

Likelihood calculations for *vsn*

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1 Introduction

This vignette contains the computations that underlie the numerical code of *vsn*. If you are a new user and looking for an introduction on how to **use** *vsn*, please refer to the vignette *Robust calibration and variance stabilization with vsn*, which is provided separately.

2 Setup and Notation

Consider the model

$$\operatorname{arsinh}(f(b_i) \cdot y_{ki} + a_i) = \mu_k + \varepsilon_{ki} \quad \mathbf{1}$$

where μ_k , for $k = 1, \dots, n$, and a_i , b_i , for $i = 1, \dots, d$ are real-valued parameters, f is a function $\mathbb{R} \rightarrow \mathbb{R}$ (see below), and ε_{ki} are i.i.d. Normal with mean 0 and variance σ^2 . y_{ki} are the data. In applications to μ array data, k indexes the features and i the arrays and/or colour channels.

Examples for f are $f(b) = b$ and $f(b) = e^b$. The former is the most obvious choice; in that case we will usually need to require $b_i > 0$. The choice $f(b) = e^b$ assures that the factor in front of y_{ki} is positive for all $b \in \mathbb{R}$, and as it turns out, simplifies some of the computations.

In the following calculations, I will also use the notation

$$Y \equiv Y(y, a, b) = f(b) \cdot y + a \quad \mathbf{2}$$

$$h \equiv h(y, a, b) = \operatorname{arsinh}(f(b) \cdot y + a). \quad \mathbf{3}$$

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The probability of the data $(y_{ki})_{k=1\dots n, i=1\dots d}$ lying in a certain volume element of y -space (hyperrectangle with sides $[y_{ki}^\alpha, y_{ki}^\beta]$) is

$$P = \prod_{k=1}^n \prod_{i=1}^d \int_{y_{ki}^\alpha}^{y_{ki}^\beta} dy_{ki} \, p_{\text{Normal}}(h(y_{ki}), \mu_k, \sigma^2) \frac{dh}{dy}(y_{ki}), \quad 4$$

where μ_k is the expectation value for feature k and σ^2 the variance.

With

$$p_{\text{Normal}}(x, \mu, \sigma^2) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{(x - \mu)^2}{2\sigma^2}\right) \quad 5$$

the likelihood is

$$L = \left(\frac{1}{\sqrt{2\pi\sigma^2}}\right)^{nd} \prod_{k=1}^n \prod_{i=1}^d \exp\left(-\frac{(h(y_{ki}) - \mu_k)^2}{2\sigma^2}\right) \cdot \frac{dh}{dy}(y_{ki}). \quad 6$$

For the following, I will need the derivatives

$$\frac{\partial Y}{\partial a} = 1 \quad 7$$

$$\frac{\partial Y}{\partial b} = y \cdot f'(b) \quad 8$$

$$\frac{dh}{dy} = \frac{f(b)}{\sqrt{1 + (f(b)y + a)^2}} = \frac{f(b)}{\sqrt{1 + Y^2}}, \quad 9$$

$$\frac{\partial h}{\partial a} = \frac{1}{\sqrt{1 + Y^2}}, \quad 10$$

$$\frac{\partial h}{\partial b} = \frac{y}{\sqrt{1 + Y^2}} \cdot f'(b). \quad 11$$

Note that for $f(b) = b$, we have $f'(b) = 1$, and for $f(b) = e^b$, $f'(b) = f(b) = e^b$.

3 Likelihood for Incremental Normalization

Here, *incremental normalization* means that the model parameters μ_1, \dots, μ_n and σ^2 are already known from a fit to a previous set of μ arrays, i.e. a set of reference arrays. See Section 4 for the profile likelihood approach that is used if μ_1, \dots, μ_n and σ^2 are not known and need to be estimated from the same data. Versions ≥ 2.0 of the *vsn* package implement both of these approaches; in versions 1.X only the profile likelihood approach was implemented, and it was described in the initial publication [1].

First, let us note that the likelihood 6 is simply a product of independent terms for different i . We can optimize the parameters (a_i, b_i) separately for each $i = 1, \dots, d$. From the likelihood 6 we get the i -th negative log-likelihood

$$-\log(L) = \sum_{i=1}^d -LL_i \quad 12$$

$$-LL_i = \frac{n}{2} \log(2\pi\sigma^2) + \sum_{k=1}^n \left(\frac{(h(y_{ki}) - \mu_k)^2}{2\sigma^2} + \log \frac{\sqrt{1 + Y_{ki}^2}}{f(b_i)} \right) \quad 13$$

$$= \frac{n}{2} \log(2\pi\sigma^2) - n \log f(b_i) + \sum_{k=1}^n \left(\frac{(h(y_{ki}) - \mu_k)^2}{2\sigma^2} + \frac{1}{2} \log(1 + Y_{ki}^2) \right) \quad 14$$

This is what we want to optimize as a function of a_i and b_i . The optimizer benefits from the derivatives. The derivative with respect to a_i is

$$\begin{aligned}\frac{\partial}{\partial a_i}(-LL_i) &= \sum_{k=1}^n \left(\frac{h(y_{ki}) - \mu_k}{\sigma^2} + \frac{Y_{ki}}{\sqrt{1 + Y_{ki}^2}} \right) \cdot \frac{1}{\sqrt{1 + Y_{ki}^2}} \\ &= \sum_{k=1}^n \left(\frac{r_{ki}}{\sigma^2} + A_{ki} Y_{ki} \right) A_{ki}\end{aligned}\quad 15$$

and with respect to b_i

$$\begin{aligned}\frac{\partial}{\partial b_i}(-LL_i) &= -n \frac{f'(b_i)}{f(b_i)} + \sum_{k=1}^n \left(\frac{h(y_{ki}) - \mu_k}{\sigma^2} + \frac{Y_{ki}}{\sqrt{1 + Y_{ki}^2}} \right) \cdot \frac{y_{ki}}{\sqrt{1 + Y_{ki}^2}} \cdot f'(b_i) \\ &= -n \frac{f'(b_i)}{f(b_i)} + f'(b_i) \sum_{k=1}^n \left(\frac{r_{ki}}{\sigma^2} + A_{ki} Y_{ki} \right) A_{ki} y_{ki}\end{aligned}\quad 16$$

Here, I have introduced the following shorthand notation for the “intermediate results” terms

$$r_{ki} = h(y_{ki}) - \mu_k \quad 17$$

$$A_{ki} = \frac{1}{\sqrt{1 + Y_{ki}^2}}. \quad 18$$

Variables for these intermediate values are also used in the C code to organise the computations of the gradient.

4 Profile Likelihood

If μ_1, \dots, μ_n and σ^2 are not already known, we can plug in their maximum likelihood estimates, obtained from optimizing LL for μ_1, \dots, μ_n and σ^2 :

$$\hat{\mu}_k = \frac{1}{d} \sum_{j=1}^d h(y_{kj}) \quad 19$$

$$\hat{\sigma}^2 = \frac{1}{nd} \sum_{k=1}^n \sum_{j=1}^d (h(y_{kj}) - \hat{\mu}_k)^2 \quad 20$$

into the negative log-likelihood. The result is called the negative profile log-likelihood

$$-PLL = \frac{nd}{2} \log(2\pi\hat{\sigma}^2) + \frac{nd}{2} - n \sum_{j=1}^d \log f(b_j) + \frac{1}{2} \sum_{k=1}^n \sum_{j=1}^d \log \sqrt{1 + Y_{kj}^2}. \quad 21$$

Note that this no longer decomposes into a sum of terms for each j that are independent of each other – the terms for different j are coupled through Equations 19 and 20. We need the following derivatives.

$$\begin{aligned}\frac{\partial \hat{\sigma}^2}{\partial a_i} &= \frac{2}{nd} \sum_{k=1}^n r_{ki} \frac{\partial h(y_{ki})}{\partial a_i} \\ &= \frac{2}{nd} \sum_{k=1}^n r_{ki} A_{ki}\end{aligned}\quad 22$$

$$\frac{\partial \hat{\sigma}^2}{\partial b_i} = \frac{2}{nd} \cdot f'(b_i) \sum_{k=1}^n r_{ki} A_{ki} y_{ki} \quad 23$$

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So, finally

$$\begin{aligned}\frac{\partial}{\partial a_i}(-PLL) &= \frac{nd}{2\hat{\sigma}^2} \cdot \frac{\partial \hat{\sigma}^2}{\partial a_i} + \sum_{k=1}^n A_{ki}^2 Y_{ki} \\ &= \sum_{k=1}^n \left(\frac{r_{ki}}{\hat{\sigma}^2} + A_{ki} Y_{ki} \right) A_{ki}\end{aligned}\tag{24}$$

$$\frac{\partial}{\partial b_i}(-PLL) = -n \frac{f'(b_i)}{f(b_i)} + f'(b_i) \sum_{k=1}^n \left(\frac{r_{ki}}{\hat{\sigma}^2} + A_{ki} Y_{ki} \right) A_{ki} y_{ki}\tag{25}$$

5 Summary

Likelihoods, from Equations 12 and 21:

$$-LL_i = \underbrace{\frac{n}{2} \log(2\pi\sigma^2)}_{\text{scale}} + \underbrace{\sum_{k=1}^n \frac{(h(y_{ki}) - \mu_k)^2}{2\sigma^2}}_{\text{residuals}} - \underbrace{n \log f(b_i) + \frac{1}{2} \sum_{k=1}^n \log(1 + Y_{ki}^2)}_{\text{jacobian}} \quad 26$$

$$-PLL = \underbrace{\frac{nd}{2} \log(2\pi\hat{\sigma}^2)}_{\text{scale}} + \underbrace{\frac{nd}{2}}_{\text{residuals}} + \underbrace{\sum_{i=1}^d \left(-n \log f(b_i) + \frac{1}{2} \sum_{k=1}^n \log(1 + Y_{ki}^2) \right)}_{\text{jacobian}} \quad 27$$

The computations in the C code are organised into steps for computing the terms “scale”, “residuals” and “jacobian”.

Partial derivatives with respect to a_i , from Equations 15 and 24:

$$\frac{\partial}{\partial a_i}(-LL_i) = \sum_{k=1}^n \left(\frac{r_{ki}}{\sigma^2} + A_{ki} Y_{ki} \right) A_{ki} \quad 28$$

$$\frac{\partial}{\partial a_i}(-PLL) = \sum_{k=1}^n \left(\frac{r_{ki}}{\hat{\sigma}^2} + A_{ki} Y_{ki} \right) A_{ki} \quad 29$$

Partial derivatives with respect to b_i , from Equations 16 and 25:

$$\frac{\partial}{\partial b_i}(-LL_i) = -n \frac{f'(b_i)}{f(b_i)} + f'(b_i) \sum_{k=1}^n \left(\frac{r_{ki}}{\sigma^2} + A_{ki} Y_{ki} \right) A_{ki} y_{ki} \quad 30$$

$$\frac{\partial}{\partial b_i}(-PLL) = -n \frac{f'(b_i)}{f(b_i)} + f'(b_i) \sum_{k=1}^n \left(\frac{r_{ki}}{\hat{\sigma}^2} + A_{ki} Y_{ki} \right) A_{ki} y_{ki}. \quad 31$$

Note that the terms have many similarities – this is used in the implementation in the C code.

References

- [1] W. Huber, A. von Heydebreck, H. Sültmann, A. Poustka, and M. Vingron. Variance stabilization applied to microarray data calibration and to quantification of differential expression. *Bioinformatics*, 18:S96–S104, 2002.
- [2] W. Huber, A. von Heydebreck, H. Sültmann, A. Poustka, and M. Vingron. Parameter estimation for the calibration and variance stabilization of microarray data. *Statistical Applications in Genetics and Molecular Biology*, Vol. 2: No. 1, Article 3, 2003. <http://www.bepress.com/sagmb/vol2/iss1/art3>