Excitable Media:

The Belousov-Zhabotinsky Chemical Reaction and the Heart

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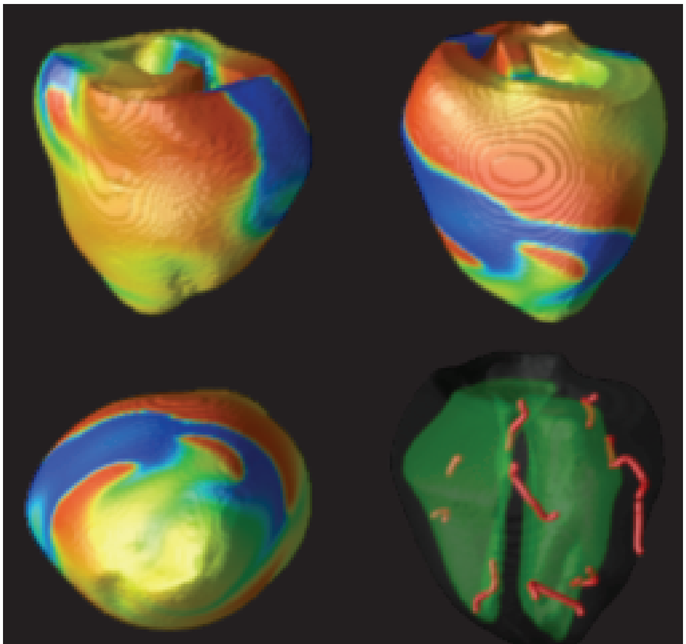


Figure 2. Simulated cardiac dynamics by Flavio Fenton and Elizabeth Cherry on a physiologically correct model of a rabbit ventricle (Vetter & McCulloch, 1998). The bottom right figure shows the cores (filaments) of multiple scroll waves present in ventricular fibrillation.

How do nerve cells behave? At the simplest level, a nerve cell receives a combination of excitatory and inhibitory inputs, and fires if their aggregate exceeds a threshold level. A nerve cell is thus an example of an excitable medium: the nerve cell returns to its resting steady state (equilibrium) after small stimuli, but a sufficiently large stimulus (above a threshold) generates an activation before the nerve cell returns to equilibrium.

There are many examples of excitable media: the cardiac electrical system is an important biological example, and the unstirred ferroin catalyzed Belousov-Zhabotinsky (BZ) (cf. Field & Burger, 1985) reaction is the prototype chemical example. There are important analogies between these systems (Glass & Mackey, 1988; Keener, 1986; Winfree, 2001); both display wave behavior — waves of high membrane potential in the cardiac electrical system, and waves of high bromous acid concentration in the BZ reaction.

The simplest description of the biological cardiac reaction is that the membrane potential of cardiac cells rises sharply when it exceeds a threshold, and "gates" are open; the rising membrane potential then causes the gates to close, which subsequently causes the membrane potential to fall. Waves propagate when a high membrane potential in one cell causes the membrane potential to rise above threshold in adjacent cells. In the BZ reaction, the concentration of bromous acid rises sharply when it exceeds a threshold dependent upon the concentration of a second chemical species, bromide ions; the rising bromous acid concentration then causes bromide ions to be produced, which subsequently cause the bromous acid concentration to fall. Waves propagate when a high bromous acid concentration in one area spreads to adjacent areas and causes the bromous acid concentration to rise above threshold there. In summary, between these two examples of excitable media, we have the following analogies:

Cardiac electrical system	Unstirred BZ reaction
Wave of high membrane potential	Wave of bromous acid concentration potential
Membrane potential (high or low)	Bromous acid concentration (high or low)
Gate status (open or closed)	Bromide ion concentration (high or low)

These analogies have been exploited by many researchers (cf. Glass & Mackey, 1988; Keener, 1986; Winfree, 2001) because it is much simpler to experiment with the BZ reaction (we do this with undergraduates in our lab at Hofstra) than with the heart.

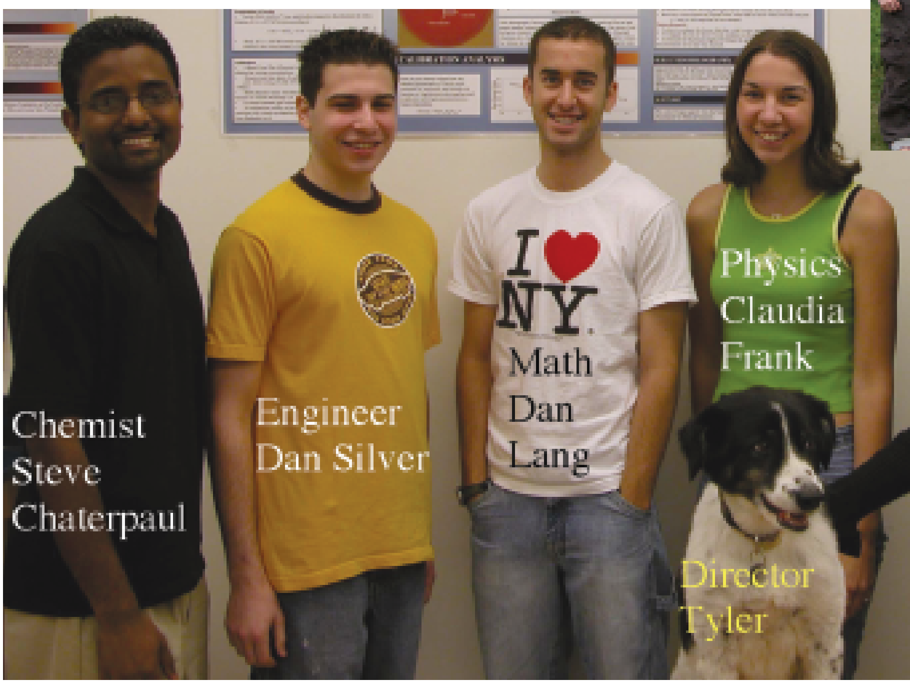
Over the last five to 10 years, my research has focused upon the dynamics of the cardiac electrical system and the BZ reaction, in combination with an outstanding group of colleagues here are Hofstra University and elsewhere. In particular Drs. Elizabeth Cherry and Flavio Fenton (research scientists in the Department of Physics at Hofstra University) have led the cardiac research program, working with Dr. Steven J. Evans (Beth Israel Medical Center), several Hofstra students (Figure 1), and me. Dr. Sabrina G. Sobel (Department of Chemistry, Hofstra University), Dr. Richard J. Field (Department of

Chemistry, University of Montana), more Hofstra as well as high school students and I have partnered in the Belousov-Zhabotinsky research program.

The heart normally behaves in a well-organized way. The heart contains a specialized group of "oscillatory" cells called the sinus node, which generate "beats" (electrical activations) approximately once per second. Under normal conditions, activation originates in the sinus node, travels first to the atria, and ultimately to the ventricles by a conductive structure called the His-Purkinj bundle. The ventricles are the main pumping chambers of the heart.

However, "spontaneous" activations can arise in the ventricles themselves, and propagate through the ventricles.

Figure 1. Our research group, Summer 2004: Front row: "Chemist" Catalina Peralta, "Photo Expert" Daniel Ravinovich, "Asst. Chemist" Arely Lemus (high school student), "Project Director" Tyler, "Chemistry Director" Sabrina Sobel, "Asst. Chemist" Fiona Yuen (high school student). Back row: "Math Theory" Christian Hilaire, "Physics Theory" Alex Zaharakis, "Physics Director" Harold Hastings, "Electrical Engineer" Carolyn Cammalleri.



Our research group, Summer 2003: Stephen Chaterpaul, Daniel Silver, Daniel Lang and Claudia Frank.

These are called ectopic beats or premature ventricular contractions (PVCs). Although ectopic beats are usually relatively harmless in the absence of underlying disease, in some cases wavefronts generated by ectopic beats can encounter refractory regions in which waves do not propagate, generated by other (sinus or ectopic) beats, yielding usually one or two wavefronts with broken ends. These broken wavefronts may generate scroll waves, which "rotate" much faster than those of the normal sinus rhythm, and thus drive the heart at rhythms much faster than the usual sinus rhythm, producing an abnormal state called ventricular tachycardia. Moreover, spiral waves in the normal heart are unstable, and meander and ultimately break down into multiple daughter waves, yielding the much less coherent state of ventricular fibrillation (Figure 2), and frequently sudden cardiac death. Sudden cardiac death is a major cause of death in the industrialized world, responsible for some 300,000 to 400,000 deaths per year in the United States alone. A better understanding of cardiac dynamics might ultimately lead to improved therapies for preventing the often fatal state of ventricular fibrillation.

In the 1980s several researchers, most notably Glass and Mackey (1988), Keener (1986) and Winfree (2001), used analogies between the cardiac electrical system and the Belousov-Zhabotinsky reaction to study the dynamics of waves of activations in both systems. The Belousov-Zhabotinsky reaction had been a surprising discovery of the 1950s: an oscillating chemical reaction. Although the existence of a chemical oscillator appears at first to bear some resemblance to a perpetual motion machine – an impossibility – a further analysis shows that one of the chemicals, malonic acid, which drives the oscillations, is consumed and the concentrations approach steady state, just as a falling weight drives oscillations of a pendulum in a grandfather clock, which continue as long as the weight continues to fall, and cease when the weight hits the floor.

Figure 3 is an illustration of pattern formation – the Belouzov-Zhabotinsky reaction was prepared as a relatively well-stirred solution; however, waves of high bromous acid concentration (represented by dark areas) appeared "spontaneously" after several minutes.

One of our major goals is to explain what causes these waves to form. For example, water vapor in a supersaturated atmosphere may condense around small dust particles to form water droplets – the dust particles nucleate droplet formation. Are analogous physical or chemical nucleating centers required for wave formation in the BZ reaction? Two careful researchers, Vidal and Pagola (1989), observed target formation in Belousov-Zhabotinsky reaction mixture containing no nucleating particles visible at a resolution of six microns (1/5000 of an inch). Their work suggested that microscopic random fluctuations might be responsible for target formation. We considered this question using a combination of theoretical, computer and experimental techniques, and have demonstrated that microscopic fluctuations can in fact nucleate target patterns.

What is a microscopic fluctuation? The ingredients in a chemical reaction are ions, atoms and molecules. For example, when carbon is oxidized to form carbon dioxide, we write

$$C + O_2 \longrightarrow CO_2$$

meaning that one atom of carbon combines with one molecule of oxygen to form one molecule of carbon dioxide. Even when we consider larger quantities, for example, when 12 grams of carbon react with 32 grams of oxygen to form 44 grams of carbon dioxide, and consider the components as continuous media, the reaction still takes place at the level of ions, atoms and molecules. The continuous description works as long as there are a large number of participating ions, atoms and molecules.

What if there are a just a few? In that case one must consider fluctuations. For a physical example of fluctuations, consider tossing a coin. The coin lands heads half of the time and tails the other half of the time. However, if we toss a coin 10 times, we will get five heads and five tails just 24.61 percent of the time. We will get four heads and six tails 20.51 percent of the time, and six heads and four tails 20.51 percent of the time. We might even get 10 heads; in fact this happens 0.09766 percent of the time. Although we get five heads on average, we sometimes get four or six heads, sometimes three or seven, and sometimes we even get zero or 10. We see fluctuations around the typical result of five heads.

We also see fluctuations in polling results. If half of the population prefers a given candidate and we poll 1,000 people from this population, we would expect 500 to answer that they prefer the given candidate. In fact, we would rarely get exactly 500 to answer this way, and in fact, 2.5 percent of the time, we would get either 469 or fewer who said they preferred the candidate, and 2.5 percent of the time we would get 531 or more who said they preferred the candidate. The difference, 531 – 500 = 31, or 3.1 percent of the 1,000 people polled, is sometimes called the margin of error. The typical fluctuation (in mathematical terms, the route mean squared fluctuation) or deviation from the expected 500 "yes" answers would be the square root of 250, or approximately 15.8.

We also see fluctuations in chemical reaction mixtures – if we expect to find 100 molecules in a small volume of solution, we would also see a typical fluctuation of size the square root of 100 (also molecules), that is, 10 molecules. Richard Field, Sabrina Sobel and I studied BZ reaction systems in which regions containing as few as 100,000,000 molecules were appropriate. In this case, a typical fluctuation was 10,000 molecules, that is, 0.01 percent, and we would sometimes see fluctuations as large as 0.06 percent. These fluctuations

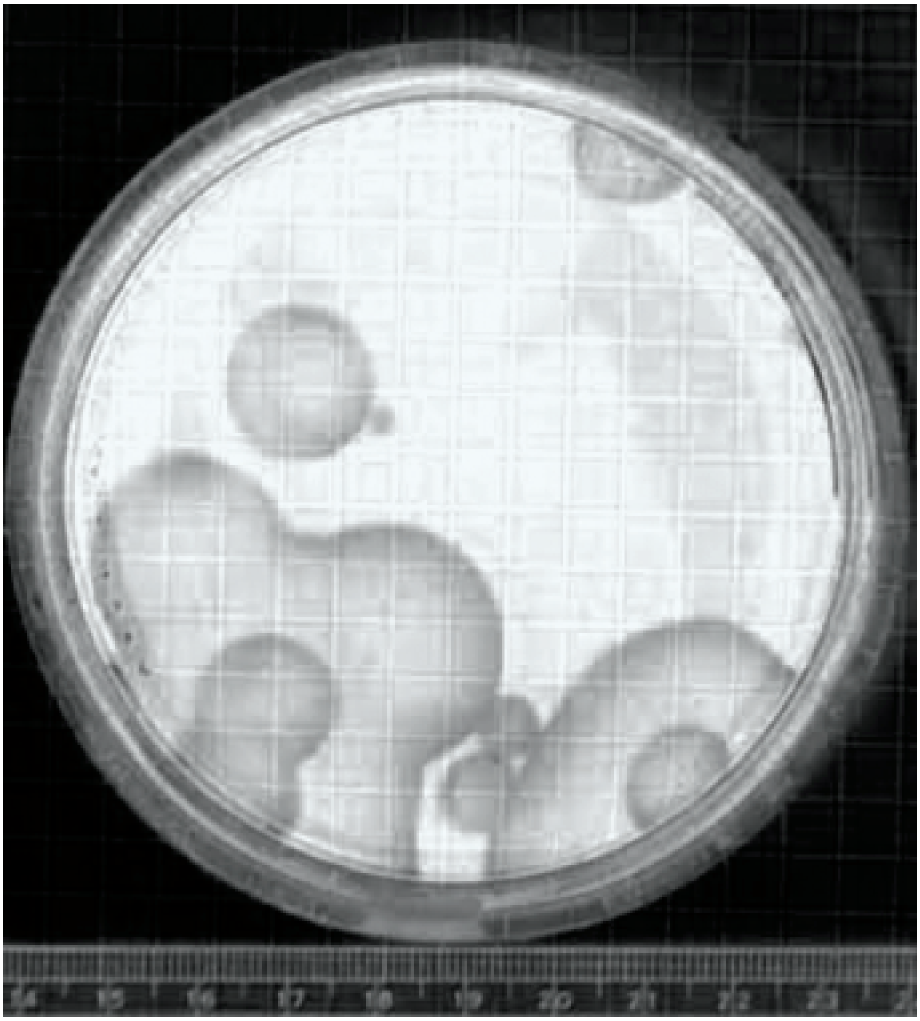


Figure 3. Photograph of the BZ reaction in an 89 mm-diameter Petri dish, from our group (Hastings, Sobel, Fenton et al., 2003). "Pacemakers" formed "spontaneously" (one in the center of each circular wave of activation) and generated the outwardly moving waves.

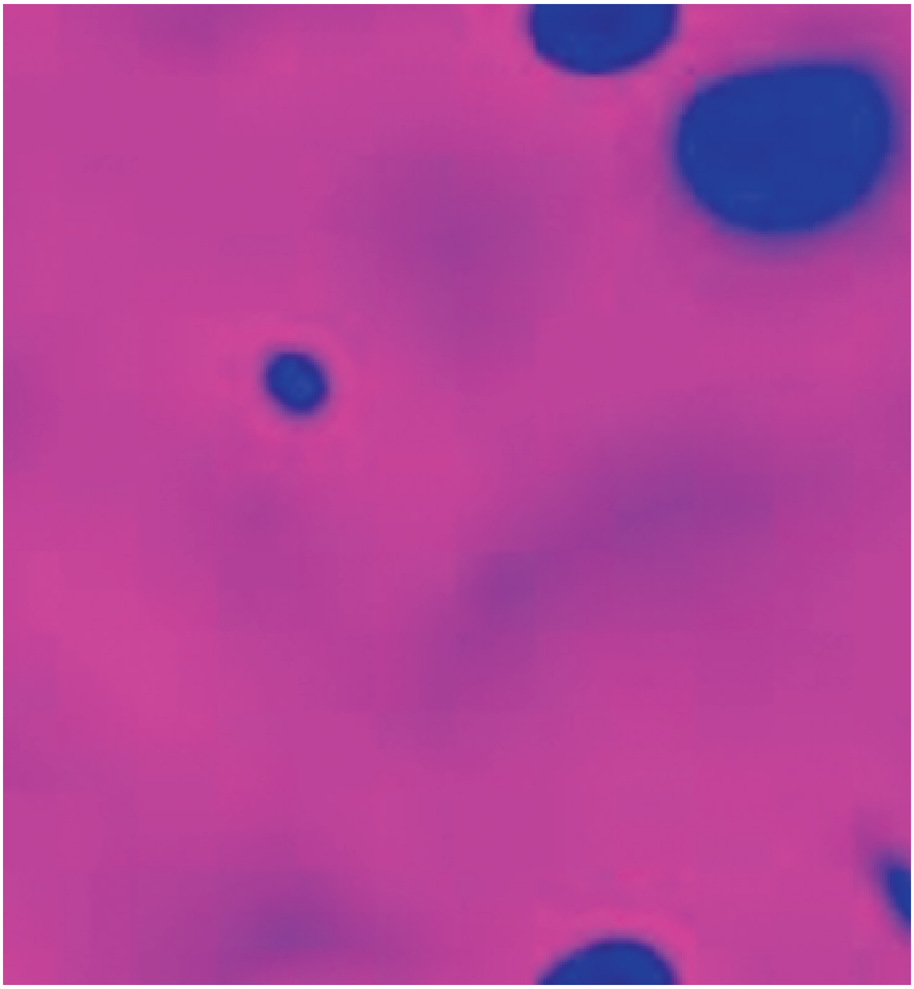


Figure 4. Computer simulation of the BZ reaction.

are called microscopic. In 2003, we showed theoretically that such small fluctuations might in some cases trigger the formation of targets, in the absence of any other larger (macroscopic) cause. I began to work on this project in the summer of 2002 when I met Richard Field at a conference at Oxford University. I walked up to him and asked if he was the "Field" of the well-established Field-Körös-Noyes (1972) theory of the BZ reaction. Dick answered that he was, and we immediately hit it off. Our discussions at the meeting continued later that summer with Sabrina Sobel, and culminated in a working session at Hofstra University in January 2003. Our paper extending work of Field, Körös and Noyes (1972) was submitted shortly thereafter to the *Journal of Physical Chemistry* and appeared that summer (Hastings, Field & Sobel, 2003).

We invite the reader to visit the Web site of the Center for Arrhythmia Research, a project of Beth Israel Medical Center and the Physics Department at Hofstra University, arrhythmia.hofstra.edu, run by Flavio Fenton, to learn more about the heart and the BZ reaction.

One of our major goals over the last two years has been to test and verify our proposed mechanism – that as the BZ reaction evolves it leaves a regime of stable dynamics and enters a "supercritical regime" in which it is very sensitive to small perturbations. One approach was to build a computer model incorporating our mathematical model together with small random fluctuations due to diffusion. Figure 4 shows the results of one such simulation of a thin film of the BZ reaction mixture, in a 10 mm square, with what we call periodic boundary conditions. That is, the top of the square is considered adjacent to the bottom and the left side adjacent to the right, so there are no edges. One can see blue areas, corresponding to oxidized ferroin, in a "sea" of pink, unoxidized ferroin, a pattern reminiscent of the first stages in target formation. This simulation was run on our new National Science Foundation-funded supercomputer, winfree.hofstra.edu, named for one of the pioneers in mathematical modeling of the heart. The supercomputer consists of 96 linked high-end Intel processors.

A related experimental component examined the generation of target patterns by small, controlled stimulations of the Beluosov-Zhabotinsky reaction. This work was led by a student, Catalina Peralta, with student co-authors Carolyn Cammalleri, Stephen Chaterpaul, Claudia Frank, Daniel Lang and Daniel Ravinovitch, with advisement from Professor Sabrina Sobel and me. The student team followed one standard approach to generating excitations – removing one chemical, bromide ions, which inhibit the reaction – analogous to causing a nerve to fire by reducing inhibitory stimuli. They did this by using positively biased silver electrode to release silver ions, which combined with bromide ions to form silver bromide, which then forms oligomers and ceases to participate in the reaction. Catalina won an award for this work (tied for second place) in the undergraduate research competition at the Fall 2004 New York Sectional Meeting of the American Physical Society.

At the same time, a second student team, Alex Zaharakis and Christian Hilaire, studied temporal patterns of ectopic activity in a simple cardiac cell model, with advisement from Drs. Elizabeth Cherry, Flavio Fenton and me. Ectopic activity in the form of premature ventricular contractions (PVCs) is relatively common in the normal heart. Although PVCs are normally harmless, sometimes (but rarely), PVCs can generate spiral waves of activation through interaction with other waves of activation, potentially progressing to ventricular tachycardia, followed by ventricular fibrillation and sudden cardiac death. This team used a computer model to study generation of PVCs by applying triggers (noise) to the generic FitzHugh-Nagumo model as substrate. Their work sought to understand the likelihood of multiple, clustered PVCs, which have been shown by others to be much more dangerous than isolated PVCs. Alex Zaharakis also won an award for this work (tied for second place) in the undergraduate research competition at the Fall 2004 New York Sectional Meeting of the American Physical Society.

We expect to continue working on both chemical excitable media and the heart over the next few years, with a goal of further understanding how apparently "spontaneous" activations arise in both systems, and perhaps ultimately gain insight on how to better control such activations. We invite the reader to visit the Web site of the Center for Arrhythmia Research, a project of Beth Israel Medical Center and the Physics Department at Hofstra University, arrhythmia.hofstra.edu, run by Flavio Fenton, to learn more about the heart and the BZ reaction.

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Harold M. Hastings began his teaching career at Hofstra University in 1968, and completed a Ph.D. in mathematics at Princeton University in 1972. Dr. Hastings is the author of 90 journal articles and book chapters, co-author of two books, and co-editor of a third book. Dr. Hastings has worked to include undergraduate students as active participants in his research program, and many of his students have presented their work at professional meetings and in research journals. His most recent book is *Fractals: A User's Guide for the Natural Sciences* (Oxford University Press, 1993; German Translation, Spektrum Akademischer Verlag, 1996), written with Dr. George Sugihara.

Dr. Hastings is now involved in two collaborative research projects. The first project, underway with Senior Research Scientists Dr. Flavio Fenton and Dr. Elizabeth Cherry from Hofstra and Dr. Steven Evans, director of cardiac electrophysiology at Beth Israel Medical Center in New York, is on the physics of the cardiac electrical system. His second project is on the dynamics of excitable chemical systems like the Belousov-Zhabotinsky reaction, discussed in the accompanying article. Dr. Hastings' present research has been supported by the National Institutes of Health and the National Science Foundation. Dr. Hastings is also principal investigator of Hofstra University's supercomputer project, funded by the National Science Foundation.

Currently, Dr. Hastings teaches courses in physics and astronomy at Hofstra, where he is professor and department chair. He has taught in many departments at Hofstra, including Biology, Computer Science, Engineering and Mathematics. Catalina Peralta and Alex Zaharakis, undergraduate students directed by Drs. Hastings, Cherry, Fenton and Sobel, won prizes for their research at the Fall 2004 New York Sectional Meeting of the American Physical Society. Dr. Hastings has served Hofstra as speaker of the faculty, as founding Arnold Saltzman mentor of Honors House (now the residential component of Honors College), and as associate dean of Hofstra College of Liberal Arts and Sciences.