Subtle Cascading Instabilities Precede Sudden Catastrophic Events in Biological Excitable Media

Biological excitable media in the heart and brain are vital for the development and sustenance of life. They provide the fastest way of transmitting information via precisely timed and directed waves of electrical activity. The precision in timing and direction at the organ level are determined by highly specialized architecture of different cell structures with different activation and recovery properties. At the level of a single cell, the electrical activity is determined by precise timing and duration of activation and recovery of intracellular ionic channels. The differentiation of electrical properties of various cell clusters and the precise relation between activation and recovery of intracellular ionic channels serve as natural “safeguards” (breaks, checkpoints) on excitable media, allowing certain patterns of excitation and blocking the others. But what happens if the “safeguards” fail? In an uncontrolled state, electrical waves of excitation can spread in different directions, rotate, or become disorganized. In a biological organism, this activity can be manifested as life-threatening cardiac arrhythmia in the heart or epileptic seizures in the brain.

Thus, a “normal” functioning of a biological organism is associated with a highly restricted and controlled state of excitable media, whereas all deviations from that state of the media are potentially fatal for the biological system. The organism can sustain the life as long as it manages to restrict and control the electrical waves of excitation.

This leads us to the question of how biological systems manage to keep control of excitable media in an ever-changing environment for so long. The short answer is that the system needs a system of multiple safeguards so that no single disturbance can break it. The safeguards include complex interactions between intracellular ionic channels, as well as a dynamic balance between cycle lengths, activation velocity, and recovery times. Only a cascade of mild disturbances can destabilize the system so gradually that the subtle changes would bypass all the safeguards and ultimately lead to the potentially fatal event.

Here we show what conditions are necessary and sufficient for the initiation and sustenance of the cascading instabilities leading to the life-threatening uncontrolled excitation.

1. Evidence from clinical and experimental studies shows that small but persisting instabilities exist up to several hours before the onset of cardiac arrhythmias or epileptic seizures [Shu Circ Res, Litt].
2. Experimental and clinical studies also show that small but persistent destabilizing influences may initiate potentially pro-arrhythmic changes in cardiac repolarization [Shu J Electr, Zipes].
3. In continuous electrocardiographic recordings from patients with life-threatening cardiac arrhythmias, enhanced temporal instability of cardiac repolarization, T-wave alternans, occur approximately 10 min before the onset of life-threatening arrhythmias, whereas irregularities in cardiac cycles occur hours before the event [Shu, Pace, 2004]. Thus, temporal repolarization instability follows persisting irregularities of cardiac cycle lengths, and it precedes imminent arrhythmia. This strongly suggests that the cascading process consists of slow accumulation of instabilities and irregularities gradually compromising the function of the protective safeguards. In general, this dynamic process has 2 parts:

1) Persisting but subtle irregularities in the stimulation cycle lengths. Experimental and clinical evidence suggests that the most likely mechanism is the changes in neurohormonal activity. In the heart, this leads to the small disturbances in the cardiac cycle lengths that persist hours before the onset of life-threatening cardiac arrhythmias. In the brain, the same process is manifested by small irregular spikes of excitation that also occur minutes to hours before the onset of epileptic seizures.
2) The recovery process, which has a slow response time relative to the changes in cycle lengths. Usually, it takes several minutes for the recovery to adjust to a change in the pacing cycle length.
However, when the irregularities in the cardiac cycles persist, the recovery properties do not have enough time to complete the adjustment, which leads to progressive increase in dispersion (heterogeneity) of recovery properties between different populations of cells. The “critical zones” are usually those places that are close to either anatomical barriers, cells with disease-induced abnormalities (ischemia), or pre-existing differences in the recovery times such as the M-cells in the heart. Those are the necessary conditions for the cascade of accumulating instabilities to begin. However, they are not sufficient for the ultimate failure of the control mechanisms and the ultimate breakup.

3) The sufficient conditions include the persisting dynamical instability that consists of:
   – irregular sequence of stimulation cycles and
   – accumulating delays and increasing spatial dispersion (asymmetry) of recovery times.

Note that the gradual character and subtlety of the destabilization are important for “disorienting” the system safeguards. For example, a very early stimulation in the heart would be blocked completely and allow the recovery properties to return to normal.

Below, we provide a plausible model of this gradually progressing cascade of events. Note that the process includes dynamics of 2 dependent sequences (irregularities in pacing cycles and recovery times) with different properties (the recovery time has a delayed adaptation to the changes in cycle lengths). Thus, this is a 2d-dynamical process, which can lead to chaos with a much smaller nonlinearity than 1d-process [May]. Is it possible that the smaller nonlinearity is the reason for much longer time that is requires for the slow temporal evolution of this destabilization?

First, we consider this process in 1d for a single cell. We show that the stimulating cycle irregularities lead to the progressive heterogeneity (asymmetry) of the action potential waveforms due to the pre-existing subtle differences in activation and recovery times. These pre-existing differences are very small so that different cells start almost at the same initial conditions but end up with completely different recovery properties. Thus, this process creates an “inter-cell” disorganization and chaos.

After that in 2d, we consider the dynamics of the propagating waves of excitation and show that this process leads to the accumulation of activation irregularities and an ultimate breakup of the propagating wave. Again, we need a long time and the “smallness” for these irregularities to produce a wave breakup.

Next, we describe the similarities between the cascades of events in the heart and brain, which lead to cardiac arrhythmias and epileptic seizures, respectively.

Finally, we show how the differences in the recovery times between the cardiac cells and the brain cells determine the differences in the radius and the period of rotation of the spiral waves in the heart and the brain.

The general plan consists of 3-4 pieces:

1) Analytical analysis of the governing system of differential equations to identify unstable states of the system and how they can be reached (changes in parameter beta).
2) Analysis of temporal dynamics of the system of ODE described above using an approximation by a simple difference equation to find the destabilization parameters.
3) Analysis of the destabilization parameters identified in Section 2 using real data.
4) Finally, we might also consider de-synchronization of cardiac cells, which are normally synchronized by intercellular coupling, but become de-synchronized when the coupling becomes weaker or breaks. This happens in a number of diseases.

Action Potentials (review)

The resting Membrane Potential

- Due to ion concentration gradients between the extracellular and intracellular fluids, most cells have a negative resting membrane potential of about -90 mV.
- This can be explained by the selective permeability of the cell membrane to certain ions, namely sodium (Na$^+$), potassium (K$^+$), and chloride (Cl$^-$).
- Look at the following figure. When K$^+$ ions diffuse out of the cell down their concentration gradient, they pull various organic anions near the cell membrane. Those anions, however, cannot cross to the extracellular fluid. The separation of the two ions thus creates a potential across the cell's membrane.

Potassium, Sodium, and Chloride ions flow down their concentration gradients.

- The membrane resting potential depends on the membrane's permeability (P) to the various ions and their concentrations inside and out of the cell. It can be estimated using the Goldman equation, itself derived from the Nernst equation:

\[ V_m = \frac{R T}{F} \ln \left( \frac{P_{Na} [Na^+]_o + P_{K} [K^+]_o + P_{Cl} [Cl^-]_o}{P_{Na} [Na^+]_i + P_{K} [K^+]_i + P_{Cl} [Cl^-]_i} \right) \]

The Action Potential

As you read along, click in the check boxes to change the images.
• Certain cells have ion channels that allow them to quickly change the cell membrane permeability to specific ions.
• Excitation of these cells usually opens Na\(^+\) channels, allowing an inrush of Na\(^+\) ions. The cell membrane potential then becomes positive. The cell is depolarized.
• As the Na\(^+\) channels begin to close, K\(^+\) channels also open. K\(^+\) ions then rush out of the cell, and the membrane potential becomes negative again. The cell is repolarized.
• After repolarization, the membrane potential is usually slightly lower than the resting membrane potential for a short period of time. The cell is said to be hyperpolarized.
• The cell then returns to its normal resting membrane potential. The sequence of events from the depolarization to the return to the normal membrane potential is the Action Potential. The relation between the action potential and the membrane permeability is illustrated in the following figure.
• It should be noted that the action potential only lasts a couple of milliseconds! This fast signal usually propagates through the cell and either causes a physiological response within it, or is transmitted to other cells. The action potential is a fast way to pass messages throughout the whole body.