Original Article

A Mathematical Model of the Pathophysiology of Reflux Esophagitis

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ABSTRACT

Background: We used a 1-dimensional cellular automaton (CA) model to investigate reflux esophagitis (RE), which is caused by increased gastroesophageal reflux. The reflux route is usually 1-way, from the stomach to the esophagus, and reflux content advances upward over time, which suggests that the next state is decided by the prior state of interaction between gastric acid and the esophageal epithelium. The present study evaluated whether a 1-dimensional CA model accurately simulated endoscopic findings from RE.

Methods: Using Microsoft Excel 2013, we programmed a 1-dimensional CA with 3 neighbors and 2 states: 0 or 1. The initial state was defined as the gastroesophageal junction, and reflux of gastric acid moved in accordance with CA calculations. Because the CA rules determined how the states of given cells changed, the rules yielded other cell states. We attempted to identify CA rules that, after repeated calculations, yielded shapes consistent with endoscopic findings of RE.

Results: Images from 1-dimensional CA resembled endoscopic findings of RE. Overall, 23 (9.0%) of 256 CA rules generated progressive growth patterns. This frequency approximates the reported prevalence of RE. Rule 232 was most likely to simulate the various patterns of mucosal breaks identified by endoscopy.

Conclusions: Endoscopic findings were readily simulated by a simple mathematical method, a 1-dimensional CA. A simple local rule between adjacent cells might predict endoscopic findings of RE.

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KEYWORDS: cellular automaton (CA), reflux esophagitis (RE), mathematical model

A cellular automaton (CA) model is constructed by using a finite number of cells.[1)] A simple 1-dimensional CA has a row of cells with 2 states: 0 or 1. The cells change from state to state over time according to the rules and calculations of the CA. The rules determine the next state of a given cell by looking at the previous states of neighboring cells. The second state of the cells is drawn below the first. After repeated calculations a 1-dimensional CA develops into a 2-dimensional shape showing the history of all states, stacked vertically. Although CAs have been used to analyze natural phenomena, including genetic algorithms, few studies have used CAs in clinical medicine. We believe that CA mathematical models are useful in predicting complex phenomena that cannot be solved by

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differential equations, especially in simulating the complex reactions of life.

In clinical practice, it is essential to predict a patient's course. Although observation without treatment is common in routine care, such observation is usually reserved for low-risk cases. More frequent observation increases the accuracy of predictions of the next state in clinical practice, and accurate prediction of disease progression is highly desirable in the management of common diseases. Although it was thought that many clinical features of disease depend on gene sequences, epigenetic phenomena may alter the clinical course of some diseases, which suggests that genes alone are not sufficient for the emergence of life. Thus, in the near future it may be possible to predict the clinical features of diseases without using genetic information. Simple rules that describe clinical features of disease would help clinicians predict the next state of a patient.

A 1-dimensional CA is a line of cells that is updated in discrete time-steps according to the rules of the CA. The evolutionary direction of the CA is fixed over time; thus, a 2-dimensional CA image is a visualization of the history of all generations, stacked vertically. It is possible that movement in a fixed direction produces distinctive forms, such as that of a river delta, where earth and sand are deposited.

The esophageal epithelium comprises a collection of cells. When an epithelial cell is regarded as a "cell" in an Excel (Microsoft Corp., Redmond, WA, USA) worksheet or a cell in a CA, the intraluminal surface of the esophagus can be expressed as a collection of such "cells". Gastric acid runs from the esophagogastric junction back to the lower esophagus.[2,3] Therefore, gastric acid will reach the adjacent grid, under the first layer, in the next generation. As time passes, the grid under the previous one will, in turn, be exposed to gastric acid.

In the present study, we used a 1-dimensional CA model of reflux esophagitis (RE) because the mechanism of onset — increased gastroesophageal reflux — is widely known. The reflux route is usually 1-way, from the stomach into the esophagus, and the reflux contents advance upward over time. Thus, the next state is decided by the prior state of interaction between gastric acid and the esophageal epithelium. This study investigated whether a 1-dimensional CA model could simulate endoscopic findings of RE.

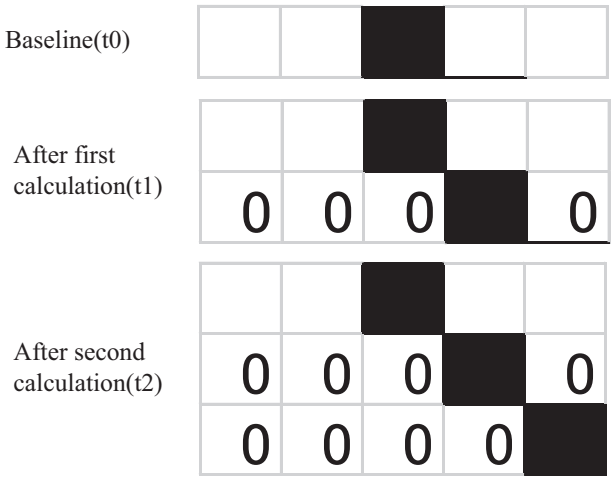


Fig. 1 A 2-dimensional image was generated by repeated calculation according to rule 120.

Methods

One-dimensional CA

A CA comprises a grid of cells and a set of transition rules. A cell has 2 states (0 or 1) and 2 adjacent neighbors. The states of cells change over time in accordance with the CA rules. At state transition, each cell gathers information on the states of its individual neighbors to the left and right. The new cell state is determined by the relationship between its own state, its neighbors' states, and the CA rules.

A center of 3 cells was defined as Ci (t) and its neighbors as Ci − 1 (t) and Ci + 1 (t). The next state generated after calculation was expressed as Ci (t1), Ci − 1 (t1), and Ci + 1 (t 1). The formula for calculating the next state at any given time t is

$$Ci\ (t1) = \delta\ [Ci - 1\ (t),\ Ci\ (t),\ Ci + 1\ (t)]$$

where δ is the state transition function. A new state was calculated and determined by the previous neighbor states. Rule 120, for example, generated a 2-dimensional image (Fig. 1) by repeated calculation.

Definition of CA rules

A 1-dimensional CA with 3 neighbors and 2 states has 3 cells, each with a state of 0 or 1. There are thus 8 possible states to be mapped to {1, 0}, and a total of 256 possible rules, because there are 8 possible states for the cell's 3 neighbors (including the central cell itself). The 2-number rule depends on the 3 cells that map the 8 possible inputs, as shown Table 1. The top row shows the states of the 3

Table 1 State transition table for rule 120

Binary		111	110	101	100	011	010	001	000
Decimal	t	7	6	5	4	3	2	1	0
	t1	0	1	1	1	1	0	0	0

Table 2 State transition table for rule 128

Binary		111	110	101	100	011	010	001	000
Decimal	t	7	6	5	4	3	2	1	0
	t1	1	0	0	0	0	0	0	0

Table 3 State transition table for rule 204

Binary		111	110	101	100	011	010	001	000
Decimal	t	7	6	5	4	3	2	1	0
	t1	1	1	0	0	1	1	0	0

Table 4 State transition table for rule 232

Binary		111	110	101	100	011	010	001	000
Decimal	t	7	6	5	4	3	2	1	0
	t1	1	1	1	0	1	0	0	0

adjacent cells, and the number in the cell is expressed as a binary value in the initial condition (t) row. The second row shows the values of the first line, expressed as decimal values. The third line shows the states of the center cells in the first line, after progressing through a 1-time interval (t1).

Table 1 shows transition rule 120, which is 01111000 in binary. The rule encodes the behavior that a cell in state 0 in the arrangements 1-0-1 and 1-0-0 should change to state 1, and that a cell in state 1 should change to state 0 only when both neighboring cells are in the same state.

Table 2 shows rule 128 (10000000 in binary), in which a cell in state 1 should change to state 0 in the next generation, unless both neighbors are in state 1. Table 3 shows rule 204, in which the initial state is not changed by the state of its neighbors. Rule 232 encodes the behavior that the state after calculation is 1 only if more than 2 of the 3 adjacent cells (*i.e.*, including itself) are in state 1 (Table 4).

Variation in the transition rules for CAs results in different 2-dimensional images. We attempted to identify CA rules that yielded shapes resembling endoscopic findings of RE after repeated calculation.

Simulation of endoscopic findings in RE

A 1-dimensional CA with 3 neighbors and 2 states was used and programmed using Microsoft Excel 2013 (Microsoft Corp.). The initial state of the upper line was virtually defined as the esophagogastric junction at time t, and gastric acid moved from the upper line, which was considered the esophageal epithelium adjacent to the esophagogastric junction, to the lower line, which includes the second state of the cell. When the second generation of cells is drawn beneath the first, and the third generation is drawn under the second, and so on, a 2-dimensional image is produced after repeated calculation. The evolution of the CA over time can be visualized on a single page. These images were compared with endoscopic findings of RE that were classified by using the Los Angeles (LA) classification.[4]

Analysis by CA

We collected 30 time-step generations from all 256 elementary rules. First, the initial state had only 1 cell in state 1, and the image generated by the CA was observed in Excel. Second, the CA image resulting from the 3 adjacent initial cells was generated and the resulting shape was evaluated with regard to its suitability in describing endo-

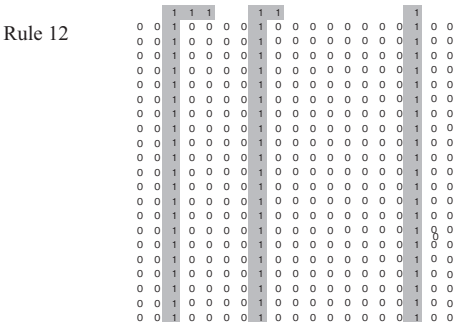


Fig. 2 Cellular automaton (CA) generated by rule 12. Initial cells in state 1 persist over time for arrangements 0-1-1 and 0-1-0 and form longitudinal lines.

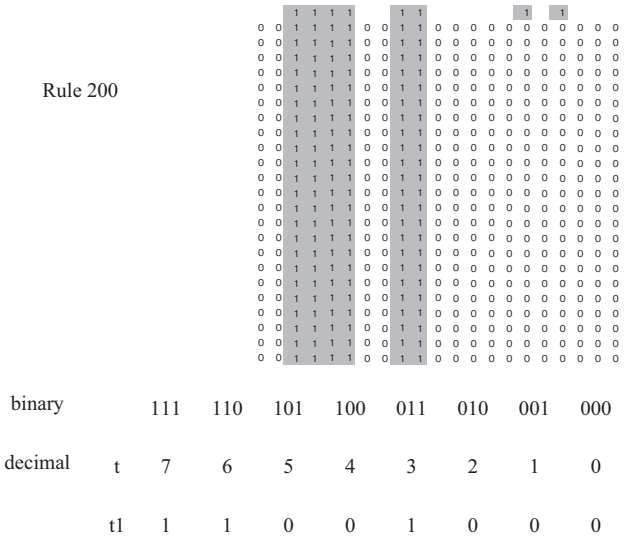


Fig. 3 Cellular automaton (CA) generated by rule 200. Although this rule produced longitudinal lines when begun with 2 or more adjacent cells in state 1, the CA did not progress when initiated with 2 nonadjacent cells in state 1.

scopic findings of RE. Next, the initial adjacent cells were changed to 1 of 2 states, 0 or 1. We examined these 3 initial conditions for all 256 rules. A rule was considered an inappropriate model for RE if the growth pattern was spiral, diffuse, widening, or showed irregular step-by-step progression.

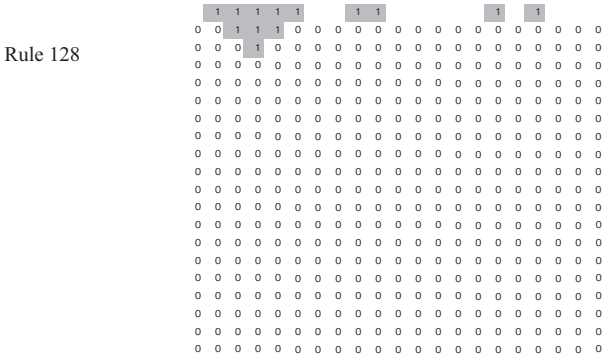
Results

Growth of adjacent initial cells

We investigated all 256 elementary rules and compared CA images with endoscopic images. Thirty iterations were collected for all 256 elementary rules. Among them, when only 1 initial cell had state 1, the initial cell developed longitudinally in 16 rules (rules 4, 12, 36, 44, 68, 76, 100, 108, 132, 140, 164, 172, 196, 204, 228, and 236). Rule 12 exhibited longitudinal growth when begun with 1, 2, or 3 adjacent cells in state 1 (Fig. 2). When the initial generation consisted of 2 cells in state 1, the 2 initial cells were able to progress over time in 7 of 16 rules (rules 12, 44, 76, 108, 140, 172, and 196). Although 3 adjacent cells in state 1 came to resemble grade B RE in rules 12, 44, 76, 108, 140, and 196, growth of the initial 3 cells stopped after 3 transitions in rule 172. Rule 172 appeared to resemble endoscopic findings of grade A RE. In contrast to rule 172, the 3 initial cells grew extensively, eventually resembling the diffuse mucosal breaks observed frequently in endoscopic examinations of patients with severe esophageal candida infection. Among the 256 rules, 5 (rules 12, 44, 76, 108, and 140) resembled grade B esophagitis and only 1 (rule 172) resembled grade A esophagitis when the width of gastric acid reflux was limited to 3 cells. Among the rules that did not generate a longitudinal CA picture when begun with only a single cell, rules 72, 200, and 232 produced a longitudinal CA picture. Figure 3 shows the image generated by rule 200. Although the 3 rules yielded a longitudinal CA picture when begun from 2 adjacent initial cells in state 1, CA did not progress with rule 72 when the CA was begun with more than 2 adjacent cells in state 1.

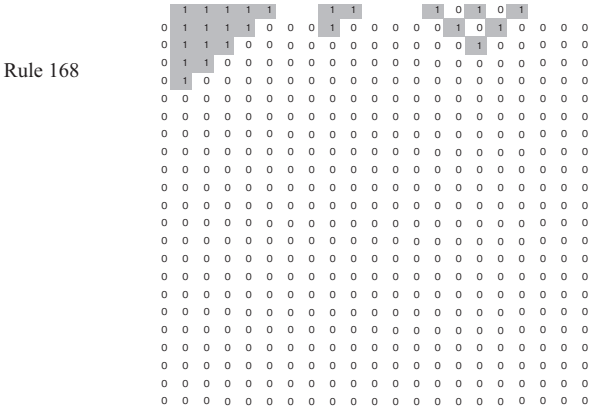
Next, we studied the rule in which a central cell remains in state 1 after calculation when all 3 serial cells are in state 1. This rule had the binary sequence 10000000 (decimal 128) and yielded a wedge shape resembling grade A esophagitis even when the number of cells was greater than 3 (Fig. 4). Rule 128 might be representative of grade A esophagitis.

Among rules that model the condition when a small amount of gastric acid regurgitates into the esophagus and 1 or 2 cells are exposed (*i.e.*, CA models starting with 1 or 2 initial cells), 18 of 256 rules (7.0%) yielded patterns resembling the longitudinal mucosal breaks of grade B esophagitis. In 9 rules, longitudinal growth from the CA occurred when starting from a single initial cell in state 1, but not from 2 adjacent cells. Four rules (136, 168, 192, and 204) produced a wedge shape when begun from 2 or more initial cells. Figures 5 and 6 show CA images generated by



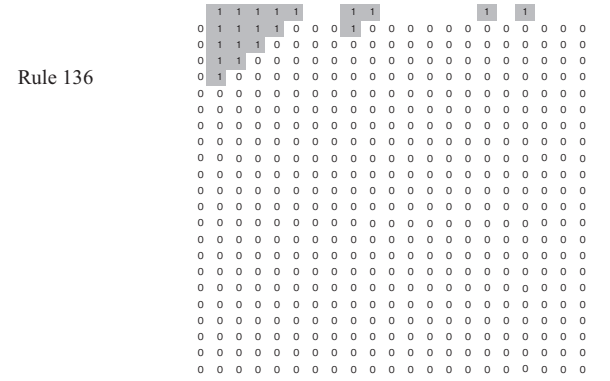
binary		111	110	101	100	011	010	001	000
decimal	t	7	6	5	4	3	2	1	0
	t1	1	0	0	0	0	0	0	0

Fig. 4 Cellular automaton (CA) generated by rule 128. A wedge shape resembling grade A esophagitis developed even if the number of adjacent cells in state 1 was greater than 3.



binary		111	110	101	100	011	010	001	000
decimal	t	7	6	5	4	3	2	1	0
	t1	1	0	1	0	1	0	0	0

Fig. 6 Cellular automaton (CA) generated by rule 168. A wedge shape developed when 2 or more adjacent initial cells were in state 1.



binary		111	110	101	100	011	010	001	000
decimal	t	7	6	5	4	3	2	1	0
	t1	1	0	0	0	1	0	0	0

Fig. 5 Cellular automaton (CA) generated by rule 136. A wedge shape developed when 2 or more adjacent initial cells were in state 1.

rules 136 and 168, respectively.

Growth of initial alternating states

We studied the growth patterns of alternating initial states such as 1-0-1-0-1. Among the 16 rules (rules 4, 12, 36, 44, 68, 76, 100, 108, 132, 140, 164, 172, 196, 204, 228, and 236) in which an initial cell progresses slowly, 10 (rules 4, 12, 44, 76, 100, 108, 132, 164, 228, and 236) grew longitudinally when begun from multiple initial cells of alternating states, such as 1-0-1-0-1. Rules 168, 204, and 232 produced a wedge-shaped CA. Overall, when gastroesophageal reflux occurred in alternating initial states, 13 rules yielded patterns resembling the mucosal breaks of grade A and B RE. In rule 72, the CA did not progress when begun from initial cells with alternating states, although a longitudinal CA image resulted when the CA was begun from 2 adjacent initial cells in state 1.

Interpretation of CA rules

1) Growth pattern for rule 104 (Fig. 7)

When any 2 of 3 initial cells, including the center cell and its 2 adjacent cells, was in state 1, the central cell is in state 0 after calculation, regardless of the previous state of the central cell. This rule had the binary sequence 01101000 (decimal 104). When calculation began with only 1 initial cell in state 1, it was always the case that a given cell would not grow in rule 104. A starting position of 2 adjacent cells in state 1 resulted only in longitudinal line-like grade B esophagitis. In contrast, 3 consecutive initial cells in state 1-1-1 always formed a wedge shape that resembled the endoscopic findings of grade A esophagitis. Surprisingly, when starting with more than 4 cells, *e.g.*, 1-1-1-1..., the cells did not grow in rule 104, even after repeated calculation. This suggests that rule 104 is a model of nonerosive reflux disease (NERD) if gastroesophageal reflux occurs widely.

2) Growth pattern for rule 232 (Fig. 8)

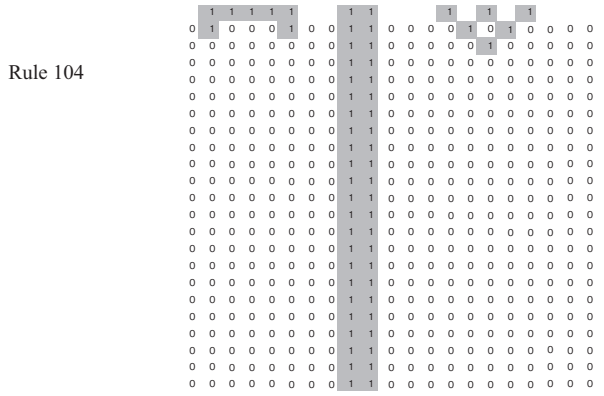


Fig. 7 Cellular automaton (CA) generated by rule 104. When calculation began with only 1 initial cell in state 1, the cell did not develop further. When starting with 2 adjacent cells in state 1, a longitudinal line was generated. Although 3 adjacent cells, *i.e.*, 1-1-1, always formed a wedge shape, the presence of more than 4 adjacent cells, *i.e.*, 1-1-1-1..., did not lead to development.

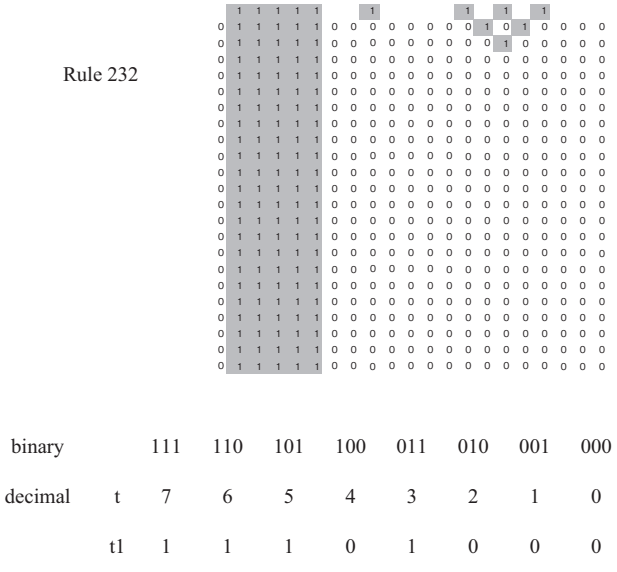


Fig. 8 Cellular automaton (CA) generated by rule 232 in which a central cell remains in state 1 after calculation if more than 2 of 3 adjacent cells are in state 1. This rule produced a longitudinal line when more than 2 cells alternated in states 0 and 1, whereas a wedge shape developed when initial cells in state 1 were nonadjacent.

When rule 232 (11101000) was used, the central cell remained in state 1 after calculation only if 2 or more neighbors were in state 1 (Table 3). The growth pattern for rule 232 resembled those for rules 72 and 200. This rule produced an image like grade B RE when more than 2 initial cells were alternately 0 and 1, and a wedge shape resembling grade A esophagitis when the initial cells in state 1 were nonadjacent.

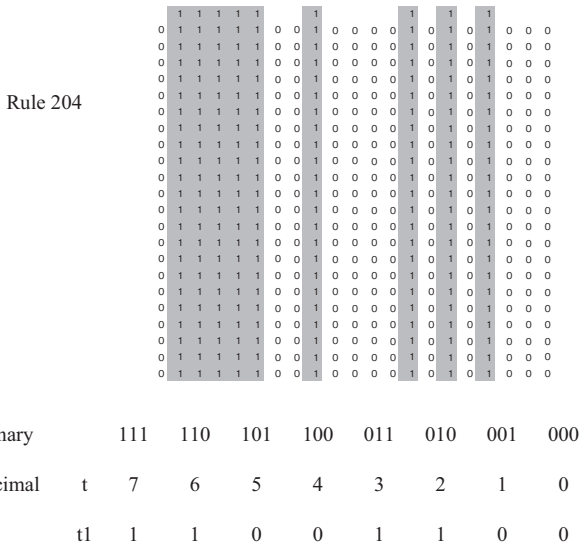


Fig. 9 Cellular automaton (CA) generated by rule 204. This rule generated only longitudinal lines.

3) Growth pattern for rule 204 (Fig. 9)

In rule 204 (11001100), decimal 204, the next state of a given cell was not influenced by the states of adjacent cells (Table 3). In other words, cells did not change state after repeated calculation. This rule yielded only narrow longitudinal lines, which suggests that it was not suitable as a model of RE development.

4) Growth pattern for rules 168 and 224

When rules 168 (Fig. 6) and 224 (binary sequences 10101000 and 11100000, respectively) were used, the cell arrangements 1-1-1, 1-0-1, or 0-1-1 resulted in a center cell in state 1 after calculation. When calculation began with only 1 initial cell in state 1, the given cell could not grow after calculation. When starting from 2 or 3 adjacent cells, an isosceles triangle formed, and CA progress stopped at the second or third generation. An isosceles triangle with its base in the initial grid was also produced after calculation when the initial cells alternated, *e.g.*, 1-0-1-0-1. Growth stopped when the number of iterations reached the number of initial cells in state 1. In contrast, the presence of 3 or more consecutive cells in state 1, *i.e.*, 1-1-1..., always formed a wedge shape resembling the endoscopic findings for grade A esophagitis. This CA also grew until the number of generations equaled the number of initial cells in

state 1.

5) Growth pattern for rules 136 and 192

Although CA rules 136 and 192 generated wedge shapes when started from 2 adjacent cells, the CA did not grow from a single initial cell in state 1 or from alternating initial cells in state 1 (1-0-1). For these rules, an initial cell remains in state 1 if the left and/or right cells are in state 1. An image of rule 136 is shown in Figure 5.

6) Growth pattern for rules 32, 40, and 96

Although rules 32, 40, and 96 did not yield useful CA images when starting from a single or more than 2 adjacent cells in state 1, a wedge shape developed when the states of initial cells alternated. These rules resulted in development if an initial cell remained in state 1 and either the left or right cells were in state 1.

7) Growth pattern for rules 8 and 64

In rules 8 and 64, an initial cell with a single neighbor in state 1 would retain its state. No growth pattern emerged when begun from any initial cell. These rules might be a model of NERD.

Frequency of RE pattern in CA rules

Twenty-three of 256 rules (9.0%) showed a progressive growth pattern resembling RE.

Discussion

The aim of this study was to determine if the simplest mathematical model, the computationally universal 1-dimensional CA, could address questions concerning RE development and progression. These questions include determining why many GERD patients present without endoscopic findings of mucosal breaks and why various shapes of mucosal breaks are observed in patients with RE, despite the same mechanisms of pathogenesis. The extent of a mucosal break is proportional to the frequency of reflux events, the duration of mucosal acidification, and the caustic potency of the refluxed fluid. In addition to injurious forces, defense mechanisms such as esophageal acid clearance and mucosal integrity are important in RE development. However, defensive mechanisms are not well understood because most patients are successfully treated with gastric-acid inhibitors in clinical practice.

There are 2 esophageal defense mechanisms: esophageal epithelial defense and pre-epithelial defense.[5,6] The former includes the capacity to change the transmural electrical potential and the barrier function of these cell layers, which is provided by apical cell membranes and adjacent intercellular junctional complexes. The latter includes the mucus layer, unstirred water layer, and bicarbonate ions trapped within these layers. The tight junctions and zonula adherens have proteins such as occludin and claudins that bridge the space between neighboring cells, which suggests that epithelial defenses should be regarded as a tissue consisting of a mass of epithelial cells.[7,8] The protective function of the esophageal epithelium should not be regarded as merely a longitudinal sequence of epithelial cells, which runs parallel to the direction of gastric acid reflux, but as a tangential one, as well. It is thought that the CA is structurally the simplest model of group defenses in esophageal epithelial cells.

Gastric acid is clearly important role in RE development, and treatment with proton pump inhibitors (PPIs) is effective in preventing GERD symptoms such as heartburn and regurgitation. However, a number of patients develop recurrence despite the marked therapeutic effect of PPIs. This suggests that the pathophysiological mechanisms of RE are not fully explained by acid reflux alone. The present results are supported by the findings of previous studies. Esophageal mucosal dilated intercellular spaces (DIS) are frequently observed in patients with NERD or RE.[9] These alterations arise with exposure to gastric acid and are improved by PPIs.[10] Displaced inflammatory cytokines and downregulated tight junction proteins subsequently induce dysfunction of the epithelial barrier.[9] When interactions between adjacent cells are changed by DIS or downregulation of tight junction proteins, it may decrease esophageal defenses and lead to longitudinal progression of mucosal breaks during gastric acid reflux. Therefore, the onset of erosive and non-erosive esophagitis and the mechanisms associated with esophagitis might be 2 sides of the same coin. Evaluation of interaction between adjacent cells in the distal esophagus is essential for the study of RE and NERD.

There are similarities between the progression of mucosal breaks in the esophagus and the development of a 1-dimensional CA over time. First, the image grows in a fixed direction. Second, a 1-dimensional CA can be virtually visualized as a 2-dimensional image. When we consider the passing of time, a 2-dimensional image is a stack of 1-dimensional CA images. The present study thus used a 1-dimensional CA to model the endoscopic findings of RE.

In this model, the different transition rules yielded a variety of images. Overall, 23 of the 256 rules (9.0%) showed a progressive growth pattern resembling RE, which sug-

gests that approximately 9% of patients with gastroesophageal reflux will develop RE if the CA rules occurred randomly with equal probability. Surprisingly, this frequency was close to the prevalence of RE (2–17.2%) reported in a number of studies.[11–13] Among the 256 rules, rules 72, 200, and 232 yielded all the types of mucosal breaks specified by the LA endoscopic classification. These rules required that a central cell remain in state 1 after evolution only if 2 or 3 of the 3 adjacent cells were in state 1. When rule 104 was applied to more than 4 adjacent cells, *i.e.*, 1-1-1-1..., the cells could not propagate after repeated calculation, even though patterns resembling grade A and grade B esophagitis were generated when starting from 2 adjacent cells and a pattern of 3 nonadjacent cells in state 1, respectively. It might be possible to successfully model NERD with a 1-dimensional CA. Although some evidence indicates that NERD development differs from that of erosive RE,[14, 15] the probability of NERD might be calculable with a CA.

Repeated daily exposure of the esophageal epithelium to acidic gastric contents does not always damage tissues. Furthermore, many patients with persistent heartburn do not have esophageal mucosal breaks when evaluated by endoscopy.[16, 17] This discrepancy between endoscopic findings and symptoms might be due to differences in esophageal defenses, including acid clearance and group defenses of esophageal epithelial cells.

The present study has some limitations. First, the transit rules for the CA were not confirmed *in vivo*, although the growth pattern of RE could follow any of the 256 rules, and the actual prevalence of RE was close to the probability obtained by the 1-dimensional CA model. Second, a 1-dimensional CA model with 3 neighbors and 2 states is quite simple. A 2-dimensional CA model with more neighbors and/or states might yield more-useful images. Nevertheless, this is the first report of the application of a CA model for clinical study.

We conclude that endoscopic findings were simulated by a simple mathematical method, a 1-dimensional CA. This suggests that a simple local rule between adjacent cells might explain the endoscopic findings of RE and NERD. Moreover, the rate of clinical RE is very similar to the rate of RE determined by CA in this study. Therefore, this new CA method may be helpful in the analysis of RE and is likely to be useful in future clinical studies.

Conflicts of interest: The authors have no conflicts of interest to disclose.

References

1) Wolfram S. Statistical mechanics of cellular automata. Rev Mod Phys. 1983; 55: 601-44.
2) Altomare A, Guarino MP, Cocca S, Emerenziani S, Cicala M. Gastroesophageal reflux disease: update on inflammation and symptom perception. World J Gastroenterol. 2013; 19: 6523-8.
3) Farré R. Pathophysiology of gastro-esophageal reflux disease: a role for mucosa integrity? Neurogastroenterol Motil. 2013; 25: 783-99.
4) Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999; 45: 172-80.
5) Chen X, Oshima T, Tomita T, Fukui H, Watari J, Matsumoto T, et al. Acidic bile salts modulate the squamous epithelial barrier function by modulating tight junction proteins. Am J Physiol Gastrointest Liver Physiol. 2011; 301: G203-9.
6) Li FY, Li Y. Interleukin-6, desmosome and tight junction protein expression levels in reflux esophagitis-affected mucosa. World J Gastroenterol. 2009; 15: 3621-30.
7) Oguro M, Koike M, Ueno T, Asaoka D, Mori H, Nagahara A, et al. Dissociation and dispersion of claudin-3 from the tight junction could be one of the most sensitive indicators of reflux esophagitis in a rat model of the disease. J Gastroenterol. 2011; 46: 629-38.
8) Capaldo CT, Farkas AE, Hilgarth RS, Krug SM, Wolf MF, Benedik JK, et al. Proinflammatory cytokine-induced tight junction remodeling through dynamic self-assembly of claudins. Mol Biol Cell. 2014; 25: 2710-9.
9) van Malenstein H, Farré R, Sifrim D. Esophageal dilated intercellular spaces (DIS) and nonerosive reflux disease. Am J Gastroenterol. 2008; 103: 1021-8.
10) Katz PO. Optimizing medical therapy for gastroesophageal reflux disease: state of the art. Rev Gastroenterol Disord. 2003; 3: 59-69.
11) Ronkainen J, Agréus L. Epidemiology of reflux symptoms and GORD. Best Pract Res Clin Gastroenterol. 2013; 27: 325-37.
12) Rosaida MS, Goh KL. Gastro-oesophageal reflux disease, reflux oesophagitis and non-erosive reflux disease in a multiracial Asian population: a prospective, endoscopy based study. Eur J Gastroenterol Hepatol. 2004; 16: 495-501.
13) Hollenz M, Stolte M, Labenz J. [Prevalence of gastro-oesophageal reflux disease in general practice]. Dtsch Med Wochenschr. 2002; 127: 1007-12. German.
14) Woodland P, Sifrim D. Oesophageal mucosal barrier: a key factor in the pathophysiology of non-erosive reflux disease (NERD) and a potential target for treatment. Gut. 2014; 63: 705-6.
15) Fujiwara Y, Arakawa T. Epidemiology and clinical characteristics of GERD in the Japanese population. J Gastroenterol. 2009; 44: 518-34.
16) Chey WD. Endoscopy-negative reflux disease: concepts and clinical practice. Am J Med. 2004; 117 Suppl 5A: 36S-43S.
17) Bashashati M, Hejazi RA, Andrews CN, Storr MA. Gastroesophageal reflux symptoms not responding to proton pump inhibitor: GERD, NERD, NARD, esophageal hypersensitivity or dyspepsia? Can J Gastroenterol Hepatol. 2014; 28: 335-41.