以生物反應器工程來解釋「喝水為治療病毒感染有效方法之一」

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摘要

由流行病學模式之推演提供對感染個體有效治療之理論基礎。喝水對病毒感染之治療是「可行策略」，尤其對仍然沒有有效醫療方法之疾病更為重要。依據模式預測，對感染之最佳被動式策略乃是限制固體食物之進食，而增加流體之攝取。此乃因為減少進食可緩和可能被感染之部位再度擴大。而持續水分之攝取對患病部位亦有降減與「清洗」之效果。相反逆向操作，限制之流體進食，而增加固體食物之攝取，反會造成病體疾病傳染之持續蔓延擴大，對病體並無基本上之人為治療效果。

關鍵詞: 病毒感染、流行病學、喝水、食物攝取、感染部位、未感染部位

Bioreactor Engineering Perspective to Interpret "Water-Drinking as an Effective Remedy for Viral Infection"

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Abstract

An epidemic model is presented to provide theoretical considerations for effective remediation of infected individuals. Water-drinking is feasible to curing of viral infection, especially as no effective medication is available. The best strategy is to limit food ingestion and increase fluid intake, since decreased ingestion reduces augmentation of susceptible components to be infected. Moreover, continuous fluid intake attenuates and washes out infected components in infected individuals. In contrast, the worst is to increase food ingestion and decrease water intake, as augmentation of susceptible components and persistence of infected component enhance "chronic" disease transmission of viral infection.

Key Words: Viral infection, Epidemic model, Water drinking, Food ingestion, Infected component, Susceptible component

I、INTRODUCTION

The purpose of this article is to show, from a bioreactor engineering perspective, that water-drinking is an effective remedy to improve health of individuals who infected with a virus. For some cases effective medication for viral infection is either known or available; however, in this study a mathematical model is used to explain why medical doctors usually suggest water-drinking (i.e. wash-out) as a feasible option of "natural attenuation" for viral infection especially if certain effective medication is pending to be approved or not available.

II、MATHEMATICAL METHOD: MODEL DEVELOPMENT

To investigate this problem, the "control volume" to be studied- an infected individual (denoted as a "biosystem") can be categorized into three portions of components: 'susceptible' or uninfected component (X), infected component (Y), and immune component (Z). The cyclic reaction, $X \xrightarrow{r_{dT}=\beta XY} Y \xrightarrow{r_Y=\nu Y} Z \xrightarrow{r_Z=\nu^* Z} X \rightarrow Y \rightarrow Z \rightarrow X \rightarrow \cdots\cdots$ ($\downarrow r_d = dY$ at Y; $\downarrow$ at Z) ([1], [2], [3], [4], [5], [6], [7], [8]) is proposed to describe infection phenomena occurring in this biosystem. It is noted that viral replication or proliferation requires significant amount of susceptible-host compartment to be established. In addition, continuous food-ingestion enhances or "enlarges" growth of susceptible to be infected. Thus, neglecting the case that surplus food-intake converts to storage components (e.g. fat), sufficient food-ingestion provides "nutrient" to be utilized and conditions to spread viral infection. The material balances for 'susceptible', 'infected' and 'immune' components and the change in the biosystem can be accounted for by:

susceptibles: $$\frac{d(VX)}{dt} = V(r_Z + r_X - r_{dT}) + F_1 \cdot X_0^1 - F_o X \,, \qquad (1)$$

infecteds: $$\frac{d(VY)}{dt} = V(r_{dT} - r_Y - r_d) - F_o Y\,, \qquad (2)$$

immunes: $$\frac{d(VZ)}{dt} = V(r_Y - r_Z) - F_o Z\,, \qquad (3)$$

overall biosystem: $$\frac{dV}{dt} = F_i - F_o\,. \qquad (4)$$

Note that F_i(l/h), F_o, and $F_1(\leq F_i)$ represent the net rate of fluid uptake, flow rate of fluid outlet, and flow rate of 'susceptible material' (e.g. food or nutrient) from surrounding, respectively. Moreover, r_X(g/l-h) is growth rate of susceptible components, r_d(g/l-h) is death rate of infected components (dY); r_{dT}(g/l-h) is disease transmission rate (βXY) which depends upon random collision between susceptible (X) and infected portions (Y); r_Y(g/l-h) denotes recovery rate of infected components (νY); r_Z(g/l-h) is rate of immunity loss (ν^*Z; e.g. r_Z=0 as permanent immunity); and V(l) is control volume of the biosystem. Based upon quasi-steady state assumption (F_i=F_o), the state equations (1), (2), (3) and (4) are generalized as follows:

'Susceptible': $$\frac{dX}{dt} = (r_Z + r_X - r_{dT}) + D_1 \cdot X_0^1 - DX\,, \qquad (5)$$

'Infected': $$\frac{dY}{dt} = (r_{dT} - r_Y - r_d) - DY\,, \qquad (6)$$

'Immune': $$\frac{dZ}{dt} = (r_Y - r_Z) - DZ\,; \qquad (7)$$

where D_1(h^{-1}) and D(h^{-1}) are defined as F_1/V and F_i/V, respectively. The term of $D_1 \cdot X_0^1$ denotes "wash-in"(or input) of susceptible material. The terms of DX, DY, and DZ express washout of susceptible, infected, and immune portion, respectively. The governing equations are shown as follows:

$$\frac{dX}{dt} = \nu^* Z + \mu X\left(1 - \frac{X}{X_m}\right) - \beta XY + D_1 X_0^1 - DX\,, \qquad (8)$$

$$\frac{dY}{dt} = \beta XY - \nu Y - dY - DY\,, \qquad (9)$$

$$\frac{dZ}{dt} = \nu Y - \nu^* Z - DZ\,; \qquad (10)$$

where $\mu X(1-X/X_m)$ in the equation (8) denotes a susceptible portion in a logistic growth; β is a disease-transmission coefficient; μ denotes the specific growth rate of X; d is the mortality

rate of Y; ν is the recovery rate constant of Y; ν^* is an immunity-loss constant; X_m is saturation value of X; and $D_1X_0^1$ is inlet 'susceptible' component from outside due to food intake. The use of D allows a stream of water to wash out all components. By setting $\left(\dot{X},\dot{Y},\dot{Z}\right)=\bar{\varnothing}=(0,0,0)$ for time-invariant steady state, one non-trivial solution [4] of X, Y, and Z is obtained as follows:

$$(X_{F^+W^+},Y_{F^+W^+},Z_{F^+W^+})=\left(\frac{\nu+d+D}{\beta},\mathrm{Y}_{\mathrm{F^+W^+}},\frac{\nu Y_{F^+W^+}}{\nu^*+D}\right);$$

where $$Y_{F^+W^+}=\frac{D_1X_0^1+(\mu-D)\left(\frac{\nu+d+D}{\beta}\right)-\frac{\mu}{X_m}\left(\frac{\nu+d+D}{\beta}\right)^2}{(d+D)\frac{\nu^*}{\nu^*+D}+(\nu+d+D)\left(\frac{D}{\nu^*+D}\right)}. \qquad (11)$$

III、DISCUSSION

In this study, four critical cases were investigated: (1) an infected person lacking food and water intake denotes as F^-W^-; (2) a person without water intake, but with food ingestion is expressed as F^+W^-. In contrast, (3) one drinks water but has no food intake denoted as F^-W^+; (4) one with water and food ingestion denotes as F^+W^+. The value of Y presents an index of viral infection to the biosystem. Asymptotic solutions of Y in the system of F^+W^+(i.e. $X_0^1\neq0$), F^-W^+(i.e.$X_0^1=0$), F^-W^-(i.e. $D\rightarrow0$), and F^+W^-(i.e. $D\rightarrow D_1$) are shown as follows:

$$Y_{F^+W^+}=\frac{D_1X_0^1+(\mu-D)\left(\frac{\nu+d+D}{\beta}\right)-\frac{\mu}{X_m}\left(\frac{\nu+d+D}{\beta}\right)^2}{(d+D)\frac{\nu^*}{\nu^*+D}+(\nu+d+D)\left(\frac{D}{\nu^*+D}\right)}, \qquad (12)$$

$$Y_{F^-W^+} = Y_{F^+W^+}\Big|_{X_0^1=0} = \frac{(\mu - D)\left(\frac{\nu + d + D}{\beta}\right) - \frac{\mu}{X_m}\left(\frac{\nu + d + D}{\beta}\right)^2}{(d+D)\frac{\nu^*}{\nu^* + D} + (\nu + d + D)\left(\frac{D}{\nu^* + D}\right)}, \qquad (13)$$

$$Y_{F^-W^-} = \lim_{D\to 0} Y_{F^+W^+}\Big|_{D_1=0} = \left(\frac{\mu}{d}\right)\left(\frac{\nu + d}{\beta}\right) - \frac{\mu}{X_m d}\left(\frac{\nu + d}{\beta}\right)^2, \qquad (14)$$

$$Y_{F^+W^-} = \lim_{D\to D_1} Y_{F^+W^+} = \frac{D_1 X_0^1}{d} + \left(\frac{\mu}{d}\right)\left(\frac{\nu + d}{\beta}\right) - \frac{\mu}{X_m d}\left(\frac{\nu + d}{\beta}\right)^2, \qquad (15)$$

According to this analysis, one may obtain the results of $Y_{F^+W^-} > Y_{F^+W^+} > Y_{F^-W^+}$ and $Y_{F^+W^-} > Y_{F^-W^-} > Y_{F^-W^+}$ (see Appendix A), provided that $\nu^2 < d^2 + d \cdot D$. It indicates that F^+W^- case is the worst to infected individual since continuous addition of nutrient that converts to the susceptible portion (X) will enhance the persistence of infection. In contrast, the case F^-W^+ is the best as washout of infected cells reduces infection and also in the absence of food uptake inlet stream removes augmentation of 'susceptibles' from surrounding.

For a particular case of viral infection of S-I-R type (i.e. Susceptibles→Infecteds→Removeds (Immunes); $\nu^*\to 0$), one may obtain the infected components as follows:

$$Y_{F^+W^+} = \frac{D_1 X_0^1 + (\mu - D)\left(\frac{\nu + d + D}{\beta}\right) - \frac{\mu}{X_m}\left(\frac{\nu + d + D}{\beta}\right)^2}{(d+D)}. \qquad (12')$$

In addition, one may obtain $\forall \Delta D \in R^+$ such that $\frac{dY_{F^+W^+}}{dD} < 0 \quad \wedge \quad \frac{dY_{F^-W^+}}{dD} < 0$; provided that $\mu > D \wedge \nu < d+D$ (also shown in Appendix A). It shows that $Y_{F^+W^+}$ is monotonically decreasing with respect to an increase in dilution rate D. It also indicates that if $\forall$ D $\wedge$ $\Delta D \in R^+$ such that $Y_{F^+W^+}|_{D+\Delta D} < Y_{F^+W^+}|_D < \lim_{D\to 0} Y_{F^+W^+}|_D = Y_{F^+W^-} \quad \wedge \quad Y_{F^-W^+}|_{D+\Delta D} < Y_{F^-W^+}|_D < \lim_{D\to 0} Y_{F^-W^+}|_D = Y_{F^-W^-}$ and also one may obtain the relation of $Y_{F^+W^-} \geq Y_{F^-W^-} > Y_{F^+W^+} > Y_{F^-W^+}$ (shown in Appendix A). This result supports that water-drinking is significant to health restoration. However, it indicates that in theoretical

basis an ‘optimal’ strategy to provide effective restoration is to drink water only and control food intake in order to accelerate washout of infected components in the control volume. Similar concepts may also be applied to describe production phenomena in bioreactor and evolutionary processes in ecosystems involving host-virus relations ([3], [4], [5]).

The purpose of this study is to provide a novel attempt to put forward, in general terms and explanations from bioreactor engineering perspectives, water-drinking likely as a viable medication for viral infection. However, as far as Su [9] addressed, certain assumptions should be addressed to exclude limitations of this generalized model. Food can be beneficial in providing energy for immune system strengthening, but in a short run surplus food tends to be stored as fat. Thus, “food” intake should compare with regular and normal diet of an average individual (ca. at least in average weight of a population). In addition, during microbial or viral infection increased catabolism of host will be expected and results in increased waste production due to metabolic responses. Increased fluid intake can stimulate renal excretion of the waste. Due to immune responses, infection usually occurs with fever, leading to mild dehydration of host. That is part of the reason why more fluid intake is often suggested and it is not only for effective remedy of viral infection but also for compensation of body-fluid loss. Therefore, the entire infection mechanism and its correlation with water and food intake may be far more complicated than what this model illustrates; at least some factors that may alter the infection phenomena are not included in this model. Nevertheless, this model still allows a better understanding in bioreactor engineering and mathematical biology aspects for why water-rich food should be present and regular water intake is of important to our life.

VI、CONCLUSION

Water drinking is a feasible alternative to cure viral infection, especially when the effective medication is not available. The most favorable strategy is to limit food ingestion

and increase fluid intake, since decreased ingestion reduces augmentation of susceptible components to be infected. Moreover, continuous fluid intake attenuates and washes out infected components in infected individuals. In contrast, the worst is to increase food ingestion and decrease water intake, as augmentation of susceptible components and persistence of infected component enhance "chronic" disease transmission of viral infection.

V、APPENDIX A

Prove that for any non-negative valued functions $Y_{F^+W^+}$, $Y_{F^-W^+}$, $Y_{F^-W^-}$ and $Y_{F^+W^-}$ *(as shown in equations (12)-(15)), there exists the relations of (A-1)* $Y_{F^+W^-} > Y_{F^+W^+} > Y_{F^-W^+}$ *and (A-2)* $Y_{F^+W^-} > Y_{F^-W^-} > Y_{F^-W^+}$ *provided that the necessary condition* ($\nu^2 < d^2 + d \cdot D$) *of (A-5) holds.*

(A-1) is proved as follow: Inequalities shown below hold:

$$\text{(A-3)} \qquad \frac{D_1 X_0^1}{d} > \frac{D_1 X_0^1}{d+D};\ \forall D \in R^+,$$

$$\text{(A-4)} \qquad \left(\frac{\mu}{d}\right)\left(\frac{\nu+d}{\beta}\right) > \left(\frac{\mu-D}{d+D}\right)\left(\frac{\nu+d+D}{\beta}\right);\ \forall D \in R^+,$$

$$\text{(A-5)} \qquad -\frac{\mu}{X_m d}\left(\frac{\nu+d}{\beta}\right)^2 > -\frac{\mu}{X_m}\frac{1}{(d+D)}\left(\frac{\nu+d+D}{\beta}\right)^2;\ \forall D \in R^+;$$

provided that the necessary condition ($\nu^2 < d^2 + d \cdot D$) of (A-5) holds. Note that the relation of (A-5) is satisfied due to severe disease (i.e. $\nu < d$) occurring in the biosystem. Hence, adding (A-3) to (A-5) the inequality of

$$Y_{F^+W^-} = \frac{D_1 X_0^1}{d} + \left(\frac{\mu}{d}\right)\left(\frac{\nu+d}{\beta}\right) - \frac{\mu}{X_m d}\left(\frac{\nu+d}{\beta}\right)^2 >$$

$$Y_{F^+W^+}^H = \frac{D_1 X_0^1}{d+D} + \left(\frac{\mu-D}{d+D}\right)\left(\frac{\nu+d+D}{\beta}\right) - \frac{\mu}{X_m}\frac{1}{(d+D)}\left(\frac{\nu+d+D}{\beta}\right)^2;\forall D \in R^+ \text{ holds;}$$

where superscript H denotes upper-bound (i.e. over-estimated) value. In addition, the contribution in the denominator of $Y_{F^+W^+}$ satisfies an inequality as follows:

$$\text{(A-6)} \qquad \frac{\nu^*}{\nu^*+D}+\left(\frac{\nu+d+D}{d+D}\right)\left(\frac{D}{\nu^*+D}\right) > \lim_{\nu^*\to\infty}\left(\frac{\nu^*}{\nu^*+D}+\left(\frac{\nu+d+D}{d+D}\right)\left(\frac{D}{\nu^*+D}\right)\right)=1.0\,.$$

Thus, the inequality of $Y_{F^+W^-} > Y_{F^+W^+}$ satisfies if the necessary condition of (A-5) holds. Combining the inequality of $Y_{F^+W^+} > Y_{F^-W^+}$, the proof of (A-1) is completed.

Similarly, (A-2) is proved as follows: as the inequalities (A-4) to (A-6) hold, the inequalities $Y_{F^+W^-} > Y_{F^-W^-} > Y_{F^-W^+}$ are obtained as follows:

$$Y_{F^-W^-}=\left(\frac{\mu}{d}\right)\left(\frac{\nu+d}{\beta}\right)-\frac{\mu}{X_m d}\left(\frac{\nu+d}{\beta}\right)^2 >$$

$$Y^H_{F^-W^+}=\left(\frac{\mu-D}{d+D}\right)\left(\frac{\nu+d+D}{\beta}\right)-\frac{\mu}{X_m}\frac{1}{(d+D)}\left(\frac{\nu+d+D}{\beta}\right)^2 >$$

$$Y_{F^-W^+}=Y^H_{F^-W^+}\times\left[\frac{\nu^*}{\nu^*+D}+\left(\frac{\nu+d+D}{d+D}\right)\left(\frac{D}{\nu^*+D}\right)\right]^{-1};\ \forall D\in R^+;$$

provided that the necessary condition ($\nu^2 < d^2 + d\cdot D$) of (A-5) holds. Combining the inequality of $Y_{F^+W^-} > Y_{F^-W^-}$, the proof of (A-2) is completed. Note that for lethal viral infection of the S-I-S type, death rate constant d is sufficiently large with respect to susceptible component inlet from the environment (i.e. $D_1X_0^1 << d$). We may obtain asymptotic behaviors of $0 < Y_{F^+W^+}\,|_{D+\Delta D} < Y_{F^+W^+}\,|_D < \lim_{D\to 0} Y_{F^+W^+}\,|_D = Y_{F^+W^-} = \frac{D_1X_0^1}{d}+Y_{F^-W^-} \cong Y_{F^-W^-} < +\infty$. It suggests that $Y_{F^+W^-}\cong Y_{F^-W^-} > Y_{F^+W^+} > Y_{F^-W^+}$ holds.

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VII、REFERENCES

1. Anderson, R.M. (1991), Discussion: The Kermack-McKendrick epidemic threshold theorem. *Bull. Math. Biol.* **53**, 3-32.
2. Chen, Bor-Yann (1995), A Study on Temperature Induction of Bacteriophage λ in *Escherichia coli*. Ph.D. Dissertation, University of California, Irvine.
3. Chen, B.-Y. and Lim, H.C. (1996), Bioreactor studies on temperature induction of the Q^- mutant of bacteriophage λ in *Escherichia coli*. *J. Biotechnol.* **51**, 1-20.
4. Chen, B.-Y. and Lim, H.C. (1998), Optimal mode of operation for temperature induction of bacteriophage λQ^- mutant in *Escherichia coli*. *Bioprocess Eng.* **19**(1), 7-10.
5. Chen, B.-Y., Chang, J.-S.(1999), Economically feasible induction of bacteriophage λQ^- mutant in *Escherichia coli*. *Bioprocess Eng.* **20**(2): 105-108.
6. Kermack, W.O. and McKendrick, A.G. (1927), Contributions to the mathematical theory of epidemics- I. *Proc. R. Soc. Edinburgh Sect.* **115A**, 700-721. [Reprinted (1991) *Bull. Math. Biol.* **53**, 33-55]
7. Kermack, W.O. and McKendrick, A.G. (1932), Contributions to the mathematical theory of epidemics- I. *Proc. R. Soc. Edinburgh Sect.* **138A**, 55-83. [Reprinted (1991) *Bull. Math. Biol.* **53**, 57-87]
8. Neumann, A.U., Lam, N.P., Dahari, H., Gretch, D.R., Wiley, T.E., Layden, T.J., Perelson A.S. (1998), Hepatitis C Viral Dynamics *in Vivo* and the Antoviral Efficacy of Interferon-α Therapy. *Science*: October 2, **282**:103-107.
9. Su, Wei-Wen (2000), Personal Communication. Internist, Chang-Hwa Christian Hospital, Taiwan.