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Deterministic Chaos: Applications in Cardiac Electrophysiology

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DETERMINISTIC CHAOS

APPLICATIONS IN CARDIAC ELECTROPHYSIOLOGY

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I. INTRODUCTION

Our universe is a complex system. It is made up of many moving parts as a dynamic, multifaceted machine that works in perfect harmony to create the natural world that allows us life. The modeling of dynamical systems is the key to understanding the complex workings of our universe. One such complexity is chaos: a condition exhibited by an irregular or aperiodic nonlinear deterministic system. Data that is generated by a chaotic mechanism will appear scattered and random, yet can be defined by a system of nonlinear equations. These mathematical equations are characterized by their sensitivity to input values (initial conditions), so that small differences in the starting value will lead to large differences in the outcome. With deterministic chaos, it is nearly impossible to make long-term predictions of results.

A system must have at least three dimensions, and nonlinear characteristics, in order to generate deterministic chaos. When *nonlinearity* is introduced as a term in a deterministic model, chaos becomes possible. These nonlinear dynamical systems are seen in many aspects of nature and human physiology. This paper will discuss how the distribution of blood throughout the human body, including factors affecting the heart and blood vessels, demonstrate chaotic behavior.

The physiological studies presented in this paper represent some of the investigations into the chaotic systems that can be found in the human body. With modern computing technologies, we are able to identify patterns that were previously thought to be random variations of regular systems, such as the heartbeat. By understanding these systems on a

mathematical level, scientists can produce mathematical models of irregular oscillations within the body. Currently, research is being conducted to develop chaos control techniques to treat patients with heart rhythm irregularities. This paper will first introduce chaos theory in a historical context, and then present some of its modern scientific applications.

II. CHAOS THEORY

In the 1880s, Henri Poincare was studying the motion of an asteroid under gravitational pull from Jupiter and the sun. The most effective way to investigate the behavior of such a system was to use nonlinear differential equations [16]. These equations were first developed by Sir Isaac Newton in the 1600s, but were heavily studied throughout the 1700s and 1800s [20]. Poincare recognized that in order to model a physical system that evolves over time, one must use a sufficient list of parameters to be able to define the state of the system at any given moment. The values of data measured in time can be made into an object in space, called *the phase space set*. In this case, the phase space set is the set of all possible positions and velocities of the asteroid. Poincare's model was known as the "return map" of the asteroid. This marked an important moment in the timeline of mathematical history by recognizing the sensitivity to initial conditions that models, such as those of the solar system, necessarily demonstrate [1]. Mathematicians studied Poincare's return map, and found that small differences in the initial conditions will lead to very large differences in final outcomes. Therefore, predictions of an asteroid's location based on estimations of its initial conditions are impossible [1]. This was the first time the existence of chaos in natural phenomena was formally recognized by the scientific community.

In the 1920s, Dutch physicist Balthasar Van der Pol modeled an oscillator with nonlinear damping by constructing elec-

Dynamical System
A mathematical model used to determine the state of a system as it moves forward in time.

Nonlinear Damping
The damping term of a differential equation is multiplied by the first derivative, causing the motion of the system to decay over time. Nonlinear damping implies that this term is not linear, so the effect of this damping fluctuates over time.

Oscillator
A generator of periodic motion or electrical currents

trical circuits according to the differential equation [16]:

$$\frac{d^2x}{dt} - \epsilon\,(1\text{-}x^2)\,\frac{dx}{dt} + x = 0$$

In this model, t is time, x is the dynamic variable, and ϵ is the parameter that can increase or decrease the influence of the nonlinear term. This can be converted to a first order system by letting y = $\frac{dx}{dt}$

$$\frac{dx}{dt} = y$$

$$\frac{dy}{dt} = -x + \epsilon(\,1 - x^2\,)y$$

The parameter ϵ allows for increased or decreased levels of non-

linearity, dependent on the system being modeled. Leonhard Euler first proposed this method of solving second order equations by reducing them to first order in the 1700s, when he developed the technique of using an integrating factor to solve differential equations [20]. Van der Pol also examined the response of the oscillator to periodic forcing, modeled as:

$$\frac{d^2x}{dt^2} - \epsilon \, (1\text{-}x^2) \, \frac{dx}{dt} + x = F \cos \frac{2\pi t}{T_{in}}$$

where ϵ determines the frequency of self-oscillations, while the $F \cos \dfrac{2\pi t}{T_{in}}$ term introduces a frequency of periodic forcing [15]. T_{in} is the term for an induced electrical current. With this system, Van der Pol found irregularities in the electrical impulses that he could hear by inserting telephone receivers into the circuits [15]. When periodic forcing is added to a system, its solutions behave seemingly unpredictably [16]. This had been seen already with Poincare's return map of the asteroid, where the periodically varying gravitational forces on the asteroid demonstrated a similar effect. Although Van der Pol did not identify the underlying structure of a chaotic system, the irregularities in his

circuit were an example of deterministic chaos, demonstrated in this system when nonlinearity is sufficiently strong [15].

In the 1960s, Edward Lorenz was studying meteorology at the Massachusetts Institute of Technology (MIT). Somewhat accidentally, Lorenz came across the phenomenon of sensitivity to initial conditions; he noted that the same calculation, when rounded to three-digit rather than six-digit figures, came to different solutions that were amplified exponentially with iterative multiplications [1].

In his study of the initial conditions and subsequent modeling of weather patterns, Lorenz saw the same results with these climate models that he had seen in the dynamics of his own calculations. Lorenz presented his models of chaotic systems in 1972, when he introduced the concept of the butterfly effect. This concept is one of sensitivity to initial conditions: the mere flap of a butterfly's wings may drastically affect global climate systems. The computer graphic of his chaotic system was the first representation of an "attractor" [1], which is a specific set of values toward which a system evolves. It was here, thanks to Lorenz, that chaos theory was born. A *Lorenz attractor* is a common model now used to represent chaotic systems similar to those of climate dynamics.

Since the 1960s and the advancement of computing technology, we have been able to create models for many systems in a similar way to Edward Lorenz's foundation of the chaotic attractor. Though much climate and biological data appear to have been generated randomly by the universe, it can actually be modeled with nonlinear dynamical systems, and often generates chaos.

Though random data sets and those that are generated by chaotic mechanisms may look very similar, there are ways to tell whether or not a system demonstrates deterministic chaos. In order to differentiate between random and chaotic data sets, one must first look at the phase space set of each system. Let each point in a phase space have coordinates $x = z\,(n)$ and $y = z\,(n+1)$. If the phase space set fills the two-dimensional space with scattered points, this would indicate that the set of data was

generated by a random mechanism. Its fractal dimension will be very high, meaning that the number of independent variables needed to determine a relationship for the data is infinite. If the set does not fill up the two-dimensional space, it will form some object (an attractor) in space with a low fractal dimension [8]. This would demonstrate a deterministic relationship between n and $n+1$. The fractal dimension of a phase space set is usually a non-integer value. The smallest integer that is greater than or equal to this value is the number of independent variables in the deterministic relationship [8].

To summarize, in a randomly generated data set there will be an infinite number of factors that determine the results, and therefore the dimension of the phase space set is infinite. In a data set that shows deterministic chaos, the fractal dimension will approach a non-integer constant [8]. This is the essence of chaos theory. As we will see, this theory is applicable to irregularities in the cardiovascular system, and can help us mathematically understand abnormalities of the human heart.

III. CHAOS IN THE CARDIOVASCULAR SYSTEM

The human heart has approximately two billion muscle cells [6]. The sinoatrial node is a group of cells in the right atrium that sends out regular electrical impulses every time the heart beats. These impulses cause the right atrium to contract, and they set a person's heart rhythm, referred to as their regular sinus rhythm. The atrioventricular node is located between the right atrium and right ventricle. This group of cells sends out a secondary set of electrical impulses, causing the ventricles to contract, but leaving enough time (about one tenth of a second) after each beat for the ventricles to fill with blood. These impulses initiate the necessary pulsing of blood throughout the body. It is a delicate system; if the electrical impulses are even slightly off, the systole and diastole (contraction and relaxation) of the heart muscle will be seriously affected. Our bodies must maintain a certain blood pressure to push essential nutrients throughout the bloodstream. Similarly, the hemoglobin in our blood, which

carries oxygen to our cells, provides for the vital functioning of our organs. Maintaining healthy blood pressure and heart rate is the essence of our well-being, which is why it is so important for scientists and medical professionals to recognize and resolve errors in the system.

Instances of chaos have been found in many cardiovascular system irregularities, including premature ventricular contractions, atrial fibrillation, bradycardia, tachycardia, and cardiac arrhythmia [11]. Premature ventricular contractions are heartbeats that begin in ventricles and disrupt normal rhythm, causing irregular or skipped beats. Atrial fibrillation is caused by the presence of too many electrical impulses in different locations within the cardiac tissue [12]. The spontaneous contraction of cardiac muscle fibers results in a lack of synchronism between the heartbeat and the pulse, so that there is not enough blood being pumped to the body's cells [12]. Ventricular tachycardia is an

Iterative Multiplications
Calculations that multiply repeatedly, using the previous output as the input for the next multiplication.

Periodic Forcing
A term that represents an external influence on the system that repeats after a defined time interval.

Isotropic Upon Rescaling
The shape of the figure remains the same despite zooming in to a small piece or zooming out to the whole object.

A PERFECT EXAMPLE OF THIS IS THE SNOWFLAKE… IT CONTAINS A SEEMINGLY INFINITE NUMBER OF CRYSTALINE PATTERNS

abnormally rapid heartbeat originating in the ventricles, while bradycardia is an abnormally slow heartbeat. Arrhythmia is a generally abnormal heart rhythm [12]. In this paper, these factors of irregularity are generally referred to as *heart rate variability.*

It is incredible to consider how the minor imperfections and complexities in all living things can in fact be defined by mathematical principles. Most objects we observe in our daily lives have continuous curves, but these curves are typically not differentiable. Self-similarity, the notion of the small patterns reflecting the larger patterns of a system, is demonstrated in abundance in the natural world. A perfect example of this is the snowflake: upon magnification, it contains a seemingly infinite number of crystalline patterns that reflect the image of the flake as a whole, so that it is isotropic upon rescaling [7]. Though we are familiar with Euclidean geometric figures, we often fail to recognize the inherent complexity of the natural structures that surround us.

Polish mathematician Benoit Mandelbrot first introduced the term *"fractal"* in 1975 to characterize these forms [7].

Like chaos, a fractal pattern cannot be effectively conveyed with estimation [7]. For example, if maps had curves that estimated the fractal dimension of a shoreline, we would not be able to accurately measure its distance or determine the shape when trying to land a ship. If the inherent complexity of the shoreline is not displayed, the necessary information is lost. Many aspects of our physiology demonstrate fractal patterns. As in the crystals of a snowflake or branches of a willow, these patterns make up our very cells. Self-similarity can be witnessed in the dendrites of nerve pathways, the blood vessels in the retina, and the bronchioles in the lungs. These self-similar patterns throughout the human body may be determined by some very basic rules in our genes. Perhaps this is how our bodies can display millions of such seemingly intricate structures with only 100,000 genes to guide their production [8]. There is evidence that the fractal branching design generates the most efficient way for blood to travel throughout the body by minimizing the work of transport between cells [5]. While the organization of the passage of fluid and electrical signals through the body can be revealed by fractal analysis, the underlying dynamics of the system can be understood by chaos theory.

In his article "Deterministic Chaos and Fractal Complexity in the Dynamics of Cardiovascular Behavior," Vijay Sharma writes, "Deterministic chaos describes a system which is no longer confined to repeating a particular rhythm, and is free to respond and adapt" [5]. Our heart is a perfect example of this phenomenon. According to Sharma, the interaction of calcium oscillators in the cytoplasm initiate rhythmic changes in the diameter of blood vessels, which exhibit chaotic behavior. Decreasing the local pressure within vessels by increasing their diameter will induce regular periodic dynamics (i.e. non-chaotic behavior). When resistance vessels are activated, chaotic

behavior will initiate. Since the sympathetic nervous system regulates the level of the resistance vessels, its activity is one of the contributing factors to chaotic behavior in vasomotion [5]. Using techniques that control initiation of the sympathetic nervous system, this chaotic behavior can be artificially induced in a lab. It has also been shown that chaotic behavior increases with increased activity in the parasympathetic nervous system. This may be due to the fact that short-term variation in heart rate is predominantly influenced by the parasympathetic nervous system. Therefore, both sympathetic and parasympathetic nerve pathways affect long-term heart rate variability, and the variability can be modeled using deterministic systems [11].

With perfusion pressure control mechanisms, the chaotic behavior can be physically increased or decreased. Various drugs that affect blood vessels can change the heart rate's sensitivity to initial conditions. Studies of mammalian blood pressure variability show that nitric oxide inhibitors, for example, decrease the chaotic behavior of the system. In 2012, Siroos Nazari and his colleagues at Payame Noor University in Tehran modeled the intrinsic pacemakers in the heart muscle: the sinoatrial (SA) node, atrioventricular (AV) node, and the His-Purkinje bundles. The SA node is recognized as the primary natural pacemaker of the heart; it is located in the right atrium and generates an electrical current of 60-100 beats per minute. The AV node and His-Purkinje bundle function as a secondary system between the right atrium and right ventricle and beat at a slower rate [12].

Nazari claims that the dynamic behavior of the heart is similar to the Van der Pol oscillator. The model they present uses the Van der Pol equations as a starting point, including a term for periodic forcing that accounts for electrical stimulation of the heart. For the purpose of this paper, I will present the models

Sensitivity to Initial Conditions
A characteristic of a system that causes minor changes in the input values to yield drastically different results. This can be tricky, since a small error in numerical approximation to initial conditions can demonstrate drastically different long-term system behavior.

Periodic Forcing
A term that represents an external influence on the system that repeats after a defined time interval.

Vasomotion:
The oscillating changes in the diameter of blood vessels. Vasomotion affects blood pressure independently from the hearbeat.

for the SA and AV nodes as follows and exclude the fifth and sixth equations for the His-Purkinje bundle [10].

Sinoatrial Node:

$$\frac{dx_1}{dt} = y_2$$

$$\frac{dy_1}{dt} = -d_1(x_1^2 - 1)y_1 - c_1 x_1 + a_1 \cos wt + R_1(x_1 - x_3)$$

Atrioventricular Node:

$$\frac{dx_3}{dt} = y_2$$

$$\frac{dy_2}{dt} = -d_2(x_3^2 - 1)y_2 - c_2 x_3 + a_2 \cos wt\ R_2(y_1 - y_2)$$

The parameter w represents external electrical stimulation and gives the term for oscillator frequency. The coefficients d_1 and d_2 affect the nonlinearity of the system and cause stability of the limit cycle. A more stable limit cycle results in values that return quickly to the attractor. c_1 and c_2 represent the frequencies of the SA node and AV node, respectively. R_1 and R_2 are the coupling coefficients between nodes. An example of this relationship would be if $R_1 = 0$ and $R_2 > 0$, then the SA node has an effect on the AV node, but not vice versa. In another case, if $R_1 > R_2$, then the AV node has a greater effect on the SA node [10].

Numerical simulations were carried out in a computer program to demonstrate that the model they developed does capture the dynamics of regular sinus rhythm. Various heart conditions were taken into account by manipulating the coupling coefficients to represent different interactions of the SA and AV nodes. Nazari and his fellow scientists concluded that their heart model could be chaotic or non-chaotic, depending on the size of the nonlinearity parameters, d_1 and d_2 [10].

Twenty years prior to Nazari's work, research concerning heart rate variability had sparked the interest of the mathematical community in North America. In 1990, Leon Glass and his colleagues at McGill University studied heart cell aggregates in chicks and the overdrive suppression evident after periodic electrical stimulation of the heartbeat. Overdrive suppression occurs when the heart rate is overstimulated to the point that the intrinsic frequency of spontaneous heart rhythm actually slows. This occurs naturally in the heart, where the spontaneous electrical activity of the SA node is of a higher frequency than the activity in other nodal firing sites, such as the AV node. The rapid firing of the SA node creates an increased level of sodium ions, resulting in a chain of chemical events that prevent the spontaneous generation of beats in the other pacemaker sites [18]. Various other ionic mechanisms play a role in overdrive suppression, including extracellular and intracellular calcium and potassium imbalance [13]. This study investigated the effects of artificial stimulation frequency, amplitude, and variation. The scientists measured the number of beats between electrical stimulations, and found that the spontaneous beats varied with the frequency of artificial stimulations. Both artificial impulses and spontaneous beats were found to be coupled in the integer ratios of 1:1, 2:1, and 2:3, depending on the frequency of artificial stimulations, demonstrating a nonlinear response [8].

The mathematicians involved in this research came up with a system of nonlinear differential equations to model their results. They began with a piecewise linear approximation to the Van der Pol equations to represent the cardiac cycle. Other biological oscillators have been modeled in this way since Van der Pol's work with simple sets of ordinary differential equations [13]. This model is written as

$$\frac{dV}{dt} = \frac{1}{\epsilon}\left[y - f(V)\right]$$

$$\frac{dy}{dt} = a(V)$$

where $V(t)$ is the experimentally observed transmembrane voltage. This is the measurement of electrical activity in the heart. Essentially, $V(t)$ is the calculation of movement of positive ions from intracellular to extracellular space. This change in voltage

is referred to as an action potential. $f(V)$ and $a(V)$ are piecewise linear functions of V. ϵ is a positive constant parameter. When ϵ is small ($0 < \epsilon << 1$), the oscillations will quickly return to the attractor [13].

Since the main assumption of this study is that overdrive suppression is a consequence of the outward electrical current, the researchers had to include a term for a history-dependent hyperpolarizing current (Z). After initiation of an action potential, the heart muscle undergoes a refractory period so that the ventricles can refill completely with blood. This is the depolarization of the heart cell membranes; they close and ionic movement becomes inactive. However, if a cell is hyperpolarized, the membrane threshold potential will become more negative and it will take a stronger than normal stimulus for the cell membrane to open and for an action potential to occur. Increasing the electrical stimulus that induces a heartbeat will increase the number of hyperpolarizing currents generated [18]. The Z term takes into account any previous hyperpolarization of the heart cells. So, with each induced stimulus, spontaneous generation of action potential is inhibited and the cardiac refractory period will be lengthened.

A term is now added to the second ordinary differential equation (the term $\beta \dfrac{Z}{Z + k}$) that affects y in the second equation, and results in a longer duration of the depolarizing phase of the cardiac cycle. This is where overdrive suppression is introduced into the model. In addition, the parameters β and y are introduced as positive constants, and ΔZ is an instantaneous positive increment that comes from the onset of action potential (at time t_{AP}) during ionic movement. δ is the Dirac delta function [21].

The final model presented in this study is as follows [13]:

$$\frac{dV}{dt} = \frac{1}{\epsilon}\left[y - f(V) \right]$$

$$\frac{dy}{dt} = a(V) - \beta\ \frac{Z}{Z + k}$$

$$\frac{dZ}{dt} = -y\ \frac{Z}{Z+k} + \Delta Z \delta\ (t\text{-}t_{AP})$$

The experiment resulted in the understanding that oscillators within the cardiovascular system demonstrate minor variability that is very sensitive to initial stimulus. The time of stimulus has a similar effect on these oscillators, as does periodic forcing on the Van der Pol oscillator. There is evidence that this

Euclidean Geometry
First introduced in Euclid's famous book *The Elements* (~300 B.C). We are familiar with the constructing of lines, circles, and regular polygons, but these figures are uncommon in the natural world. Non-Euclidean geometry includes the fractal patterns discussed in this paper.

Piecewise Function
A function made up of smaller functions on sequential intervals that make up the domain of the function as a whole.

complex evolution of the rhythmic pattern may apply to other oscillating biological systems under periodic stimulation [19].

IV. CONCLUSION

Throughout our world, the intrinsic value of natural biological processes can be seen through chaos theory. From the fractal patterns in the naked branches of trees to the orbiting asteroids in outer space, deterministic chaos plays a role in the character of life. With this century's modern computing methods, we are able to capture and model these systems in a way that scientists never could before, allowing for medical innovations that may change how humans respond to physiological concerns.

Original methods used artificial pacemakers that induced large electrical currents to force the heart out of irregularities [8]. We can, however, use smaller electrical currents that are applied at specific intervals computed from the deterministic relationship between these stimulations and heartbeats. Chaos control techniques can now be employed by scientists to fix the medical complications caused by abnormal heart rate variability. Smaller impulses in pacemakers can be used to stabilize the heartbeat; the technique of subtle perturbations can be used to stabilize any biological oscillator that demonstrates chaotic behavior [11]. By explicitly modeling the impulses of the human heart, we are able to apply chaos control techniques to modern pacemakers, and attempt to reduce the risk of heart attacks and other potentially life-threatening cardiovascular problems.
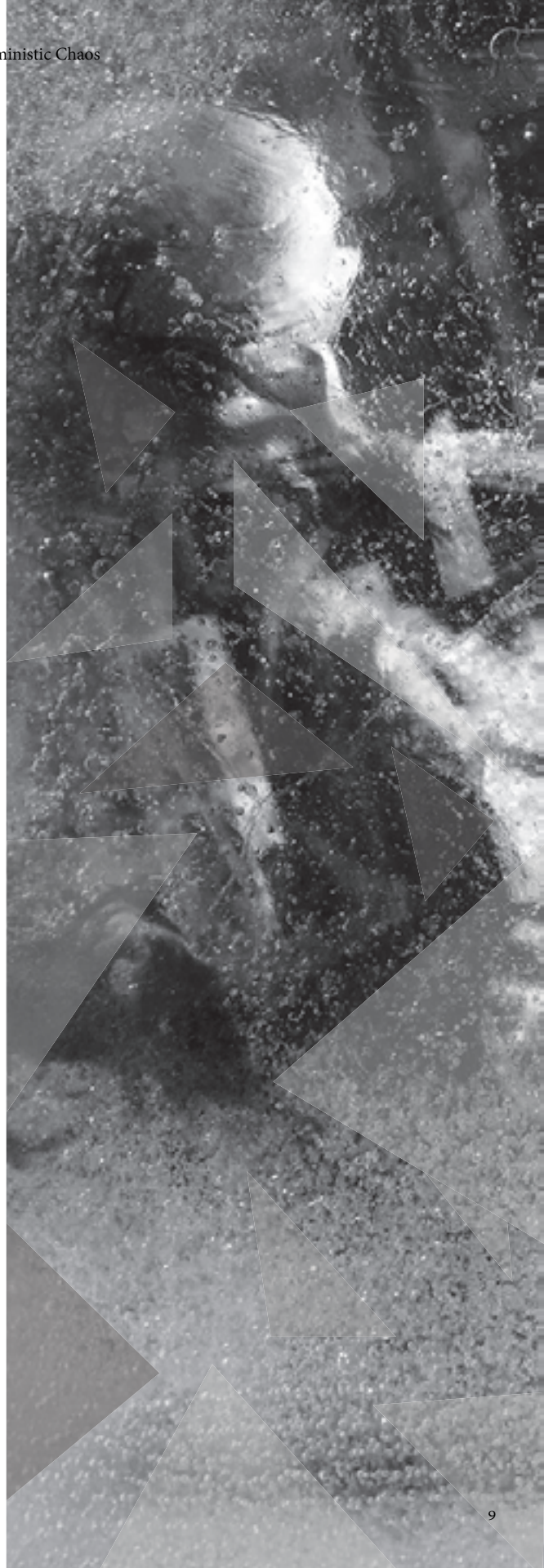
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