

Long Tailed functions

Long tail functions are desirable for fitting many physiological data sets. A general example is fitting the response of a system to an impulse input. Most passive systems have uni-modal right-skewed response functions. In multiple indicator dilution studies, the input is a brief solute injection pulse into the arterial inflow to the organ and the output is the concentration curve vs. time in the outflowing blood. The complexity of intraorgan handling of the solute gives rise to a large variety of outflow curve forms. Those for untransformed solutes tend to be uni-modal but the tails are prolonged, often being multiexponential or even fractal with power law scaling.

The particular long tail functions modeled here are composed of two parts: an initial uni-modal probability density function (PDF), $F(t)$, and a tail function, $T(t)$, either the sum of decaying exponentials or the sum of decaying power law functions. The tail functions are joined to the downslope side of the PDFs. The functions $F(t)$ and $T(t)$ have matching values and slopes where they are joined so there is no apparent discontinuity.

A graphical user interface (GUI) for LTFs allows changing many parameters (Figure 1). The selections made with the GUI are: (1) the type of PDF (“PDF”), (2) the type of tail function, exponential or power law, (“expORpow”, and (3) the place on the PDF where the tail is attached (“tORfr”), specified as either a specific time, $tJoin$, or as a fraction of the peak height, $frJoin$.

Function Generator fgen_1

Domain	t
Function	Longtail

PDF	LagNormal	w4	.015625
area	1	k1	1
tMean	5	k2	.25
RD	.3	k3	.0625
skewn	1.3	k4	.015625
frPeak	1E-6	nPow	1
upslope	Regular	wpow1	1
tORfr	frJoin	wpow2	.5
tJoin	10	wpow3	.25
frJoin	.3	wpow4	.125
expORpow	Exponential	beta1	2
nExp	1	beta2	1.5
w1	1	beta3	1
w2	.25	beta4	.5
w3	.0625	timeToRepeat	0

Figure 1: Graphical User Interface for the long tailed functions showing default parameters.

PDF parameters:

Click on “PDF” to choose the leading part of a long tailed function. The choices are (1) Lagged Normal Density, (2) Gaussian, (3) Poisson, (4) Random Walk and (5) Gamma Variate. PDFs are described in detail at http://www.physiome.org/jsim/docs/User_Fgen.html where limitations on the

parameters are given. The default choice for PDF is the Lagged Normal density function, a Gaussian distribution lagged by a single exponential. The parameters used for the various PDFs and their default values are summarized in Table 1. The “area” is the integrated area for the leading part of the curve before joining the long tail to it. Eventually “area” will be used to normalize the entire curve including the tail. The mean transit time of the curve, “tMean” is usually slightly later than where the peak occurs, except when the Gaussian PDF is chosen. “RD”, the relative dispersion, is the square root of the variance of the curve, normalized by the mean transit time. The skewness of the curve is given by “skewn”. The fraction of the peak height, “frPeak”, is the cutoff for calculating the PDF. The “upslope” parameter is only used for the Lagged Normal Density curve to replace the beginning of the curve with a linear upslope for this particular PDF.

Table 1: Default parameters for the PDFs.

PDF parameters	Lag Normal Density	Gaussian	Poisson	Random Walk	Gamma Variate
area	1	1	1	1	1
tMean	5	5	5	5	5
RD	0.3	0.3	0.3	0.3	0.3
skewn	1.3	Not used	Not used	1	1.3
frPeak	1E-6	1E-6	1E-6	1E-6	1E-6
upslope	Regular	Not used	Not used	Not used	Not used

Area under the LTF:

The user defines the “area” that is used to normalize the entire curve. The LTF is brought to an end when $T(t)$ is less than frPeak, the fraction of the peak height of $F(t)$, the PDF. The normalization accounts exactly for the incompleteness of $T(t)$ going to zero, and the area is exactly what the user has chosen. The parameter frPeak is usually set to less than .010.

Continuity at the joining point:

A key condition for smoothness at the joining point is that the functions match and their derivatives match.

$$F(t=tJoin)=T(t=tJoin) \quad \text{and} \quad \frac{dF(t=tJoin)}{dt}=dT(t=tJoin)/dt.$$

To enforce the continuity conditions, the weights ($w_i's$) and the decay rates ($k_i's$) for the sum of exponentials are scaled. For the power functions, the weights ($wpow_i's$) are scaled and the arguments to the power function are time-shifted as described below. The user has the option of

specifying at what time ($tJoin$) or at what fraction of the peak height ($frJoin$) the long tailed function will join the chosen PDF. This choice is labeled **tORfr**. The default choice is $frJoin$ which is set at 25% of the peak height.

Multiexponential and power law tail functions:

The user can choose either exponential or power law functions for the extended tail. This choice is labeled **expORpow** and the default setting is exponential. The exponential choice allows sums of up to four exponentials. The power law choice allows sums of up to four power law curves of the form

$$w \cdot (t - tJoin + shift)^{-\beta}.$$

Single or multiexponential functions for T(t):

The user can specify from 1 to 4 exponential functions all of which are positive functions decaying with time. The exponential functions have amplitudes (w_i , $i=1$ to $nExp$) and decay rates (k_i , $i=1$ to $nExp$). The actual function joined to the PDF at either $tJoin$ or $frJoin$ is given by

$$T(t) = a \cdot \sum_{i=1}^n w_i \cdot \exp(-b \cdot k_i \cdot (t - tJoin))$$

where $tJoin$ is either the specified time, or the time where $frJoin$ occurs and $nExp = n$, is the number of exponentials wanted. Designating $F(tJoin) = F$ and $dF(t)/dt = S$ at $t = tJoin$, the constants a and b are chosen so that at the joining point, the value of the PDF and its derivative are matched.

$$T(t=tJoin) = a \cdot \sum_{i=1}^n w_i = F \quad \text{and} \quad dT(t=tJoin)/dt = a \cdot \sum_{i=1}^n -b \cdot w_i \cdot k_i = S$$

from which we derive

$$a = \frac{F}{\sum_{i=1}^n w_i} \quad \text{and} \quad b = \frac{-S \cdot \sum_{i=1}^n w_i}{F \cdot \sum_{i=1}^n w_i \cdot k_i}.$$

If the weights are chosen so that $\sum_1^n w_i = 1$, then

$$a = F \quad \text{and} \quad b = \frac{-S}{F \cdot \sum_{i=1}^n w_i \cdot k_i}.$$

For simplicity, the k_i 's should be ordered in descending magnitude. It is important to remember the the weights and the decay rates are relative to each other, not absolute. All the chosen rate constants are modified by b , and b does not change the weighting scheme, the w_i 's. If adhering to specific rate

constants is important, then b can be set equal to 1 by adjusting the weights so that

$$\sum_{i=1}^n w_i \cdot k_i = -S/F \quad \text{and} \quad \sum_{i=1}^n w_i = 1.$$

For $n=2$, this requires that $k_1 > -S/F > k_2$ in order that both w_1 and w_2 are positive.

Single or multiple power law functions for T(t):

If the **expORpow** choice is set to PowerLaw, a sum of power law functions are used for the long tail extension. The parameter $nPow = n$ is the number of power law functions used and can range from 1 to 4. We will use w_i for convenience here to represent $wpow_i$ set by the user in the GUI (Figure 1).

We use the previous definitions of F , the value of $F(tJoin)$, and S , the derivative $dF(t)/dt$ at $t=tJoin$ and derive

$$T(t) = a \cdot \left(\sum_{i=1}^n w_i \cdot (t - tJoin + ts_i)^{-\beta_i} \right), \quad ts_i = \frac{-\beta_i \cdot F}{S}, \quad \text{and} \quad a = \frac{F}{\left(\sum_{i=1}^n w_i \cdot ts_i^{-\beta_i} \right)}.$$

The coefficient a can be expanded as

$$a = \frac{F}{\frac{w_1}{ts_1^{\beta_1}} + \frac{w_2}{ts_2^{\beta_2}} + \dots + \frac{w_n}{ts_n^{\beta_n}}}$$

which becomes

$$a = \frac{F \cdot ts_1^{\beta_1} \cdot ts_2^{\beta_2} \cdot \dots \cdot ts_n^{\beta_n}}{w_1 \cdot ts_2^{\beta_2} \cdot \dots \cdot ts_n^{\beta_n} + ts_1^{\beta_1} \cdot w_2 \cdot ts_3^{\beta_3} \cdot \dots \cdot ts_n^{\beta_n} + \dots + ts_1^{\beta_1} \cdot ts_2^{\beta_2} \cdot \dots \cdot ts_{n-1}^{\beta_{n-1}} \cdot w_n}$$

When $t=tJoin$, the sum becomes

$$T(tJoin) = \sum_{i=1}^n a \cdot w_i \cdot ts_i^{-\beta_i}.$$

which is then equal to

$$T(tJoin) = \sum_{i=1}^n \frac{F \cdot ts_1^{\beta_1} \cdot ts_2^{\beta_2} \cdot \dots \cdot w_i \cdot ts_i^{\beta_i} \cdot ts_i^{-\beta_i} \cdot \dots \cdot ts_n^{\beta_n}}{w_1 \cdot ts_2^{\beta_2} \cdot \dots \cdot ts_n^{\beta_n} + ts_1^{\beta_1} \cdot w_2 \cdot ts_3^{\beta_3} \cdot \dots \cdot ts_n^{\beta_n} + \dots + ts_1^{\beta_1} \cdot ts_2^{\beta_2} \cdot \dots \cdot ts_{n-1}^{\beta_{n-1}} \cdot w_n}$$

with each $ts_i^{\beta_i}$ being canceled by $ts_i^{-\beta_i}$ in the numerator of the i 'th term. The sum of the terms in the numerator when divided by the denominator equals F .

The derivative at $t=t_{Join}$ is given by

$$\frac{dT(t_{Join})}{dt} = \sum_{i=1}^N \frac{a \cdot w_i \cdot (-\beta_i) \cdot ts_i^{-\beta_i}}{ts_i}$$

Choosing $ts_i = \frac{-\beta_i \cdot F}{S}$, the part of the term

$$\frac{(-\beta_i)}{ts_i} = \frac{-\beta_i}{-\beta_i \cdot F} = \frac{S}{F}$$

and the summation becomes

$$\frac{dT(t_{join})}{dt} = \frac{\sum_{i=1}^n a \cdot w_i \cdot S \cdot ts_i^{-\beta_i}}{F} = \frac{S}{F} \cdot \sum_{i=1}^n a \cdot w_i \cdot ts_i^{-\beta_i} = S$$

Examples of the LTFs using default parameters from Figure 1 are displayed in Figure 2. ExpORpow has been switched from Exponential to PowerLaw to produce the curves.

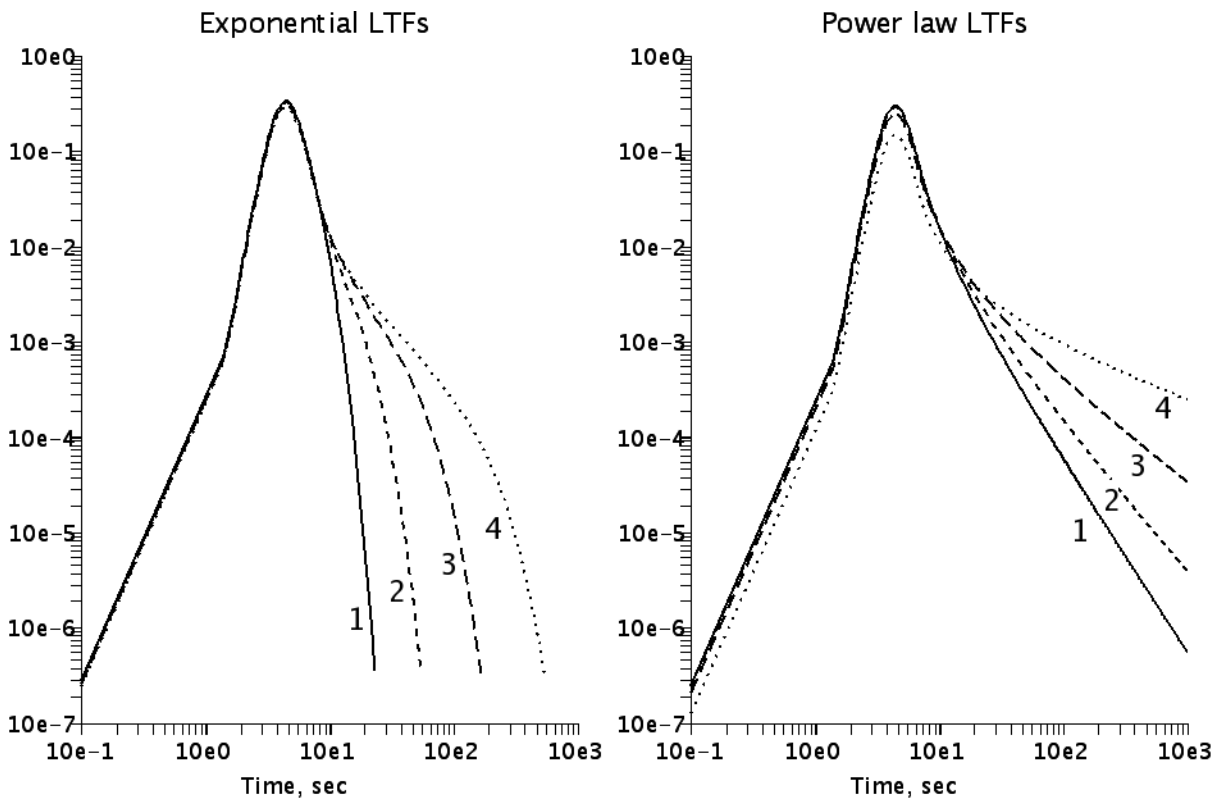


Figure 2: LTFs using default parameters. The number of exponentials, n_{Exp} , and the number of power law functions, n_{Pow} are varied from 1 to 4 and indicated by the numbers adjacent to the curves.

Caveats about optimization:

Do not attempt to optimize with *frJoin*. The routine for finding the fraction of a peak returns the index of the point, not the time when this occurs. Hence small perturbations around the value of *frJoin* will return the same point and there will be no model sensitivity to perturbing *frJoin*. Optimize with *tJoin* instead.

If using exponential functions with *nExp*=1, it is pointless to attempt to optimize *wI* and *kI* because they get normalized out of the equation.

$$T(t, nExp=1) = F \cdot \exp\left(\frac{S \cdot t}{F}\right).$$

If optimizing with two exponential functions, it is best to optimize only one weight and one decay rate. As the exponentials have high covariance with each other and the resultant confidence limits will be unacceptably large.

Similarly, if using one power law function, it is pointless to optimize *wPowI* because it is normalized out of the equation. Normalizing on *betaI* is useful.

$$T(t, nPow=1) = ts_i^{\beta_i} \cdot (t - tJoin + ts_i)^{\beta_i}$$

Optimizing excessive numbers of exponentials or power functions manifests itself in overly large confidence limits with the covariance matrix returning Infs and NaNs. Don't use more than you need.