Extrapolation of Threshold-Limited Null Measurement Frequencies

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Abstract

The total measurable level of a pathogen is due to many sources, which produce a variety of pulses, overlapping in time, that rise suddenly and then decay.

What is measured is the level of the total contribution of the sources at a given time. But since we are only capable of measuring the total level above some threshold $x_0$, we would like to predict the distribution below this level.

Our principal model assumption is that of the asymptotic exponential decay of all pulses. We show that this implies a power law distribution for the frequencies of low amplitude observations. As a consequence, there is a simple extrapolation procedure for carrying the data to the region below $x_0$.

Keywords: exponential decay; power-law distribution; completion of data

1 Introduction

Acquiring sufficient data of sufficient accuracy is the standard problem in the use of applicable mathematics. Reliance upon null measurements—i.e., an answer of yes or no—is often an intelligent way of attending to the latter desideratum, as in the familiar limiting dilution assays [Lefkowitz and Waldman, 1979]. But the former frequently is controlled by experimental inability, or perhaps excessive expense, in dealing with some region of data. If enough is surmised about the structure of the data, such regions can be reduced by suitable extrapolation, but the implicit assumption [for an elegant presentation, see Berman, 2006] of some sort of analytic structure runs the
risk of being too much of a mathematical band-aid unless it is justified by a versatile underlying model.

In this note, we address a situation of some generality. It is that in which an organism, biological or mechanical, is continually subjected to transient defects, e.g. pathogenic molecular species, internally or externally incited but soon eliminated. These inhibit its ability to effectively deal with its environment. We imagine that the net pathogen level $A$ is measurable at occasional time intervals, but only if it exceeds some threshold $x_0$ (i.e. $A \geq x_0$). A null measurement sequence would then give the relative frequency $G(x_0)$ of measurements falling below the threshold $x_0$. We would want e.g. to obtain from this the density function $\rho(A)$ of amplitudes of the pathogen aggregate level, $A$, with particular attention to the unavailable low amplitudes. The total pathogen load $A$ at a given measurement would be expected to be the resultant of the current amplitudes of each of the sources; these sources may be imagined as time-displaced versions of a discrete set of types, and this is the model that we will study in detail. The model was originally used in a somewhat different context, that of the significance of “blips” in HIV viral level in patients undergoing multi-drug therapy. [see Percus et al, 2003]

What we can adjust in this scenario is the threshold level above $x_0$, and then observe the null frequency $G(x)$ for $x \geq x_0$. The relationship between the intrinsic $\rho(A)$ and $G(x)$ is obvious

$$G(x) = \int_{0}^{x} \rho(A) \, dA, \quad (1)$$

just the cumulative distribution of $A$. Our task is now to obtain the form of $\rho(A)$.
from the model assumptions and use this e.g. to extrapolate the available $G(x)$ for $x \geq x_0$ to values $0 < x < x_0$.

2 The Underlying Model

![Figure 1: Parameters of Typical Pulse Shape](image)

We imagine that the arriving pulses are all translations in time of a basic set of shapes indexed by $\lambda$

$$F_\lambda(t), \ a < t < b$$  \hspace{1cm} (2)

These shapes are non-negative functions such that

$$\int_a^b F_\lambda(t) \, dt \ \text{is finite,}$$

Now, place each of these functions, independently on the interval $(-T, T)$, $(-T < a < b < T)$ $\nu_\lambda$ times. To do this, let $\hat{\tau}$ be a random variable uniformly distributed on the interval $(-T, T)$ and $\hat{\nu}_\lambda$ a Possion random variable with mean $2Tq_\lambda$, i.e.

$$h_\lambda(\nu_\lambda) \equiv P\{\hat{\nu}_\lambda = \nu_\lambda\} = \frac{(2Tq_\lambda)^{\nu_\lambda}}{\nu_\lambda!} e^{-2Tq_\lambda}.$$  \hspace{1cm} (3)
The location in time of $F_\lambda$ is determined, for example, so that its maximum is at the origin (see Fig. 1). The time coordinate of the maximum point of the $i^{th}$ occurrence of $F_\lambda$ is then denoted by $\tilde{\tau}_\lambda$, $i = 1, \ldots, \nu_\lambda$.

The equation of the $i^{th}$ occurrence of the curve $F_\lambda$ is then

$$\hat{A}_{\lambda_i} = F_\lambda (t - \tilde{\tau}_{\lambda_i}).$$

The total amplitude at any specified time, say $t = 0$, is

$$\hat{A} = \sum_\lambda \nu_\lambda \sum_{j=1}^{\nu_\lambda} F_\lambda (-\tilde{\tau}_{\lambda_j}).$$  \hspace{1cm} (4)

We would like to find the probability density of the random variable $\hat{A}$. Let $\rho(A)$ be the probability density function of the random variable $\hat{A}$ i.e.

$$\rho(A) = (\partial/\partial A) Pr (\hat{A} \leq A)$$  \hspace{1cm} (5)

We will assume a steady state distribution of “pathogens” in the course of measurements. This is a limitation of our approach: often the life-time of the organism may be comparable to the “decay” of pathogen. Then the system is translation-invariant in time, which is why we can choose, without loss of generality, the observation time $t = 0$, as in (4).

Let us construct the generating function for $\rho(A)$

$$w(\alpha) \equiv E \left( e^{-\alpha \hat{A}} \right)$$  \hspace{1cm} (6)

Then

$$w(\alpha) = \int_0^\infty e^{-\alpha A} \rho(A) dA.$$  \hspace{1cm} (7)
We need
\[ E \left( e^{-\alpha F_{\lambda}(\tau)} \right) = \frac{1}{2T} \int_{-T}^{T} e^{-\alpha F_{\lambda}(\tau)} d\tau, \]  
so that
\[ w(\alpha) = E \left( \prod_{\lambda} \left( \frac{1}{2T} \int_{-T}^{T} e^{-\alpha F_{\lambda}(\tau)} d\tau \right)^{\nu_{\lambda}} \right). \]  
But from (8), \( E \left( Y^{\nu_{\lambda}} \right) = e^{2T q_{\lambda}(Y-1)} \), and we see at once that
\[ w(\alpha) = \prod_{\lambda} \exp \left[ q_{\lambda} \int_{-T}^{T} \left( e^{-\alpha F_{\lambda}(\tau)} - 1 \right) d\tau \right], \]  
or letting \( T \to \infty \),
\[ \int_{0}^{\infty} e^{-\alpha A} \rho(A) dA = \exp \sum_{\lambda} \left[ q_{\lambda} \int_{-\infty}^{\infty} \left( e^{-\alpha F_{\lambda}(\tau)} - 1 \right) d\tau \right], \]  
which is our basic expression.

Eq. (11) can be expressed more concisely. Define \( \Delta \tau_{\lambda}(F) \) (see Fig. 1) as the total time that the ordinate \( F_{\lambda}(\tau) \geq F \) i.e. \( \Delta \tau_{\lambda}(F) \equiv \int \theta \left( F_{\lambda}(\tau) - F \right) d\tau \) where
\[ \theta(x) = \begin{cases} 0 & \text{if } x < 0 \\ 1 & \text{if } x \geq 0 \end{cases}. \]

Also note that \( \Delta \tau_{\lambda}'(F) \equiv \frac{d}{dF} \Delta \tau_{\lambda}(F) = -\delta \left( F_{\lambda}(\tau) - F \right) \) where \( \delta(x) \) is the Dirac \( \delta \) function. Then for any function \( f \) we have
\[ \int f(F) \Delta \tau_{\lambda}'(F) dF = -\int f(F) \int \delta \left( F_{\lambda}(\tau) - F \right) d\tau dF = -\int f \left( F_{\lambda}(\tau) \right) d\tau. \]

It follows that
\[ \int_{-\infty}^{\infty} \left( e^{-\alpha F_{\lambda}(\tau)} - 1 \right) d\tau = \int_{0}^{\infty} \left( 1 - e^{-\alpha F} \right) \Delta \tau_{\lambda}'(F) dF, \]  
so that if
\[ \tau(F) \equiv \sum_{\lambda} q_{\lambda} \Delta \tau_{\lambda}(F), \]
we have the simple equality
\[
\int_0^\infty e^{-\alpha A} \rho(A) dA = \exp \int_0^\infty \left(1 - e^{-\alpha F}\right) \tau'(F) dF.
\] (14)

3 Rationale for Extrapolation

Eq. (14) can of course be solved for \(\rho(A)\) in nominal closed form by applying the inverse Laplace transform. But a less formal path is to use (14) to set up an equation that \(\rho(A)\) satisfies. For this purpose, take the logarithm of the equality (14) and apply the operation \(-\partial/\partial \alpha\) to both sides, yielding

\[
\int_0^\infty e^{-\alpha A} A \rho(A) dA = \int_0^\infty e^{-\alpha F} (-F \tau'(F)) dF \int_0^\infty e^{-\alpha A} \rho(A) dA
\]
\[
= \int_0^\infty \int_0^\infty Q(F) e^{-\alpha F + A} \rho(A) dA dF
\]
\[
= \int_0^\infty \int_0^\infty Q(F) e^{-\alpha A} \rho(A - F) dF dA
\]
\[
\text{where } Q(F) = -F \tau'(F)
\] (15)

and we have used the fact that \(\rho(A) = 0\) for \(A < 0\). Now the inverse Laplace transform (loosely, take the coefficient of \(e^{-\alpha A}\) on both sides) establishes that

\[
A \rho(A) = \int_0^A Q(F) \rho(A - F) dF.
\] (16)

Our interest is in the behavior of \(\rho(A)\), or \(G(X)\), for small values of \(A\), or \(X\); since \(F \leq A\) in (3.2), this corresponds to small values of \(F\). Now the anticipated nature of the pulse profiles comes into play. A pulse form of type \(\lambda\) will be initiated (see Fig. 1) at some time \(-b_\lambda\). If it is thereafter determined by any standard chemical kinetic sequence leading to its eventual disappearance, it will asymptotically decay
as $C_{\lambda} e^{-a_{\lambda} t}$ for some $a_{\lambda}$. Hence the low amplitude level $F$ duration will be given by

$$\tau_{\lambda}(F) = -b_{\lambda} - \frac{1}{a_{\lambda}} \ell n\left(\frac{F}{C_{\lambda}}\right).$$

Consequently, we have for the total weighted duration

$$\tau(F) = \sum_{\lambda} q_{\lambda} \left( -b_{\lambda} + \frac{1}{a_{\lambda}} \ell n C_{\lambda} \right) - \left( \sum_{\lambda} \frac{q_{\lambda}}{a_{\lambda}} \right) \ell n F,$$

from which $Q(F)$ of (3.1) has the constant value

$$Q(F) = Q \equiv \sum_{\lambda} q_{\lambda}/a_{\lambda}.$$

Eq. (16), with $\rho(F) = 0$ for $F < 0$ then becomes

$$A \rho(A) = Q \int_{0}^{A} \rho(F) dF,$$

or in terms of the null measurement cumulant $G(x)$ of (1.1), $x G'(x) = Q G(x)$, with the solution

$$G(x) = C x^Q.$$

We conclude that

$$\ell n G(x) = \ell n C + Q \ell n x,$$

so that a standard linear extrapolation of $\ell n G$ vs $\ell n x$ is valid at sufficiently small $x$.

Let us take a hypothetical example. It is that of chronic parasitic infection of an organism, with continual birth of clusters of parasites, each of which is quenched by the immune system. There is a large fluctuation in parasite load $A$, sampled sequentially in equivalent test volumes, measurable if above the threshold $x_0$. If the data is acquired via null measurements of the load above virtual thresholds $\{x \geq x_0\}$,
we want to extrapolate the ensuing $G(x)$ to $x < x_0$. Choose as typical population spike, (with origin at $\tau = 0$ rather than at max $F_\lambda$—it makes no difference) the form

$$F_\lambda(-\tau) = C_\lambda e^{-a_\lambda \tau} \left(1 - e^{-d_\lambda \tau}\right),$$  \hspace{1cm} (23)

and for definiteness, $1 \leq c_\lambda \leq 5$, $1 \leq a_\lambda \leq 3$, $1 \leq d_\lambda \leq 5$ over a period $0 \leq \tau \leq 10$, with parameters distributed uniformly in their domains, and all $q_\lambda = 1$. Evaluating $A$ of Eq. (6) for 1000 runs, the resulting $\ln G(x)$ is plotted against $\ln x$ in Fig. 2. The feasible linear extrapolation region is indeed very large.

The conclusion (22) is not without assumptions that have been pointed out, but it appears to be a result of some generality, exemplifying the assertion that extrapolation is a model-dependent procedure, and that recognition of this fact has important operational significance.
Figure 2: Typical Dependence of $\ln G$ on $\ln A$
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