THE ROLE OF DISTRIBUTIONS OF CELL CYCLE TIMES AND NOISE IN DETERMINING THE STABILITY OF CELLULAR POPULATIONS VERSION OF 11 JUNE, 1994 FILE: NOISEDEL.TEX[1] 999

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ABSTRACT

Here we consider the role of a distribution of cell cycle times and noise in determining the dynamics of a population of cells that are capable of simultaneous proliferation and maturation. The equations describing the cellular population numbers are stochastic first order partial integro-differential equations (transport equations) in which there is an explicit temporal retardation as well as a nonlocal dependence in the maturation variable due to cell replication.

I. Introduction. THIS SECTION WILL CONTAIN A BRIEF REVIEW OF CELL CYCLE KINETICS, AND THE MODELLING ATTEMPTS THAT HAVE BEEN MADE TO LOOK AT THEIR DYNAMICS.

II. The Model.

The assumption that cellular maturation proceeds simultaneously with cellular replication has been shown to be sufficient to explain existing cell kinetic data for erythroid and neutrophilic precursors in several mammals (Mackey and Dörmer, 1981, 1982). Furthermore, the hypothesis is consistent with recent data related to the labeling index of neutrophil precursor cells in patients receiving human recombinant GM-CSF during the terminal phase of various carcinomas (REFERENCE HERE). Thus, we consider a population of cells capable of both proliferation and maturation. We assume that these cells may be either actively proliferating or in a resting (G_0) phase.

The Proliferating Phase. Actively proliferating cells are those committed to the replication of their DNA and the ultimate passage through mitosis and cytokinesis with the eventual production of two daughter cells. The position of one of these cells within the cell cycle is denoted by a (cell *age*), which is assumed to range from $a = 0$ (the point of commitment) to $a = \tau$ (the point of cytokinesis). The age τ at which cytokinesis takes place is not, however, identical for all cells (REF). Thus we assume that τ is distributed with a density f_τ on an interval $[\tau_L, \tau_U]$ with $0 < \tau_L \leq \tau_U < \infty$. Since f_τ is a density, $\int_{\tau_L}^{\tau_U} f_\tau(\tau)d\tau = 1$. The particular case when $\tau_L \equiv \tau_U$ so f_τ is a dirac delta function, $f_\tau(\tau) = \delta(\tau - \tau_L)$, has been considered by a number of investigators (REF).

The *maturation* variable is labeled by m which ranges from $m = 0$ to $m = m_F < \infty$. (For concreteness one could think of erythroid precursor cells and associate the maturation variable with the intracellular hemoglobin concentration which is maintained at cytokinesis.) However, many of the considerations here generalize to the case that m is *not* restricted to this specific assumption that the maturation variable is a conserved quantity, (cf. Mackey and Rudnicki, 1994.)

We assume that proliferating cells age with unitary velocity so $(da/dt) = 1$, that cells in this phase are lost at a stochastic rate $\delta_P(t)$, and both proliferating and non-proliferating cells mature with a stochastic velocity $V(t, m)$. We

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assume that the velocity of maturation is given by $V(t,0) = 0$, $V(t,m) = r(t) > 0$ for $m \in (0, m_F)$ and $V(t, m_F) = 0$, where $r(t)$ is understood to be a stochastic variable.

Denote the number of actively proliferating cells at time t, maturation level m, and age a by $p(t,m,a)$. Then the conservation equation for $p(t,m,a)$ is

$$\frac{\partial p(t,m,a)}{\partial t} + \frac{\partial p(t,m,a)}{\partial a} + \frac{\partial [V(t,m)p(t,m,a)]}{\partial m} = -\delta_P(t)p(t,m,a), \tag{1}$$

in conjunction with an initial condition $p(0,m,a) = \Gamma(m,a)$ for $(m,a) \in [0,m_F] \times [0,\tau_U]$. The total number of proliferating cells at a given time and maturation level is given by

$$P(t,m) = \int_{\tau_L}^{\tau_U} f_\tau(\tau) \int_0^\tau p(t,m,a)\, da d\tau, \tag{2a}$$

and the total population of proliferating cells is

$$\mathcal{P}(t) = \int_0^{m_F} P(t,m) dm. \tag{2b}$$

The Resting Phase. After cell division, both daughter cells are assumed to enter the resting G_0 phase. The cellular age in this population ranges from $a = 0$, when cells enter, to $a = \infty$. We assume that if the maturation of the mother cell at cytokinesis is m, then the maturation of a daughter cell at birth is $m/2$ so there is a strict division and conservation of the maturation variable m. Let the number of cells in this stage be $n(t,m,a)$, so the total number of resting stage cells of maturation m is

$$N(t,m) = \int_0^\infty n(t,m,a)\, da, \tag{2c}$$

while the total number of resting phase cells at all maturation levels is

$$\mathcal{N}(t) = \int_0^{m_F} N(t,m)\, dm. \tag{2d}$$

We make the assumption that the non-proliferating cells also age with unitary velocity, and that they may exit from the resting stage either by being lost at a stochastic rate $\delta_R(t)$, or by re-entering proliferation. We take the rate of re-entry into proliferation to be given by $\beta(t)\mathcal{R}(\mathcal{N}, m)$ (in agreement with the existing data on the regulation of cell kinetics), where $\beta(t)$ is the stochastic maximal re-entry rate, while $\mathcal{R} : [0,\infty] \times [0, m_F] \to [0,1]$ is the fractional re-entry rate. Then the conservation equation for $n(t,m,a)$ is given by

$$\frac{\partial n(t,m,a)}{\partial t} + \frac{\partial n(t,m,a)}{\partial a} + \frac{\partial [V(t,m)n(t,m,a)]}{\partial m} = -[\delta_N(t) + \beta(t)\mathcal{R}(\mathcal{N}(t), m)]n(t,m,a), \tag{3}$$

again with an initial condition $n(0,m,a) = \mu(m,a)$ for $(m,a) \in [0,m_F] \times [0,\infty)$. We assume that $\lim_{a\to\infty} \mu(m,a) = 0$.

Boundary Conditions. There are two natural boundary conditions for this problem that come from the biology. The first of these relates the equality of the cellular efflux following cytokinesis to the input flux of the resting compartment, and is

$$n(t,m,0) = 2\int_{\tau_L}^{\tau_U} f_\tau(\tau)p(t,2m,\tau)d\tau \quad \text{for } m \le m_F. \tag{4}$$

The second boundary condition, equating the efflux from the resting population to the proliferative population influx, is

$$p(t,m,0) = \int_0^\infty \beta(t)\mathcal{R}(\mathcal{N}(t), m)n(t,m,a)\, da = \beta(t)\mathcal{R}(\mathcal{N}(t), m)N(t,m). \tag{5}$$

The Stochastic Parameters. . We have already introduced the stochastic nature of the cell cycle time τ, and to proceed further we must, at this point, specify the nature of the other four stochastic variables in the model–namely δ_P, δ_N, r, and β. We assume that each of these variables has a mean value given by $\bar{\delta}_P$, $\bar{\delta}_N$, $\bar{r}$, and $\bar{\beta}$ respectively and that

$$\begin{aligned}
\delta_P(t) &= \bar{\delta}_P + \sigma_P \frac{dw_P(t)}{dt},\\
\delta_N(t) &= \bar{\delta}_N + \sigma_N \frac{dw_N(t)}{dt},\\
r(t) &= \bar{r} + \sigma_r \frac{dw_r(t)}{dt},\\
\beta(t) &= \bar{\beta} + \sigma_\beta \frac{dw_\beta(t)}{dt},
\end{aligned}$$

where each $w_i(t)$ is a Wiener process distributed with amplitude σ_i, density f_i, and $i = P, N, r, \text{or}\, \beta$. The densities f_i are assumed to be supported on an interval of R^+ and such that any one of the four variables δ_P, δ_N, r, and β may never assume a negative value due to fluctuations.

Equations for P and N. We now turn to a derivation of the evolution equations for $P(t,m)$ and $N(t,m)$ from the conservation equations (1) and (3), and the associated initial and boundary conditions.

Integrating equation (1) over the age variable and then averaging with respect to τ gives

$$\begin{aligned}
&\frac{\partial P(t,m)}{\partial t} + \frac{\partial [V(t,m)P(t,m)]}{\partial m}\\
&\qquad = -\delta_P(t)P(t,m) - \left\{ \int_{\tau_L}^{\tau_U} f_\tau(\tau) p(t,m,\tau)d\tau - p(t,m,0) \right\},
\end{aligned} \tag{6}$$

while integrating (3) over the age variable yields

$$\begin{aligned}
&\frac{\partial N(t,m)}{\partial t} + \frac{\partial [V(t,m)N(t,m)]}{\partial m}\\
&\qquad = -[\delta_N(t) + \beta(t)\mathcal{R}(\mathcal{N}(t),m)]N(t,m) - \left\{ \lim_{a\to\infty} n(t,m,a) - n(t,m,0) \right\}.
\end{aligned} \tag{7}$$

To proceed further, we must have the functions $p(t,m,a)$ and $n(t,m,a)$, the solutions of (1) and (3) in conjunction with their initial conditions. Since the equations along the characteristics of (1) and (3) are now rather simple stochastic differential equations, this is straightforward. We set

$$\tilde{m}(t,m) \equiv m - \bar{r}t - \sigma_r w_r(t)$$

for notational convenience and find that the general solution of (1) is

$$p(t,m,a) = \begin{cases} \Gamma(\tilde{m}(t,m), a-t)e^{-\bar{\delta}_P t}e^{-\sigma_P w_P(t)} & 0 \le t < a \\ p(t-a, \tilde{m}(t,m), 0)e^{-\bar{\delta}_P a}e^{-\sigma_P w_P(a)} & a \le t, \end{cases} \tag{8}$$

and for (3)

$$n(t,m,a) = \begin{cases} \mu(\tilde{m}(t,m), a-t)e^{-[\bar{\beta}\mathcal{R}(\mathcal{N}(t),m)+\bar{\delta}_N]t}e^{-[\sigma_\beta w_\beta(t)\mathcal{R}(\mathcal{N}(t),m)+\sigma_N w_N(t)]} & 0 \le t < a \\ n(t-a, \tilde{m}(t,m), 0)e^{-[\bar{\beta}\mathcal{R}(\mathcal{N}(a),m)+\bar{\delta}_N]a}e^{-[\sigma_\beta w_\beta(a)\mathcal{R}(\mathcal{N}(a),m)+\sigma_N w_N(a)]} & a < t. \end{cases} \tag{9}$$

If the initial conditions satisfy $\mu(m,0) = 2\Gamma(2m,\tau)$ and $\Gamma(m,0) = \beta\mathcal{R}(\mathcal{N}(0),m)N(0,m)$, then from the boundary conditions (4) and (5) it follows that both p and n are continuous functions. Further, since $\lim_{a\to\infty}\mu(m,a) = 0$ by assumption, we also have $\lim_{a\to\infty} n(t,m,a) = 0$.

Using the boundary condition (5), equation (8) can be used to give

$$p(t,m,\tau) = \begin{cases} \Gamma(\tilde{m}(t,m), \tau-t)e^{-\bar{\delta}_P t}e^{-\sigma_P w_P(t)} & 0 \le t < \tau \\ \beta(t-\tau)\mathcal{R}(\mathcal{N}_\tau(t), \tilde{m}(t,m))N_\tau(t, \tilde{m}(t,m))e^{-\bar{\delta}_P \tau}e^{-\sigma_P w_P(\tau)} & \tau \le t, \end{cases} \tag{10}$$

where $\mathcal{N}_\tau(t) \equiv \mathcal{N}(t-\tau)$ and $N_\tau(t, \tilde{m}(t,m)) \equiv N(t-\tau, \tilde{m}(t,m))$. Using (10) and (5) in equation (6) we find that the dynamics of $P(t,m)$ is governed by the delayed first order partial differential equation

$$\boxed{\begin{aligned} &\frac{\partial P(t,m)}{\partial t} + \frac{\partial [V(t,m)P(t,m)]}{\partial m} \\ &\quad = -\,\delta_P(t)P(t,m) \\ &\quad\quad + \beta(t)N(t,m)\mathcal{R}(\mathcal{N}(t),m) \\ &\quad\quad - \begin{cases} e^{-\bar{\delta}_P t}e^{-\sigma_P w_P(t)} \int_{\tau_L}^{\tau_U} f_\tau(\tau)\Gamma(\tilde{m}(t,m),\tau - t)d\tau & 0 \le t < \tau \\ \int_{\tau_L}^{\tau_U} f_\tau(\tau)\beta(t-\tau)\mathcal{R}(\mathcal{N}_\tau(t),\tilde{m}(t,m))N_\tau(t,\tilde{m}(t,m))e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau & \tau \le t. \end{cases} \end{aligned}} \tag{11}$$

Further, from the other boundary condition (4) in conjunction with (10), followed by (5), equation (8) for N becomes

$$\boxed{\begin{aligned} &\frac{\partial N(t,m)}{\partial t} + \frac{\partial [V(t,m)N(t,m)]}{\partial m} \\ &\quad = -[\delta_N(t) + \beta(t)\mathcal{R}(\mathcal{N}(t),m)]N(t,m) \\ &\quad\quad + 2\begin{cases} e^{-\bar{\delta}_P t}e^{-\sigma_P w_P(t)} \int_{\tau_L}^{\tau_U} f_\tau(\tau)\Gamma(\tilde{m}(t,2m),\tau - t)d\tau & 0 \le t < \tau \\ \int_{\tau_L}^{\tau_U} f_\tau(\tau)\beta(t-\tau)\mathcal{R}(\mathcal{N}_\tau(t),\tilde{m}(t,2m))N_\tau(t,\tilde{m}(t,2m))e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau & \tau \le t. \end{cases} \end{aligned}} \tag{12}$$

The interesting thing about equations (11) and (12) is that although the dynamics of P depends on N, the converse is not true. Thus the dynamics of N evolves independently of what is going on in the proliferative phase, and the dynamics in the proliferating phase is in a sense "driven" by the dynamics of the nonproliferative cells. This illustrates the central importance of the resting phase cells in any regulatory consideration of cell cycle dynamics. This same feature has been found in a number of other models of the cell cycle.

Maturation Independent Proliferation Control. Another interesting feature of this model is the following. In the special case that the proliferative control function $\mathcal{R}$ is independent of the maturation level m, then even simpler equations for the dynamics may be obtained since the maturation completely disappears!

To see how this works is quite simple, since integrating (11) over the maturation variable, and remembering the properties of V, gives

$$\begin{aligned} \frac{\partial \mathcal{P}(t)}{\partial t} = &-\,\delta_P(t)\mathcal{P}(t) + \beta(t)\mathcal{N}(t)\mathcal{R}(\mathcal{N}(t)) \\ &- \begin{cases} e^{-\bar{\delta}_P t}e^{-\sigma_P w_P(t))} \int_0^{m_F}\int_{\tau_L}^{\tau_U} f_\tau(\tau)\Gamma(\tilde{m}(t,m),\tau - t)d\tau dm & 0 \le t < \tau \\ \int_{\tau_L}^{\tau_U} f_\tau(\tau)\beta(t-\tau)\mathcal{R}(\mathcal{N}_\tau(t))\mathcal{N}_\tau(t)e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau & \tau \le t, \end{cases} \end{aligned} \tag{13}$$

while the corresponding operation on (12) yields

$$\begin{aligned} \frac{\partial \mathcal{N}(t)}{\partial t} = &-\,[\delta_N(t) + \beta(t)\mathcal{R}(\mathcal{N})]\mathcal{N} \\ &+ 2\begin{cases} e^{-\bar{\delta}_P t}e^{-\sigma_P w_P(t)} \int_0^{m_F}\int_{\tau_L}^{\tau_U} f_\tau(\tau)\Gamma(\tilde{m}(t,2m),\tau - t)d\tau dm & 0 \le t < \tau \\ \int_{\tau_L}^{\tau_U} f_\tau(\tau)\beta(t-\tau)\mathcal{R}(\mathcal{N}_\tau(t))\mathcal{N}_\tau(t)e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau & \tau \le t. \end{cases} \end{aligned} \tag{14}$$

The types of equations we want to look at the stability of. Thus, the bottom line equation that we have to study the stability of is either (12), written in the form [for $\tau < t$]

$$\boxed{\begin{aligned} &\frac{\partial N(t,m)}{\partial t} + \frac{\partial [V(t,m)N(t,m)]}{\partial m} \\ &\quad = -[\delta_N(t) + \beta(t)\mathcal{R}(\mathcal{N}(t),m)]N(t,m) \\ &\quad\quad + 2e^{-\bar{\delta}_P t}e^{-\sigma_P w_P(t)}\int_{\tau_L}^{\tau_U} f_\tau(\tau)\beta(t-\tau)\mathcal{R}(\mathcal{N}_\tau(t),\tilde{m}(t,2m))N_\tau(t,\tilde{m}(t,2m))e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau. \end{aligned}} \tag{15}$$

or the maturation independent case (14) written as

$$\boxed{\begin{aligned}\frac{\partial \mathcal{N}(t)}{\partial t} =& - [\delta_N(t) + \beta(t)\mathcal{R}(\mathcal{N})]\mathcal{N} \\ &+ 2\int_{\tau_L}^{\tau_U} f_\tau(\tau)\beta(t-\tau)\mathcal{R}(\mathcal{N}_\tau(t))\mathcal{N}_\tau(t)e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau.\end{aligned}} \tag{16}$$

I am afraid that (15) may be too difficult, and maybe we should stick to (16) initially—though I freely admit that I haven't thought about it too much at this point.

Random (no pun intended) Thoughts Related to Equation (16) Without Noise.

Equation (16) is a nonlinear stochastic functional integro-differential equation, and as such sees quite difficult to deal with. As a start, we will look at the linearized version of (16) to try to see how the stability of the situation in the absence of noise *but still with the distribution of time delays* is modified by the presence of this distribution of delays. Thus we first determine what the steady states of (16) in the absence of any fluctuations are by taking $\sigma_i \equiv 0$ for $i = P, N, r$, or β.

One of the steady states in the absence of noise is the trivial one of $\mathcal{N}_* \equiv 0$, while the second is determined from the implicit relation

$$\bar{\beta}\mathcal{R}(\mathcal{N}_*) = \frac{\bar{\delta}_N}{2\mathcal{I}-1}, \tag{17}$$

where

$$\mathcal{I} \equiv \int_{\tau_L}^{\tau_U} f(\tau)e^{-\bar{\delta}_P\tau}d\tau \tag{18}$$

satisfies (for $\bar{\delta}_P \geq 0$)

$$0 \leq e^{-\bar{\delta}_P\tau_U} \leq \mathcal{I} \leq e^{-\bar{\delta}_P\tau_L} \leq 1. \tag{19}$$

(Remember that, since f is a density it is normalized.) Thus, if $\mathcal{R}(\mathcal{N}_*) > 0$, then we must have $\mathcal{I} > \frac{1}{2}$.

If we set $g(\mathcal{N}) = \mathcal{N}\mathcal{R}(\mathcal{N})$, then in the neighborhood of either of the steady states the linearized version of (16) in the absence of fluctuations is given by

$$\frac{dz}{dt} = -[\bar{\delta}_N + \bar{\beta}g'(\mathcal{N}_*)]z + 2\bar{\beta}g'(\mathcal{N}_*)\int_{\tau_L}^{\tau_U} f(\tau)z(t-\tau)e^{-\bar{\delta}_P\tau}d\tau, \tag{20}$$

where $z(t) \equiv \mathcal{N}(t) - \mathcal{N}_*$ is the deviation of $\mathcal{N}$ from the steady state $\mathcal{N}_*$. This means that the eigenvalue equation will be given by

$$\lambda = -[\bar{\delta}_N + \bar{\beta}g'(\mathcal{N}_*)] + 2\bar{\beta}g'(\mathcal{N}_*)\int_{\tau_L}^{\tau_U} f(\tau)e^{-(\lambda+\bar{\delta}_P)\tau}d\tau. \tag{21}$$

1. Note that if f is a delta function $f(\tau) = \delta(\tau - \tau_L)$, then (21) takes the simpler form

$$\frac{\lambda + A}{B} = e^{-(\lambda+\bar{\delta}_P)\tau_L}, \tag{22}$$

where

$$A = \bar{\delta}_N + \bar{\beta}g'(\mathcal{N}_*) \qquad \text{and} \qquad B = 2\bar{\beta}g'(\mathcal{N}_*).$$

Using well established techniques (c.f. Hale), it can be shown that $\mathrm{Re}\lambda < 0$ when

$$\tau_L < \frac{\cos^{-1}\left(\dfrac{Ae^{\bar{\delta}_P\tau_L}}{B}\right)}{Be^{-\bar{\delta}_P\tau_L}\sqrt{1-\left(\dfrac{Ae^{\bar{\delta}_P\tau_L}}{B}\right)^2}}. \tag{23}$$

If the inequality (23) is replaced by an equality, then $\mathrm{Re}\lambda \equiv 0$.

2. However, if f is not a delta function, then (21) can be rewritten in the equivalent form (A and B are as defined above)

$$\begin{aligned}\frac{\lambda + A}{B} &= \int_{\tau_L}^{\tau_U} f(\tau)e^{-(\lambda+\bar{\delta}_P)\tau}\,d\tau \\ &= E\left(e^{-(\lambda+\bar{\delta}_P)\tau}\right) \\ &= \sum_{m=0}^{\infty} \frac{(-1)^m}{m!}(\lambda+\bar{\delta}_P)^m E(\tau^m). \end{aligned} \tag{24}$$

This doesn't look too useful to me.

2. Alternately, if we change variables so $u = \tau + \tau_L$, then the eigenvalue problem can be rewritten in the form

$$\begin{aligned}\lambda &= -[\bar{\delta}_N + \bar{\beta}g'(\mathcal{N}_*)] + 2\bar{\beta}g'(\mathcal{N}_*)\int_0^{\tau_U-\tau_L} f(u-\tau_L)e^{-(\lambda+\bar{\delta}_P)(u-\tau_L)}\,du \\ &= -[\bar{\delta}_N + \bar{\beta}g'(\mathcal{N}_*)] + 2\bar{\beta}g'(\mathcal{N}_*)e^{(\lambda+\bar{\delta}_P)\tau_L}\int_0^{\tau_U-\tau_L} f(u-\tau_L)e^{-(\lambda+\bar{\delta}_P)u}\,du. \end{aligned} \tag{25}$$

If we assume that the data are such that we can take $\tau_U - \tau_L$ to be quite large, then the last equation becomes

$$\begin{aligned}\lambda &\simeq -[\bar{\delta}_N + \bar{\beta}g'(\mathcal{N}_*)] + 2\bar{\beta}g'(\mathcal{N}_*)e^{(\lambda+\bar{\delta}_P)\tau_L}\lim_{\tau_U-\tau_L\to\infty}\int_0^{\tau_U-\tau_L} f(u-\tau_L)e^{-(\lambda+\bar{\delta}_P)u}\,du \\ &= -[\bar{\delta}_N + \bar{\beta}g'(\mathcal{N}_*)] + 2\bar{\beta}g'(\mathcal{N}_*)e^{(\lambda+\bar{\delta}_P)\tau_L}\mathcal{L}_{\lambda+\bar{\delta}_N}[f(u-\tau_L)], \end{aligned} \tag{26}$$

where the notation $\mathcal{L}_s[f(t)]$ denotes the Laplace transformation of f with respect to the complex variable s. This means that we should be able to drag out all of the machinery to do with Laplace transformations to look at the eigenvalue problem.

3. In terms of trying to obtain workable results, it may be necessary to pick a certain density f to work with. HOWEVER, IT WOULD ALSO BE NICE IF WE COULD MAKE GENERIC STATEMENTS ABOUT STABILITY FOR ANY DENSITY IF ANY OF IRINA'S RESULTS THAT SHE WROTE UP IN FEBRUARY ARE WORKABLE. I THINK THAT THE ANDERSON RESULTS ARE USABLE HERE, BUT NOT SURE.

4. One possible density we could take is the density of the gamma distribution, viz.

$$f(\tau) = \kappa(\tau-\tau_L)^n e^{-a(\tau-\tau_L)} \tag{27}$$

for $\tau_L < \tau$, and κ is a suitably defined normalization constant. Actually, κ has the value

$$\kappa = \frac{a^{n+1}}{\Gamma(n+1)} \qquad n > 0, \tag{28a}$$

where Γ is the gamma function, or

$$\kappa = \frac{a^{n+1}}{n!} \tag{28b}$$

when n is an integer. Integer n might be OK, because I think we can always fit data pretty well this way. If we have integer n, then a few computations show that the mean delay is given by

$$\xi_\tau = \tau_L + \frac{n+1}{a} = \tau_L + \bar{\tau}, \tag{29}$$

where $\bar{\tau} = (n+1)/a$, and the variance $D_\tau^2 =< (\tau - \xi_\tau)^2 >$ is given by

$$D_\tau^2 = \frac{\bar{\tau}}{a} = \frac{\bar{\tau}^2}{n+1}. \tag{30}$$

For integer n, the eigenvalue equation becomes

$$\lambda = -[\bar{\delta}_N + \bar{\beta}g'(\mathcal{N}_*)] + 2\bar{\beta}g'(\mathcal{N}_*)\int_0^{\infty} f(\tau)e^{-(\lambda+\bar{\delta}_P)\tau}\,d\tau, \tag{31}$$

where the lower limit can be taken to be zero since $f(\tau)$ is identically zero for $\tau < \tau_L$. Using the fact that the integral on the right hand side of (31) is a Laplace transform with respect to $\lambda + \bar{\delta}_P$ we can write the eigenvalue equation, when f is the density of the gamma distribution, as

$$\boxed{\lambda + [\bar{\delta}_N + \bar{\beta} g'(\mathcal{N}_*)] = 2\bar{\beta} g'(\mathcal{N}_*) \frac{a^{n+1} e^{-(\lambda+\bar{\delta}_P)\tau_L}}{(\lambda + \bar{\delta}_P + a)^{n+1}},} \tag{32}$$

or

$$\boxed{\left[\lambda + \bar{\delta}_N + \bar{\beta} g'\right] \left[\lambda + \bar{\delta}_P + a\right]^{n+1} = 2\bar{\beta} g' a^{n+1} e^{-(\lambda+\bar{\delta}_P)\tau_L}.} \tag{33}$$

It turns out that something close to this eigenvalue equation has been analyzed by S.P. Blythe, R.M. Nisbet, and W.S.C. Gurney in "The dynamics of population models with distributed maturation periods", *Theor. Popul. Biol.* (1984), **25**, 289-311. Unfortunately, in our particular case things do not work out to be quite as tidy as with Blythe et al.

To see this, divide (33) by $(\bar{\delta}_P + a)^{n+1}$ and define

$$A = \bar{\delta}_N + \bar{\beta} g' \qquad \text{and} \qquad \rho = 2\bar{\beta} g' \left[\frac{a}{\bar{\delta}_P + a}\right]^{n+1} e^{-\bar{\delta}_P \tau_L}. \tag{34}$$

Then the eigenvalue equation (33) becomes

$$(\lambda + A)\left(1 + \frac{\lambda}{\bar{\delta}_P + a}\right)^{n+1} = \rho e^{-\lambda\tau_L}. \tag{35}$$

If we assume that λ is pure imaginary, $\lambda = i\omega$, then this takes the form

$$(i\omega + A)\left(1 + i\frac{\omega}{\bar{\delta}_P + a}\right)^{n+1} = \rho e^{-i\omega\tau_L}. \tag{36}$$

Define φ by

$$\frac{\omega}{\bar{\delta}_P + a} = \tan\varphi, \tag{37}$$

so the eigenvalue equation becomes

$$(i\omega + A)\left[\frac{\cos\varphi + i\sin\varphi}{\cos\varphi}\right]^{n+1} = \rho\left[\cos(\omega\tau_L) + i\sin(\omega\tau_L)\right]. \tag{38}$$

Remembering that $[\cos\varphi + i\sin\varphi]^{n+1} = \cos[(n+1)\varphi] + \sin[(n+1)\varphi]$, and separating the real and imaginary parts of the eigenvalue equations gives us

$$A - \omega\tan[(n+1)\varphi] = \rho\frac{\cos^{n+1}\varphi\cos(\omega\tau_L)}{\cos[(n+1)\varphi} \tag{39a}$$

$$A\tan[(n+1)\varphi] + \omega = \rho\frac{\cos^{n+1}\varphi\sin(\omega\tau_L)}{\cos[(n+1)\varphi}. \tag{39b}$$

This latter pair of equations is simply a linear system in (A, ρ), which is easily solved. To do this I first defined

$$\alpha = \frac{\cos^{n+1}\varphi\cos(\omega\tau_L)}{\cos[(n+1)\varphi} \qquad \text{and} \qquad \beta = \frac{\cos^{n+1}\varphi\sin(\omega\tau_L)}{\cos[(n+1)\varphi}, \tag{40}$$

and cranked the whole mess through to eventually obtain

$$A = -\frac{\omega}{\tan[\omega\tau_L + (n+1)\varphi]} \tag{41a}$$

$$\rho = -\frac{\omega}{\cos^{n+1}\varphi\sin[\omega\tau_L + (n+1)\varphi]}. \tag{41b}$$

How can these be simplified? I haven't had much luck, but one should note that since $\tan\varphi = \omega/(\bar{\delta}_P + a)$, it then follows that

$$\cos\varphi = \frac{1}{\sqrt{1 + \left(\frac{\omega}{\bar{\delta}_P + a}\right)^2}} \tag{42}$$

Furthermore, if the solutions for A and ρ are written in the form

$$A\sin[\omega\tau_L + (n+1)\varphi] = -\omega\cos[\omega\tau_L + (n+1)\varphi] \tag{43a}$$

$$\rho\sin[\omega\tau_L + (n+1)\varphi]\cos^{n+1}\varphi = -\omega, \tag{43b}$$

and we then square and add we obtain

$$\cos^{n+1}\varphi = \frac{\omega^2 + A^2}{\rho^2}. \tag{44}$$

However,

$$\cos^{2(n+1)}\varphi = \left[1 + \left(\frac{\omega}{\bar{\delta}_P + a}\right)^2\right]^{-(n+1)}, \tag{45}$$

so the latter expression becomes

$$\boxed{\left(\frac{\omega^2 + A^2}{\rho^2}\right)\left[1 + \left(\frac{\omega}{\bar{\delta}_P + a}\right)^2\right]^{(n+1)} = 1.} \tag{46}$$

Furthermore, if we divide the equations for A and ρ we then obtain

$$\cos[\omega\tau_L + (n+1)\varphi]\cos^{n+1}\varphi = \frac{A}{\rho}, \tag{47}$$

or

$$\boxed{\cos\left[\omega\tau_L + (n+1)\tan^{-1}\left(\frac{\omega}{\bar{\delta}_P + a}\right)\right] = \frac{A}{\rho}\left[1 + \left(\frac{\omega}{\bar{\delta}_P + a}\right)^2\right]^{(n+1)/2}.} \tag{48}$$

These two boxed equations have to be dealt with to determine the stability, if I haven't made a mistake somewhere—which is more than possible.

5. Another specific density for the distribution of delays that we could pick is one that is piecewise constant, i.e.,

$$f(\tau) = \begin{cases} \dfrac{1}{\tau_U - \tau_L} & \tau_L \le \tau \le \tau_U \\ 0 & \text{otherwise.} \end{cases} \tag{49}$$

For this especially simple choice, if we define the width of the density as $\Delta\tau \equiv \tau_U - \tau_L$ then the mean delay is

$$\xi_\tau = \tau_L + \frac{1}{2}\Delta\tau = \frac{\tau_L + \tau_U}{2}, \tag{50}$$

while the variance can be calculated as

$$D_\tau^2 \equiv \frac{(\Delta\tau)^2}{12}. \tag{51}$$

It is also trivial to show that

$$\tau_L = \xi_\tau - \Delta\tau \qquad \text{and} \qquad \tau_U = \xi_\tau + \Delta\tau. \tag{52}$$

In this particular case, the eigenvalue equation

$$\lambda = -[\bar{\delta}_N + \bar{\beta}g'(\mathcal{N}_*)] + 2\bar{\beta}g'(\mathcal{N}_*)\int_{\tau_L}^{\tau_U} f(\tau)e^{-(\lambda+\bar{\delta}_P)\tau}\,d\tau, \tag{53}$$

now takes the form

$$\frac{\lambda + \bar{\delta}_N + \bar{\beta} g'}{2\bar{\beta} g'} = \frac{e^{-(\lambda+\bar{\delta}_P)\xi_\tau}}{\Delta\tau(\lambda + \bar{\delta}_P)} \left\{ e^{-(\lambda+\bar{\delta}_P)\Delta\tau} - e^{+(\lambda+\bar{\delta}_P)\Delta\tau} \right\}. \tag{54}$$

If we set $\rho = \Delta\tau(\lambda + \bar{\delta}_P)$, i.e., just shift and scale the eigenvalues, and define constants

$$\alpha = \frac{1}{2\bar{\beta} g' \Delta\tau}, \quad \theta = \frac{\bar{\delta}_N + \bar{\beta} g' - \bar{\delta}_P}{2\bar{\beta} g'}, \quad \text{and} \quad R = \frac{\Delta\tau}{\xi_\tau}, \tag{55}$$

[Question: Is this R like the "relative variance" that Bob Anderson talks about in his papers? Answer: Very similar, since he takes the relative variance to be σ^2/ξ^2.] then (54) takes the form

$$\boxed{\rho[\alpha\rho + \theta] = e^{-\rho/R}\left\{e^{-\rho} - e^{\rho}\right\}.} \tag{56}$$

Thus the eigenvalue problem depends on the parameter vector (α, θ, R).

6. While talking to Ira on 3 May, 1994, I realized that if one goes back to the original linearized equation (20):

$$\frac{dz}{dt} = -[\bar{\delta}_N + \bar{\beta} g'(\mathcal{N}_*)]z + 2\bar{\beta} g'(\mathcal{N}_*) \int_{\tau_L}^{\tau_U} f(\tau) z(t-\tau) e^{-\bar{\delta}_P \tau} d\tau, \tag{20}$$

and sets $a = -[\bar{\delta}_N + \bar{\beta} g'(\mathcal{N}_*)]$ and $b = 2\bar{\beta} g'(\mathcal{N}_*)$ then we can use the integrating factor $\exp(at)$ to rewrite this as

$$\frac{d(ze^{at})}{dt} = b \int_{\tau_L}^{\tau_U} f(\tau) z(t-\tau) e^{a(t-\tau)} e^{a\tau} e^{-\bar{\delta}_P \tau} d\tau. \tag{20a}$$

If we define a new variable $y(t) = z(t)\exp(at)$, then (20a) takes the equivalent form

$$\frac{dy}{dt} = b \int_{\tau_L}^{\tau_U} f(\tau) y(t-\tau) e^{(a-\bar{\delta}_P)\tau} d\tau, \tag{20b}$$

and then maybe some of the work that Ira found can be used to examine the stability of y. Once we know the stability of y, it is trivial to determine the linear stability of x.

Steady States and Stability in the Presence of Noise.

Lets return to the original equation (16) and not neglect the noise. Thus we have, writing it in the more traditional form of a stochastic equation,

$$\begin{aligned} d\mathcal{N}(t) =& -\bar{\delta}_N \mathcal{N}(t)dt - \bar{\beta}\mathcal{R}(\mathcal{N}(t))\mathcal{N}(t)dt \\ &+ 2\int_{\tau_L}^{\tau_U} f_\tau(\tau)\bar{\beta}\mathcal{R}(\mathcal{N}_\tau(t))\mathcal{N}_\tau(t) e^{-\bar{\delta}_P\tau} e^{-\sigma_P w_P(\tau)} d\tau \ dt \\ &- \sigma_N \mathcal{N}(t) dw_N(t) - \sigma_\beta \mathcal{R}(\mathcal{N}(t))\mathcal{N}(t) dw_\beta(t) \\ &+ 2\int_{\tau_L}^{\tau_U} f_\tau(\tau)\sigma_\beta\mathcal{R}(\mathcal{N}_\tau(t))\mathcal{N}_\tau(t) e^{-\bar{\delta}_P\tau} e^{-\sigma_P w_P(\tau)} d\tau \ dw_\beta(t). \end{aligned} \tag{57}$$

Integrating (57) from 0 to t gives

$$\begin{aligned} \mathcal{N}(t) - \mathcal{N}(0) =& -\int_0^t \bar{\delta}_N \mathcal{N}(t)dt - \int_0^t \bar{\beta}\mathcal{R}(\mathcal{N}(t))\mathcal{N}(t)dt \\ &+ 2\int_0^t \left[\int_{\tau_L}^{\tau_U} f_\tau(\tau)\bar{\beta}\mathcal{R}(\mathcal{N}_\tau(t))\mathcal{N}_\tau(t) e^{-\bar{\delta}_P\tau} e^{-\sigma_P w_P(\tau)} d\tau\right] \ dt \\ &- \int_0^t \sigma_N \mathcal{N}(t) dw_N(t) - \int_0^t \sigma_\beta \mathcal{R}(\mathcal{N}(t))\mathcal{N}(t) dw_\beta(t) \\ &+ 2\int_0^t \left[\int_{\tau_L}^{\tau_U} f_\tau(\tau)\sigma_\beta\mathcal{R}(\mathcal{N}_\tau(t))\mathcal{N}_\tau(t) e^{-\bar{\delta}_P\tau} e^{-\sigma_P w_P(\tau)} d\tau\right] \ dw_\beta(t). \end{aligned} \tag{58}$$

and now taking the mathematical expectation of both sides we have

$$\begin{aligned} E(\mathcal{N}(t)) - E(\mathcal{N}(0)) = &- E\left(\int_0^t [\delta_N(s) + \beta(s)\mathcal{R}(\mathcal{N}(s))]\, \mathcal{N}(s)ds\right) \\ &+ 2E\left(\int_0^t \left[\int_{\tau_L}^{\tau_U} f_\tau(\tau)\beta(s-\tau)\mathcal{R}(\mathcal{N}_\tau(s))\mathcal{N}_\tau(s)e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau\right]\, ds\right) \\ = &- E\left(\int_0^t \bar{\delta}_N\mathcal{N}(s)ds\right) - E\left(\int_0^t \bar{\beta}\mathcal{R}(\mathcal{N}(s))\mathcal{N}(s)ds\right) \\ &+ 2E\left(\int_0^t \left[\int_{\tau_L}^{\tau_U} f_\tau(\tau)\bar{\beta}\mathcal{R}(\mathcal{N}_\tau(s))\mathcal{N}_\tau(s)e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau\right]\, ds\right) \\ &- E\left(\int_0^t \sigma_N\mathcal{N}(s)dw_N(s)\right) - E\left(\int_0^t \sigma_\beta\mathcal{R}(\mathcal{N}(s))\mathcal{N}(s)dw_\beta(s)\right) \\ &+ 2E\left(\int_0^t \left[\int_{\tau_L}^{\tau_U} f_\tau(\tau)\sigma_\beta\mathcal{R}(\mathcal{N}_\tau(s))\mathcal{N}_\tau(s)e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau\right]\, dw_\beta(s)\right). \end{aligned} \tag{59}$$

However, since

$$E\left(\int_\alpha^\beta f(s)dw(s)\right) \equiv 0, \tag{60}$$

(cf. Lasota and Mackey, equation (11.4.2)) the last three integrals in equation (59) vanish and we are left with

$$\begin{aligned} E(\mathcal{N}(t)) - E(\mathcal{N}(0)) = &- E\left(\int_0^t \bar{\delta}_N\mathcal{N}(s)ds\right) - E\left(\int_0^t \bar{\beta}\mathcal{R}(\mathcal{N}(s))\mathcal{N}(s)ds\right) \\ &+ 2E\left(\int_0^t \left[\int_{\tau_L}^{\tau_U} f_\tau(\tau)\bar{\beta}\mathcal{R}(\mathcal{N}_\tau(s))\mathcal{N}_\tau(s)e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau\right]\, ds\right). \end{aligned} \tag{61}$$

Now denote the expectation of a quantity $\mathcal{J}(t)$ by

$$E(\mathcal{J}(t) \equiv < \mathcal{J}(t) >,$$

and differentiate (61) with respect to time t to obtain

$$\begin{aligned} \frac{d < \mathcal{N}(t) >}{dt} = &- \bar{\delta}_N < \mathcal{N}(t) > - \bar{\beta} < \mathcal{R}(\mathcal{N}(t))\mathcal{N}(t) > \\ &+ 2\bar{\beta}\left\langle \int_{\tau_L}^{\tau_U} f_\tau(\tau)\mathcal{R}(\mathcal{N}_\tau(t))\mathcal{N}_\tau(t)e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau \right\rangle . \end{aligned} \tag{62}$$

In analogy with the situation without noise, we define a stochastic steady state $\mathcal{N}_*$ as one in which

$$\frac{d < \mathcal{N}(t) >}{dt} \equiv 0 \tag{63}$$

so

$$\bar{\delta}_N\mathcal{N}_* = -\bar{\beta}\langle\, \mathcal{R}(\mathcal{N}(t))\mathcal{N}(t)\, \rangle + 2\bar{\beta}\langle\, \mathcal{R}(\mathcal{N}(t))\mathcal{N}(t)\, \rangle \int_{\tau_L}^{\tau_U} f_\tau(\tau)e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau\ . \tag{64}$$

We now return to equation (57), and linearize it in the neighborhood of a stochastic steady state defined implicitly by (64). As previously, we define

$$\mathcal{R}(\mathcal{N}(t))\mathcal{N}(t) \equiv g(\mathcal{N}(t))$$

to simplify matters, thus obtaining

$$\begin{aligned} d\mathcal{N}(t) = &- \delta_N(t)\mathcal{N}(t)dt - \beta(t)g(\mathcal{N}(t))dt \\ &+ 2\left[\int_{\tau_L}^{\tau_U} f_\tau(\tau)\beta(t-\tau)g(\mathcal{N}_\tau(t))e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau\right]\, dt \\ \simeq &- [\bar{\delta}_N dt + \sigma_N dw_N(t)]\mathcal{N}(t) - [\bar{\beta}dt + \sigma_\beta dw_\beta(t)][g(\mathcal{N}_*) + g'(\mathcal{N}_*)(\mathcal{N}(t) - \mathcal{N}_*)] \\ &+ 2g(\mathcal{N}_*)\int_{\tau_L}^{\tau_U} f_\tau(\tau)[\bar{\beta}dt + \sigma_\beta dw_\beta(t)]e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau\ dt \\ &+ 2g'(\mathcal{N}_*)\int_{\tau_L}^{\tau_U} f_\tau(\tau)[\bar{\beta}dt + \sigma_\beta dw_\beta(t)][\mathcal{N}_\tau(t) - \mathcal{N}_*]e^{-\bar{\delta}_P\tau}e^{-\sigma_P w_P(\tau)}d\tau\ dt \end{aligned} \tag{65}$$

Integrating equation (65) from 0 to t, taking the mathematical expectation of the result in conjunction with relation (60), and then once again differentiating with respect to time t results in

$$\begin{aligned} d < \mathcal{N}(t) > \simeq & - \bar{\delta}_N < \mathcal{N}(t) > \ dt - \bar{\beta}[g(\mathcal{N}_*) + g'(\mathcal{N}_*)(< \mathcal{N}(t) > - \mathcal{N}_*)] \ dt \\ & + 2\bar{\beta} g(\mathcal{N}_*) \int_{\tau_L}^{\tau_U} f_\tau(\tau) e^{-\bar{\delta}_P \tau} e^{-\sigma_P w_P(\tau)} d\tau \ dt \\ & + 2\bar{\beta} g'(\mathcal{N}_*) \left\langle \int_{\tau_L}^{\tau_U} f_\tau(\tau) [\mathcal{N}_\tau(t) - \mathcal{N}_*] e^{-\bar{\delta}_P \tau} e^{-\sigma_P w_P(\tau)} d\tau \right\rangle \ dt. \end{aligned} \tag{66}$$

Using the notation g defined above, now rewrite (64) in the equivalent form

$$\bar{\delta}_N \mathcal{N}_* = -\bar{\beta} \langle \ g(\mathcal{N}(t)) \ \rangle + 2\bar{\beta} \langle \ g(\mathcal{N}(t)) \ \rangle \int_{\tau_L}^{\tau_U} f_\tau(\tau) e^{-\bar{\delta}_P \tau} e^{-\sigma_P w_P(\tau)} d\tau \ , \tag{67}$$

and define the deviation of $< \mathcal{N}(t) >$ from the stochastic steady state $\mathcal{N}_*$ by

$$z(t) \equiv < \mathcal{N}(t) > - \mathcal{N}_*.$$

Using (67) and the definition of z we can rewrite (66) in the form

$$\begin{aligned} dz(t) = & - [\bar{\delta}_N + \bar{\beta} g'(\mathcal{N}_*)] z(t) \ dt + 2\bar{\beta} g'(\mathcal{N}_*) \ < \int_{\tau_L}^{\tau_U} f_\tau(\tau) z_\tau(t) e^{-\bar{\delta}_P \tau} e^{-\sigma_P w_P(\tau)} d\tau \right\rangle \ dt \\ & + \bar{\beta}[\langle \ g(\mathcal{N}(t)) \ \rangle - g(\mathcal{N}_*)] \left\{ 1 - 2 \int_{\tau_L}^{\tau_U} f_\tau(\tau) e^{-\bar{\delta}_P \tau} e^{-\sigma_P w_P(\tau)} d\tau \right\} \ dt. \end{aligned} \tag{68}$$

Our next task is to calculate

$$\left\langle \int_{\tau_L}^{\tau_U} f_\tau(\tau) z_\tau(t) e^{-\bar{\delta}_P \tau} e^{-\sigma_P w_P(\tau)} d\tau \right\rangle,$$

and I think that the following derivation is correct. PLEASE CHECK THIS CAREFULLY IRA. THANK YOU. I have mostly used Gardiner here ('Handbook of Stochastic Methods'–we have it in my office or yours).

Using a modification of Gardiner equation (4.2.38) we have

$$d(e^{-\sigma_P w_P(\tau)}) = e^{-\sigma_P w_P(\tau)} \left[\frac{\sigma_P^2}{2} d\tau - \sigma_P dw_P(\tau) \right],$$

so

$$e^{-\sigma_P w_P(\tau)} d\tau = \frac{2}{\sigma_P^2} d(e^{-\sigma_P w_P(\tau)}) + \frac{2}{\sigma_P} e^{-\sigma_P w_P(\tau)} dw_P(\tau).$$

Consequently, we can write

$$\begin{aligned} & \left\langle \int_{\tau_L}^{\tau_U} f_\tau(\tau) z_\tau(t) e^{-\bar{\delta}_P \tau} e^{-\sigma_P w_P(\tau)} d\tau \right\rangle \\ & = \frac{2}{\sigma_P} \left\langle \int_{\tau_L}^{\tau_U} f_\tau(\tau) z_\tau(t) e^{-\bar{\delta}_P \tau} e^{-\sigma_P w_P(\tau)} dw_P(\tau) \right\rangle \\ & \quad + \frac{2}{\sigma_P^2} \left\langle \int_{\tau_L}^{\tau_U} f_\tau(\tau) z_\tau(t) e^{-\bar{\delta}_P \tau} d\left(e^{-\sigma_P w_P(\tau)} \right) \right\rangle \\ & = 0 + \frac{2}{\sigma_P^2} \left\langle \int_{\tau_L}^{\tau_U} f_\tau(\tau) z_\tau(t) e^{-\bar{\delta}_P \tau} d \left[1 + \sum_{i=1}^{\infty} \frac{(-\sigma_P)^n}{n!} (w_P(\tau))^n \right] \right\rangle \\ & = \frac{2}{\sigma_P^2} \left\langle \int_{\tau_L}^{\tau_U} f_\tau(\tau) z_\tau(t) e^{-\bar{\delta}_P \tau} \left[-\sigma_P dw_P(\tau) + \frac{\sigma_P^2}{2} d\tau \right] \right\rangle \\ & = \left\langle \int_{\tau_L}^{\tau_U} f_\tau(\tau) z_\tau(t) e^{-\bar{\delta}_P \tau} d\tau \right\rangle, \end{aligned} \tag{69}$$

and the linearized equation (68) thus takes the form

$$dz(t) = -\,[\bar{\delta}_N + \bar{\beta}g')z(t)\ dt + 2\bar{\beta}g' \int_{\tau_L}^{\tau_U} f_\tau(\tau) z_\tau(t) e^{-\bar{\delta}_P\tau} d\tau \ \ dt$$
$$+\, \bar{\beta}[\langle g(\mathcal{N}(t))\rangle - g(\mathcal{N}_*)] \left\{1 - 2\int_{\tau_L}^{\tau_U} f_\tau(\tau) e^{-\bar{\delta}_P\tau} e^{-\sigma_P w_P(\tau)} d\tau\right\} dt. \tag{70}$$

Now note in (70) that when $z(t) \equiv 0$, it reduces to

$$\bar{\beta}[\langle g(\mathcal{N}(t))\rangle - g(\mathcal{N}_*)] \left\{1 - 2\int_{\tau_L}^{\tau_U} f_\tau(\tau) e^{-\bar{\delta}_P\tau} e^{-\sigma_P w_P(\tau)} d\tau\right\} \equiv 0 \tag{71}$$

for all times t, and thus (70) takes the form

$$dz(t) = -[\bar{\delta}_N + \bar{\beta}g')z(t)\ dt + 2\bar{\beta}g' \int_{\tau_L}^{\tau_U} f_\tau(\tau) z_\tau(t) e^{-\bar{\delta}_P\tau} d\tau \ \ dt, \tag{72}$$

which is identical to the linearized equation (20) in the absence of any fluctuations. **Thus we conclude that the linear stabillity of the deterministic steady states given in (17) is identical with the stability of the stochastic steady states defined by (64).**