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Calibration, Error Analysis, and Ongoing Measurement Process Monitoring for Mass Spectrometry

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Abstract

We consider problems of quantifying and monitoring accuracy and precision of measurement in mass spectrometry, particularly in contexts where there is unavoidable day-to-day/period-to-period changes in instrument sensitivity. First we consider the issue of estimating instrument sensitivity based on data from a typical calibration study. Simple method-of-moments methods, likelihood-based methods, and Bayes methods based on the one-way random effects model are illustrated. Then we consider subsequently assessing the precision of an estimate of a mole fraction of a gas of interest in an unknown. Finally, we turn to the problem of ongoing measurement process monitoring and illustrate appropriate set-up of Shewhart control charts in this application.

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1 Calibration: Precision of Estimated Device Sensitivities and Estimation of Variance Components

In the calibration of a mass spectrometer, several (say m) specimens of a pure gas of interest are first analyzed. Measured for each are a pressure (P^*), a temperature (T^*), and an integral of current over time (A^*). (We will use the asterisk on symbols as a reminder that the corresponding measurements are made on a pure gas.) This produces m data vectors $\left(P_j^*, T_j^*, A_j^*\right)$. From these, single estimated device sensitivity values are available as

$$DS_j = \frac{\left(\dfrac{P_j^* V}{T_j^* R}\right)}{A_j^*} = \left(\frac{V}{R}\right)\left(\frac{P_j^*}{A_j^* T_j^*}\right)$$

for $j = 1, 2, \ldots, m$ (where R is the gas constant and the volume, V, is assumed to be fixed/known for the particular instrument under study). The ratios

$$r_j^* = \frac{P_j^*}{A_j^* T_j^*}$$

are in some sense the fundamental "measurements" produced in calibration of the instrument.

If one averages $DS_1, DS_2, \ldots, DS_m$ (or equivalently averages $r_1^*, r_2^*, \ldots, r_m^*$), a sample mean sensitivity is

$$\overline{DS} = \left(\frac{V}{R}\right)\overline{r^*} \quad . \tag{1.1}$$

Further, if s_{DS} is the sample standard deviation of the values $DS_1, DS_2, \ldots, DS_m$ (or equivalently, s_{r^*} is the sample standard deviation of the values $r_1^*, r_2^*, \ldots, r_m^*$), a standard error for $\overline{DS}$ is then

$$\mathrm{SE}_{\overline{DS}} = \frac{s_{DS}}{\sqrt{m}} = \left(\frac{V}{R}\right)\frac{s_{r^*}}{\sqrt{m}} \quad . \tag{1.2}$$

In cases where the scenario above is repeated on several (say, I) occasions over time (with possibly varying sample sizes, m_t, $t = 1, 2, \ldots, I$) there is the question of how to use the resulting $\sum m_t$ observations to state a single estimated sensitivity for the device and a corresponding precision for that estimated sensitivity. A class of possible answers to these questions can be based on the one-way random effects model. This model says that

$$DS_{tj} = \text{the sensitivity computed from specimen } j \text{ in batch } t$$

can be decomposed as

$$DS_{tj} = \mu_S + \delta_t + \varepsilon_{tj} \quad,$$

where μ_S is a fixed unknown constant (the "true" sensitivity of the device), the (daily) deviations δ_t for $t = 1, 2, \ldots, I$ are iid $N(0, \sigma_\delta^2)$ random variables, independent of the (specimen deviations) ε_{tj}, that are iid $N(0, \sigma^2)$.

A computationally simple way of estimating μ_S in the random effects model is as

$$\widehat{DS} = \frac{1}{I} \sum_{t=1}^{I} \overline{DS}_t$$

(where in the obvious way $\overline{DS}_t$ is the estimated sensitivity based on the m_t specimens on occasion t). Vardeman and Wendelberger (2003) note that (in spite of the possibility that daily sample size is not constant) if $s_{\overline{DS}}$ is the simple sample standard deviation of $\overline{DS}_1, \overline{DS}_2, \ldots, \overline{DS}_I$, a standard error for $\widehat{DS}$ is

$$\text{SE}_{\widehat{DS}} = \frac{s_{\overline{DS}}}{\sqrt{I}} \quad.$$

Vardeman and Wendelberger (2003) further observe that if $s_{DS\,t}^2$ is the usual sample variance of the sample device sensitivity values $DS_{t1}, DS_{t2}, \ldots, DS_{tm_t}$ at period t, then

$$s_{DS\text{ pooled}}^2 = \frac{1}{\sum m_t - I} \sum_{t=1}^{I} (m_t - 1) s_{DS\,t}^2$$

is a pooled sample variance of the individual specimen sensitivity values DS_{tj} and the square root of this is an estimate of σ. And a simple estimate of σ_δ can be built on the sample variances $s_{\overline{DS}}^2$ and $s_{DS\ \text{pooled}}^2$. That is (see again Vardeman and Wendelberger (2003)) a sensible point estimate of σ_δ is

$$\hat{\sigma}_\delta = \sqrt{\max\left(0, s_{\overline{DS}}^2 - s_{DS\ \text{pooled}}^2 \left(\frac{1}{I}\sum_{t=1}^{I}\frac{1}{m_t}\right)\right)} \quad .$$

A second and more refined possibility for estimating μ_S (and assessing the precision of estimation through either a standard error or confidence limits) and estimating the standard deviations σ_δ and σ is via use of a (linear) mixed effects routine like that in R (or Splus). The R function lme will produce likelihood-based estimates and standard errors of estimation for this problem.

A third possibility for estimating μ_S (and assessing the precision of the estimation) and estimating σ_δ and σ is via a Bayes analysis implemented in software like WinBUGS. Diffuse/large-variance priors should produce inferences not wildly different from those produced by using more common likelihood-based methods.

There are also other methods of inference in the one-way random effects model (besides the simple method-of-moments, likelihood-based, and Bayes methods mentioned above). See, for example, pages 473-475 of Searle (1971) for some explicit formulas for other possible estimators. The ones we have mentioned here and proceed to illustrate have been chosen for their simplicity (in the method-of-moments case) or optimality properties (in the other two cases).

To illustrate the forgoing, consider the sensitivity values (DS_{tj}) obtained from 44 pure Argon specimens (on three different days) represented in Table 1.

Table 1. Argon Sensitivities for a Particular Device Computed from 44 Specimens
Analyzed Over 3 Days (units are Moles/(Amp·Sec))

Day 1	Day 2	Day 3
31.3	32.5	31.7
31.0	32.2	29.8
29.4	31.9	29.6
29.2	30.2	29.0
29.0	30.2	28.8
28.8	29.5	29.6
28.8	30.8	28.9
27.7	30.5	28.3
27.7	28.4	28.3
27.8	28.5	28.3
28.2	28.8	29.2
28.4	28.8	29.7
28.7	30.6	31.1
29.7	31.0	
30.8		
30.1		
29.9		
$m_1 = 17$	$m_2 = 14$	$m_3 = 13$
$\overline{DS}_1 = 29.21$	$\overline{DS}_2 = 30.28$	$\overline{DS}_3 = 29.41$
$\text{SE}_{\overline{DS}_1} = \dfrac{1.132}{\sqrt{17}} = .275$	$\text{SE}_{\overline{DS}_2} = \dfrac{1.355}{\sqrt{14}} = .362$	$\text{SE}_{\overline{DS}_3} = \dfrac{1.039}{\sqrt{13}} = .288$

Simple method-of-moments estimates based on these values are a device sensitivity of

$$\widehat{DS} = \frac{29.21 + 30.28 + 29.41}{3} = 29.63 \quad ,$$

with corresponding standard error

$$SE_{\widehat{DS}} = \frac{.570}{\sqrt{3}} = .329 \quad .$$

The pooled standard deviation that can be used to estimate σ is

$$s_{DS\ \text{pooled}} = \sqrt{\frac{16(1.132)^2 + 13(1.355)^2 + 12(1.039)^2}{44 - 3}} = 1.183$$

and an elementary point estimate of σ_δ is

$$\hat{\sigma}_\delta = \sqrt{(.570)^2 - (1.183)^2 \left(\frac{1}{3}\left(\frac{1}{17} + \frac{1}{14} + \frac{1}{13}\right)\right)} = .493$$

Notice that even these elementary calculations reveal substantial day-to-day variation in sensitivity that is "missed" or unaccounted for if one uses only a single $\overline{DS}_t$ (with corresponding standard error $SE_{\overline{DS}_t}$) in the calibration.

A more refined analysis of these data based on the random effects model can be done using standard "linear mixed effects" routines that rely on likelihood (and "REML") methods. An example output from the R package follows.

```
> sens<-c(31.3,31.0,29.4,29.2,29.0,28.8,28.8,27.7,27.7,27.8,28.2,28.4,
+ 28.7,29.7,30.8,30.1,29.9,32.5,32.2,31.9,30.2,30.2,29.5,30.8,30.5,28.4,
+ 28.5,28.8,28.8,30.6,31.0,31.7,29.8,29.6,29.0,28.8,29.6,28.9,28.3,28.3,
+ 28.3,29.2,29.7,31.1)
day<-c(1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,2,2,2,2,2,2,2,2,2,2,2,2,2,2,
+ 3,3,3,3,3,3,3,3,3,3,3,3)
> DAY<-as.factor(day)
> DAY
 [1] 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 3 3 3 3 3 3 3
[39] 3 3 3 3 3 3
Levels: 1 2 3
> sensmixed<-lme(sens~1,random=~1|DAY)
> summary(sensmixed)
Linear mixed-effects model fit by REML
 Data: NULL
       AIC      BIC    logLik
  148.6772 153.9608 -71.33858

Random effects:
 Formula: ~1 | DAY
        (Intercept) Residual
StdDev:    0.480316 1.182519
```

```
Fixed effects: sens ~ 1
             Value Std.Error DF  t-value p-value
(Intercept) 29.6245 0.3301128 41 89.74054       0

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-1.42150019 -0.81682237 -0.01345281  0.52247011  2.04567367

Number of Observations: 44
Number of Groups: 3
> intervals(sensmixed)
Approximate 95% confidence intervals

 Fixed effects:
              lower     est.     upper
(Intercept) 28.95782 29.6245 30.29117
attr(,"label")
[1] "Fixed effects:"

 Random Effects:
  Level: DAY
                    lower      est.     upper
sd((Intercept)) 0.1199656 0.480316 1.923081

 Within-group standard error:
   lower      est.     upper
0.952379 1.182519 1.468273
> fixed.effects(sensmixed)
(Intercept)
   29.6245
> random.effects(sensmixed)
  (Intercept)
1  -0.3085896
2   0.4564536
3  -0.1478639
> predict(sensmixed)
       1        1        1        1        1        1        1        1
29.31591 29.31591 29.31591 29.31591 29.31591 29.31591 29.31591 29.31591
       1        1        1        1        1        1        1        1
29.31591 29.31591 29.31591 29.31591 29.31591 29.31591 29.31591 29.31591
       1        2        2        2        2        2        2        2
29.31591 30.08095 30.08095 30.08095 30.08095 30.08095 30.08095 30.08095
       2        2        2        2        2        2        2        3
30.08095 30.08095 30.08095 30.08095 30.08095 30.08095 30.08095 29.47663
       3        3        3        3        3        3        3        3
29.47663 29.47663 29.47663 29.47663 29.47663 29.47663 29.47663 29.47663
       3        3        3        3
29.47663 29.47663 29.47663 29.47663
attr(,"label")
[1] "Fitted values"
```

Among other things, the parts of the printout in bold show that the standard mixed effects analysis produces inferences for the sensitivity μ_S of

$$\hat{\mu}_S = 29.62 \text{ with 95\% limits } (28.96, 30.29) \quad,$$

inferences for σ (measuring specimen-to-specimen variation in sensitivity within a single day) of

$$\hat{\sigma} = 1.183 \text{ with 95\% limits } (0.952, 1.468) \quad,$$

and inferences for σ_δ (measuring day-to-day variation in sensitivity) of

$$\hat{\sigma}_\delta = 0.480 \text{ with 95\% limits of } (0.120, 1.923) \quad.$$

These inferences are, not surprisingly, consistent with the story told by the simple estimates. In particular, it seems the day-to-day variation in sensitivity is not ignorable.

A Bayes analysis of the data of Table 1 can be accomplished using WinBUGS. A summary of a sample WinBUGS session follows.


```
list(sens=c(31.3,31.0,29.4,29.2,29.0,28.8,28.8,27.7,27.7,27.8,28.2,28.4,28.7,29.7,30.8,3
0.1,29.9,32.5,32.2,31.9,30.2,30.2,29.5,30.8,30.5,28.4,28.5,28.8,28.8,30.6,31.0,31.7,29.8
,29.6,29.0,28.8,29.6,28.9,28.3,28.3,28.3,29.2,29.7,31.1),ind=c(1,1,1,1,1,1,1,1,1,1,1,1,1,1
,1,1,1,2,2,2,2,2,2,2,2,2,2,2,2,2,2,3,3,3,3,3,3,3,3,3,3,3,3,3),N=44)

list(mu=c(3,3,3),tau=1,muS=0,taudelta=1)

model;
{
  for(i in 1:N) {
    sens[i]~dnorm(mu[ind[i]],tau)
  }
  for(i in 1:3) {
    mu[i]~dnorm(muS,taudelta)
  }
  tau~dgamma(0.001,0.001)
  sigma<-1/sqrt(tau)
  muS~dnorm(0.0,1.0E-6)
  taudelta~dgamma(0.001,0.001)
  sigmadelta<-1/sqrt(taudelta)
}
```

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
mu[1]	29.38	0.2845	9.197E-4	28.8	29.39	29.91	100001	500000
mu[2]	29.97	0.3488	0.001272	29.35	29.96	30.68	100001	500000
mu[3]	29.5	0.2847	7.398E-4	28.91	29.51	30.04	100001	500000
muS	29.62	0.8746	0.001392	**28.56**	**29.62**	**30.69**	100001	500000
sigma	1.221	0.1397	2.354E-4	**0.9833**	**1.208**	**1.529**	100001	500000
sigmadelta	0.6365	1.292	0.004277	**0.03682**	**0.3937**	**2.699**	100001	500000

The Bayes analysis is in substantial agreement with all that has gone before (though is perhaps somewhat less optimistic about the precision with which μ_S has been determined than are the other analyses). In particular, there is evidence of substantial day-to-day variation in device sensitivity in the reported posterior mean and median for "sigmadelta."

2 Assessing Precision in the Determination of an Unknown

When one or more (say, n) specimens of a new mixture of gases are analyzed, values of pressure, temperature, and integrated current are obtained. That is, one is presented with new data vectors $\left(P_i, T_i, A_i\right)$ for $i = 1, 2, \ldots, n$. (Notice that in contrast to the previous section, we use no asterisks on these symbols. These are measurements not on a pure gas, but on samples of a mixture of gases.) Let

$$q_i = \frac{P_i}{A_i T_i}\left(\frac{V}{R}\right) \quad,$$

and in the obvious way, let $\bar{q}$ stand for the sample mean of these values. Then for $\hat{\mu}_S$ some estimate of instrument sensitivity, an estimated mole fraction of the gas of interest is

$$X = \frac{\hat{\mu}_S}{\bar{q}} \quad . \tag{2.1}$$

An important question is "How may one state a precision for X?"

Stating a precision for an estimate like (2.1) requires that one make explicit one's assumptions about how $\bar{q}$ and $\hat{\mu}_S$ are related probabilistically. We proceed to do that for two possible scenarios, the first where $\bar{q}$ and $\hat{\mu}_S$ are based on measurements collected on a single day, and the second where the estimate of device sensitivity is based on data

from days different from the day on which the n values $q_1, q_2, \ldots, q_n$ are observed. After making the modeling explicit, we offer two types of assessments of the precision of (2.1), namely

1. in terms of standard errors based on simple "delta method"/propagation of error/Taylor linearizations and the output of the estimation methods discussed in Section 1, and
2. in terms of Bayes posterior distributions

based on the probability modeling.

2.1 Modeling Measurement Response for a Mixture of Gases

We continue with the one way random effects model for individual sample sensitivities introduced in Section 1. There is then the question of how to model "responses" q_i for a gas mixture with a fraction f of the gas of interest, on a day t_0 when device sensitivity is $\mu_{\mathrm{S}} + \delta_{t_0}$. We will adopt a regression assumption and suppose that

$$q_i = \frac{\mu_{\mathrm{S}} + \delta_{t_0}}{f} + \gamma_i \quad , \tag{2.2}$$

where the γ_i are iid $\mathrm{N}\left(0, \sigma_\gamma^2\right)$ independent of δ_{t_0} (and all ε_{tj} and any δ_t with $t \neq t_0$). (Note that we are assuming that the mean of the q_i depends on the daily deviation in sensitivity, but that the standard deviation is approximately constant in that deviation.)

Notice then that under a scenario where both calibration runs and measurement of the mixture are made on a single day, the estimated sensitivity (2.1) is most naturally the ratio

$$X = \frac{\overline{DS}_{t_0}}{\overline{q}} = \frac{\mu_{\mathrm{S}} + \delta_{t_0} + \overline{\varepsilon}}{\frac{1}{f}\left(\mu_{\mathrm{S}} + \delta_{t_0}\right) + \overline{\gamma}} = \frac{f\mu_{\mathrm{S}} + f\delta_{t_0} + f\overline{\varepsilon}}{\mu_{\mathrm{S}} + \delta_{t_0} + f\overline{\gamma}} \quad . \tag{2.3}$$

So analysis of the precision of (2.1) can proceed through the analysis of the variance of (2.3), a function of the 3 independent random variables $\delta_{t_0}, \overline{\gamma}$, and $\overline{\varepsilon}$.

In a second case, where calibration runs come from days different from the one on which the measurements of the mixture are made, we suppose that $\hat{\mu}_S$ is independent of $\overline{q}$, with mean μ_S and standard deviation $\sigma_{\hat{\mu}_S}$. Then the estimated sensitivity (2.1) is the ratio

$$X = \frac{\hat{\mu}_S}{\overline{q}} = \frac{\hat{\mu}_S}{\frac{1}{f}\left(\mu_S + \delta_{t_0}\right) + \overline{\gamma}} = \frac{f\hat{\mu}_S}{\mu_S + \delta_{t_0} + f\overline{\gamma}} \quad . \tag{2.4}$$

So analysis of the precision of (2.1) can proceed through the analysis of the variance of (2.4), a function of the 3 independent random variables $\delta_{t_0}, \overline{\gamma}$, and $\hat{\mu}_S$.

2.2 Simple Standard Errors of Estimation of a Mole Fraction

The well-known "propagation of error"/"delta method" approximation says that for independent random variables U, W, and Z and a differentiable function g,

$$\operatorname{Var} g(U, W, Z) = \left(\frac{\partial g}{\partial u}\right)^2 \operatorname{Var} U + \left(\frac{\partial g}{\partial w}\right)^2 \operatorname{Var} W + \left(\frac{\partial g}{\partial z}\right)^2 \operatorname{Var} Z$$

where the partial derivatives are evaluated at $(\mathrm{E}U, \mathrm{E}W, \mathrm{E}Z)$. Applying this first to (2.3) and recalling that all of $\delta_{t_0}, \overline{\gamma}$, and $\overline{\varepsilon}$ have mean 0, one has that

$$\operatorname{Var} \frac{f\mu_S + f\delta_{t_0} + f\overline{\varepsilon}}{\mu_S + \delta_{t_0} + f\overline{\gamma}} \approx f^2\left(\frac{\sigma^2}{m\mu_S^2} + \frac{f^2\sigma_\gamma^2}{n\mu_S^2}\right) = f^2\left(\frac{\operatorname{Var}\overline{\varepsilon}}{\left(\mathrm{E}\,\overline{DS}\right)^2} + \frac{\operatorname{Var}\overline{\gamma}}{\left(\mathrm{E}\,\overline{q}\right)^2}\right)$$

and so a reasonable standard error for (2.3) is

$$\mathrm{SE}_X = X\sqrt{\frac{s_{DS}^2}{m\left(\overline{DS}\right)^2} + \frac{s_q^2}{n\left(\overline{q}\right)^2}} \quad , \tag{2.5}$$

where in the obvious way, s_q is the sample standard deviation of $q_1, q_2, \ldots, q_n$. Note in passing that in (2.5) the sample coefficient of variation $s_q / \overline{q}$ can be computed as the sample coefficient of variation for values $X_i^{-1} = q_i / \hat{\mu}_S$ for any fixed estimate of device sensitivity $\hat{\mu}_S$. (This is potentially useful where the most natural way to report the result

of an individual measurement on an unknown is as an estimated mole fractions of the gas of interest, instead of as a value q_i.)

Then applying the delta method to (2.4) one has

$$\text{Var} \frac{f\hat{\mu}_S}{\mu_S + \delta_{t_0} + f\bar{\gamma}} \approx f^2 \left(\frac{\text{Var}\,\hat{\mu}_S}{\mu_S^2} + \frac{f^2 \sigma_\gamma^2}{n\mu_S^2} + \frac{\sigma_\delta^2}{\mu_S^2} \right) = f^2 \left(\frac{\text{Var}\,\hat{\mu}_S}{\mu_S^2} + \frac{\text{Var}\,\bar{\gamma}}{(E\bar{q})^2} + \frac{\sigma_\delta^2}{\mu_S^2} \right) \ .$$

So assuming that (multiple day) calibration data has been processed (for example as in Section 1) to produce estimates $\hat{\sigma}_\delta, \hat{\mu}_S$, and $\text{SE}_{\hat{\mu}_S}$, a standard error for (2.4) is

$$\text{SE}_X = X \sqrt{\left(\frac{\text{SE}_{\hat{\mu}_S}}{\hat{\mu}_S} \right)^2 + \frac{s_q^2}{n(\bar{q})^2} + \left(\frac{\hat{\sigma}_\delta}{\hat{\mu}_S} \right)^2} \ . \tag{2.6}$$

Comparison of (2.5) and (2.6) shows that the second standard error is inflated over the first by the addition under the square root of a squared coefficient of variation of the daily device sensitivities. This accounts for the fact that the unknown is analyzed on a day different from those on which the calibration takes place.

To illustrate the foregoing, consider the $n = 6$ measured Argon mole ratio values in Table 2. These were obtained from a single mixture of gases on a single day, and we will assume that (consistent with the calculations in Section 1) an Argon sensitivity of $\hat{\mu}_S = 29.63$ was used in the development of these values, $\text{SE}_{\hat{\mu}_S} = .329$, and $\hat{\sigma}_\delta = .493$.

Table 2. Estimated Argon Mole Fractions Collected on a Single Day

Estimated Mole Fractions $X_i = \dfrac{\hat{\mu}_S}{q_i}$ and Their Reciprocals $X_i^{-1} = \dfrac{q_i}{\hat{\mu}_S}$

.103   (9.709)

.103   (9.709)

.104   (9.615)

.097   (10.309)

.097   (10.309)

.098   (10.204)

$$\overline{\left(\frac{q}{\hat{\mu}_S}\right)} = \frac{1}{6}\sum X_i^{-1} = 9.9759$$

$$X = \frac{1}{\overline{\left(\dfrac{q}{\hat{\mu}_S}\right)}} = .1002$$

$$s_{\frac{q}{\hat{\mu}_S}} = .3308$$

Applying formula (2.6) (and the fact that the sample coefficient of variation $s_q/\overline{q}$ can be computed as the sample coefficient of variation for values $X_i^{-1} = q_i/\hat{\mu}_S$), we find that $X = .1002$ has standard error

$$\mathrm{SE}_X = X\sqrt{\left(\frac{\mathrm{SE}_{\hat{\mu}_S}}{\hat{\mu}_S}\right)^2 + \frac{s_{\frac{q}{\hat{\mu}_S}}^2}{n\,\overline{\left(\dfrac{q}{\hat{\mu}_S}\right)}^2} + \left(\frac{\hat{\sigma}_\delta}{\hat{\mu}_S}\right)^2}$$

$$= .1002\sqrt{\left(\frac{.329}{29.63}\right)^2 + \frac{1}{6}\left(\frac{.3308}{9.9759}\right)^2 + \left(\frac{.493}{29.63}\right)^2}$$

$$= .1002(.0242)$$

$$= .0024 \quad.$$

2.3 Bayesian Assessment of Precision of Estimation of a Mole Fraction

The modeling assumptions adopted in this discussion provide a complete statistical model for the calibration data DS_{tj} and observations q_i on the unknown, this model having parameters $\mu_S, \sigma_\delta^2, \sigma^2, f, \sigma_\gamma^2$ (where in the analysis of an unknown, it is the parameter f that is of most interest). In theory, standard statistical tools of likelihood estimation could be applied to estimate f and state a standard error of estimation (as an alternative to the sensible, but somewhat ad hoc adoption of X and standard error (2.5) or (2.6) discussed in Section 2.2). But the model is not a simple mixed linear model, and we presently do not see how to handle the estimation and assessment of precision from this point of view.

On the other hand, using modern Bayesian software, it is straightforward to make a Bayes analysis and use a posterior distribution for f to assess what the data tells one about an unknown mole fraction. The following is an example of a summary of a WinBUGS session made using the data of Tables 1 and 2. Notice that limits of the posterior 95% interval for f indicated in bold are somewhat less optimistic (in terms of precision of determination), but roughly consistent with the cruder analysis presented in Section 2.2. Under the modeling assumptions of Section 2.1 it seems that an estimated mole fraction of roughly .1003 can be thought of as good to within perhaps $\pm.0084$.

```
list(sens=c(31.3,31.0,29.4,29.2,29.0,28.8,28.8,27.7,27.7,27.8,28.2,28.4,28.7,29.7,30.8,30.1,29.
9,32.5,32.2,31.9,30.2,30.2,29.5,30.8,30.5,28.4,28.5,28.8,28.8,30.6,31.0,31.7,29.8,29.6,29.0,28.
8,29.6,28.9,28.3,28.3,28.3,29.2,29.7,31.1),ind=c(1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,2,2,2,2,2,2,2,2
,2,2,2,2,2,2,3,3,3,3,3,3,3,3,3,3,3,3,3),q=c(287.7,287.7,284.9,305.5,305.5,302.3),N=44)

list(mu=c(30,30,30,30),tau=1,muS=0,taudelta=1,taugamma=1,f=.1)

model;
{
  for(i in 1:N) {
    sens[i]~dnorm(mu[ind[i]],tau)
  }
  for(i in 1:4) {
    mu[i]~dnorm(muS,taudelta)
  }
```

```
muq<-mu[4]/f
for(i in 1:6) {
  q[i]~dnorm(muq,taugamma)
}
tau~dgamma(0.001,0.001)
sigma<-1/sqrt(tau)
muS~dnorm(0.0,1.0E-6)
taudelta~dgamma(0.001,0.001)
sigmadelta<-1/sqrt(taudelta)
taugamma~dgamma(0.001,0.001)
sigmagamma<-1/sqrt(taugamma)
f~dunif(0,1)
}
```

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
f	0.1005	0.004836	3.748E-5	**0.09318**	**0.1003**	**0.1087**	1100001	2500000
mu[1]	29.38	0.2848	4.93E-4	28.8	29.4	29.91	1100001	2500000
mu[2]	29.98	0.348	7.342E-4	29.36	29.96	30.68	1100001	2500000
mu[3]	29.51	0.285	3.911E-4	28.91	29.52	30.04	1100001	2500000
mu[4]	29.68	1.329	0.01101	27.72	29.63	31.85	1100001	2500000
muS	29.64	0.7558	0.002962	28.61	29.62	30.73	1100001	2500000
sigma	1.221	0.1397	1.165E-4	0.9832	1.208	1.53	1100001	2500000
sigmadelta	0.6306	1.129	0.007227	0.03678	0.3939	2.664	1100001	2500000
sigmagamma	11.66	4.917	0.004159	6.118	10.51	24.06	1100001	2500000

3 Ongoing Measurement Process Monitoring

It is important to monitor the performance of any measurement system to assure that it continues to function as expected over time. Elementary statistical quality control techniques applied to the measurement process are helpful in this regard. In the particular context of monitoring the performance of a mass spectrometer, we assume that samples of a fixed gas mixture (potentially a pure gas, but not necessarily so) are analyzed at regular time intervals, say m_t specimens at period t, giving rise to ratios

$$q_{tj} = \frac{P_{tj}}{A_{tj}T_{tj}}\left(\frac{V}{R}\right)$$

or, equivalently, should the same fixed sensitivity value μ_S be used for calculation at each period, the measured mole fractions

$$X_{tj} = \frac{\mu_S}{q_{tj}} \quad .$$

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In light of the day-to-day variation seen in even the calibration data of Table 1, it seems clear that a sensible process monitoring scheme in this context must allow for period-to-period variation in the q_{tj}'s or X_{tj}'s as legitimate/unavoidable. The following suggestions are thus based on a one-way random effects model for any of these values.

That is, let Y_{tj} stand for q_{tj} or X_{tj} (depending upon exactly what variable one wishes to use in ongoing process monitoring). Assume (in a way analogous to what was done in Section 1) that Y_{tj} may be decomposed as

$$Y_{tj} = \mu + \tau_t + \eta_{tj} \quad ,$$

where μ is a fixed constant (the "true" mean of the variable being monitored), the (daily) deviations τ_t are iid $N(0, \sigma_\tau^2)$ random variables, independent of the (specimen deviations) η_{tj}, that are iid $N(0, \sigma_\eta^2)$. In what follows, we assume that values for the model parameters μ, σ_τ, and σ_η have been established. This will almost always involve the analysis of values Y_{tj} from days $t = 1, 2, \ldots, I$ in the style of Section 1, leading to estimates that are subsequently employed as if they were parameter values.

After establishing parameter values for the measurement process running in an acceptable fashion, the m_{new} observations $Y_{new\,i}, Y_{new\,2}, \ldots, Y_{new\,m_{new}}$ from a subsequent period can be summarized in terms of a mean $\overline{Y}_{new}$ and a standard deviation s_{new}. These can then be compared to "control limits" to ascertain whether they clearly indicate a change in the measurement process.

A sample mean outside the control limits

$$LCL_{\overline{Y}_{new}} = \mu - 3\sqrt{\sigma_\tau^2 + \frac{\sigma_\eta^2}{m_{new}}} \quad \text{and} \quad UCL_{\overline{Y}_{new}} = \mu + 3\sqrt{\sigma_\tau^2 + \frac{\sigma_\eta^2}{m_{new}}} \tag{3.1}$$

or a sample standard deviation outside the control limits

$$LCL_{s_{new}} = B_5 \sigma_\eta \quad \text{and} \quad UCL_{s_{new}} = B_6 \sigma_\eta \tag{3.2}$$

(for "control chart constants" B_5 and B_6 chosen for sample size m_{new} from a standard table of such constants) indicate a change in the measurement process and the need for intervention of some sort. The limits (3.1) monitor primarily for a change in mean Y and secondarily for changes in day-to-day or within-day variation in Y. The role of limits (3.2) is to monitor only for changes in within-day variation in Y.

Consider two examples of the above development, the first where what is to be monitored are individual sensitivity values produced from pure gas specimens, and the second where what is to be monitored are estimated mole fractions for a particular gas in a fixed mixture of gases. The data in Table 1 provide a basis for the first example.

Table 1 contains data from only $I = 3$ periods/days. Ideally, one would like to have data from $I = 20$ or more periods to estimate process parameters before setting up control charts for subsequent routine process monitoring. However, for illustration purposes, we will simply use the (simple method-of-moments) estimates derived from limited data in Table 1 as if they had been derived from a more substantial data set. That is, we consider monitoring Argon sensitivity values ($Y_{tj} = DS_{tj}$ in our earlier notation), based on an assumption that

$$\mu = 29.63 (= \hat{\mu}_S), \ \sigma_\tau = .493 (= \hat{\sigma}_\delta), \text{ and } \sigma_\eta = 1.183 (= s_{DS \text{ pooled}}) \quad .$$

And for sake of illustration, suppose that a sample size of $m_{new} = 6$ will be used in ongoing process monitoring. (On a day when device performance is to be checked, 6 pure Argon specimens will be run and corresponding sensitivities $Y_{new\,j} = q_{new\,j} = DS_{new\,j}$ computed.)

Then following from equations (3.1) are control limits

$$LCL_{\bar{Y}_{new}} = 29.63 - 3\sqrt{(.493)^2 + \frac{(1.183)^2}{6}} \quad \text{and} \quad UCL_{\bar{Y}_{new}} = 29.63 + 3\sqrt{(.493)^2 + \frac{(1.183)^2}{6}} \quad .$$

These are limits of 29.63 ± 2.07 for a sample average Argon sensitivity on any single day (based on 6 specimens). Since for sample size 6, $B_5 = .029$ and $B_6 = 1.874$ (see, for

example, Table A.1 page 509 of Vardeman and Jobe (1999)), following from equations (3.2) are control limits

$$LCL_{s_{new}} = .029(1.183) = .034 \quad \text{and} \quad UCL_{s_{new}} = 1.874(1.183) = 2.217$$

for the sample standard deviation calculated from 6 Argon sensitivities computed on any single day.

As a second example, consider the estimated mole fractions of Methane in a fixed gas mixture, collected on $I = 6$ different days recorded in Table 3. (Once again, one would like to have on the order of 20 days' worth of data to estimate parameters and set up control charts for ongoing measurement process monitoring, but these will suffice to illustrate the concepts and calculations.)

Table 3. Estimated Methane Mole Fractions in a Fixed Gas Mixture Collected on 6 Different Days

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
.4076	.4059	.3940	.3970	.3950	.4020
.4060	.4074	.4030	.4000	.3960	.4030
.4086	.4073	.4040	.4020	.3970	.4040
.4088		.4080	.3900	.3860	
		.4090	.3920	.3860	
		.4080	.3940	.3870	
				.3900	
				.3940	
$m_1 = 4$	$m_2 = 3$	$m_3 = 6$	$m_4 = 6$	$m_5 = 8$	$m_6 = 3$
$\overline{Y}_1 = .40775$	$\overline{Y}_2 = .40687$	$\overline{Y}_3 = .40433$	$\overline{Y}_4 = .39583$	$\overline{Y}_5 = .39138$	$\overline{Y}_6 = .40300$
$s_1 = .00128$	$s_2 = .00084$	$s_3 = .00561$	$s_4 = .00467$	$s_5 = .00466$	$s_6 = .00100$

Then using the simple method-of-moments estimators as in Section 1, we have

$$\hat{\mu} = \frac{1}{6}(.40775 + .40687 + .40433 + .39583 + .39138 + .40300) = .40153 \quad,$$

and

$$\hat{\sigma}_\eta = \sqrt{s^2_{Y\ pooled}}$$

$$= \sqrt{\frac{3(.00128)^2 + 2(.00084)^2 + 5(.00561)^2 + 5(.00467)^2 + 7(.00466)^2 + 2(.00100)^2}{3+2+5+5+7+2}}$$

$$= .00422 \quad,$$

and since

$$s_{\bar{Y}} = \sqrt{\frac{(.40775 - .40153)^2 + (.40687 - .40153)^2 + (.40433 - .40153)^2 + (.39583 - .40153)^2 + (.39138 - .40153)^2 + (.40300 - .40153)^2}{6-1}} = .00652 \quad,$$

also

$$\hat{\sigma}_\tau = \sqrt{(.00652)^2 - (.00422)^2 \left(\frac{1}{6}\left(\frac{1}{4} + \frac{1}{3} + \frac{1}{6} + \frac{1}{6} + \frac{1}{8} + \frac{1}{3}\right)\right)} = .00620 \quad.$$

We proceed to use these as if they were process parameters and compute control limits for the sample mean and standard deviation of $m_{new} = 6$ new estimated Methane mole fractions for this fixed gas mixture made on some future day.

First, following from equations (3.1) are control limits

$$LCL_{\bar{Y}_{new}} = .40153 - 3\sqrt{(.00620)^2 + \frac{(.00422)^2}{6}} \quad \text{and} \quad UCL_{\bar{Y}_{new}} = .40153 + 3\sqrt{(.00620)^2 + \frac{(.00422)^2}{6}} \quad,$$

These are limits of $.40153 \pm .01930$ for a sample average Methane mole fraction on any single day (based on 6 specimens). Then, following from equations (3.2) are control limits

$$LCL_{s_{new}} = .029(.00422) = .00012 \quad \text{and} \quad UCL_{s_{new}} = 1.874(.00422) = .00791$$

for the sample standard deviation calculated from 6 Methane mole fractions computed on any single day.

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