Integrated Functions for Four Basic Models of Indirect Pharmacodynamic Response

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Received April 24, 1997. Final revised manuscript received August 18, 1997.

Abstract The integrated solutions (ABEC, area between baseline and effect curve) of four basic models of indirect pharmacodynamic responses are developed. These models assume that drug can inhibit or stimulate the production or loss of the response variable. For two models (I and III) with monoexponential drug disposition, explicit formulas for the ABEC were obtained, where ABEC is a function of $\ln \left(1 + \frac{D}{V}\right)IC_{50}$ or $\ln \left(1 + \frac{D}{V}\right)SC_{50}$ where $D = \text{dose}$, $V = \text{volume}$, and $IC_{50}$ or $SC_{50} = 50\%$ effective concentration. Two other models (II and IV) were treated asymptotically with respect to small and large doses. Approximate formulas [e.g., $\text{ABEC} = \text{constant}(1) \cdot \ln \left(1 + \frac{D}{V}\right)IC_{50} + \text{constant}[2]$] were derived and the asymptotic behavior of the ABEC was established. In addition, simulations were performed to assess the effects of drug absorption rates and polyexponential disposition on ABEC values. These models show how pharmacokinetic and pharmacodynamic factors jointly determine the net response to a single dose of drug.

Theoretical Section

An indirect mechanism produces a measured response $R$ to a drug (Figure 1). The rate of change of the response is

$$\frac{dR}{dt} = k_{in}(1 + H_1(t)) - k_{out}(1 + H_2(t))R$$

Parameter $k_{in}$ represents the zero-order constant for production of the response, and $k_{out}$ defines the first-order rate constant causing loss of the response. Functions $H_1$ and $H_2$ specify the type of mechanism, which may be either stimulation or inhibition of the response. Four basic models are considered:

Inhibition of $k_{in}$: $H_1(t) = I(t)$ and $H_2(t) = 0$, Model I (3)

Inhibition of $k_{out}$: $H_1(t) = 0$ and $H_2(t) = I(t)$, Model II (4)

Stimulation of $k_{in}$: $H_1(t) = S(t)$ and $H_2(t) = 0$, Model III (5)

Stimulation of $k_{out}$: $H_1(t) = 0$ and $H_2(t) = S(t)$, Model IV (6)

where $I(t)$ and $S(t)$ are functions responsible for inhibition and simulation according to:

$$I(t) = -\frac{I_{max}C(t)}{IC_{50} + C(t)}$$

and

$$S(t) = \frac{S_{max}C(t)}{SC_{50} + C(t)}$$

where $C(t)$ is the plasma concentration of the drug, $0 < I_{max} < 1$ and $S_{max} > 0$ are parameters related to maximum inhibition and stimulation, and $IC_{50}$ and $SC_{50}$ are the drug concentrations which produce 50% of maximum inhibition and stimulation.

The initial condition is the baseline response:

$$R(0) = R_0 = \frac{k_{in}}{k_{out}}$$


\[
\frac{dR}{dt} = k_{in} \cdot \{1 + H_2(t)\} + k_{out} \cdot \{1 + H_2(t)\} \cdot R
\]

**Model**  | \(H_1(t)\)  | \(H_2(t)\)  | Condition
--- | --- | --- | ---
I  | \((\frac{I_{max} \cdot C_0}{IC_{50} + C_p})\)  | 0  | \(0 < I_{max} \leq 1\)
II  | 0  | \((\frac{I_{max} \cdot C_0}{IC_{50} + C_p})\)  | \(0 < I_{max} \leq 1\)
III  | \((\frac{S_{max} \cdot C_0}{SC_{50} + C_p})\)  | 0  | \(0 < S_{max}\)
IV  | 0  | \((\frac{S_{max} \cdot C_0}{SC_{50} + C_p})\)  | \(0 < S_{max}\)

Key:  | IC_{50} Inhibition  | SC_{50} Stimulation

Figure 1—Four basic indirect response models representing processes that inhibit (Models I and II) or stimulate (Models III and IV) the factors controlling drug response.

A pharmacological effect E is defined as the change of the response R with respect to the baseline response \(R_0\):

\[
E = |R - R_0|
\]  

From eq 2 it follows that:

\[
\frac{dE}{dt} = k_{in} |H_1(t) - H_2(t)| - k_{out} (1 + H_2(t)) E
\]

and eq 3 implies:

\[
E(0) = 0
\]

Because of the nonlinear form of \(H_1(t)\) and \(H_2(t)\), the solution of eq 11 cannot be represented in terms of elementary functions. A solution of eqs 11 and 12 is of the form:

\[
E(t) = k_{in} \int_{0}^{t} |H_1(\tau) - H_2(\tau)|e^{(t-\tau)\mu(\tau)} d\tau
\]

where

\[
\mu(t) = k_{out} \int_{0}^{t} (1 + H_2(\tau)) d\tau
\]

The area between effect curve (ABEC) parameter is defined as:

\[
ABEC = \int_{0}^{\infty} E(t) dt
\]

For Models I and III, an explicit formula for ABEC is derived. For Models II and IV the asymptotic behavior of ABEC as \(D \to 0\) and \(D \to \infty\) is presented.

**Methods**

Integration of eq 11 was carried out using principles of asymptotic expansion theory. Computer simulations were performed by the Runge-Kutta method of numerical integration. Parameter values of dose (as indicated), V of 90 L, \(k_{el}\) of 0.3 h^{-1}, \(IC_{50}\) or \(SC_{50}\) of 100 ng/mL, \(I_{max}\) or \(S_{max}\) of 1.0 (unless indicated otherwise), \(k_{in}\) of 9 unit/h, and \(k_{out}\) of 0.3 h^{-1} were employed in examining the effect of dose on ABEC values.

Further simulations were performed to assess the effects of polyexponential rather than monoexponential disposition on ABEC. In this case, the pharmacokinetic function employed was:

\[
C_p = C_1 e^{-k_1 t} + C_2 e^{-k_2 t}
\]

where \(k_2\) values were assigned to produce an absorption \(t_{1/2}\) ranging from 0 to 7 h.

**Results**

For Models I and III, the function \(H_2 = 0\). Equation 13 implies that:

\[
ABEC = R_0 \int_{0}^{\infty} |H_1(t)| dt
\]

If the concentration function \(C(t)\) is of the form (1), then the integral in eq 18 can be evaluated and has the following exact solutions:

\[
\begin{align*}
ABEC &= \left\{ \begin{array}{ll}
R_0 - \frac{I_{max}}{K_{el}} \ln \left(1 + \frac{D V}{IC_{50}}\right), & \text{Model I} \\
R_0 - \frac{S_{max}}{K_{el}} \ln \left(1 + \frac{D V}{SC_{50}}\right), & \text{Model III}
\end{array} \right.
\end{align*}
\]

For Models II and IV the function \(H_1 = 0\). Hence, from eq 13:

\[
ABEC = k_{in} \int_{0}^{\infty} \int_{0}^{t} |H_2(\tau)| e^{(t-\tau)\mu(\tau)} d\tau dt
\]

Let parameters \(I_{max}, S_{max}, k_{el}, k_{in}\), and \(k_{out}\) be fixed. For Model II, if \(I_{max} = 1\), then:

\[
ABEC = \frac{R_0 \ D V}{k_{el} \ IC_{50}} + O\left(\frac{(DV)^2}{IC_{50}}\right) \text{ as } \frac{DV}{IC_{50}} \to 0
\]

where the symbol \(O(\cdot)\) means that the relative error between the exact and the approximate values is proportional to the expression between the parentheses (for more detailed definition see Olver). If \(0 < I_{max} < 1\), then:

\[
ABEC = \frac{R_0}{k_{el} \ IC_{50}} \frac{I_{max}}{1 - I_{max}} \ln \left(1 + \left(1 - I_{max}\right) \frac{DV}{IC_{50}}\right) + O\left(\frac{(DV)^2}{IC_{50}}\right) \text{ as } \frac{DV}{IC_{50}} \to 0
\]
For Model IV:

\[
\text{ABEC} = \frac{R_0}{k_\text{el}} \frac{S_{\text{max}}}{1 + S_{\text{max}}} \ln \left( 1 + (1 + S_{\text{max}}) \frac{D/V}{SC_{50}} \right) + \frac{O\left( \left( \frac{D/V}{SC_{50}} \right)^2 \right)}{\text{as } \frac{D/V}{SC_{50}} \to 0} \quad (24)
\]

Proof of eqs 22–24 is presented in Appendix A. Similar approximate formulas can be obtained for large doses. For Model II,

\[
\text{ABEC} = \begin{cases} 
R_0 \frac{k_{\text{out}}}{k_{\text{el}}} \frac{1}{1 - I_{\text{max}}} \ln \left( 1 + \frac{D/V}{IC_{50}} \right) + A + \epsilon \left( \frac{D/V}{IC_{50}} \right), & \text{if } I_{\text{max}} = 1 \\
R_0 \frac{k_{\text{out}}}{2k_{\text{el}}} \ln^2 \left( 1 + \frac{D/V}{IC_{50}} \right) + A + \epsilon \left( \frac{D/V}{IC_{50}} \right), & \text{if } I_{\text{max}} = 1
\end{cases} \quad (25)
\]

where, if \( I_{\text{max}} = 1 \), the value of the constant \( A \) is:

\[
A = -\frac{R_0 k_{\text{out}}^2}{k_{\text{el}}^2 (1 - I_{\text{max}})} \int_0^\infty \frac{y^{(k_{\text{out}} / k_{\text{el}}) - 1} (1 + t)^{1/(k_{\text{out}} / k_{\text{el}}) - 1} y^{(k_{\text{out}} / k_{\text{el}}) - 1} \, dt \, dy
\]

If \( I_{\text{max}} = 1 \), then:

\[
A = -\frac{R_0 k_{\text{out}}^2}{2k_{\text{el}}^2} \int_0^\infty y (1 + y)^2 \ln y \, dy - \frac{R_0 k_{\text{out}}}{k_{\text{el}}} \int_0^\infty y^{(k_{\text{out}} / k_{\text{el}}) - 1} \left( \frac{\ln y}{(1 + y)^{k_{\text{out}} / k_{\text{el}}}} - \frac{1}{(1 + y)^{k_{\text{out}} / k_{\text{el}}}} \right) \, dy
\]

The error term is:

\[
\frac{O\left( \left( \frac{D/V}{IC_{50}} \right)^{-1} \right)}{\text{as } \frac{D/V}{IC_{50}} \to \infty}, \quad \text{if } I_{\text{max}} \neq 1 \text{ and } k_{\text{el}} \neq k_{\text{out}} \quad (29)
\]

\[
\frac{O\left( \left( \frac{D/V}{IC_{50}} \right)^{-1} \right) \ln \left( \frac{D/V}{IC_{50}} \right)}{\text{as } \frac{D/V}{IC_{50}} \to \infty}, \quad \text{otherwise} \quad (30)
\]

Appendix B provides the rationale for the magnitude of the error terms. For Model IV:

\[
\text{ABEC} = \frac{R_0}{k_{\text{el}}} \frac{S_{\text{max}}}{1 + S_{\text{max}}} \ln \left( 1 + \frac{D/V}{SC_{50}} \right) + A + \epsilon \left( \frac{D/V}{SC_{50}} \right)
\]

where

\[
A = \frac{R_0 S_{\text{max}} k_{\text{out}}^2}{k_{\text{el}}^2 (1 + S_{\text{max}})} \int_0^\infty \int_0^\infty y^{(k_{\text{out}} / k_{\text{el}}) - 1} (1 + t)^{S_{\text{max}}(k_{\text{out}} / k_{\text{el}}) - 1} y^{-S_{\text{max}}(k_{\text{out}} / k_{\text{el}}) - 1} \, dt \, dy
\]

and

\[
\epsilon \left( \frac{D/V}{IC_{50}} \right) = \begin{cases} 
O\left( \left( \frac{D/V}{IC_{50}} \right)^{-1} \right) \text{ as } \frac{D/V}{IC_{50}} \to \infty, & \text{if } S_{\text{max}} \neq 1 - \frac{k_{\text{el}}}{k_{\text{out}}} \\
O\left( \left( \frac{D/V}{IC_{50}} \right)^{-1} \right) \ln \left( \frac{D/V}{IC_{50}} \right) \text{ as } \frac{D/V}{IC_{50}} \to \infty, & \text{if } S_{\text{max}} = 1 - \frac{k_{\text{el}}}{k_{\text{out}}}
\end{cases} \quad (33)
\]

The proof of eqs 25, 26, and 31 is presented in Appendix B. These equations provide information about behavior of ABEC for large values of the ratios (D/V)/IC_{50} and (D/V)/SC_{50} for Models II and III. The error term \( \epsilon \) is then small, so one can use eqs 25, 26, and 31 as approximate values of ABEC.

For Models I and III, which account for inhibition or stimulation of k_{el} (Figure 1), the ABEC has exact solutions as indicated in eqs 19 and 20. These equations show that a plot of ABEC versus \ln (1 + (D/V)/IC_{50}) or \ln (1 + (D/V)/SC_{50}) should be linear with a slope of R_0 I_{max}/k_{el} or R_{0 S_{\text{max}}}. At high doses, ABEC is simply proportional to \ln D^2.

Equations 22–26 and 31 served practically as approximations of ABEC. If D/V \ll IC_{50} (or D/V \ll SC_{50}), then eqs 22 and 23 (or 24 and 25) apply; if D/V \gg IC_{50} (D/V \gg SC_{50}), then eqs 25 and 26 (or 31) are valid. Figure 2 shows the modest differences between ABEC_{approx} and ABEC for different dose levels for Models II and IV. The maximum errors found were 9% for Model II and <1% for Model IV.

Figure 3 shows the pharmacokinetic profiles obtained by converting to a polyexponential function or having first-order input to a one-compartment model. Families of curves were generated for one dose level and scaled to other doses with an assumption of linear kinetics. The effect of increasing V_t values on the ABEC values for the four
indirect response models is shown in Figure 4. Modest polyexponential curvature of the plasma concentration versus time curve produces slight changes in ABEC, but eventually the prolongation in \( t_{1/2} \) results in a marked increase in ABEC, especially at higher doses. This increase is because drug concentrations are being held above the IC\(_{50}\) or SC\(_{50}\) for longer periods, causing an enhancement in response. In general, however, there remain similar relationships between ABEC and dose for each set of pharmacokinetic parameters (\( V_c, V_T, C L_d, \) and CL) are constant). At larger doses ABEC is proportional to ln dose.

Figure 5 shows the effects of varying the drug absorption rate constant on ABEC values for each model. Extending the absorption phase with smaller \( k_a \) values produces an increase in ABEC values at larger doses. Again, this result is due to longer periods of drug concentrations greater than the IC\(_{50}\) or SC\(_{50}\). A nearly linear relationship is maintained between ABEC and \( \ln D \) for larger doses with each set of pharmacokinetic parameters (\( V, k_{el}, k_a \)).

Discussion

The ABEC summarizes the influence of primary pharmacokinetic (\( k_{el}, V \)) and pharmacodynamic (\( R_0, I_{max} \) or \( S_{max} \), IC\(_{50}\) or SC\(_{50}\)) variables on the net pharmacologic response for drugs with four basic indirect mechanisms of action. This parameter is typically calculated from experimental data and can be related to various doses of administered drug.\(^2,4\)

The ABEC parameter depends on the dose \( D \) through the combination \( (D/V)/IC_{50} \) or \( (D/V)/SC_{50} \), which means that the effective influence on ABEC is the ratio \( (D/V)/IC_{50} \) or \( (D/V)/SC_{50} \), rather than the dose itself. However, at high ratios of \( D/V \) to IC\(_{50}\) (or SC\(_{50}\)), the initial drug concentration (\( C_0 \)) or dose becomes the major determinant of ABEC. Because \( C_0 \) and AUC and D are correlated when clearance is constant, ABEC will also be proportional to log AUC.

For Models II and IV, which account for inhibition or stimulation of \( k_{out} \) (Figure 1), the ABEC has approximate solutions. If \( V \) and IC\(_{50}\) (or SC\(_{50}\)) are fixed and \( D \) is varied, then the error terms in eqs 22 and 23 (or 24) and 25 and 26 (or 31) can be considered as \( D \to 0 \) and \( D \to \infty \), respectively.
One can observe from eqs 19, 20, 26, and 31 that ABEC is proportional to ln D as D → ∞, except for Model II when $I_{\text{max}} = 1$:

\[ \text{ABEC} \sim \frac{I_{\text{max}}}{K_{\text{el}}} \ln D, \quad \text{Model I} \]  
\[ R_0 \frac{1}{1 - I_{\text{max}}} \ln D, \quad \text{Model II, } I_{\text{max}} = 1 \]  
\[ R_0 \frac{S_{\text{max}}}{K_{\text{el}}} \ln D, \quad \text{Model III} \]  
\[ R_0 \frac{S_{\text{max}}}{1 + S_{\text{max}}} \ln D, \quad \text{Model IV} \]

For Model II with $I_{\text{max}} = 1$, eq 26 implies that ABEC is proportional to ln$^2$ D:

\[ \text{ABEC} \sim R_0 \frac{k_{\text{out}}}{2k_{\text{el}}} \ln^2 D \text{ as } D \rightarrow \infty \]  

Numerical simulations were also carried out previously to demonstrate the relationships of ABEC to ln (D) for the four models. The present equations confirm the pattern found earlier and indicate the general net behavior of indirect response models in the absence of specific assumptions about pharmacodynamic model parameters.

The ABEC for Model I was derived previously over the time interval 0 to $t_1$, where $t_1$ is a specified time. Our solution is simpler and reflects the total duration of the response (time 0 to $\infty$). The present solution is obtained from that found previously if $t_1 \rightarrow \infty$. It is interesting to note that ABEC for Models I and III are essentially identical to that for drug providing a direct response according to: $E = E_{\text{max}}/(EC_{50} + C(t))$, where C(t) is defined in eq 1. Wagner\textsuperscript{4} derived a similar formula that contained $E_{\text{max}}$ in place of $R_0 I_{\text{max}}$ or $R_0 S_{\text{max}}$. Thus, these formulae have some generality in pharmacodynamics.

The exact solutions for ABEC for Models I and III and the approximate solutions for Models II and IV could be obtained in the case of simple monoeponential disposition (eq 1) of the drug. The derivations for Model II and IV are complicated because of the presence of the nonlinear H(t) function attached to the $k_{\text{out}}$ parameter in eq 2 producing the complex integrals shown in eqs B4 and B10. This permits only approximate solutions under conditions of small or large doses.

Identification of the exact or approximate values of ABEC is of value in pharmacokinetic/pharmacodynamic (PK/PD) modeling for both conceptual and practical reasons. Here-to-føre, the role of pharmacokinetic (V, $k_{\text{el}}$) and pharmacodynamic ($I_{\text{max}}$, $S_{\text{max}}$, and $IC_{50}$ or $SC_{50}$) values in controlling indirect responses required exploration by simulation\textsuperscript{2,4} or via partially integrated solutions.\textsuperscript{5} This requirement remains true in assessing the time-course of responses, but the determinants of net response can now be readily found in the ABEC equations. In Models I and III, ABEC relates to $R_0 I_{\text{max}}$ or $S_{\text{max}}$, and $k_{\text{el}}$ in a direct and linear fashion (eqs 19 and 20). The roles of D, V, and $IC_{50}$ or $SC_{50}$ are slightly obscured by their nonlinear role in the ABEC equation. Nevertheless, a basic tenet of pharmacology that the ABEC is proportional to log D holds true for indirect response models.

Unfortunately, the ABEC equations cannot be generalized to relate clearly to diverse pharmacokinetic models. Further, such derivations pose difficulties in their even greater complexity. Thus, the extension of these ABEC concepts to polyexponential and biphasic plasma concentration versus time profiles was done by simulations. These simulations (Figures 3–5) show basic similarities to the simpler pharmacokinetic situation and some interesting differences. All of the ABEC profiles maintain shapes with a dose threshold and then a nearly proportional increase with log dose. However, at larger doses, an extended duration of drug exposure by increasing the terminal $t_{1/2}$ (even with CL constant) or slowing drug absorption produces greater net responses. The latter would also apply in the case of drug infusions because the biphasic profile is similar. Thus, duration of drug exposure at values greater than $IC_{50}$ or $SC_{50}$ is a fifth determinant of ABEC.

The present derivations also enhance the value of ABEC in practical analysis of PK/PD data. For Models I and III, it becomes possible to use ABEC values at two or more dose levels to estimate $I_{\text{max}}$ (or $S_{\text{max}}$) and $IC_{50}$ (or $SC_{50}$) by regression analysis providing that $k_{\text{el}}$ and V are supplied as secondary variables. The ABEC has been used in simulations to express total drug effects\textsuperscript{2,10} and as a comparator in examining changes in responses in studies of disease effects\textsuperscript{11} and drug interactions.\textsuperscript{12,13}

Often the ABEC is expressed as a ratio with normalization by baseline responses, (viz., ABEC/$R_0$). The present derivations validate this practice as a means of removal of intersubject or treatment variation in $R_0$. Another adjustment is factoring (ABEC/$R_0$) × $k_{\text{el}}$ to reflect the role of $I_{\text{max}}$, D/V, and $IC_{50}$ in determining net response:

\[ \frac{\text{ABEC} k_{\text{el}}}{R_0} = I_{\text{out}} \ln(1 + D/V) \]  

This factoring may be helpful in drug interaction studies where, if D/V is constant, the pharmacodynamic alterations in ABEC can be isolated. On the other hand, calculating ABEC/AUC at low doses does not clearly isolate and reflect the pharmacodynamic parameters because of the complex fashion in which D/V and $k_{\text{el}}$ control ABEC. At high doses, however, ABEC/ln D is largely reflects the ratio of $R_0 I_{\text{max}}$, $k_{\text{el}}$ or $R_0 S_{\text{max}}/K_d$ (eqs 35–38). These considerations indicate some of the advantages and caution needed in examining ABEC values for experimental data.

Appendix A

**Proof of Equations 22–24 for Models II and IV**—The integral $\int_0^\infty H_2(t)/(1 + H_2(t)) dt$ can be evaluated by substitution of $u = e^{-kt}$. The results are the leading terms in eqs 23–25. Because for some positive M > 0: $1 + H_2 \geq 1/M$, then

\[ \left| \int_0^\infty \frac{H_2(t)}{(1 + H_2(t))^2} \int_0^t H_2(r) e^{-u - t} dr dt \right| \leq M^2 \int_0^\infty H_2(t) \int_0^t H_2(r) dr dt \]  

(A1)

The signs of $H_2$ and $H_2'$ are fixed. This allows evaluation of:

\[ \int_0^\infty H_2(t) \int_0^t H_2(r) dr dt = \int_0^\infty H_2(t)^2 dt \]  

(A2)

For Model II:

\[ \int_0^\infty H_2(t)^2 dt \leq \frac{DN}{IC_{50}} e^{2k_{\text{el}}} dt \]  

(A3)
An analogous inequality holds for Model IV. Hence, for Model II:

\[
\int_0^\infty \frac{H_2(t)}{(1 + H_2(t))^2} \int_0^t |H_2(r)| e^{\epsilon(t-r)} \, dr \, dt = O\left(\frac{D/N}{IC_{50}}\right)^2 \quad \text{as} \quad \frac{D/N}{IC_{50}} \to 0 \quad (A4)
\]

The same statement is true for Model IV, which completes the proof.

**Appendix B**

**Proof of Equations 25, 26, and 31 for Models II and IV**—The proof is carried out for Model II because the case for Model IV is analogous. Integration by parts transforms eq 21 into:

\[
\text{ABEC} = R_0 \int_0^\infty \frac{|H_2(t)|}{1 + H_2(t)} \, dt + R_0 \int_0^\infty \frac{H_2(t)}{(1 + H_2(t))^2} \int_0^t |H_2(r)| e^{\epsilon(t-r)} \, dr \, dt \quad (B1)
\]

The first integral in eq B1 dominates the second as \(\frac{D/N}{IC_{50}} \to \infty\), and it can be evaluated explicitly, yielding the leading terms in eqs 25 and 26. The remainder terms come from the second integral in eq B1. To simplify calculations, it is convenient to introduce nondimensional parameters:

\[
\alpha = \frac{D/N}{IC_{50}}, \quad \beta = \frac{k_{out}}{k_{el}}, \quad \gamma = \frac{k_{out}}{k_{el}} i_{\text{max}} \quad (B2)
\]

Substitute \(\eta = e^{k_{el} t}\) and \(z = e^{k_{el} t}\) into the second integral in eq B1 and let \(y = \alpha^{2} \eta^{1/2}\) and \(x = \alpha^2 \eta\). Then, the integral, if \(\beta - \gamma > 0\), becomes:

\[
-R_0 \max_{k_{out}} \frac{y^{\gamma/\beta - 1}}{k_{el}^2} \int_0^\infty y^{\gamma/\beta - 1}(1 + t)^{-1}(1 + \gamma) y^{-\gamma} y^{\gamma} \, dt \, dy \quad (B3)
\]

If \(\beta - \gamma = 0\), then:

\[
-R_0 \max_{k_{out}} \frac{y^{\gamma/\beta - 1}}{k_{el}^2} \int_0^\infty y^{\gamma/\beta - 1}(1 + t)^{-1}(1 + \gamma) y^{-\gamma} y^{\gamma} \, dt \, dy \quad (B4)
\]

Let \(\beta - \gamma > 0\). Because

\[
\int_0^\gamma y^{\gamma-1}(1 + t)^{-1} \, dt = \begin{cases} O(y^{\gamma-1}) & \text{as } y \to \infty, \text{ if } \beta - \gamma \neq 1 \quad (B5) \\ O(ln y) & \text{as } y \to \infty, \text{ if } \beta - \gamma = 1 \quad (B6) \end{cases}
\]

one can transform the integral in eq B3 to the following form:

\[
\int_0^\gamma y^{\gamma-1}(1 + t)^{-1}(1 + \gamma) y^{-\gamma} y^{\gamma} \, dt \, dy = \int_0^\gamma \int_0^\gamma y^{\gamma-1}(1 + t)^{-1}(1 + y)^{-\gamma} y^{\gamma} \, dt \, dy + \epsilon(\alpha, \beta, \gamma) \quad (B7)
\]

where \(\epsilon\) satisfies the following equations:

\[
\epsilon(\alpha, \beta, \gamma) = \begin{cases} O\left(\frac{1}{\alpha}\right) & \text{as } \alpha \to \infty, \text{ if } \beta - \gamma > 0, \beta - \gamma \neq 1 \quad (B8) \\ O\left(\frac{\ln \alpha}{\alpha}\right) & \text{as } \alpha \to \infty, \text{ otherwise} \quad (B9) \end{cases}
\]

Let \(\beta - \gamma = 0\). The leading integral in eq B1 evaluated in terms of \(\alpha, \beta, \gamma\) is equal to:

\[
\frac{1}{2} \frac{\alpha}{1 + \alpha} \ln^2 \alpha - \frac{1}{2} \frac{\ln \alpha}{\alpha} \int_0^\infty (1 + y)^{-2} \ln y \, dy \quad (B10)
\]

The asymptotic expansion of the expression in eq B10 is:

\[
\frac{1}{2} \ln^2 \alpha - \frac{1}{2} \int_0^\infty (1 + y)^{-2} \ln^2 y \, dy + O\left(\frac{\ln \alpha}{\alpha}\right) \quad (B11)
\]

Note that \(\ln^2 \alpha = \ln^2 (1 + \alpha) + O(\ln \alpha) \alpha \to \infty\). Because

\[
\int_0^\infty t^{-1}(1 + t)^{-1}(1 + \gamma) y^{-\gamma} \, dt \, dy = \int_0^\infty \int_0^\infty t^{-1}(1 + t)^{-1}(1 + y)^{-\gamma} \, dt \, dy + O\left(\frac{\ln \alpha}{\alpha}\right) \quad (B13)
\]

Thus, the proof of eqs 25, 26, and 31 is completed.

**References and Notes**


**Acknowledgments**

This work was supported in part by Grant No. 24211 from the National Institute of General Medical Sciences, National Institute of Health.

J S970168R