Topological Chaos: 
When Topology Meets Medicine

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(Received April 2002; accepted May 2002)

Abstract—In the present note, the chaotic behaviour of a class of infinite system of linear ODEs  
(with variable coefficients) describing the population of neoplastic cells divided into subpopulations  
characterized by different levels of resistance to drugs is discussed. The result of [1] is extended to a  
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Keywords——Chaos, Infinite system of linear ODEs, Gene amplification.

TOPOLOGICAL CHAOS

In the past two decades, it was observed that some processes in physiology and medicine display  
chaotic behaviour [2,3]. However, as Hill [4] noticed, “By now these words (“chaos” and “chaos theory”)  
have appeared in more than 7000 mathematical and scientific books, dictionaries, and papers.  
Unfortunately the technical meanings are themselves confused, and there is no agreement on  
definition.” The most popular and widely utilized definition of chaos (for discrete in time  
dynamical systems) is due to Devaney [5]: a map \( f : X \rightarrow X \), where \((X, d)\) is a metric space, is  
chaotic on \( X \) if it has three ingredients—it is topologically transitive, its set of periodic points  
is dense in \( X \), and it satisfies the condition of sensitive dependence on initial conditions (SDIC).  
These properties describe irreducibility (indecomposability), some regularity, and unpredictability,  
respectively.

The paper [6] demonstrates that under some weak assumptions the last condition (SDIC) is  
implied by the remaining two. Therefore, despite its sense of intuitiveness, the condition SDIC  
should be left out of Devaney’s definition of chaos. Moreover, the result of Banks et al. [6] shows
that chaos is a topological property and it is not related directly to the metric properties of the space.

The papers [7,8] suggested some modifications of the definition of chaos. Crannell [7] considered a slightly more intuitive concept—blending—as an alternative to transitivity. Touhey [8] proposed a definition of chaos, equivalent to Devaney's: a map \( f : X \to X \) is chaotic on \( X \) if it mixes together, via periodic trajectories, any finite number of nonempty open subsets in infinitely many ways.

Recently, it was observed [9-11] that chaos, typically related to nonlinear dynamics, can also occur in (discrete or continuous in time) linear dynamical systems provided that they are infinite-dimensional. In [10], chaotic semigroups are associated with the idea of exactness.

In the present paper, we consider the continuous in time linear dynamical systems. Let \( \{T_t\}_{t \geq 0} \) be a strongly continuous semigroup of bounded linear operators (\( C_0 \)-semigroup) on a Banach space \( X \).

**DEFINITION 1.** The \( C_0 \)-semigroup \( \{T_t\}_{t \geq 0} \) is topologically transitive on \( X \) if for any two nonempty open sets \( U, V \subset X \), there exists \( t_0 \geq 0 \) such that \( (T_{t_0} U) \cap V \neq \emptyset \).

**DEFINITION 2.** The \( C_0 \)-semigroup \( \{T_t\}_{t \geq 0} \) is topologically chaotic on \( X \) if

(i) it is topologically transitive;

(ii) its set of periodic points is dense in \( X \).

The original proof of [6] for discrete in time systems can be repeated with slight modifications for continuous in time systems in nondegenerate metric spaces—see [12]. Conditions (i) and (ii) of Definition 2 imply SDIC and Definition 2 is a continuous time version of Devaney's definition.

In each separable Banach space, the notion of topological transitivity is equivalent to the notion of hypercyclicity (see [11,12]).

**DEFINITION 3.** The \( C_0 \)-semigroup \( \{T_t\}_{t \geq 0} \) on \( X \) is hypercyclic if for some \( x \in X \) the trajectory \( \bigcup_{t \geq 0} \{T_t x\} \) is dense in \( X \).

Desch et al. [11] provide two important theorems allowing the identification of certain classes of chaotic and nonchaotic semigroups. The theorems deliver useful criteria in terms of the spectral properties of the infinitesimal generator. The criteria were used in the paper [1] and are also the base in the present paper.

**AMPLIFICATION-DEAMPLIFICATION PROCESS**

Gene amplification is by now a well-documented phenomenon in cancer (see [13,14] and references therein).

Following [15,16], we consider a population of cancer cells characterized by different levels of drug resistance. The cells of type 0 (belonging to 0th subpopulation) are sensitive to antineoplastic drugs. The cells of type \( n = 1, 2, 3, \ldots \) (belonging to \( n \)th subpopulation) are resistant with increasing level of resistance (for \( n \) increasing). Each subpopulation contains the cells characterized by a number of copies of a drug resistance gene. The more copies of the gene that exist, the more resistant the cell is, with the understanding that it can survive under higher concentration of the drug [15,16]. Because the number of gene copies in cancer cells can be very large, it is reasonable to use a model with an infinite number of cell subpopulations. The process considered in [15,16] is gene amplification-deamplification process characterized by two components: the conservative one and the proliferative one. The conservative component of the process describes the mutations of cells: \( b_n \Delta t + o(\Delta t) \), for \( n \geq 0 \), is the chance of one mutation in the \( n \)th-subpopulation shifting the mutated cell to the \((n + 1)\)th-subpopulation and \( d_n \Delta t + o(\Delta t) \), for \( n \geq 1 \), is the chance of one mutation in the \( n \)th-subpopulation shifting the mutated cell to the \((n - 1)\)th-subpopulation (we assume that \( d_0 = 0 \)). The proliferative component of the process is related to the assumption that the moment of death represents the moment of cell division and
that the average life-span is given by the coefficient \( \lambda_n \) for the \( n \)-th subpopulation \((n \geq 0)\). The model is defined by the following infinite system of ODEs:

\[
\dot{f}_n = (Lf)_n, \quad n = 0, 1, 2, \ldots ,
\]

where \( L \) is the infinite tridiagonal matrix given by

\[
\begin{align*}
(Lf)_0 &= (\lambda_0 - b_0)f_0 + d_1f_1, \\
(Lf)_n &= (\lambda_n - b_n - d_n)f_n + b_{n-1}f_{n-1} + d_{n+1}f_{n+1}, \quad n = 1, 2, \ldots ,
\end{align*}
\]

and \( f = \{f_n(t)\}_{n \geq 0} \) is the distribution function.

**MAIN RESULTS**

With the above interpretation the proper Banach space for the process defined by equation (1) is \( l^1 \), where the norm \( \|f\|_1 = \sum_{n=0}^{\infty} f_n \) of any element \( f \) in the positive cone \( l^1_+ = \{ f \in l^1 : f_n \geq 0, \forall n = 0, 1, 2 \ldots \} \), represents the total number of cells. We consider the (complex) Banach spaces \( l^p \), \( 1 \leq p < \infty \), with norms \( \|f\|_p = (\sum_{n=0}^{\infty} |f_n|^p)^{1/p} \), and \( c_0 \) -- the (complex) Banach space of all sequences \( f \) converging to 0, with the norm \( \|f\|_0 = \sup_{n=0, 1, \ldots} |f_n| \). We denote \( X(p) = l^p \), \( 1 \leq p < \infty \), and \( X(0) = c_0 \).

The paper [17] dealt with equation (1) for \( b_n = 0 \) for all \( n = 0, 1, \ldots \). In the paper [1], the general equation (1) has been considered under the assumption that the coefficients \( \lambda_n, b_n, d_n \) (for \( n = 0, 1, 2, \ldots \)) are such that

\[
\begin{align*}
\lim_{n \to \infty} d_n &= d, \\
\inf_{n=1, 2, \ldots} \frac{d_k}{d} &> 0, \\
b_n &\geq 0, \quad n = 1, 2, \ldots, \\
a_n &= b_n + d_n - \lambda_n \geq 0, \quad n = 0, 1, 2, \ldots \quad \text{and} \quad \lim_{n \to \infty} a_n = a, \quad \text{for some } a \in ]0, \infty[, \\
0 &< a < d,
\end{align*}
\]

where \( q_0 \in ]0, 1[ \) is a critical constant.

Note that (A1), (A2), and (A5) imply \( \lim_{n \to \infty} b_n = 0 \).

Let \( L_p \) be the operators defined by the matrix \( L \) (cf. (2)) in the spaces \( X(p) \), for \( p \in [1, \infty[ \cup \{0\} \). The operators \( L_p \) are bounded, hence, they generate \( C_0 \)-semigroups \( \{T_t^{(p)}\}_{t \geq 0} \) in \( X(p) \). In [1], the following theorem was proved.

**THEOREM 1.** There exists a critical constant \( q_0 > 15/100 \) such that if the sequences \( \{\lambda_n\}, \{b_n\}, \{d_n\} \) satisfy Assumptions (A1)-(A5), then the semigroups \( \{T_t^{(p)}\}_{t \geq 0} \) solving system (1) in \( X(p) \), \( p \in [1, \infty[ \cup \{0\} \), are topologically chaotic.

Theorem 1 ensures the occurrence of topological chaos for large deamplification ("death") rates and small amplification ("birth") rates, i.e., for the process which is subcritical in terminology of [15, 16]. References to the experiments confirming that the process described in the previous section is indeed subcritical can be found in [15, 16].

In this paper, we show that the critical constant \( q_0 \) can be chosen \( q_0 > (\sqrt{3} - 1)/2 > 36/100 \).
THEOREM 2. There exists a critical constant $q_0 > (\sqrt{3} - 1)/2$ such that if the sequences $\{\lambda_n\}$, $\{b_n\}$, $\{d_n\}$ satisfy Assumptions (A1)–(A5), then the semigroups $\{T^{(p)}_t\}_{t \geq 0}$ solving system (1) in $X^{(p)}$, $p \in [1, \infty] \cup \{0\}$, are topologically chaotic.

PROOF. One of the main steps in the proof of Theorem 1 (cf. Lemma 3.5 in [1]) was the estimate

$$\Theta_n \leq \sum_{k=1}^{\infty} S_{1,k},$$

where

$$S_{j,k} = S_{j,k}(q) = \sum_{j_1,j_2,\ldots,j_k \leq j \leq j_1 \leq j_2 \leq \ldots \leq j_k} q^{j_1+j_2+\cdots+j_k},$$

and we have

$$S_{j,k} = q^k S_{0,k}.$$ (4)

Using (3) and (4), for $0 < q < 1$, we obtain

$$S_{0,k+1} = \sum_{j_1=0}^{\infty} q^{j_1} S_{j_1,k} = \sum_{j_1=0}^{\infty} q^{j_1+j_k} S_{0,k} = \frac{1}{1 - q^{k+1}} S_{0,k},$$

and

$$S_{0,1} = \frac{1}{1 - q}.$$ (5b)

Therefore, for $0 \leq q < 1$,

$$S_{0,k} = \prod_{j=1}^{k} \frac{1}{1 - q^j}, \quad k \geq 1,$$ (6)

from (4)

$$S_{1,k} = q^k S_{0,k} = \prod_{j=1}^{k} \frac{q}{1 - q^j}, \quad k \geq 1,$$ (7)

consequently

$$S_{1,k} \leq \frac{q}{1 - q} \frac{q^{k-1}}{(1 - q^2)^{k-1}}, \quad k \geq 1,$$ (8)

and the estimate is sharp for $0 < q < 1$ and $k > 2$. Hence, defining $\Gamma(q) = \sum_{k=1}^{\infty} S_{1,k}(q)$, we obtain

$$\Theta_n \leq \Gamma(q) < \frac{q}{1 - q} \sum_{k=0}^{\infty} \frac{q^k}{(1 - q^2)^k} = \frac{q(1 + q)}{1 - q - q^2},$$ (9)

for $0 < q < (\sqrt{3} - 1)/2$. It follows that $\Gamma((\sqrt{3} - 1)/2) < 1$, and thus, by the continuity of $\Gamma$ there exists $q_0 > (\sqrt{3} - 1)/2$ such that

$$\Theta_n < 1,$$ (10)

for $0 \leq q < q_0$. The rest of the proof follows from [1].

As all the results above have been proved using the spectral theory that requires complex Banach space setting, it seems that we have departed far from the real applications. However, as we shall see now, chaotic behaviour in complex Banach spaces has its direct counterpart in their real parts. We start by introducing some terminology.

Let $X$ be a complex Banach space and $X$ a real linear subspace of $X$ (that is, a subset of $X$ being a linear subspace over the field of real numbers) such that there exist continuous real linear projectors $R, I : X \to X$, with $R + I = \text{id}_X$, $R(X) = X$, and $I(X) = iX$. Thus, $X$ is a real Banach space (the "real part" of $X$) and $X$ can be treated as the complexification of $X$ (see e.g., [18]). The projection $R$ is called the real part operator and vectors of $X$ are called the real vectors.
A linear operator $A$ with the domain $D(A)$ in $X$ is called real if $A(D(A) \cap X) \subset X$ and $\mathcal{R}(D(A)) \subset D(A)$. Thus, if $A$ is bounded, then $A$ is real iff $A\mathcal{R} = \mathcal{R}A$. If $A$ is real, then $A$ is determined by its restriction $A\mathcal{R}$ to the space $X$ (with the domain $D(A) \cap X$).

Suppose that $\{T(t)\}_{t \geq 0}$ is a $C_0$-semigroup on $X$ and that $A$ is its infinitesimal generator. Then $A$ is real iff $\{T(t)\}_{t \geq 0}$ is real (i.e., $T(t)$, for each $t \geq 0$, is real). Moreover, if $\{T(t)\}_{t \geq 0}$ is real, then $\{(T(t))\mathcal{R}\}_{t \geq 0}$ is a $C_0$-semigroup on $X$ generated by $A\mathcal{R}$. These facts are easy to prove, when $A$ is bounded. In the general case, the Yosida approximation [19] can be used.

It turns out that the "complex chaos" implies the "real chaos" for real semigroups.

**Proposition 3.** Suppose that $\{T(t)\}_{t \geq 0}$ is a real topologically chaotic $C_0$-semigroup in $X$. Then $\{(T(t))\mathcal{R}\}_{t \geq 0}$ is topologically chaotic in $X$.

**Proof.** Since $\{T(t)\}_{t \geq 0}$ is chaotic, it has a dense trajectory in $X$ and the set of periodic points (initial values that give periodic solutions) is dense in $X$. We have to prove that the same is true in $X$. We have $\mathcal{R}T(t) = T(t)\mathcal{R}$, thus the real part of the trajectory corresponding to $x \in X$ is the real trajectory corresponding to $\mathcal{R}x \in X$. But $\mathcal{R}$ is continuous and $\mathcal{R}(X) = X$. Therefore, the real part of a dense trajectory in $X$ is a dense real trajectory in $X$, and the set of real parts of periodic points in $X$ is a dense set consisting of real periodic points in $X$.

We can apply the above result to the (complex) space $X = \mathbb{X}^p$ with $\mathcal{R}x$ being the usual real part of the complex sequence $x$ (then $X$ is the real space $\mathbb{R}^p$, $1 \leq p < \infty$, or $\mathbb{C}_0$, $p = 0$) and $A = \mathcal{L}_p$. Of course, $A$ is real since the matrix $L$ has real entries.

It is fair to note that the chaotic properties discussed in this paper refer to the whole-space structure of solutions whereas in most applications only positive solutions make sense. For example, the wandering trajectory mentioned in Definition 3 is dense in the whole space, that is, it passes arbitrarily close to all positive, negative and indeterminate values, and as such has no physical meaning (the distribution function $f$ must be nonnegative). Thus, chaos in the sense of this paper, being important, e.g., in the analysis of the stability of numerical schemes, does not necessarily say anything important about the actual behaviour of "physical" trajectories. In each of the spaces $\mathbb{X}^p$, $p \in [1, \infty] \cup \{0\}$, the positive cone $\mathbb{X}_+^p$ has an empty interior, that is, arbitrarily close to any positive element $f$ there are nonpositive elements. Therefore, all the initial values close to $f$, that cause chaos in the sense of Devaney’s definition, may be nonpositive, and thus, in principle, all positive solutions could be regular. At present we don’t know to which extent the results on chaos for the whole space $\mathbb{X}^p$ are inherited by its positive cone.

**References**