Appendix 1

Three Agent Model

1.1 Introduction

The anesthetic state is produced through combination of analgesics and sedatives/hypnotics. Often this requires two drugs, but occasionally uses three, as in the case of Short et al.[1] Three or more drugs have been used in other disease states such as AIDS.[2] For this reason Minto et al. proposed a three drug model in their appendix.[3] Like their two-agent model, they used polynomials to describe the overall interaction. These polynomials accommodated differences in Hill-based pharmacodynamic changes. Comparison of different interactions, or interaction properties, cannot be attained by this method.

We believe a three drug model with parameters linked to specific curve-shape properties is ideal. With parameter inspection, an immediate idea of the nature of the interaction is observed. This is especially important in a three-drug interaction model. A three-drug response surface is a four-dimensional object, plotting the three drug concentrations against the effect. This is difficult to both interpret and plot. Understanding of four dimensional curve shape can be found by inspecting the parameters, not just by plotting an isosurface, or trying to find a way to plot a four-dimensional surface.

In addition the properties mentioned above, we would like regulatory conditions satisfied:

1. Parameters representing type/intensity of three-drug interaction, symmetry and curve shape.
2. Reduce to the two drug model when one of the three drugs is absent.
3. When two drugs are the same, have the model reduces to the two drug model.

4. When all three drugs are the same reduce to the appropriate Hill-model.

1.2 Materials and methods

1.2.1 Three agent additivity

When a three-agent interaction is additive, the 50% effect-slice follows the equation:

$$1 = \frac{[A]}{A_{50}} + \frac{[B]}{B_{50}} + \frac{[C]}{C_{50}} \qquad (1.1)$$

Here, [*X*] represents the concentration of drug *X*. X_{50} represents the concentration of drug *X* acting alone at where 50% of the effect occurs. Often these quantities are referred to as EC_{50} values.

This type of additivity was originally proposed to overcome the sham-drug experiment; two identical drugs predicting either synergism or antagonism "in combination." This can be proved algebraically. Assuming drugs *A* and *B* are the same drug, say *D*, then the EC_{50} values are the same: $D_{50}=A_{50}=B_{50}$. Under these conditions Equation 1.1 reduces to:

$$1 = \frac{[A]+[B]}{D_{50}} + \frac{[C]}{C_{50}}$$

The total amount of drug *D* is [*A*]+[*B*], so this reduces to the two-drug additive condition:

$$1 = \frac{[D]}{D_{50}} + \frac{[C]}{C_{50}}$$

This sort of sham-drug outcome must also hold when there is a three-agent intraction.

1.2.2 Deriving the three agent model

Overall three drug base interaction

When deriving the three drug model, the obvious place to start is adding the corresponding two drug models:

$$1 = \frac{1}{\left(\frac{E-E_0}{E_{max}(\theta_{p,A},\theta_{p,B})-E_0}\right)^{1/\gamma(\theta_{p,A},\theta_{p,B})}} \left[\begin{array}{l} \frac{[A]}{A_{50}} + \frac{[B]}{B_{50}} + \frac{[C]}{C_{50}} \\ \quad +\alpha_{AB} f_{AB,\alpha} \sqrt{\frac{[A][B]}{A_{50}B_{50}}} \\ \quad +\alpha_{AC} f_{AC,\alpha} \sqrt{\frac{[A][C]}{A_{50}C_{50}}} \\ \quad +\alpha_{BC} f_{BC,\alpha} \sqrt{\frac{[B][C]}{B_{50}C_{50}}} \end{array} \right] \quad (1.2)$$

This alone fails the sham-drug experiment. Consider the case when two "drugs" are actually the same compound; [*A*] and [*B*] represent the sham combination of the overall concentration of the same drug, [*D*]. The drug being the same implies a few conditions: $D_{50} = A_{50} = B_{50}$, $\alpha_{DC} = \alpha_{AC} = \alpha_{BC}$, $f_{DC,\alpha} = f_{AC,\alpha} = f_{BC,\alpha}$, and α_{AB}=0 among others. Dealing with the interaction terms inside the parenthesis of Equation 1.2, and applying these conditions, gives:

$$\alpha_{AD} f_{AD,\alpha} \sqrt{\frac{[A][C]}{D_{50}C_{50}}} + \alpha_{AD} f_{AD,\alpha} \sqrt{\frac{[B][C]}{D_{50}C_{50}}} = \alpha_{AD} f_{AD,\alpha} \sqrt{\frac{[C]}{D_{50}C_{50}}} \left[\sqrt{[A]} + \sqrt{[B]}\right] \quad (1.3)$$

To reduce to the proper form Equation 1.3 should reduce to:

$$\alpha_{AD} f_{AD,\alpha} \sqrt{\frac{[C]}{D_{50}C_{50}}} \left[\sqrt{[A]+[B]}\right] = \alpha_{AD} f_{AD,\alpha} \sqrt{\frac{[C]([A]+[B])}{D_{50}C_{50}}}$$

$$= \alpha_{AD} f_{AD,\alpha} \sqrt{\frac{[D][C]}{D_{50}C_{50}}}$$

This requires famous triangle inequality to be an equality. Rather, it remains as:

$$\sqrt{[A]} + \sqrt{[B]} \geq \sqrt{[A] + [B]}$$

The triangle inequality is only equal when [*A*] and [*B*] are zero. When [*A*] and [*B*] are the same drug, Equation 1.3 overcomes the sham-combination when multiplied by:

$$\frac{\sqrt{[A] + [B]}}{\sqrt{[A]} + \sqrt{B}}$$

All three possible sham combinations need to be multiplied by a slightly different quantity. Depending on the sham drug combination, the possible quantities to multiply by are:

$$v_{AB} = \frac{\sqrt{[A] + [B]}}{\sqrt{[A]} + \sqrt{[B]}} \quad (1.4)$$

$$v_{AC} = \frac{\sqrt{[A] + [C]}}{\sqrt{[A]} + \sqrt{[C]}} \quad (1.5)$$

$$v_{BC} = \frac{\sqrt{[B] + [C]}}{\sqrt{[B]} + \sqrt{[C]}} \quad (1.6)$$

These need to be multiplied at the appropriate time. By assessing whether the combination is a sham, this can eventually be accomplished. When two drugs are actually the same (say *X* and *Y*), three general conditions apply. First, the Hill constants are equal: $X_{50} = Y_{50}$, $\gamma_X = \gamma_Y$ and $E_{\max,X} = E_{\max,Y}$. Second, the interaction between the sham drug and the other drug (say *Z*) are equal: $\alpha_{XZ} f_{XZ,\alpha} = \alpha_{YZ} f_{YZ,\alpha}$, $\beta_{XZ} f_{XZ,\beta} = \beta_{YZ} f_{YZ,\beta}$, and $\zeta_{XZ} f_{XZ,\zeta} = \zeta_{YZ} f_{YZ,\zeta}$. Last the interaction between the two sham drugs is nonexistent as well as the interaction between the three drugs, or $\alpha_{XY} = \beta_{XY} = \zeta_{XY} = \alpha_{XYZ} = \beta_{XYZ} = \zeta_{XYZ} = 0$. With this in mind, a set of functions that are zero when two drugs are a sham combination are given by:

$$\begin{aligned} s_{AC} = {} & \alpha_{AC}^2 + \beta_{AC}^2 + \zeta_{AC}^2 + \alpha_{ABC}^2 + \beta_{ABC}^2 + \zeta_{ABC}^2 \\ & + (A_{50} - C_{50})^2 + (\gamma_A - \gamma_C)^2 + (E_{max,A} - E_{max,C})^2 \\ & + (\alpha_{AB} f_{AB,\alpha} - \alpha_{BC} f_{BC,\alpha})^2 + (\beta_{AB} f_{AB,\beta} - \beta_{BC} f_{BC,\beta})^2 \\ & + (\zeta_{AB} f_{AB,\zeta} - \zeta_{BC} f_{BC,\zeta})^2 \end{aligned} \quad (1.7)$$

$$s_{AB} = \alpha_{AB}^2 + \beta_{AB}^2 + \zeta_{AB}^2 + \alpha_{ABC}^2 + \beta_{ABC}^2 + \zeta_{ABC}^2 + (A_{50} - B_{50})^2 + (\gamma_A - \gamma_B)^2 + (E_{max,A} - E_{max,B})^2 + (\alpha_{AC} f_{AC,\alpha} - \alpha_{BC} f_{BC,\alpha})^2 + (\beta_{AC} f_{AC,\beta} - \beta_{BC} f_{BC,\beta})^2 + (\zeta_{AC} f_{AC,\zeta} - \zeta_{BC} f_{BC,\zeta})^2 \quad (1.8)$$

$$s_{BC} = \alpha_{BC}^2 + \beta_{BC}^2 + \zeta_{BC}^2 + \alpha_{ABC}^2 + \beta_{ABC}^2 + \zeta_{ABC}^2 + (B_{50} - C_{50})^2 + (\gamma_B - \gamma_C)^2 + (E_{max,B} - E_{max,C})^2 + (\alpha_{AB} f_{AB,\alpha} - \alpha_{AC} f_{AC,\alpha})^2 + (\beta_{AB} f_{AB,\beta} - \beta_{AC} f_{AC,\beta})^2 + (\zeta_{AB} f_{AB,\zeta} - \zeta_{AC} f_{AC,\zeta})^2 \quad (1.9)$$

The s_{XY} functions are zero when *X* and *Y* are the same drug. The following multiplicative factors overcome the sham-drug combination concern:

$$\omega_{AB} = \frac{s_{BC}}{s_{AC} + s_{BC}} v_{AC} + \frac{s_{AC}}{s_{AC} + s_{BC}} v_{BC} \quad (1.10)$$

$$\omega_{AC} = \frac{s_{BC}}{s_{AB} + s_{BC}} v_{AB} + \frac{s_{AB}}{s_{AB} + s_{BC}} v_{BC} \quad (1.11)$$

$$\omega_{BC} = \frac{s_{AC}}{s_{AB} + s_{AC}} v_{AB} + \frac{s_{AB}}{s_{AB} + s_{AC}} v_{AC} \quad (1.12)$$

These are applied to Equation 1.2:

$$1 = \frac{1}{\left(\frac{E - E_0}{E_{max}(\theta_{p,A}, \theta_{p,B}) - E_0}\right)^{1/\gamma(\theta_{p,A}, \theta_{p,B})}} \left[\begin{array}{l} \frac{[A]}{A_{50}} + \frac{[B]}{B_{50}} + \frac{[C]}{C_{50}} \\ + \alpha_{AB} f_{AB,\alpha} \omega_{AB} \sqrt{\frac{[A][B]}{A_{50} B_{50}}} \\ + \alpha_{AC} f_{AC,\alpha} \omega_{AC} \sqrt{\frac{[A][C]}{A_{50} C_{50}}} \\ + \alpha_{BC} f_{BC,\alpha} \omega_{BC} \sqrt{\frac{[B][C]}{B_{50} C_{50}}} \end{array} \right] \quad (1.13)$$

This overcomes the sham combination problem. Additionally, when one drug is absent, it becomes the suitable two-agent interaction.

E_{max} and γ three drug interaction base

E_{max} and γ interactions are defined in a different manner. The first obvious step in determining

the three-agent interaction base is to add the interaction terms:

$$(k_A\theta_{p,A} + k_B\theta_{p,B} + k_C\theta_{p,C})(1 + \kappa_{AB}f_{AB,\kappa} + \kappa_{AC}f_{AC,\kappa} + \kappa_{BC}f_{BC,\kappa}) \quad (1.14)$$

Here k_X represents the constant associated with drug X acting alone. This constant is related to either E_{max} or γ. Similarly κ_{XY} represents the constant of interaction for drugs X and Y. The $f_{XY,\kappa}$ represents the interaction function between X and Y for the constant related to either E_{max} or γ.

When a sham drug experiment is performed, the interaction defined by Equation 1.14 is weighted by two. An additional limitation of the classification comes when one drug is absent; the interaction does not represent the previous model of two drugs interacting together. To overcome this, the following fractions are defined and used:

$$\Omega_{AB} = \frac{s_{AB}\sqrt{\frac{[A][B]}{A_{50}B_{50}}}}{s_{AB}\sqrt{\frac{[A][B]}{A_{50}B_{50}}} + s_{AC}\sqrt{\frac{[A][C]}{A_{50}C_{50}}} + s_{BC}\sqrt{\frac{[B][C]}{B_{50}C_{50}}}} \quad (1.15)$$

$$\Omega_{AC} = \frac{s_{AC}\sqrt{\frac{[A][C]}{A_{50}C_{50}}}}{s_{AB}\sqrt{\frac{[A][B]}{A_{50}B_{50}}} + s_{AC}\sqrt{\frac{[A][C]}{A_{50}C_{50}}} + s_{BC}\sqrt{\frac{[B][C]}{B_{50}C_{50}}}} \quad (1.16)$$

$$\Omega_{BC} = \frac{s_{BC}\sqrt{\frac{[B][C]}{B_{50}C_{50}}}}{s_{AB}\sqrt{\frac{[A][B]}{A_{50}B_{50}}} + s_{AC}\sqrt{\frac{[A][C]}{A_{50}C_{50}}} + s_{BC}\sqrt{\frac{[B][C]}{B_{50}C_{50}}}} \quad (1.17)$$

The s_{xy} equations (Equations 1.7-1.9) overcomes the sham drug combination problem. The factors $\sqrt{\frac{[X][Y]}{X_{50}Y_{50}}}$ allows the same two-agent interaction when one drug is absent. These multiplicative factors are then applied to Equation 1.14:

$$(k_A\theta_{p,A} + k_B\theta_{p,B} + k_C\theta_{p,C})(1 + \kappa_{AB}f_{AB,\kappa}\Omega_{AB} + \kappa_{AC}f_{AC,\kappa}\Omega_{AC} + \kappa_{BC}f_{BC,\kappa}\Omega_{BC}) \quad (1.18)$$

In terms of the γ and E_{max} functions, this function becomes:

$$\begin{aligned}\gamma(\theta_{p,A},\theta_{p,B}) &= [\gamma_A\theta_{p,A}+\gamma_B\theta_{p,B}+\gamma_C(1-\theta_{p,A}-\theta_{p,B})]\times \\ &\quad (1+\beta_{AB}\Omega_{AB}f_{AB,\beta}+\beta_{AC}\Omega_{AC}f_{AC,\beta}+\beta_{BC}\Omega_{BC}f_{BC,\beta}) \\ E_{max}(\theta_{p,A},\theta_{p,B}) &= [E_{max,A}\theta_{p,A}+E_{max,B}\theta_{p,B}+E_{max,C}(1-\theta_{p,A}-\theta_{p,B})]\times \\ &\quad (1+\zeta_{AB}\Omega_{AB}f_{AB,\zeta}+\zeta_{AC}\Omega_{AC}f_{AC,\zeta}+\zeta_{BC}\Omega_{BC}f_{BC,\zeta})\end{aligned} \quad (1.19)$$

Two agent interaction functions

The two agent interaction functions are defined in the main text. However, there could be some ambiguity in whether the three-agent potency fractions are used, or the two-agent potency fraction should be used. The three-agent potency fractions can be written as:

$$\theta_{p,A}=\frac{[A]/A_{50}}{[A]/A_{50}+[B]/B_{50}+[C]/C_{50}} \quad (1.20)$$

$$\theta_{p,A}=\frac{[A]/A_{50}}{[A]/A_{50}+[B]/B_{50}+[C]/C_{50}} \quad (1.21)$$

$$\theta_{p,A}=\frac{[A]/A_{50}}{[A]/A_{50}+[B]/B_{50}+[C]/C_{50}} \quad (1.22)$$

The two-agent interaction functions are defined as:

$$f_{XY}=f_{XY}(m_{XY},w_{XY},\theta_{p,X},\theta_{p,Y})=\tau(m_{XY},w_{XY},\theta_{p,X})\cdot\tau(1-m_{XY},w_{XY},\theta_{p,Y})$$

(1.23)

The τ function in Equation 1.23 is defined by:

$$\tau(m,w,\theta_p)=\left(\frac{\theta_p}{m}\right)^w\exp\left[-w\left(\frac{\theta_p-m}{m}\right)\right] \quad (1.24)$$

The three-agent potency fractions are used because the interaction function decreases upon addition non-modeled agent. For example, the amount of interaction between *A* and *B* is decreased when $\theta_{p,C}$ increases, as shown in Figure 1.1.

Three agent interaction function

Using the τ function defined by Equation 1.20 with two asymmetry parameters, a function for f_{ABC} can be given:

$$f_{ABC} = \tau\left(m_{A,ABC}, w_{ABC}, \frac{[A]/A_{50}}{[A]/A_{50}+[B]/B_{50}}\right) \times \tau\left(m_{B,ABC}, w_{ABC}, \frac{[B]/B_{50}}{[B]/B_{50}+[C]/C_{50}}\right) \times \tau\left(1-m_{C,ABC}, w_{ABC}, \frac{[C]/C_{50}}{[A]/A_{50}+[C]/C_{50}}\right) \quad (1.25)$$

In the three-agent interaction model, the maximum interaction locations should coincide. If the two drug interaction functions are held constant, as shown in Figure 1.2, the two lines intersect and the third can be determined. If the three drug interaction fractions are fixed, as shown in Figure 1.3, the only intersect in specialized circumstances. For this reason, Equation 1.21 uses the two drug fractions over the three drug fractions.

The third maximum interaction point can be determined from the other two. To allow a geometrical interpretation of this situation, an equilateral triangle, with axes of the three maximum interaction points is used. Each edge of the triangle represents the location of maximum interaction, which ranges from 0 to 1. To allow asymmetry, each triangle point is the start of one scale, and the end of another. With this triangle in place, any point on the axis will define a line of maximum interaction from that point to the opposite vertex. With two axis points, the corresponding two lines will intersect. The line from the unused triangle vertex to the intersection of the two lines will give the location of the third maximum interaction parameter, $m_{C,ABC}$. This is shown graphically is Figure 1.3.

To solve this problem, the corresponding triangle was drawn with lines on a Cartesian *x*-*y* plane. The *x*-axis represents the value of the $m_{C,ABC}$ coordinate. The lines for the other coordinates are given by:

$$y_{A,ABC} = \tan\left(\frac{\pi}{3}\right) \cdot x$$
$$y_{B,ABC} = \tan\left(\frac{\pi}{3}\right) - \tan\left(\frac{\pi}{3}\right) \cdot x$$

The line from $m_{A,ABC}$ to the tip of the triangle opposite the coordinate axis at (1,0) is given by:

$$y = \frac{m_{A,ABC}\sqrt{3}(x-1)}{m_{A,ABC}-2} \quad (1.26)$$

The lines from $m_{B,ABC}$ to the tip of the triangle opposite the coordinate axis at (0,0) is given by:

$$y = \frac{x\sqrt{3}(1-m_{B,ABC})}{1+m_{B,ABC}} \quad (1.27)$$

The Cartesian coordinate for the tip of the triangle opposite the *x*-axis is given by $(\frac{1}{2}, \frac{\sqrt{3}}{2})$. The line that passes through this vertex and the intersection of Equations 1.26 and 1.27, is given by:

$$y = \sqrt{3}\frac{m_{A,ABC}m_{B,ABC} + xm_{A,ABC} - 2xm_{A,ABC}m_{B,ABC} - x}{m_{A,ABC} + m_{B,ABC} - 1}$$

Solving this equation for x when $y = 0$ gives the $m_{C,ABC}$ value, that is:

$$m_{C,ABC} = \frac{m_{A,ABC}m_{B,ABC}}{2m_{A,ABC}m_{B,ABC} - m_{A,ABC} - m_{B,ABC} + 1} \quad (1.28)$$

Finalizing the three drug interaction model

The final three-agent model is obtained adding the triple interaction to Equation 1.13, giving:

$$1 = \frac{1}{\left(\frac{E-E_0}{E_{max}(\theta_{p,A},\theta_{p,B})-E_0}\right)^{1/\gamma(\theta_{p,A},\theta_{p,B})}} \left[\begin{array}{l} \frac{[A]}{A_{50}} + \frac{[B]}{B_{50}} + \frac{[C]}{C_{50}} \\ \quad +\alpha_{AB}f_{AB,\alpha}\omega_{AB}\sqrt{\frac{[A][B]}{A_{50}B_{50}}} \\ \quad +\alpha_{AC}f_{AC,\alpha}\omega_{AC}\sqrt{\frac{[A][C]}{A_{50}C_{50}}} \\ \quad +\alpha_{BC}f_{BC,\alpha}\omega_{BC}\sqrt{\frac{[B][C]}{B_{50}C_{50}}} \\ \quad +\alpha_{ABC}f_{ABC,\alpha}\sqrt[3]{\frac{[A][B][C]}{A_{50}B_{50}C_{50}}} \end{array} \right] \quad (1.29)$$

This is performed with the γ and E_{max} functions as well:

$$\gamma(\theta_{P,A},\theta_{p,B}) = (\gamma_A\theta_{p,A} + \gamma_B\theta_{p,B} + \gamma_C\theta_{p,C}) \begin{bmatrix} 1 + \beta_{AB}f_{AB,\beta}\Omega_{AB} \\ +\beta_{AC}f_{AC,\beta}\Omega_{AC} \\ +\beta_{BC}f_{BC,\beta}\Omega_{BC} \\ +\beta_{ABC}f_{ABC,\beta} \end{bmatrix}$$

$$E_{max}(\theta_{P,A},\theta_{p,B}) = (E_{max,A}\theta_{p,A} + E_{max,B}\theta_{p,B} + E_{max,C}\theta_{p,C}) \begin{bmatrix} 1 + \zeta_{AB}f_{AB,\zeta}\Omega_{AB} \\ +\zeta_{AC}f_{AC,\zeta}\Omega_{AC} \\ +\zeta_{BC}f_{BC,\zeta}\Omega_{BC} \\ +\zeta_{ABC}f_{ABC,\zeta} \end{bmatrix} \quad (1.30)$$

The two drug interaction models $f_{XY,\alpha}$, $f_{XY,\beta}$, and $f_{XY,\zeta}$ are defined by Equation 1.23. The symmetry and curve shape are not explicitly stated in Equations 1.29-1.30. Notationally, these constants are defined by $w_{XY,\alpha}$ and $m_{XY,\alpha}$ for $f_{XY,\alpha}$; $w_{XY,\beta}$ and $m_{XY,\beta}$ for $f_{XY,\beta}$; finally, $w_{XY,\zeta}$ and $m_{XY,\zeta}$ for $f_{XY,\zeta}$. These constants are applied for every possible two drug combination: *AB*, *AC*, and *BC*. With the inclusion of the type/intensity parameters, there are 27 parameters for the two drug interactions. These are often not necessary in describing the interactions. For this reason, the *m* values are set to be symmetric (*m* = 0.5). Additionally a moderate curve shape is assumed, ω = 1. Unless the data proves otherwise, the different types/intensities of interactions are assumed to be non-existent. $\alpha_{XY} = \beta_{XY} = \zeta_{XY} = 0$.

The three drug interaction functions are defined by Equation 1.25. Each interaction has two symmetry parameters $m_{A,ABC,\alpha}$ and $m_{B,ABC,\alpha}$ for $f_{ABC,\alpha}$; $m_{A,ABC,\beta}$ and $m_{B,ABC,\beta}$ for $f_{ABC,\beta}$; finally, $m_{A,ABC,\zeta}$ and $m_{B,ABC,\zeta}$ for $f_{ABC,\zeta}$. The three-parameter interaction also has only one curve-shape parameter per function, $w_{ABC,\alpha}$ for $f_{ABC,\alpha}$; $w_{ABC,\beta}$ for $f_{ABC,\beta}$; finally, $w_{ABC,\zeta}$ for $f_{ABC,\zeta}$. As with the two drug case, we will assume symmetry (all *m* values =0.5), and moderate curve shape (all ω values =1), unless the data has evidence for the parameter.

1.3 Results

This three-agent model has many desirable attributes, they are:

1. If [*A*], [*B*], or [*C*] are zero, then the model reduces to the previous model for the remaining two drugs.
2. If only one of the drugs are present, [*A*], [*B*], and [*C*], the model reduces to the standard Hill form.
3. If there are no interactions between the three drugs, the resulting interaction should be a plane between the three constants that define drugs acting alone. Therefore, for γ, the no-interaction standard should be the plane between γ_A, γ_B, and γ_C. Note that this applies for the γ and E_{max} functions directly from the multiplicative line. Whenever there are no interactions, this becomes the plane between the three constants. The interaction is not as obvious, but by the convergence to Minto's additivity conditions, it implies a plane between the three E_{50} values, like a U=1 constant for the Minto model. [3]
4. The sham experiment where drugs *B* and *C* are actually the same drug, should show the same interaction between *A* and *B* as between *A* and *C*. This can be proved algebraically, showing the model reduces to the appropriate two-agent model.
5. When two drugs are absent, the model converges to the standard Hill-equation.
6. This equation is symmetrical when values of *m* are excluded by setting them equal to 0.5. When *m* is not excluded, the equation is asymmetric, which is a benefit in describing certain curves.

1.4 Discussion

1.4.1 Parameter meanings

Parameters retain the same sort of meaning as in the two-agent interaction case. For example,

a positive α_{ABC} parameter value represents an overall increase in synergy (Figure 1.4); zero value, no change (Figure 1.5); or negative value, increase in antagonism (Figure 1.6). However, each of these parameters also apply with drugs that have complex two-drug interactions. In the case of the α_{ABC}, for instance, an increase in synergy (Figure 1.7), no change in interaction (Figure 1.8), and a increase in antagonism (Figure 1.9) are observed. These properties can be observed by carefully looking at the isosurfaces or the contour-plot of the isosurfaces for the complex interactions (Figures 1.7-1.9), but the same properties are more easily observed in both the isosurfaces and the contour plots in the isosurfaces of simpler two-agent interactions (Figures 1.4-1.5). Therefore, in this discussion, in an attempt to simplify parametric visualization, we will use figures that show simple additive two-drug interactions.

The symmetry parameters represent the location of the two agent interactions. Figures 1.10-1.12 vary $m_{A,ABC}$ while keeping $m_{B,ABC}$ symmetric. Notice that when $m_{A,ABC}$ is asymmetric, the corresponding $m_{C,ABC}$ parameter is also asymmetric. Both $m_{A,ABC}$ and $m_{B,ABC}$ can also be asymmetric, as shown in Figure 1.13-Figure 1.14. With these two parameters various forms of three-agent interaction symmetry can be described. The exception is a three-agent interaction that has multiple types of interactions on the same effect-slice. With the large number of parameters, and relatively unstudied different types of interactions on the same effect-slice, this type of interaction was neglected in the derivation.

The last three-agent parameter affecting the three-parameter interaction is the ω_{ABC} parameter. Like it's two-agent counterpart it represents how fast the interaction changes from no-interaction to maximum interaction. Lower values represent almost immediate transitions from no interaction to maximum interaction. High values represent transition from no interaction to maximum interaction only around the maximum interaction value. This is illustrated in Figures 1.15-1.17.

These same parameter meanings cross over to the γ and E_{max} functions. Because of the similar meanings, and difficulty of representation of the fourth-dimensional functions, no

graphical representation of these parameters are given. The $w_{ABC,\beta}$ and $w_{abc,\zeta}$.

1.4.2 Parameter ranges

The two agent parameters retain both their meaning and their range. The three agent symmetry parameters, $m_{A,ABC,\alpha}$, $m_{B,ABC,\alpha}$, $m_{A,ABC,\beta}$, $m_{B,ABC,\beta}$, $m_{A,ABC,\zeta}$, and $m_{B,ABC,\zeta}$, can range from 0 to 1. The curve shape parameter $w_{ABC,\alpha}$ is greater or equal to zero. The curve shape parameter $w_{ABC,\beta}$ and $w_{ABC,\zeta}$ is only greater than zero. The type/intensity of interaction range cannot be solved in a closed form. The range of each value depends on the two-agent parameter values and the symmetry of the two-drug interaction as well as the three-drug symmetries. However, we can obtain the minimum values that are possible for each parameter. If we assume that there is no two-drug interaction, and that the maximum occurs at the point of symmetry we can derive a general relation for a minimum value for α_{ABC}. First, we note that:

$$\frac{[A]}{A_{50}} = \frac{m_{A,ABC,\alpha}}{1-m_{A,ABC,\alpha}}\frac{[B]}{B_{50}} \tag{1.31}$$

$$\frac{[C]}{C_{50}} = \frac{m_{B,ABC,\alpha}}{1-m_{B,ABC,\alpha}}\frac{[B]}{B_{50}} \tag{1.32}$$

These are the conditions that occur when the interaction is at the triple maximum interaction point. Applying this, along with the assumption of additive interactions, to the 50% effect point of the final form of the model, gives:

$$\begin{aligned} 1 &= \frac{m_{A,ABC,\alpha}}{1-m_{A,ABC,\alpha}}\frac{[B]}{B_{50}} + \frac{[B]}{B_{50}} + \frac{1-m_{B,ABC,\alpha}}{m_{B,ABC,\alpha}}\frac{[B]}{B_{50}} + \\ &\quad \alpha_{ABC}\sqrt[3]{\frac{m_{A,ABC,\alpha}(1-m_{B,ABC,\alpha})}{m_{B,ABC,\alpha}(1-m_{A,ABC,\alpha})}}\left(\frac{[B]}{B_{50}}\right)^3 \\ &= \frac{[B]}{B_{50}}\left(1 + \frac{m_{A,ABC,\alpha}}{1-m_{A,ABC,\alpha}} + \frac{1-m_{B,ABC,\alpha}}{m_{B,ABC,\alpha}} + \alpha_{ABC}\sqrt[3]{\frac{m_{A,ABC,\alpha}(1-m_{B,ABC,\alpha})}{m_{B,ABC,\alpha}(1-m_{A,ABC,\alpha})}}\right) \end{aligned} \tag{1.33}$$

For Equation 1.33 to be true, the terms inside the parenthesis must be positive. Hence the

lowest value that α_{ABC} can attain under these conditions is:

$$\alpha_{ABC} = -\frac{1+\frac{m_{A,ABC,\alpha}}{1-m_{A,ABC,\alpha}}+\frac{1-m_{B,ABC,\alpha}}{m_{B,ABC,\alpha}}}{\sqrt[3]{\frac{m_{A,ABC,\alpha}(1-m_{B,ABC,\alpha})}{m_{B,ABC,\alpha}(1-m_{A,ABC,\alpha})}}} \quad (1.31)$$

When this is symmetric, the minimum value that α_{ABC} can attain is -3. Positive two-drug interaction decrease this value to below -3. Negative two-drug interaction values increase this value to above -3. However, the positive upper bound of α_{ABC} is limitless. Still values approaching -3 are extremely antagonistic and hence values greater than -3 are often more reasonable.

The β and ζ parameters have a minimum value of -1 under the same conditions described above. For β this is a requirement, but for ζ this is only a requirement if you wish to maintain either a positive or negative effect (depending on the E_{max} value).

1.4.3 Model limitations

The first limitation of the model is the number of parameters that can be used. Still, these parameters are not all necessarily used. Rather these parameters are used to try to be complete and flexible in interaction modeling. Many cases these parameters are not going to be significant enough to include in the model building procedure. Therefore, the number of parameters allows flexible modeling of surfaces with just the number of interaction parameters needed through a step-up regression.

Second, all the three agent interaction parameters are relative to pseudo-additive surface. This psuedo-additive surface is the interaction surface described by Equation 1.13, or the interaction just assuming that the two-drug interactions are all that affect the interaction. Therefore the parameters do not tell of antagonism, synergism or additivity, in the Loewe or even Minto sense, but rather tells how the three drug affects the overall interaction.

Third, there is only one type of triple drug interaction possible. Therefore an antagonistic and synergistic interaction on the same triple-interaction surface is not possible. With triple drug interactions not being studied as much as two-drug interactions, this may or may not prove to be a problem. We think that with the number of parameters needed to have a more complex triple-drug interaction, the more complex interactions will not have enough data to completely characterize this interaction, and therefore could not be assessed.

In summary, this three drug interaction model allows asymmetric interactions with different curve shapes for both the three and two drug interactions. Additionally, the interaction parameters are constant from the two-drug interaction to the three-drug interaction.

References

1. Short TG, Plummer JL, Chui PT: Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. Br J Anaesth 1992; 69: 162-7
2. Gulick R: Combination therapy for patients with HIV-1infection: the use of dual nucleoside analoguse with protease inhibitors and other agents. AIDS Suppl 1998; 12: S17-22
3. Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL: Response surface model for anesthetic drug interactions. Anesthesiology 2000; 92: 1603-16

Figure 1.1: The effect of adding a third agent to the interaction function, *f*. Notice how the function dies down upon addition of the third agent. In this case *t* represents $\theta_{p,A}$ and *t*2 represents $\theta_{p,C}$

Figure 1.2: The lines on the 50% additive isosurface show the fixed two drug fractions of 0.25, 0.5, and 0.75.

Figure 1.3: Triangle showing how the $m_{C,ABC,\alpha}$ parameter is determined. When two locations of maximum interaction are chosen, the line that bisects the the other two chooses the third, as shown in this figure.

Figure 1.4: This shows the 50% isosurface for the three parameter synergistic interaction when α_{ABC}=2. All other constants are set to additivity α_{AB}=α_{AC}=α_{BC}=0, with EC_{50} values set equal to one, A_{50}=B_{50}=C_{50}=1.

Figure 1.5: This shows the 50% isosurface for the thee parameter synergistic interaction when α_{ABC}=0. All other constants are set to additivity α_{AB}=α_{AC}=α_{BC}=0, with EC_{50} values set equal to one, A_{50}=B_{50}=C_{50}=1.

Figure 1.6: This shows the 50% isosurface for the three parameter synergistic interaction when α_{ABC}=-0.9. All other constants are set to additivity $\alpha_{AB}=\alpha_{AC}=\alpha_{BC}=0$, with EC_{50} values set equal to one, $A_{50}=B_{50}=C_{50}=1$.

Figure 1.7: This shows the 50% isosurface for the three parameter increase in synergism when α_{ABC}=2, even with complex two-drug interactions. The EC_{50} values are set equal to one, $A_{50}=B_{50}=C_{50}=1$. Complex two-agent interactions are formed by $\alpha_{AB}=-\frac{1}{2}$, $m_{AB}=\frac{1}{2}$, w_{AB}=10, $\alpha_{AC}=-\frac{1}{2}$, $m_{AC}=\frac{1}{4}$, w_{AC}=1, α_{BC}=2, $m_{BC}=\frac{1}{10}$, and w_{BC}=1.

Figure 1.8: This shows the 50% isosurface for the three parameter interaction when α_{ABC}=0, even with complex two-drug interactions. The EC_{50} values are set equal to one, $A_{50}=B_{50}=C_{50}=1$. Complex two-agent interactions are formed by $\alpha_{AB}=-\frac{1}{2}$, $m_{AB}=\frac{1}{2}$, w_{AB}=10, $\alpha_{AC}=-\frac{1}{2}$, $m_{AC}=\frac{1}{4}$, w_{AC}=1, α_{BC}=2, $m_{BC}=\frac{1}{10}$, and w_{BC}=1.

Figure 1.9: This shows the 50% isosurface for the three parameter decrease in antagonism when α_{ABC}=-0.9, even with complex two-drug interactions. The EC_{50} values are set equal to one, $A_{50}=B_{50}=C_{50}=1$. Complex two-agent interactions are formed by $\alpha_{AB}=-\frac{1}{2}$, $m_{AB}=\frac{1}{2}$, w_{AB}=10, $\alpha_{AC}=-\frac{1}{2}$, $m_{AC}=\frac{1}{4}$, w_{AC}=1, α_{BC}=2, $m_{BC}=\frac{1}{10}$, and w_{BC}=1.

Figure 1.10: A description of the three agent symmetry parameters when

$$m_{A,ABC,\alpha} = \frac{1}{4}; m_{B,ABC,\alpha} = \frac{1}{2}$$

Figure 1.11: A description of the three agent symmetry parameters when

$$m_{A,ABC,\alpha} = m_{B,ABC,\alpha} = \frac{1}{2}$$

Figure 1.12: A description of the three agent symmetry parameters when

$$m_{A,ABC,\alpha} = \frac{3}{4}; m_{B,ABC,\alpha} = \frac{1}{2}$$

Figure 1.13: A description of the three agent symmetry parameters when

$$m_{A,ABC,\alpha} = m_{B,ABC,\alpha} = \frac{1}{4}$$

Figure 1.14: A description of the three agent symmetry parameters when

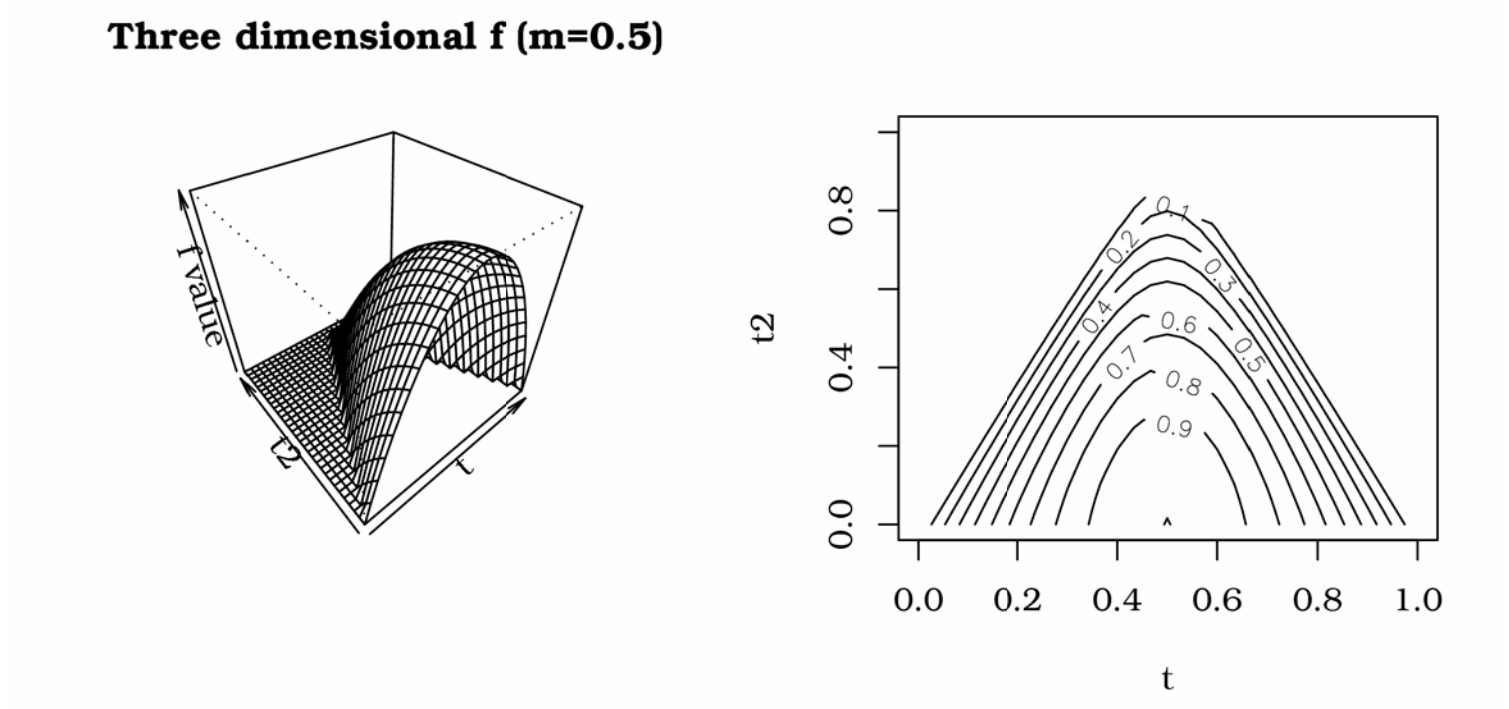
$$m_{A,ABC,\alpha} = \frac{1}{4}; m_{B,ABC,\alpha} = \frac{3}{4}$$

Figure 1.15: There is almost immediate interaction when $w_{ABC,\alpha} = 0$.

Figure 1.16: When $w_{ABC,\alpha} = 1$ the transition from no interaction to maximum interaction occurs slower than the $w_{ABC,\alpha} = 0$. The value of $w_{ABC,\alpha} = 1$ is assumed unless the data shows otherwise.

Figure 1.17: When the $w_{ABC,\alpha}$ value is large the interaction is basically only around the maximum interaction location. This is mostly true in this case when $w_{ABC,\alpha} = 5$.

Figure 1. 1


Three dimensional f (m=0.5)
f value
t2
t
t2
t
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0.4
0.6
0.8
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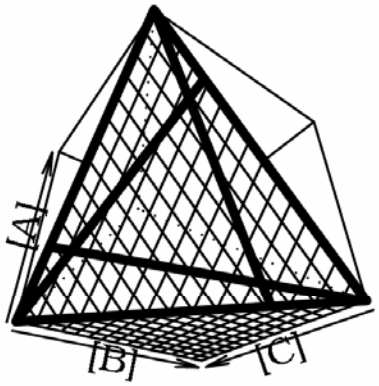
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9

Fixed double drug fractions of 0.25



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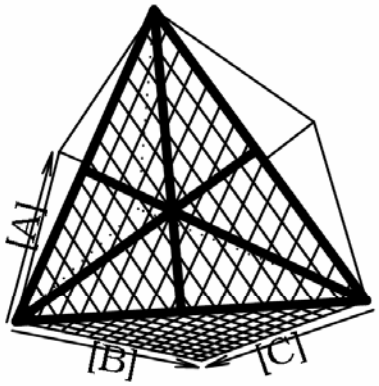
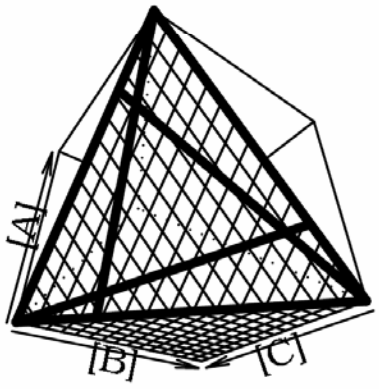


Fixed double drug fractions of 0.75



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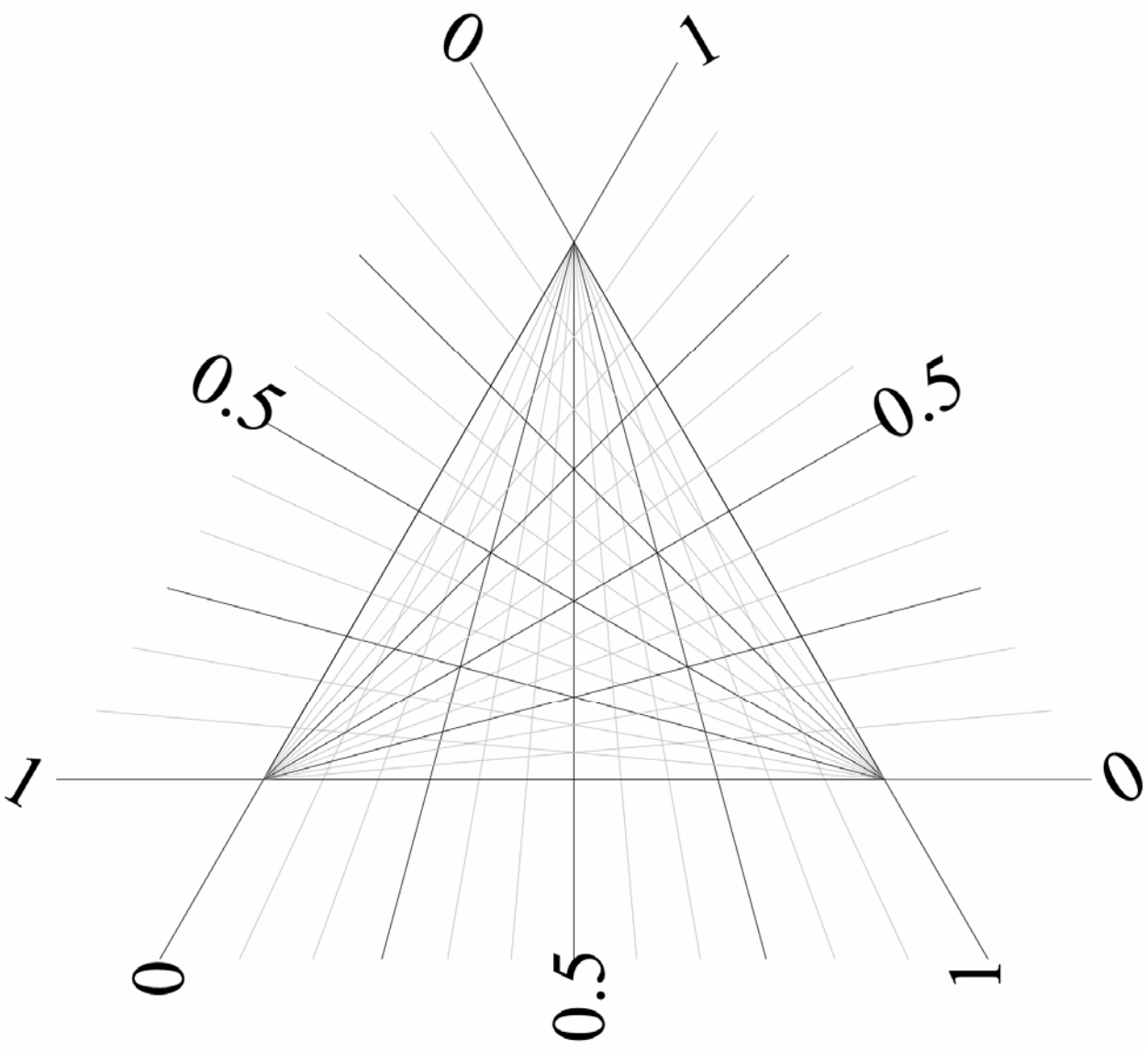

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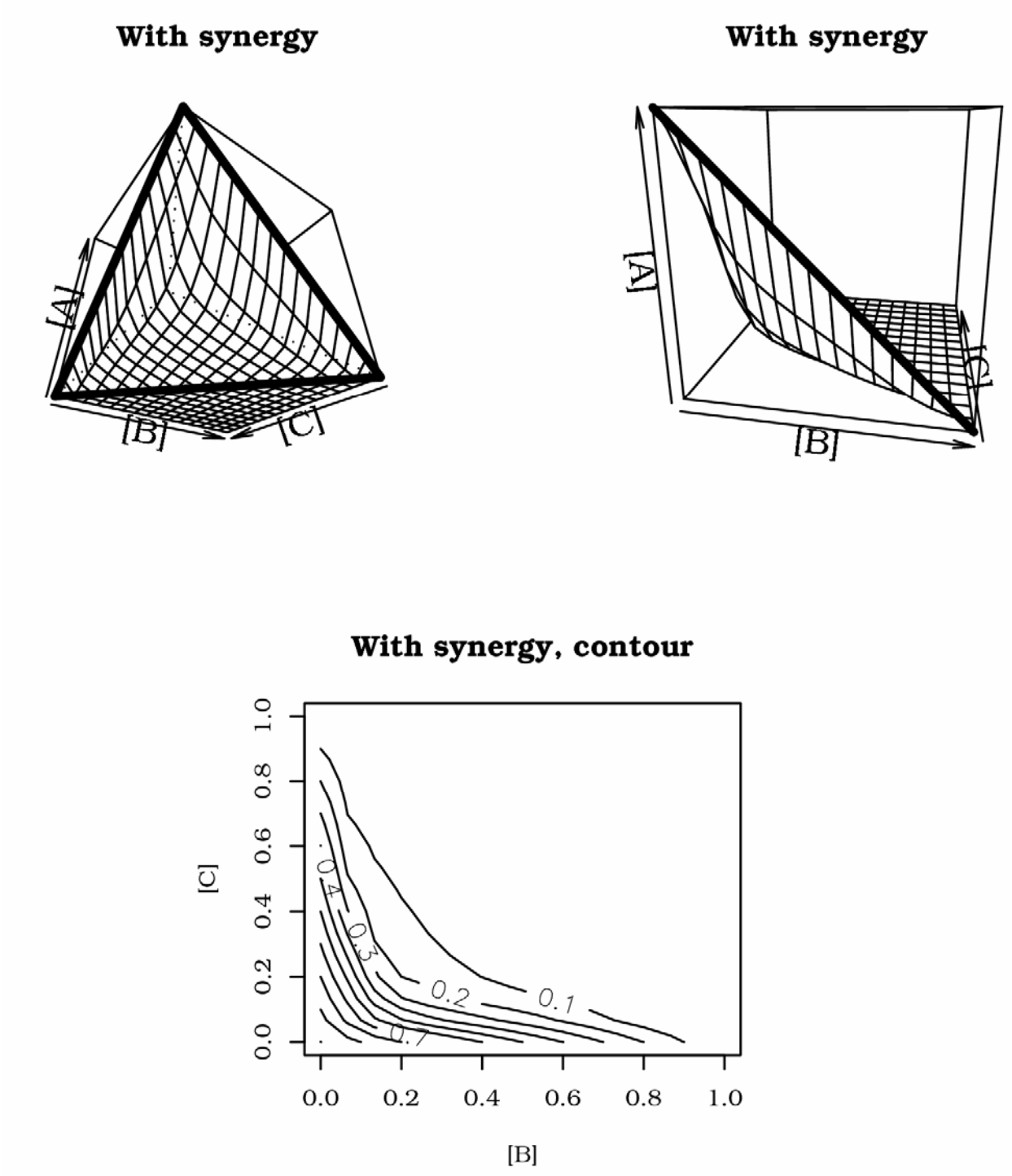
With synergy
With synergy
[A]
[B]
[C]
[A]
[B]
[C]
With synergy, contour
[C]
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0.2
0.4
0.6
0.8
1.0
0.4
0.3
0.2
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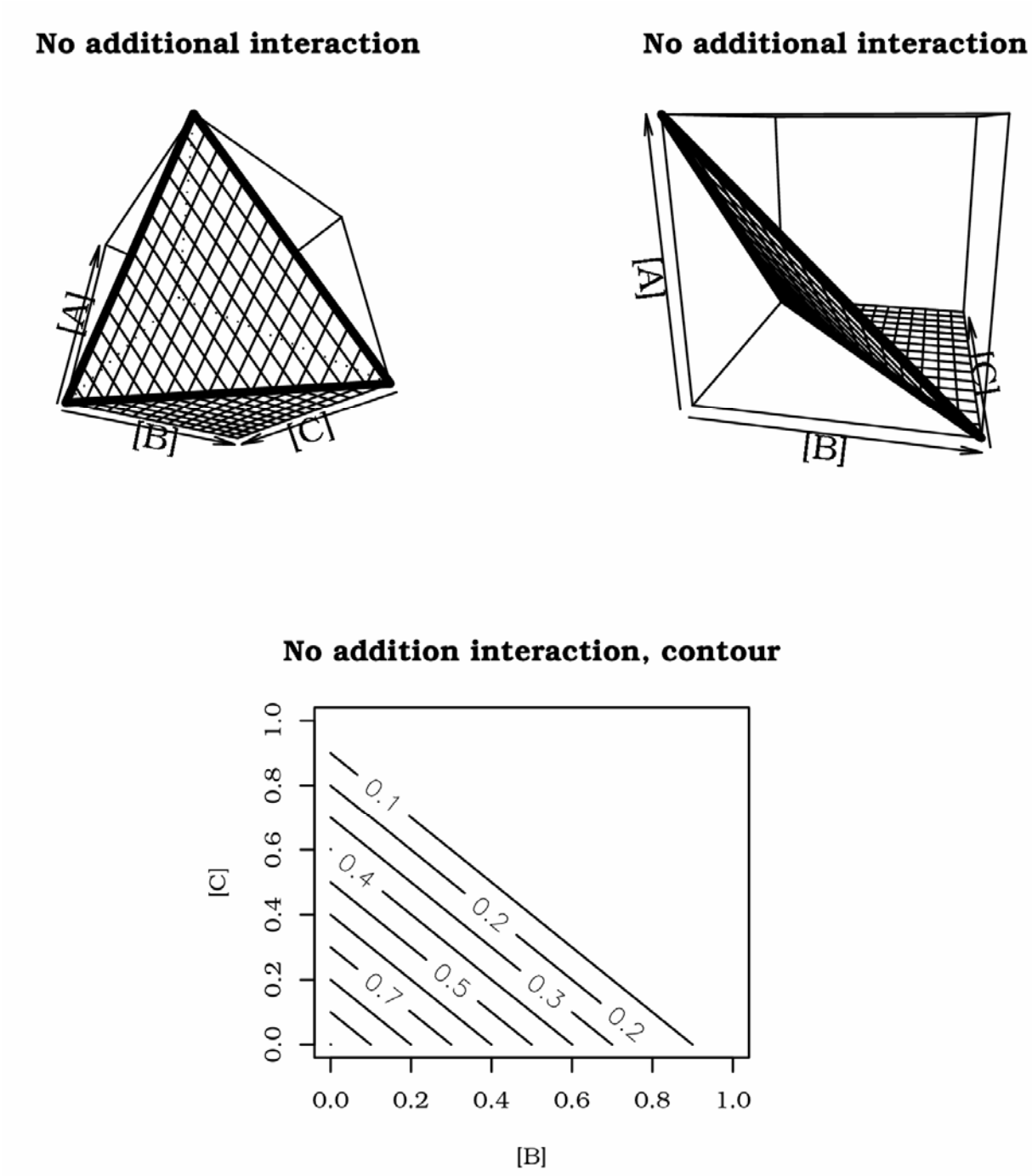
0.6
0.8
1.0
[B]

Figure 1. 4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No addition interaction, contour
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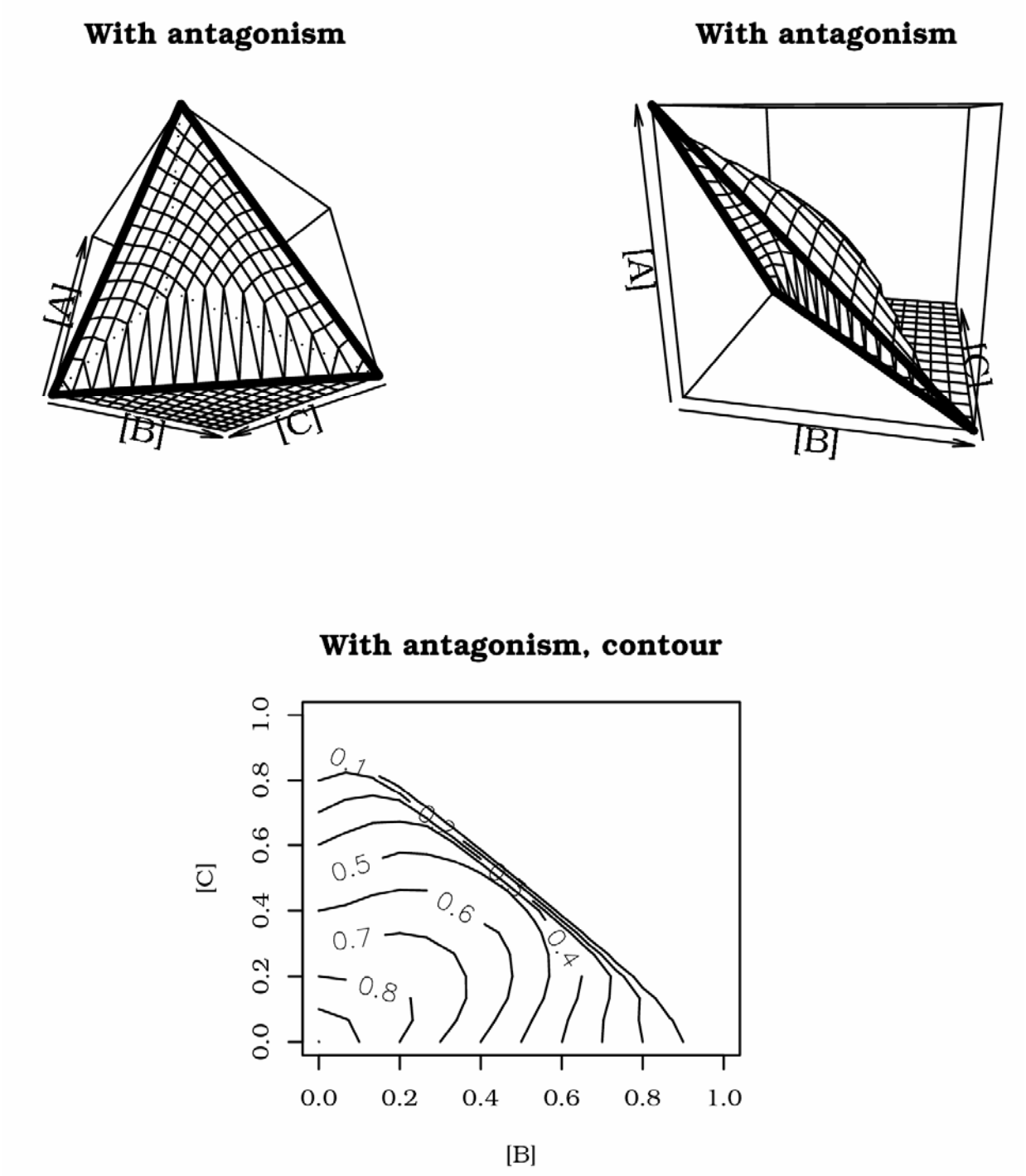
0.2
[B]

Figure 1. 5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With antagonism
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[B]
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With antagonism, contour
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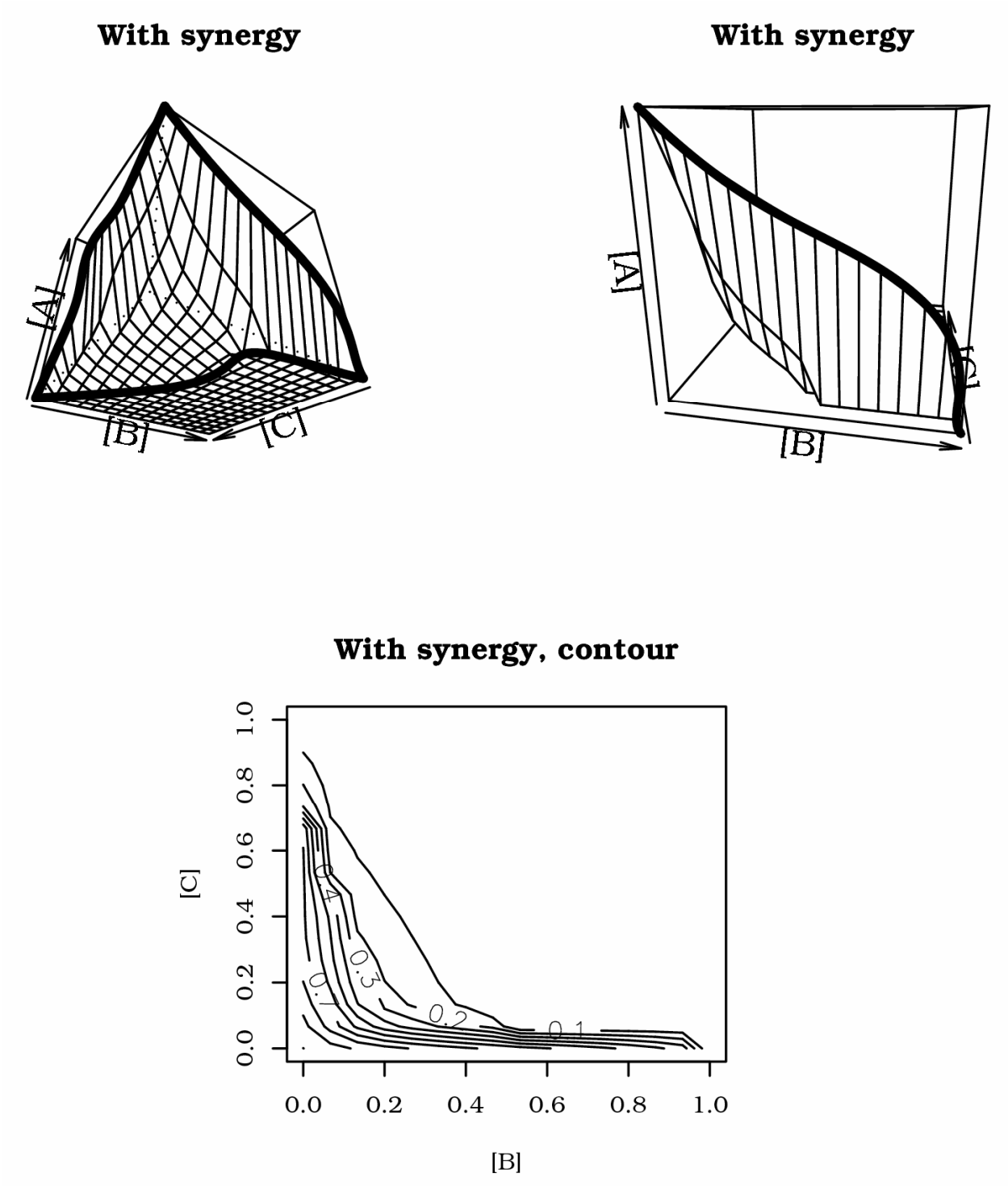
Figure 1. 6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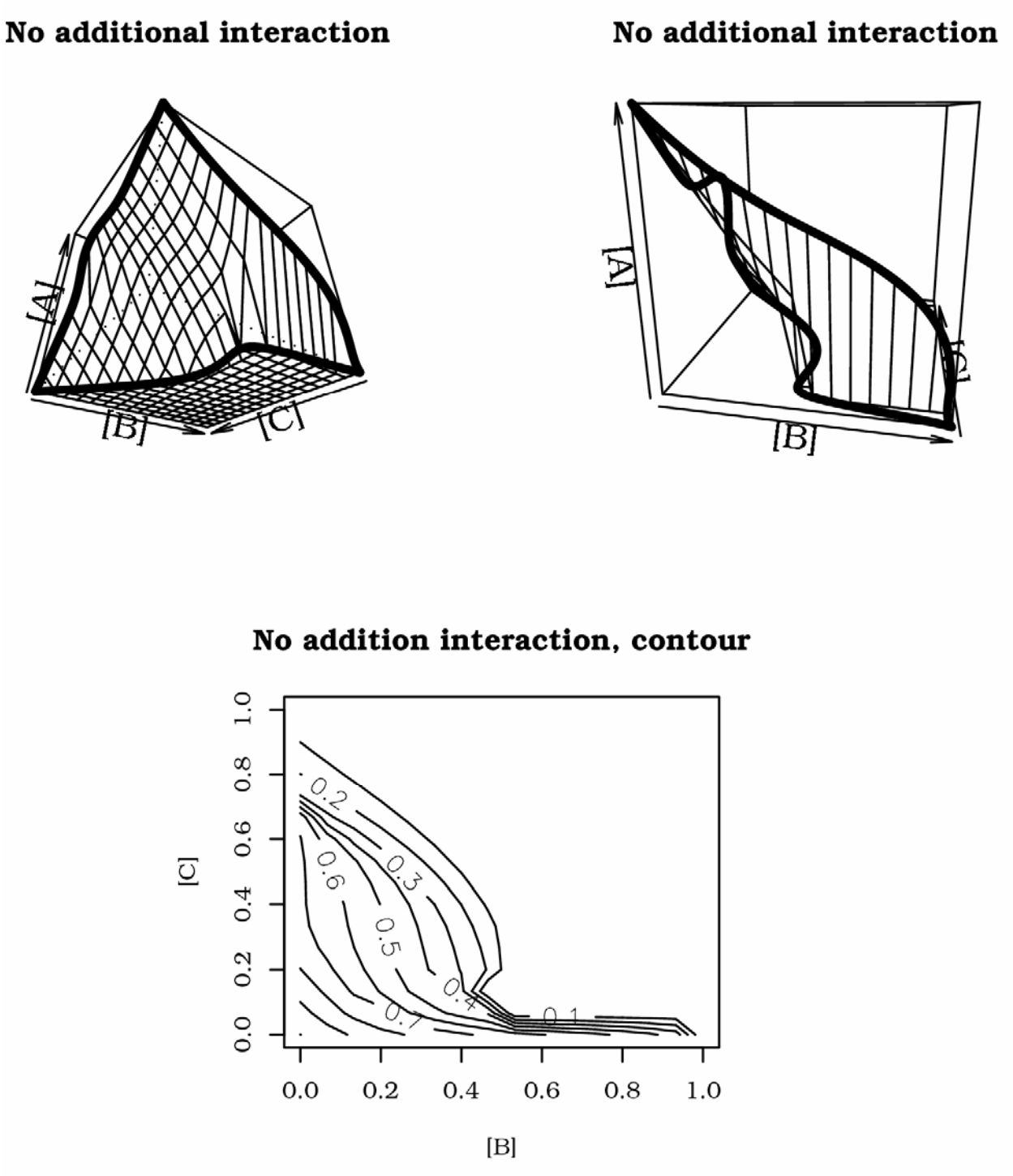
0.1
0.7

Figure 1. 7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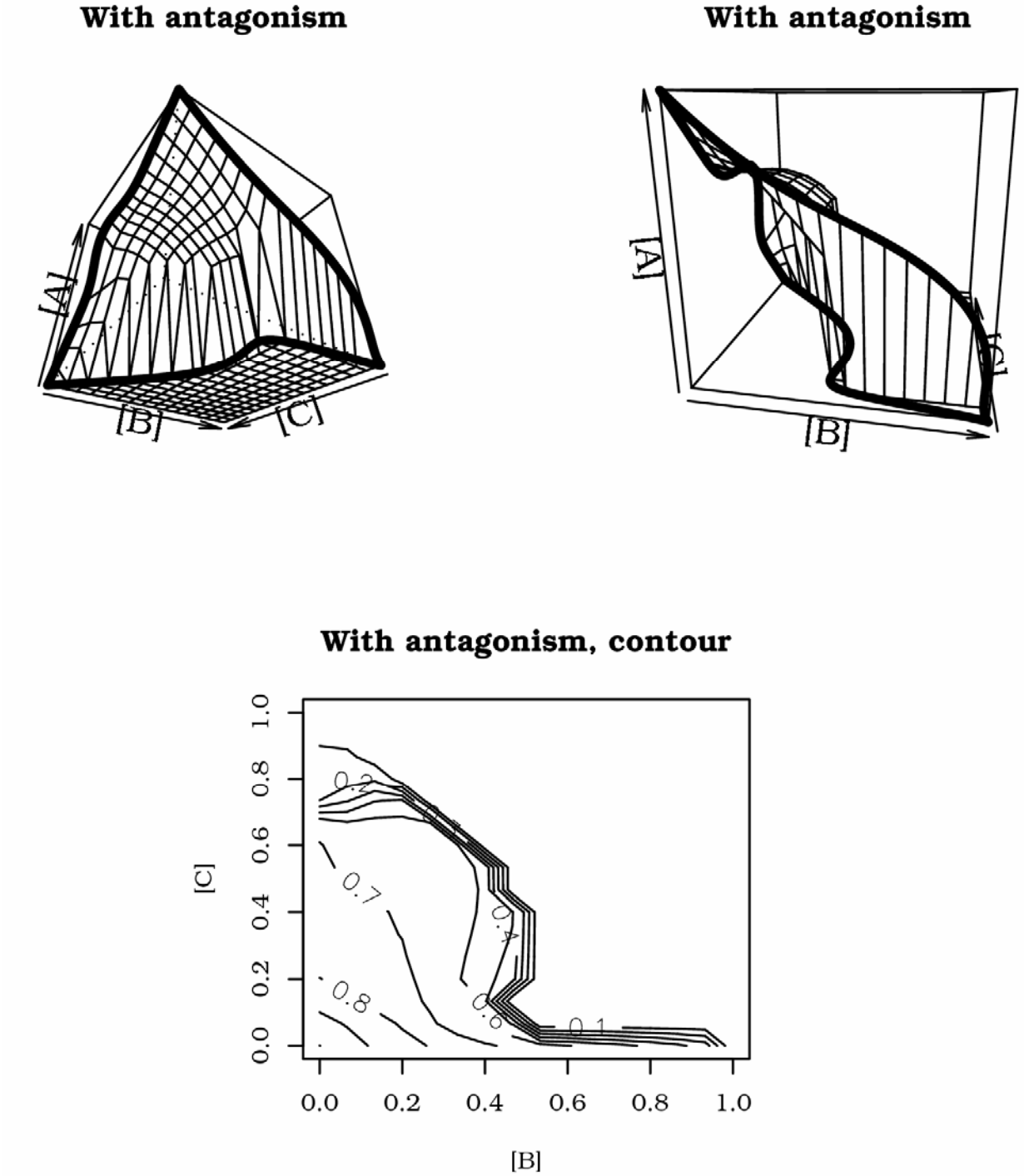
0.7
0.1
[B]

Figure 1. 8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With antagonism
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With antagonism, contour
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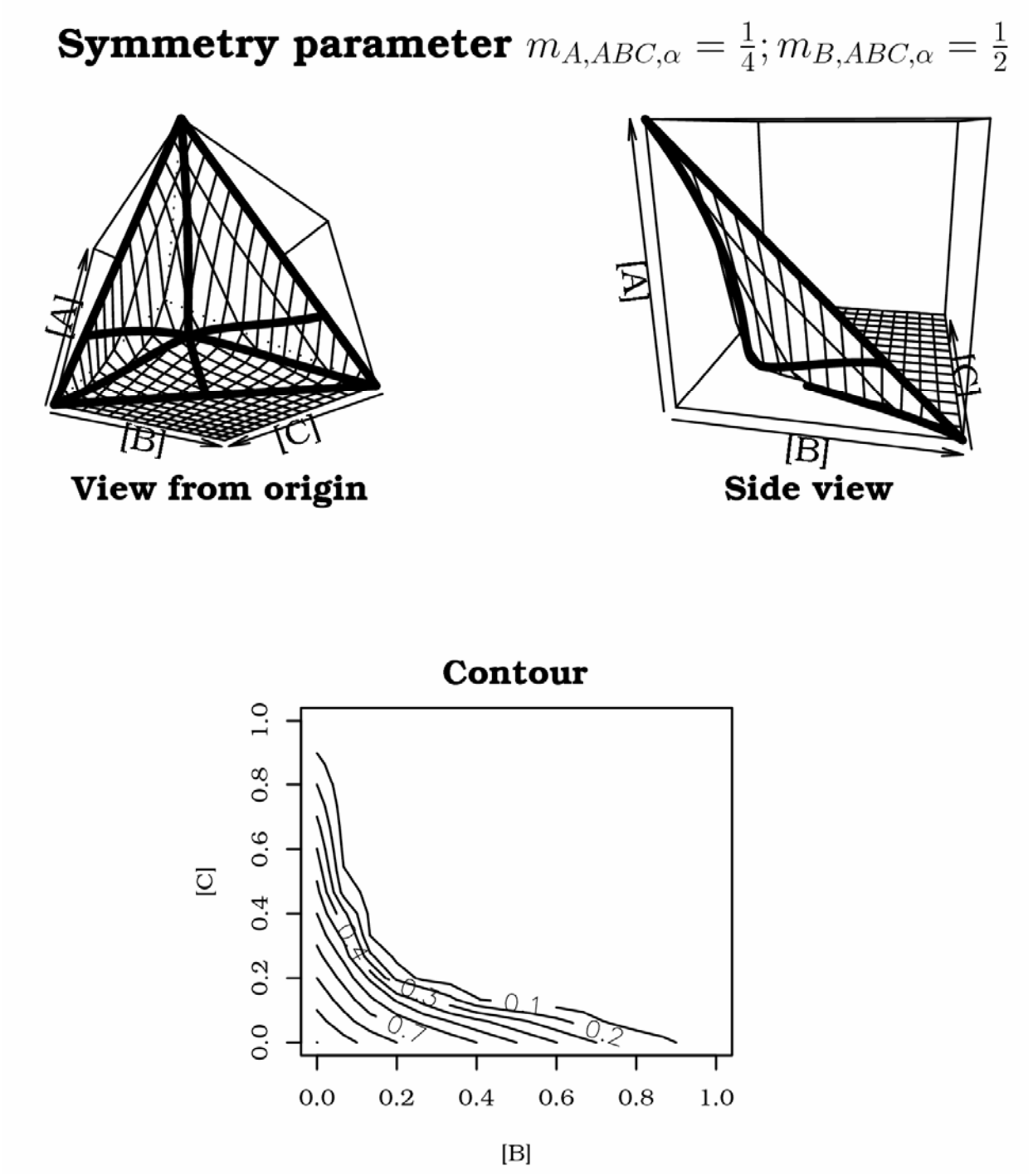
Figure 1. 9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Side view
Contour
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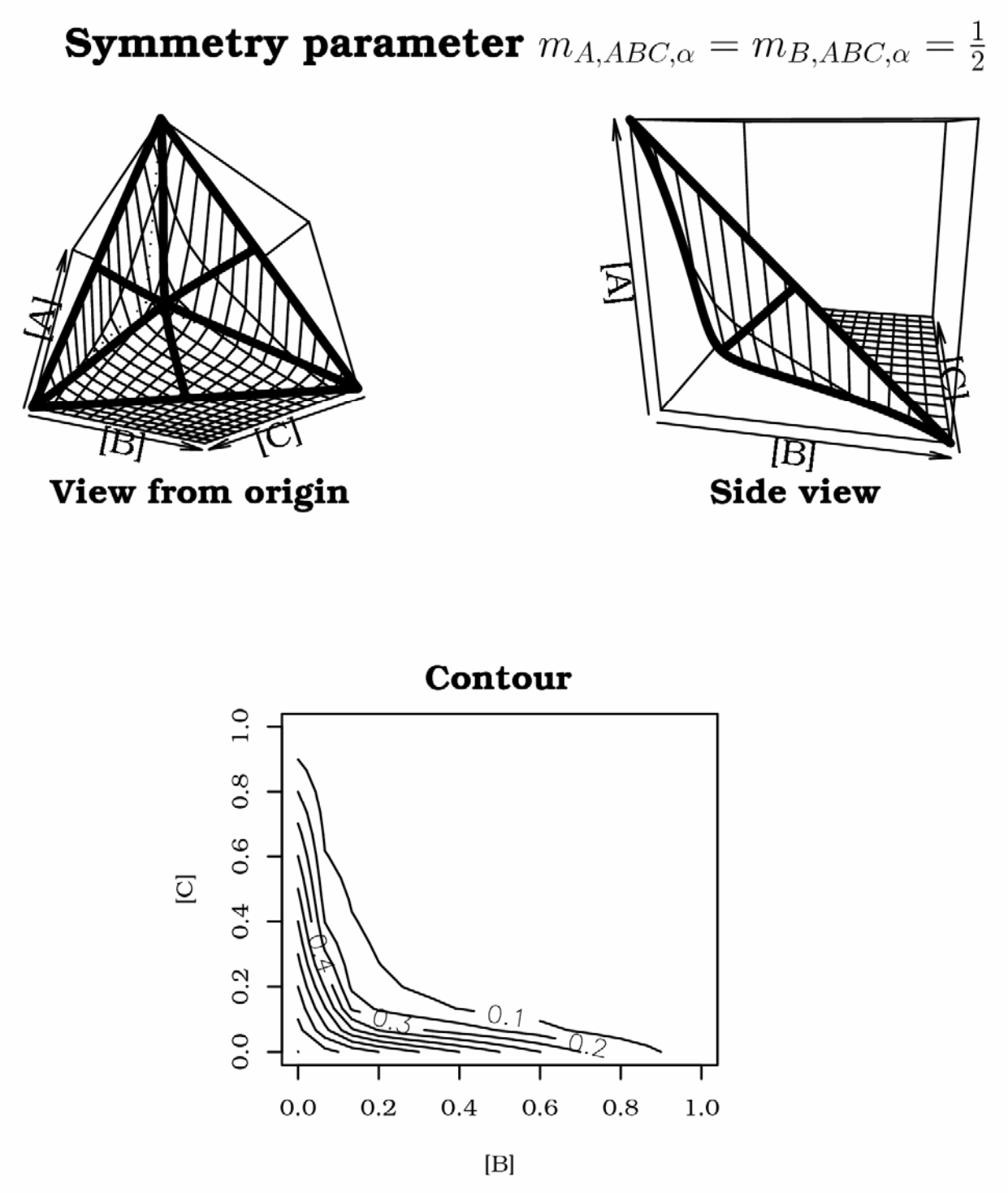
0.2
0.7

Figure 1. 10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Side view
Contour
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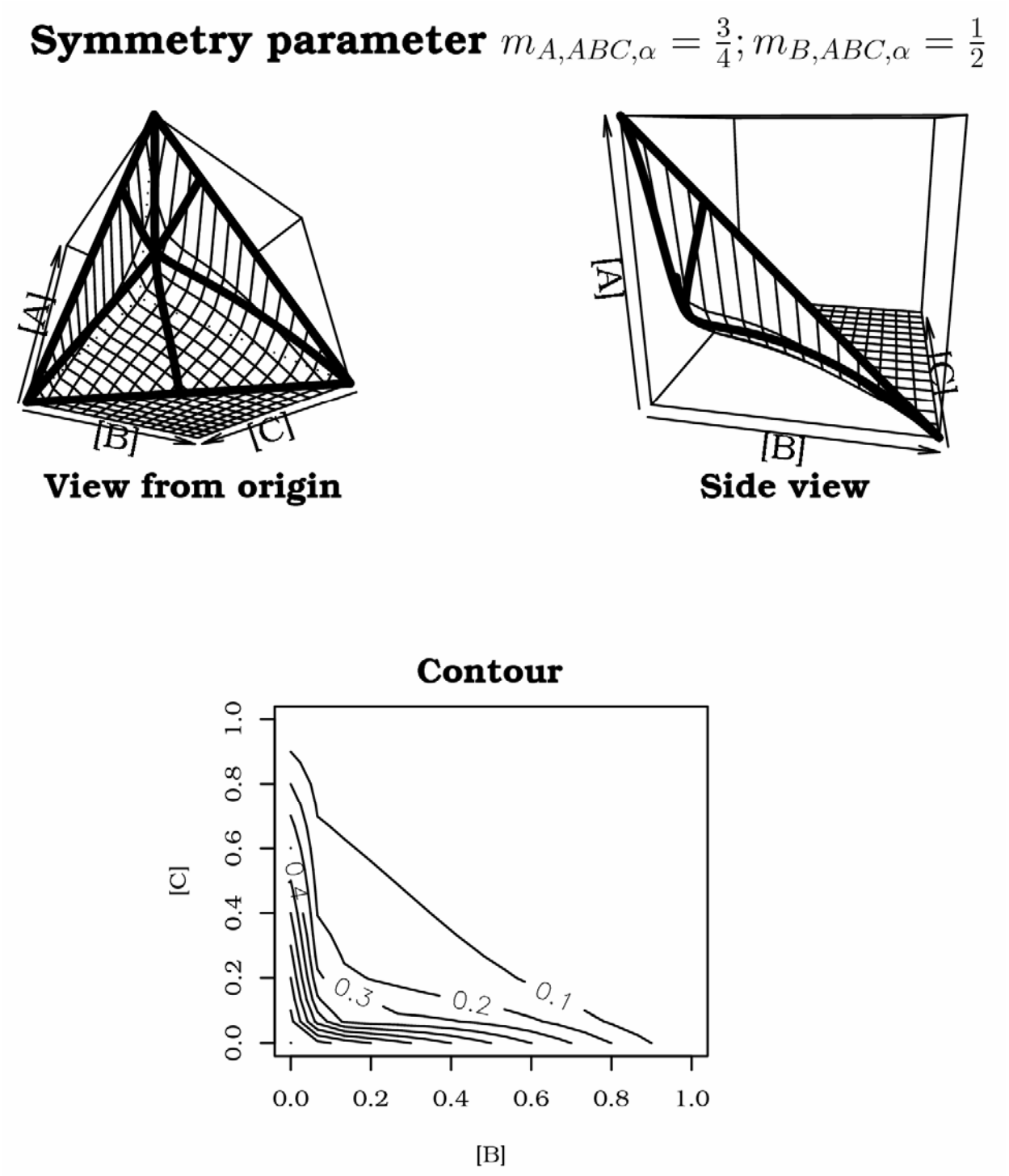
0.4
[B]

Figure 1. 11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Side view
Contour
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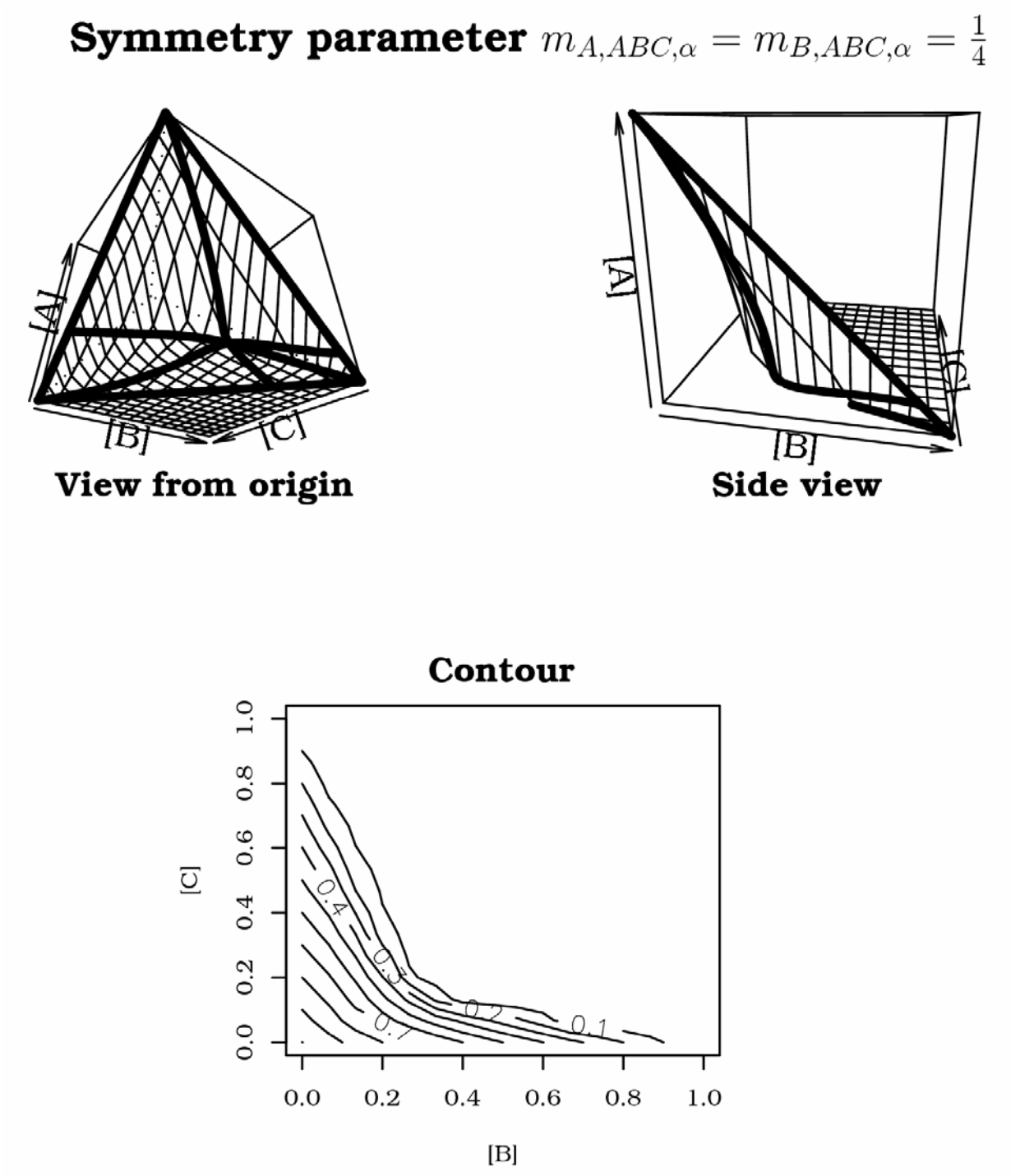
Figure 1. 12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Side view
Contour
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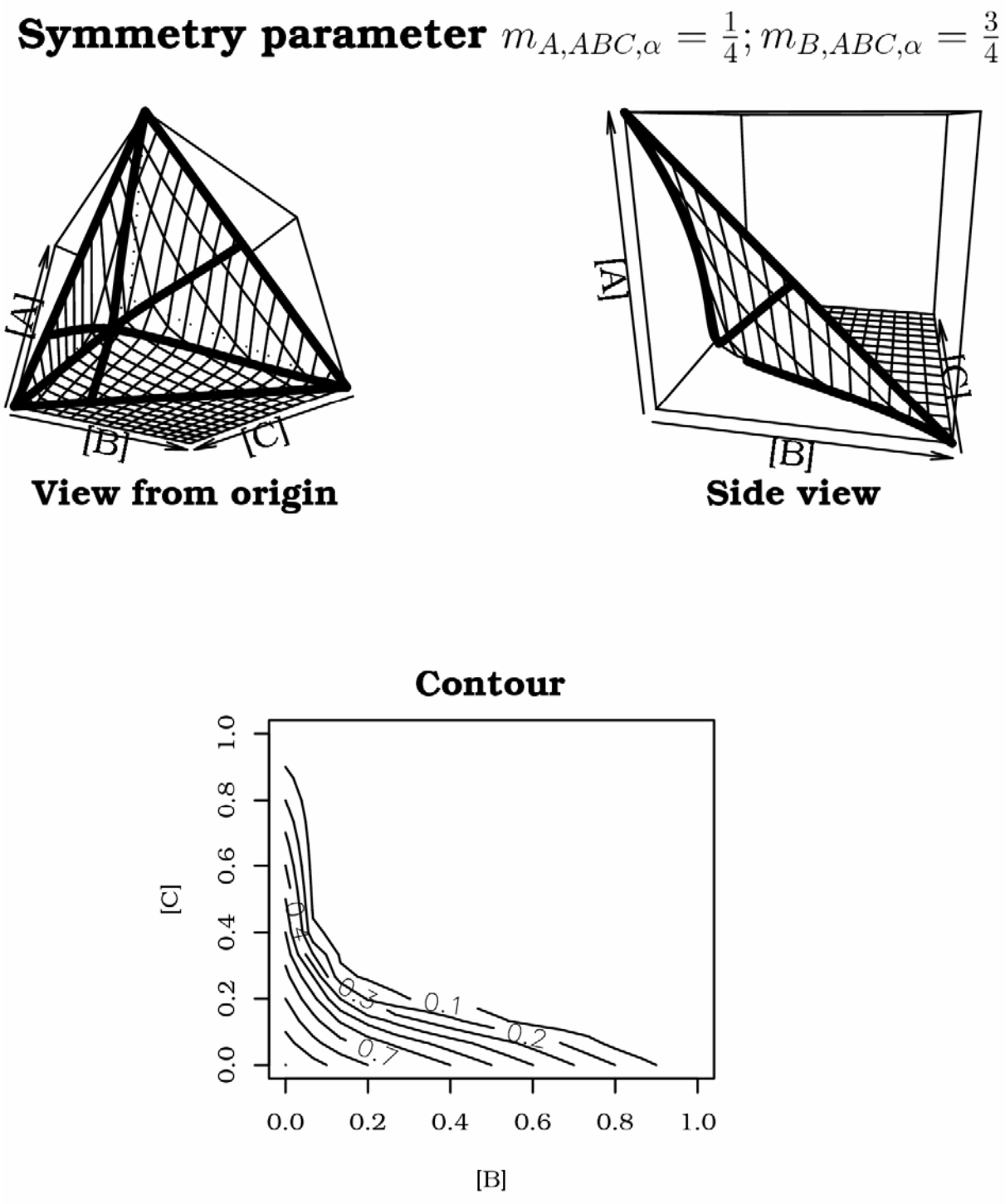
0.7
[B]

Figure 1. 13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View from origin
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Side view
Contour
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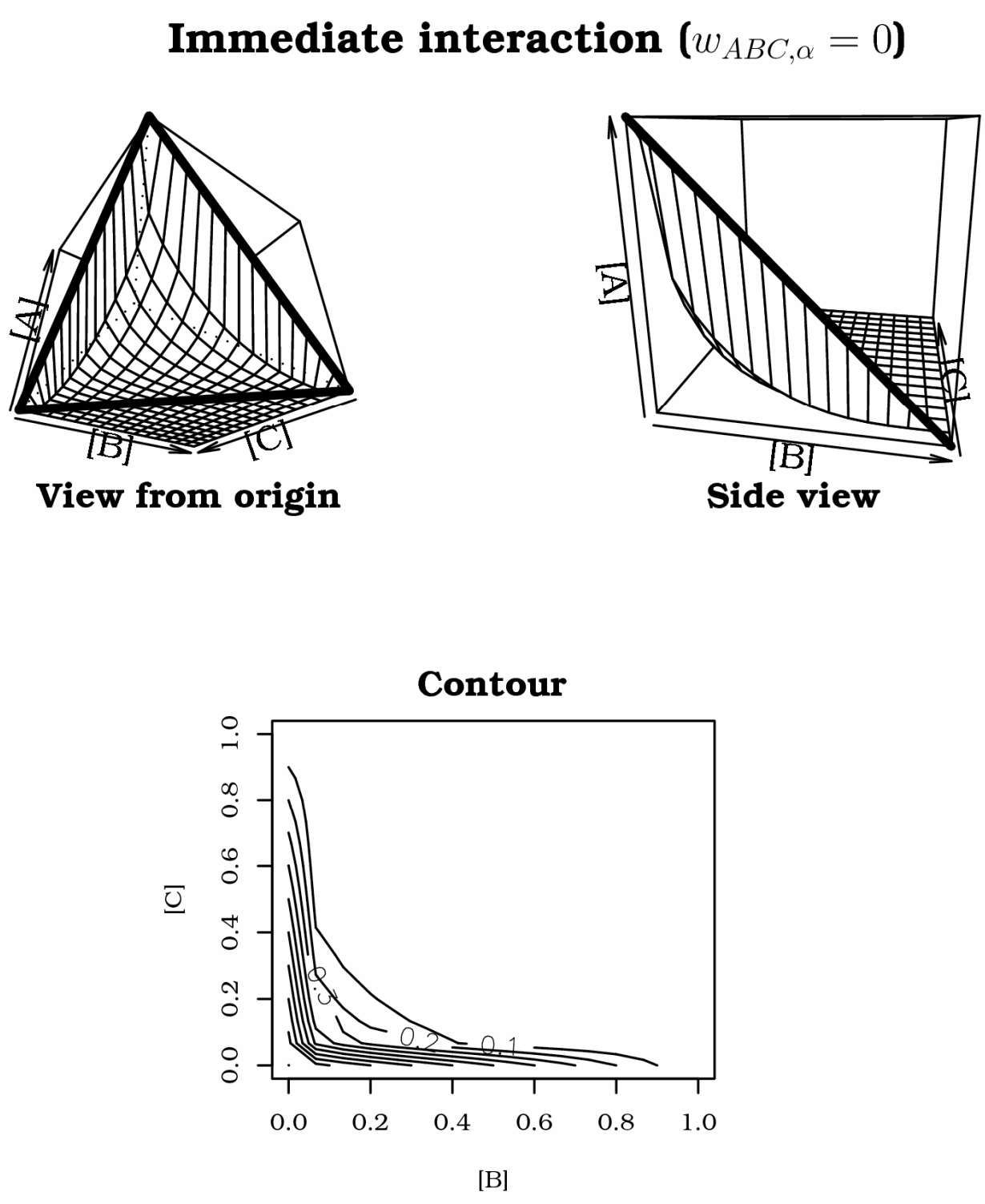
0.7

Figure 1. 14


Immediate interaction ($w_{ABC,\alpha} = 0$)
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[C]
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Side view
Contour
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0.6
0.8
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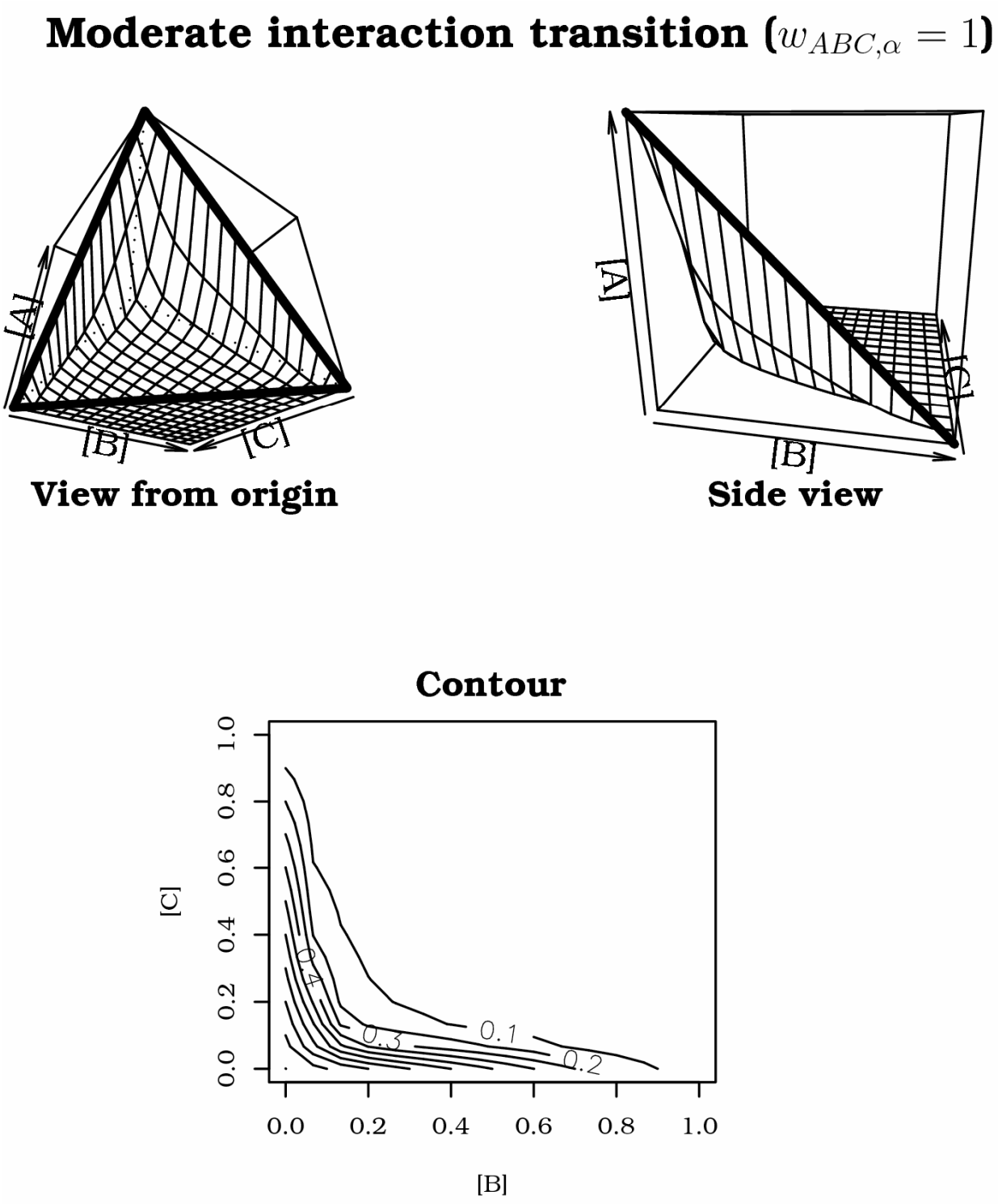
1.0
[B]

Figure 1. 15


Moderate interaction transition ($w_{ABC,\alpha} = 1$)
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View from origin
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Side view
Contour
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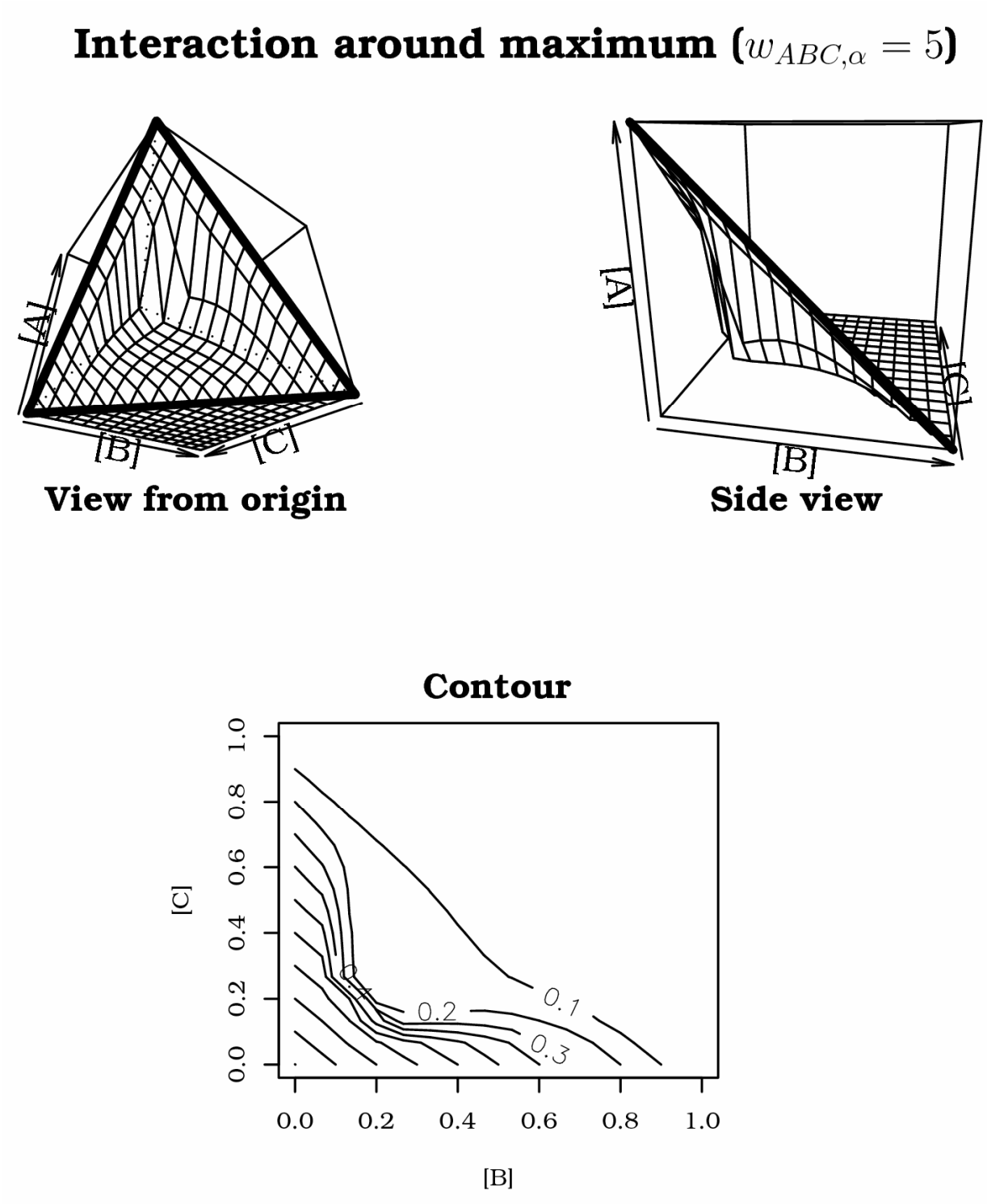
1.0
[B]

Figure 1. 16


Interaction around maximum ($w_{ABC,\alpha} = 5$)
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[C]
View from origin
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Side view
Contour
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0.6
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1.0
[B]

Figure 1. 17