Using Cellular Automata Experiments to Model Periodontitis: A First Step Towards Understanding the Nonlinear Dynamics of the Disease

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Cellular automata (CA) are time and space discrete dynamical systems that can model biological systems. The aim of this study is to simulate by CA experiments how the disease of periodontitis propagates along the dental root surface. Using a Moore neighborhood on a grid copy of the pattern of periodontal ligament fibers (PDLF) supporting and anchoring the teeth to bone, we investigate the fractal structure of the associated using all possible outer-totalistic CA rules. On the basis of the produced propagation patterns, CA rules are classified in 3 groups, according to whether the disease was spreading, remaining constant or receding. These are subsequently introduced in a finite state Markov model as probabilistic “state-rules” and the model is validated using datasets retrieved from previous studies.

Based on the maximum entropy production principle, we identified the “state-rule” that most appropriately describes the PDLF pattern, showing a power law distribution of periodontitis propagation rates with exponent 1.3. Entropy rates and mutual information of Markov chains were estimated by extensive data simulation. The scale factor of the PDLF used to estimate the conditional entropy of Markov chains was seen to be nearly equal 1.85. This possibly reflects the fact that a dataset representing tooth percentage with bone loss equal to 50% or more of their root length, is found to have a fractal dimension (FD) of about 1.84. Similarly, datasets of serum neutrophil, basophil, eosinophil, monocyte counts and IgG, IgA, IgM levels taken from periodontitis patients, showed a FD ranging from 1.82 to 1.87.

Our study presents the first mathematical model to our knowledge that suggests periodontitis is a nonlinear dynamical process. Moreover, the model we propose implies that the entropy rate of the immune-inflammatory host response dictates the rate of periodontitis progression. This is validated by clinical data and suggests that our model can serve as a basis for detecting periodontitis susceptible individuals and shaping prognosis for treated periodontitis patients.
1. Introduction

The inability of innate and adaptive host responses to impede the infectious process of periodontitis, has long been recognized and addressed as a characteristic of the disease [Page, 1994]. Clinically, the progression of periodontitis is measured by the loss of attached tissue between successive measurements using a probe in the vertical direction. To reduce false-positive readings during manual probing, we usually select a resolution of about 2 mm difference between successive measurements at a site, in order to determine disease progression [Lindhe et al., 1989].

In his histological studies, Waerhaug [1977] showed that periodontitis advances apically along the dental root surface. He actually identified the dental root surface as the attractor of periodontitis, since an attractor by definition is the set of points on which the motion of a system eventually settles. It is estimated that there are 30000 periodontal ligament collagen fibers (PDLF) per mm² of root surface [Bosshardt & Selvig, 1997], which are responsible for anchoring the tooth root to the alveolar bone. Periodontitis is recognized as a bacterial driven chronic inflammatory disease and the inflammation process leads to the destruction of these collagen fibers [Ishikawa, 2007]. It is also considered a complex disease [Loos et al., 2008], with 3 main categories of aetiological factors playing a role: 1) Genetic factors (as multiple genes play simultaneously a role in modifying the disease), 2) environmental factors (pathogenic and non-pathogenic bacteria and possibly viruses occur in dental plaque biofilms), 3) lifestyle factors (i.e., smoking, dietary habits, stress). Two forms of periodontitis are currently recognized: aggressive periodontitis and chronic periodontitis [Armitage, 1999].

Periodontitis is found to progress in episodes, with periods of activity alternating with intervals of quiescence [Lindhe et al., 1983]. To explain the progression rate of periodontitis several models have been introduced, as e.g. the random burst, asynchronous multiple burst or continuous progression models [Socransky et al., 1984]. Jeffcoat & Reddy [Jeffcoat & Reddy, 1991], using an automated probe that could detect changes as low as 0.2 mm between successive measurements, found that 76 percent of the measured sites were well fitted by a linear model for probing the attachment loss. The authors concluded that sites might experience continuous loss at a slow rate, short bursts or become quiescent after a period of months or years of continuous attachment loss.

Clearly, our inability to directly observe and measure a physical or biological process, leads to the need to introduce an appropriate model in order to understand and explain the process. In the current study, we employ cellular automata (CA) to simulate how periodontitis spreads along the dental root surface. CA are time and space discrete dynamical systems that can be used to simulate real life processes [Ben, 2004; Mainzer & Chua, 2012]. They were introduced by von Neumann [1951] in the early '50s and are characterized by the following attributes: 1) They model arrays of cells, 2) identify the possible states the cells can attain and 3) provide transition rules that can be applied simultaneously to all cells over successive iterations.

In general, the behaviour of a system can be described by all the different states it can occupy and a set of rules that dictate how it moves from one state to another. If the next step in its evolution depends only on the current state, this evolution can be represented by a Markov process [Rabiner, 1989]. If the space is discrete, the term Markov chain is employed. Thus, a finite state Markov model is frequently used for modelling sequential biological observations or describing physical processes [Liao & Seaman, 2004]. Such biological sequences, therefore, can be modelled as the output of a stochastic process, which progresses through a series of states.

Shannon [1948] introduced the concept of informational entropy as a measure of uncertainty in trying to estimate the probabilities for a given discrete random variable to take a specified set of values. Thus, entropy is considered as a measure of the inherent randomness of a probability distribution. In probabilistic CA (PCA) experiments [Billings & Yang, 2002], Markov chains have been used to analyse the transition
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behaviour of CA states. PCA are primarily used for the description of dynamical systems which are unpredictable and irreversible [Lucia , 2008]. In the analysis of PCA, it is of fundamental importance to classify CA local rules into groups representing “state-rules”.

CA local rules update deterministically cell states in a way that is always the same for a given configuration of cell states in the neighbourhood. However, “state-rules” incorporate also a probabilistic element in them. Rather than dictating the state that a cell will take, “state-rules” give the probability of a cell to be in a number of states. The concept of entropy can thus be utilized to describe the exponential growth of Markov chains. According to the maximum entropy production principle for nonequlibrium systems [Martynushev & Selzneve, 2006], the sequence of states is selected from a probability distribution that maximizes entropy production under certain constraints, for instance expected value and variance.

A recent comprehensive review [Preshaw & Taylor, 2011] suggests that the host immune-inflammatory response is the major determinant of the onset and progression of periodontitis. The same review emphasizes the paradoxical fact that the inflammatory response is responsible for much of the periodontal tissue destruction. PDLF are decomposed by the induction of destructive enzymes. On the other hand, it has been found histologically that an inflammatory infiltrate is contained within 1-2 mm from the bacterial biofilm front, while the process follows an apical and lateral direction [ Waerhaug, 1977].

Based on the above, we suggest that periodontitis, as a biological process, behaves like a nonlinear dynamical system, with the host immune-inflammatory response determining its motion. By motion we mean the described apical and lateral spread of inflammation that results in PDLF degradation by the induction of destructive enzymes. The purpose of this study, therefore, is to use CA experiments to investigate the patterns of periodontitis progression along the dental root surface. Based on these experiments we propose a mathematical model of periodontitis dynamics for better understanding the pathophysiology of the disease. The paper is structured as follows: Section 2 describes materials & methods, section 3 presents the results of the methods and section 4 contains our conclusions.

2. Materials and Methods

2.1. CA experiments

To conduct CA experiments, we employ a 2-dimensional lattice with 9 neighbours (Moore neighbourhood) and use periodic boundary conditions [Cheung & Perez-Pelgardo, 2010]. The latter means that opposing boundaries wrap around, creating the topological equivalent of a torus. The central lattice site of the grid interacts with the surrounding 8 sites using local transition rules, which gives each lattice site 8 orientations.

The initial configuration is copied from a micrograph of human cementum with PDLF inserting [Bosshardt & Selvig, 1997] at a magnification (see Fig. 1).

To start the CA experiment, we consider a nucleus of infection (some PDLF have become infected and/or inflamed) and then apply the transition rules over all sites simultaneously at each iteration to see how the infection will evolve. The nucleus of the infection is hypothesized to be the area of the first contact of the bacterial biofilm front with PDLF inserting the dental root cementum, after the breach of the junctional epithelium. Periodontitis then progresses in an apical and lateral direction. PDLF are destroyed by the induction of destructive enzymes by the host immune-inflammatory response. Thus, the lattice sites can occupy any one of three states: 1) healthy PDLF (“off state”), 2) inflamed PDLF (“on state”); and 3) vacant, either initially from the layout of the PDLF or having become vacant due to the inflammatory process that destroys the PDLF.

Transition rules are called “outer totalistic” when they rely only on sites of the neighbourhood that are at the “on state” (as well as the central sites own state). We denote these transition rules as follows: (i) “Survived 0 / Newly Inflamed 1”, implying that all inflamed sites (“on state”) become vacant in the next iteration and a healthy one (“off state”) becomes inflamed, if it is found to have exactly one neighbour site inflamed (“on state”), (ii) “Survived 1 / Newly Inflamed 1 2”, meaning that the inflamed sites (“on state”) will remain inflamed in the next iteration (survive), if and only if exactly one neighbour site is found inflamed (“on state”) and healthy sites (“off state”) will become inflamed in the next iteration, when exactly one or exactly two neighbour sites are found inflamed (see Fig. 2). In a similar way, we denote all possible combinations that can arise as “Survived 0 / Newly Inflamed 1 2 3...m” and “Survived
**Figure 1**

Panel A: A micrograph of periodontal ligament fibers inserting into cementum, see [Bosshardt & Selvig, 1997], divided in 240 boxes to measure the fractal dimension of periodontal ligament. Fibers are identified as gray circles. Panel B: Log-log plot of numbers of fibers against the reciprocal of the magnification factor, used in computing the input probability P(X) in the Markov model. It also represents the fractal dimension (FD = 1.85) of the periodontal ligament, given by the slope of the regression line. Panel C: This is a copied from the micrograph presented in panel A. The open circles represent 310 fibers distributed over a grid of 960 cells. We gave x and y coordinates for each fiber and doubled the vertical and horizontal lines. Panel D: The size of the grid is increased so that each site contains up to four fibers. Panel E: Example of a cellular automata experiment over the grid presented in panel C, for the local rule: “Survived 1 / Newly Inflamed” (see Materials and Methods). The surface within the rectangular area bordered by the dotted lines represents the nucleus of infection. The numbers indicate the sequence of iterations and are placed over fibers destroyed by inflammation. Open circles without numbers represent healthy fibers. The local rule stopped at the 19th iteration reaching a state of stable equilibrium.

1 2...n / Newly Inflamed 1 2 3...m", where n, m = 1,2,...,8, yielding a total of 72 possible rules.
Fig. 2. Cellular automata experiments on the grid of Fig. 1D producing three patterns of disease propagation that were introduced in the Markov model as three state-rules: The increasing rate state-rule ($S_1$), the constant rate state-rule ($S_2$) and the decreasing rate state-rule ($S_3$). Panel A: $S_1$ represents equivalent local transition rules as Survived 1/Newly Inflamed 1, Survived 12/Newly Inflamed 1, Survived 12/Newly Inflamed 12, etc. The element defining this rule is the number 1 in the Newly Inflamed section. We find 8 such rules. Dotted lines include an area considered as the infection nucleus. Panel B: $S_2$ represents equivalent local transition rules as Survived 1/Newly Inflamed 2, Survived 12/Newly Inflamed 23 or Survived 123/Newly Inflamed 234 etc. There are 57 such rules. Panel C: $S_3$ represents an equivalent set of local transition rules as Survived 0/Newly Inflamed 2 Survived 0/Newly Inflamed 23 or Survived 0/Newly Inflamed 234 etc., with 0 being the defining element with the concomitant absence of number 1 in the Newly Inflamed section. We find 7 such rules. Panel D: Distribution of the propagation rate of periodontitis induced by $S_1$. Log-log plot of the number of destroyed fibers against the number of iterations is shown. The slope of the regression line (=1) provides the factor $\kappa$ in (4). Panel E: As in panel D for the rule $S_2$. The slope of the regression line is again 1. Panel F: As in panel D for the rule $S_3$. Here the slope of the regression line is 0.92.

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If local transition rules fail to exhibit disease propagation when one site of the grid corresponds to one fiber, we repeat the experiments, only this time we quadruple the size of the grid (see Fig. 1D), so that a site can now contain from one up to four fibers. Applying then local transition rules one more time, we treat all possibly included fibers in a grid site as one entity. When no further iterations are produced by any of the 72 possible local transition rules after an initial number of iterations, we describe the system as being at a stable equilibrium. Equilibrium is a state which does not change in time and is considered stable if the system always returns to it after small disturbances [Ives, 1995]. If the system moves away upon disturbance, the equilibrium is considered unstable.

There are two basic steps for building a finite state Markov model (FSMM): 1) Design the directed graph that describes the topology of the model (number of states, connections between states) and 2) assign transmission and emission probabilities [Rabiner, 1989]. Recall that the deterministic CA local transition rules are classified on the basis of the pattern of propagation they produce. The classification results in 3 groups identified by “state-rules” corresponding to increasing, constant or decreasing rates of fiber destruction (see Fig. 2) and the resulting FSMM is called ergodic, if starting from any “state-rule” any other “state-rule” can follow (see Fig. 3A).

2.2. Probabilistic Analysis

We, therefore, proceed with the hypothesis that the immune-inflammatory response determines the periodontitis progression, since it is responsible for the destruction of collagen fibers. Next, to compute probabilities in building up the model, we may use reliability theory [Rausand & Hoyland, 2004]. The starting input probability for the FSMM is selected by the complementary cumulative distribution function given by the exponential distribution:

\[ P(x > X) = S_{eq}(x) = e^{x\lambda} \]  

which estimates the probability of \( x \) being larger than \( X \), with \( X \) representing the host immune-inflammatory response level and \( \lambda \) the rate factor of the distribution. Conventionally, and for the rest of this study, we shall denote \( P(x > X) \) by \( P(X) \). The exponential distribution is the only continuous and memoryless random distribution available with the largest entropy production [Sheldon, 2009]. It describes the time for a continuous process to change state as a Poisson process in which events occur continuously and independently at a constant rate. The probability that the event occurs between two dates \( t \) and \( t + \Delta t \) is proportional to \( \Delta t \), while the rate factor \( \lambda \) of the distribution is the constant of proportionality.

One method to estimate \( \lambda \) is by plotting on a log - log scale failure data (number of destroyed fibers) vs. time. In our case, events (fiber destruction) evolve on the dental root surface. The method for estimating \( \lambda \) from the micrograph of Fig. 1A involves counting the numbers of fibers (NF) in squares of size 1 by 1, 2 by 2, 3 by 3, etc., up to 15 by 15, with a respective magnification factor (MF) of 1, 2, 3, 4, etc, up to 15 [Sarkar & Chaudhuri, 1994], as shown in Fig. 1B. The slope of the regression line of the log-log plot of NF against the reciprocal of MF is an estimate of \( \lambda \). Here this estimate also represents the fractal dimension (FD) of the PDLF. Thus, the survival function of the exponential distribution gives us the probability that the immune-inflammatory response will remain above a certain level past a certain time.

The next step in constructing the FSMM is to calculate the probability to be in one of the 3 “state-rules” (see Fig. 3A). This is defined as the joint probability \( P(Y, X) \) computed by the chain rule as:

\[ P(Y, X) = P(Y|X)P(X) \]  

where \( X \) is the input symbol (inflammatory host response level), \( Y \) the output symbol (rate of fiber destruction) in the process of building up the Markov model and \( P(Y|X) \) the conditional probability of \( Y \) given \( X \). To continue with the first iteration of the Markov model (see Fig. 3A), we need to know the probability with which a “state-rule” \( S_n, n = 1, 2, 3 \), progresses steadily through the iteration process, defined as the invariant state duration probability. Duration probabilities \( P(S_n) \) are given by the complementary cumulative hazard function expressed in terms of the Weibull distribution as follows [Mishalany & Madanat, 2002]:

\[ P(S_n) = 1 - [-log(S_{wd}(x))] \]
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Figure 3

Fig. 3. Panel A: Ergodic Markov Chain diagram: At every iteration, a state-rule assigns a duration probability $P(S_n)$ to itself and $(1 − P(S_n))/2$ to the other two rules. Panel B: A trace plot presenting the results of 32000 iterations of the Markov chains of the three state-rules for aggressive periodontitis with $X = 0.99$ and chronic periodontitis with $X = 1.23$ (see Table 1). Arrows indicate the starting points of the two groups of chains. According to the maximum entropy production principle, the increasing rate state-rule ($S_1$) is distinguished along the way for both groups of chains. The traces for both groups converge after around 11000 iterations to their stationary distribution. Panel C: The plot of conditional entropy and mutual information (MI) rates against host immune response ($X$), created by simulating entropy rate data for 300 different values of ($X$) within the range 0.01-3.00. If MI = 0, then $X$ and $Y$ behave independently. If MI = 1, then all the information for the system is given by $X$ alone.

where $S_{wd}(x)$ is the exponential part of the Weibull probability distribution, i.e.

$$S_{wd}(x) = exp[-(x/\lambda)^\kappa]$$  \hspace{1cm} (4)
$S_n$ and $S_{wd}$ are functions of the variable $x$ (host defence) the scale factor $\lambda$ and a third parameter $\kappa$, called the shape factor. The Weibull distribution is widely used to model the behaviour of real life data. It characterizes a set of failure data (destroyed fibers in our case) as increasing, constant or decreasing in time. Various methods have been devised to estimate this shape factor such as probability plots, rank regression or maximum likelihood techniques. In our CA experiments, by plotting time vs. failure data (destroyed fibers) on a log-log scale, we get a regression line, whose slope is the shape factor $\kappa$, as shown in Fig. 2.

The shape factor $\kappa$ is different for each of the 3 classes of “state-rules” and thus may be used to distinguish between increasing, constant and decreasing fiber destruction rates. It is determined by the PDLF destruction rate induced by each “state-rule” from one iteration to the next (Fig. 2D, 2E and 2F). The cumulative hazard function gives us the conditional probability that a change occurs in the “state-rule” of fiber loss, given the probability that the “state-rule” has survived at a specified time. Consequently, the complement of this is the probability that the “state-rule” will continue performing past the specified time. From iteration to iteration, a “state-rule” is assigned its duration probability $P(S_n)$ with $(1 - P(S_n))/2$ assigned to each of the other two “state-rules” (see Fig. 3A).

Simulating data as in [Arnold et al., 2006] for a range of values of input $X$ we estimated the mutual information $MI$ and entropy rates $H(Y)$ and $H(Y|X)$ of the Markov chains defined as in [Han & Marcus, 2006] by:

$$MI = \frac{1}{N} \sum_{i=0}^{N} [H(Y_i) - H(Y_i|X_i)]$$

$$H(Y) = -\frac{1}{N} \sum_{i=0}^{N} p(Y_i) \log p(Y_i)$$

$$H(Y|X) = -\frac{1}{N} \sum_{i=0}^{N} p(Y_i|X_i) \log p(Y_i|X_i)$$

for $i = 1, 2, \ldots, N$ such experiments. The conditional entropy rate $H(Y|X)$ represents the exponential decay constant of the Markov chains [Holliday et al., 2006]. Mutual information (MI) is a measure of the amount of information one random variable contains about another [Zuk et al., 2006]. In other words, it is a measure of the reduction in uncertainty over time for a random variable given the knowledge of another. A high MI shows a large reduction in our uncertainty, while a low MI represents a small reduction. To make the case for periodontitis, we are interested in measuring MI when we ask how much we could learn about the progression rate of periodontitis from knowing the level of the immune-inflammatory response.

The level of host immune-inflammatory response $X$ used in simulations of periodontitis progression was estimated using data files retrieved from three previous studies [Loos et al., 2000; Takahashi et al., 2001; Graswinckel et al., 2004]. For the purpose of the present study we wish to discriminate between chronic periodontitis (CP) and aggressive periodontitis (AgP). Thus, we took periodontitis patients from two studies [Loos et al., 2000; Graswinckel et al., 2004] and reclassified them as follows: those older than 35 at the time of diagnosis are listed as CP and those less than or equal to 35 years old as AgP. We also used the results of a third study [Takahashi et al., 2001] concerning patients with localized early onset periodontitis (EOP) and generalized EOP and found that they could be classified as AgP, while patients with an original diagnosis of adult periodontitis were classified as CP. Mean values and standard deviations (SD) for all parameters were computed and outlying values ($\pm$ 3SD from the mean) excluded.

Using these mean values of immunological parameters, the host response ($X$) was estimated by comparing periodontitis patients to healthy controls using the “ratio of means” method (see Table 1). According to this method [Friedrich et al., 2008], the ratio of the mean value of each parameter for patients over the corresponding mean value for healthy controls is estimated and then transformed to its natural logarithm. Subsequently the transformed ratios are aggregated using the generalized inverse variance model and then back transformed to obtain a pooled ratio with a 95% confidence interval.
2.3. Biological implications

To validate the model, we looked for possible intrinsic self-similarity patterns [Han & Marcus, 2006] in various datasets [Loos et al., 2000] of radiographic bone loss measurements (tooth percentage with bone loss equal to or more than 50% of their root length) and in datasets of several immunological parameters [Takahashi et al., 2001; Graswinckel et al., 2004]. For alveolar bone loss severity measurements, we suggest that the self-similarity scaling factor of the attractor (related to its fractal dimension FD) reflects a similar pattern on the dataset. Furthermore, if the severity of periodontitis is determined by the entropy rate H(Y|X) of the immune response, the scaling factor involved in the calculations of the entropy rate should reflect again a self-similar pattern in the immune parameter datasets. To test these hypotheses, the bone loss severity data were sorted by the patients’ ascending age and the immunological data were sorted in ascending order according to the patients’ bone loss severity. Subsequently, the FD of each dataset was estimated using the vector quantization method [Kumaraswamy et al., 2004]. Data was divided in clusters of varying sizes and the error produced by this approximation was estimated by evaluating

\[ D = \sqrt{E[(X - \bar{X})^2]} \]  

(8)

The log-log plot of D against the size of the clusters produced a regression line, the slope of which is negative and inversely proportional to the FD of the dataset (see Fig. 4). To simulate the progression of periodontitis requires an estimate of vertical disease progression in mm at a given time. For this purpose, we based our probing attachment loss (PAL) calculations on the available micrograph of PDLF shown in Fig. 1A. It is reported [Bosshardt & Selvig, 1997] that there are around 30000 fibers contained within 1 mm², therefore the 310 PDLF within the micrograph are contained in a square with sides equal to 310/30000 = 0.01033mm.

From the CA experiments we observed that 13 iterations cover this surface, leading to the suggestion that a vertical advancement of periodontitis of 0.01033 mm represents 13 iterations. Thus, we can deduce that one iteration represents 0.01033/13 = 0.00079 mm of vertical advancement. To bring this into a time perspective, we take from the literature that the mean annual PAL per tooth site in chronic periodontitis patients is 0.1 mm, as has been almost consistently observed in untreated human populations [Socransky et al., 1984; Papapanou et al., 1989]. Thus, one iteration takes place in approximately 0.00079mm × 365days/0.1 mm = 2.88days. The decay rate of the initial joint probabilities P_t(Y, X) is then obtained from

\[ P_t(Y, X) = P_0(Y, X)e^{-H(Y|X)t} \]  

(9)

where \( P_t(Y, X) \) is the reduced probability at time \( t \) and \( H(Y|X) \) the decay constant [Holliday et al., 2006]. The convergence of three Markov chains was first visually inspected in trace plots. Second, the Gelman & Rubin [1992] convergence diagnostics were used. The method compares the variance within each chain to the variance between chains and leads to the computation of the potential scale reduction factor (PSRF). A large PSRF indicates that the variance between chains is substantially greater than the variance within chains, so that longer runs of the chains are needed to reach the target stationary distribution. If PSRF is close to 1, we can conclude that the chains have stabilized and are likely to have reached their stationary distribution.

3. RESULTS

To model mathematically the dynamics of periodontitis propagating along the dental root surface, we employed probabilistic CA experiments. When each site of the grid corresponds to one fiber (as in Fig. 1C), all 72 possible local transition rules failed to show disease propagation beyond a number of iterations, leading to a state of stable equilibrium (Fig. 1E). By contrast, when we increased the size of the grid sites so that each site could contain from one to up four fibers (see Fig. 1D), all 72 possible transition rules produced iterations that classified them into three categories: 1) an increasing rate type including 8 of the 72 rules, 2) a constant rate type containing 57 of the 72 rules and 3) a decreasing rate type with the rest 7 rules (see Fig. 2A, 2B and 2C). These categories were taken as three “state-rules” (S_1, S_2 and S_3) in the FSMM (Fig. 3A). The rate factor \( \lambda \) of the exponential distribution of \( P(X) \) was estimated to be 1.85.
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There is, however, one fundamental difference: There is no probability for an isolated collagen fiber to be sure, our model does resemble similar models devised to simulate forest fires [Turcotte, 1987]. To be sure, our model does resemble similar models devised to simulate forest fires [Turcotte et al., 2007].

The tooth is a unique, non-shedding organ piercing the epithelial barrier. Once

The disease is started, a dissipative process arises that lies far from equilibrium [Martyushev & Seleznev, 1987]. Futhermore, the shape factor \( \kappa \) of the Weibull distribution for \( S_1 \) was estimated at 1.3 (Fig. 2D), while \( \kappa \) for \( S_2 \) was 1 (Fig. 2E) and for \( S_3 \) it was 0.92 (Fig. 2F).

Based on data files of cross sectional studies investigating several immunological parameters in relation to periodontitis, we have obtained values for \( X \) (host immune-inflammatory response) corresponding to CP and AgP (Table 1). The “ratio of means” method was used to estimate that the average \( X \) for CP is 1.23, while for AgP the corresponding value is 0.99. With these values as starting points we proceeded to construct the FSMM. Calculations of probabilities and entropy rates in building the FSMM are presented in Table 2 A. For \( X = 1.23 \) (CP) and \( X = 0.99 \) (AgP) we used formula (7) and calculated the entropy rates \( H(Y|X) \) of these two types of periodontitis as 0.0750 and 0.0904 respectively for the \( S_1 \) “state-rule”.

Depending on different values of \( X \) and based on the maximum entropy production principle, the entropy rates \( H(Y|X) \) we computed suggest that the most probable hidden path is to stay within the \( S_1 \) “state-rule” for all values of \( X \) up to 1.85. However, above this value, the \( S_3 \) “state-rule” was distinguished instead. For both CP \( (X = 1.23) \) and AgP \( (X = 0.99) \) we observed in data simulations that the three classes of “state-rules” converge to their stationary distribution after around 11000 iterations (Fig. 3B). At this point the PSRF convergence diagnostic is computed as 0.99992 for CP and 0.99989 for AgP, which is highly indicative that the chains have reached their stationary distribution. As we see in Fig. 3C, when \( X \) increases the entropy rate \( H(Y|X) \) and mutual information \( MI \) both decrease. Using Eq. 2, 7 and 9, we thus find that AgP shows \( 0.00285/0.00117 \times e^{-0.0904+0.075} \approx 2.4 \) times higher decay rate than CP (see Table 2 A).

To simulate clinical progression of periodontitis we showed that the initial 1000 iterations for chronic periodontitis resulted in 0.00079 \( \times 1000 = 0.79 \) mm of attachment loss in a vertical direction. Therefore, by taking 0.1 mm as the mean annual rate of chronic periodontitis per tooth site (as explained in the previous section), we can deduce that this attachment loss occurred after about 0.79/0.1 \( \approx 8 \) years (Table 2). Hence, these simulations show that disease activity for aggressive periodontitis cases terminates on average at the age of 52 (Table 2 B).

The datasets exhibiting percentage of teeth with bone loss more or equal to 50% of their root length, showed a FD of about 1.84 (Fig. 4). Similarly, datasets of serum neutrophil, basophil, eosinophil, monocyte counts and IgA, IgG, IgM levels from all periodontitis patients also had a similar FD ranging from 1.82 to 1.87 (see Fig. 4). The above results appear to support the implications of our model that: (a) The attractor of periodontitis is a periodontal ligament with a FD of about 1.85, and (b) the entropy rate of the immune system dictates the rate of the progression of the disease.

4. DISCUSSION

Cellular automata (CA) consist of an array of finite geometrical cells that evolve in discrete time by transition rules that are simultaneously applied over all cells [Cheung & Perez-Pelgado, 2010]. The popularity of CA as a model for dynamical systems can be explained by the fact that physical and biological systems, just as CA, consist of many simple identical elementary units. As is well-known, CA may exhibit several characteristic features observed in complex systems, such as fractal geometry, 1/f noise and power laws [Bak et al., 1987].

Complexity emerges in a manner that does not depend on finely tuning parameters of the system, meaning that variables can change significantly without affecting the emergence of critical phenomena (such as phase transitions with power law behaviour and scale invariance). Moreover, local transition rules produce an irreversible process and generate self-organized states that arise spontaneously from initially disordered forms. Our study shows that, while aggressive and chronic periodontitis obey the same transition rules (since a strange attractor implies scale invariance), differences in initial probabilities and decay rates can reflect the occurrence of different clinical cases.

In periodontitis we face a unique anatomical situation in which the body’s defence cannot eliminate the disease permanently. The tooth is a unique, non-shedding organ piercing the epithelial barrier. Once the disease is started, a dissipative process arises that lies far from equilibrium [Martyshev & Seleznev, 2006]. To be sure, our model does resemble similar models devised to simulate forest fires [Turcotte et al., 2007]. There is, however, one fundamental difference: There is no probability for an isolated collagen fiber...
Using Cellular Automata Experiments to Model Periodontitis: A First Step Towards Understanding the Nonlinear Dynamics of the Disease

Fig. 4. Estimation of the fractal dimension (FD) of various datasets. We present here the log-log plot of the size of the data clusters produced by vector quantization, against the error of the quantizer. FD is given by the inverse of the negative slope of the regression line and ranges from 1.83 to 1.87. This validates the indication of the model that entropy rates of the immune system dictate the rate of disease progression. Bone loss refers to tooth percentage with bone loss greater or equal to half of their root length.

to get infected by bacteria, in contrast to an isolated tree that can catch fire. Histological measurements showed that the connective tissue inflammatory infiltrate is confined to an area 1-2 mm apical/lateral from the bacterial plaque biofilm front [Waerhaug, 1977]. Thus, one may think of several nuclei of infection that work simultaneously with the apical and lateral spread of the inflammation. CA models have also been used to simulate the local and systemic spread of HIV infection [Moonchail et al., 2010]. However; the lymph node tissues and blood circulation are completely different structures compared to the periodontium.

No matter how complex periodontitis might be in its pathophysiology, the literature is conclusive that
bacteria are the driving force of the inflammatory process [Loos et al., 2008; Preshaw & Taylor, 2011]. Pathogenic bacteria in the subgingival biofilm initiate an unfavorable host response in subjects susceptible to periodontitis and maintain the course of periodontitis when untreated. The paradoxical characteristic of the process is that the elicited inflammatory response, which is supposed to be protective, is also responsible for the collagen fiber destruction. It has been reported that the mean absolute counts of 40 bacterial species in supragingival and subgingival plaque were higher in subjects with periodontitis than in periodontally healthy subjects [Socransky & Haffajee, 2005].

CA experiments in this study showed that when each site of the grid contains one fiber, after some iterations, progression stops for any possible rule. We have to quadruple the size of the cell to continue with the CA experiments. The size of the site then intuitively corresponds to the bacterial load necessary to begin or, in case of a treated disease, to reinitialize the process. Below a certain threshold of bacterial load (it is as yet unknown what this load represents in quantitative and qualitative terms), small perturbations may occur, but the state of equilibrium is stable representing no progression of disease. On the other hand, the bacterial load cannot expand indefinitely and for that matter the same is true for the size of the sites of the grid. Eventually, they have to reach the maximum climax pathogenic community described in the literature [Socransky & Haffajee, 2005], which also represents a state of stable equilibrium.

The nonlinear mathematical model of periodontitis progression proposed in this study is validated by a number of clinical reports found in the literature. For example, Baer [1971] reported that juvenile periodontitis (now identified in the literature with AgP) attains a 3-4 times higher disease rate. He also reported the possibility of a spontaneous stop of AgP progression, at some point during the course of the disease. Furthermore, in longitudinal studies of untreated populations regarding periodontitis progression, there have been interesting clinical observations which support our model. For example, a 6-year longitudinal study [Albandar, 1990] reported a steady increase in the rate of alveolar bone loss from the age of 24 years to the mid-fifties, and a decrease in the rate of bone loss in a group of patients above the mid-fifties.

Based on two radiographic examinations of subjects of a general population sample performed 17 years apart [Hugoson & Laurell, 2000], longitudinal mean bone loss scores (% of tooth length) were estimated as follows: those aged initially 15, 20, 30, 40, 50 and 60 yr respectively showed a bone loss of 2.8%, 2.1%, 3.1%, 2.4%, 1.6% and 2.4%. This shows a slowing down of periodontitis rate in the age range 50 to 60 years, which again rises to previous levels after the age of 60. We suggest that this can be explained by a termination of the disease progression in aggressive cases around the age of 50, which is later balanced by a continuation in disease activity in chronic periodontitis patients at older ages.

Using our model, we have estimated that the mean probing attachment loss (PAL) for all periodontitis cases at the age of 31 is 2.27 mm, at the age of 39 is 3.41 mm and at the age of 47 is 4.55 mm (see Table 2 B). These results are in good agreement with reported measurements of disease progression in the literature. For instance, a radiographic study [Papapanou et al., 1989] reported at the age of 30 yr 2.08 mm mean interproximal bone loss, at the age of 40 yr 3.29 mm and 4.3 mm at the age of 50 yr. Notably, comparing simulated PAL to clinically obtained measures of radiographic bone loss from the latter study, we find that they differ only by 0.2 mm.

Additional intuition is provided in Fig. 3B and 3C. Here we observe a clear convergence of the traces of the three distributions for AgP after about 11000 iterations, meaning that the Markov chains come to their stationary distribution and disease activity terminates [Holliday et al., 2006]. Moreover, increasing the host immune-inflammatory response level X we find lower rates of disease. For example, for X = 1.85 we notice by the maximum entropy production principle that the state-rule of decreasing rates S3 is prominent. This suggests that at an even higher level of host defence, disease progression might stop altogether.

We also tried to capture the intricacies of the immune system [Garlet, 2010] by using the “ratio of means” method, comparing periodontitis patients to healthy controls, in an attempt to quantify the overall host immune response. Our findings (Table 1) indicate that CP patients exhibit an elevated immune response compared to healthy controls, while AgP cases show an immune profile similar to healthy controls. Previous studies have also reported similar results [Lopatin et al., 1991; Chen et al., 1991; Sigusch et al., 1998].

Finally, the FD of a dataset can be seen as a measure of the spread of data [Kumaraswamy et al., 2004]. It is used in data mining tasks, data clustering, formulating classification schemes or disclosing
learning patterns. Our finding that the bone loss severity measurements dataset presents a FD of 1.84, can be interpreted on the basis that periodontitis has a strange attractor with a FD of this magnitude. This simply means that whether we look upon individual PDLF or bundles of PDLF, the model applies to both equally. A slight variation in the FD of PDLF can be expected among individuals. Thus, while lower dimensions could be incompatible with a sustainable tooth structure, higher dimensions can result in easier initiation and/or progression of the disease. This clearly merits further investigation to which we intend to return in a future publication.

We also wish to point out that there is an extensive list of CA software in the literature, which can be used for a better representation of our results, especially with regard to two-dimensional (2D) models. In particular, we mention the 2D CA free software available at Discrete Dynamics Lab (www.ddlab.com) and the very interesting books [Deutsch, A. & Dormann, S., 2005; McIntosh, H.V., 2009; Wuensch & Lesser, 1992; Wuensche, 2011]. As suggested by the referees, we intend in a future paper to look more closely at such models, in view of a more global study of periodontitis in other continents beyond Europe and a broader characterization of our results in terms of attractors with specific basins.

In conclusion, we have attempted in this study to mathematically model periodontitis as a nonlinear dynamical system using CA experiments and have presented a model that is validated by clinical data. Simulations of disease progression based on our model are consistent with reports of a spontaneous halt of aggressive periodontitis. Thus, the proposed model can serve as a basis towards a quantified immune-inflammatory response to detect periodontitis susceptible individuals and shape the prognosis for treated periodontitis patients.

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References


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REFERENCES


Table 1. Mean ± standard deviations for host response parameters for healthy control subjects and patients with chronic periodontitis (CP) or aggressive periodontitis (AgP) for data retrieved from previous study populations [Loos et al., 2000; Graswinckel et al., 2004; Takahashi et al., 2001]. For the host response parameters, the ratio of the mean of CP or AgP over the mean of the healthy controls, is presented in parentheses. The average of these ratios (with 95% confidence interval), i.e. the ratio of means [Friedrich et al., 2008] represents the host response factor X in simulation of periodontitis progression.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy controls</th>
<th>Chronic periodontitis(CP)</th>
<th>Aggressive periodontitis(AgP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leukocytes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (10^9/L)</td>
<td>2.94 ± 0.75</td>
<td>3.88 ± 1.43(1.32)</td>
<td>3.83 ± 1.75(1.30)</td>
</tr>
<tr>
<td>Basophils (10^9/L)</td>
<td>0.06 ± 0.02</td>
<td>0.06 ± 0.02(1.00)</td>
<td>0.05 ± 0.02(0.84)</td>
</tr>
<tr>
<td>Eosinophils (10^9/L)</td>
<td>0.18 ± 0.11</td>
<td>0.16 ± 0.08(0.89)</td>
<td>0.11 ± 0.08(0.61)</td>
</tr>
<tr>
<td>Monocytes (10^9/L)</td>
<td>0.48 ± 0.13</td>
<td>0.47 ± 0.16(0.98)</td>
<td>0.41 ± 0.14(0.85)</td>
</tr>
<tr>
<td><strong>Lymphocytes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3 (%)</td>
<td>72.29 ± 7.77</td>
<td>61.03 ± 9.70(0.84)</td>
<td>65.09 ± 12.05(0.90)</td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>41.38 ± 11.24</td>
<td>41.63 ± 7.51(1.01)</td>
<td>37.28 ± 10.98(0.90)</td>
</tr>
<tr>
<td>CD4/CD8 ratio</td>
<td>1.59 ± 0.89</td>
<td>2.38 ± 0.86(1.50)</td>
<td>1.92 ± 2.13(1.21)</td>
</tr>
<tr>
<td>CD20 (%)</td>
<td>12.53 ± 5.67</td>
<td>16.38 ± 9.33(1.31)</td>
<td>9.28 ± 5.22(0.74)</td>
</tr>
<tr>
<td><strong>Host response molecules</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1 (pg/ml)</td>
<td>118.42 ± 104.59</td>
<td>189.42 ± 147.30(1.60)</td>
<td>141.61 ± 163.82(1.20)</td>
</tr>
<tr>
<td>IL-2 (U/ml)</td>
<td>3.42 ± 1.59</td>
<td>5.13 ± 2.34(1.50)</td>
<td>3.56 ± 1.94(1.04)</td>
</tr>
<tr>
<td>IL-4 (pg/ml)</td>
<td>11.41 ± 6.01</td>
<td>14.88 ± 8.88(1.30)</td>
<td>9.01 ± 6.70(0.79)</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>293.28 ± 461.43</td>
<td>503.19 ± 616.78(1.72)</td>
<td>218.77 ± 395.85(0.75)</td>
</tr>
<tr>
<td>TNFα (pg/ml)</td>
<td>448.86 ± 237.78</td>
<td>628.23 ± 380.74(1.40)</td>
<td>358.15 ± 383.65(0.80)</td>
</tr>
<tr>
<td>IFNγ (U/ml)</td>
<td>42.92 ± 54.48</td>
<td>54.32 ± 68.91(1.27)</td>
<td>72.39 ± 84.98(1.69)</td>
</tr>
<tr>
<td>IgG (g/L)</td>
<td>9.57 ± 2.02</td>
<td>10.03 ± 2.39(1.05)</td>
<td>10.59 ± 2.59(1.11)</td>
</tr>
<tr>
<td>IgA (g/L)</td>
<td>2.12 ± 0.96</td>
<td>2.23 ± 1.96(1.05)</td>
<td>1.70 ± 0.75(0.80)</td>
</tr>
<tr>
<td>IgM (g/L)</td>
<td>1.32 ± 0.59</td>
<td>1.49 ± 0.66(1.13)</td>
<td>1.76 ± 1.19(1.33)</td>
</tr>
</tbody>
</table>

“Ratio of means” (X)(95%CI) \[ X = 1.23(0.94 - 1.56) \] \[ X = 0.99(0.72 - 1.27) \]
Table 2. Calculated probabilities in building up the Finite State Markov Model (FSMM) (Part A) and simulation of periodontitis progression (Part B): two values of \( X \) for host defense (see Table 1) represent different levels of disease activity.

**Part A: construction of Finite State Markov Model**

<table>
<thead>
<tr>
<th>Ratio of means</th>
<th>Chronic periodontitis</th>
<th>Aggressive periodontitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( X = 1.23 )</td>
<td>( X = 0.99 )</td>
</tr>
<tr>
<td>Starting input probability ( P(X) )</td>
<td>0.1028</td>
<td>0.1602</td>
</tr>
<tr>
<td>&quot;State-rule&quot; (( S_1 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial joint probability ( P(Y,X) )</td>
<td>0.0012</td>
<td>0.0029</td>
</tr>
<tr>
<td>Entropy rate ( H(Y</td>
<td>X) )</td>
<td>0.0750</td>
</tr>
<tr>
<td>Mutual information (MI)</td>
<td>0.2729</td>
<td>0.2810</td>
</tr>
<tr>
<td>Duration probability ( P(S_n) )</td>
<td>0.7446</td>
<td>0.8074</td>
</tr>
</tbody>
</table>

**Part B: simulation of periodontitis progression**

<table>
<thead>
<tr>
<th>Chronic periodontitis</th>
<th>Aggressive periodontitis</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td># iterations(^1)</td>
<td>PAL (mm)(^2)</td>
<td># iterations(^1)</td>
</tr>
<tr>
<td>1000</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>1.58</td>
<td></td>
</tr>
<tr>
<td>3000</td>
<td>2.37</td>
<td></td>
</tr>
<tr>
<td>4000</td>
<td>3.16</td>
<td></td>
</tr>
<tr>
<td>4583</td>
<td>3.62</td>
<td></td>
</tr>
<tr>
<td>continues terminated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)One iteration represents approximately 0.00079 mm of vertical advancement of periodontitis along the root surface (see Materials & Methods).

\(^2\)Aggressive periodontitis has 2.4 times higher decay rate of the Markov chain (see Materials & Methods). PAL= probing attachment loss.

\(^3\)We use the survival function of the Pareto distribution taking 1.3 as the power law of disease progression and from the ratio of initial joint probabilities between aggressive and chronic periodontitis patients, we calculate that aggressive periodontitis patients account for approximately 31.4% of all patients: \(0.0029/0.0012)^{-1.3} \approx 0.314; \) therefore the remainder, approximately 68.6% represent chronic periodontitis patients.

\(^4\)Based on reports in the literature, we consider the mean annual PAL per tooth site to be 0.1 mm for chronic periodontitis. Therefore 0.79 mm (1000 iterations) occur within 0.79/0.1 \( \approx \) 8 years.