An Introduction to Second-Order Random Variables in Human Health Risk Assessments

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Abstract

When performing a human health risk assessment using probabilistic methods, risk assessors need a way to distinguish, analyze, and visualize both the variability and the uncertainty in a quantity. As described by many previous authors, first-order random variables represent variability, i.e., the heterogeneity or diversity in a well-characterized population which is usually not reducible through further measurement or study. Growing in popularity, second-order random variables also include uncertainty, i.e., partial ignorance or lack of perfect knowledge about a poorly characterized phenomenon which may be reducible through further study. In this manuscript, we explore second-order random variables as a way to encode and propagate variability and uncertainty separately.

The Deterministic Paradigm

When estimating the incremental lifetime cancer risk, R, from an environmental exposure to a single carcinogenic chemical via a single exposure pathway, risk assessors often assume that risk is directly proportional to positive real variables X_i (for i = 1, ... , I) and inversely proportional to positive real variables Y_j (for j = 1, ... , J) by using equations of this multiplicative form:

$$R = \frac{\prod_{i=1}^{I} X_i}{\prod_{j=1}^{J} Y_j} \qquad \text{Eqn 1}$$

where $\prod$ indicates a product over the indices. This is a special case of a more general model $R = f(X_1, ..., X_i, ..., X_I, Y_1, ..., Y_j, ..., Y_J)$. [EndNote 1].

In this discussion, we assume that X_1 is the exposure point concentration (EPC), X_I is the Cancer Slope Factor (CSF), and all the remaining variables on the right hand side (RHS) of the equation are other exposure variables. Adapting ideas published by the National Academy of Sciences in 1983 (NAS, 1983), the US Environmental Protection Agency (US EPA) has published many such equations for use in human health risk assessments at hazardous waste sites (e.g., US EPA, 1989, HHEM). In all but rare instances, the US EPA has developed its formulae in the deterministic paradigm in which all variables on the RHS of Eqn 1 are positive real numbers, i.e., deterministic or point values that do not express either the variability or the uncertainty in a quantity.

Variability and Uncertainty

Definitions

As a practical matter, most risk assessors agree that all the variables on the RHS of Eqn 1 contain both variability and uncertainty:

- Variability (V) represents heterogeneity or diversity in a well-characterized population which is usually not reducible through further measurement or study. For example, different people in a population have different body weights, no matter how carefully we weigh them.

- Uncertainty (U) represents ignorance about a poorly characterized phenomenon which is sometimes reducible through further measurement or study. For example, the analyst may be able to reduce her or his uncertainty about the volume of wine consumed in a week by different people through a survey of the population. [EndNote 2].

On the one hand, V represents the diversity found in nature, and it is fundamentally a (bounded) property of the population being studied in the risk assessment. On the other hand, U represents the state of partial knowledge or partial ignorance present in the analyst, and it is fundamentally an (bounded) property of the risk assessor. It is usually easier for an analyst to quantify the V found in nature than to quantify the U found in herself or himself. After all, who among us can quantify what we do not now know? And who among us can reliably predict the future?

While it is difficult -- if not impossible -- for an analyst to describe all that she or he does not know, several authors have published taxonomies that disaggregate the U found in a risk assessment into more manageable components. For example, Morgan and Henrion (1990, p. 56 et seq.) identify 7 subcategories of U, while the US EPA (1992, EG, p. 22925 et seq.) identify even more subcategories. While no two taxonomies are identical, they often have some similarities. For example, the taxonomies presented by Morgan and Henrion and by the US EPA include categories for (i) model uncertainty (viz., is Eqn 1 correct?) and (ii) parameter uncertainty (viz., how well does the analyst know the parameters of the probability distributions used to quantify the V in the population?). While model uncertainty is indisputably important (see, e.g., Cooke and Kraan, 1996; French, 1995; Morgan and Henrion, 1990), we restrict our focus to parameter uncertainty in this manuscript so we can show how various methods help the risk assessor analyze and communicate variability and parameter uncertainty in risk assessments to members of the public and to risk managers.

Encoding and Propagating Variability and Uncertainty

Since V and U arise from different sources, have different interpretations, and have different consequences in decisionmaking, many risk assessors have sought a way to encode and propagate them separately. At the end of a long calculation, it is highly desirable for the risk assessor to be able to segregate the total V from the total U so the risk manager could make appropriate decisions. In particular, the risk manager can do little to reduce the total V in an assessment, but she or he can often reduce the total U in an assessment by commissioning further studies. This approach integrates smoothly with benefit/cost analysis (Freeman, 1993) and with the value-of-information (VOI) approach used in decision analysis (Clemen, 1991).

Until recently, most publications about probabilistic risk assessments made no attempt to encode or propagate V and U separately. However, there are new methods that allow the risk assessor to encode V and U separately in the same (second-order) probability distribution. While the new methods allow for random variables to contain some V and some U, they also allow for distributions that contain only V or only U.

Progression from First- to Second-Order Random Variables

We first discuss the use of first-order random variables to model V in a population. First-order random variables are described using probability density functions (PDFs) or cumulative distribution functions (CDFs) with fixed or constant parameters (Freund, 1971). Most modelers use ordinary (first-order) random variables to represent and analyze V (Morgan and Henrion, 1990; Cooke, 1991), although some authors use fuzzy or hybrid numbers as a way to represent and analyze variability (Kaufmann and Gupta, 1991; Ferson, Millstein, and Mauriello, 1994; Ferson and Ginzburg, 1995).

Next we discuss the use of second-order random variables to model the analyst's U about the V in a population (Frey, 1992; NCRP, 1996; IAEA, 1989). Second-order random variables are sometimes described as "distributions of distributions" because the random variables describing V have uncertain parameters described, in turn, by PDFs or CDFs. This paper extends ideas in the literature on second-order random numbers for modeling parameter uncertainty (e.g., Frey, 1992) and on finite mixture distributions (Titterington, Smith, and Makov, 1985).

The First-Order Probabilistic Paradigm

Using First-Order Random Variables to Model Variability

In the first-order probabilistic paradigm, we ignore model uncertainty by assuming that the form of Eqn 1 remains appropriate. However, in this first-order probabilistic framework, we assert that each of the variables on the RHS of Eqn 1 is a positive first-order random variable represented by an ordinary probability density function (PDF) or a cumulative distribution function (CDF) (see, e.g., Freund, 1971). To emphasize this change in perspective, we rewrite Eqn 1 as Eqn 2 and with underscored symbols to denote that each variable is now a first-order random variable that expresses the V in a quantity:

$$\underline{R} = \frac{\prod_{i=1}^{I} \underline{X}_i}{\prod_{j=1}^{J} \underline{Y}_j} \qquad \text{Eqn 2}$$

This is a special case of a more general model $\underline{R} = f(\underline{X}_1, ..., \underline{X}_i, ..., \underline{X}_I, \underline{Y}_1, ..., \underline{Y}_j, ..., \underline{Y}_J)$.

We continue to denote deterministic variables (point values) without the underscore. With knowledge of the distributions of all the $\underline{X}_i$ and $\underline{Y}_j$, an analyst can calculate a closed form expression for the distribution $\underline{R}$ in a few special cases with independent variables (Springer, 1979). In most practical cases, including those cases with correlated or jointly distributed random variables on the RHS, the analyst can simulate a numerical approximation to the distribution $\underline{R}$ (Rubenstein, 1981; Morgan, 1984).

Some First-Order Random Variables

Figures 1, 2, and 3 illustrate three examples of first-order random variables often used in risk assessments. See Johnson, Kotz, and Balakrishnan (1994; 1995) for more families of parametric probability distributions.

First, the two panels in Figure 1 show the PDF and CDF for a Uniform (or Rectangular) distribution (Evans et al, 1993):

$$\underline{X} \quad \sim \quad \text{Uniform(min, max)} \qquad \text{Eqn 3}$$

with min = 2 and max = 6. This distribution has an expected value $E[\underline{X}] = \frac{\text{min + max}}{2} = 4$.

Second, the three panels in Figure 2 show the PDF, the CDF, and the Normal Probability Plot (NPP) for a Normal (or Gaussian) probability distribution (Evans, Hastings, and Peacock, 1993):

$$\underline{X} \quad \sim \quad \text{Normal}(\mu, \sigma) \quad > \quad 0 \qquad \text{Eqn 4}$$

with μ (= the arithmetic mean of the random variable) = 5 and σ (= the arithmetic standard deviation of the random variable) = 1. Note that $\underline{X}$ is truncated to keep it positive. If not truncated, this random variable has $E[\underline{X}] = \mu = 5$.

Third, the three panels in Figure 3 show the PDF, the CDF, and the LogNormal Probability Plot (LNPP) for a LogNormal probability distribution (Evans, Hastings, and Peacock, 1993; Crow and Shimizu, 1988; Aitchison and Brown, 1957):

$$\underline{X} \quad \sim \quad \exp[\, \text{Normal}(\mu, \sigma) \,] \qquad \text{Eqn 5}$$

which is equivalent to

$$\ln[\,\underline{X}\,] \sim \quad \text{Normal}(\,\mu, \sigma\,) \qquad \text{Eqn 5'}$$

with μ (= the arithmetic mean of the natural logarithm of the random variable) = 0.5 and σ (= the arithmetic standard deviation of the natural logarithm of the random variable) = 0.6. this random variable has $E[\underline{X}] = \exp[\,\mu + 0.5 \bullet \sigma^2\,] = 1.97$.

Degenerate Distributions

Under suitable conditions, each first-order random variable can degenerate to a constant (point value). For instance, $\underline{X}$ in Eqn 4 tends towards its average value, μ, in the limit as σ -> 0, and $\underline{X}$ in Eqn 5 tends to its median, exp(μ), in the limit as σ -> 0. These two examples reveal a larger point: the deterministic paradigm is a degenerate version of the first-order probabilistic paradigm.

The Second-Order Probabilistic Paradigm

Using Second-Order Random Variables to Model Variability and Parameter Uncertainty

In the second-order probabilistic paradigm, we again ignore model uncertainty by assuming that the form of Eqn 1 remains appropriate. However, in this second-order probabilistic framework, we assert that each of the variables on the RHS of Eqn 1 is a positive second-order random variable. To emphasize this change in perspective, we re-write Eqn 1 as Eqn 6 with doubly underscored symbols to denote that each variable is now a second-order random variable that encodes both the V in a population and the U in the analyst's knowledge of its parameters:

$$\underline{\underline{R}} = \frac{\prod_{i=1}^{I} \underline{\underline{X}}_i}{\prod_{j=1}^{J} \underline{\underline{Y}}_j} \qquad \text{Eqn 6}$$

This is a special case of a more general model $\underline{\underline{R}} = f(\underline{\underline{X}}_1, \ldots, \underline{\underline{X}}_i, \ldots, \underline{\underline{X}}_I, \underline{\underline{Y}}_1, \ldots, \underline{\underline{Y}}_j, \ldots, \underline{\underline{Y}}_J)$.

We continue to denote real variables (point values) without the underscore and first-order random variables with a single underscore. In most practical cases, including those cases with correlated or jointly distributed random variables on the RHS, the analyst can simulate a numerical approximation to the distribution $\underline{\underline{R}}$, as discussed below.

Some Second-Order Random Variables

Figures 4, 5, and 6 illustrate three examples of second-order random variables often used in risk assessments. The graphs of these three distributions show that the uncertain parameters create uncertainty "bands" around the related first-order random variable in Figures 1, 2, and 3, respectively.

Figure 4 shows a second-order random variable with a Uniform distribution representing the V in the population where each parameter is, in turn, a Uniform distribution representing the U in the analyst:

$$\underline{\underline{X}} \quad \sim \quad \text{Uniform}(\ \underline{\text{min}},\ \underline{\text{max}}\ ) \qquad \text{Eqn 7}$$

with $\underline{\text{min}}$ ~ Uniform(2, 3) and with $\underline{\text{max}}$ ~ Uniform(4, 9), i.e., the uncertain parameters in Eqn 7 are represented by first-order random variables with constant parameters. The second-order random variable in Eqn 7 is related to the first-order random variable in Eqn 3. The two panels in Figure 4 show 25 realizations from Eqn 7 in a format analogous to the two panels in Figure 1 for Eqn 3. In fact, the complete graphs of the second-order random variable in Eqn 7 would have an infinite number of realizations so that the reader would see solid black regions (with sharp boundaries) in the panels in Figure 4 instead of the 25 lines portrayed. Of course, it is possible to create different second-order random variables by using different parametric distributions -- perhaps Triangular distributions or others-- to represent the uncertain parameters in Eqn 7.

Figure 5 shows a second-order random variable with a Normal distribution representing the V in the population where each parameter is, in turn, a Normal distribution representing the U in the analyst:

$$\underline{\underline{X}} \quad \sim \quad \text{Normal}(\ \underline{\mu},\ \underline{\sigma}\ ) \qquad \text{Eqn 8}$$

with $\underline{\mu}$ ~ Normal(5, 0.5) and with $\underline{\sigma}$ ~ Normal(1, 0.5). Here, the distribution for $\underline{\sigma}$ is truncated to keep it positive. The second-order random variable in Eqn 8 is related to the first-order random variable in Eqn 4. The three panels in Figure 5 show 25 realizations from Eqn 8 in a format analogous to the three panels in Figure 2 for Eqn 4. The complete graphs of the second-order random variable in Eqn 8 would have an infinite number of realizations so that the reader would see black regions (fading into gray without sharp boundaries) in the panels in Figure 5 instead of the 25 lines portrayed. Of course, it is possible to create different second-order random variables by using different parametric distributions -- perhaps Beta distributions or others -- to represent the uncertain parameters in Eqn 8.

Figure 6 shows a second-order random variable with a LogNormal distribution representing the V in the population where each parameter is, in turn, a Normal distribution representing the U in the analyst:

$$\underline{\underline{X}} \quad \sim \quad \exp[\ \text{Normal}(\ \underline{\mu},\ \underline{\sigma}\ )\ ] \qquad \text{Eqn 9}$$

with $\underline{\mu}$ ~ Normal(0.5, 0.15) and with $\underline{\sigma}$ ~ Normal(0.6, 0.2). Here, the distribution for $\underline{\sigma}$ is truncated to keep it positive. Rewritten in more generality, Eqn 9 is a special case of the more general formulation in Eqn 10:

$$\underline{\underline{X}} \quad \sim \quad \exp[\ \text{Normal}(\ \text{Normal}(\ \mu_{\mu},\ \sigma_{\mu}\ ),\ \text{Normal}(\ \mu_{\sigma},\ \sigma_{\sigma}\ )\ )\ ] \qquad \text{Eqn 10}$$

where μ_{μ}, σ_{μ} (> 0), μ_{σ} (> 0), and σ_{σ} (> 0) is each a constant.

The second-order random variable in Eqn 9 is related to the first-order random variable in Eqn 5. The three panels in Figure 6 show 25 realizations from Eqn 9 in a format analogous to the three panels in Figure 3 for Eqn 5. The complete graphs of the second-order random variable in Eqn 9 would have an infinite number of realizations so that the reader would see black regions (fading into gray without sharp boundaries) in the panels in Figure 6 instead of the 25 lines portrayed. Of course, it is possible to create different second-order random variables by using different parametric distributions -- perhaps Trapezoidal distributions or others -- to represent the uncertain parameters in Eqn 9.

Degenerate Special Cases to Encode Pure V or Pure U

Although the second-order random variables in Eqns 7, 8, and 9 contain nonzero V and nonzero U, each of them has degenerate special cases that represent (i) nonzero V (with zero U) or (ii) nonzero U (with zero V). For example, here are three degenerate special cases of Eqn 9:

(a) $\underline{\underline{X}}$ contains only V in the limit as $\underline{\mu} \to \mu_0$, a constant, and as $\underline{\sigma} \to \sigma_0 > 0$, a positive constant. In this special case, $\underline{\underline{X}}$ in Eqn 9 degenerates gracefully to a first-order random variable containing only nonzero V.

(b) $\underline{\underline{X}}$ contains only U in the limit $\underline{\sigma} \to 0$ as long as $\underline{\mu}$ remains a nondegenerate distribution. In this special case, $\underline{\underline{X}}$ in Eqn 9 degenerates to an uncertain constant containing only nonzero U.

(c) $\underline{\underline{X}}$ contains neither V nor U in the limit $\underline{\mu} \to \mu_0$, a constant, and as $\underline{\sigma} \to 0$. In this special case, $\underline{\underline{X}}$ in Eqn 9 degenerates to a positive constant without V and without U.

These three examples illuminate a much larger point: Just as the deterministic paradigm (with means or medians) is a degenerate special case of the first-order probabilistic paradigm, both the deterministic paradigm and the first-order probabilistic paradigm are degenerate special cases of the second-order probabilistic paradigm. Thus, we see a set of "nested" paradigms, with the deterministic paradigm as the zeroth-order paradigm.

A Discussion of the Constants in Eqn 10

In Eqn 10, the constants μ_μ and σ_μ control the location and the spread, respectively, of the intercept (at z = 0) of the straight lines on the LNPP in Figure 6, and the constants μ_σ and σ_σ control the location and the spread, respectively, of the slope of the straight lines on the LNPP in Figure 6.

Propagation of Variability and Uncertainty in Equation 6

Propagation of Variability and Uncertainty with LogNormal Distributions

We investigate a special case -- the input variables $\underline{\underline{X}}_i$ and $\underline{\underline{Y}}_j$ are each independent second-order LogNormal random variables (that express variability) with independent random parameters that express parameter uncertainty. Each of the input variables follows one of these forms:

$$\underline{\underline{X}}_i \sim \exp[\text{ Normal}(\underline{\mu}_i , \underline{\sigma}_i)] \quad \text{for } i = 1,..., I \qquad \text{Eqn 11}$$

$$\underline{\underline{Y}}_j \sim \exp[\text{ Normal}(\underline{\mu}_j , \underline{\sigma}_j)] \quad \text{for } j = 1, ..., J \qquad \text{Eqn 12}$$

With no other restrictions except the constraint $\underline{\sigma} > 0$, we find that the incremental lifetime cancer risk, $\underline{\underline{R}}$, is a second-order LogNormal random variable expressing both the V and the U. The independent uncertain LogNormal input variables in Eqns 11 and 12 propagate through Eqn 6 to create the second-order LogNormal random variable $\underline{\underline{R}}$ in Eqn 13:

$$\underline{\underline{R}} \sim \exp[\text{ Normal}(\underline{\mu}_R, \underline{\sigma}_R)] \qquad \text{Eqn 13}$$

where:

$$\underline{\mu}_R \sim \sum \underline{\mu}_i - \sum \underline{\mu}_j \qquad \text{Eqn 14}$$

$$\underline{\sigma}_R \sim \text{Sqrt}[\sum (\underline{\sigma}_i)^2 + \sum (\underline{\sigma}_j)^2] \qquad \text{Eqn 15}$$

Eqns 14 and 15 hold over all the values of the indices. [EndNote 3].

Calculating or Approximating the Distribution $\underline{\mu}_R$

Many students of probability or statistics study the properties of sums and differences of random variables. For example, if all the $\underline{\mu}_i$ and $\underline{\mu}_j$ in Eqn 14 are jointly Normal random variables, perhaps with a nonzero covariance matrix, then $\underline{\mu}_R$ is also a Normal random variable. In particular, when the $\underline{\mu}_i$ and $\underline{\mu}_j$ in Eqn 14 are independent and jointly Normal random variables,

$$\underline{\mu}_R \quad \sim \quad \text{Normal}(\ (\ \sum \mu_{\mu,i}\ -\ \sum \mu_{\mu,j}\ )\ ,\ \text{Sqrt}[\ \sum (\sigma_{\mu,i})^2 + \sum (\sigma_{\mu,j})^2\ ]\ ) \qquad \text{Eqn 16}$$

With mutually independent nonNormal random variables, an analyst may sometimes calculate $\underline{\mu}_R$ using convolutions (Parzen, 1960) or approximate $\underline{\mu}_R$ using Fast Fourier Transforms (FFTs; see, e.g., Ramirez, 1985). When the conditions of the Central Limit Theorem hold, $\underline{\mu}_R$ tends to a Normal distribution as the sum I+J grows large.

Approximating the Distribution $\underline{\sigma}_R$

Few people have studied the properties of the square root of sums of squares of random variables, much less the square root of sums of squares of random variables constrained to remain positive. [EndNote 4]. In fact, we could find no general results in the literature. However, a colleague (Korsan, 1995) wrote routines using Fast Fourier Transforms (FFTs) and Laplace transforms in Mathematica® (Wolfram, 1991) to help us investigate the behavior of Eqn 15 with different mutually independent inputs.

Figures 7, 8, and 9 show some of the results from the FFT calculations for some special cases of Eqn 15 when all the $\underline{\sigma}_i$ and $\underline{\sigma}_j$ are independent, identically distributed (iid) random variables. As inputs to Eqn 15, we consider cases with the sum I+J = 4, 8, and 16 for three input distributions: (i) a Uniform distribution (Figure 7), (ii) symmetric Triangular distribution (Figure 8), and (iii) a truncated Normal distribution (Figure 9). These distributions are, respectively:

$$\underline{\sigma}_i\ ,\ \underline{\sigma}_j \quad \sim \quad \text{Uniform}(\ 0,\ 1\ ) \qquad \text{Eqn 17}$$

$$\underline{\sigma}_i\ ,\ \underline{\sigma}_j \quad \sim \quad \text{Triangular}(\ 0,\ 0.5,\ 1\ ) \qquad \text{Eqn 18}$$

$$\underline{\sigma}_i\ ,\ \underline{\sigma}_j \quad \sim \quad \text{truncateNormal}(\ 0.5,\ 0.25\ ) \qquad \text{Eqn 19}$$

[EndNote 5].

In Figures 7, 8, and 9, none of the distributions are Normal distributions, even though each has a bell shape. Looking at the graphs for a fixed value of the sum I+J for these special cases, we see that the shape of the input distribution causes some subtle changes in the shape of distribution $\underline{\sigma}_R$. Looking at the graphs for a fixed type of input distribution, we see that the location of the distribution $\underline{\sigma}_R$ shifts to the right as the sum I+J grows, but that the shape and spread of the distribution remain approximately the same for this special case.

In Figure 7 for iid Uniform inputs, the bottom panel for I+J = 16 shows an important phenomenon. From first principles, we know the support for this $\underline{\sigma}_R$ is [0, 4], but the distribution has most of its mass over the interval [1.8, 3]. The expected value of this distribution is ~2.37 (a value larger than the square root of the sum of the squares of the arithmetic means of the input distributions). This same phenomenon also holds for the other special cases in Figures 8 and 9, and it holds for other input distributions as well.

Propagation of Variability and Uncertainty in Other Distributions

Although direct analytical and/or transform methods work in special cases, it is possible to approximate the second-order random variable $\underline{\underline{R}}$ in Eqn 6 using Monte Carlo (MC) or Latin Hypercube (LH) sampling in nested loops to maintain the isolation between V and U (Frey, 1992). [EndNote 6].

Begin Outer Loop for **Uncertainty** (N_{outer} =1,000, say)

> Pick one set of point values from each distribution representing Uncertainty
>
> Begin Inner Loop for **Variability** (N_{inner} = 1,000, say)
>
> > Compute this one simulation
> >
> > Store desired information
>
> End Inner Loop

End Outer Loop

Algorithms based on nested loops have high computational costs ($\propto N_{outer} \cdot N_{inner}$). However, this class of algorithms -- sometimes called 2-dimensional simulations -- can approximate $\underline{\underline{R}}$ while maintaining the separation between V and U even when the input variables have a complicated correlation structure and/or dependency structure among and within the distributions encoding V and/or U. Note that the uncertain parameters in a second-order random variable become the outer loop in this nested simulation.

Visualizing the Inputs and the Outputs of a Second-Order Simulation

When $N_{outer} = N_{inner} = O[10^3]$ in the nested-loop algorithm, how can the risk assessor understand the $O[10^6]$ results? Harder still, how can the risk assessor communicate the inputs to and the results from a calculation to the risk managers and to the members of the public? Using Mathematica® (Wickham-Jones, 1994), we introduce three new types of graphs as possible answers to these questions.

First, we illustrate the three graphs as a way to visualize one input distribution to a second-order simulation. Each of the three panels in Figure 10 presents a different visualization of the same second-order distribution, $\underline{\underline{X}}$ in Eqn 9, using the nested-loop algorithm to simulate the distribution.

The top panel in Figure 10 shows 25 lines for realizations drawn from Eqn 9; this LNPP has the same axes as the one in the bottom panel in Figure 6. [EndNote 7]. In this graph, we interpret the abscissa as z_V, the z-score for V in the second-order distribution, and we interpret the vertical dispersion among the 25 lines as a measure of U in the distribution. Notice that the 25 lines increasingly diverge as $|z_V|$ increases. This means that the analyst's uncertainty in $\underline{\underline{X}}$ grows ever more important in the tails of this distribution. Conversely, this means that the analyst's confidence in the results decreases in the tails of this distribution. In Eqn 10, the constant σ_σ controls the fanning of the lines on the LNPP.

The center panel in Figure 10 shows the isopleths for z_U conditional at the given value of z_V. By slicing the top graph vertically at a particular place, say, $z_V = 1$, we find that a histogram of the 25 values from the 25 cut lines approximates a bell-shaped distribution. Similarly, by slicing the top graph vertically at a different place, say, $z_V = 2$, we find that a histogram of the 25 different values from the 25 cut lines approximates a different bell-shaped distribution, i.e., one with a larger mean and a larger standard deviation. In the special case of the second-order distribution in Eqn 9, each vertical slice at a particular z_V in the top graph yields a histogram of cut values that closely approximates a Normal distribution. By realizing a large number of lines in the top graph (i.e., $N_{outer} = 500$

different realizations of U in the algorithm), we rank the values at any vertical slice (at any particular z_V) and compute a z_U conditional at the particular z_V, i.e., the z-score for the uncertainty in the 500 lines cut by the particular vertical slice. The center panel in Figure 10 shows this plot of z_U conditional on z_V. While it is more abstract, this "zzPlot" reduces the tangle and overlap of lines seen in the top graph. [EndNote 8].

The bottom panel in Figure 10 shows the same information as the center panel, but in a 3D plot. Here the {x, y, z}-axes become, respectively, the {z_V, z_U, ln[•]}-axes. [EndNote 9]. In this plot, as in the center plot, z_U is conditional on z_V, that is, z_U shows the degree of U conditioned on a value for V. The heavy line shows the locus of $z_U = 0$.

The three panels in Figure 11 parallel those in Figure 10 for this simplified problem with three second-order random variables. Here we model the uncertain parameters using symmetric or almost symmetric distributions.

$$\underline{\underline{R}} = \frac{\underline{\underline{X}}_1 \bullet \underline{\underline{X}}_2}{\underline{\underline{Y}}_1} \qquad \text{Eqn 20}$$

with

$\underline{\underline{X}}_1$ ~ exp[Normal($\underline{\mu}$, $\underline{\sigma}$)] Eqn 21

~ exp[Normal(Normal(μ_μ, σ_μ), truncateNormal(μ_σ, σ_σ))]

~ exp[Normal(Normal(0.60, 0.05), truncateNormal(0.10, 0.01))]

$\underline{\underline{X}}_2$ ~ exp[Uniform($\underline{\text{min}}$, $\underline{\text{max}}$)] Eqn 22

~ exp[Uniform(Triangular(a, b, c), Triangular (d, e, f))]

~ exp[Uniform(Triangular(1.8, 2.0, 2.2), Triangular (2.7, 3.0, 3.3))]

$\underline{\underline{Y}}_1$ ~ exp[Normal($\underline{\mu}$, $\underline{\sigma}$)] Eqn 23

~ exp[Normal(Normal(μ_μ, σ_μ), truncateNormal(μ_σ, σ_σ))]

~ exp[Normal(Normal(4.2, 0.1), truncateNormal(0.2, 0.02))]

The three panels in Figure 12 parallel those in Figure 11, except that we have added positive correlation between two of the variables. In this simulation, $\rho_V(\underline{\underline{X}}_1, \underline{\underline{Y}}_1) = 0.9$, a reasonable assumption for the correlation between the V in (i) the skin surface area and (ii) the body weight of an adult (Murray and Burmaster, 1992). In this simulation, $\rho_V(\underline{\underline{X}}_1$,

$\underline{\underline{Y}}_1$) is a constant, but we could easily make it an uncertain constant using the formalism developed earlier. Similarly, while we have only considered correlation in the variability of $\underline{\underline{X}}_1$ and $\underline{\underline{Y}}_1$, we could also add correlation in the analyst's uncertainty about $\underline{\underline{X}}_1$ and $\underline{\underline{Y}}_1$.

The Expected Value of a Second-Order Random Variable

In a first course on probability or statistics, students learn how to compute the expected value of a first-order random variable. To paraphrase Freund (1971), mathematical expectation was introduced in connection with games of chance, and it is the product of a player's potential gain and the probability that the gain will actually be realized. Countless authors have extended this concept to discrete and continuous first-order random variables using well-known sums and integrals (e.g., Parzen, 1960) to compute an expected value (a point value) for a full distribution. Taking care to avoid various pitfalls, the same concept may be further extended to compute an expected value (also a point value) for a second-order random variable. [EndNote 10].

By Integration

Viewing $\underline{\underline{X}}$ as a random variable conditioned on random variables $\underline{\mu}$ and $\underline{\sigma}$, we compute its expected value by adapting standard methods for expected values of conditional random variables (Burgess, 1996; Mood, Graybill, and Boes, 1974).

$$E[\,\underline{\underline{X}}\,] = \int_{\mu=-\infty}^{\infty} \int_{\sigma=-\infty}^{\infty} \left[\int_{x=-\infty}^{\infty} x \bullet f_{X|\mu,\sigma}(x|\mu,\sigma)\, dx \right] f_{\mu,\sigma}(\mu,\sigma)\, d\mu\, d\sigma$$

Eqn 24

To illustrate this method, we chose the following example with an easy analytical solution, but the method works with numerical quadrature for more difficult integrals. Let $\underline{\underline{X}}$ be this second-order random variable:

$$\underline{\underline{X}} \sim \exp[\,\text{Normal}(\,\underline{\mu},\,\underline{\sigma}\,)\,]$$ Eqn 25

with $\underline{\mu}$ and $\underline{\sigma}$ distributed independently as

$\underline{\mu}$ ~ Uniform(0, 1) and

$\underline{\sigma} \quad \sim \quad \text{Triangular}(0, \sqrt{2}, \sqrt{2})$

Exact Method: In this example, $f_{\mu,\sigma}(\mu,\sigma) = f_\mu(\mu) \bullet f_\sigma(\sigma) = 1 \bullet \sigma$ for $0 \le \mu \le 1$ and $0 \le \sigma \le \sqrt{2}$ and the inner integral (over x) = exp[$\mu + 0.5\ \sigma^2$], so

$$E[\underline{\underline{X}}] = \int_{\mu=0}^{1} \int_{\sigma=0}^{\sqrt{2}} \exp[\mu + 0.5\,\sigma^2]\, f_\mu(\mu)\, f_\sigma(\sigma)\, d\mu\, d\sigma \qquad \text{Eqn 26}$$

$$= \int_{\mu=0}^{1} \int_{\sigma=0}^{\sqrt{2}} \exp[\mu + 0.5\,\sigma^2]\, 1\, \sigma\, d\mu\, d\sigma$$

$$= \int_{\mu=0}^{1} \exp[\mu]\, d\mu \int_{\sigma=0}^{\sqrt{2}} \exp[0.5\,\sigma^2]\, \sigma\, d\sigma$$

$$= (e - 1) \bullet (e - 1) = 2.95$$

Alternate Exact Method: For this example, we offer an alternative:

$$E[\underline{\underline{X}}] = E[\exp[\underline{\mu} + 0.5\,\underline{\sigma}^2]] \qquad \text{Eqn 27}$$

$$= E[\exp[\text{Uniform}(0, 1) + 0.5\,(\text{Triangular}(0, \sqrt{2}, \sqrt{2}))^2]]$$

$$= E[\exp[\text{Uniform}(0, 1) + \text{Uniform}(0, 1)]]$$

$$= E[\exp[\text{Triangular}(0, 1, 2)]]$$

Let w = exp[Triangular(0, 1, 2)]. This LogTriangular distribution has this PDF:

$$f_W(w) = \begin{cases} 0, & w < 1 \\ \ln[w] / w, & 1 \le w < e \\ (2 - \ln[w]) / w, & e \le w < e^2 \\ 0, & e^2 \le w \end{cases} \qquad \text{Eqn 28}$$

The expectation of this ordinary random variable follows with modest effort:

$$E[\underline{\underline{X}}] = E[w] \qquad \text{Eqn 29}$$

$$= e^2 - 2e + 1 = (e - 1)^2 \qquad \text{as before.}$$

Incorrect Method. We note that the $E[\underline{\underline{X}}]$ for Eqn 25 cannot be computed as follows:

$$E[\underline{\underline{X}}] \neq \exp[E[\mu] + 0.5 (E[\sigma])^2] \qquad \text{Eqn 30}$$

$$\neq \exp[0.5 + 0.5 \bullet \frac{8}{9}] = 2.57$$

By Monte Carlo Simulation

To continue the example, we also estimate the expected value of $\underline{\underline{X}}$ in Eqn 25 using Monte Carlo simulation to draw random pairs (μ, σ) from the independent PDFs for $\underline{\mu}$ and $\underline{\sigma}$:

$$E[\underline{\underline{X}}] = \text{AMean}[\exp[\underline{\mu} + 0.5\, \underline{\sigma}^2]] \qquad \text{Eqn 31}$$

After 10 sets of 1,000 iterations each of this method, we find 10 different estimates of $E[\underline{\underline{X}}]$: 2.878, 2.914, 3.045, 2.948, 2.974, 2.980, 2.977, 2.954, 2.917, and 2.916. After 10 sets of 4,000 iterations each of this method, we find another 10 estimates of $E[\underline{\underline{X}}]$: 2.936, 2.944, 2.906, 2.959, 2.950, 2.950, 2.954, 2.935, 2.960, and 2.944.

More generally, when using the nested loop algorithm, the risk assessor may estimate the expected value for $\underline{\underline{R}}$ by (i) computing one arithmetic mean for each call to inner loop (just before exiting the loop), and then (ii) computing a grand arithmetic mean over all the calls to the inner loop. The accuracy and precision of the estimated expected value increase as N_{outer} and N_{inner} increase.

When $\underline{\mu}$ and $\underline{\sigma}$ are not independent -- as may often happen -- the analyst may use this simulation method to compute $E[\underline{\underline{X}}]$.

Discussion, Limitations, and Next Steps

In this manuscript, we give an introduction to the use of the second-order probabilistic paradigm in human health risk assessment. This second-order paradigm contains both the first-order probabilistic paradigm and the deterministic paradigm within it.

The second-order paradigm allows the risk assessor to encode the variability in natural populations and the uncertainty in the analyst separately. While computationally expensive, nested-loop algorithms allow the risk assessor to propagate the variability and parameter uncertainty separately, so that the analyst can communicate the different components to risk managers and to the public. Although this manuscript is not the right forum to present our arguments, we think that V and U have rather different management implications, so it is important that the risk assessor, the risk manager, and the members of the public understand their relative and absolute contribution to the distributions of exposure and risk.

Several limitations attend this manuscript. First, second-order random variables do not and cannot capture model uncertainty in Eqn 6 and its generalization. While this is major limitation in some risk assessments, it is not a major limitation for most exposure assessments. Second, without customized software, calculations with second-order random variables are difficult, especially when complex correlations and dependencies are present. The results in this manuscript rest on custom software (called Risk2D) written in Mathematica®.

In the future, risk assessors need to develop new methods for developing (fitting) second-order random variables to describe the variability found in a population and the uncertainty found in the analyst. In our profession, risk assessors now have good methods to fit parametric distributions to measured data for variability, but we do not have adequate methods to quantify the uncertainty in the parameters. Surely, professional judgment is and will remain the key tool for quantifying parameter uncertainty for the foreseeable future.

Finally, we risk assessors also need to develop new ways to visualize the results from 2-dimensional simulations so we can communicate the results to risk managers and to members of the public. While this manuscript presents several novel graphs for risk communication, we ask others to join the search for new ways to visualize and communicate the results from these calculations.

EndNotes

1. For noncarcinogens, the exposure methods are the same as for carcinogens.

2. In defining U, we follow the lead of many other authors (e.g., Bogen, 1990; Frey, 1992; Hoffman and Hammonds, 1994; NAS, 1994).

3. These closed-form results have another basic use -- they provide a closed-form special case so an analyst can make sure that his or her nest-loops are running properly.

4. Mathai and Provost (1992) have studied quadratic forms in random variables. For example, under suitable conditions, the sum of squares of Normal random variables is distributed as a convolution of NonCentral ChiSquare distributions. Since a ChiSquare distribution is a special case of a Gamma distribution, some results in Bondesson (1992) may be useful.

5. The PDF for truncateNormal(0.5, 0.25) equals

$$f_X(x) \quad = \quad \frac{\dfrac{1}{0.25\sqrt{2\,\pi}} \bullet \exp\left[-\,\dfrac{1}{2}\left(\dfrac{x - 0.5}{0.25} \right)^2 \right]}{0.97725}$$

over the support $[0, \infty)$. This distribution has an expected value of ~0.514

6. The analyst may implement these nested loops in many different software languages. As always, some languages have more power and speed than others. It is especially challenging to implement complex correlation structures in all but a full-strength programming language like Mathematica®.

7. The 25 lines in this top panel are not perfectly straight due to "sampling error." For each of the 25 lines in this graph, we use straight line segments to interpolate between knots with these z values {z = -3.00, -2.35, -2.05, -1.45, -0.92, -0.56, -0.27, 0., 0.27, 0.56, 0.92, 1.45, 2.05, 2.35, and 3.00}.

8. The isopleths in the center panel of Figure 10 become smooth curves in the limit as N_{outer} and N_{inner} each tend to infinity. When Eqn 10 holds, and when the truncation caused by the constraint $\underline{\sigma} > 0$ is not severe, we see:

$$\ln[\underline{\underline{X}}]\,[\, z_U \mid z_V \,] \quad \doteq \quad \mu_\mu + z_V \bullet \mu_\sigma + z_U \bullet \sqrt{(\sigma_\mu)^2 + (z_V \bullet \sigma_\sigma)^2}$$

where $\ln[\underline{\underline{X}}]\,[\, z_U \mid z_V \,]$ denotes the point value at z_U conditional on z_V. In this equation, the symbol "$\doteq$" denotes "is approximately equal to." Thus, to approximate the point value for the 67th percentile of uncertainty on the 95th percentile of variability of the LogNormal distribution in Eqn 10, first evaluate this equation with $z_V = 1.645$ and $z_U = 0.440$ and then exponentiate the result.

9. In a risk assessment for a hazardous waste site, we suggest using common logarithms (base 10) instead of natural logarithms (base e) in any graphs for the estimated incremental lifetime cancer risk attributable to exposure to compounds regulated as carcinogens. The US EPA and other regulatory agencies often specify the range of acceptable risk using powers of 10, so common logarithms make sense for risk communication.

10. We include these new results for several reasons. First, we are unaware of any previous publication of these results for second-order random variables. Second, we show the types of analytical and simulation methods useful in computing summary statistics for second-order random variables. The methods here, for example, may be easily extended to computing the expected value of the Uncertainty for a particular percentile of the Variability. Finally, we hasten to add that we do not recommend that risk managers use $E[\underline{\underline{X}}]$ as the sole or principal criterion for making risk management decisions.

Trademarks and Licenses

We performed most of the calculations and simulations in this manuscript in Risk2D, a set of custom software packages developed by Alceon Corporation using Mathematica® (Wolfram, 1991; Wickham-Jones, 1994) and RiskQ (Bogen, 1992).

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Dedication

We dedicate this manuscript in memory of Jerry B. Keiper of Wolfram Research, Inc.

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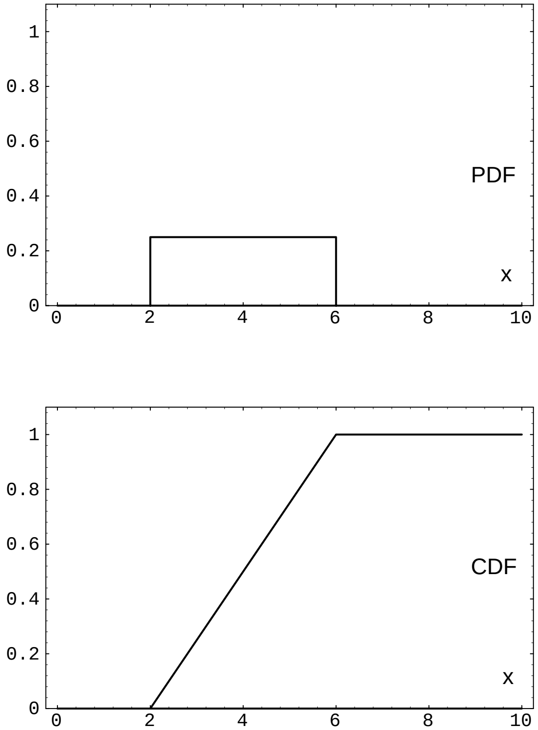


Figure 1
Uniform

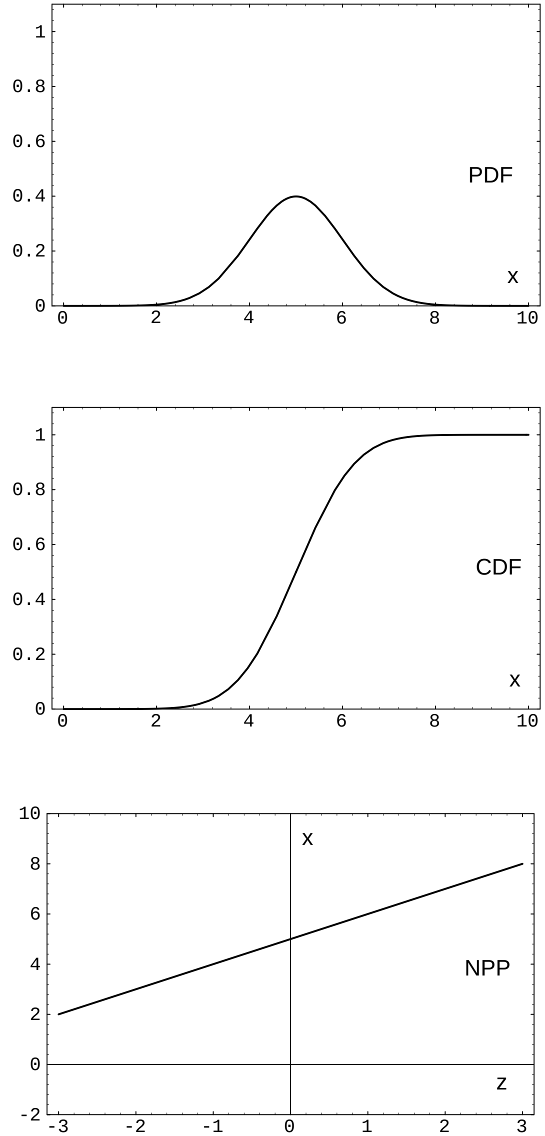


Figure 2
Normal

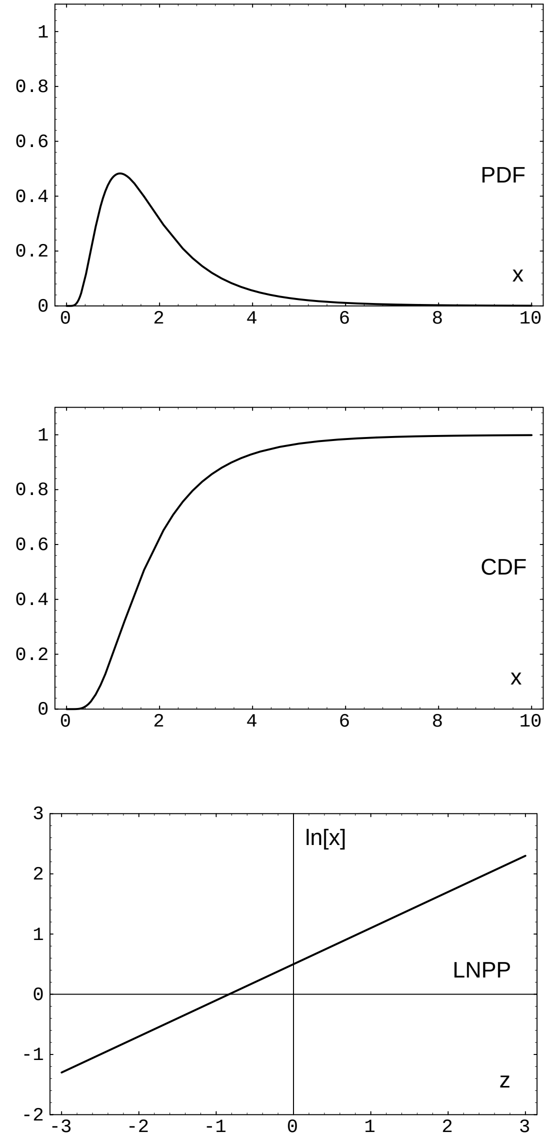
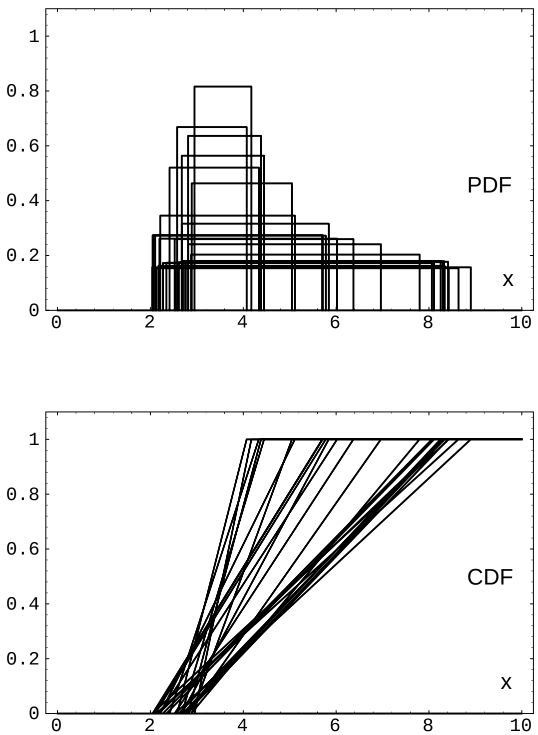


Figure 3
LogNormal

Alceon



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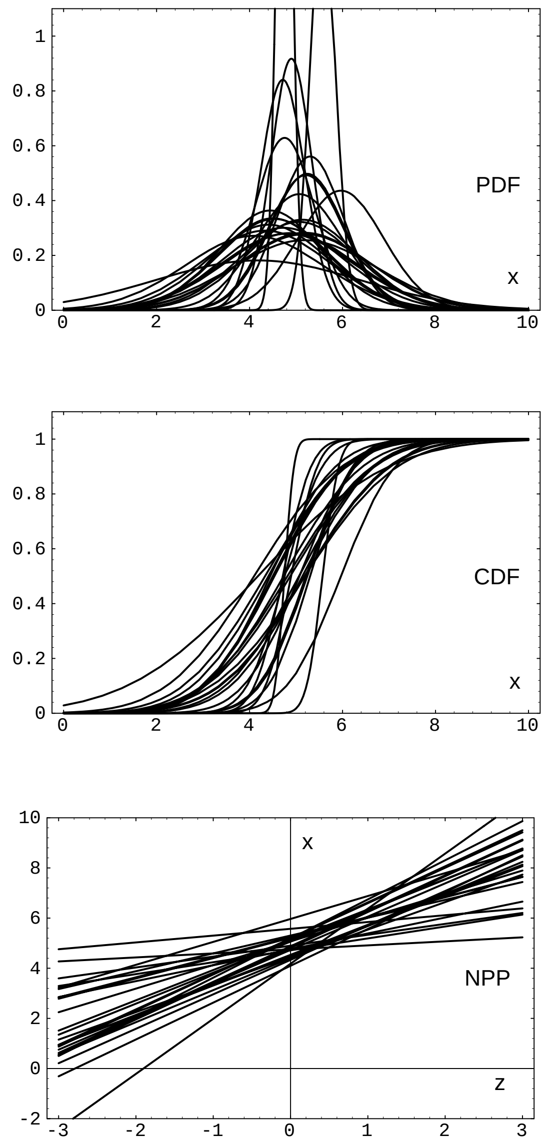

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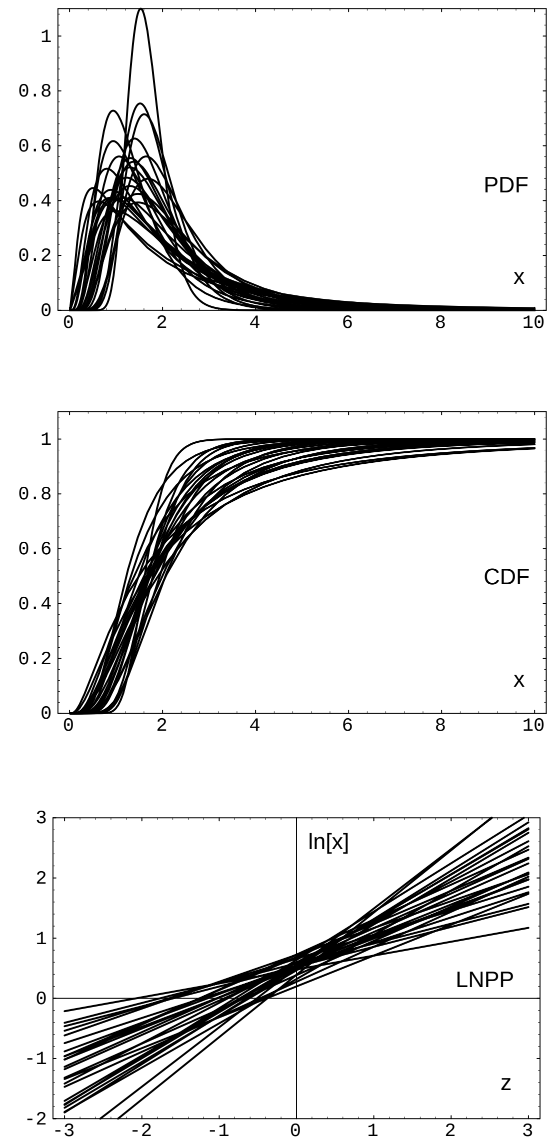


Figure 6
LogNormal

Alceon

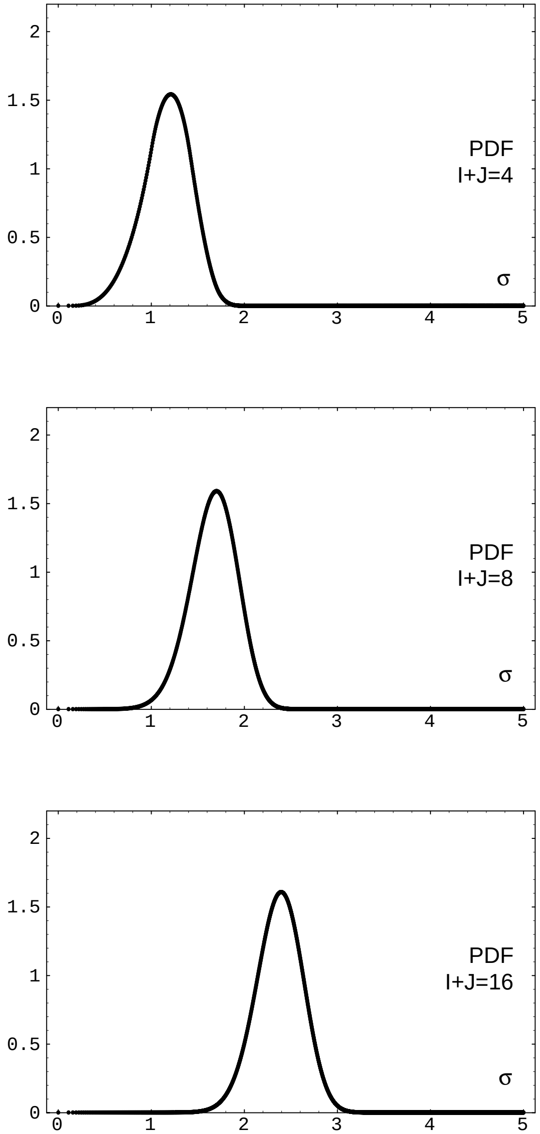
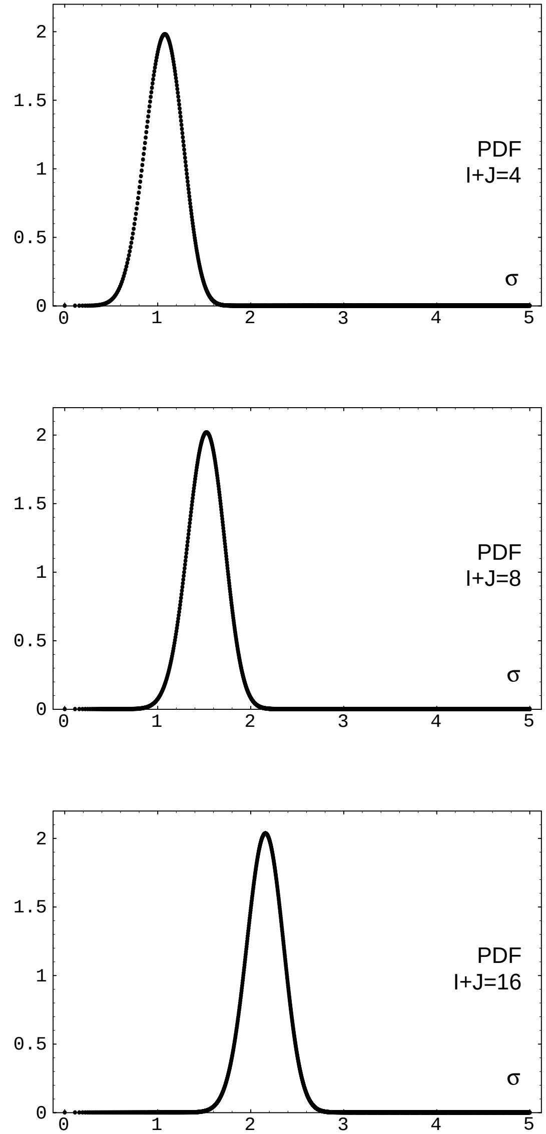


Figure 7
Uniform



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Triangular

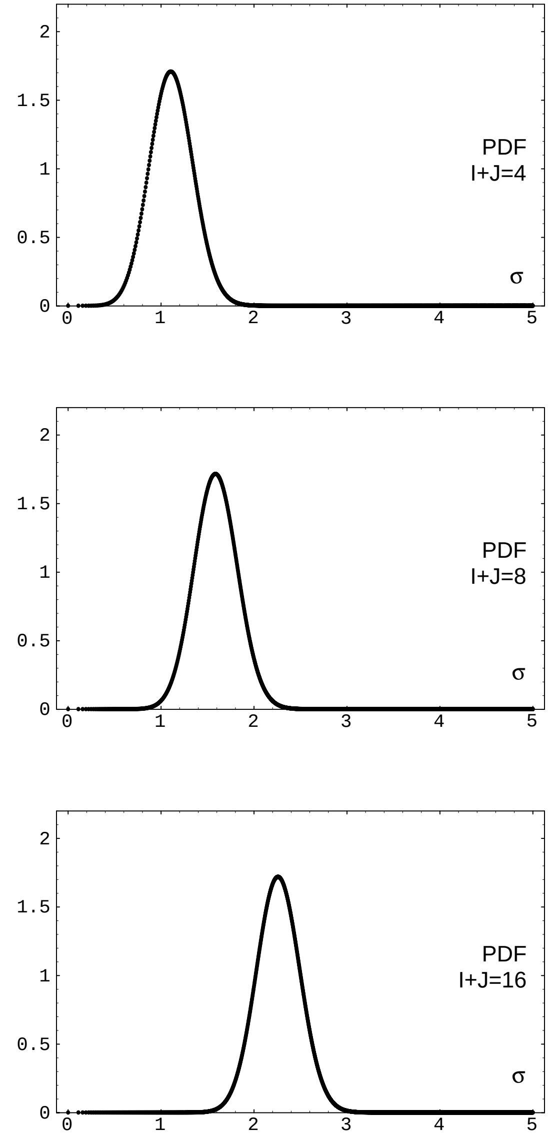

Figure 9
truncateNormal

Alceon

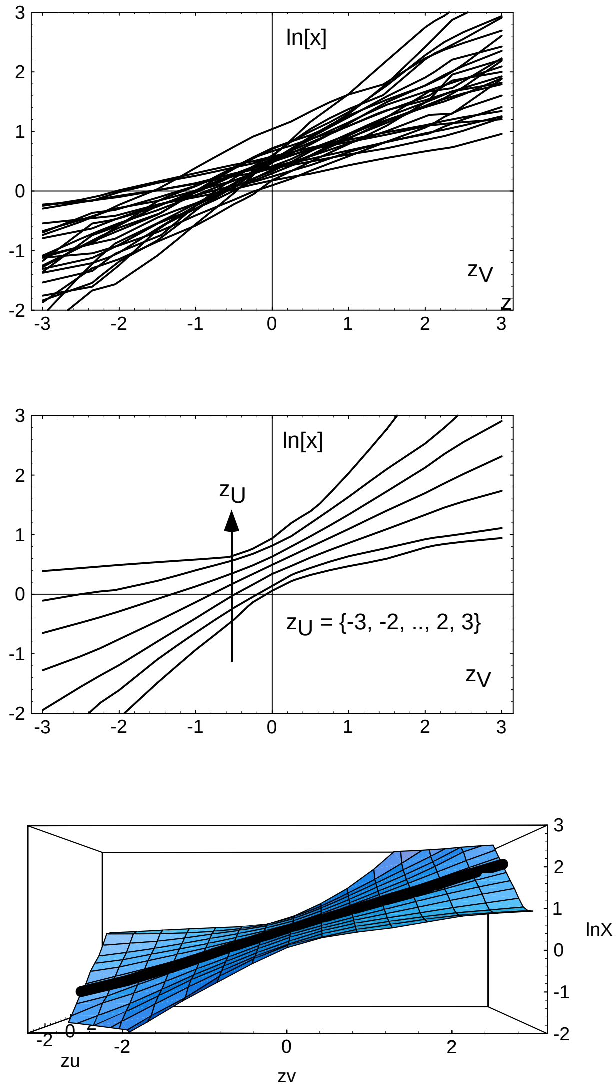

Figure 10

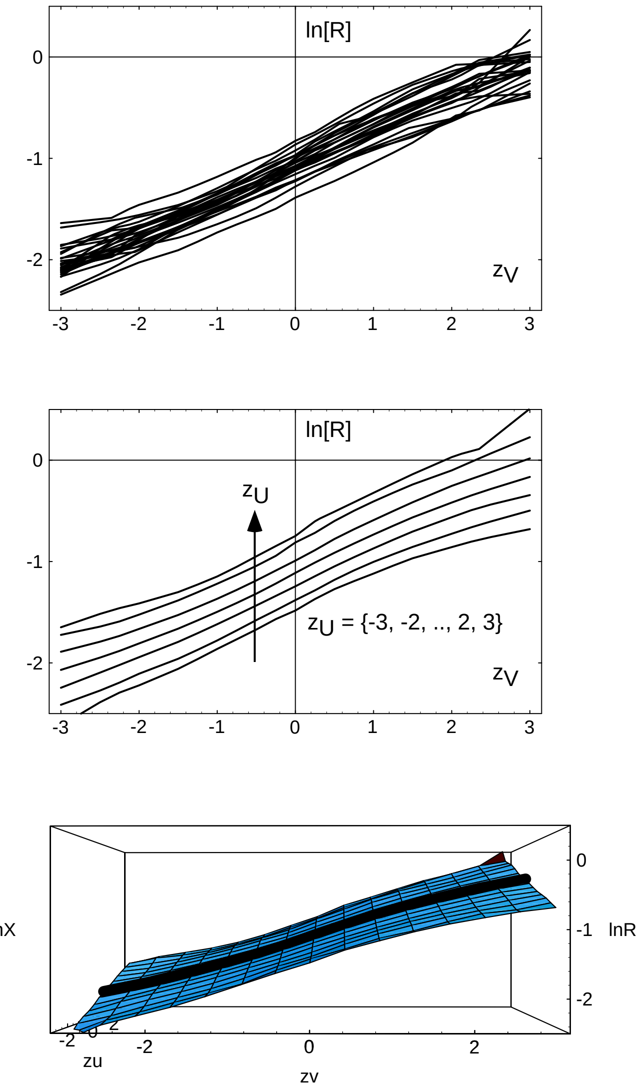

Figure 11

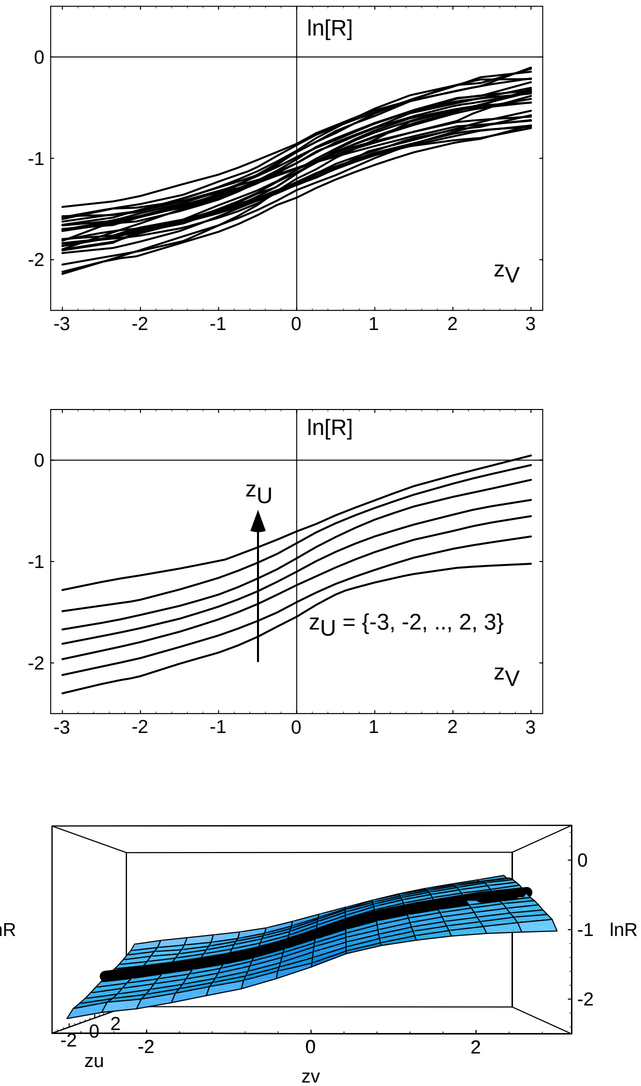

Figure 12

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