A Population Growth Model of Dissolution

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Received March 9, 1997; accepted June 12, 1997

Purpose. To develop a new approach for describing drug dissolution which does not require the presuppositions of time continuity and Fick's law of diffusion and which can be applied to both homogeneous and heterogeneous media.

Methods. The mass dissolved is considered to be a function of a discrete time index specifying successive "generations" (n). The recurrence equation: $\Phi_{n+1} = \Phi_n + r(1 - \Phi_n)(1 - \Phi_n X_0/\theta)$ was derived for the fractions of dose dissolved Φ_n and Φ_{n+1}, between generations n and $n + 1$, where r is a dimensionless proportionality constant, X_0 is the dose and θ is the amount of drug corresponding to the drug's solubility in the dissolution medium.

Results. The equation has two steady state solutions, $\Phi_{ss} = 1$ when $(X_0/\theta) \leq 1$ and $\Phi_{ss} = \theta/X_0$ when $(X_0/\theta) > 1$ and the usual behavior encountered in dissolution studies, i.e, a monotonic exponential increase of Φ_n reaching asymptotically the steady state when either $r < \theta/X_0 < 1$ or $r < 1 < \theta/X_0$. Good fits were obtained when the model equation was applied to danazol data after appropriate transformation of the time scale to "generations". The dissolution process is controlled by the two dimensionless parameters θ/X_0 and r, which were found to be analogous to the fundamental parameters *dose* and *dissolution number*, respectively. The model was also used for the prediction of fraction of dose absorbed for highly permeable drugs.

Conclusions. The model does not rely on diffusion principles and therefore it can be applied under both homogeneous and non-homogeneous conditions. This feature will facilitate the correlation of *in vitro* dissolution data obtained under homogeneous conditions and *in vivo* observations adhering to the heterogeneous milieu of the GI tract.

KEY WORDS: dissolution; model; growth; fraction absorbed; *in vitro-in vivo* correlations.

INTRODUCTION

Dissolution testing is generally accepted as the most useful physicochemical test to assess drug release from solid oral dosage forms (1). In addition, it is used to predict *in vivo* performance and as a surrogate for bioavailability and bioequivalence (1,2).

Due to the importance of drug dissolution, numerous studies have been carried out to identify the factors affecting drug dissolution rate. Among the factors associated with the dissolution system, stirring conditions have been found to be of major significance (3). Thus, dissolution experiments are always carried out under well defined hydrodynamic conditions (4) which ensure a homogeneous dispersion of the dissolved drug in the dissolution medium. Accordingly, all expressions used to describe the rate of dissolution presuppose a homogeneous dissolution medium where Fick's law of diffusion can be applied.

Under *in vivo* conditions, however, the hydrodynamic conditions are controlled by gastrointestinal (GI) motility and have not been well characterized. Furthermore, motility patterns in the GI tract and therefore *in vivo* hydrodynamic conditions are dependent on GI contents (fasted or fed state, type of meal, caloric content of meal etc) (5). Consequently, the assumptions of homogeneity and well stirred medium routinely used in *in vivo* drug dissolution are not valid given the anatomical complexity of the GI tract and the variable composition and hydrodynamics of GI fluids. Moreover, Fick's law of diffusion cannot be applied in these understirred media with topological constraints (6). Finally, the concept of time continuity inherently linked with the differential equations describing drug dissolution rate under homogeneous conditions may not be appropriate for processes taking place in heterogeneous and understirred media. It is worth mentioning that space and time have been considered independent and discrete in a recent cellular automata model of dissolution (7).

Our objective in this study was to develop a new approach for describing drug dissolution which can be applied to both homogeneous and heterogeneous media, does not require the presuppositions of Fick's law of diffusion, and does not rely on the concept of time continuity.

THEORY

The most common equation used to describe drug dissolution rate, is based on the very old work of Noyes and Whitney (8) and Nernst and Brunner (9), as modified by Levich (4):

$$\frac{dW}{dt} = \frac{D}{h} A(C_s - C) \tag{1}$$

where W is the amount of drug dissolved at time t, D is the diffusion coefficient, h is the thickness of the effective diffusion boundary layer, A is the total or more precisely the effective surface area of the solid, C_s is the saturation solubility of drug in the dissolution medium and C is the concentration of the dissolved drug at time t. Eq. 1 relies on Fick's first law of diffusion and presupposes that the parameters D, A, C_s, and h remain constant throughout the process while hydrodynamic conditions are well defined and ensure homogeneous agitation and laminar flow (4).

However, the dissolution of drug under *in vivo* conditions is a very complex phenomenon which cannot be described by a simple differential equation. In order to face the problem of complexity and circumvent describing the system completely, discrete time is used in this study. Thus, only instants of the system's behavior are considered and what happens in the meanwhile is ignored. The jump from one instant to the next is done by a logical rule, which is not of course a physical law, but some expression that works and gives realistic results based on logical assumptions. In our approach the variable of interest (mass dissolved) is not considered a continuous function of time, but is a function of a discrete time index specifying successive "generations". Defining X_n and Y_n as the populations of the drug molecules in the solid state and in solution in the n^{th} generation, respectively, the following finite difference

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0724-8741/97/0900-1122$12.50/0

equation describes the change of Y_n between generations n and $n + 1$:

$$Y_{n+1} = Y_n + rX_n = Y_n + r(X_0 - Y_n) \quad (2)$$

where r is a proportionality constant and X_0 is the population of the drug molecules in the solid state corresponding to dose, Figure 1. The growth of Y_n is not unlimited since the solubility of drug in the medium restricts the growth of Y_n. However, the growth rate is a function of the population level and it can be assumed to decrease with increasing population in a linear manner:

$$r \rightarrow r(Y_n) = r\left(1 - \frac{Y_n}{\theta}\right) \quad (3)$$

where θ is the saturation level of the population i.e the number of drug molecules corresponding to saturation solubility. Thus, the recursion relation 2 is replaced with the nonlinear discrete equation:

$$Y_{n+1} = Y_n + r(X_0 - Y_n)\left(1 - \frac{Y_n}{\theta}\right) \quad (4)$$

Dividing both sides of Eq. 4 with θ one gets the dimensionless difference equation:

$$Z_{n+1} = Z_n + r\left(\frac{X_0}{\theta} - Z_n\right)(1 - Z_n) \quad (5)$$

where $Z_n = Y_n/\theta$.

RESULTS AND DISCUSSION

For the purposes of derivation X_n and Y_n, in Eqs. 4 and 5, refer to the populations of the drug molecules in the solid state and in solution, respectively. However, it is rather obvious that, the undissolved and dissolved amounts of drug are proportional to the values of X_n and Y_n, respectively. Similarly, the dose expressed in mass units corresponds to the number of drug molecules in solid state, X_0, whereas the dissolved amount of drug corresponding to saturation solubility is proportional to θ. Hence, Eqs 4 and 5 describe, in essence, in an absolute and a relative manner, respectively, the continuous increase of the dissolved amount of drug in the successive "generations".

Substituting in Eq. 5, Z_{n+1} and Z_n with the steady state value Z_{ss}, two fixed points are found: $Z_{ss} = 1$ and $Z_{ss} = X_0/\theta$. This means that the system either reaches saturation ($Z_{ss} = 1$ since $Y_{ss} = \theta$) when $X_0/\theta \geq 1$ or the bulk of the initial quantity (dose) is dissolved ($Z_{ss} = X_0/\theta$) when $X_0/\theta < 1$.

In practice, however, *in vitro* dissolution profiles are routinely presented as percent or fraction dissolved versus time curves. To this end, Eq. 4 can be normalized in terms of dose by dividing both sides by X_0:

$$\frac{Y_{n+1}}{X_0} = \frac{Y_n}{X_0} + r\left(1 - \frac{Y_n}{X_0}\right)\left(1 - \frac{Y_n}{\theta}\right) \quad (6)$$

which can be written more conveniently using $(Y_n/X_0) = \Phi_n$ and $(Y_{n+1}/X_0) = \Phi_{n+1}$:

$$\Phi_{n+1} = \Phi_n + r(1 - \Phi_n)\left(1 - \frac{\Phi_n X_0}{\theta}\right) \quad (7)$$

where Φ_n and Φ_{n+1} are the dissolved fractions of drug at "generations" n and $n + 1$, respectively. Eq. 7 has two steady-state solutions, $\Phi_{ss} = 1$ when $X_0/\theta \leq 1$ and $\Phi_{ss} = \theta/X_0$ when $X_0/\theta > 1$. Since difference equations can exhibit dynamic behaviour under certain conditions (10,11), the stability of the fixed points of Eq. 7 are explored in the Appendix. As it is shown, both fixed points are stable, when $r < 2/(1 - (X_0/\theta))$ for $\theta/X_0 > 1$ and $r < 2/((X_0/\theta) - 1)$ for $\theta/X_0 < 1$. Because of the nature of Eq. 7, the first step always gives $\Phi_{n=1} = r$; hence, r is always lower than 1 i.e the theoretical top boundary of Φ_n. For the interval $\theta/X_0 < r < 2/((X_0/\theta) - 1)$, the first step is higher than the plateau value followed by a progressive diminution to the plateau, Figure 2. This diminution can either be smooth when θ/X_0 and r are close enough or it can take the form of a fading oscillation when r is close to $2/((X_0/\theta) - 1)$. When r exceeds $2/((X_0/\theta) - 1)$ the fixed point becomes unstable bifurcating to a double period stable fixed point. So we have both the unstable main point and the generated double period stable point. This mechanism is called bifurcation and is very common to dynamical systems (11). For our purposes, however, this particular case has no physical meaning since it generates a stable state over the saturation level θ/X_0. As a matter of fact, Eq. 7 has the usual behavior encountered in dissolution studies i.e a mono-

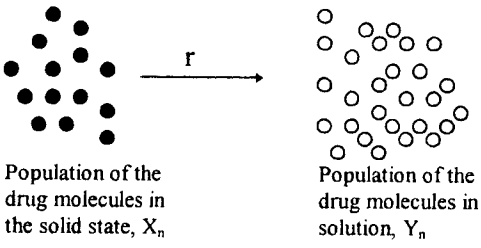

Fig. 1. A schematic representation of the population growth model of dissolution; r denotes a proportionality constant.

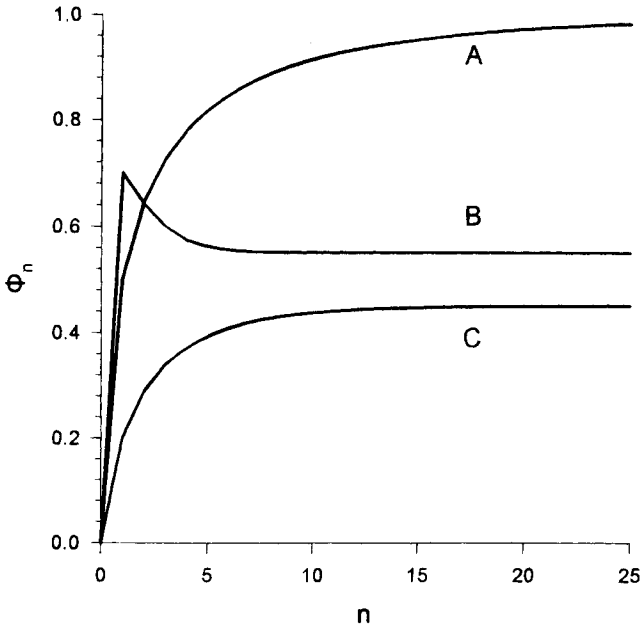

Fig. 2. Plot of the dissolved fraction Φ_n as a function of generations (n) using Eq. 7 with: $r = 0.5$, $\theta/X_0 = 1.2$ (A); $r = 0.7$, $\theta/X_0 = 0.55$ (B); $r = 0.2$, $\theta/X_0 = 0.45$ (C).

tonic exponential increase of Φ_n reaching asymptotically a limit, when either $r < \theta/X_0 < 1$ or $r < 1 < \theta/X_0$, Figure 2.

Equation 7 can be used to estimate the proportionality constant r and the quotient θ/X_0 from experimental data by plotting the fraction dissolved (Φ_n) as a function of the "generations", n. Prior to plotting the sampling times are transformed to "time units" defining arbitrarily a constant sampling interval as a "time unit". By doing so, an initial estimate for r can be derived by reading the value of Φ_n corresponding to the first datum point. Obviously, the value of r is dependent on the definition of the "time unit" in relation to chronological time (see below). An initial estimate for the quotient $\theta/X_0 < 1$ can be obtained from the highest value of the dissolved fraction at the end of the dissolution run. However, an estimate for θ/X_0 cannot be derived from visual inspection when $\theta/X_0 \geq 1$ since $\Phi_{ss} = 1$ in all cases. The initial estimates for r and θ/X_0 can be further used as starting points in a computer fitting program to derive the best parameter estimates. A number of fitting examples are shown in Figure 3 for the danazol data taken from Shah *et al.* (12) by defining 15 minutes as a "time unit". Table I lists the estimates for r and θ/X_0 derived from the computer analysis of danazol data utilizing an algorithm minimizing the sum of squares deviation between experimental and theoretical values.

The approach developed for the analysis of drug dissolution is of particular interest for water-insoluble drugs since the two independent dimensionless variables r and θ/X_0 control drug absorption. The parameter X_0/θ corresponds to the dose/solubility ratio when a volume of 250 mL is considered for the population (amount) θ of the dissolved drug molecules (13,14). This ratio has been termed *dose number* and it has been found, together with the *dissolution number*, to be the key parameters

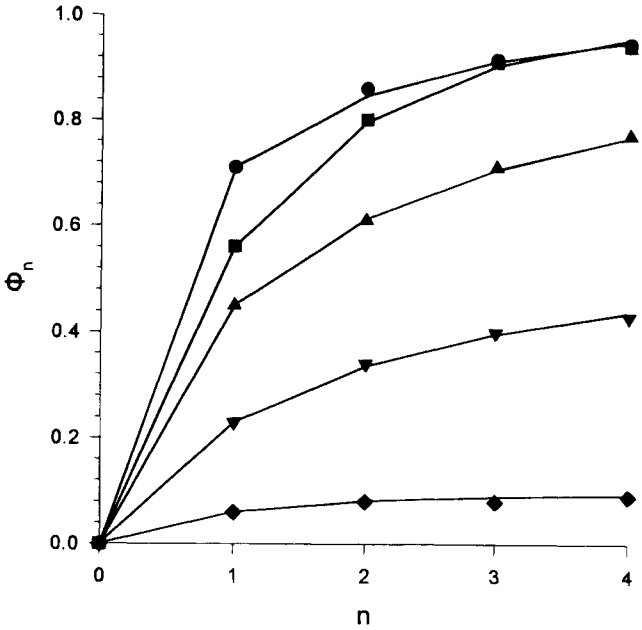

Fig. 3. The fraction of dose dissolved as a function of generations n, where (—) represents the fittings of Eq. 7 to danazol data (12). Symbols represent experimental points transformed to the discrete time scale for graphing and fitting purposes assigning one generation equal to 15 minutes. Key (% sodium lauryl sulfate in water as dissolution medium): ● 1.0; ■ 0.75; ▲ 0.50; ▼ 0.25; ◆ 0.10.

Table I. Estimates for r and θ/X_0 Derived from the Fitting of Eq. 7 to Danazol Data (12)

Dissolution medium	r	θ/X_0	R^{2a}
0.10% SLS/W[b]	0.06	0.10	0.993
0.25% SLS/W[b]	0.23	0.55	0.9993
0.50% SLS/W[b]	0.45	1.33	0.9999
0.75% SLS/W[b]	0.56	12.92	0.9995
1.00% SLS/W[b]	0.71	2.14	0.9996

[a] Correlation coefficient.
[b] Sodium lauryl sulfate in water.

controlling the magnitude of the fraction of dose absorbed for drugs exhibiting dissolution limited absorption (13). Although a fixed value for the dose/solubility ratio X_0/θ has been used so far, separate analysis of *in vitro* and *in vivo* dissolution data (obtained via deconvolution for highly permeable drugs) on the basis of Eq. 7 will allow estimation of two values for X_0/θ under the two different conditions. Such an approach will facilitate the development of *in vitro-in vivo* correlations since i) the *in vivo* solubility value can be drastically different from that usually employed i.e solubility at pH 6.5 (13) and ii) the volume of GI contents may differ from the 250 mL usually assigned to those calculations dealing with the *dose number* (13,14). Furthermore, the proportionality constant, r, can be considered to be analogous to the *dissolution number* since both parameters are dimensionless and both express globally the rate of the dissolution process. The dimensionless character of r allows comparisons to be made for r estimates obtained for a drug studied under different *in vitro* and *in vivo* conditions e.g. various dissolution media, fasted or fed state. This will certainly facilitate the proper analysis of *in vitro-in vivo* correlation studies.

Under *in vivo* conditions, the birth rate of the dissolved molecules, r, includes all drug physicochemical characteristics as well as the physiological factors involved without strict assumptions being made. On the contrary, the presuppositions associated with the use of Eq. 1 delineated above are not fulfilled under both *in vitro* and *in vivo* conditions. Moreover, the present approach does not rely on various assumptions associated either with the use of the *dissolution number* (13) or the similarity and/or the constancy of hydrodynamic conditions in *in vitro-in vivo* correlation studies (15). Therefore, this model can be applied in *in vitro-in vivo* correlation studies involving data for drugs with different physicochemical properties. Such a multi-drug correlation study may reveal the dissolution media most akin to *in vivo* conditions and/or identify potential cut-off values of solubility and permeability appropriate for correlation purposes.

Caution should be exercised though with the definition of the "time unit" when the present model is applied to studies involving more than one set of data. It is advisable to utilize an approach with universal applicability in order to make the estimates for r of various drugs and formulations in miscellaneous dissolution media comparable and meaningful. It is suggested to analyze the data equating 15 minutes with a "time unit" regardless of the sampling design utilized. Based on this definition, Eq. 7 was used to calculate the fraction of dose dissolved in 180 minutes (equivalent to 13 "generations"), which approximately corresponds to the mean small intestine

transit time (16,17), as a function of various values of r and θ/X_0, Figure 4. The plot shows that the fraction of dose dissolved is higher than 0.8 when $\theta/X_0 > 1$ and $r > 0.5$. Figure 4 can be used to predict the fraction of dose absorbed for highly permeable drugs as does the corresponding plot between fraction of dose absorbed as a function of *dose number* and *dissolution number* (13). In reality, the two plots can be considered to be complementary to one another since the calculations of *dose*, *dissolution* and *absorption numbers* are based on the physicochemical properties of drugs (13) while the use of Figure 4 requires dissolution data. For comparative and predictive purposes, and because of the dimensionless character of the parameters (θ/X_0, *dose number*) and (r, *dissolution number*) one can co-plot the data in a common system of coordinates including the contour plots of the surfaces of the three dimensional plots.

Some examples are shown in Figure 5, using the contour plot of Figure 4 and fitting estimates for r and θ/X_0 derived from analysis of dissolution studies of digoxin formulations (18) along with the danazol data (Table I). Based on the visual inspection of digoxin data, complete absorption is anticipated for the "Lanoxin-new formulation" while the fraction of dose absorbed from the other two digoxin formulations is roughly 0.55, Figure 5. Although exact estimates for the fractions of dose absorbed from the digoxin formulations are not available, these predictions seem to be in accord with the actual *in vivo* observations (19). The different dissolution characteristics of danazol in the various dissolution media, (Figure 3 and Table I), lead to predictions for the fraction of dose absorbed ranging from 0.1 to 1, Figure 5. However, a very limited absorption of danazol is expected in humans since absolute bioavailability values 5 to 6% in dogs and rats have been reported in literature (20,21). Therefore, the dissolution data obtained in sodium lauryl sulphate (0.1%) seem to be the most suitable for the prediction of fraction of danazol absorption.

CONCLUSIONS

The model developed (Eq. 7) utilizes the usual information available in dissolution studies i.e the amount dissolved at certain fixed intervals of time. The time points of all observations need to be transformed to equally spaced values of time and furthermore to take the values 0, 1, 2, . . . By doing so, the model was found to be capable of analysing dissolution data. In addition, the model does not rely on diffusion principles and therefore can be applied to both the homogeneous and non-homogeneous conditions. This is of particular value for the correlation of *in vitro* dissolution data obtained under homogeneous conditions and *in vivo* observations adhering to the heterogeneous milieu of the GI tract. The dimensionless parameters r and θ/X_0, which were found to control the dissolution process, are qualitatively similar to the fundamental dimensionless parameters *dose* and *dissolution numbers* (13) which control the fraction of dose absorbed for highly permeable drugs. This adds to the prediction potential of the previous approach for the fraction of dose absorbed (13) since dissolution data of drug's formulations can be combined with the values of *dose* and *dissolution numbers* for predictive purposes.

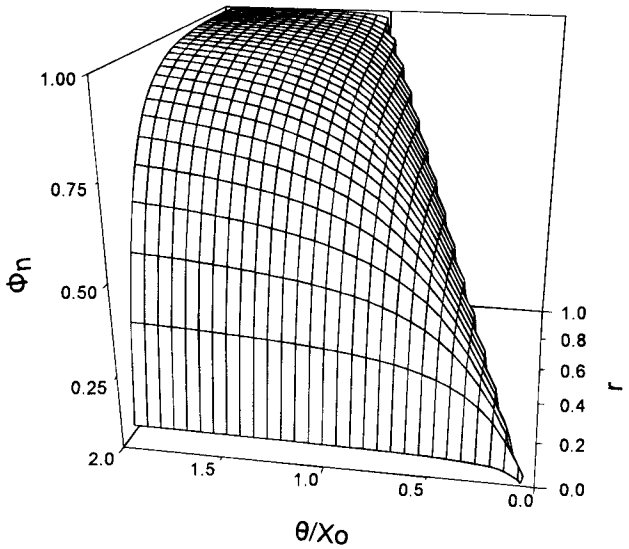

Fig. 4. Estimated fraction of dose dissolved in 180 minutes *versus* r and θ/X_0 using Eq.7 and assigning one generation equal to 15 minutes.

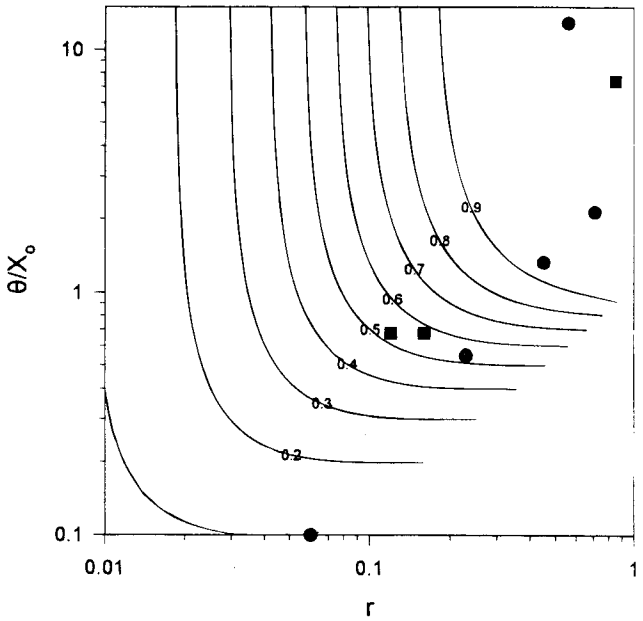

Fig. 5. Contour plot of the surfaces of Figure 4 for the estimation of fraction dose absorbed for highly permeable drugs. Circles represent the danazol data quoted in Table I. Squares represent digoxin data calculated by fitting Eq. 7 to dissolution data points reported in literature (18) assigning one generation equal to 15 minutes. Key (digoxin formulation, r, θ/X_0): Lanoxin "new formulation", 0.85, 7.42; Lanoxin "old formulation", 0.16, 0.68; Second brand, 0.12, 0.68).

APPENDIX

Initially we present a simplified general approach based on the perturbation theory to examine the stability of a system in the vicinity of a given value (11).

Let us consider the general case of a mapping rule:

$$y_{n+1} = f(y_n) \tag{1A}$$

and let y_{ss} be a fixed point:

$$y_{ss} = f(y_{ss}) \tag{2A}$$

We are interested in the stability of Eq. 1A at that fixed point i.e to find out whether for a starting point near y_{ss} the system

converges to y_{ss} (stable) or diverges from it (unstable). Let us consider a small change ξ_n added to y_{ss}. We rewrite Eq. 1A using the transformation: $y_{n+1} = y_{ss} + \xi_{n+1}$, $y_n = y_{ss} + \xi_n$:

$$y_{ss} + \xi_{n+1} = f(y_{ss} + \xi_n) \quad (3A)$$

We use the Taylor expansion of $f(y_{ss} + \xi_n) = g(\xi_n)$ at $\xi_n = 0$ and keep only the first order term to linearize Eq. 3A.

$$g(\xi_n) = g(0) + \xi_n g'(\xi_n)|_{\xi_n=0} + \text{higher order terms} \quad (4A)$$

Rewriting the function $f(y_{ss} + \xi_n)$ in accord with Eq. 4A:

$$f(y_{ss} + \xi_n) = f(y_{ss}) + \xi_n f'(y_{ss} + \xi_n)|_{\xi_n=0} \quad (5A)$$

Using Eq. 5A, Eq. 3A can be expressed:

$$y_{ss} + \xi_{n+1} = f(y_{ss}) + \xi_n f'(y_{ss} + \xi_n)|_{\xi_n=0} \quad (6A)$$

and because of Eq. 2A:

$$\xi_{n+1} = \xi_n f'(y_{ss} + \xi_n)|_{\xi_n=0} \quad (7A)$$

According to Eq. 7A, y_{ss} is a stable solution if the absolute value of the derivative is less than the unity since ξ_n will converge to zero as $n \to \infty$. Otherwise the system is unstable at y_{ss}.

This methodology can be applied to Eq. 7. The derivative of the right hand side of Eq. 7 is:

$$1 - r\left(1 - \frac{2\Phi_n X_0}{\theta} + \frac{X_0}{\theta}\right)$$

The absolute value of the derivative is compared with unity for each fixed point. There are two cases:

a) If $\theta/X_0 > 1$ then $\Phi_{ss} = 1$; hence, the derivative is equal to $1 - r(1 - (X_0/\theta))$. The condition for stability of the fixed point $\Phi_{ss} = 1$ is

$$\left|1 - r\left(1 - \frac{X_0}{\theta}\right)\right| < 1$$

The last inequality yields $0 < r < 2/((X_0/\theta) - 1)$. Therefore, when $0 < r < 2/((X_0/\theta) - 1)$ the system is stable at $\Phi_{ss} = 1$.

b) If $\theta/X_0 < 1$ then $\Phi_{ss} = \theta/X_0$; hence, the derivative is equal to $1 - r((X_0/\theta) - 1)$. The condition for stability of the fixed point $\Phi_{ss} = \theta/X_0$ is

$$\left|1 - r\left(\frac{X_0}{\theta} - 1\right)\right| < 1$$

The last inequality yields $0 < r < 2/(1 - (X_0/\theta))$. Therefore, when $0 < r < 2/(1 - (X_0/\theta))$ the system is stable at $\Phi_{ss} = \theta/X_0$.

In the special case $\theta/X_0 = 1$, Eq.7 collapses to

$$\Phi_{n+1} = \Phi_n + r(1 - \Phi_n)^2 \quad (8A)$$

with a double root at steady state $\Phi_{ss} = 1$. The derivative of the right hand side of Eq. 8A is equal to unity and therefore the steady state is neither stable or unstable (11).

ACKNOWLEDGMENTS

Supported in part by the General Secretariat for Research and Technology (PENED Grant 70/3/2824).

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