MULTI-SUBSTANCE SPECIES SENSITIVITY DISTRIBUTIONS & NON-INTERACTIVE ACTIONS: A BIVARIATE EXAMPLE

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Introduction & Non-Interactive Action

Species sensitivity distributions (SSDs) are usually considered univariately, i.e. for a single toxicant. If we have two toxicants: A & B, then SSD modelling and risk measurement must incorporate interactions of the substances in order to adequately estimate the potentially affected fraction (PAF; see Traas et al. 2002) of species. At log-toxicant exposure x, the PAF is G(x) (defined for a prescribed species community), where G is known as the SSD (on the log-scale). We explore the extension of this concept for two non-interacting toxicants; in Traas et al. (2002) this was called the multi-substance PAF; denoted msPAF (where here, multi = 2).

Non-interactive joint action, as defined by Plackett and Hewlett (1952), can be classified into two (extreme) categories: **concentration addition** (**CA**; a.k.a. simple similar action) and **response addition** (**RA**; a.k.a. independent action); later they also hypothesised a continuum state of **partial similarity** between these two extremes. In 1959 they proposed two models, although for single-species dose-response curves, which can be extended to separate the modelling of the bivariate-SSD from the regions of determination (functions dependant on the mechanism of joint-action) for calculating the msPAF. They also introduced the concept of partial similarity for joint actions which were partially similar.

1. $P\left[\{\lambda'\delta_1 + \delta_2 \geq 1\} \cup \{\delta_1 + \lambda'\delta_2 \geq 1\}\right]$ for $\lambda' \in [0,1]$

2. $P\left[\delta_1^{1/\lambda''} + \delta_2^{1/\lambda''} \geq 1\right]$ for $\lambda'' \in (0,1]$

where $\log(\delta_i) = x_i^* - Y_i$; λ' and λ'' are similarity parameters; and Y_i is a random variable drawn from the SSD for substance i. For λ' = λ'' = 1 one admits CA; and λ' = 0, λ'' → 0 admits RA. Cases in between are known as partial similarity.

Figure 1 illustrates a hypothetical case of a bivariate SSD centred at mean (μ_1, μ_2) and evaluated at log-environmental concentration (EC) (x_1^*, x_2^*). The coloured lines correspond to the lines of determination for some examples of binary non-interactive joint actions. In other words, these lines determine the region of the SSD one numerically integrates over to determine the msPAF for different types of joint action.

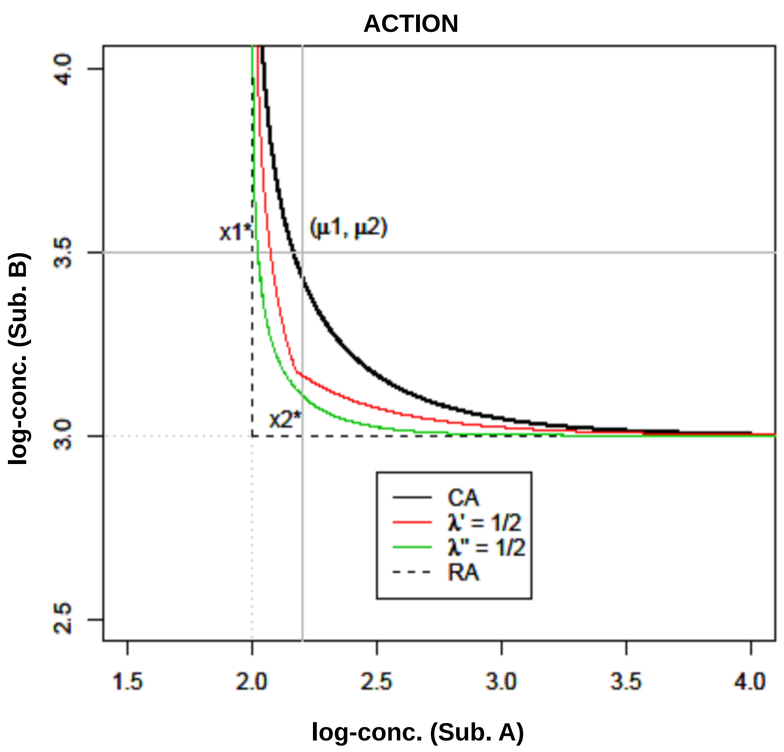

Figure 1. Plackett and Hewlett's lines of determination for an environmental exposure of (x_1^*, x_2^*). Integrating a hypothetical bivariatly distributed SSD, centred with mean (μ_1, μ_2), below the region of determination yields the msPAF given the type of joint-interaction.

Bivariate SSD & Some Special Cases of RA

Separation of the region of determination from the joint SSD means that there is *no* prerequisite in regards to its covariate structure. A natural extension of the univariate normal SSD is the bivariate normal SSD: F(x_1, x_2; μ_1, μ_2, σ_1, σ_2, ρ) where (μ_i, σ_i) are the univariate SSD mean and standard deviation parameters for substance i; and (x_1, x_2) are the log-ECs to be evaluated. The parameter ρ is the correlation coefficient of the SSDs. For the basic case of **RA** we have:

ρ = +1: msPAF(x_1, x_2) = max(p_1, p_2)

ρ = 0: msPAF(x_1, x_2) = $p_1 + p_2 - p_1p_2$

ρ = -1: msPAF(x_1, x_2) = min($p_1 + p_2$, 1)

where p_i is the univariate-SSD PAF for toxicant i acting alone.

Figure 2 shows the consequence of altering the correlation coeffcient ρ on the msPAF evaluated at (known) hazardous concentrations: HCp_1 and HCp_2 for all $p_1 = p_2 \in (0, 1)$. The case of $p_1 = p_2 = 1/2$, i.e. the msPAF evaluated at the univariate median hazardous concentrations to substances A & B: (μ_1, μ_2) is equivalent to:

$$\text{msPAF}(\mu_1, \mu_2; \rho) = 1 - \frac{1}{\pi}\arctan\left(\sqrt{\frac{1+\rho}{1-\rho}}\right);$$

this case is highlighted as the black curve in Figure 2.

There is no apparent reason why a bivariate normal SSD should be the obvious choice for the joint SSD, especially since ρ can only capture linear correlation.

Proposition: It makes logical sense that a risk assessor would expect to obtain their univarite SSD by marginalising their bivariate SSD. This is a property of the bivariate normal SSD. Therefore, we want to capture the correlation separately. This is most elegantly done using the statistical structure of copulas.

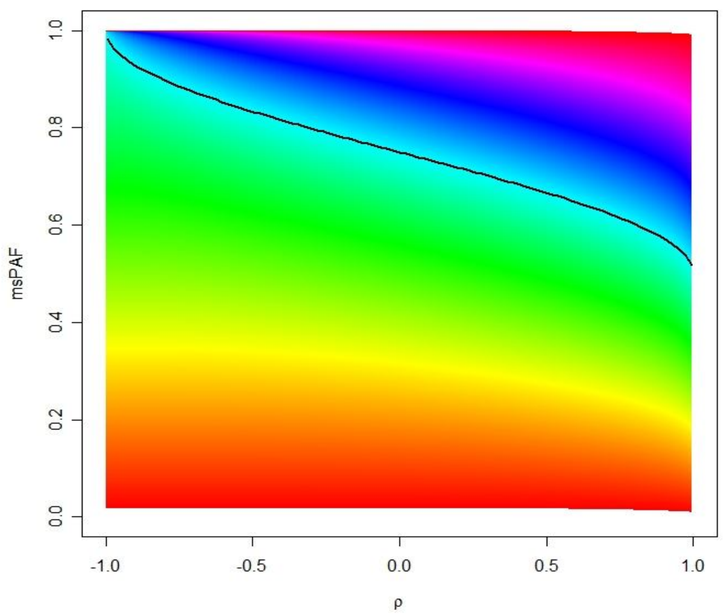

Figure 2. Plot of msPAF(HCp_1, HCp_2) against ρ for all $p_1 = p_2$ based on response addition. Low values of p_i are indicated by red; increasing towards p_i = 1/2 around the light blue region. Blue to pink indicates p_i > 0.5 region. The black solid line indicates the special case where p_i = 1/2.

Graeme Hickey's Ph.D. research is jointly funded by grants from The Food and Environment Research Agency (Seedcorn grant), and the Engineering and Physical Sciences Research Council.

Copula Modelling

It can be shown that F(x_1, x_2; θ) = C($F_1(x_1)$, $F_2(x_2)$; θ) uniquely where F is the **bivariate SSD**, C is a (bivariate) copula (Nelson, 2006), and θ is a *dependency parameter*. Therefore the copula encodes the dependency *separately* from the **marginal SSDs**. The bivariate normal distribution is a special case of a Gaussian SSD with univariate normal marginals.

There are lots of other well known copulas which exhibit different measures of association, and which can all be parameterised through non-parametric measures of rank correlation; e.g. Frank's copula, Gumbel's copula; Clayton's copula; etc. Complete independence of the bivariate SSD would reduce to the *independence copula*.

Fitting models to data can be done in many ways: e.g. maximum likelihood; method of moments (e.g. Traas et al. 2002); inference for margins (IFM; fit the marginal SSDs first, then θ conditional on the former); semi-parametrically, etc. Uncertainty can be captured via Monte-Carlo methods or Bayesian analysis. Note that we do not use dose-response curves per-species, just their substance-pairwise EC50 values.

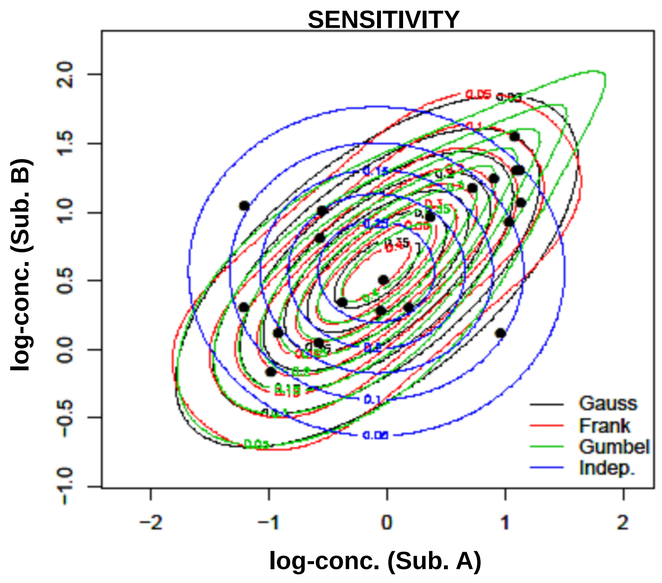

Figure 3. Estimated bivariate SSDs based on different copulas (as an example only) using IFM parameter estimation (discussed above) with normal margins. Data is EC50s for two substances from an RIVM database.

Applying Plackett and Hewlett's joint-action model we ascertain that the msPAF at a log-EC = (-1, 0) is:

	Gauss	Frank	Gumbel	Indep.
RA	0.250	0.253	0.252	0.299
CA	0.341	0.349	0.320	0.352

The Gaussian copula was often preferred, in this example, by copula selection (e.g. Anderson-Darling criteria). With normal margins, this is equivalent to the bivariate normal distribution.

Conclusions

- The independence copula typically infers a higher risk relative to other copulas.
- The independence copula is strongly rejected by copula selection techniques for data analysed for fish from an RIVM toxicity database.
- The methods proposed in Traas et al. (2002) for RA relies on independence, but this assumption may therefore be invalid and therefore misleading, but protectively cautious nonetheless.
- Using copulas for ≥3 substances will lead to much more complex SSD modelling and domains of determination. Whereas the procedure of Traas et al. (2002) is very simple to use in general for many substances. Adequate copula selection requires a lot of data.

References

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