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THE STATA JOURNAL

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Abstract. This article describes a substantial update to mvis, which brings it more closely in line with the feature set of S. van Buuren and C. G. M. Oudshoorn's implementation of the MICE system in R and S-PLUS (for details, see

http://www.multiple-imputation.com). To make a clear distinction from mvis, the principal program of the new Stata release is called ice. I will give details of how to use the new features and a practical illustrative example using real data. All the facilities of mvis are retained by ice. Some improvements to micombine for computing estimates from multiply imputed datasets are also described.

Keywords: st0067_1, ice, mvis, uvis, micombine, mijoin, misplit, missing data, missing at random, multiple imputation, multivariate imputation, regression modeling

1 Introduction

Royston (2004) introduced mvis, an implementation for Stata of a method of multiple multivariate imputation of missing values under missing-at-random (MAR) assumptions. The method is known as MICE, an acronym for multiple imputation by chained equations (van Buuren et al. 1999). See van Buuren's article for details of the theory behind MICE and his interesting web site http://www.multiple-imputation.com for abundant literature references, reports, information, and software links. The material will not be repeated here.

Royston (2004) presented five ado-files: mvis to create multiple multivariate imputations; uvis to impute missing values of a single variable as a function of several covariates, each with complete data; micombine to fit a wide variety of regression models to a multiply imputed dataset, combining the estimates using Rubin's rules (1987); and misplit and mijoin, utilities to inter-convert datasets created by mvis and by Carlin et al.'s miset routine (2003).

In this article, I will describe a substantial update to mvis, which brings it more closely in line with the feature set of S. van Buuren and C. G. M. Oudshoorn's implementation of MICE in R and S-PLUS (for details, see

http://www.multiple-imputation.com). To avoid confusion with mvis, the principal program of the new Stata release is called ice. I will give details of how to use the new features and a practical illustrative example using real data. All the facilities of mvis are retained by ice. Some improvements to micombine are also described.

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 $\mathrm{st0067_1}$

2 Syntax

ice mainvarlist using filename[.dta] [if exp] [in range] [weight] [, <u>bo</u>ot[(varlist)] cc(ccvarlist) <u>cm</u>d(cmdlist) <u>cycles(#) draw[(varlist)]</u> <u>dryrun eq(eqlist) genmiss(string) id(string) m(#) on(varlist) noconstant <u>noshoweq passive(passivelist) sub</u>stitute(sublist) replace <u>seed(#)</u>]</u>

uvis regression_cmd yvar xvarlist [if exp] [in range] [weight], gen(newvarname) [noconstant boot draw replace seed(#)]

where *regression_cmd* may be logistic, logit, mlogit, ologit, or regress. All weight types supported by *regression_cmd* are allowed.

```
micombine regression_cmd [yvar] [covarlist] [if exp] [in range] [weight] [,
    br <u>noconstant detail eform(string) genxb(newvarname) impid(varname)
    lrr obsid(varname) regression_cmd_options]</u>
```

where *regression_cmd* may be clogit, cnreg, glm, logistic, logit, poisson, probit, qreg, regress, rreg, xtgee, streg, stcox, ologit, oprobit, or mlogit. All weight types supported by *regression_cmd* are allowed.

mijoin [filestubname], clear [m(#) impid(varname)]

misplit, clear [m(#) impid(varname)]

The options are described in the help files. Features new to mvis and now in ice are discussed in some detail in the next section. New features of micombine are discussed in the section Changes to micombine.

3 Options

I shall give details here only of options that are new or modified from the previous release of the suite of programs.

3.1 New options for ice

dryrun does a "dry run"; that is, ice reports the prediction equations it has constructed from the various inputs. No imputation is done, and no files are created. It is not mandatory to specify an output file with using for a dry run. The prediction equation setup needs to be carefully checked before running what may be a lengthy imputation process.

eq(eqlist) allows customization of prediction equations for any subset of variables in mainvarlist. The eq() option, particularly when used with passive(), allows great flexibility in the possible imputation schemes. The syntax of eqlist is varname1:varlist1 [, varname2:varlist2 ...] where each varname# (or varlist#) is a member or subset of mainvarlist. It is your responsibility to ensure that each equation is sensible. ice places no restrictions except to check that all variables mentioned are indeed in mainvarlist, and that an equation is not defined for a variable specified to be passively imputed (see the passive() option). Note that eq() takes precedence over all default definitions and assumptions about the way a given variable in mainvarlist will be imputed. The default, if the passive() and substitute() options are not invoked, is that each variable in mainvarlist with any missing data is imputed from all the other variables in mainvarlist.

noshoweq suppresses the presentation of the prediction equations.

- passive(passivelist) allows the use of "passive" imputation of variables that depend on other variables, some of which are imputed. The syntax of passivelist is varname: exp [\varname: exp ...]. Here exp denotes a valid Stata expression (see help exp in Stata). Notice the requirement to use '\' as a separator between items in passivelist, rather than the usual comma; the reason is that a comma may be a valid part of an expression. The option is most easily explained by example. Suppose that x1 is a categorical variable with 3 levels, and that two dummy variables x1a and x1b have been created by the commands
 - . generate byte x1a=(x1==2)
 - . generate byte x1b=(x1==3)

Now suppose that x1 is to be imputed by the mlogit command and is to be treated as the two dummy variables x1a and x1b when predicting other variables. Use of mlogit is achieved by the option cmd(x1:mlogit). When x1 is imputed, we want x1a and x1b to be updated with new values that depend on the imputed values of x1. This may be achieved by specifying passive(x1a:x1==2\x1b:x1==3). It is necessary also to remove x1 from the list of predictors when variables other than x1 are being imputed, and this is done by using the substitute() option; in the present example, you would specify substitute(x1:x1a x1b). In this example, the generate statements given above will make x1a take the (possibly unintended) value of 0 when x1 is missing. However, ice is careful to ensure that x1a and x1b inherit the missingness of x1 and are passively imputed following active imputation of missing values of x1. If this were not done, incorrect results could occur. The responsibility of the user is to create x1a and x1b before running ice such that their missing values are identical to those of x1. The values they assume initially are irrelevant since ice recalculates them anyway.

A second example is multiplicative interactions between variables, say, between x1 and x2 (e.g., x12=x1*x2); this could be implemented through passive(x12:x1*x2).

It would cause the interaction term x12 to be omitted when either x1 or x2 was being imputed since it would make no sense to impute x1 from its interaction with x2. The substitute() option is not needed here. It should be stressed that variables to be imputed passively must be included in *mainvarlist*; otherwise, they will not be recognized.

substitute(sublist) is typically used with the passive() option to represent multilevel categorical variables as dummy variables in models for predicting other variables. See passive() for more details. The syntax of sublist is varname: dummyvarlist [,varname: dummyvarlist ...], where varname is the name of a variable to be substituted and dummyvarlist is the list of dummy variables representing it.

3.2 Options for uvis, mijoin, misplit, micombine

None of the options for uvis, mijoin, misplit have been changed. Details of some changes to micombine are given in the section *Changes to micombine*.

4 What is new?

The changes to mvis implemented in ice mainly affect two areas:

- 1. The flexibility of the prediction equations used in the system of chained equations and
- 2. The way the program handles categorical variables, interactions, and transformations.

4.1 Flexible prediction equations

The earlier program mvis is restricted to imputing missing observations for each variable in *mainvarlist* from all the other members of *mainvarlist*. While this is sensible in many applications, there are many other cases in which greater flexibility is needed. I will give a relatively simple example in the section *Example: Fetal size*. With the eq() option of ice, an equation (i.e., a list of right-hand-side variables, comprising part of a model) may be specified in order to impute any variable in *mainvarlist* from any subset of *mainvarlist*. The eq() option overrides all automatic behavior invoked by the passive() and substitute() options (described in context below), giving the user ultimate control over the prediction equations.

4.2 Categorical variables

mvis does not handle categorical variables in an ideal fashion. For example, suppose that x1 is continuous and x2 is a three-level unordered categorical variable taking the values 0, 1, 2, both variables having missing data. It would be preferable to impute x1 by linear regression on dummy variables x21 and x22 indicating values of 1 and 2,

respectively, of x^2 . A natural way to impute x^2 is by multinomial logistic regression (mlogit command) of x^2 on x^1 . A possible way to achieve this with mvis may be thought to be

. generate byte x21=(x2==1) if x2<.
. generate byte x22=(x2==2) if x2<.
. mvis x1 x2 using temp, m(5) cmd(x2:mlogit)</pre>

However, although appropriate for predicting x^2 , this approach predicts x^1 from x^2 but not from the dummy variables x^{21} and x^{22} , which are not used. An alternative scheme with dummy variables for x^2 ,

```
. mvis x1 x21 x22 using temp, m(5) cmd(x21 x22:logit)
```

does not allow constrained imputation of x2 (as would be achieved by using mlogit). The result could be inconsistent estimates of the missing values of x2 when the latter is reconstructed from the original and imputed values of x21 and x22. For example, suppose that x2 = 2 in a particular observation. Then x21 = 0 and x22 = 1. Suppose that x2 were missing for this observation and that x21 and x22 were imputed independently, as in the command above. It could happen by chance that x21 = 1 and x22 = 1, which do not encode a possible value of x2. An appropriate solution with ice is

. ice x1 x2 x12 x22 using temp, m(5) cmd(x2:mlogit)
 passive(x21:x2==1\x22:x2==2) substitute(x2:x21 x22)

The logic here is worth spelling out. *mainvarlist* must include all variables that are involved in the imputation; hence x2 and both its dummy variables are listed. However, we do not wish to predict x1 from x2 x12 x22, but only from x12 x22. This is achieved by the option substitute(x2:x21 x22), which replaces x2 with x21 x22 whenever x2 is a predictor and removes redundant mentions of variables already included. Finally, it is necessary to construct imputed values of x21 and x22 from imputed values of x2, the latter being obtained internally via the model mlogit x2 x1. This is done by the option passive(x21:x2==1\x22:x2==2), which recalculates the dummy variables from the newly imputed values of x2.

Although it may at first sight appear complicated, the approach is consistent. The options passive(), substitute(), and eq() together cover all practical possibilities with categorical variables in a unified syntax. More generally, passive imputation (a term coined, I believe, by Steff van Buuren) is an important feature of the MICE system for dealing flexibly with categorical covariates, interactions, transformations and the like. The substitute() option is mainly a convenience feature, since substitution could be achieved explicitly by use of the eq() option, for example, eq(x1:x21 x22) instead of substitute(x2:x21 x22).

4.3 Interactions

Correct imputation involving multiplicative interactions requires the passive() option. Suppose that we plan to impute continuous variables x1 and x2 and a binary variable

z. Suppose also that there are good reasons for imputing x^2 from the main effects and interaction of x^1 with z, that is from x^1 , z, and a new variable $x^1z = x^1*z$. How do we impute x^1 and z in this situation? If we were to specify

```
. generate x1z=x1*z
. ice x1 x2 z x1z using temp, m(5)
```

we would get x2 imputed from x1, z, and x1z (as required); x1 from x2, z, and x1z; and z from x1, x2, and x1z. However, it makes no sense to impute a variable from its interaction with another variable. We wish to eliminate the interaction term x1z from the prediction equations for x1 and z. Even if the problem were tackled by using the eq() option, because of the danger of inconsistency we do not want the imputation of x1z to be treated independently of the imputation of its components, x1 and z. The way to solve the problem is to use the passive() option. Note also the dryrun option that allows us to see and check the prediction equations but not yet to run the imputations:

. ice x1 x2 z x1z using temp, m(5) passive(x1z:x1*z) dryrun					
Variable	Command	Prediction equation			
x1 x2 z x1z	regress mlogit	[No missing data in estimation sample] x1 z x1z x1 x2 [Passively imputed from x1*z]			

End of dry run. No imputations were done, no files were created.

As seen above, ice automatically removes the composite passive variable x1z from the relevant prediction equations. When it discerns that x1z is computed from x1 and z, it knows to exclude x1z from the prediction equations for imputing x1 and z. This would happen with any variable that is a combination of others.

4.4 Transformations

Simple or complex transformations may be handled by combining the passive() and eq() options. Here is a fairly complicated but realistic example, which prefigures the example presented in detail in the section *Example: Fetal size*. Suppose that we have three continuous variables y1, y2, and x, all with missing values. Preliminary analysis indicates that the following prediction equations are appropriate:

$$E(y_1) = \beta_1 x^{-2} + \beta_2 x^{-1}$$
$$E(y_2) = \gamma_1 x + \gamma_2 x^2$$
$$E(x) = \delta_1 y_1 + \delta_2 y_2$$

In other words, in expectation, y1 is a fractional polynomial function of x with powers (-2, -1), y2 is a quadratic function of x, and x is a linear function of y1 and y2. You may imagine y1 and y2 to be two response variables linked to a common covariate, x. With this imputation scheme, missing values may be imputed in *ice* as follows:

```
. generate xa=x^-2
```

```
. generate xb=x^-1
```

```
. generate xc=x^2
. ice y1 y2 x xa xb xc using temp, m(5) passive(xa:x^-2\xb:x^-1\xc:x^2)
> eq(y1:xa xb, y2:x xc, x:y1 y2)
    Variable
                Command
                                 Prediction equation
           v1
                 regress
                                 xa xb
           y2
                 regress
                                 x xc
                                 y1 y2
           х
                 regress
                                 [Passively imputed from x<sup>-2</sup>]
           xa
           xb
                                 [Passively imputed from x<sup>-1</sup>]
           xc
                                 [Passively imputed from x<sup>2</sup>]
```

Here the equation for each variable must be defined explicitly, and this is easily done by using the eq() option.

4.5 More on passively imputed variables

Passive (passively imputed) variables in general are computed directly as a function of one or more active (actively imputed) variables. They inherit their missing values from their component active variables. An active variable is a member of *mainvarlist* that is not defined as passive and that has at least one missing value in the estimation sample. Finally, there is a third class of fully observed variables that have no missing values within the estimation sample defined by if, in, and weights.

It is sometimes convenient to create passive variables as a function of other passive (and perhaps also of active and fully observed) variables. This will work fine provided that the chain of computation of passive variables is correctly reflected in the order of the variables presented in *mainvarlist*. For example, the command

. ice y x z xa xaz using temp, m(5) passive(xa:x^-2\xaz:xa*z) eq(y:xa z xaz, x:y z, z:y xa)

will compute xa=x⁻² followed by xaz=xa*z, which is appropriate since x and z precede xa and xa precedes xaz in *mainvarlist*. On the other hand, on reversing xa and xaz in *mainvarlist*, namely

```
. ice y x z xaz xa using temp, m(5) passive(xa:x^-2\xaz:xa*z)
eq(y:xa z xaz, x:y z, z:y xa)
```

will cause *ice* to recalculate *xaz* before *xa* has been updated from *x*. This will give incorrect results. The rule is simple: structure *mainvarlist* such that primary passive variables (that is, variables that are derived only from active variables) precede secondary passive variables (which depend on primary passive variables) and the latter precede tertiary passive variables (which involve secondary passive variables), and so on. The order of definition of passive variables in the *passive()* option is immaterial.

Note that secondary and higher-order passive variables are not traced back to their original active variables and are therefore not automatically removed from the prediction equations of the relevant active variables. Consider the example

```
. ice x1 x2 z z1 z2 x2z1 x2z2 using temp, replace m(5) substitute(z:z1 z2)
> passive(z1:z==1\z2:z==2\x2z1:x2*z1\x2z2:x2*z2)
```

Variable	Command	Prediction equation		
x1 x2 z1 z2 x2z1 x2z1 x2z2	regress regress mlogit	x2 z1 z2 x2z1 x2z2 x1 z1 z2 x1 x2 x2z1 x2z2 [Passively imputed from z==1] [Passively imputed from z==2] [Passively imputed from x2*z1] [Passively imputed from x2*z2]		

We see that z is inappropriately going to be predicted from x1, x2, and z's interaction with x2, expressed indirectly through the interaction between x2 and z1, z2. Here, x2z1 and x2z2 are defined as secondary passive variables. To correct the problem, you could either specify the equation for z directly, e.g., eq(z:x1 x2) or define only primary passive variables, as in $passive(z1:z=1\backslashz2:z=2\backslashx2z1:x2*(z==1)\backslashx2z2:x2*(z==2))$. The second solution is perhaps cleaner, though more laborious.

5 Example: Fetal size

5.1 Data

I will present an example that is rather different from the usual sort of imputation problem encountered in clinical biostatistics and epidemiology. Some 15 years ago, Altman and Chitty (1993) designed and performed an influential study of the growth of the fetus. The aim was to establish gestational age-specific reference intervals ("normal ranges") for each of a large number of in-utero "parameters" (anthropometric measurements) of fetal size. In each of 649 singleton pregnancies, ultrasound scanning of the abdomen was carried out once on each mother according to a predefined study schedule. The intention was adequately to cover the important gestational period between 12 and 42 weeks, and this was largely achieved. The dataset is therefore cross-sectional in character. A longitudinal study of growth was also performed, but I will not consider that here.

In this example, I will consider a subset of the study dataset comprising just 4 variables: gestational age (ga) in weeks (measured to the nearest day), and three fetal-size measurements: abdominal circumference (ac), head circumference (hc), and mandible (jawbone) length (ml). The pairwise rank correlations and relative sample sizes are shown in table 1.

The data for ac and hc are > 90% complete, whereas only about a quarter of fetuses had mandible measurements. The clinical reason is that it is difficult to make accurate measurements of this structure. Values taken after 28 weeks' gestation are regarded by ultrasonographers as unreliable and have been discarded. Note the high rank correlations among all four variables.

Table 1: Rank correlations among variables in the fetal-size dataset (n = 649), based on available pairs of nonmissing observations. Values in parentheses are the percentage of complete observations for the variable or pair of variables in question. Only ga had complete data

Variable	ac	hc	ml	ga
ac	1.000~(94%)			
hc	0.991~(86%)	1.000~(92%)		
ml	0.948~(25%)	0.951~(25%)	1.000~(26%)	
ga	0.988~(94%)	0.989~(92%)	0.947~(26%)	1.000 (100%)

5.2 Developing the imputation model

I will use the data to illustrate certain aspects of multiple imputation and the use of ice. Imagine that we wished to get some idea of what mandible length looks like after 28 weeks. Such a result would clearly be an extrapolation beyond observed data and should not be regarded as reliable. However, the strong relationships among the body-structure measurements indicated by table 1 makes it appealing to investigate what (if anything) can be done with ml.

All three fetal-size variables show variance increasing with ga, the trend being largely removed by log transformation of fetal size. I will therefore work with the logarithmic transformations lnac, lnhc, and lnml. Investigation of the relationships between each log fetal-size variable and the others and ga was done with Stata's mfp command for multivariable fractional polynomial (MFP) modeling. To avoid instability, the log transformed variables were not further transformed in the model-building phase, whereas gawas allowed up to a second degree FP transformation. Further, due to the large proportion (74%) of missing data in ml, it seemed sensible to exclude lnml from the prediction of lnac and lnhc. Model selection was performed at the $\alpha = 0.05$ significance level. For lnac, for example, the command was

```
. mfp lnac lhhc ga, select(0.05) df(1, ga:4) \,
```

FP2 functions of ga were selected, with powers of (-2, 3) for lnac and (0, 2) for lnhc. For predicting lnml, only lnac and lnhc were needed, ga being eliminated as not significant at the 0.05 level, conditional on lnac and lnhc. Variance explained by the model was 99% for lnac and lnhc and 94% for lnml. Gestational age was complete and therefore required no imputation model.

5.3 Imputation

The prediction-equation matrix for lnac, lnhc, and lnml obtained by MFP modeling is shown in table 2.

Variable	Predictor				
	lnac	lnhc	lnml	ga	
lnac	_	Linear	-	FP2(-2,3)	
lnhc	Linear	—	—	FP2(0, 2)	
lnml	Linear	Linear	—	—	
ga	_	—	—	-	

Table 2: Prediction equations for the fetal-size dataset

The transformations FP2(-2,3) and FP2(0,2) were applied to x = ga denoting, respectively, the models $\beta_0 + \beta_1 x^{-2} + \beta_2 x^3$ and $\beta_0 + \beta_1 \ln x + \beta_2 x^2$. The implementation in ice is as follows: first, the FP transformations are computed and then the imputation itself. For present purposes, we will create just one imputation and store the data in a new file called fetalimp.dta. The following commands are required:

. generate ga_1=ga^-2 . generate ga_2=ga^3 . generate ga_3=ln(ga) . generate ga_4=ga^2 . ice lnac lnhc lnml ga_1 ga_2 ga_3 ga_4 using fetalimp, m(1) genmiss(m_) > eq(lnac:lnhc ga_1 ga_2, lnhc:lnac ga_3 ga_4, lnml:lnac lnhc) Variable Prediction equation Command lnac regress lnhc ga_1 ga_2 lnac ga_3 ga_4 lnhcregress lnml regress lnac lnhc [No missing data in estimation sample] ga_1 ga_2 [No missing data in estimation sample] ga_3 [No missing data in estimation sample] ga_4 [No missing data in estimation sample]

Imputing 1..file fetalimp.dta saved

The results for lnml are shown as a graph of lnml against ga in figure 1.

(Continued on next page)



Figure 1: Original and imputed values of log mandible length using prediction matching

Although all missing values of lnml have been replaced, the results are unsatisfactory since a constant has been imputed for ga > 30 weeks. The reason is that, by default, ice has used prediction matching to obtain imputed values. Since the distribution of lnml is not represented in the data beyond 28 weeks' gestation, ice has been forced to match according to the predictions at the highest available ga values for which lnml is not missing.

To make the imputation more realistic and useful, prediction matching may be replaced by random draws from the posterior distribution of the log fetal-size variables. This is achieved by adding the option draw(lnac lnhc lnml) to the ice command. The plot equivalent to figure 1 is shown in figure 2.

(Continued on next page)



Figure 2: Original and imputed values of log mandible length using random draws from the posterior distribution of the three log fetal-size variables

The results are visually much more satisfactory. Mean log mandible length continues to increase smoothly right to the end of pregnancy, flattening off as the birth size of the fetus is approached. It should of course be stressed once again that the behavior seen in figure 2 is an extrapolation based on the assumption that the relationship between the four variables is similar in the extrapolation region to that in the region where data are observed. This is a strong assumption and, in the present example, is essentially uncheckable. However, the example does show the ability of *ice* to produce what seem to be reasonable estimates of unobserved quantities, with a plausible amount of random variation injected.

If ga had missing values, the ice command would need to include the option passive(ga_1:ga^-2\ga_2:ga^3\ga_3:ln(ga)\ga_4:ga^2). The revised command would create the prediction equation lnac lnhc lnml for ga.

6 Changes to micombine

6.1 New options

There are two new options for micombine: impid(*varname*) and br. Both have been added in response to user requests. The first of these options allows data created outside of ice to be analyzed by using micombine. *varname* is the name of a variable identifying the imputations. The number of imputations is determined as the number of unique values of *varname*. The default *varname* is _j, the name used by ice when creating a dataset of imputations. The second new option, br, defines more precise degrees of freedom (d.f.) and confidence interval for each estimated regression coefficient.

The method is due to Barnard and Rubin (1999), hence the acronym br. Note that br is implemented for all models fit by micombine, not just linear regression, even though the methodology was developed in a linear regression context. Whether this is an improvement over the default inference and confidence intervals in the nonlinear-regression case remains to be investigated.

6.2 Postestimation aspects

Stata's ereturn local, ereturn scalar, and ereturn matrix commands set e() macros, scalars, and matrices returned by estimation commands. micombine respects this convention. It stores the sample size for one imputation (i.e., of the original data); mean regression coefficients; and estimated variance-covariance matrix, calculated according to the Rubin rules for multiple imputation, in e(N), e(b), and e(V), respectively. The test and testparm commands work as expected following use of micombine, giving Wald tests of the desired parameters. Furthermore, micombine stores in $e(m_df)$ the model d.f. and in e(11) and e(chi2) the mean log likelihood and the mean model χ^2 statistic, each averaged over the *m* imputations.

The predict command evaluates predictions for all observations in the estimation sample using the parameters stored in e(b) and e(V). Since the data vary across imputations, the predictions will vary correspondingly. The same principle applies to other postestimation commands that work at the level of the individual observations.

7 Conclusion

The methodology originally developed by Donald Rubin (1976) and others in the late 1970s and brilliantly implemented as the MICE system for more general use by Stef van Buuren and colleagues in the late 1990s is finally coming of age for the practitioner. I believe that this latest development will prove useful to Stata users. I hope also that it will provide a platform on which further numerical experiments in multiple imputation may be carried out. There are many outstanding questions to be tackled in the practical use of multiple imputation, including, for example, how to select an appropriate model and how to do regression diagnostics.

8 Acknowledgments

I thank numerous email correspondents and, in particular, Jennifer Hill for suggesting improvements and new features for mvis and micombine, and equally important, for pointing out unwanted "features" of the software. Without such helpful feedback, it is that much more difficult to develop flexible, reliable, and useful software.

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About the Author

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