication of degradation. For now, mathematics cannot fully explain the phenomenon, but it can reproduce it in a multi-component model and point to possibly critical parameters and threshold values. In such a way, Sherman's work has indeed motivated many experimental and theoretical investigations (see Fig. 5).

The Phylogenetic Heritage

Our insulin-producing β-cells are among the most differentiated of all human cells. They are closely packed with a zoo of different types of organelles. Insulinlike peptides can be detected in our distant invertebrate ancestors who have been around for more than 600 million years. Something resembling pancreases with a kind of insulin-producing β-cells already exist in the hagfish, which has been around for more than 500 million years. So, any new observed process or measured quantity may be irrelevant, a relic, a ruin of historical development that has no importance any longer. Of course, this type of confusion was also met in the history of physics. How long did it take to assign to meteors and comets their place in our conception of the solar system, or to remove Pluto from the list of planets? However, although the ruins and relics ideally sharpen the mind in simple research fields such as physics and astronomy, they can be extremely confusing and even completely block medical research. Again and again one senses that we mathematicians coming from the outside are possibly too early. Perhaps we had better wait another 150 or 200 years, until the research has separated essential processes from nonessential processes, before we at last can begin the serious work.

Lack of Universality

What strikes me most in mathematical cell physiology is the lack of any *universality* or *scale invariance*. In the world of physics, Maxwell's equations apply for both high-frequency

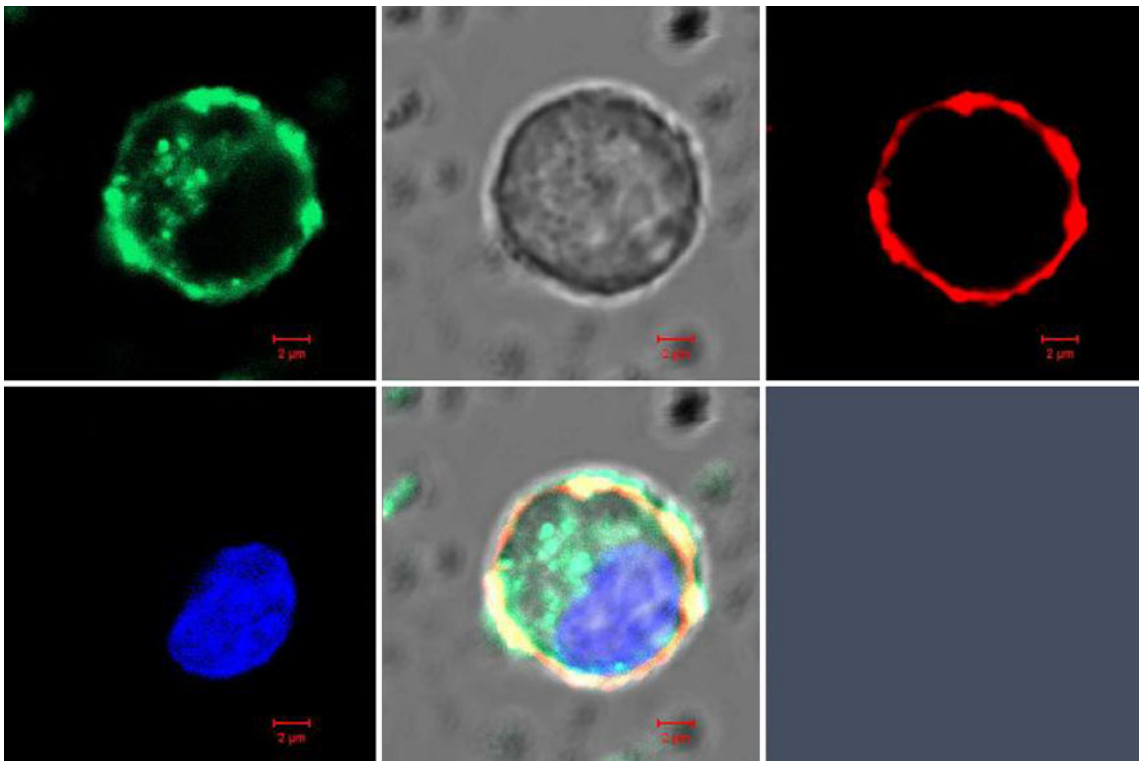

Figure 4. Three-colour confocal microscopy of magnetic nanoparticles (MNPs) nondestructively entered into a pancreatic β-cell by low-frequency magneto-manipulation. Green: MNPs; red: cell membrane; blue: cell nucleus (courtesy E. Renström and M. Koch). This crucial experiment delivered the proof-of-concept of the envisaged long-time (up to 10 minutes), precise and localizable capturing of intracellular dynamics of pancreatic β-cells, namely by manipulating and tracking MNPs in vivo – without damaging the cell or blocking its function. (Note that live imaging is at the cost of the high resolution obtainable by electron tomography of fixed [frozen] objects; compare fig. 2 and fig. 8).

radio waves and low-frequency voltage in power plants; the Navier-Stokes equations apply for both the continental atmospheric phenomena and the whirling around a ship hull. In mathematical physics, we have concepts (such as fields and ergodicity) relating point measurements with spatially widespread events. We noted reluctance, even resistance, in the cell physiology community to such global concepts when we published an article incorporating such ideas.[3] They were perceived as abstract, imaginary, speculative, and immaterial.

Of course there are cross connections in medicine between what we know on different length scales, about β-cell function and our genetic data, the mode of operation of single organs (such as the pancreas) and a body's, an organism's behavior and the performance of a whole population. For example, genetic data are collected by epidemiological studies of large populations, and the feedback is well studied between nutrient intake, liver and brain response, and the secretion signaling. But – apart from the universality of the applied statistical methods for parameter estimation and hypothesis testing – all the methods used are closely tied to a specific biological level, a particular length, and a time scale. We know such a hopeless situation also from mathematical physics with the seeming incompatibility between the mathematical theories of gravitation and quantum mechanics. That might be considered a wound in physics, but it is a unique wound. In diabetes research, we have hundreds of such cracks and ditches where no one knows whether there is a bridge, and if so, how it would be built.

Volatility

Medical biology, as it is conducted today, is a huge undertaking with myriad articles published every year. Not many of them will be quoted 2 years later. That's probably the reason why a key parameter for bibliometric research information, the impact factor, only examines the current references to papers that are not more than 2 years old. To be sure, the overall goal, the understanding of life and death, of health and illness, is long-term. But the angles of attack change constantly and appear frequently, dictated by some observational techniques that have just now come into use. The subject seems to be characterized by the absence of established and general traditions. As practiced today, cell physiology is a young subject that is just now establishing itself. Accidental discoveries seem to play a major role. We recognize that fact also from physics, where, for example, the discovery of high-temperature superconductivity in conventional insulating ceramic materials by Bednorz and Müller in 1986 could hardly be characterized as the result of deep theoretical

[3]D. Apushkinskaya et al., *Geometric and electromagnetic aspects of fusion pore making*, in ref. [1] in footnote 1, pp. 505-538.

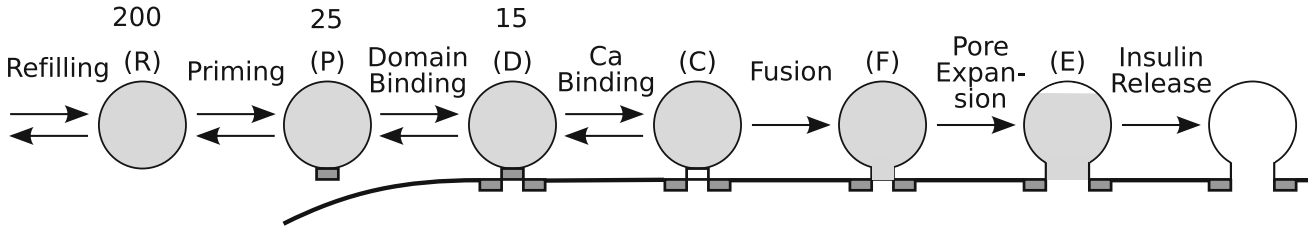

Figure 5. Extended six-pool compartment model, incorporating Ca-binding, of Y. D. Chen, S. Wang, and A. Sherman, "Identifying the targets of the amplifying pathway for insulin secretion in pancreatic beta cells by kinetic modeling of granule exocytosis," *Biophys. J.*, 95/5 (Sept. 2008), 2226-2241. In a beautiful piece of analysis, the authors were able to reproduce the typical two-phase insulin secretion of healthy β-cells by tuning the transition rates in their system of six coupled ordinary differential equations. Cell physiology and electron tomography support the authors' claim of six distinguishable pools of insulin-packed vesicles. Whether the values of the found rates can be given a biophysical interpretation is still an open question. It is also an open question as to whether the present author's global electromagnetic part model, of the making of the fusion pore in joint work with D. Apushkinskaya, et al. in ref. [1] in footnote 1, pp. 507-538, supplements or contradicts the compartment model. Figure drawn by H. Larsen, Roskilde. From B. Booss-Bavnbek, "Geometry and dynamics on nano scale: Towards a nano geometry?" *Contemp. Math.* 584 (2012), 147-162, http://dx.doi.org/10.1090/conm/584/11600, p. 159, reproduced with permission. Original figure © *Amer. Math. Soc.*

considerations. However, random breakthroughs certainly occur more often in biomedicine.

Systems Thinking Versus Reductionism

It goes without saying that a strictly reductionist program is needed in medical research, if the current packing of medical ignorance in ad-hoc assumptions is to be replaced by falsifiable references to basic physical laws. But I must also acknowledge that most bodily functions and processes involve many different cell components, neighboring cells, various organs, and the whole organism in an interaction. Understandably, the holistic slogan of systems biology has become popular, and great expectations are attached to it.

Both programs will reveal exciting new facts and relations. Both approaches offer the mathematician rich working opportunities. To me, the most promising direction is somewhere in the middle: maybe a focused systems biology will show its ability to touch the wall, knock a hole in it, and achieve a breakthrough. That has not happened yet. The hope is to develop a medicine and a biology that simplifies in a reductionist way, fearlessly ignores some probably relevant aspects, and focuses on a limited range of processes – but in turn lets itself holistically and equally fearlessly be confronted at a multitude of levels and a diversity of length and time scales all at once.

Mathematical Helping Hand

What, then, can a mathematician do in this environment?

The Daily Practice

Just as in engineering, economics, or anywhere else, also in cell physiology the daily mathematical exercise consists of the estimation of some parameters, testing the significance of some hypotheses, and designing compartment models for the dynamics of coupled quantitative variables. Often the role of mathematics is to check whether a random discovery delivers what it promised.

Numerical problems can rapidly pile up when, for example, one wants to simulate a fusion process of a simple insulin vesicle to the plasma membrane of the β-cell throughout the process: the bending of the plasma membrane into a dimple, the coupling of the vesicle to the dimple, the coalescence of vesicle and plasma membrane during the hemifusion, the formation of the fusion pore for emitting the insulin molecules, and dissolving the vesicle remains into the plasma membrane. The reason for the numerical problems is that we are at a mesoscale: the characteristic lengths vary from 1 nm for the lipid heads, to 7 nm for the strength of the membrane bilayers of lipids – to 100-250 nm for the insulin vesicle diameters. Thus, the relevant lengths of regulated exocytosis considerably exceed the lengths that chemists have mastered using *Molecular Dynamics* (MD). It is even worse with the time scale, because a simple β-cell responds to glucose stimulation by insulin secretion over 25-30 minutes. And everything is in three dimensions (see Fig. 6). This requires the development of special software to aggregate both space and time intervals to something that current computers can work with.[4]

The Dual Role of Mathematicians

A mathematician coming from the outside must be humble in front of the immense calibration and programming work that underlies such models. It's hard not to succumb to the fascination of the "lively" graphical output of such simulations. Respectfully and humbly, we should make our tool box available and fearlessly lend a hand when needed. But we must not abandon our mathematical way of viewing, our acquired competence to inquire into the basis for the modeling and the simulations. We must remain skeptical and question everything by cross-checking calculations, insisting

[4] J. Shillcock, *Probing cellular dynamics with mesoscopic simulations*, in ref. [1] in footnote 1, pp. 459-473.

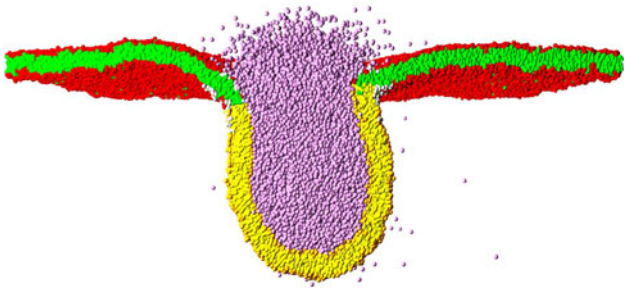

Figure 6. Cross section of the fusion of a vesicle of 28 nm diameter and a 100 × 100 nm^2 plane lipid bilayer in computer simulation; instantaneous snapshot 300 ns after the first vesicle-membrane contact. The simulation of a complete fusion event requires 4 CPU days on a processor. From Shillcock (2011) in ref. [1] in footnote 1, p. 468. Original figure reproduced with permission © Springer-Verlag.

on relating corresponding phenomena with each other, and using our imagination to devise quite simple physical mechanisms that have the ability to generate the world of complex phenomena that we observe.

The Falsifying and Heuristic Function of Mathematics

There are many jokes about the sharp-nosed mathematicians who check up on something and afterward, sometimes annoyed, sometimes smiling, note that the biologists' data and assumptions do not fit together. This gives mathematicians a reputation of pettiness and pedantry, but it is perhaps our most important contribution to all biomedical fields. With such a know-all tone, between 1616 and 1628, William Harvey falsified the prevalent notions about the cardiovascular system and discovered the arithmetic existence of the blood capillaries that connect arteries and veins – 40 years before Marcello Malpighi's light microscope confirmed their histological reality.[5]

Similarly, for example, a harmonic analysis[6] of observed electrical vibrations (calcium oscillations) in β-cells just before secretion indicates that these fluctuations are not only an expression of pulsing influx of calcium ions through the plasma membrane, but – contrary to common perception – may also result from a pulsing violent "splashing" of these ions between the cell's internal calcium organelles such as mitochondria and the endoplasmic reticulum. Hence, a purely mathematical realization of an inconsistency can move the focus from, I must admit, more easily and directly measurable local electrical membrane processes (measurement of the change of the static potential over time using the patch clamp) to cell-internal global and long-range electrodynamic processes (measurement of fluctuating magnetic field strengths) and give the exocytose research a new approach.[7]

Model-Based and Simulated Measurements

Many biomedical quantities cannot be measured directly. That is due to the subject matter, here the nature of life, partly because most direct measurements will require some type of fixation, freezing and killing of the cells, partly due to the small length scale and the strong interaction between different components of the cell. Just as in physics since Galileo Galilei's determination of the law of falling bodies by calculating "backwards" from the inclined plane, one must also in cell physiology master the art of model-based experiment design. Let us, for example, look at the 8000 to 12,000 densely packed insulin vesicles in a single β-cell. They all must reach the plasma membrane, within a maximum of 30 minutes after stimulation, to pour out their contents. Let us ignore the many processes taking place simultaneously in the cell and consider only the basic physical parameter for transport in liquids, namely the viscosity of the cell cytosol. From measurements of the tissue (consisting of dead cells) we know the magnitude of viscosity of the protoplasma, namely about 1 millipascal-seconds (mPa s); that is, it is of the same magnitude as water at room temperature. But now we want to measure the viscosity in living cells: before and after stimulation, deep in the cell's interior and near the plasma membrane, for healthy and stressed cells. By the way, I found that such an investigation is difficult to finance, and funds are required, not so much for mathematics but for performing the laboratory work. Funding agencies hesitate, because it is a new question, and we don't know in advance whether viscosity differences will show up and, if so, whether they are relevant. But let's keep with the example.

It serves no purpose to kill the cells and then extract their cytosol. We must carry out the investigation in vivo and in loco, by living cells and preferably in the organ where they are located. The medical question is clear. So is the appropriate technological approach, because techniques have been developed that allow iron oxide nanoparticles of a diameter up to 100 nm to be brought inside these most vulnerable β-cells without destroying them. It happens with a low-frequency (around 10 Hz) electromagnetic dynamic field generator that makes nanoparticles "roll" on the surface of the cells until they hit a willing receptor and attain an approach to the cell interior across the plasma membrane. These particles are primed with appropriate antigens and with a selected color protein, so that their movements within the cell can be observed with a confocal multibeam laser microscope that can produce up to 40 frames per second (see again Fig. 4). The periods of observations are only relatively short – perhaps a maximum of 8-10 minutes – before these particles are captured by cell endosomes and delivered to the cells' lysosomes for destruction and consumption of their color proteins.[8]

The simplest mathematical method to determine the viscosity of the cytosol in vivo would be just to pull the magnetized particles with their fairly well-defined radius a

[5]For details, see the box *Harvey's arithmetical microscope* in J. T. Ottesen, *The mathematical microscope – making the inaccessible accessible*, in ref. [1] in footnote 1, pp. 97-118, specifically p. 99.

[6]L. E. Fridlyand and L. H. Philipson, *What drives calcium oscillations in β-cells? New tasks for cyclic analysis*, in ref. [1] in footnote 1, pp. 475-488.

[7]D. Apushkinskaya, et al., loc. cit.

[8]Details will be disclosed in a U.S. patent in preparation by M. Koch, et al.

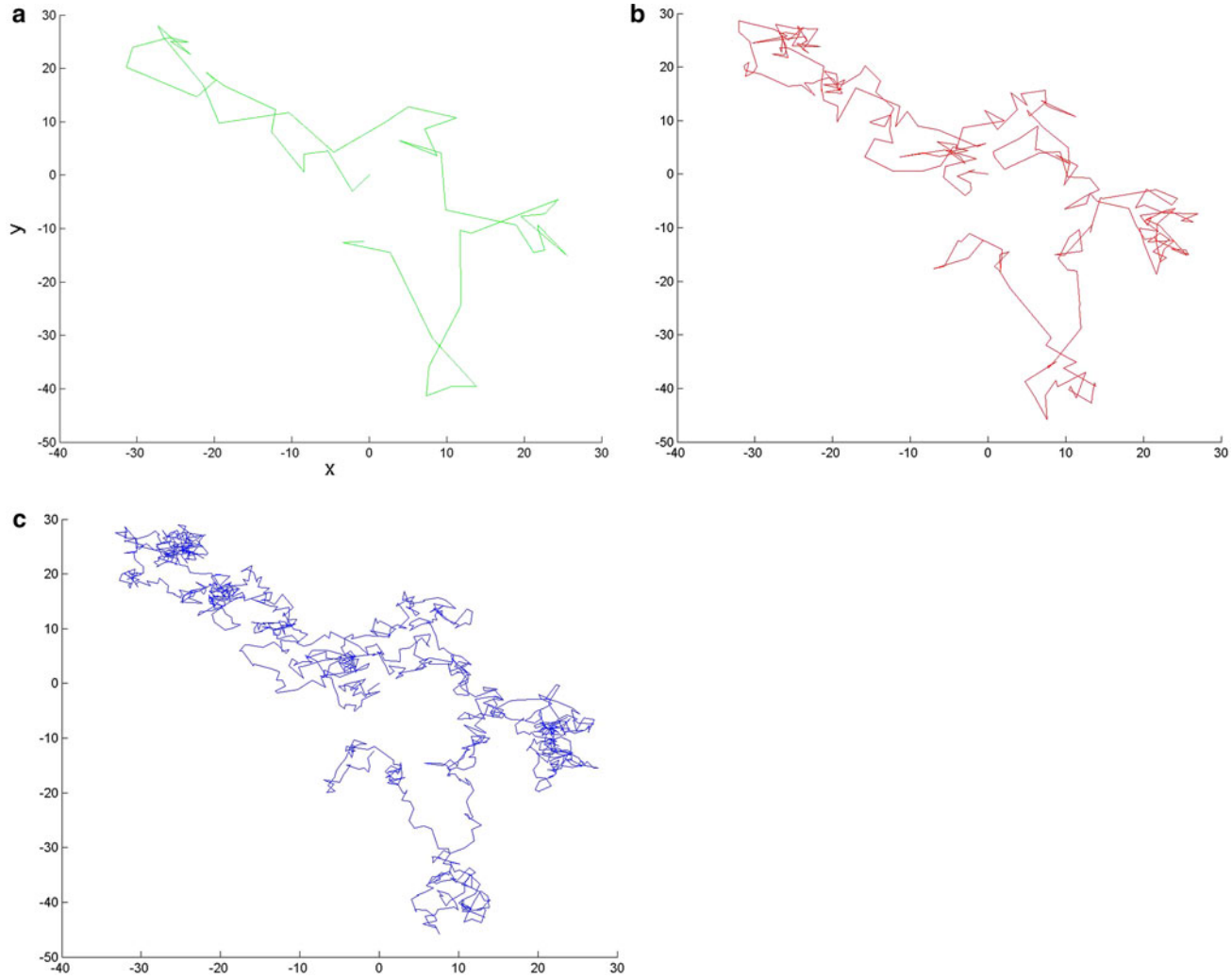

Figure 7(a-c). 2-dimensional projection of a computer simulation: (a) Low-resolution, (b) middle-resolution, (c) high-resolution track of the same Brownian motion. In (c), we registered twice as many observations per time unit as in (b), and four times as many as in (a). Because of the self-similarity property of Wiener processes, faster tracking of a Brownian motion does not yield greater precision for estimating diffusion coefficients than correspondingly many repetitions of the low-resolution track. Computer simulations might convince experimentalists of the vainness of their cry for ever better and faster equipment. Mathematics can say, "Stop, enough is enough," and prove, against intuition, that many blurred pictures yield a sharp one, as in this case. (MatLab program, courtesy of A. Gyurov and R. Tokin, Roskilde.)

with constant velocity v through the liquid and measure the applied electromagnetic force F. Then the viscosity η is obtained from Stokes's Law $F = 6\pi a \eta v$. The force and the speed must be small so as not to pull the particles out of the cell before the speed is measured and kept constant. Collisions with insulin vesicles and other organelles must be avoided. It can only be realized with a low-frequency alternating field. But then Stokes's Law must be rewritten for variable speed, and the mathematics begins to be advanced. In addition, at low velocity we must correct for the spontaneous Brownian motion of particles. Everything can be done mathematically: write down the associated stochastic Langevin equations and solve them analytically or approximate the solutions by Monte Carlo simulation.[9] However, we rapidly approach the equipment limitations, both regarding the laser microscope's resolution and the lowest achievable frequency of the field generator.

So we might as well turn off the field generator and be content with intermittently recording the pure Brownian motion of a single nanoparticle in the cytosol! As shown in the two famous 1905 and 1906 papers by Einstein,[10] the motion's variance (the mean-square displacement over a time interval

[9]F. Schwabl, *Statistical Mechanics*, Springer, Berlin-Heidelberg-New York, 2006; A. R. Leach, *Molecular Modelling – Principles and Applications*, Pearson Education Ltd., Harlow, 2001, Chapter 7.8.

[10]A. Einstein, "Über die von der molekularkinetischen Theorie der Wärme geforderte Bewegung von in ruhenden Flüssigkeiten suspendierten Teilchen," *Ann. Phys.* 17 (1905) 549-561; "Zur Theorie der Brownschen Bewegung," *Ann. Phys.* 19 (1906) 371-381. Both papers have been reprinted and translated several hundred times.

of length τ) $\sigma^2 = \langle \mathbf{x}^2 \rangle = \mathrm{E}(|\mathbf{x}(t_0 + \tau) - \mathbf{x}(t_0)|^2)$ of a particle dissolved in a liquid of viscosity η is given by $\sigma^2 = 2D\tau$, where

$$D = \frac{k_B T}{6\pi a \eta}$$

denotes the diffusion coefficient with Boltzmann constant k_B, absolute temperature T, and particle radius a. In statistical mechanics, one expects 10^{20} collisions per second between a single colloid of 1 μm diameter and the molecules of a liquid. For nanoparticles with a diameter of perhaps only 30 nm, we may expect only about 10^{17} collisions per second, still a figure large enough to preclude registration. There is simply no physically observable quantity $\langle \mathbf{x}^2 \rangle$ at the time scale $\tau = 10^{-17}$ seconds. But since the Brownian motion is a Wiener process with self-similarity, we obtain approximately the same diffusion coefficient and viscosity estimate, if we, for example, simply register 40 positions per second. So few measurements per second are enough. "Enough is enough," we can explain to the experimentalist, if he or she constantly demands better and more expensive apparatus.

This is beautifully illustrated by a small MatLab program (see Fig. 7), which first generates a Wiener process with a given variance σ^2 and then estimates the variance from the zigzag curves generated by taking all points or every second or fourth. Note that σ^2 also can be estimated by the corresponding 2-dimensional Wiener process of variance $3/2\ \sigma^2$, consisting of the projections of the 3-dimensional orbits, as the experimental equipment also will do.[11]

Beautiful, but it is still insufficient for laboratory use: There we also must take into account the non-Newtonian character of the cytosol of β-cells. These cells are, as mentioned, densely packed with insulin vesicles and various organelles and 1-dimensional structures (microtubules and actin filaments). Because the electric charge of iron oxide particles is neutral, we can as a first approximation assume a purely elastic impact between particles and obstacles. It does not change the variance in special cases, as M. Smoluchowski figured out 100 years ago for strong rejection of particles by reflection at an infinite plane wall.[12] Here also, computer simulations have their place to explore the impact of different repulsion and attraction mechanisms on the variance and the change of the dynamics of suspended nanoparticles and insulin vesicles due to the presence of guiding 1-dimensional structures.

Now one can hardly bring just a single nanoparticle into a cell. There will always be many simultaneously. Thus it may be difficult or impossible to follow a single particle's zigzag path in a cloud of particles by intermittent observation. Also here, rigorous mathematical considerations may help, namely the estimation of the viscosity by a periodic counting of all particles in a specified "window."[13]

The goal of model-based measurements and computer simulations is both to obtain the desired quantity from available or realizable observations *and* to become familiar with the expected laboratory conditions. Calculations and simulations can put us on intimate terms with the expected results, can support the exploration of a range of a priori unknown conditions, and can help to identify the best choice of free parameters such as particle diameter, temperature, area of focus, and so forth.

New Mathematical Ideas

I have described how important a wide, solid mathematical competence is for success in everyday practice, both for the verification and falsification of current assumptions, and for model-based measurements and simulation. Overview and literature study are required, not originality.

But there is also a need for radically new mathematical ideas, especially ideas that can integrate the otherwise isolated and local observations and perceptions that characterize molecular biology. How do localized events propagate from a position at the plasma membrane into a global process involving a myriad of ions, proteins, and organelles far away and across the cell to let the essential event take place: the secretion back at the plasma membrane? How does communication take place: the spread of a singularity, the amplification of a signal, and finally the creation of new forms? For instance, we may need hard mathematical tools to disclose the biophysical meaning of observed branching of mitochondria upon glucose stimulation (Fig. 8). Many mathematical disciplines have something to offer, from algebraic geometry, stochastic processes, and complex dynamics, to parabolic and hyperbolic differential equations and free boundary-value problems.[14]

Conclusion

How Deep Is the Gap Between Mathematics and Medicine?

Most mathematicians who have tried to work with doctors will confirm that cooperation is fairly smooth. You soon find a common language and common understanding in spite of widely different backgrounds. Understandably, one should not and cannot overstretch the patience of a clinical physician who has his or her patient here and now.

The relationship between mathematics and medicine has varied throughout the history of science. Such important mathematicians and physicists as R. Descartes, D. Bernoulli, J. d'Alembert, H. Helmholtz, E. Schrödinger, I. Gelfand, and R. Thom have been attracted to biomedical questions and

[11]M. von Smoluchowski, "Zur kinetischen Theorie der Brownschen Molekularbewegung und der Suspensionen," *Ann. Phys.* 21 (1906), 756-780, §9 gives – erroneously – the correction factor $4/\pi$, that is, the reciprocal value of the average shortening of a cylindrical 3D-length in 2D-projection.

[12]M. von Smoluchowski, "Einige Beispiele Brownscher Molekularbewegung unter Einfluß äußerer Kräfte," *Bull. Int. Acad. Sc. Cracovie, Mat.-naturw. Klasse A* (1913), 418-434.

[13]M. von Smoluchowski, "Studien über Molekularstatisktik von Emulsionen und deren Zusammenhang mit der Brownschen Bewegung," *Sitzber. Kais. Akad. Wiss. Wien, Mat.-naturw. Klasse* 123/IIa (Dec. 1914), 2381-2405. All three papers by Smoluchowski cited here are available on http://matwbn.icm.edu.pl/spis.php?wyd=4&jez=en.

[14]For the last mentioned approach, cf. D. Apushkinskaya, et al. 2012, loc. cit. For a more fundamental approach to the geometry of biological amplification processes, see also M. Gromov's many related and quite varied contributions from the last decade.

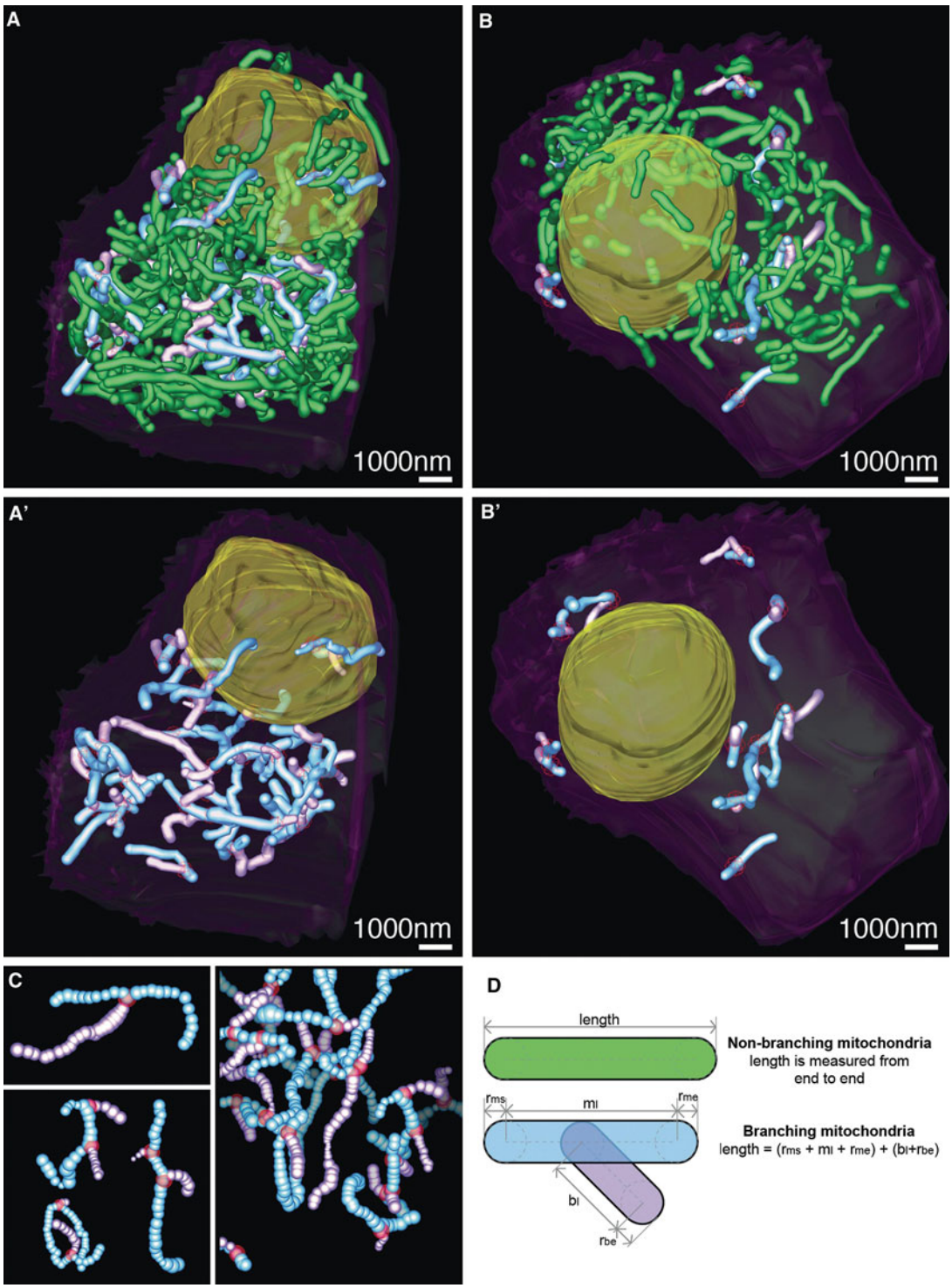

Figure 8. Significant differences in the number, distribution, and branching of mitochondria, determined by quantitative analysis of whole-cell electron tomograms, reflect β-cell heterogeneity in response to glucose-stimulation. *Top*: 3-dimensional models showing the number, size, and distribution of branched versus unbranched mitochondria. Color-coding: unbranched mitochondria (green); branched mitochondria (main lengths: light blue; branches: pink; branch points: red); plasma membrane (purple); nucleus (yellow). *Middle*: The relative difference in the number of branched mitochondria in each cell is more evident when branched mitochondria are displayed alone as a subset. *Bottom left*: Examples of variations in mitochondrial morphology from the 3-dimensional models displayed in (A′ & B′) are presented. *Bottom right*: A cartoon demonstrating how mitochondrial length and branching was quantified. Scale bars: 1000 nm. *Stochastic geometry* supports distinguishing and estimating numbers of stratified objects; *global analysis* of electromagnetic field equations offers explanation of the advantage of branched mitochondria for building up electromagnetic field waves. After Marsh (2011) in ref. [1] in footnote 1, p. 167. Original figure reproduced with permission, © Springer-Verlag.

observations, but they have also expressed their reservations. Important doctors – for examples one need only go through the list of Nobel Laureates – have apparently not suffered from math phobia, but rather have retained a lifelong fondness for mathematical ideas and ways of seeing.

Maybe this understanding between physicians and mathematicians has deep roots in the past: counting and healing was, by all accounts, the mysterious privilege of magicians and medicine men in prescientific cultures. Both subjects were, however, unlike the previous conjuration spirit and belief in magic and the good or evil ghosts, carried by the same rationalistic spirit throughout Greek and Roman antiquity (perhaps beside the Asclepiades). Geometric and arithmetic ratios should be explained and not adored or cursed! In the same spirit, Greek medicine has established itself as a strictly materialistic subject that described the course of a disease in purely objective, observable terms, and also envisioned solely objective reasons and pure physical treatment.[15]

Tasks for Mathematics Education

All higher educational institutions within mathematics have, in recent years, seen more than half of their graduates go to work in the financial sector, especially in the mathematically delicate evaluation of options and other derivatives. Some university teachers have been just as pleased as their students at these quick appointments. Some went so far as to point to this new job market as an argument to attract new math students to their universities.

I agree with the series of critical contributions in *The Mathematical Intelligencer*: there is no reason to be proud at having trained some of our best students for that task.[16] One alternative is to train our students in pure mathematics at its best. Perhaps an even better alternative is to direct students' attention to the many fascinating possibilities of cooperation in the medical world – at the population level, for example, in the study of infectious diseases and antibiotic resistant bacteria; at the organism and organ level, for example, in the study of cardiovascular diseases; or at the cellular level, for example, in the study of β-cells and other highly differentiated cell types.

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[15]Paul Diepgen, *Geschichte der Medizin. Die historische Entwicklung der Heilkunde und des ärztlichen Lebens*, Vol. 1, Walter de Gruyter & Co., Berlin, 1949, pp. 67-158; Fridolf Kudlien, *Der Beginn des medizinischen Denkens bei den Griechen, Von Homer bis Hippokrates*, Artemis, Zürich and Stuttgart, 1967; Fritz Jürss, *Geschichte des wissenschaftlichen Denkens im Altertum*, Akademie-Verlag, Berlin, 1982.

[16]M. Rogalski, ''Mathematics and finance: An ethical malaise,'' *Mathematical Intelligencer* 32/2 (2010), 6-8; I. Ekeland, ''Response to Rogalski,'' *Mathematical Intelligencer* 32/2 (2010), 9-10; J. Korman, ''Finance and mathematics: A lack of debate,'' *Mathematical Intelligencer* 33/2 (2011), 4-6. Related questions have been addressed in *SIAM-News* and *Mitt. Deutsch. Math.-verein*.