A MATHEMATICAL MODEL FOR CHAOTIC CANCER EVOLUTION

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Abstract- It is well accepted that cancer evolution is chaotic. However in literature serious mathematical proofs or other theoretic verifications are still lacking. In this paper, we present a mathematical model for the cancer evolution and prove that cancer evolution is chaotic in the sense of Devaney. We also discuss the Lyapunov exponent for this chaotic system and present an estimation of the maximal Lyapunov exponent. This quantity estimation may have potential implication in cancer treatment.

I. INTRODUCTION

It is well accepted that cancer evolution is chaotic. e.g. Williams et al [12] revealed that the apparently chaotic growth of a cancer tumor follows a power law pattern. Recently, Vogt et al reported in [11] that a single base substitution in one allele of the PIK3CA gene (encoding the catalytic subunit p110 of PI3K which is one of the most frequently mutated oncogenes in solid cancers) in a human breast epithelial cell not only leads to a gene expression profile similar to that of basal breast cancer, but also causes extensive remodeling of gene signatures that are not known to be connected to the activity of that gene. In other words, this mutation induces an extensive cellular reorganization that far exceeds the known signaling activities of PI3K. The changes are highly diverse, with examples in structural protein levels, the DNA repair machinery, and sterol synthesis. Gene set enrichment analysis reveals a highly significant concordance of the genes differentially expressed in MCF-10A-H1047R cells and the established protein and RNA signatures of basal breast cancer. No such concordance was found with the specific gene signatures of other histological types of breast cancer. On the other hand, although the chaotic behaviors of cancer evolution were supported many experiments and observation in laboratory [18]-[26], theoretic proof is still lacking in literature. Solving this issue is the goal of this paper.

A. The limitation of predictability

The physicist James Lighthill, commenting on the impact of chaos on unpredictability, expresses this point as follows: We are all deeply conscious today that the enthusiasm of our forebears for the marvelous achievements of Newtonian mechanics led them to make generalizations in this area of predictability which, indeed, we may have generally tended to believe before 1960, but which we now recognize were false. ([8], p. 38). Similarly, Weingartner ([10], p. 50) says that the new discovery now was that a dynamical system obeying Newtons laws can become chaotic in its behavior and practically unpredictable. Chaos is discussed in dynamical systems theory. A dynamical system is a mathematical model consisting of a phase space X, the set of all possible states of the system, and evolution equations that describe how solutions evolve in phase space. Dynamical systems often model natural systems.

The unpredictability of cancer poses a threat to personalized cures. Although cancer is studied as a chaotic system, the shape of its unpredictability, known as the strange attractor, is unclear. Dhruba [6] discussed a conceptual model, building on the strange attractor in cancer phase space and defined the 10-dimensional phase space and then, using an abstract expressionist approach, represents the strange attractor, which twists and turns in multi dimensions, indicating the unpredictability of cancer. Williams et al [12] revealed that the apparently chaotic growth of a cancer tumour follows a power law pattern. Vogt et al reported in [11] that a single base substitution in one allele of the PIK3CA gene in a human breast epithelial cell not only leads to a gene expression profile similar to that of basal breast cancer, but also causes extensive remodeling of gene signatures that are not known to be connected to the activity of that gene. All these observations support the idea that cancer cell evolution is chaotic.

B. Main features of Chaos theory

Deterministic system is defined by no randomness. One obvious feature is that the same initial input will produce the same outcomes. Deterministic system can be understood that their future behavior is fully determined by their initial conditions, with no random elements involved [1], [9].

1. Chaos are deterministic systems (When the present determines the future) with no random,, but the approximate present does not approximately determine the future.
2. Highly sensitive (butterfly effect, When a tiny variation change the result of a system dramatically (over a period of time), this sensitivity is called the butterfly effect. Does the Flap of a Butterflys Wings in Brazil set off a Tornado in Texas?.
3. Unpredictable on long term because they are very complex and sensitive (unpredictability on long term).

C. Macro-predictable yet micro-unpredictable?

behavior is a broad and interesting topic in physics. For instance, in statistical mechanics, systems are often macro-predictable but micro-unpredictable. Here, we concentrate only on whether there is any combination of macro-predictability and micro-unpredictability in chaotic systems that other deterministic systems do not have. To gain an understanding of this third proposed answer, recall the Lorenz Equations. These equations exhibit macro-predictability: the solutions are attracted by an attractor, a small region of phase space. There is also micro-unpredictability since the motion on the attractor exhibits SDIC. Smith [16] argues that this combination of macro-predictability and micro-unpredictability is a new implication of chaos for unpredictability.

We propose that a more reasonable pattern is micro-unpredictability, macro-predictability and Cosmo-unpredictability; very short-term unpredictability, short-term predictability and long-term unpredictability.

This type of combination of large-scale order with small scale disorder, of macro-predictability with the micro-unpredictability due to sensitive dependence, is one paradigm of what has come to be called chaos. So error inflation by itself is entirely old-hat. The novelty in the new-fangled chaotic cases that will concern us is, to repeat, the combination of exponential error inflation with the tight confinement of trajectories by an attractor (Smith [16], pp. 13-5, original emphasis). Here, macro-predictability means that the system eventually shows the behavior corresponding to the motion on the attractor, a proper subset of phase space. Micro-unpredictability is understood as the unpredictability implied by exponential error inflation. Therefore, micro-unpredictability has to be interpreted as a weaker notion, e.g. asymptotic unpredictability.[4]

II. MATHEMATICAL MODEL

It is important to determine whether a system is chaotic. There are several mathematical approaches or analytical techniques to do it, including topological spaces or measure theory. The following is such an approach defined by Devaney [5], which we will use in the sequel.

The following construction is mainly due to Bahi [2]. However, by this structure, the conclusion, presented in [2], that (human) DNA mutations have a chaotic behaviour may not be proper. In addition, a key factor which makes their structure workable is the assumption that the mutation sequence (the definition see below) is infinite. They did not make the crucial assumption in an explicitly way. Here we will put their structure in a correct way and show that cancer cell evolution is chaotic.

A. Devaney's chaotic dynamical systems

We consider a topological space (X,τ) and a continuous function $f : X \to X$.

Definition 1 . Function f is said to be topologically transitive if, for any pair of non-empty open sets $U,V \subseteq X$, there exists k> 0 such that the intersection and $f^k(U)$ and V is not empty.

Definition 1 is also called Topological mixing: The map defined by x4x(1 - x) and y(x + y) mod 1 also displays topological mixing. Here, the blue region is transformed by the dynamics first to the purple region, then to the pink and red regions, and eventually to a cloud of vertical lines scattered across the space. Topological mixing (or topological transitivity) means that the system will evolve over time so that any given region or open set of its phase space will eventually overlap with any other given region. This mathematical concept of "mixing" corresponds to the standard intuition, and the mixing of colored dyes or fluids is an example of a chaotic system.

Topological mixing is often omitted from popular accounts of chaos, which equate chaos with only sensitivity to initial conditions. However, sensitive dependence on initial conditions alone does not give chaos. For example, consider the simple dynamical system produced by repeatedly doubling an initial value. This system has sensitive dependence on initial conditions everywhere, since any pair of nearby points will eventually become widely separated. However, this example has no topological mixing, and therefore has no chaos. Indeed, it has extremely simple behavior: all points except 0 will tend to positive or negative infinity.

Definition 2. The point $x \in X$ is a periodic point for f of period n , if $f^n(x) = x$.

Definition 3 Function f is said to be regular on (X,τ) if the set of periodic points for f is dense in X: for any point x in X, any neighborhood of x contains at least one periodic point.

Definition 3 is also called having dense periodic orbits. For a chaotic system to have dense periodic orbits means that every point in the space is approached arbitrarily closely by periodic orbits.[18] The one-dimensional logistic map defined by $x \mapsto 4x(1-x)$ is one of the simplest systems with density of periodic orbits. The Li and Yorke[15] proof that any one-dimensional system that exhibits a regular cycle of period three will also display regular cycles of every other length, as well as completely chaotic orbits.

Definition 4 A function f is said to be chaotic on (X,τ) if f is regular and topologically transitive.

In cases where the topology can be described by a

metric d, the chaos property is strongly linked to the notion of sensitivity, defined on a metric space (X,τ) by:

Definition 5 Function f has sensitive dependence on initial conditions if there exists δ > 0 such that, for any $x \in X$ and any neighborhood V of x, there exists $y \in X$ and n > 0 such that $d(f^n(x), f^n(y)) > \delta$. Then δ is called the constant of sensitivity of f.

B. Formalization of DNA Mutation Evolution

Following [2], a genome having N nucleotides is formalized here as a sequence of N integers belonging in {1, 2, 3, 4}, where 1 (resp. 2, 3, and 4) refers to the adenine (resp. cytosine, guanine, and thymine). The benefit of using integers 1, 2, 3, 4 instead of {A;C; G; T} is justified by the construction of a metric for the mutation process. An evolution under nucleotide mutations of this genome is a sequence of couples of [1,N] x [1, 4], where we infer that:

- time has been divided into a sequence $\{t_0, t_1, \cdots, t_n, \cdots\}$ such that at most one mutation can occur between two time intervals,
- the i^{th} couple of the mutation sequence is equal to (m; n) if and only if the m^{th} nucleotide of the genome is replaced into the nucleotide n. If the mth nucleotide was n, then no mutation has occurred at time t_i.

Such a sequence will be called mutations sequence in the remainder of this paper.

Main Assumption: In general speaking, for an organism, the length of mutation sequence has an upper bound, otherwise, the individual would die. But because cancer cells is out of control, we assume that the length of mutation sequence is infinite. which is supported by many experiments [17]-[26]. Thus we introduce the following:

$S_N = \bigcup_n ([1,N]\times[1,4])^n$ denotes the infinite set of all possible mutations finite sequences, and write $\aleph_N = [1,4]^N \times S_N$.

Again following [2], we introduce the initial and shift operators i and σ defined respectively by

$$i : S_N \to [1.N]\times[1,4]$$
$$(s^0, s^1, \cdots, s^m) \mapsto s^0$$

and

$$\sigma : S_N \to S_N$$
$$S = (s^0, \cdots, s^m) \mapsto \sigma(S) = (s^1, \cdots s^m).$$

The mutation operation M can be written as follows:

$$M; \aleph_N \to \aleph_N$$
$$((G_1, \cdots, G_N), S) \mapsto$$
$$((G_1, \cdots, G_{i(S)_1 - 1}, i(S)_2, G_{i(S)_1 + 1}, \cdots G_N), \sigma(S)).$$

Define a metric distance on $\aleph_N$ ([2]):

$$\forall X, Y \in \aleph_N, d(x,Y) = d_G(X_1, Y_1) + d_S(X_2, Y_2)$$

,

where $d_G(X_1, Y_1) = \sum_{k=1}^{N} \delta(X_1^k, Y_1^k)$ and

$d_S = \frac{1}{N}\sum_{k=1}^{\infty} \frac{F(X_2^k, Y_2^k)}{10^{k+1}}$, where δ is the discrete metric on R and $F : R^2 \to R$ is defined by $F(x_1, x_2) = |x_1| + \delta(0, x_2)$.

Note that

1) $\forall X, Y \in \aleph_N$, either $d_G(X_1, Y_1) \geq 1$ or equal to zero.

2) $\sum_{k=1}^{\infty} \frac{F(X_2^k, Y_2^k)}{10^{k+1}} \leq \sum \frac{N+1}{10^{k+1}}$

3) $d_S(X_2, Y_2) \geq \frac{1}{N}\frac{F(X_2^0, Y_2^0)}{10^n}$

Thus we have

4) if d(X; Y) < 1, then X1 = Y1 and

$d(X,Y) < \frac{1}{10^N}$, then

the first term of X2 is the same as the first one of Y2.

The properties 3) and 4) will be used in the proof of Proposition below.

Proposition ([2]) 1) The function d is a metric and the mutation M is continuous on $\aleph_N$;

2) The mutation M is (strong) topologically transitive and regular on $(\aleph_N, d)$.

Tumor heterogeneity describes the observation that different tumor cells can show distinct morphological and phenotypic profiles, including cellular morphology, gene expression, metabolism, motility, proliferation, and metastatic potential. The heterogeneity of cancer cells introduces significant challenges in designing effective treatment strategies. Thus the heterogeneity of cancer cells can be regarded as a consequence of chaotic cancer evolution. Numerous experiments and observations in

laboratory [18]-[26] supply strong evidence that cancer mutation sequence is infinite. Thus we have

Theorem Cancer cell evolution is chaotic according to Devaney.

It was claimed in [2] that (human) genome mutation have a chaotic behavior according to Devaney. In contrast, we claim the following

Corollary Assuming that external or internal environment keeps constant, the evolution of human DNA is not chaotic.

C. Estimation of The Lyapunov exponent

The Lyapunov exponent measures the sensitivity to initial conditions. Given two starting trajectories in the phase space that are infinitesimally close, with initial separation δZ_0 end up diverging at a rate given by $|\delta Z(t)| \approx e^{\lambda t} |\delta Z_0|$ where t is the time and λ is the Lyapunov exponent. The rate of separation depends on the orientation of the initial separation vector, so a whole spectrum of Lyapunov exponents exist. The number of Lyapunov exponents is equal to the number of dimensions of the phase space, though it is common to just refer to the largest one. For example, the maximal Lyapunov exponent (MLE) is most often used because it determines the overall predictability of the system. A positive MLE is usually taken as an indication that the system is chaotic. Also, other properties relate to sensitivity of initial conditions, such as measure-theoretical mixing (as discussed in ergodic theory) and properties of a K-system.[5] The Lyapunov spectrum can be used to give an estimate of the rate of entropy production of the considered dynamical system. In particular from the knowledge of the Lyapunov spectrum it is possible to obtain the so-called Kaplan-Yorke dimension D_{ky} , which is defined as follows:

$$D_{ky} = k + \sum_{i=1}^{k} \frac{\lambda_k}{|\lambda_{k+1}|}$$

k is the maximum integer such that the sum of the k largest exponents is still non-negative. D_{ky} represents an upper bound for the information dimension of the system [13]. Moreover, the sum of all the positive Lyapunov exponents gives an estimate of the Kolmogorov-Sinai entropy accordingly to Pesin's theorem [14].

The multiplicative inverse of the largest Lyapunov exponent is sometimes referred in literature as Lyapunov time. For chaotic orbits, the Lyapunov time will be finite, whereas for regular orbits it will be infinite [14]. Thus the Lyapunov exponent or Lyapunov characteristic exponent of a dynamical system is a quantity that characterizes the rate of separation of infinitesimally close trajectories. quantitatively, two trajectories in phase space with initial separation diverge (provided that the divergence can be treated within the linearized approximation) at a rate given by $e^{\lambda t}$ where λ is the Lyapunov exponent. The rate of separation can be different for different orientations of initial separation vector. Note that an arbitrary initial separation vector will typically contain some component in the direction associated with the MLE, and because of the exponential growth rate, the effect of the other exponents will be obliterated over time. Thus we have

$$\lambda = \lim_{t\to\infty} \lim_{\delta Z_0 \to 0} \frac{1}{t} \ln \frac{|\delta Z(t)|}{|\delta Z_0|} = \mu$$

CONCLUSION

In this paper, we have proven that cancer evolution is chaotic in a strict mathematical sense and then discuss the maximal Lyapunov exponent of this system. In mathematical terms, the random looking, poorly periodic oscillations observed in the mutation-induced new variants originate from either a stochastic (nondeterministic and random) or a chaotic (deterministic and predictable) system. Stochastic behavior is nondeterministic in that precise knowledge of the state of the system is not sufficient to determine the next state; no underlying law exists, and the outcome is random and unpredictable. In contrast, chaotic behavior originates from deterministic systems, which implies that a well-defined law governs the evolution of the system and each state is sufficient to determine the next. However, sensitivity to the initial condition in chaotic systems means that tiny differences can have drastic effects, thus limiting predictability to a short time-scale. Importantly, chaotic systems are able to produce an infinite number of dynamic behaviors, both periodic and nonperiodic, in nature. A common feature of determinism is that one state of the system is similar to a previous state, and this can be measured mathematically by using a number of tests, including recurrence plots. Our estimation of the maximal Lyapunov exponent of this chaotic cancer evolution may have implications in cancer treatment.

ACKNOWLEDGMENT

The authors would like to thank the Australian Research Council for the Discovery Project (T.T. DP120104460). T.T. is also an ARC Future Fellow (FT100100748).

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