VIEWPOINT

Integrating beat rate variability: From single cells to hearts

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Introduction

The timescales of variations in cardiac pacemaker rhythmicity expressed as heart rate variability (HRV) are similar in nature to those of other biological processes driven by ultradian, circadian, and infradian clocks.[1] To this end, pacemakers have been defined as "that part of the circadian system … conferring … the ability to persist in rhythmicity without rhythmic environmental input. Without rhythmic input the period of the rhythm expressed by the system will reflect thus its physical-chemico properties."[2]

Consideration of the origins of HRV requires a discussion of fractality, self-similarity, and power-law relations. *Fractals* are "objects or processes whose small pieces resemble the whole"[3]; that is, a fractal is an object or quantity displaying the property of self-similarity on all scales. *Self-similarity* means that an object or a time series is composed of subunits and sub-sub-units on multiple levels that (statistically) resemble the structure of the whole object. The object need not exhibit exactly the same structure at all scales, but the same "types" of structures must appear. Whereas magnification of a nonfractal object reveals no new features (Figure 1A, upper row), as a fractal object is magnified, ever-finer features are seen whose shapes resemble those of the larger features thus demonstrating the concept of self-similarity (Figure 1A lower row, Figure 1B). Prototypical examples of fractals exhibiting self-similarity are listed as follows:

1. *The coastline:* In Figure 1C the length of a Great Britain coastline is measured with different length rulers; the shorter the ruler, the greater the length measured.[3] Furthermore, a double logarithmic plot of the length of the ruler vs the measured length of the coastline provides a straight line whose slope (a number between 1 and 2) describes the power law.
2. *Natural phenomena with fractal features:* Frost crystals forming on cold glass (Figure 1D), Romanesco cauliflower (Figure 1E), and lung airways (Figure 1F).

KEYWORDS Heart rate variability; Beat rate variability; Fractals; Self-similarity; Induced pluripotent stem cell-derived cardiomyocytes
ABBREVIATIONS **BRV** = beat rate variability; **hESC-CM** = human embryonic stem cell-derived cardiomyocytes; **HRV** = heart rate variability; **iPSC-CM** = induced pluripotent stem cell-derived cardiomyocytes; **SAN** = sinoatrial node; **SR** = sarcoplasmic reticulum
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Heart rate variability and beat rate variability

The power spectral density of HRV incorporates several power bands: The high-frequency band is mainly associated with parasympathetic activity, the low-frequency band with sympathetic activity, and the very low and ultralow frequencies are associated with slow oscillations influenced by thermoregulation, hormonal activity, and other less-defined factors. The very low and ultralow bands in the human heart manifest a property—the power-law behavior—which is common to many representations in nature, such as scale of hurricanes and earthquakes, volcanic eruptions and floods, meteorites size, physiologic measurements, and heart rate fluctuations. Specifically, applying a line-fitting algorithm to the measures of log power on log very low and ultralow frequencies of the power spectrum provides a line with a slope denoted by β. A β of 1 is also known as 1/f, or power-law relation. Different slopes can be distinguished in settings such as myocardial infarction, heart transplant, and aging.[4,5]

Consistent with the behavior of the in situ heart, our recent findings indicated that "human embryonic stem cell-derived cardiomyocytes (hESC-CM) and induced pluripotent stem cell-derived cardiomyocytes (iPSC-CM) exhibit beat rate variability (BRV) and power-law behavior," resembling HRV in the human sinoatrial node (SAN).[6] Specifically, hESC-CM and iPSC-CM exhibit self-similar

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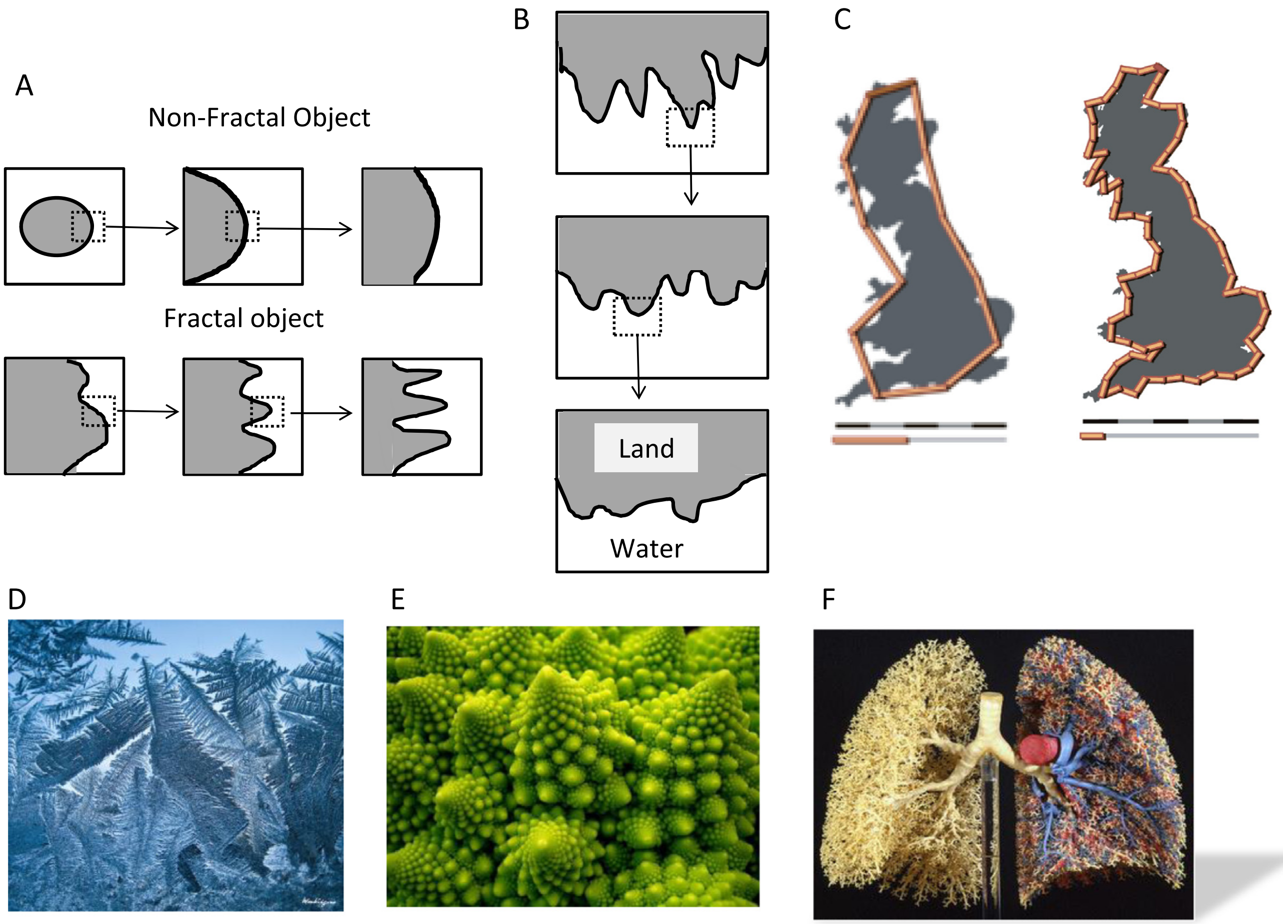

Figure 1 Presentation of the basic concept of fractality and selfsimilarity. **A:** A schematic illustration depicting the difference between a fractal and a nonfractal object. **B:** A schematic illustration depicting the concept of selfsimilarity. Both illustrations are adopted from Reference 3 by permission of Oxford University Press, USA. **C:** An example of the coastline paradox. If the coastline of Great Britain is measured by using fractal units 100 km (62 mi) long, then the length of the coastline is approximately 2800 km (1700 mi). With 50 km (31 mi) units, the total length is approximately 3400 km (2100 mi), approximately 600 km (370 mi) longer (http://en.wikipedia.org/wiki/Coastline_paradox). Natural phenomena with fractal features: frost crystals formed naturally on cold glass (http://www.flickr.com/photos/monteregina/6635078819) (**D**), Romanesco broccoli (**E**) (http://www.flickr.com/photos/sasha_kopf/2063282413), and lung airways (**F**).

long-range oscillations having fractal-like features of the beat rate time series as does the SAN.[7,8] Although hESC-CM and iPSC-CM grow in culture devoid of neural and humoral inputs, both share the feature of fractal behavior with the in situ SAN, suggesting that the origin of this power-law behavior is an *intrinsic* feature of pacemaker cells. These findings are consistent with previous studies, showing that the rhythmicity of spontaneously beating cardiomyocytes in culture[9–11] and the rhythmicity of other excitable cells (eg, single presynaptic neurons in feline rostral ventrolateral medulla) exhibit self-similarity and fractality.[12]

An important issue raised by these findings is whether BRV and HRV have the same mechanism and origin. A robust body of research shows that “steady-state” characteristics of biological systems result from the integration of oscillations, rhythms, and clocks, which are essential for the regulated function of an organism.[1] Hence, the sources for HRV of the in situ heart might be considered in terms of the non-steady-state firing patterns of individual cardiac pacemakers, the interactions among neighboring pacemakers in a cluster, and the external environment’s influences on all these.

Relating HRV to BRV

While relating HRV to BRV, we first consider the fractal behavior of hESC-CM and iPSC-CM and use the SAN as a model for comparison. In the normal heart, HRV reflects the modulation of the SAN pacemaker function mainly by the autonomic nervous system activity. However, in hearts lacking direct autonomic neural input, cardiac rhythm dynamics are sufficiently altered to suggest roles for other intrinsic cardiac regulatory mechanisms and for circulating neurohumors.[4]

Hence, we asked whether HRV is simply the in situ manifestation of BRV, with the impact of the sympathetic and parasympathetic nervous systems and of extracardiac inputs added to it. This simple question requires us to dissect a complex subject—the origin of the oscillatory activity and pacemaker activity in the heart. Oscillatory activity is a