Multivariate Optimizing Up and Down Design

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Abstract: Suppose we are interested in finding the optimal dose of two drugs (for example, Tylenol and Aspirin), that is, we are interested in determining the dose combination that maximizes the probability of patients' success. We assume responses are binary, either failure or success, and that the treatments to be used in the study are selected from a lattice of combination drugs. We extend the univariate Optimizing Up-and-Down Design of Kpamegan (2001), using ideas from stochastic approximation, in a way that the number of subjects at each stage is independent of the number of predictor variables (e.g. drugs).

keywords and phrases: Simultaneous perturbation stochastic approximation, Adaptive designs, Optimal dose, Phase II clinical trials, Markov chain, combination therapy, random walk, up-and-down designs, dose finding.

1 INTRODUCTION

In univariate up-and-down designs, the next treatment is determined such that it is one level higher, one level lower, or the same level as the current treatment. Many authors have studied univariate up-and-down designs for use when the probability of response is increasing (*cf.* Flournoy, 2001). But suppose we are interested in determining the dose combination of two drugs (for example, Tylenol and Aspirin) that maximizes the probability of success. Assume responses are binary, either failure or success, and the treatments to be used are selected from a lattice of combination drug levels.

Our technical approach is to extend the univariate Optimizing Up-and-Down Design Kpamegan (2001) using ideas from stochastic approximation procedures. Recursive

estimation of the maximum (minimum) of regression functions started with papers of Robbins and Monro (1951) and Kiefer and Wolfowitz (1952). Stochastic approximation has become increasingly important due to its wide range of applications, including the targeting of weapon systems, signal timing for vehicle traffic control, and locating buried objects using electrical conductivity (Spall, 1998), queueing systems (Hill, 1995 and Fu, 1997), industrial quality improvement (Rezayat, 1995), pattern recognition (Maeda, et al., 1995), neural network training (Cauwenberghs, 1994), adaptive control of dynamic systems (Spall and Cristion, 1994 and Spall and Cristion, 1997), statistical model parameter estimation and fault detection (Alessandri and Parasini, 1997) and traffic management (Chin and Smith, 1994).

Different algorithms are available for finding the maxima (minima) using stochastic approximation. Spall (2000) reviews two main techniques: the gradient-free technique (using a finite differencing approach) originating with Kiefer and Wolfowitz and the gradient-based method originating with Robbins and Monro. Spall (1987) modified the Kiefer-Wolfowitz procedure by introducing perturbations so that the number of subjects at each stage is independent of the number of predictor variables (e.g. drugs). In these stochastic approximation procedures, predictor variables are continuous

In this paper, we develop a multidimensional extension of Kpamegan's up-and-down procedure using Spall's idea. In Kpamegan's procedure, treatment continuations are restricted to a lattice points and a treatment assignment never more than one level distant from the prior assignment.

2 REVIEW OF UNIVARIATE OPTIMIZING UP-AND-DOWN DESIGNS

For response functions that are unimodal with respect to one explanatory variable, a class of up-and-down designs modelled after the Kiefer-Wolfowitz procedure was suggested by Durham, Flournoy and Li (1998). Let there be a constant interval between doses $\Delta = x_j - x_{j-1}$ for $j = 2, ..., K$ and $c = b\frac{\Delta}{2}$, where b is a positive integer. Let $X(n)$ be the midpoint of the dose interval for the nth pair of subjects, where $X(n) \in \Omega_x = \{x_1, ..., x_K\}$. So subjects are treated at $X^L(n) = X(n) - c$ and $X^U(n) = X(n) + c$, for some constant $c > 0$. Kpamegan (2001) analyzed these designs assuming $b = 1$. The sequences $X^L(n)$ and $X^U(n)$, $n \geq 1$, are called the *lower* and *upper sequences*, respectively. Let $Y^L(n)$ and $Y^U(n)$ be corresponding Bernoulli random variables with $Y^i(n) = 1$ indicating that a success is obtained for subject of the nth pair on $X^i(n)$, and $Y^i(n) = 0$ otherwise, $i = L, U$.

The Optimizing Up-and-Down Design prescribes that the midpoint of the $(n + 1)$th pair be determined recursively by

$$X(n + 1) = X(n) + \Delta V(n), \tag{2.1}$$

where

$$V(n) = \begin{cases} -1 & \text{if } Y^L(n) = 1 \text{ and } Y^U(n) = 0 \\ 0 & \text{if } Y^L(n) = Y^U(n) \\ 1 & \text{if } Y^L(n) = 0 \text{ and } Y^U(n) = 1 \end{cases},$$

that is, doses are increased if there is a success in the upper sequence and a failure in the

lower sequence; doses are decreased if there is a success in the lower sequence and a failure in the upper sequence and are not changed otherewise.

Let p_k, q_k, and r_k, denote, respectively, the probability that the treatment dose for the lower sequence of subjects will move down from level $x_k - \frac{\Delta}{2}$ to $x_{k-1} - \frac{\Delta}{2}$, up from level $x_k - \frac{\Delta}{2}$ to $x_{k+1} - \frac{\Delta}{2}$, and stay at level $x_k - \frac{\Delta}{2}$, with $p_k + q_k + r_k = 1$. Define $\alpha(x) = P(success \mid x)$ to be the success probability function with $\bar{\alpha}(x) = 1 - \alpha(x)$. Then for the lower sequence, the treatment transition probabilities that result from using the Optimizing Up-and-Down Design are

$$\begin{aligned} p_k &= P\left\{X^L(n+1) = x_{k-1} - \frac{\Delta}{2} | X^L(n) = x_k - \frac{\Delta}{2}\right\} \\ &= P(Y^L(n) = 1 | X^L(n) = x_k - \frac{\Delta}{2}) \times P(Y^U(n) = 0 | X^U(n) = x_k + \frac{\Delta}{2}) \\ &= \alpha(x_k - \frac{\Delta}{2})\bar{\alpha}(x_k + \frac{\Delta}{2}),\ k = 2, \ldots, K; \end{aligned}$$

$$\begin{aligned} q_k &= P\left\{X^L(n+1) = x_{k+1} - \frac{\Delta}{2} | X^L(n) = x_k - \frac{\Delta}{2}\right\} \\ &= P(Y^L(n) = 0 | X^L(n) = x_k - \frac{\Delta}{2}) \times P(Y^U(n) = 1 | X^U(n) = x_k + \frac{\Delta}{2}) \\ &= \bar{\alpha}(x_k - \frac{\Delta}{2})\alpha(x_k + \frac{\Delta}{2}),\ k = 1, \ldots, K-1; \\ r_k &= 1 - p_k - q_k. \end{aligned}$$

For treatment spaces Ω_x with a finite number of points, boundary conditions are needed. One possibility is to set $p_1 = q_K = 0$, and let treatments stay on the boundary when the general rule would move them outside the range of Ω_x.Then $r_1 = 1 - q_1 = 1 - \bar{\alpha}(x_k - \frac{\Delta}{2}) \times \alpha(x_k + \frac{\Delta}{2})$ and $r_K = 1 - p_K = 1 - \alpha(x_k - \frac{\Delta}{2}) \times \bar{\alpha}(x_k + \frac{\Delta}{2})$. The resulting transition probability matrix for the lower sequence of treatments is

$$\mathbf{P} = \begin{bmatrix} r_1 & q_1 & 0 & \cdots & 0 & 0 \\ p_2 & r_2 & q_2 & & & 0 \\ 0 & p_3 & r_3 & q_3 & & \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ \vdots & \cdots & \cdots & p_{K-1} & r_{K-1} & q_{K-1} \\ 0 & \cdots & 0 & 0 & p_K & r_K \end{bmatrix}.$$

The corresponding transition probabilities for the upper sequence, denoted (p'_k, q'_k, and r'_k), are equivalent as the paired of treatment sequences are deterministically linked.

Now, define the *n*th step transition probability:

$$p_{ik}(n) = \sum_j p_{ij}(n-1)p_{jk}(1) = \sum_{j=k-1}^{k+1} p_{ij}(n-1)p_{jk}(1).$$

Then so long as $\{p_k\}$ and $\{q_k\}$ are bounded away from 0 and 1, $\lim_{n\to\infty} p_{ik}(n) = \pi_k$, $k = 1, 2, , \ldots, K$, that is the stationary treatment distribution exists and is solution to the

balance equations $\pi_k = \pi_{k-1}q_{k-1} + \pi_k r_k + \pi_{k+1}p_{k+1}$:

$$\pi_k = \pi_1 \prod_{j=2}^{k} \frac{\bar{\alpha}(x_{j-1} - \frac{\Delta}{2})}{\bar{\alpha}(x_j + \frac{\Delta}{2})},\ j = 2, \ldots, k,$$

where

$$\pi_1^{-1} = 1 + \sum_{k=2}^{K} \prod_{j=2}^{k} \frac{\bar{\alpha}(x_{j-1} - \frac{\Delta}{2})}{\bar{\alpha}(x_j + \frac{\Delta}{2})}.$$

Kpamegan (2001) reports results from his dissertation (2000), including the finding that, when $\alpha(x)$ is unimodal, the sequence generated by $X(n)$ converges to a stationary distribution that is unimodal with its mode in a close neighborhood of the mode of the success probability function. For this reason, the procedure is called an Optimizing Up-and-Down Design. In several examples with finite samples, Kpamegan (2001) showed that the up-and-down designs yield estimates of the optimal dose that converge faster and have smaller mean square error than does stochastic approximation. This is not surprising in view of the exponential convergence rate of Markov chains.

3 GRADIENT FREE STOCHASTIC APPROXIMATION

Gradient free stochastic approximation procedures do not require direct gradient measurements of the response function. A gradient free procedure, when the response function is unknown, is based on finite difference estimates of the derivatives of the response function with respect to the explanatory variable(s). The finite difference approach is also known as the Kiefer and Wolfowitz algorithm because they were the first to formulate it and prove its convergence (*cf.* Kushner and Yin, 1997).

Suppose the study involves p drugs where subjects are treated in pairs. Let $\mathbf{X}(n)$ be the treatment midpoint for the nth subject pair. Hence, $\mathbf{X}(n)$ is a point in the p-dimensional space spanned by these drugs. The multivariate finite difference approach is based on a finite difference approximation to the gradient of the response function.

Consider a small perturbation of $\mathbf{X}(n)$ in each of its coordinates. Let a subject be given the drug combination prescribed by each of these 2^p possible perturbations at each stage, $n \geq 1$, of the experiment. Note this procedure requires 2^p subjects to make a single finite difference approximation of the gradient which will determine where the next 2^p subjects are to be treated.

The components of the finite difference approximation are obtained by differencing the pair of $Y(.)$ values and then dividing by the difference interval along each coordinate of $X(n)$. Define $\widehat{g}(\mathbf{X}(n)) = (\widehat{g}_1(X(n)), \ldots, \widehat{g}_p(X(n)))$ to be a p-dimensional vector of the finite difference approximation; the ith component of $\widehat{g}(\mathbf{X}(n))$, $i = 1, ..., p$, is given by

$$\widehat{g}_i(\mathbf{X}(n)) = \frac{Y(\mathbf{X}(n) + c(n)\mathbf{e}_i) - Y(\mathbf{X}(n) - c(n)\mathbf{e}_i)}{2c(n)}, \tag{3.1}$$

where $\mathbf{e}_i$ is a vector whose elements are 1 in the ith place and 0 elsewhere. The sequence $\{c(n)\}$ consists of positive numbers that get smaller as n gets larger. Update $\mathbf{X}(n)$ by

$$X(n+1) = X(n) + a(n)\widehat{g}(X(n)). \tag{3.2}$$

Using a finite difference approach, the number of subjects needed at each stage increases with the dimensionality p. Thus Kiefer-Wolfowitz procedure quickly becomes infeasible as the number of drugs increase. A solution is simultaneous perturbation stochastic approximation (SPSA) which was introduced by Spall (1987) and more fully developed in Spall (1992). SPSA requires only two subjects at each stage, independently of p. Therefore, this procedure is more efficient than the finite difference approach with high dimensional response surfaces (e.g. when multiple drugs are to be evaluated in combination).

4 SIMULTANEOUS PERTURBATION STOCHASTIC APPROXIMATION (SPSA)

SPSA is a method of allocating treatments so that the treatment's distribution converges to the maximum of a differentiable response function. Take the response function to be the probability of success, which varies with the doses of p drugs, $p \geq 2$. Assuming too little treatment is ineffective and too much is harmful, the probability of success is assumed to be a unimodal function on the treatment space. The maximum of the response function occurs at a drug combination we call the *optimal dose*.

Let two subjects be treated with a pair of p dimensional treatments in the nth stage of the experiment. Let $X(n)$ be the p-dimensional average of the nth treatments for these two subjects. We define $\widehat{g}(X(n))$ to be a random approximation of the unknown gradient $g(X(n))$. One of the nth pair is treated at $\mathbf{X}(n) - c(n)\mathbf{U}(n)$ and one at $\mathbf{X}(n) + c(n)\mathbf{U}(n)$, where $\mathbf{U}(n) = (u_1^{-1}(n), ..., u_p^{-1}(n))$ is a vector of random variables called the *simultaneous perturbation vector* and defined such that $E\left|u^{-1}(n)\right|$ exists and $c(n)$ is a non-random sequence of values that decreases with n. Denote the responses to the treatment pair by $\mathbf{Y}(n) = (Y^1(n), Y^2(n))$, where $Y^1(n) = Y(X(n) + c(n)U(n))$ and $Y^2(n) = Y(X(n) - c(n)U(n))$.

Now we can define the randomized gradient approximation of the response function:

$$\widehat{g}(\mathbf{X}(n)) = \frac{Y(X(n) + c(n)U(n)) - Y(X(n) - c(n)U(n))}{2c(n)} \begin{bmatrix} u_1^{-1}(n) \\ \vdots \\ u_p^{-1}(n) \end{bmatrix}. \qquad (4.1)$$

The recursive formula for updating $X(n)$ is given by (3.2), where $a(n)$ is the decreasing step size that goes to zero as n goes to infinity. We use $a(n) = a/\ (A + n)^{\alpha}$ and $c(n) = c/n^{\gamma}$ and call them *gain sequences*, where a, c, A, α and γ are non-negative coefficients that are initialized at $n = 1$. See Spall (1998) regarding the choice of initial values for the gain coefficients. Asymptotically optimal values of α and γ are 1.0 and $1/6$, respectively (Fabian, 1971, and Chin, 1997). The value of A, the *stability constant*, is chosen such that it is much less than the number of stages in the experiment.

4.1 SPSA with a Bivariate Normal Success Probability Function

We illustrate the functionality of the SPSA using a dose-response situation in which there

are two drugs, that is, $p = 2$. In this example, the randomized gradient approximation is

$$\widehat{g}(\mathbf{X}(n)) = \frac{1}{2c(n)} \left(Y \begin{bmatrix} X_1(n) + c(n)u_1(n) \\ X_2(n) + c(n)u_2(n) \end{bmatrix} - Y \begin{bmatrix} X_1(n) - c(n)u_1(n) \\ X_2(n) - c(n)u_2(n) \end{bmatrix} \right) \begin{bmatrix} u_1^{-1}(n) \\ u_2^{-1}(n) \end{bmatrix},$$

where we take the outcomes of $u(n)$ to be equally likely with

$$\begin{bmatrix} u_1(n) \\ u_2(n) \end{bmatrix} \in \left\{ \begin{bmatrix} 1 \\ 1 \end{bmatrix}, \begin{bmatrix} 1 \\ -1 \end{bmatrix}, \begin{bmatrix} -1 \\ 1 \end{bmatrix}, \begin{bmatrix} -1 \\ -1 \end{bmatrix} \right\}. \tag{4.2}$$

Use the recursion formula (3.2) to update treatment midpoints separately for each possible realization of the simultaneous perturbation vector.

For $a(n)/2c(n) = 1$, Figure 1 shows the possible directions in which the treatment midpoints change and they are labeled: (1) both treatment midpoints increase, (2) Treatment 1 midpoint increases while Treatment 2 midpoint decreases, (3) Treatment 1 midpoint decreases while Treatment 2 midpoint increases and (4) both treatment midpoints decrease.

For continuous response functions, $Y^1(n) - Y^2(n) = 0$ with probability zero and $\widehat{g}(X(n))$ equals zero with probability zero. If $Y(n)$ is discrete, however, and in particular if it binary, the positive probability that the treatment process does not change causes significant deterioration in the performance of the procedure. This problem is addressed later. First we demonstrate how the procedure identifies a maxima with a deterministic response function.

As an example, consider a deterministic response function $Y(z_1, z_2) = \phi(\mu_1, \mu_2, \sigma_1, \sigma_2, \rho)$ with doses measured on a logarithmic scale, where

$$\phi(\mu_1, \mu_2, \sigma_1, \sigma_2, \rho) = \frac{1}{2\pi\sigma_1\sigma_2\sqrt{1-\rho^2}} \exp\left\{ -\frac{1}{2(1-\rho^2)} \left[z_1^2 - 2\rho z_1 z_2 + z_2^2 \right] \right\}, \tag{4.3}$$

$$z_1 = \frac{(x_1 - \mu_1)}{\sigma_1} \text{ and } z_2 = \frac{(x_2 - \mu_2)}{\sigma_2},$$

$\sigma_1$and σ_2 are scale parameters, and $\mu_1$and μ_2 are location parameters controlling the probability of success as functions of Treatments 1 and 2, respectively. In this example a standard bivariate normal function is used, that is, $Y(z_1, z_2) = \phi(0, 0, 1, 1, 0)$ is a deterministic function.

One SPSA sample path of $X(n)$ is shown in Figure 2. To obtain it, we set $a = 1$, $A = 1$, $\alpha = .1$, $\gamma = \frac{1}{6}$, and $c = 1$. The simultaneous perturbation vector, $U(n)$, is generated using Bernoulli random variables taking values ± 1 with probability $\frac{1}{2}$. The SPSA algorithm terminates if there is little change several subsequent iterations or the maximum number of trials has been reached. We choose to start with a low dosage, $X(1) = (-2, -3)'$are the treatment midpoints for the first pair of subjects. For our illustration, the first perturbation vector we generated was $u(1) = (1, -1)$. So

$$Y \begin{pmatrix} -2+1 \\ -3-1 \end{pmatrix} = \frac{1}{2\pi} \exp\left\{ -\frac{1}{2} \left[(-1)^2 + (-4)^2 \right] \right\},$$

and

$$Y \begin{pmatrix} -2-1 \\ -3+1 \end{pmatrix} = \frac{1}{2\pi} \exp\left\{ -\frac{1}{2} \left[(-3)^2 + (-2)^2 \right] \right\}$$

and

$$\widehat{g}(X(1)) = \frac{1}{2c(1)} \left(\frac{1}{2\pi} \exp\left\{ -\frac{1}{2} [17] \right\} - \frac{1}{2\pi} \exp\left\{ -\frac{1}{2} [13] \right\} \right) \begin{bmatrix} 1 \\ -1 \end{bmatrix}$$

$$= \begin{bmatrix} -0.00012 \\ 0.00012 \end{bmatrix}.$$

Updating the treatments according to (3.2), yields $X(2) = (-2.000, -2.999)$. Using (3.2) we continued until $n = 100$. As can be seen in Figure 2, after getting out of the tail of the response function, convergence is fast and the number of trials required to converge to the optimal dose is much less than the maximum number of trials we specified. Complete convergence on both treatment midpoints took approximately 30 pairs of subjects.

From this point, we study (3.2) and (4.1) with a binary response. In sections 6.2 and 6.3 we model P(sucess| treatment combination)= $\phi(0, 0, 1, 1, 0)$. In section 6.4, we use skewed sucess probability models.

5 BIVARIATE OPTIMIZING UP-AND-DOWN DESIGNS: GENERAL FORMATION

As SPSA is a multivariate extension of the Kiefer-Wolfowitz method, we draw on it to extend the Optimizing Up-and-Down Design to two dimensions. The extension to higher dimensions in conceptually straightforward, but notationally cumbersome. In the Kiefer-Wolfowitz procedure subjects are treated in groups of 2^p, where p is the dimension of the treatment space whereas in the SPSA procedure subjects are treated in pairs independently of p. The Optimizing Up-and-Down Design differs from these methods in that the treatment space is a lattice and the dose increments are constant.

We now construct an Optimizing Up-and-Down Design in the bivariate setting i.e. $p = 2$. Consider a lattice $\{x_{11} < x_{12} < \cdots < x_{1K_1}\} \times \{x_{21} < x_{22} < \cdots < x_{2K_2}\}$ in which the sets $\{x_{11}, x_{12}, \cdots, x_{1K_1}\}$ and $\{x_{21}, x_{22}, \cdots, x_{2K_2}\}$ are midpoints between the pairs of possible doses on Treatments 1 and 2, respectively. Let the interval between possible midpoints be a positive constant for each treatment, i.e., $x_{ij} - x_{ij-1} = \Delta_i$ for $i = 1, 2$ and $j = 2, \ldots, K_i$. For the two subjects, let δ_i be the interval between doses on Treatment i, $i = 1, 2$, where $\delta_i = \frac{\Delta_i}{2}$. Define $t^1_{1k} = x_{1k} - \delta_1$, $t^2_{1k} = x_{1k} + \delta_1$, $t^1_{2l} = x_{2l} - \delta_2$ and $t^2_{2l} = x_{2l} + \delta_2$, for dose levels $k = 1, \ldots, K_1$ and $l = 1, \ldots, K_2$. Then the marginal dose space for Treatment 1 is $\Omega_{x_1} = \left\{t^1_{11}, t^2_{11}, t^2_{12}, \cdots, t^2_{1K_1}\right\}$, and the marginal dose space for Treatment 2 is $\Omega_{x_2} = \left\{t^1_{21}, t^2_{21}, t^2_{22}, \cdots, t^2_{1K_2}\right\}$: $\Omega_{x_1} \times \Omega_{x_2}$ is the joint treatment space.

Define the vectors $\boldsymbol{\Delta} = (\Delta_1, \Delta_2)$ and $\boldsymbol{\delta} = (\delta_1, \delta_2)$, and let $\mathbf{X}(n) = (X_1(n), X_2(n))$ be the treatment midpoint for the nth subject pair and let $\mathbf{T}(n)$ be the actual doses for subjects in the nth pair:

$$\mathbf{T}(n) = \begin{bmatrix} \mathbf{T}^1(n) \\ \mathbf{T}^2(n) \end{bmatrix} = \begin{bmatrix} (T^1_1(n), T^1_2(n)) \\ (T^2_1(n), T^2_2(n)) \end{bmatrix},$$

where $\mathbf{T}^1(n)$ and $\mathbf{T}^2(n)$ are the dose combinations for subjects 1 and 2 of the nth pair, respectively; $T^1_1(n)$ and $T^2_1(n)$ take on values in Ω_{x_1}, whereas T^1_2 and $T^2_2(n)$ take on values in Ω_{x_2}. If $X_1(n) = (x^1_{1k}, x^1_{2l})$, then $\mathbf{T}^1(n)$ takes on a value from $\{x_{1k} \pm \delta_1, x_{2l} \pm \delta_2\}$ depending on the outcome of $\mathbf{U}(n)$, which is the simultaneous perturbation vector given by (5.1). Likewise, $\mathbf{T}^2(n)$ takes on a value from $\{x_{1k} \pm \delta_1, x_{2l} \pm \delta_2\}$ depending on the outcome of $\mathbf{U}(n)$.

Denote the responses to treatments $T^1(n)$ and $T^2(n)$ by $Y^1(n)$ and $Y^2(n)$, respectively,

where

$$Y^j(n) = \begin{cases} 1 \text{ if success} \\ 0 \text{ if failure} \end{cases} \quad j = 1, 2.$$

Define

$$\mathbf{V}(n) = \left[Y^1(n) - Y^2(n)\right] * \mathbf{U}^{-1}(n), \tag{5.1}$$

where $\mathbf{U}(n)$ the simultaneous perturbation vector. Now, extending (2.1) to the bivariate treatment space, we give the general form of the Bivariate Optimizing Up-and-Down Design.

If the nth pair were treated at X(n)=($\mathbf{X}_1(n)$,$\mathbf{X}_2(n)$), then treat the (*n+1*)th pair at

$$\mathbf{X(n+1)} = \mathbf{X(n)} + \mathbf{\Delta V(n)}. \tag{5.2}$$

Equation (5.2) must be modified at the boundaries of the treatment space. Except on the boundaries of the treatment space, the treatment midpoints $X_1(n)$ and $X_2(n)$ both stay constant for the $(n+1)$th pair of subjects if $V(n) = [0, 0]$; both treatment midpoints increase if $V(n) = [1, 1]$; the midpoint of Treatment 1 increases and the midpoint of Treatment 2 decreases if $V(n) = [1, -1]$; the midpoint of Treatment 1 decreases and the midpoint of Treatment 2 increases if $V(n) = [-1, 1]$ and both midpoints decrease if $V(n) = [-1, -1]$. Alternative designs are obtained by changing the distribution of $\mathbf{U}(n)$ and by changing (5.2) at the boundaries.

5.1 Transition Probabilities for Treatment Midpoints and Their Associated Perturbations

Let subscripts of the form $(1_i, 2_j)$ denote the ith level of Treatment 1 and the jth level of Treatment 2. Define $p_{(1_i 2_j, 1_k 2_l, u\ u_w)}(n+1)$ to be the probability that the $(n+1)$th treatment midpoint is at (x_{1_k}, x_{2_l}) and perturbation u_w around the midpoint given that the nth treatment midpoint is at $\left(x_{1_i}, x_{2_j}\right)$ and treatments have perturbation u around the midpoint. Define $p_{(1_i 2_j, 1_k 2_l, u\ )} = p_{(1_i 2_j, 1_k 2_l, u)}(1)$. The transitions of the paired treatment midpoints coupled with their associated perturbation determines the next pair of treatments. Transitions from the treatment pair with perturbation u around midpoints (X_{1i}, X_{2j}) to a perturbation $u_w$around midpoints (X_{1k}, X_{2l}) are Markovian, depending only on the probability of sucess at (X_{1i}, X_{2j}).

To restrict treatment midpoints to only change one level at a time in Up-and-Down Designs, we require

$$p_{(1_i 2_j, 1_k 2_l, u)} = 0 \quad \text{if} \left\{ \begin{array}{c} |i-k| > 1 \\ or \\ |j-l| > 1 \end{array} \right\}, \tag{5.3}$$

for all u and $(i, k) = 1, \ldots, K_1$, $(j, l) = 1, \ldots, K_2$. Also, designs are constructed with boundary conditions so that the probability of treating outside the specified treatment space is zero.

5.2 Stationary Distribution of Treatments

Let $\pi_{(1_r 2_s)} \in [0, 1]$, $r = 1, \ldots, K_1$ and $s = 1, \ldots, K_2$, denote the stationary probability of the $(1_r 2_s)$ midpoint and with at least one π positive and $\sum_{r=1}^{K_1} \sum_{s=1}^{K_2} \sum_u \pi_{(1_r 2_s, u)} = 1$. Assuming the stationary distribution for treatment midpoints and their associated

perturbations exists,

$$\pi_{(1_k 2_l, u_w)} = \sum_{r=1}^{K_1} \sum_{s=1}^{K_2} \sum_{u} \pi_{(1_r 2_s, u)} p_{(1_r 2_s u, 1_k 2_l u, u_w)} = \sum_{r=k-1}^{k+1} \sum_{s=l-1}^{l+1} \sum_{u} \pi_{(1_r 2_s, u)} p_{(1_r 2_s u, 1_k 2_l u, u_w)}. \tag{5.4}$$

Let **P**=$(1_i 2_j, 1_k 2_l, u, u_w)$ denote the 3x3 matrix of transition probabilities for treatment midpoints and their associated perturbations. The associated stationary distribution can be approximated to any desired degree of accuracy by exponentiating **P**. We consider stationarity to be attained for m trials when all rows of $\mathbf{P}^m$agree to 4 decimal places.

Since a particular orientation of treatments around the midpoint may coincide with another particular orientation around another midpoint, we must aggregate their probabilities to obtain the total stationary probability for that treatment. For example, suppose that treatment midpoints take on values from $\{-1, 0, 1\}$, and hence, the actual treatments take on values from $\{\frac{-3}{2}, \frac{-1}{2}, \frac{1}{2}, \frac{3}{2}\}$. Furthermore, suppose that u is given by (4.2). Figure 3 shows that the treatment can be at $(\frac{-1}{2}, \frac{-1}{2})$ when treatment midpoints are at 4 different locations. A treatment midpoint at $(0, -1)$ with perturbation $(-1, 1)$; a treatment midpoint at $(0, 0)$ with perturbation $(-1, -1)$; a treatment midpoint $(-1, -1)$ with perturbation $(1, 1)$; and a treatment midpoint at $(-1, 0)$ with perturbation $(1, -1)$. The stationary probabilities of these four outcomes must be summed to obtain the asymptotic proportion of subjects treated at $(\frac{-1}{2}, \frac{-1}{2})$. This type of aggregation must be done for all orientations and treatment levels.

6 EXAMPLE OF A BIVARIATE OPTIMIZING UP-AND-DOWN DESIGN

First, in Section 6.1 we describe the transitions of treatment midpoints on the interior of the design space. In Section 6.2, when a transition according to (5.2) would move the next treatment outside of $\Omega_{x_1} \times \Omega_{x_2}$, the next treatment is held constant instead. In Section 6.3, when a transition according to (5.2) would move the treatment outside the prescribed treatment space, the treatment randomly stays the same or one treatment stays fixed and the other changes one level within $\Omega_{x_1} \times \Omega_{x_2}$, with each of the possible events having equal probability.

In sections 6.2 and 6.3, we illustrate the Bivariate Optimizing Up-and-Down Design in which the ith subject of the nth pair has responses

$$Y^j(n) = \begin{cases} 1 & \text{if success} \\ 0 & \text{if failure} \end{cases} \quad j = 1, 2,$$

where $P(Y^j(n) = 1 \mid Z_1, Z_2) = E(Y^j(n) \mid Z_1, Z_2) = \phi(0, 0, 1, 1, 0)$ as given by (4.3). We let $\Delta_1 = \Delta_2 = \Delta = 1$, and $\delta_1 = \delta_2 = \delta = \frac{\Delta}{2} = \frac{1}{2}$. In Section 6.4, we consider skewed response functions.

6.1 Midpoint Transitions on the Interior of the Design Space

The stochastic algorithm used is given by (5.2) with perturbations given by (4.2), except on

the boundaries. As used by Spall (1998) for SPSA, we used the perturbation vector

$$\mathbf{U}^{-1}(n) = \left[u_1^{-1}(n), u_2^{-1}(n)\right] \in \{[-1,-1]\,,\ [1,1]\,,\ [1,-1]\,,\ [-1,1]\}\,,$$

with probability of $\frac{1}{4}$ for each outcome pair. From (5.1), we have $\mathbf{V}(n) \in \{[0,0]\,,[1,1]\,,[1,-1]\,,[-1,1]\,,[-1,-1]\}$. Figure 4 shows a schematic of the possible transitions of a treatment midpoint from $\mathbf{X}(n) = (X_{1k}, X_{2l})$. It is shown that treatment midpoints under Design 1 can only move diagonally or stay put. Let $\mathbf{\Delta}$ be the step size between treatment midpoints. Depending on the outocme of the process, the transitions at the midpoint $(\mathbf{X(n)} = (\mathbf{X}_1(\mathbf{n}), \mathbf{X}_2(\mathbf{n}))$ can take are in one of four possible directions; $(\mathbf{X}_1(\mathbf{n}) - \mathbf{\Delta}, \mathbf{X}_2(\mathbf{n}) + \mathbf{\Delta})$, $(\mathbf{X}_1(\mathbf{n}) - \mathbf{\Delta}, \mathbf{X}_2(\mathbf{n}) - \mathbf{\Delta})$, $(\mathbf{X}_1(\mathbf{n}) + \mathbf{\Delta}, \mathbf{X}_2(\mathbf{n}) - \mathbf{\Delta})$,or $(\mathbf{X}_1(\mathbf{n}) + \mathbf{\Delta}, \mathbf{X}_2(\mathbf{n}) + \mathbf{\Delta})$.

Let E_{ij} indicate a possible event from one trial in the Bivariate Optimizing Up-and-Down procedure, where $i = 0$ if $\mathbf{X}(n)$ does not change, $i = 1$ if both components of $\mathbf{X}(n)$ decrease, $i = 2$ if both components of $\mathbf{X}(n)$ increase, $i = 3$ if $X_1(n)$ decreases while $X_2(n)$ increases and $i = 4$ if $X_1(n)$ increases while $X_2(n)$ decreases. The subscript j indicates different ways in which these treatment changes can occur. The different perturbations of the treatments around their midpoint as shown in Table 1.

Define $\alpha(T^1(n), T^2(n)) = P(success|T^1(n), T^2(n))$ to be the success probability function with $\overline{\alpha}(T^1(n), T^2(n)) = 1 - \alpha(T^1(n), T^2(n))$. Given treatment at $(T^1(n), T^2(n))$, Table 2 shows the possible events for this Bivariate Optimizing Up-and-Down Design on the interior of the treatment space, with their associated probabilities, where up, down and stay put are denoted by $\uparrow, \downarrow$ *and* $\circlearrowleft$, respectively. For example,

$$\begin{aligned}
&P(E_{01} \mid T^1(n), T^2(n)) \\
&\quad = P(Y^1(n) = 0, Y^2(n) = 0, \mathbf{U}(n) = [1,1] \mid T^1(n), T^2(n)) \\
&\quad = P(U(n) = [1,1]) P(Y^1(n) = 0, Y^2(n) = 0 \mid T^1(n), T^2(n)) \\
&\quad = \frac{1}{4}\overline{\alpha}(T^1(n))\overline{\alpha}(T^2(n));
\end{aligned}$$

$$\begin{aligned}
&P(E_{05} \mid T^1(n), T^2(n)) \\
&\quad = P(Y^1(n) = 1, Y^2(n) = 1, \mathbf{U}(n) = [1,1] \mid T^1(n), T^2(n)) \\
&\quad = P(U(n) = [1,1]) P(Y^1(n) = 1, Y^2(n) = 1 \mid T^1(n), T^2(n)) \\
&\quad = \frac{1}{4}\alpha(T^1(n))\alpha(T^2(n)).
\end{aligned}$$

The probabilities of the other transitions in Table 2 are obtained analogously. Note that the conditional probability that $X(n+1) = X(n)$ is equal to

$$\begin{aligned}
P(V(n) = [0,0] | T^1(n), T^2(n)) &= \sum_{j=1}^{8} P(E_{0j} \mid T^1(n), T^2(n)) \\
&= \alpha(T^1(n))\alpha(T^2(n)) + \overline{\alpha}(T^1(n))\overline{\alpha}(T^2(n)).
\end{aligned}$$

The transition probabilities on the interior of the design space can be written in terms of the response function probabilities. For example, the probability of treatment midpoints staying

put with perturbation $\mathbf{U}(n) = u = [-1, -1]$ is

$$\begin{aligned} p_{(\circlearrowleft\circlearrowleft,u)} &= p(_{1_i2_j,1_i2_j}, u) \\ &= P(Y^1(n) = 0, Y^2(n) = 0, \mathbf{U}(n) = u | T^1(n), T^2(n)) \\ &+ P(Y^1(n) = 1, Y^2(n) = 1, U(n) = u | T^1(n), T^2(n)) \\ &= P(U(n) = u) P(V(n) = [0, 0] \mid T^1(n), T^2(n)) \\ &+ P(U(n) = \mathbf{u}) P(V(n) = [0, 0] \mid T^1(n), T^2(n)) \\ &= \frac{1}{4}\overline{\alpha}(T^1(n))\overline{\alpha}(T^2(n)) + \frac{1}{4}\alpha(T^1(n))\alpha(T^2(n)). \end{aligned} \tag{6.1}$$

The transition probability that both treatment midpoints move up with perturbation $\mathbf{U}(n) = u = [-1, -1]$ is

$$\begin{aligned} p_{(\uparrow\uparrow,u)} &= p(_{1_i2_j,1_{i+1}2_{j+1}}, u) \\ &= P(Y^1(n) = 0, Y^2(n) = 1, \mathbf{U}(n) = u | T^1(n), T^2(n)) \\ &= P(U(n) = u) P(V(n) = [1, 1] \mid T^1(n), T^2(n)) \\ &= \frac{1}{4}\overline{\alpha}(T^1(n))\alpha(T^2(n)), \end{aligned} \tag{6.2}$$

and the transition probability that both treatment midpoints move up and $\mathbf{U}(n) = u = [1, 1]$ is

$$\begin{aligned} p_{(\uparrow\uparrow,u)} &= p(_{1_i2_j,1_{i+1}2_{j+1}}, u) \\ &= P(Y^1(n) = 1, Y^2(n) = 0, \mathbf{U}(n) = u | T^1(n), T^2(n)) \\ &= P(U(n) = u) P(V(n) = [1, 1] \mid T^1(n), T^2(n)) \\ &= \frac{1}{4}\alpha(T^1(n))\overline{\alpha}(T^2(n)); \end{aligned} \tag{6.3}$$

Other transition probabilities are calculated similarily yielding

$$p_{(\downarrow\downarrow,u)} = \frac{1}{4}\alpha(T^1(n))\overline{\alpha}(T^2(n)),\ u = [-1, -1],$$

$$p_{(\downarrow\downarrow,u)} = \frac{1}{4}\overline{\alpha}(T^1(n))\alpha(T^2(n)),\ u = [1, 1],$$

$$p_{(\downarrow\uparrow,u)} = \frac{1}{4}\overline{\alpha}(T^1(n))\alpha(T^2(n)),\ u[1, -1],$$

$$p_{(\downarrow\uparrow,u)} = \frac{1}{4}\alpha(T^1(n))\overline{\alpha}(T^2(n)),\ u[-1, 1],$$

$$p_{(\uparrow\downarrow,u)} = \frac{1}{4}\alpha(T^1(n))\overline{\alpha}(T^2(n)),\ u[1, -1],$$

and finally,

$$p_{(\uparrow\downarrow,u)} = \frac{1}{4}\overline{\alpha}(T^1(n))\alpha(T^2(n)),\ u[-1, 1].$$

6.2 A Bivariate Normal Response Function with Curtailment at the Boundary

In this section, we evaluate the bivariate up-and-down design with curtailment at the

boundary. That is, when a transition would move the next treatment outside the prescribed treatment space, the next treatment is held constant instead.

Suppose that treatment midpoints belong to the space $\{-1, 0, 1\} \times \{-1, 0, 1\}$, and hence, the treatments belong to the space $\{-\frac{3}{2}, -\frac{1}{2}, \frac{1}{2}, \frac{3}{2}\} \times \{-\frac{3}{2}, -\frac{1}{2}, \frac{1}{2}, \frac{3}{2}\}$. The interval between midpoints Δ is set equal to 1 and the interval between treatments is $\delta = \frac{\Delta}{2} = \frac{1}{2}$. We calculated the transition probabilities of the treatments considering their orientation around their midpoints to obtain a numerical evaluation of the transition probability matrix $\mathbf{P}$ given P($Y^j = 1|T^1, T^2$)=$\phi(0, 0, 1, 1, 0)$, $j = 1, 2$. The asymptotic proportion of subjects treated at each dose combination was then computed by summing the midpoint perturbation combinations that were actually the same treatment combination as described in Section 6.2. These treatment allocation proportions are shown in Table 3. The relative frequency at the mode of the treatment distribution is described in terms of the probability of the modal set which consists of the doses that have the highest stationary probabilities. Note that the optimal dose is at the point $(0, 0)$, which is surrounded by the modal set in the treatment distribution. The modal set in this example consist of the 4 points that surround the point $(0, 0)$, which are $(-\frac{1}{2}, -\frac{1}{2})$, $(\frac{1}{2}, \frac{1}{2})$, $(\frac{1}{2}, -\frac{1}{2})$ and $(-\frac{1}{2}, \frac{1}{2})$. The stationary probability at the modal set is the sum of the probabilities of the 4 modal points surrounding $(0, 0)$ which is 0.28.

This design follows SPSA closely. However, there are undesirable results. First, the probability that treatment midpoints stay put is high (this would not be so with continuous response variables). Furthermore, all treatment midpoints do not communicate with each other. There are two seperate paths for the treatment midpoints depending on the starting treatment as can be seen in Figure 4. However, all treatments can be reached through the perturbations. These facts cause most of the transition probability mass to lie on a narrow diagonal band of $\mathbf{P}$, which causes slow convergence. Indeed, it took $m = 100$ (pairs of subjects) for the rows of the $\mathbf{P}$ matrix to become equal to four decimal places. Hence, we change the boundary conditions in Section 6.3 to address these problems.

6.3 A Bivariate Normal Response Function with Transitions Along the Boundary

In order to speed convergence, modifications are made on the boundaries that reduce the probabilities of no transition and make all treatment midpoints communicate with each other (See Figure 5). When a transition according to (5.2) would move the treatment outside the prescribed treatment space, the treatment randomly stays the same, or one treatment stays fixed and the other changes one level within $\Omega_{x_1} \times \Omega_{x_2}$, with each possible change having equal probability. This design allows all treatment midpoints to communicate and also allows a transition in the midpoint of one treatment while the other treatment midpoint is held constant.

This modification puts less mass near the diagonal of $\mathbf{P}$ than in Section 6.2. Hence, fewer trials are required to reach stationarity. Considering the same sample space and success response function described in Section 6.2, the stationary distribution is approximated well by $\mathbf{P}^{10}$, that is, only 10 pairs of subjects were required for the rows of $\mathbf{P}$ to be equal to 4 decimal places. Hence, the stationary distribution resulting from this design is applicable to combination therapy dose-finding trials with small sample sizes. The asymptotic proportion of subjects treated at each dose combination is given in Table 4.

Note that the optimal dose is at $(0, 0)$, which is represented by 4 points in the modal set of the treatment distribution and these points are $(-\frac{1}{2}, -\frac{1}{2})$, $(\frac{1}{2}, \frac{1}{2})$, $(\frac{1}{2}, -\frac{1}{2})$ and $(-\frac{1}{2}, \frac{1}{2})$. Hence, the stationary probability at the modal set is equal to 0.51,up from 0.28 with curtailment at the boundary.

Now, we consider the bivariate normal response function, operating on a larger treatment space. Let treatment midpoints take on values from $\{-2, -1, 0, 1, 2\} \times \{-2, -1, 0, 1, 2\}$. The dose space for Treatment 1 is given by $\Omega_{x_1} = \left\{\frac{-5}{2}, \frac{-3}{2}, \frac{-1}{2}, \frac{1}{2}, \frac{3}{2}, \frac{5}{2}\right\}$ and the dose space for Treatment 2 is given by $\Omega_{x_2} = \left\{\frac{-5}{2}, \frac{-3}{2}, \frac{-1}{2}, \frac{1}{2}, \frac{3}{2}, \frac{5}{2}\right\}$. Treatments for the sequence of subjects are selected from $\left\{\frac{-5}{2}, \frac{-3}{2}, \frac{-1}{2}, \frac{1}{2}, \frac{3}{2}, \frac{5}{2}\right\} \times \left\{\frac{-5}{2}, \frac{-3}{2}, \frac{-1}{2}, \frac{1}{2}, \frac{3}{2}, \frac{5}{2}\right\}$. The resulting asymptotic proportion of subjects treated at each dose combination is shown in Table 5.

Note again that the modal set of the treatment distribution surrounds the optimal dose which is zero. Twenty one percent of subjects are treated at the modal set. The number of subject pairs required for stationarity is 30.

6.4 Alternative Success Probability Functions

In this section, we will compare asymptotic treatment distributions resulting from three different response functions which we call SPF-1, SPF–2, and SPF-3. First, let (m_1, m_2) indicate the optimal dose combination of Treatments 1 and 2. Also let $(\widehat{m}_1, \widehat{m}_2)$ indicate the empirical mode of the asymptotic treatment distribution of Treatments 1 and 2.
In the symmetric case (SPF-1), we will refer to the mode by the modal set, since the mode consist of 4 points surrounding the optimal dose. We let the step size between treatment midpoints be $\Delta_1 = \Delta_2 = \Delta = 1$ and we let the space of both treatment midpoints be equal to $\{2, -1, 0, 1, 2\}$. Hence, the dose space for Treatment 1 is given by $\Omega_{x_1} = \left\{\frac{-5}{2}, \frac{-3}{2}, \frac{-1}{2}, \frac{1}{2}, \frac{3}{2}, \frac{5}{2}\right\}$ and the dose space for Treatment 2 is given by $\Omega_{x_2} = \left\{\frac{-5}{2}, \frac{-3}{2}, \frac{-1}{2}, \frac{1}{2}, \frac{3}{2}, \frac{5}{2}\right\}$. Table 6 summarizes design characteristics of each success probability function.

Figure 2 shows SPF-1 and Figure 6 shows a 3 dimensional bar graph of the asymptotic treatment distribution using SPF-1. The modal set consist of treatments $(-\frac{1}{2}, -\frac{1}{2})$, $(\frac{1}{2}, -\frac{1}{2})$, $(-\frac{1}{2}, \frac{1}{2})$ and $(\frac{1}{2}, \frac{1}{2})$. These points are within $\pm\frac{\Delta}{2}$ from the optimal dose is $(0, 0)$.

A left skewed response function (SPF-2) is shown in Figure 7. The optimal dose for this function is $(1, 1)$. The treatments converge to a distribution shown in Figure 8. The mode of the stationary distribution is at the point $(\frac{1}{2}, \frac{1}{2})$ and the mode is within $\pm\frac{\Delta}{2}$ from the optimal dose.

Figure 9 shows a right skewed success response function SPF-3, with optimal dose at (-1,-1). Figure 10 shows the asymptotic treatment distribution with its mode at the point $(-\frac{1}{2}, -\frac{1}{2})$ which is also within $\pm\frac{\Delta}{2}$ from the optimal dose.

The three different examples of the success probability functions show treatments converging to a distribution whose mode is in a close neighborhood of the optimal dose.

7 Conclusion

In this paper we have shown how to extend Kpamegan's (2000, 2001) Optimizing Up-and-Down Design to accomodate combination therapies using an idea of Spall (1998); and we show how this can be done with two subjects at each step regardless of the dimension

of the treatment space. We emphasize that analytically, rather than by simulation, one can compute treatment allocation probabilities.

We have analytically evaluated the performance of the Optimizing Up-and-Down Design for combination therapy with two different boundary conditions. Allowing transitions along the boundaries is clearly superior to curtailment at the boundary. More subjects were assigned near the optimal dose and stationarity was reached faster. Optimal boundary rules present an open problem which is important for small treatment spaces. Larger treatment spaces require more subject pairs for stationarity to be attained. We have been rather explicit in describing the calculations needed to evaluate the Optimizing Up-and-Down designs in our illustrations so that these calculations can be readily adopted to the treatment lattice and types of response functions that one expects to encounter in other situations.

8 Acknowledgment

We would like to thank Dr. Tawfiq Diab for his help in developing the code. We would like to thank Dr. Helaine Resnick for her encouragement and valuable support.

Table 1: Midpoint Transitions according to Perturbation Outcomes			
Midpoint	**Perturbation**	**Sequence 1**	**Sequence 2**
$\mathbf{X(n)} = (x_{1k},\ x_{2l})$	$\mathbf{U}(n) =$	$\mathbf{T}^1\mathbf{(n)} =$	$\mathbf{T}^2\mathbf{(n)} =$
	$[-1,-1]$	$\{x_{1k} + \delta a[1], x_{2l} + \delta a[2]\}$	$\{x_{1k} - \delta a[1], x_{2l} - \delta a[2]\}$
		$= \{x_{1k} - \delta, x_{2l} - \delta\}$	$= \{x_{1k} + \delta, x_{2l} + \delta\}$
	$[1,1]$	$\{x_{1k} + \delta b[1], x_{2l} + \delta b[2]\}$	$\{x_{1k} - \delta b[1], x_{2l} - \delta b[2]\}$
		$= \{x_{1k} + \delta, x_{2l} + \delta\}$	$= \{x_{1k} - \delta, x_{2l} - \delta\}$
	$[1,-1]$	$\{x_{1k} + \delta c[1], x_{2l} + \delta c[2]\}$	$\{x_{1k} - \delta c[1], x_{2l} - \delta c[2]\}$
		$= \{x_{1k} + \delta, x_{2l} - \delta\}$	$= \{x_{1k} - \delta, x_{2l} + \delta\}$
	$[-1,1]$	$\{x_{1k} + \delta d[1], x_{2l} + \delta d[2]\}$	$\{x_{1k} - \delta d[1], x_{2l} - \delta d[2]\}$
		$= \{x_{1k} - \delta, x_{2l} + \delta\}$	$= \{x_{1k} + \delta, x_{2l} - \delta\}$

Table 2:Possible Transition for the Bivariate Optimizing Up-and-Down Design on the Interior						
Event	$\mathbf{Y}^1\mathbf{(n)}$	$\mathbf{Y}^2\mathbf{(n)}$	$\mathbf{U(n)}$	$\mathbf{V(n)}$	$\mathbf{X(n+1)}$	$\mathbf{P}(\mathbf{E}_{ij} \mid \mathbf{T}^1\mathbf{(n)}, \mathbf{T}^2\mathbf{(n)})$
E_{01}	0	0	$[1,1]$	$[0,0]$	$[\circlearrowright, \circlearrowleft]$	$\frac{1}{4}\overline{\alpha}(T^1(n))\overline{\alpha}(T^2(n))$
E_{02}	0	0	$[-1,-1]$	$[0,0]$	$[\circlearrowright, \circlearrowleft]$	$\frac{1}{4}\overline{\alpha}(T^1(n))\overline{\alpha}(T^2(n))$
E_{03}	0	0	$[1,-1]$	$[0,0]$	$[\circlearrowright, \circlearrowleft]$	$\frac{1}{4}\overline{\alpha}(T^1(n))\overline{\alpha}(T^2(n))$
E_{04}	0	0	$[-1,1]$	$[0,0]$	$[\circlearrowright, \circlearrowleft]$	$\frac{1}{4}\overline{\alpha}(T^1(n))\overline{\alpha}(T^2(n))$
E_{05}	1	1	$[1,1]$	$[0,0]$	$[\circlearrowright, \circlearrowleft]$	$\frac{1}{4}\alpha(T^1(n))\alpha(T^2(n))$
E_{06}	1	1	$[1,-1]$	$[0,0]$	$[\circlearrowright, \circlearrowleft]$	$\frac{1}{4}\alpha(T^1(n))\alpha(T^2(n))$
E_{07}	1	1	$[-1,-1]$	$[0,0]$	$[\circlearrowright, \circlearrowleft]$	$\frac{1}{4}\alpha(T^1(n))\alpha(T^2(n))$
E_{08}	1	1	$[-1,1]$	$[0,0]$	$[\circlearrowright, \circlearrowleft]$	$\frac{1}{4}\alpha(T^1(n))\alpha(T^2(n))$
E_{11}	0	1	$[1,1]$	$[-1,-1]$	$[\downarrow, \downarrow]$	$\frac{1}{4}\overline{\alpha}(T^1(n))\alpha(T^2(n))$
E_{12}	1	0	$[-1,-1]$	$[-1,-1]$	$[\downarrow, \downarrow]$	$\frac{1}{4}\alpha(T^1(n))\overline{\alpha}(T^2(n))$
E_{21}	1	0	$[1,1]$	$[1,1]$	$[\uparrow, \uparrow]$	$\frac{1}{4}\alpha(T^1(n))\overline{\alpha}(T^2(n))$
E_{22}	0	1	$[-1,-1]$	$[1,1]$	$[\uparrow, \uparrow]$	$\frac{1}{4}\overline{\alpha}(T^1(n))\alpha(T^2(n))$
E_{31}	1	0	$[-1,1]$	$[-1,1]$	$[\downarrow, \uparrow]$	$\frac{1}{4}\alpha(T^1(n))\overline{\alpha}(T^2(n))$
E_{32}	0	1	$[1,-1]$	$[-1,1]$	$[\downarrow, \uparrow]$	$\frac{1}{4}\overline{\alpha}(T^1(n))\alpha(T^2(n))$
E_{41}	1	0	$[1,-1]$	$[1,-1]$	$[\uparrow, \downarrow]$	$\frac{1}{4}\alpha(T^1(n))\overline{\alpha}(T^2(n))$
E_{42}	0	1	$[-1,1]$	$[1,-1]$	$[\uparrow, \downarrow]$	$\frac{1}{4}\overline{\alpha}(T^1(n))\alpha(T^2(n))$

Table 3: Asymptotic Proportion of Subjects with Curtailment at the Boundary				
	Treatment 2			
Treatment 1	$\mathbf{1.5}$	$\mathbf{0.5}$	$\mathbf{-0.5}$	$\mathbf{-1.5}$
$\mathbf{1.5}$	0.06	0.07	0.06	0.05
$\mathbf{0.5}$	0.08	0.07	0.07	0.05
$\mathbf{-0.5}$	0.08	0.07	0.07	0.05
$\mathbf{-1.5}$	0.08	0.05	0.06	0.06

Table 4: Asymptotic Proportion of Subjects with Transitions Along the Boundary				
	Treatment 2			
Treatment 1	$\mathbf{1.5}$	$\mathbf{0.5}$	$\mathbf{-0.5}$	$\mathbf{-1.5}$
$\mathbf{1.5}$	0.02	0.05	0.05	0.02
$\mathbf{0.5}$	0.05	0.13	0.13	0.05
$\mathbf{-0.5}$	0.05	0.13	0.13	0.05
$\mathbf{-1.5}$	0.02	0.05	0.05	0.02

Table 5: Asymptotic Proportion of Subjects with Transitions Along the Boundary						
	Treatment 2					
Treatment 1	$\mathbf{2.5}$	$\mathbf{1.5}$	$\mathbf{0.5}$	$\mathbf{-0.5}$	$\mathbf{-1.5}$	$\mathbf{-2.5}$
$\mathbf{2.5}$	0.01	0.015	0.02	0.02	0.02	0.01
$\mathbf{1.5}$	0.02	0.04	0.04	0.04	0.04	0.02
$\mathbf{0.5}$	0.02	0.04	0.05	0.05	0.04	0.02
$\mathbf{-0.5}$	0.02	0.04	0.05	0.05	0.04	0.02
$\mathbf{-1.5}$	0.02	0.04	0.04	0.04	0.04	0.02
$\mathbf{-2.5}$	0.01	0.02	0.02	0.02	0.02	0.01

Table 6: Characteristics of Different Success Probability Functions			
SPF-	**Optimal Dose**	**Stationary**	**Mode**
	(m_1, m_2)	**Distribution**	$(\widehat{m}_1, \widehat{m}_2)$
1: Figure 2	$(0, 0)$	Figure 6	$(-\frac{1}{2}, -\frac{1}{2}), (\frac{1}{2}, -\frac{1}{2}), (-\frac{1}{2}, \frac{1}{2}), (\frac{1}{2}, \frac{1}{2})$
2: Figure 7	$(1, 1)$	Figure 8	$(\frac{1}{2}, \frac{1}{2})$
3: Figure 9	$(-1, -1)$	Figure 10	$(-\frac{1}{2}, -\frac{1}{2})$

Figures

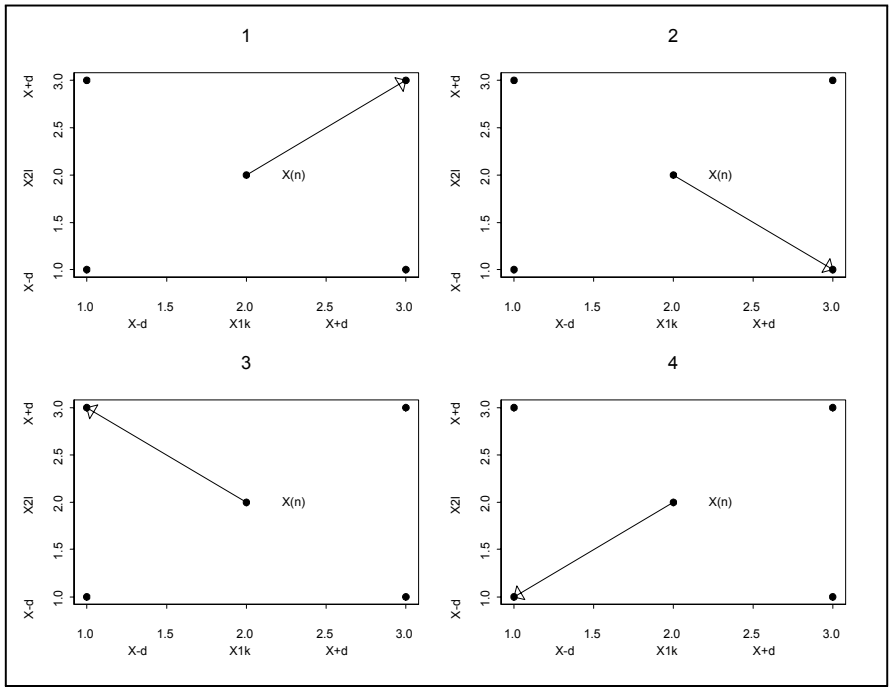

Figure 1. Possible Directions of the Treatment Midpoint X(n).

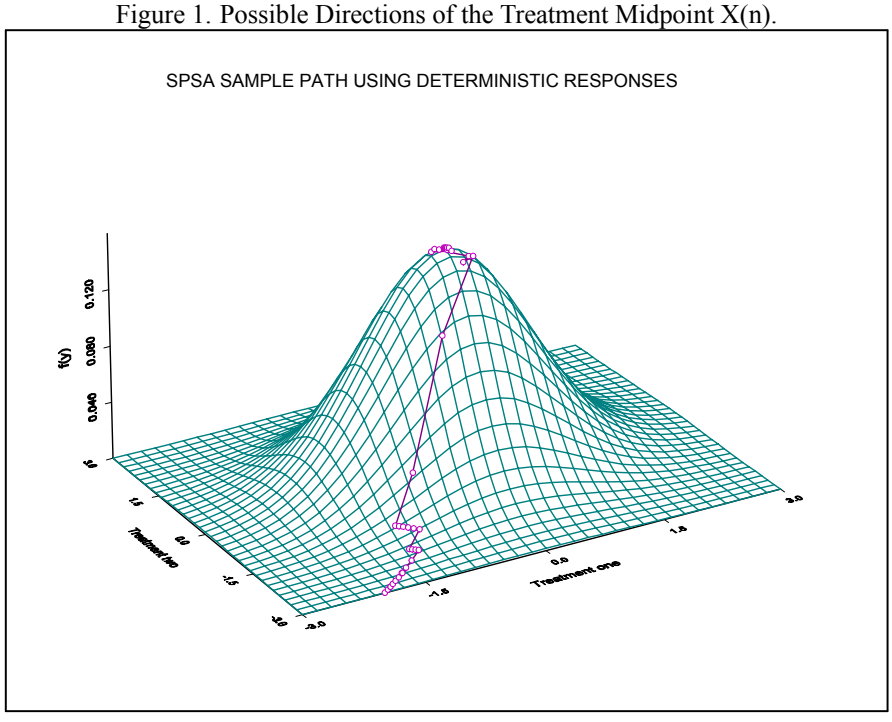

Figure 2. (eg.Bivariate Normal)

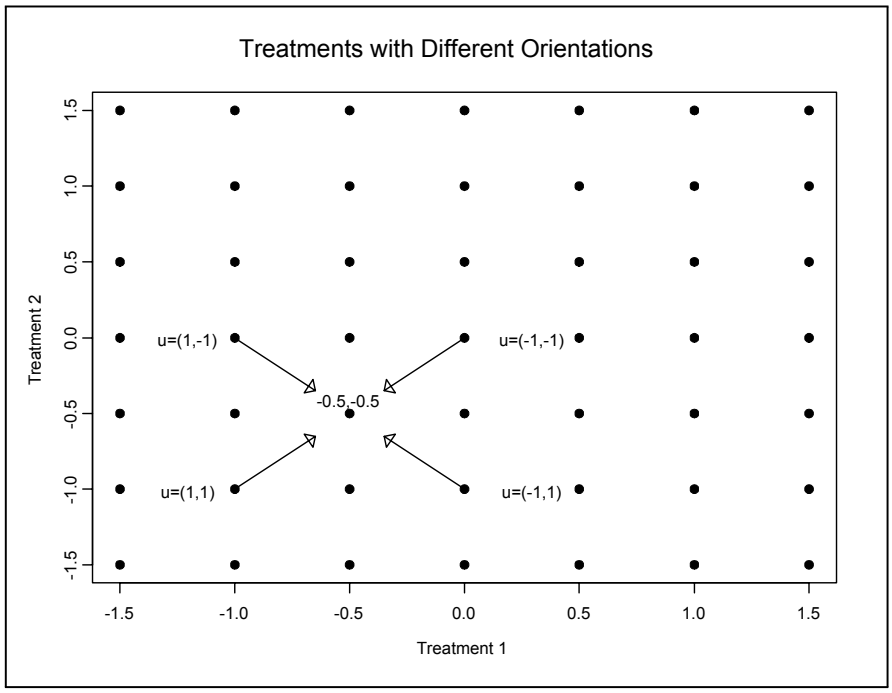

Figure 3. Treatments with Different Orientations.

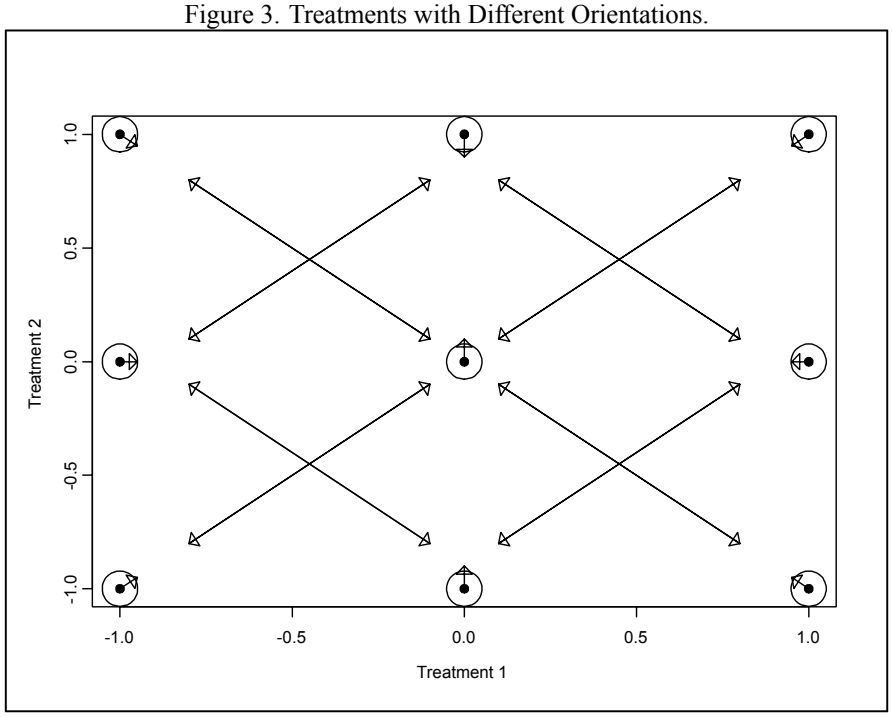

Figure 4. Possible Midpoint Transitions of X(n) with Curtailment at the Boundary.

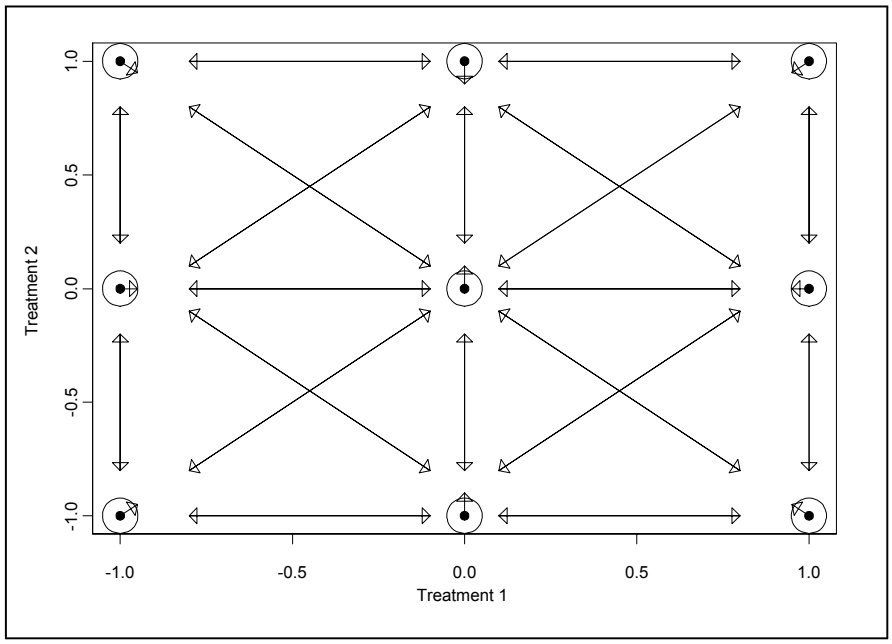

Figure 5. Possible Midpoint Transitions of X(n) with Transitions Along the Boundary.

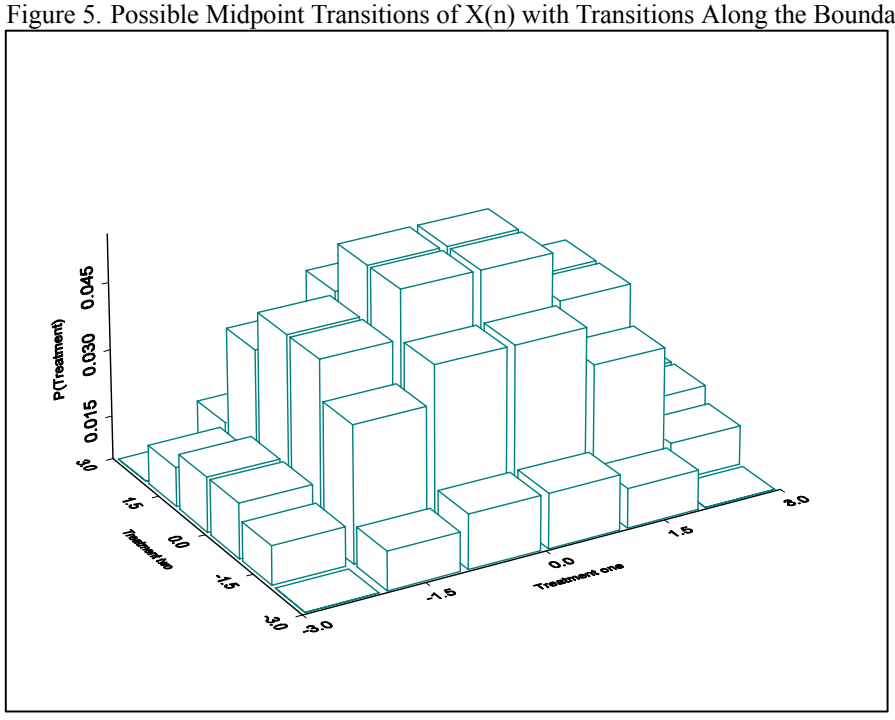

Figure 6. Stationary Distribution under SPF-1.

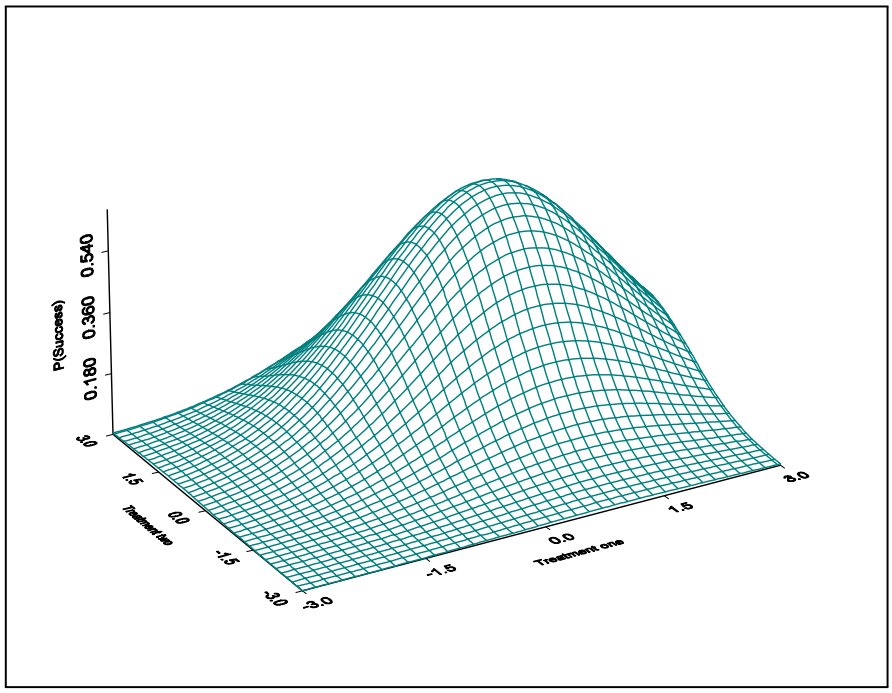

Figure 7. Left Skewed Response Function SPF-2.

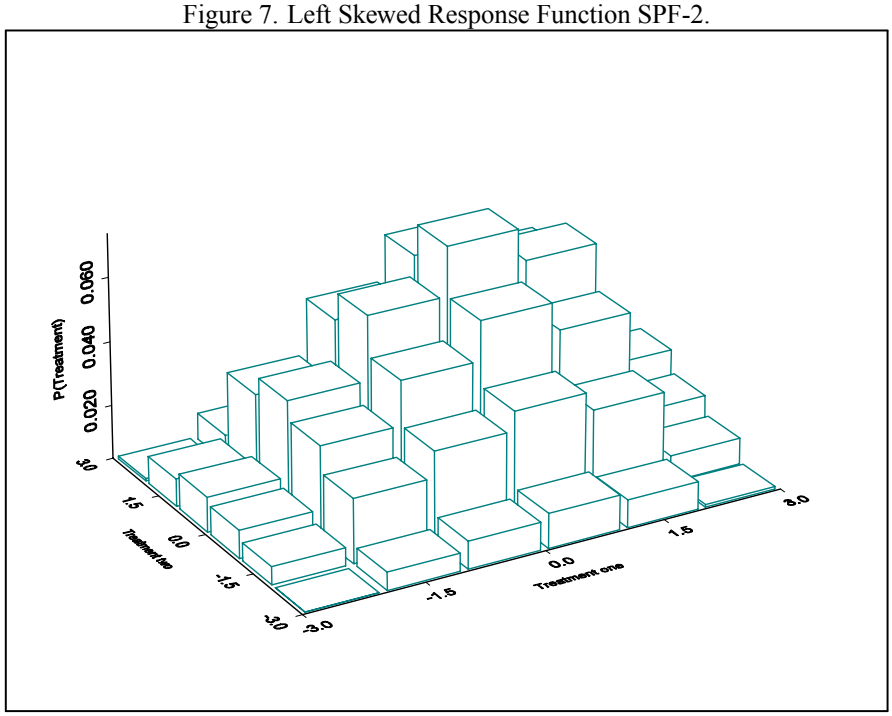

Figure 8. Stationary Distribution under SPF-2.

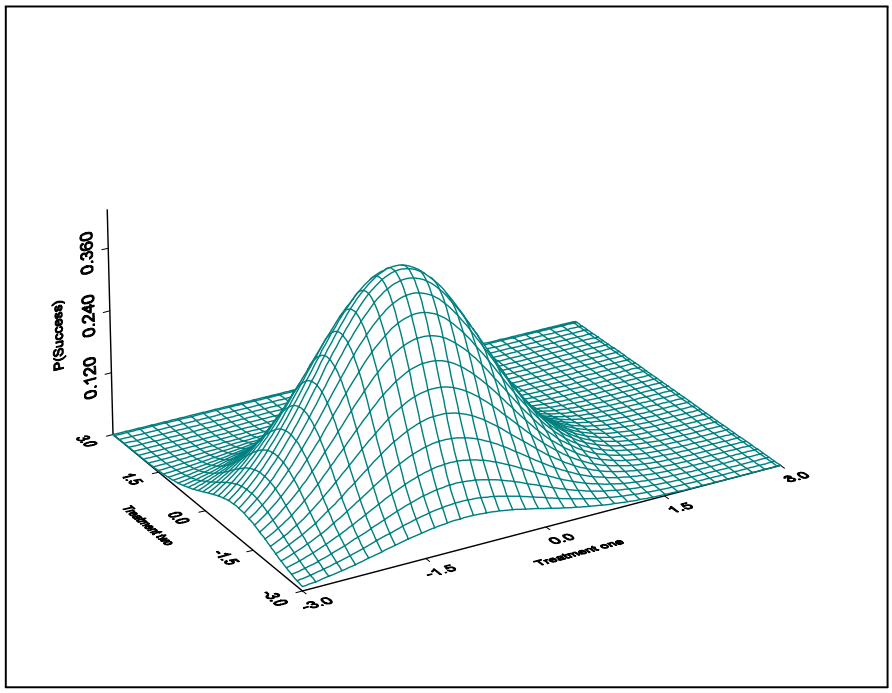

Figure 9. Right Skewed Response Function SPF-3.

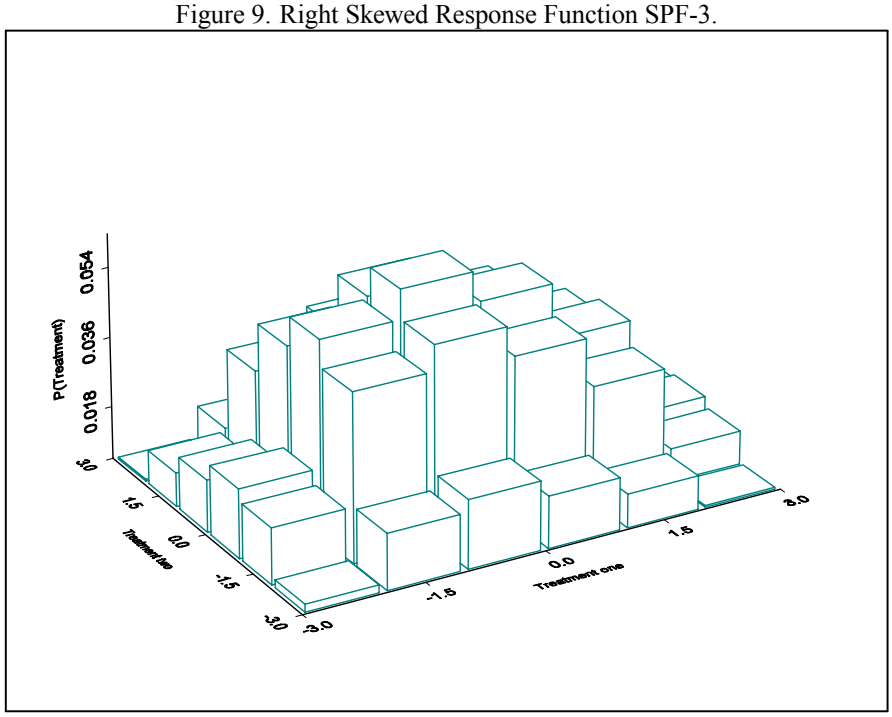

Figure 10. Stationary Distribution under SPF-3.

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