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Simulation of Dynamic Changes of Human T-Cell Leukemia Virus Type I Carriage Rates

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The human T-cell leukemia virus type I (HTLV-I) is transmitted via breast milk, semen, or blood transfusion. The last route was not responsible for HTLV-I infection before the advent of modern medicine, nor will it be a major route in the future because anti HTLV-I antibody-positive blood is now screened out. Thus, the carriage rates in various areas of Japan have to be explained by the former two transmission methods. Based on the relationship between the two modes of transmission and carriage rates, several simulation experiments were performed. These experiments revealed that: (a) No population with a vertical transmission rate lower than 50% can be maintained as endemic for the virus. (b) Slight differences in horizontal transmission rates can cause a large change of the carriage rates. (c) A 1,000-fold carriage rate difference would become indistinguishable within a hundred generations if both modes of transmission were operating at nearly the same rate. (d) The probability of a formerly non-endemic population becoming endemic due to a single female carrier is not negligible. (e) Prevention of vertical transmission is much more effective in lessening the carriage rate within a short period of time than is prevention of horizontal transmission. A simulation for a real population is also presented.

Key words: HTLV-I carriage rate — Computer simulation

The causative agent of adult T-cell leukemia (ATL)[1] is human T-cell leukemia virus type-I (HTLV-I),[2,3] which is transmitted via breast milk,[4] semen,[5] and blood transfusion.[6]

Other possible transmission routes such as via insect bite, sexual transmission from female to male, and vertical transmission other than via milk, are not proven as yet. Among the three proven routes, blood transfusion was not a route in the not-so-distant past, nor will it be a major route in the future because anti HTLV-I antibody-positive blood is now screened out. Thus, the existence of HTLV-I endemic areas needs to be explained by vertical and horizontal transmission via the other two routes, if further alternative routes really do not exist.

It is less than a decade since the identification of HTLV-I,[2,3] and the present can be seen as an exceptional era due to the presence of the blood transfusion route in the recent past as well as incidental prevention of HTLV-I transmission by artificial feeding of babies and by the usage of contraceptives. Therefore, it is impossible to estimate the "natural" features of HTLV-I transmission from epidemiological findings alone. However, to develop an appropriate eradication program for HTLV-I, it is of importance to determine whether or not there are really no other routes. In addition, an estimate is required of the "natural" vertical and horizontal transmission rates, and of the extent to which the use of prophylactic maneuvers can change the HTLV-I carriage rates among descendants.

To answer these questions, simulation models were developed based on the known transmission routes.

The abbreviations used are: HTLV-I, human T-cell leukemia virus type I; ATL, adult T-cell leukemia.

MATERIALS AND METHODS

Simulation models Two kinds of simulation models, deterministic and stochastic, were developed. The former models were used for populations where both the population size and the carrier numbers were so large that methods for infinite numbers could be applicable. The latter models were applied for populations where carrier numbers and/or population size were rather small. The cycle times for the simulation experiments were either a generation or a year.

Basic parameters and their definitions The basic parmeters and their definitions are as follows. (a) Carriage rate (Pp). This is not the carriage rate of the whole population but that of young people before beginning reproductive life and is assumed to be the same for both sexes. (b) Vertical transmission rate (Pv). (c) Horizontal transmission rate (Ph). This is determined as the cumulative probability of a formerly non-carrier mother becoming infected from carrier partner(s) at the time of cessation of breast-feeding.

Assumptions To make models, some assumptions other than the basic parameters are necessary. The assumptions used were: (a) The average number of offspring is independent of the carrier status of the parents. (b) The

survival rates of carriers and non-carriers are the same, at least within the reproductive period. (c) Selection of the partner is independent of the carrier status.

Derived parameters and their definitions From the basic parameters and the assumptions, two derived parameters and their functional relationships were determined. These were the carriage rate among mothers (Pm) and the initial carriage rate of the next generation (Pc). The relationship between them was:

$$Pm = Pp + (1 - Pp)PhPp \quad (1),$$
$$Pc = PmPv \quad (2).$$

Computers used For running the models, computers at Kyoto University Data Processing Center and an NEC-PC9801-VX21 desk top computer were used.

RESULTS

Carriage rate in equilibrium phase When Pv and Ph remain stable throughout the generations, the carriage rate converges to one particular value irrespective of the initial carriage rate. The mathematical proof of the convergence is given in the appendix.

In such a case, the carriage rate of the former generation has to be the same as that of the next generation. Then, from equations (1) and (2) we can obtain the equation

$$Pp = \{Pp + (1 - Pp)PpPh\}\, Pv.$$

Accordingly, for $Pp > 0$

$$Pv(1 + Ph - PpPh) = 1 \quad (3).$$

Equation (3) indicates that, if one of the three parameters is given, the relation between the other two parameters can be drawn on a curve. The curves for several given values of Pp (Fig. 1A), Pv (Fig. 1B), and Ph (Fig. 1C) are shown.

Fig. 1A indicates that if the combined value of Pv and Ph lies below the curve for $Pp=0.0$, and if there is no other transmission route, then HTLV-I carriers will vanish. Further, if Pv is lower than 0.5, then carriage cannot be maintained at any level.

When Pp is low, a slight change of Ph may cause a large change of Pp (Fig. 3B). On the other hand, when Pp is high, the influence of a change in Ph is not so large.

The relationship between Pp and Pv is close to a straight line (Fig. 1C).

Chronological changes of carriage rate Suppose that there are two populations with the same Pv and Ph but the carriage rates are different. It could be supposed that the two populations will reach the same equilibrium carriage rate. A simulation experiment to show the chronological changes of Pp was performed. In this experiment, the initial carriage rate was set as 100% for one population and 0.1% for the other. The theoretical carriage rate at equilibrium was fixed as 25%. Two combinations of Pv and Ph were then simulated for a hundred

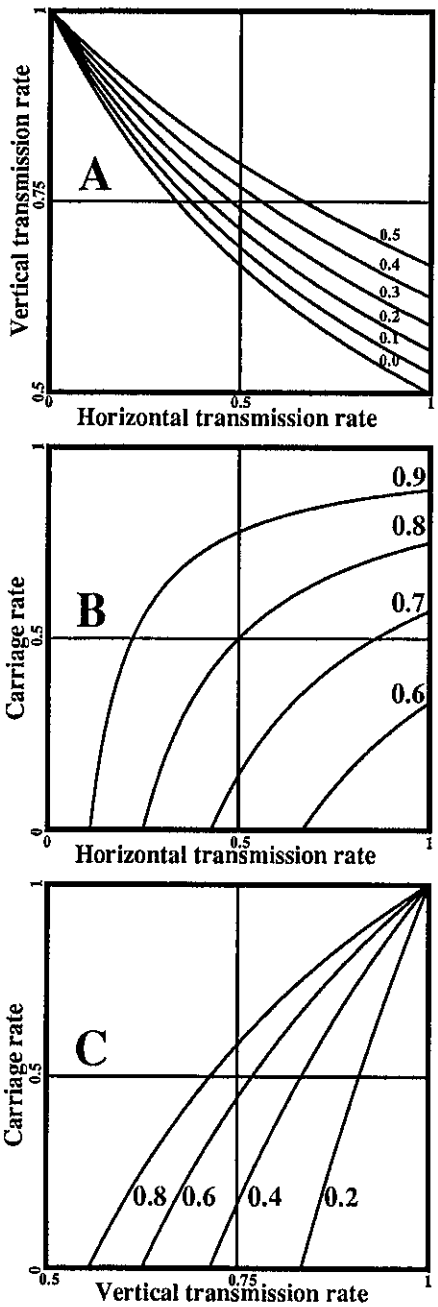

Fig. 1. Relation between Pv and Ph (A), Pp and Ph (B), and Pp and Pv (C), at equilibrium. Numbers in the figure are, Pp (A), Pv (B), and Ph (C), respectively.

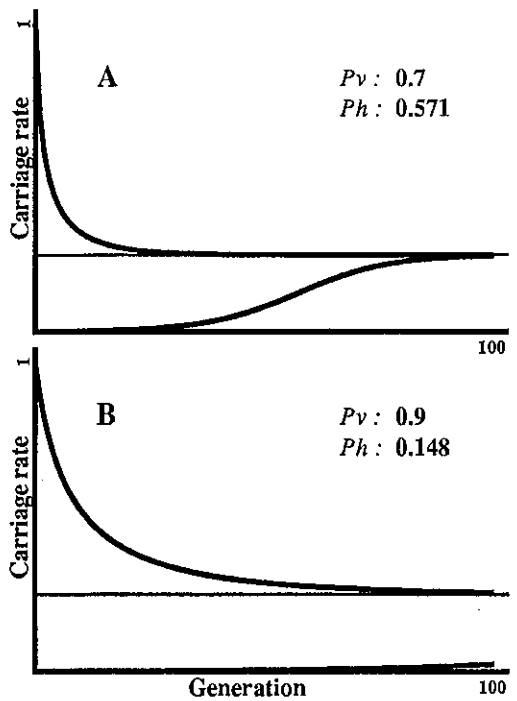

Fig. 2. Chronological change of carriage rate in initially high (100%) and low (0.1%) carriage rate populations. The theoretical carriage rate at equilibrium was set at 25%.

generations (Fig. 2). Fig. 2A shows that if *Ph* is relatively high, the carriage rates of both groups will be indistinguishable within a hundred generations. If *Ph* is very low compared with *Pv* (Fig. 2B), the chronological changes of carriage rate will be slow and a hundred generations will not be long enough for the population with an initial carriage rate of 0.1% to reach equilibrium.

Fate of a population challenged by a single carrier female

All former simulations were based on the implicit assumption that the population and the number of carriers were so large that theories only applicable to infinite numbers could be used. However, in certain situations, such an implicit assumption is no longer applicable. One of these situations is the fate of a formerly non-endemic population challenged by a single female carrier. This does not necessarily mean that the female carrier came from an endemic population, since an accidental contact with a foreign male carrier may cause the same situation. The purpose of this simulation experiment was to estimate the probability of a formerly non-endemic population changing to endemic due to a single female carrier. Simulation of such situation needs stochastic models, i.e., models based on random numbers. Furthermore, several additional assumptions are necessary, i.e., the sex ratio, the size and growth rate of the population, the distribution of numbers of offspring, and the average number and distribution of the partners for a male. Criteria for determining that a population is endemic are also necessary. The parameters chosen were a 1:1 sex ratio, a population size so large that the probability of a carrier male pairing with a carrier female was negligible, a zero population growth rate, and the Poisson distribution for numbers of offspring (as in most simulations handling discrete small numbers). In order to simplify the model, the number of partners for a male was fixed at one. The mean number of offspring who would participate in reproductive activity would then become two from the 1:1 sex ratio and the zero population growth rate. People not having children were neglected in this experiment because they would not affect the carriage rate of the future generations. The generations were cycled until carriers either vanished or exceeded a hundred. The latter case was considered to be endemic. The simulation cycle was as follows: (a) For each carrier female, the number of offspring was determined. (b) For each offspring, sex and carrier status were determined based on *Pv*. (c) For each carrier male, his wife's carrier status was determined based on *Ph*. If his wife become infected, the number, sex, and carrier status of their offspring were determined as in (a) and (b). (d) The carrier offspring constituted the next generation.

Table I. Simulation of the Fate of a Formerly Non-endemic Population Challenged by Single Carrier Female

$Pv^{a)}$	$Ph^{b)}$	$Pp^{c)}$	Probability of becoming endemic	
0.6	0.8888	0.25	0.216	(0.191–0.242)[d]
0.7	0.5714	0.25	0.162	(0.140–0.186)
0.8	0.3333	0.25	0.128	(0.108–0.150)
0.9	0.1481	0.25	0.067	(0.053–0.084)
0.6	0.7407	0.10	0.089	(0.072–0.108)
0.7	0.4762	0.10	0.076	(0.061–0.094)
0.8	0.2777	0.10	0.041	(0.030–0.054)
0.9	0.1235	0.10	0.027	(0.018–0.038)

a) Vertical transmission rate.
b) Horizontal transmission rate.
c) Calculated carriage rate at equilibrium.
d) Numbers in parentheses gives 95% confidence intervals.

Several sets of *Pv* and *Ph* were simulated. For ease of comparison, *Pv* and *Ph* were selected so that the estimated carriage rate at equilibrium was either high (0.25) or low (0.1). A thousand simulation experiments were performed for each set. Table I summarizes the given parameters and the estimated probability of an endemic population arising in each case. When the estimated carriage rate at the equilibrium is the same, a relatively low *Pv* and high *Ph* gives a higher probability of an endemic population developing than a relatively high

Pv and low *Ph*. It became apparent from this simulation that a single female carrier could convert a formerly non-endemic population to an endemic one with a not negligible degree of probability.

If the population growth rate is positive, in other words, if the mean number of offspring is larger than two, the probability of developing an endemic population becomes larger than in this simulation. Also if the mean number of partners for a male is greater than one, the probability will become higher. Thus, the probability estimated in this simulation could be considered as the lower limit. Of course, if the population growth rate is negative, the probability will be less than in this simulation. However, such a population is outside the scope of this work.

Simulating a real population The former models are satisfactory to estimate the long-term changes of HTLV-I carriage rate. However, to simulate the changes within a short period such as a few generations, models which can describe a real population become necessary. That is, such models have to determine the population size, the age- and sex-specific survival rates, as well as the mean and distribution of the age of marriage for both sexes, and of mothers' ages at delivery. A model to simulate yearly changes of carriage rate in a given population was developed with the following specifications. (a) A population with up to 2,000 females was simulated using a personal computer. (b) Each female in the population had the following characteristics determined: age, carrier status, age of marriage, age difference from her husband, and carrier status of her husband. (c) The cycle time for this simulation was a year. (d) For males, only the age-specific carriage rates were determined. (e) Parameters were given from the keyboard at run time. (f) Zero population growth rate was assumed.

The run time parameters were, *Pv*, *Ph*, mean and standard deviation for females' age of marriage, age difference from husband, and mothers' age at delivery. *Ph* can be a function of the duration of marriage. In this experiment, the probability of a non-carrier female becoming infected by her carrier husband was assumed to be $\{1-(1-x)^n\}Ph$, where n is the duration of marriage in years and x is a new parameter representing the yearly horizontal transmission rate from a carrier husband having donor activity. Thus, in this experiment, *Ph* was the proportion of males with donor activity among male carriers.

The simulation was performed as follows: (a) The necessary parameters were obtained from the keyboard. (b) Age- and sex-specific one-year survival rates[7] were obtained from a file. (c) The age and age of marriage for each female (and if her age was above her age of marriage, her husband's age) were determined based on parameters. (d) The initial carriage rate was set as 1.0 for both sexes. (e) Cyclic simulation was continued until the population reached equilibrium or the carriers vanished. (f) If the population reached equilibrium, the characteristics of each (age, age of marriage, carrier status, as well as husband's age and carrier status when necessary) and the age-specific carriage rates of males were stored. (g) Using the population at equilibrium, the chronological changes of carriage rates for different sets of *Pv* and *Ph* were simulated.

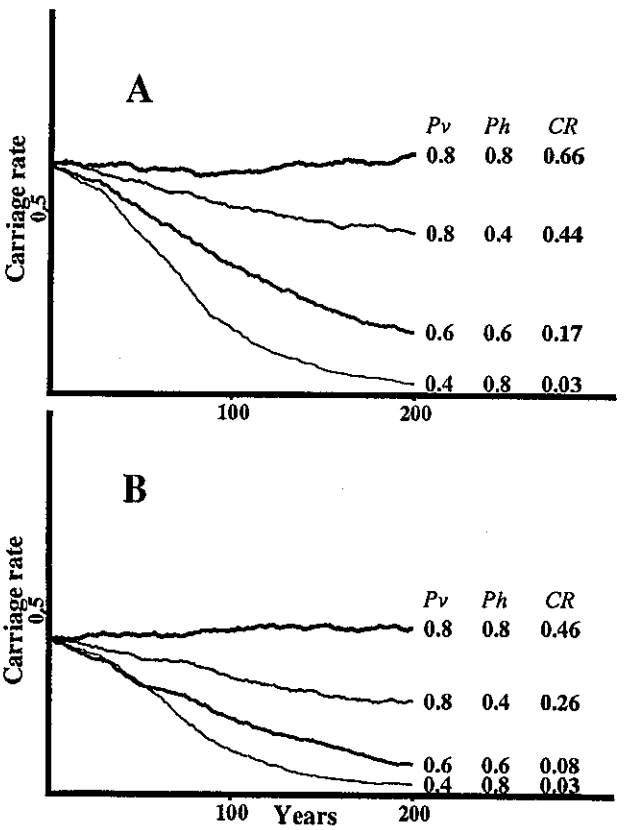

Fig. 3. Simulating a real population. The initial population was at equilibrium with both *Pv* and *Ph* 0.8, females' age of marriage 25 ± 3 years old, age difference from husband 3 ± 3 years old, and mothers' age at delivery 29 ± 5 years old for both A and B. The yearly horizontal transmission rate (x) was 0.5 for A and 0.2 for B.

Fig. 3 shows some examples. The mean and standard deviation of the females' age of marriage, the age difference from the husbands, and the mothers' age at delivery, as well as *Pv* and *Ph* were all the same in Figs. 3A and 3B. The yearly horizontal transmission rates (x) are shown to be 0.5 in Fig. 3A and 0.2 in Fig 3B, while the female carriage rates at equilibrium are 0.63 and 0.43, respectively. It is apparent that prevention of vertical transmis-

sion is much more effective than prevention of horizontal transmission in reducing the carriage rate within a short period.

DISCUSSION

The known characteristics of HTLV-I infection make it relatively easy to develop simulation models. These are the following. 1) Once infected, no natural eradication of HTLV-I has been observed. 2) There are no individuals immunized against HTLV-I infection. 3) The incidence rate of ATL among carriers is quite low and could be regarded as negligible among female carriers of a reproductive age. 4) Troublesome considerations of differing background factors between carriers and non-carriers (e.g., number of offspring, age of marriage, survival rate within the reproductive age) can be omitted. 5) The epidemiologically proven and ongoing transmission routes, i.e., vertical transmission from the mother and horizontal transmission from the male, are easy to simulate. On the other hand, a cohort study of at least several generations would be necessary to get adequate information about HTLV-I infection from a survey on a real population. Also simulation is the only method that can be used to estimate the influence of changed transmission rates on the carriage rate of the descendants.

No epidemiological estimate of the horizontal transmission rate is available yet. Also, the diversity among estimates of vertical transmission by breast-feeding is so large that it is not yet possible to select a realistic value. Furthermore, even if both rates are constants in reality, they may be functions of several social factors that have varied in different eras. That is, vertical transmission rate may be a function of the mean duration of breast-feeding, and the influence of horizontal transmission on the next generation's carriage rate would vary with the mean duration from starting sexual activity to delivery or cessation of breast-feeding, the average number of partners of a female, and the use of contraceptives.

Therefore, I first treated both transmission rates as variables. The simulation based on the functional relationship between transmission rates by both methods and carriage rate at equilibrium showed several important features of the nature of HTLV-I infection. A population with less than a 0.5 vertical transmission rate cannot be maintained as endemic even if the horizontal transmission rate is 1.0 (Fig. 1A). Slight differences of the horizontal rate may result in large differences of the carriage rate if carriage rates are low (Fig. 1B). This might be one of the reasons for geographical difference of carriage rate in Japan.

Second, the chronological changes of carriage rate in two populations with the same vertical and horizontal transmission rates were simulated. The initial carriage rate in one population was set at 1,000 times higher than that of the other. When the difference between *Pv* and *Ph* was small, the carriage rates of both populations became indistinguishable within a hundred generations (Fig. 2 A). On the other hand, if *Pv* was very high and *Ph* was very low, a hundred generations was not long enough for the initially very low carriage rate population to reach equilibrium (Fig. 2B). Although the vertical transmission rate used in the former example (0.7, Fig. 2A) was higher than the estimates from epidemiological surveys,[8-13] the former example is more likely to be close to reality than the latter one. This suggests that the major determinant of carriage rates in various areas in Japan today is not the carriage rates in ancient times, e.g., the Yayoi era, but the different vertical and horizontal transmission rates.

The third model was of an extreme situation, i.e., the probability of a formerly non-endemic population becoming endemic to a single female carrier. The estimated probability was not negligible (Table I). This suggested that the distribution of HTLV-I carriage today might differ from that in earlier times, and that non-endemic populations today are not totally safe from the risk of becoming endemic.

We know of two major transmission routes for HTLV-I and both could be controlled by available methods. The final model simulated a real population which was initially at equilibrium and then had the transmission rates changed. The major result of interest from this model was that lessening the vertical transmission rate was much more effective than lessening the horizontal transmission rate in reducing the carriage rate within a relatively short period (Fig. 3). From this model, other ways to lessen the carriage rate would appear to include decreasing the average time span from starting sexual activity to delivery and prevention of contact with HTLV-I positive semen if pregnancy is not desired (compare Figs. 3A and 3B).

A slight modification of the program is adequate to simulate existing populations with up to 2,000 females, so that instead of the computer-generated population at equilibrium, data about real females and the age-specific carriage rate of real males in a population could be used.

Most of the transmission rates used in this work were higher than the epidemiological estimates, because it is almost impossible to explain the existence of an endemic population on the basis of the epidemiological estimates if vertical and horizontal transmission are the only routes available to HTLV-I. Several hypotheses can account for this discrepancy. One is that some HTLV-I carriers do not have a detectable level of anti HTLV-I antibody so that the "carriage rate" determined from anti HTLV-I antibody-positive rate is an underestimate. This might be true. However, if such "anti HTLV-I antibody-negative HTLV-I carriers" had donor activity, many more carrier

offspring from anti HTLV-I antibody-negative mothers should have been reported. It is also possible the contribution of such "anti HTLV-I antibody-negative carrier mothers" to the carriage rate of the next generation could be negligible. The second hypothesis is that there are unknown transmission route(s) in addition to the vertical and horizontal transmission routes. However, this hypothesis is also disfavored for the same reason as given above, as well as the fact that transmission of HTLV-I needs direct contact with infected lymphocytes. The final hypothesis is that both vertical and horizontal transmission rates have fallen considerably within the last few decades. This seems likely, because most of the changes of lifestyle in recent decades have been likely to decrease transmission. The use of artificial feeding for babies obviously lowers the vertical transmission rate, while the increase of the average age of females at marriage, the fall in the age of mothers at the delivery of their last child, and the use of the contraceptives all decrease the horizontal transmission rate. Therefore, it is possible to explain the discrepancy in terms of this last hypothesis.

It is hoped that the simulation models presented here will be of use in planning an eradication program for HTLV-I.

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APPENDIX

Proof of the convergence of the carriage rate: Let us denote $P0$ as the initial carriage rate and Pn as the carriage rate at the nth generation. Then, from equations (1) and (2), we obtain the equation

$$P(n+1)=\{Pn+(1-Pn)PnPh\}Pv \qquad (4).$$

If we let $PvPh=a$ and $(1+Ph)/Ph=b$, then we obtained the equation

$$P(n+1)=a(b-Pn)Pn \qquad (5).$$

If we then let $Xn=Pn/b$ and $k=ab$, equation (5) is transformed into

$$bx(n+1)=ab^2(1-Xn)Xn \qquad (6).$$

Because $0<Ph<1$, it follows that $b>2$. This means that equation (6) is equivalent to

$$X(n+1)=k(1-Xn)Xn \qquad (7).$$

Because $0<Pv<1$ and $0<Ph<1$, then it fullows that $0<k<2$ and $0<X0<0.5$. These values and equation (7) limit the range of Xn to $0<Xn<0.5$. Now we should consider the signs of $Xn-X(n+1)$ and $X(n+1)-X(n+2)$. From equation (7), we can obtain the equations

$$Xn-X(n+1)=Xn(1-k+kXn) \qquad (8),$$

and

$$X(n+1)-X(n+2)=X(n+1)(1-kXn)(1-k+kXn) \qquad (9).$$

Because Xn, $X(n+1)$, and $1-kXn$ are all limited to positive values, $Xn-X(n+1)$ and $X(n+1)-X(n+2)$ have the same sign. This indicates to us that Xn will increase monotonously, decrease monotonously, or be constant when $1-k+kXn<0$, $1-k+kXn>0$, or $1-k+kXn=0$, respectively. Because the range of Xn is limited for both sides and Xn monotonously changes as n increases, Xn will always converge irrespective of the initial value.

One more question remained to be solved; i.e., whether Xn converged to one particular value irrespective of the initial value ($X0$).

When $0<X0<(k-1)/k$, Xn monotonously increases because $1-k+kX0<0$. If we assume that $Xn>(k-1)/k$, Xn will monotonously decrease because $1-k+kXn>0$. This contradicts the former statement. Then, let us take the upper limit of Xn as $(k-1)/k$. If we assume that Xn converges to c and $X0<c<(k-1)/k$, i.e., $\lim Xn=c$, then $\lim X(n+1)/Xn=\lim k(1-Xn)=k(1-c)$ should equal 1. This contradicts our assumption that $c<(k-1)/k$. Thus, Xn always converges to $(k-1)/k$ when $0<X0<(k-1)/k$.

When $X0>(k-1)/k$ and $k>1$, Xn monotonously decreases because $1-k+kXn>0$. Also, by the same logic as above, the lower limit of Xn is $(k-1)/k$ and Xn does not converge to c when $c>(k-1)/k$. Thus, Xn always converges to $(k-1)/k$ when $X0>(k-1)/k$ and $k>1$.

When $k\leqq 1$, then Xn decreases monotonously irrespective of $X0$ because $1-k+kXn>0$. If we assume Xn converges to c and $0<c$, then $\lim X(n+1)/Xn=\lim k(1-Xn)=k(1-c)$ should equal 1. However, $k(1-c)$ is always less than 1 in this setting because $k\leqq 1$ and $1-c<1$. Therefore, Xn always converges to 0 when $k\leqq 1$.

Thus, the thesis "Xn always converges to one particular value" was proved to be true, and this thesis is equivalent to the original thesis "Pn always converges to one particular value."

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