Research Article

International Journal of Cardiology and Cardiovascular Disorder

A Mathematical Theory of Heartbeat

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Submitted : 5 Aug 2023 ; Published : 24 Apr 2024

Citation: Lewis, T. G.(2024) A Mathematical Theory of Heartbeat. I J cardio & card diso; 5(2):1-4.

Abstract

This article develops a novel mathematical theory of pacemaker operation using complexity theory and network science ideas. Specifically, the author claims that pacing is a byproduct of emergence of a self-synchronizing electrical network in humans (and animals) based on a fundamental property of feedback networks – aperiodicity. The exceptional resilience and reliability of the ordinary heartbeat may be due to the emergence of a self-organized network in the sinoatrial node and the particular property of aperiodic networks. Clinical studies should be performed to verify the model.

Using simulation, we show that aperiodic synchronization arises almost naturally in random network structures due to the presence of many feedback loops with lengths that are relatively prime to each other. Furthermore, we show that nearly any random network of sufficient density "naturally" forms an aperiodic subset of nodes that synchronize to provide a reliable and resilient "clock" for regulating biological rhythms such as heartbeat.

Keywords: Heartbeat, sinoatrial node, complex networks in cardiology, aperiodic network, self-correcting network, network resilience.

A Novel Theory

The human heart performs remarkably reliably and resiliently for more than 2.5 billion beats in a normal lifespan. It relentlessly repeats a rhythmic pulse regardless of occasional mis-beats and under a variety of heart conditions called "remodeling." The question posed here is "how does heartbeat work at the basic level and why is it so reliable and resilience?"

Briefly, heartbeat begins in the sinoatrial node (SAN) — the natural pacemaker of the heart. The SAN pulses the heart about once every second or two, under normal conditions, but when something goes wrong, a SAN dysfunction (SND) occurs. Until recently the pathophysiology was incompletely understood, "After over 100 years of studying the SAN and its disease we are still uncovering new insights into pacemaker function. Ion channel remodeling is now thought to be a major contributor to SND and the pattern of remodeling in different diseases can be wide and complex." (Choudhury et al., 2015).

We propose a novel mathematical theory of heartbeat focusing on the SAN. This theory is mathematically sound but lacking in clinical proof. We hope that by modeling heartbeat as a mathematical system using network science our results will stimulate additional studies into the electrical network of the sinus node to unravel its secrets and improve treatment of SNDs.

The SAN

The sinoatrial node is located in the upper anterior region of the heart's right atrial. The node consists of clusters of pacemaker myocytes arranged in parallel rows with short fingerlike protuberances that interconnect forming a network with the surrounding atrial tissue. These specialized cells are interspersed with nerves and capillaries and supported by dense connective tissue to form the *SN pacemaker complex* that drive the rhythmic contraction of the heart muscles to pump blood (John, & Kumar, 2016; Boyett et al., 2000).

In 2016 researchers presented a heart modeled as an elastic-fluid biphasic material. They explained the rhythmic beating is due to "strong stiffness dependence in both the heartbeat velocity and strain in isolated hearts, as well as the strain for a hydrogel-cultured cardiac myocyte, in quantitative agreement with recent experiments" (Chiou et al., 2016). This mechanical model does not explain how heartbeat maintains rhythmic perpetual motion on its own but does illustrate the plausibility of mechanical contraction approximating the actual action of a heart.

We know that multiple electrical currents are involved in pacing the SN. While the electrochemical interactions are well known, the detailed circuitry has not been studied in detail. There is

no published network description of the inner workings of the sinus node, tracing rhythmic beating to the node's circuitry. For example, we do not know all of the wiring among and between the pacemaker myocytes. Also, remodeling of the pacemaker complex heavily impacts the pacemaker's ability to perform reliably and resiliently. This hints at the possibility of discovering deeper mechanisms within the pacemaker complex.

More recently, researchers have applied *network science* to cardiology in order to understand the heart's complexity and its complex operations – among them, the complexity of heartbeat. Network analysis was used in (Sama et al., 2020) to identify protein–protein interaction networks associated with heart failure caused by restricted blood flow. Network science proved to be a useful tool for modeling the flow.

The notion of synchronization within a network began to appear in the literature circa 2019 when researchers reported the dynamics of synchronized networks and heartbeat-evoked responses, i.e., how heartbeat is processed at the brain's cortical level (Kim & Jeong, 2019). The researchers studied the brain's interaction with heartbeat rather than the sinus node. The topology of the electrical network of the SAN remains unknown, however, at this time.

Shao was perhaps the first to apply network analysis directly to the study of the human heartbeat for the purposes of diagnosis (Shao, 2010). Shao was interested in the statistical properties of both networks and heartbeats rather than the topological network structure of the sinus node re: its operation. On the other hand, the author is interested in the relationship between heartbeat and network structure – a topic more akin to complex network science.

More to the point, network science is a branch of complexity science which embraces emergence as a force, and sometimes replacement, for traditional formulas and equations as models of reality in physical systems. Emergence of structure from non-structure or randomness is a form of self-organization that the author believes contributes to understanding how the biological pacemaker evolved and works every minute of every day. How does the SAN "know" went to beat, and how does it recover from miss-beats?

The remainder of this article develops a novel mathematical theory of pacemaker operation using complexity theory and network science ideas. Specifically, the author claims that pacing is the byproduct of emergence of a self-synchronizing electrical network in humans (and animals) based on a fundamental property of feedback networks – *aperiodicity*. The exceptional resilience and reliability of heartbeat may be due to the emergence of self-organization and the particular property of aperiodic networks.

The following mathematical theory has not been verified clinically. It is the author's desire that this theoretical work be followed up by research to verify the theory. We make no claims beyond the fact that mathematical properties of aperiodic networks match the rhythmic and incessant beating of the human heart.

The Theory

Network science may be applied to understand how heartbeat works by abstracting away details of myocytes and ion channels in the sinus node and modeling the interior structure of the sinoatrial node as a network system. We assume the following:

- Electrical potentials (created electrochemically) flow through channels that, taken together, form a network of nodes (myocytes) and links (channels).
- Multiple nodes combine potentials to amass enough potential to stimulate the heart muscles into contracting.
- The network of nodes and links form a structure that intrinsically "beats" due to its structure. That is, rhythmic pulsing is a direct product of network structure, i.e., its topology or connection matrix.
- In theory, it is possible to predict the rhythmic pulsing by careful study of network topology as it applies to the SAN.
- Theory is converted into a working computer model by simulating the network and adding up the total response potential of nodes in the network. The computer model is run, and the results compared with the rhythmic beat of a heart.

The Mathematics

Watts (Watts, 2003) describes the behavior of a certain species of cricket found in South America to illustrate how an unstructured network synchronizes and becomes an orderly network simply because of nearest-neighbor connections. Crickets listen, chirp, listen, chirp, etc. at random, initially. Over time, they all listen at the same time and chirp at the same time. That is, they synchronize without any central authority or external control mechanism. Hagberg and others (Hagberg & Schult, 2008; Lewis, 2009) have subsequently shown that the transition from chaotic chirping to orchestrated chirping is inevitable in some networks and not in others, depending on the topology of the interconnections. We show that a very simple test can determine under what conditions a given network synchronizes.

We use the chirping crickets metaphor to guide the design of a mathematical model of the sinoatrial node with its cluster of specialized pacemaker cells. Furthermore, we speculate that these cells are wired together into a network interconnected in such a way that they behave like chirping crickets. That is, they pulse, wait, pulse, and wait in a never-ending sequence.

A simulation of the chirping and potential synchronization of a network was programed to illustrate the theory and mathematics. In this simulation, pulsing nodes are colored red and a non-pulsing cell is colored white as illustrated in Figure 1. At each point in time, simulated by an interval timer, the entire network of interconnected nodes is updated. Nodes that were previously red, turn white, and white nodes with at least one red node connected to the white node are turned red.

Synchronization occurs when nodes turn red (white) at the same time.

We assume the connections point in a direction (of electrical flow). Whenever a cell detects a signal from any one of its incoming links, it will pulse (red) in the subsequent time frame and then go dormant for one time period before it repeats the process – either turning red or white for a time interval. The "all on" versus "all off" state of the network is what forms a pulse that in turn, stimulates a heart.

The network must self-synchronize because there is no watchman watching to polarize each node to make sure it pulses on time. Furthermore, in order for the sinoatrial node to produce enough electric shock to pace the heart, all of the cells must "chirp" together. Thus, the signal coming from the sinus node is the sum of potentials of all pacemaker cells. If fewer than all 100% pulse in harmony, the heartbeat will be weak and at some point it may not be able to make a heart pump.

Aside from the actions of the chirping network, the mathematical model is simply to sum up all pacemaker cell states to provide enough charge to polarize the walls of both atrial and ventricle chambers. Heartbeat H(t) at time t is simply the sum of n cell potentials, where cellj represents the "color" or potential of the jth pacemaker cell (node) in the network.

$$H(t) = \frac{1}{n} \sum_{all\ cells} cell_j\,(t)$$

$$cell_j(t) = \begin{Bmatrix} 1 & ;\ if\ pulsing\ (red) \\ 0; & otherwise\ (white) \end{Bmatrix}$$

Networks containing nodes that repeat rhythmically and pulse in unison are said to synchronize. If one node fails to synchronize the network must automatically re-synchronize. A partial fractional sum H(t) is possible and common, but an uncoordinated and chaotic pulsing leads to pathologies such as arrhythmia, and death. H(t) for synchronized networks is constant and has a rhythmic period as shown in Figure 1.

Alternatively, unstable or chaotic networks are inherently un-synchronizable. When the nodes behave erratically over a short period of time before stabilizing, we call such behavior chaotic – a temporary-only condition of inherently stable networks. Thus, the goal of a pacemaker is to self-correct if an error occurs and re-synchronize.

"How does a biological system such as the myocytes in the SAN organize themselves into a state of perpetual oscillation, even when occasional errors occur? The answer is the same for hearts as it was for Watts and crickets. The wiring of a directed network must form an aperiodic network in order for it to synchronize and oscillate, forever. And an *aperiodic network* is one in which the length of its feedback loops, counted as the number of links around the loop, are relatively prime numbers. That is, their greatest common denominator, GCD, is one.

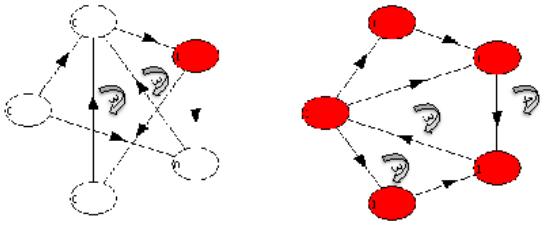
Figure 2 illustrates periodic versus aperiodic. The test is simple. An aperiodic network is guaranteed to synchronize regardless of initial state, while a periodic network is not. For example, in Figure 1a, there are two feedback loops of length 3 each. GCD(3, 3) = 3, therefore, the network is periodic and does not synchronize. In fact, if any nodes are initially pulsed, they eventually dissipate and pulsing ceases.

The two networks in Figure 2 are nearly identical. Only the wiring differs, slightly, but the difference is enough to change the network from periodic to aperiodic. The periodic network will repeat a pattern of activated nodes but will never synchronize with all nodes active at once.

(a). H(t) of a healthy heartbeat (simulation).

(b). H(t) of a sick sinus node (simulation).

Figure 1: Examples of oscillations that synch versus one that does not. (a) Illustrates the constant rhythmic output H(t). (b). Illustrates an uneven output H(t) even though pulsing may be rhythmic.

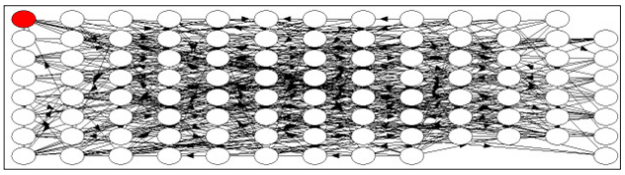


(a). Periodic GCD(3, 3) = 3 (b). Aperiodic GCD(3, 4) = 1

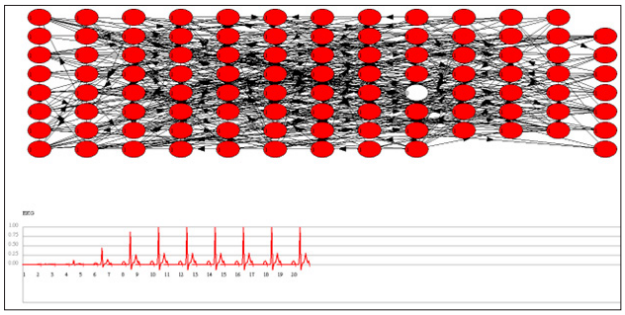
Figure 2: Two nearly identical networks with n = 5 nodes and m = 7 links, each. (a). A periodic network with GCD(3, 3) = 3 fails to synchronize. (b). An aperiodic network with GCD(3, 4) = 1 synchronizes.

#nodes	#links	Density	%Synched
100	150	0.030	25
100	200	0.040	88
100	300	0.060	92
100	400	0.080	99 - 100

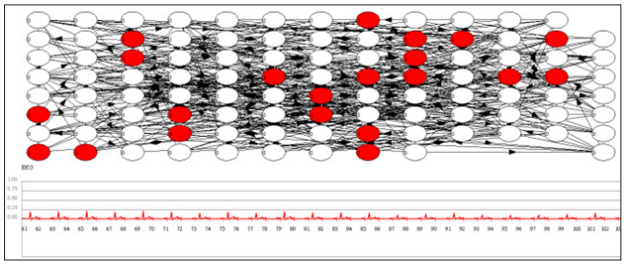
Table 1: Synchronization of random networks versus density.



(a) Initial state with one pulsed node. The "wiring" is random in the sense that connections obey a Binomial distribution.



(b). Steady state is quickly reached and stabilizes with 99% of nodes pulsing.



(c). Degraded synchronization when probability of fault in pulsing is 65%, e.g., the signal is not passed forward.

Figure 3: A random network with 100 nodes, 400 links quickly synchronizes and remains in sync even when up to 65% of the pulses fail to reach the next node. Note the lower value of H(t) when the fault rate is 65%.

Results

How common are aperiodic (synchronizing) networks in biological systems? That is, how likely is a biological organism to form an aperiodic network to control rhythmic motions such as flapping wings, breathing, and beating of a heart? As it turns out, aperiodic topology is common, arising in random networks of sufficient density. That is, the likelihood of aperiodic cycles forming in a random network increases with its density. Also, the number of nodes that synchronize increases with density, see Table 1 and Figure 3.

Dense random networks easily synch and stay synched under relatively high fault rates, but topology matters. For example, scale-free networks are just the opposite – they are difficult to synch and quickly fail under modest fault rates. (Chiou et al., 2016). This is due to the difficulty in forming cycles in a typical scale-free network.

The evolutionary path from non-pulsing heartbeat to one regulated by a network of myocytes and their interconnection is not difficult to conjecture. A random network with sufficient density is highly likely to be aperiodic. Starting with a shock that randomly pulses some nodes and not others a random network can quickly self-organizes into a rhythmic synchronization – all it takes is one pulsed node to start a chain reaction, if the topology is aperiodic.

This is a theoretical result. It needs clinical verification before we can say that heartbeat is regulated by an aperiodic SAN. If, however, it is verified, the treatment for some forms of SND are obvious.

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