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Implementing ODA from Within Stata: An Application to Dose-Response Relationships (*Invited*)

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This paper describes how dose-response relationships can be evaluated using the new Stata package for implementing ODA.

Recent papers[1,2] introduced the new Stata package called **oda**[3] for implementing ODA from within the Stata environment. This package is a wrapper for the MegaODA software[4], and therefore the megaODA.exe file must be loaded on the computer for the **oda** package to work (ODA software is available at https://odajournal.com/resources/). To download the **oda** package, at the Stata command line type: "ssc install oda" (without the quotation marks).

In this paper, I demonstrate how the **oda** package can be used to evaluate the relationship between various doses of an exposure and a response variable, which is a generalization of the multivalued treatments problem.[5,6]

Linear statistical models, such as analysis of variance (ANOVA), generalized estimating equations (GEE), or multilevel models are widely used for estimating dose-response relationships. As a family, these parametric models share several drawbacks when used in dose-response studies. First, they assume a linear relationship exists between the dose and the response. Given that orderly, linear relationships rarely exist in health care data, such models may over- or under-estimate the true dose-response relationship at various points across the range of doses studied. Second, only a limited number of doses are typically tested in most dose-response studies, thus requiring interpolation or extrapolation for any dose not studied. Third, conventional statistical methods are intended for estimating treatment effects at the population level, are generally inaccurate when applied to small samples, and are inappropriate when used for making point predictions concerning the response effect for individuals.[7]

In **oda** we evaluate dose-response relationships by simply specifying the dose as the *class* variable and the outcome as the *attribute*. Further, if we assume the relationship increases in tandem (i.e., the response increases as dose is increased) we can speed up the algorithmic processing time by specifying the *directional* option (which computes one-sided *P*-values).[4]

Methods

Data

Data from Lang et al[8] measure the responses of blood flow in the forearm to the intra-arterial administration of isoproterenol in seven escalating doses (0, 10, 20, 60, 150, 300, 400 ng/min)

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in 9 normotensive black men and 13 normotensive white men. This study found that forearm blood-flow responses to isoproterenol were markedly attenuated in normotensive blacks, whereas the responses were approximately linear in white subjects. It was hypothesized that the mechanisms responsible for blunted vasodilatation in response to the administration of isoproterenol may contribute to enhanced vascular reactivity, thereby influencing the pathogenesis of hypertension in blacks.

Analytic Process

I repeat the ODA analyses performed previously on these data (Linden, Yarnold and Nallomothu[7] give a comprehensive description), that generate three separate models–one pooled, and two separately by race. All three models used forearm blood flow (attribute) to predict assignment to each dose level (class variable). All models are directional (i.e., "one-sided"), with the *a priori* hypothesis being that dose would increase with increasing forearm blood flow. *P* values are estimated by permutation tests with 25,000 iterations.

A statistically significant *P* value derived from these models indicates only that a dose-response relationship exists somewhere in the data, but it does not tell us where that relationship is. Therefore, after estimating the overall model, we perform all 21 pairwise tests to assess where the dose-response relationship is statistically significant, using the Sidak adjustment for multiple testing as specified in **oda** using the **sidak(#)** option, where # indicates the number of comparisons to be made.

I also conduct LOO analysis to assess the potential cross-generalizability of each ODA model when used to classify individuals other than those in the original study sample.

Pooled Model

Using the entire sample, **oda** is implemented with the following syntax (see the help file for **oda** for a complete description of the syntax options):

```
oda dose fbf, pathoda("C:\ODA\")
store("C:\ODA\output") iter(25000) loo
direction(lt 0 10 20 60 150 300 400)
seed(1234)
```

The above syntax is explained as follows: The variable "dose" is the *class* variable; the outcome variable "fbf" (forearm blood flow) is the *attribute*; the directory path where the megaODA.exe file is located on my computer is "C:\ODA\"; the directory path where the output and other files generated during the analysis should be stored is "C:\ODA\output"; the number of iterations (repetitions) for computing a permutation *P*-value is 25,000; leave-one-out (LOO) analysis should be performed; the analysis should be directional (one-sided) with the assumption that fbf increases as dose increases; and the seed should be set to 1234 (any seed value will suffice) to ensure replication of the permutation results.

The **oda** package produces an extract of the total output produced by the ODA software (the complete output is stored in the specified directory with the extension ".out").

As seen in the **oda** output, the ODA model is interpreted as follows: "if fbf <= 2.53, then predict that the dose is 0. If fbf is between 2.53 and 2.95, predict that the dose is 10. If fbf is between 2.95 and 6.86, predict the dose is 20. If fbf is between 6.86 and 7.36, predict the dose is 60. If fbf is between 7.36 and 9.85, predict the dose is 150. If fbf is between 9.85 and 21.0, predict the dose is 300. And, if fbf is > 21.0, predict that the dose is 400."

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```
ODA model:
----------
IF FBF <= 2.52999995 THEN DOSE = 0
IF 2.52999995 < FBF <= 2.94500005 THEN DOSE = 10
IF 2.94500005 < FBF <= 6.855 THEN DOSE = 20
IF 6.855 < FBF <= 7.355 THEN DOSE = 60
IF 7.355 < FBF <= 9.8500002 THEN DOSE = 150
IF 9.8500002 < FBF <= 21.0 THEN DOSE = 300
IF 21.0 < FBF THEN DOSE = 400


Summary for Class DOSE  Attribute FBF
---------------------------------------

Performance Index           Train    LOO
-----------------          ------  ------
Overall Accuracy            41.50%  38.10%
PAC DOSE=0                  66.67%  66.67%
PAC DOSE=10                 28.57%  28.57%
PAC DOSE=20                 71.43%  71.43%
PAC DOSE=60                  4.76%   0.00%
PAC DOSE=150                23.81%  14.29%
PAC DOSE=300                57.14%  47.62%
PAC DOSE=400                38.10%  38.10%
Effect Strength PAC         31.75%  27.78%
PV DOSE=0                   60.87%  60.87%
PV DOSE=10                  60.00%  60.00%
PV DOSE=20                  32.61%  32.61%
PV DOSE=60                  16.67%   0.00%
PV DOSE=150                 38.46%  23.08%
PV DOSE=300                 37.50%  33.33%
PV DOSE=400                 47.06%  44.44%
Effect Strength PV          32.19%  25.72%
Effect Strength Total       31.97%  26.75%


Monte Carlo summary (Fisher randomization):
-------------------------------------------
Iterations:  25000
Estimated p: 0.000000


Results of leave-one-out analysis
---------------------------------
147 observations
(P-values are computed for binary class variables only)
```

The effect strength for sensitivity (ESS) is labelled in the output as "Effect Strength PAC" (Percentage Accurate Classification). In the training data the ESS is 31.75% and in the LOO analysis it is 27.78% (moderate effects).[9] The permutation *P*-value for the training sample was < 0.00001, while no *P*-value can be computed in LOO analyses with > 2 treatment (*class* variable) levels. In summary, ODA was able to find a model that moderately discriminated between doses, and was statistically significant.

Table 1 presents the *P* values and Sidak adjusted *P* values for all pairwise comparisons between doses. As shown, some pairwise comparisons (e.g. 0 *vs*. 10, 60 *vs*. 150, 150 *vs*. 400, etc.) are not statistically significant--either in the permutation P (training data) or in the LOO or both, and with adjustment for 21 tests, the bar for achieving significance is made more difficult. It is evident that forearm blood flow does not increase linearly with dose.

Table 1: *P* values and Sidak adjusted *P* values for all pairwise comparisons between doses – pooled data.

Dose Pairs	P (Perm)	Adj P (Perm)	P (LOO)	Adj P (LOO)
0,10	0.151	0.968	0.061	0.732
0,20	<0.001	0.001	0.001	0.014
0,60	<0.001	<0.001	0.552	1.000
0,150	<0.001	<0.001	0.552	1.000
0,300	<0.001	<0.001	0.821	1.000
0,400	<0.001	<0.001	0.552	1.000
10,20	0.002	0.047	0.001	0.014
10,60	<0.001	<0.001	<0.001	0.000
10,150	<0.001	<0.001	0.862	1.000
10,300	<0.001	<0.001	0.470	1.000
10,400	<0.001	<0.001	0.862	1.000
20,60	0.007	0.145	0.002	0.037
20,150	0.000	0.003	0.000	0.001
20,300	<0.001	<0.001	0.000	0.001
20,400	<0.001	0.001	0.000	0.000
60,150	0.657	1.000	1.000	1.000
60,300	0.048	0.646	0.031	0.482
60,400	0.100	0.891	0.253	0.998
150,300	0.097	0.881	0.059	0.721
150,400	0.168	0.979	0.170	0.980
300,400	0.472	1.000	0.253	0.998

Analysis Limited to White Patients

The **oda** syntax for analyzing data of the white patients only is as follows:

```
oda dose fbf if race==1, pathoda("C:\ODA\")
store("C:\ODA\output") iter(25000) loo
direction(lt 0 10 20 60 150 300 400)
seed(1234)
```

As can be seen, the syntax is nearly identical to that used in the prior example, with the only difference being the addition of the [if] specification: ***"if race==1"*** which indicates that

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the analysis should be limited to race = white. The **oda** output for this model is as follows:

```
ODA model:
----------
IF FBF <= 2.14999995 THEN DOSE = 0
IF 2.14999995 < FBF <= 3.95000005 THEN DOSE = 10
IF 3.95000005 < FBF <= 7.29999995 THEN DOSE = 20
IF 7.29999995 < FBF <= 12.05 THEN DOSE = 60
IF 12.05 < FBF <= 17.4499995 THEN DOSE = 150
IF 17.4499995 < FBF <= 21.1999995 THEN DOSE = 300
IF 21.1999995 < FBF THEN DOSE = 400


Summary for Class DOSE  Attribute FBF
--------------------------------------

Performance Index           Train    LOO
-----------------          ------  ------
Overall Accuracy            48.81%  39.29%
PAC DOSE=0                  50.00%  50.00%
PAC DOSE=10                 58.33%  50.00%
PAC DOSE=20                 66.67%  58.33%
PAC DOSE=60                 41.67%  25.00%
PAC DOSE=150                33.33%  25.00%
PAC DOSE=300                33.33%  25.00%
PAC DOSE=400                58.33%  41.67%
Effect Strength PAC         40.28%  29.17%
PV DOSE=0                   66.67%  66.67%
PV DOSE=10                  58.33%  50.00%
PV DOSE=20                  61.54%  46.67%
PV DOSE=60                  41.67%  27.27%
PV DOSE=150                 33.33%  25.00%
PV DOSE=300                 40.00%  27.27%
PV DOSE=400                 43.75%  35.71%
Effect Strength PV          40.88%  29.77%
Effect Strength Total       40.58%  29.47%


Monte Carlo summary (Fisher randomization):
-------------------------------------------
Iterations:  25000
Estimated p: 0.000000


Results of leave-one-out analysis
---------------------------------
84 observations
(P-values are computed for binary class variables only)
```

As shown in the **oda** output, the ODA model can be interpreted as follows: "if fbf <= 2.15, then predict that the dose is 0. If fbf is between 2.15 and 3.95, predict the dose is 10. If fbf is between 3.95 and 7.30, predict the dose is 20. If fbf is between 7.30 and 12.05, predict the dose is 60. If fbf is between 12.05 and 17.45, predict the dose is 150. If fbf is between 17.45 and 21.20, predict the dose is 300. If fbf is > 21.20, predict the dose is 400."

In the training data the ESS is 40.28% and in the LOO analysis it is 29.17% (moderate effects).[9] The permutation *P*-value for the training sample was < 0.00001. In summary, in the sample limited to white subjects, ODA was able to find a model that moderately discriminated between doses, and was statistically significant. It is evident from the data in Table 2 that forearm blood flow does not increase linearly with dose.

Table 2: *P* values and Sidak adjusted *P* values for all pairwise comparisons between doses – white patients only.

Dose Pairs	P (Perm)	Adj P (Perm)	P (LOO)	Adj P (LOO)
0,10	0.457	1.000	0.200	0.991
0,20	0.001	0.016	0.002	0.034
0,60	<0.001	0.001	<0.001	0.001
0,150	<0.001	0.001	<0.001	0.001
0,300	<0.001	<0.001	0.370	1.000
0,400	<0.001	<0.001	<0.001	0.000
10,20	0.001	0.021	0.006	0.121
10,60	<0.001	0.002	<0.001	0.007
10,150	<0.001	<0.001	0.002	0.034
10,300	<0.001	<0.001	<0.001	0.001
10,400	<0.001	<0.001	<0.001	0.001
20,60	0.004	0.075	0.020	0.340
20,150	0.004	0.077	0.050	0.658
20,300	<0.001	<0.001	<0.001	0.007
20,400	<0.001	0.001	<0.001	0.001
60,150	0.481	1.000	0.893	1.000
60,300	0.127	0.943	0.034	0.520
60,400	0.048	0.641	0.342	1.000
150,300	0.488	1.000	0.903	1.000
150,400	0.125	0.940	0.200	0.991
300,400	0.468	1.000	0.950	1.000

Analysis Limited to Black Patients

The **oda** syntax for analyzing data of the black patients only is as follows:

```
oda dose fbf if race==2, pathoda("C:\ODA\")
store("C:\ODA\output") iter(25000) loo
direction(lt 0 10 20 60 150 300 400)
seed(1234)
```

As can be seen, the syntax is nearly identical to that used in the prior example, with the only difference being the addition of the [if]

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specification: ***"if race==2"*** which indicates that the analysis should be limited to race = black. The **oda** output for this model is as follows:

```
ODA model:
----------
IF FBF <= 2.52999995 THEN DOSE = 0
IF 2.52999995 < FBF <= 2.94500005 THEN DOSE = 10
IF 2.94500005 < FBF <= 3.68000005 THEN DOSE = 20
IF 3.68000005 < FBF <= 4.08500005 THEN DOSE = 60
IF 4.08500005 < FBF <= 4.375 THEN DOSE = 150
IF 4.375 < FBF <= 18.950001 THEN DOSE = 300
IF 18.950001 < FBF THEN DOSE = 400


Summary for Class DOSE  Attribute FBF
---------------------------------------

Performance Index           Train    LOO
-----------------          ------  ------
Overall Accuracy            49.21%  39.68%
PAC DOSE=0                  77.78%  66.67%
PAC DOSE=10                 44.44%  33.33%
PAC DOSE=20                 44.44%  44.44%
PAC DOSE=60                 33.33%  33.33%
PAC DOSE=150                33.33%   0.00%
PAC DOSE=300               100.00%  88.89%
PAC DOSE=400                11.11%  11.11%
Effect Strength PAC         40.74%  29.63%
PV DOSE=0                   63.64%  60.00%
PV DOSE=10                  57.14%  42.86%
PV DOSE=20                  57.14%  50.00%
PV DOSE=60                  50.00%  33.33%
PV DOSE=150                 42.86%   0.00%
PV DOSE=300                 37.50%  38.10%
PV DOSE=400                100.00% 100.00%
Effect Strength PV          51.38%  37.38%
Effect Strength Total       46.06%  33.51%


Monte Carlo summary (Fisher randomization):
-------------------------------------------
Iterations:  25000
Estimated p: 0.000000


Results of leave-one-out analysis
---------------------------------
63 observations
(P-values are computed for binary class variables only)
```

As seen in the **oda** output, the ODA model for black patients only is very similar to that of the pooled sample (whereas the white subset of patients differed). In the training data the ESS is 40.74% and in the LOO analysis it is 29.63% (a moderate effect).[9] The permutation *P*-value for the training sample was < 0.00001. In summary, in the sample limited to black subjects, ODA was able to find a model that moderately discriminated between doses, and was statistically significant.

Table 3 indicates that, like the pooled and white patient sample, forearm blood flow does not increase linearly with dose in the black patient sample.

Table 3: *P* values and Sidak adjusted *P* values for all pairwise comparisons between doses – black patients only.

Dose Pairs	P (Perm)	Adj P (Perm)	P (LOO)	Adj P (LOO)
0,10	0.152	0.969	0.173	0.982
0,20	0.016	0.291	0.077	0.813
0,60	<0.001	0.009	0.002	0.035
0,150	<0.001	<0.001	<0.001	<0.001
0,300	<0.001	<0.001	<0.001	<0.001
0,400	<0.001	<0.001	<0.001	<0.001
10,20	0.149	0.966	0.173	0.982
10,60	0.003	0.053	0.008	0.148
10,150	<0.001	0.009	0.002	0.035
10,300	<0.001	<0.001	<0.001	0.004
10,400	<0.001	0.009	0.002	0.035
20,60	0.016	0.292	0.008	0.148
20,150	0.003	0.060	0.025	0.411
20,300	<0.001	0.007	0.008	0.148
20,400	0.003	0.060	0.025	0.411
60,150	0.379	1.000	0.681	1.000
60,300	0.065	0.757	0.077	0.813
60,400	0.384	1.000	0.681	1.000
150,300	0.177	0.983	0.827	1.000
150,400	0.803	1.000	0.897	1.000
300,400	0.900	1.000	0.500	1.000

Discussion

This paper demonstrates how the new Stata package **oda** can be used to evaluate dose-response relationships. ODA should be considered the preferred approach over commonly-used parametric models because ODA avoids the assumptions required of parametric models, is insensitive to skewed data or outliers, and has the ability to handle any variable metric including categorical, Likert-type integer, and real number measurement scales.[4] Moreover, in contrast to regression or ANOVA models, ODA also has the distinct ability to ascertain where the optimal (maximum-accuracy) cutpoints are on the outcome

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variable, which in turn, facilitates the use of measures of predictive accuracy. Moreover, ODA can perform cross-validation using LOO which allows for assessing the cross-generalizability of the model to potentially new study participants or non-participants.

Finally, the findings continue to support our recommendation to employ the ODA and CTA frameworks to draw causal inferences regarding treatment effects in observational data, and in data from randomized controlled trials.[6,7,10-25] A large, ever-increasing body of evidence supports the use of ODA and CTA to evaluate the efficacy of health-improvement interventions and policy initiatives.[26-29]

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Author Notes

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