Multivariate Bioequivalence

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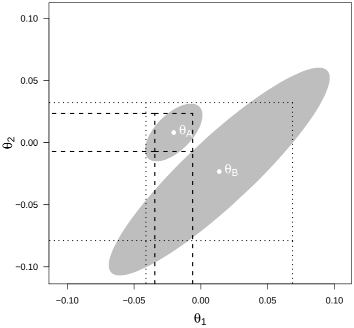
Is Greenland farther north, south, west, east than Iceland?

https://brilliantmaps.com/greenland-v-iceland/

Confidence intervals vs. regions

Example: 95% simultaneous confidence intervals and joint regions around two bivariate normal vectors $\boldsymbol{\theta}_A = (\theta_{A1}, \theta_{A2})$ and $\boldsymbol{\theta}_B = (\theta_{B1}, \theta_{B2})$ based on 100 simulations

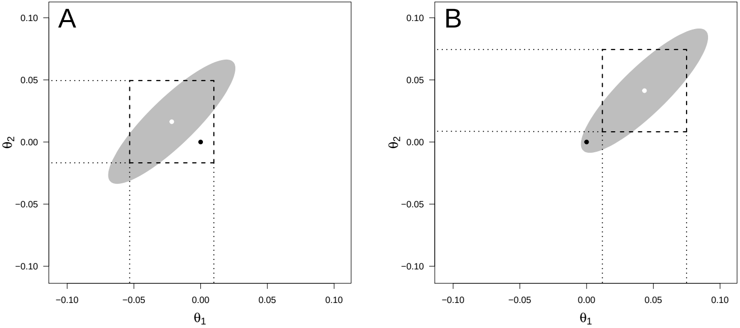


The intervals around $\boldsymbol{\theta}_A$ are contained in those around $\boldsymbol{\theta}_B$ but the regions do not overlap at all!

Confidence intervals vs. regions

Example: 95% simultaneous confidence intervals and joint region around a bivariate normal vector $\boldsymbol{\theta} = (\theta_1, \theta_2)$ based on 100 simulations

Confidence intervals and regions may "disagree" at first sight...



...but they answer different questions

Confidence intervals vs. regions

Interval: what are plausible locations of θ_1 and θ_2 (with joint error rate control)?

Region: what is a plausible joint location of $\boldsymbol{\theta} = (\theta_1, \theta_2)$?

Intervals are easier to summarise and report and (therefore?) much more widely used than regions but…

"…the 'joint' message of individual confidence intervals should be regarded with caution" (Draper & Smith 1998)

Is there a role for joint confidence regions in multi-parameter bioequivalence problems? (Pallmann & Jaki 2017)

Multi-parameter bioequivalence

Almost all bioequivalence problems are multi-parameter problems!

European Medicines Agency

London, 20 January 2010
Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

Guidance for Industry

Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations

Several PK parameters to be shown bioequivalent:

- Europe (EMA), Canada (HC), Japan (JGA): $AUC_{0\text{-}t}$, C_{max}
- US (FDA): $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}

Common analysis: separate TOSTs (or CI inclusion approach) per parameter

Multi-parameter bioequivalence

Single parameter:

$$\mathrm{H}_0\colon \Delta_l > \theta \ \vee \ \Delta_u < \theta$$

$$\mathrm{H}_A\colon \Delta_l \leq \theta \leq \Delta_u$$

Multiple parameters: $i = 1, \ldots, p$

$$\mathrm{H}_0\colon \exists\, i\colon \Delta_l^i > \theta_i \ \vee \ \Delta_u^i < \theta_i$$

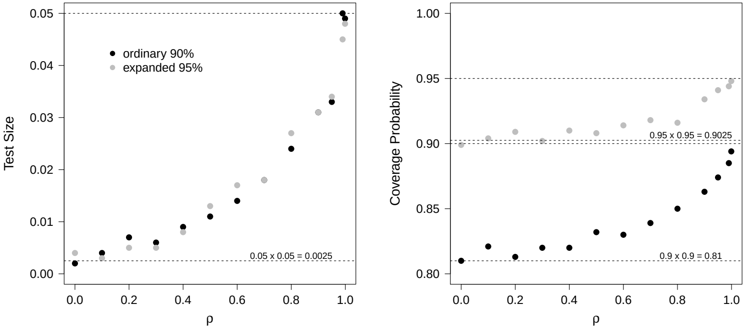
$$\mathrm{H}_A\colon \Delta_l^i \leq \theta_i \leq \Delta_u^i \ \forall\, i$$

Type I error rate control due to the intersection-union principle because all (not just any) PK parameters are to be shown bioequivalent (Berger 1982)

Practical and sufficient for simultaneous but disjoint assessment

Multiple TOSTs are conservative

Simulated test size and coverage probability of 2 simultaneous TOST procedures for $\theta_1 = \theta_2 = \log(1.25)$, $\sigma_1^2 = \sigma_2^2 = 0.1$ and $n = 20$ with varying ρ (10,000 runs)



Confidence ellipses

The “standard” $100(1-\alpha)\%$ confidence region around multivariate normal mean vector $\boldsymbol{\theta}$ is an ellipse in 2D and an ellipsoid in >2D

$$C^0(\mathbf{X}, \widehat{\boldsymbol{\Sigma}}) = \left\{ \boldsymbol{\theta} \colon n(\mathbf{X} - \boldsymbol{\theta})' \widehat{\boldsymbol{\Sigma}}^{-1} (\mathbf{X} - \boldsymbol{\theta}) \leq \frac{\nu p}{\nu - p + 1} F_{1-\alpha, p, \nu - p + 1} \right\}$$

with $\mathbf{X}$ a random variable following a p-variate normal distribution $\mathcal{N}_p(\boldsymbol{\theta}, \boldsymbol{\Sigma})$, sample size n and ν DF

The left-hand part is Hotelling’s T^2 statistic

Proposed for assessment of bioequivalence (Wang *et al.* 1999)

Towards an "optimal" confidence region

The ellipse is easy to compute and interpret—but is it "optimal"?

Depends on how you define optimality (Efron 2006)

One definition: minimum expected effective length (Tseng 2002)

Another definition: minimum expected volume (Brown *et al.* 1995)

The $100(1-\alpha)$% confidence region around a multivariate normal mean vector $\boldsymbol{\theta}$

- that minimises the expected volume at prespecified $\boldsymbol{\theta}_0$
- and thus always contains $\boldsymbol{\theta}_0$

has the boundary shape of the Limaçon of Pascal

Digression: the Limaçon of Pascal

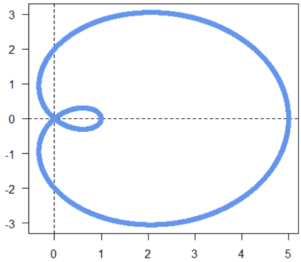
Polar coordinates: $r = a\cos\theta + b$

Cartesian coordinates: $(x^2 + y^2 - ax)^2 - b^2(x^2 + y^2) = 0$

Parametrically: $x = a(\cos\theta)^2 + b\cos\theta$

$$y = a\cos\theta\sin\theta + b\sin\theta$$

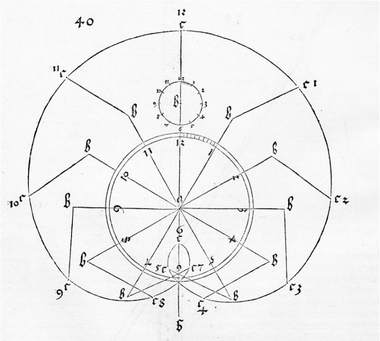
With $a = 3$, $b = 2$:



Named after  and Ètienne Pascal ($\sim$1637)

Further digression: the first Limaçons

Albrecht Dürer's "spider curve":



Underweysung der messung mit dem zirckel und richtscheyt in Linien ebnen unnd gantzen corporen (1525)

The Limaçon confidence region

For covariance matrix $\mathbf{I}$:

$$C^{Lim}(\mathbf{X}) = \left\{\boldsymbol{\theta}\colon (\boldsymbol{\theta}-\boldsymbol{\theta}_0)(\mathbf{X}-\boldsymbol{\theta}_0)' > |\boldsymbol{\theta}-\boldsymbol{\theta}_0|\left(|\boldsymbol{\theta}-\boldsymbol{\theta}_0| - \Phi^{-1}(1-\alpha)\right)\right\}$$
$$= \left\{\boldsymbol{\theta}\colon |\boldsymbol{\theta}-\boldsymbol{\theta}_0| \leq \Phi^{-1}(1-\alpha) + |\mathbf{X}-\boldsymbol{\theta}_0|\cos\beta\right\}$$

with β the angle between $\boldsymbol{\theta}-\boldsymbol{\theta}_0$ and $\mathbf{X}-\boldsymbol{\theta}_0$

For (known) covariance matrix $\boldsymbol{\Sigma}$:

$$C^{Lim}(\mathbf{X}) = \left\{\boldsymbol{\theta}\colon |\boldsymbol{\eta}| \leq \Phi^{-1}(1-\alpha) + |\widehat{\boldsymbol{\eta}}|\cos\beta\right\}$$

with $\boldsymbol{\eta}' = \boldsymbol{\Sigma}^{-\frac{1}{2}}(\boldsymbol{\theta}-\boldsymbol{\theta}_0)'$ and $\widehat{\boldsymbol{\eta}}' = \boldsymbol{\Sigma}^{-\frac{1}{2}}(\mathbf{X}-\boldsymbol{\theta}_0)'$ and β the angle between $\boldsymbol{\eta}$ and $\widehat{\boldsymbol{\eta}}$

The Limaçon confidence region

Natural choice: $\theta_0 = \mathbf{0}$

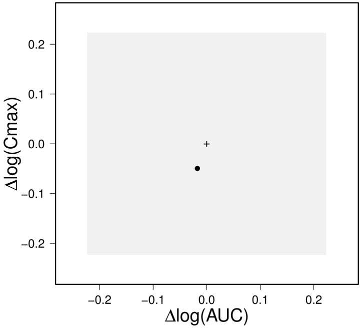
Assuming known covariance (Brown *et al.* 1995):

$$C^{Lim}(\mathbf{X}) = \left\{ \boldsymbol{\theta} \colon \frac{\boldsymbol{\theta}'\boldsymbol{\Sigma}^{-1}\mathbf{X}}{\sqrt{\boldsymbol{\theta}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\theta}}} + z_{1-\alpha} > \sqrt{\boldsymbol{\theta}'\boldsymbol{\Sigma}^{-1}\boldsymbol{\theta}} \right\}$$

Assuming unknown covariance (Berger & Hsu 1996):

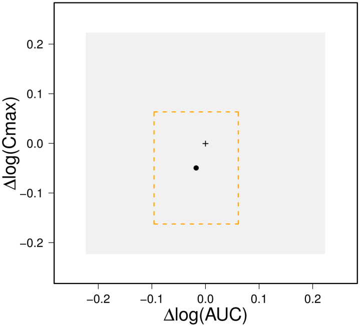
$$C^{Lim}(\mathbf{X}, \widehat{\boldsymbol{\Sigma}}) = \left\{ \boldsymbol{\theta} \colon \frac{\boldsymbol{\theta}'\mathbf{X}}{\sqrt{\boldsymbol{\theta}'\widehat{\boldsymbol{\Sigma}}\boldsymbol{\theta}/n}} + t_{1-\alpha,\nu} > \frac{\boldsymbol{\theta}'\boldsymbol{\theta}}{\sqrt{\boldsymbol{\theta}'\widehat{\boldsymbol{\Sigma}}\boldsymbol{\theta}/n}} \right\}$$

The Limaçon confidence region



The Limaçon confidence region

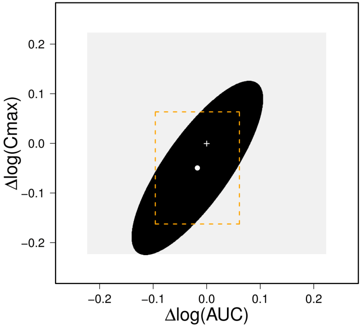
TOST



The Limaçon confidence region

TOST

Ellipse

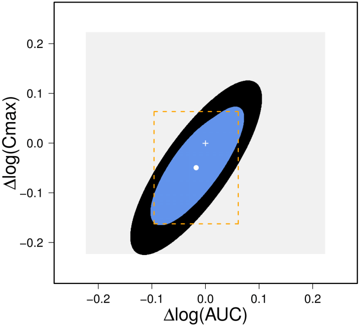


The Limaçon confidence region

TOST

Ellipse

Limaçon (known Σ)



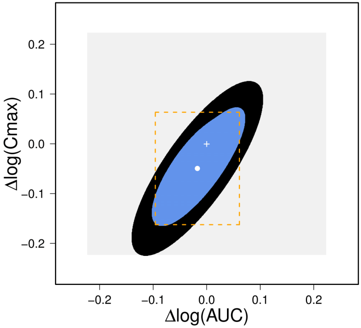
The Limaçon confidence region

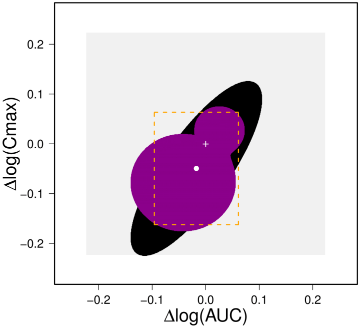
TOST

Ellipse

Limaçon (known Σ)

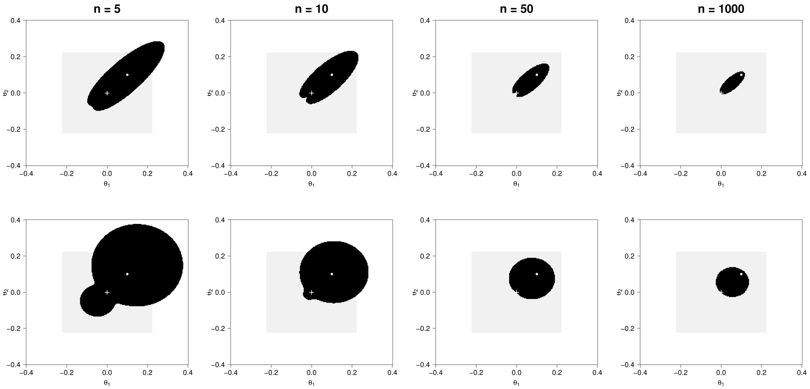
Limaçon (unknown Σ)





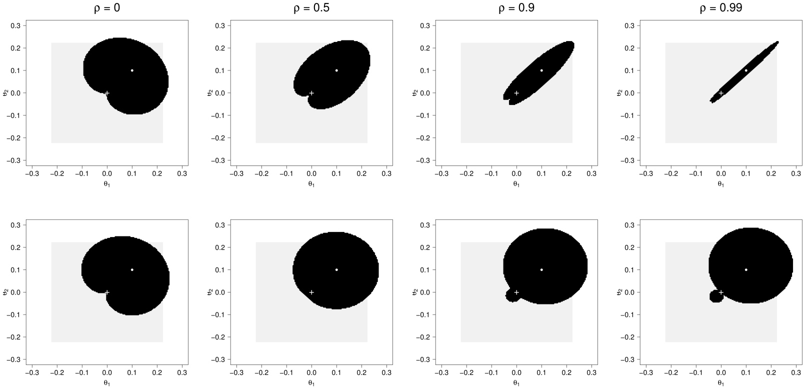
The Limaçon confidence region

90% confidence regions for $\boldsymbol{\theta}_0 = \mathbf{0}$, $\theta_1 = \theta_2 = 0.1$, $\sigma_1 = \sigma_2 = 0.1$ and $\rho = 0.8$ with varying n



The Limaçon confidence region

90% confidence regions for $\boldsymbol{\theta}_0 = \mathbf{0}$, $\theta_1 = \theta_2 = 0.1$, $\sigma_1 = \sigma_2 = 0.1$ and $n = 10$ with varying ρ



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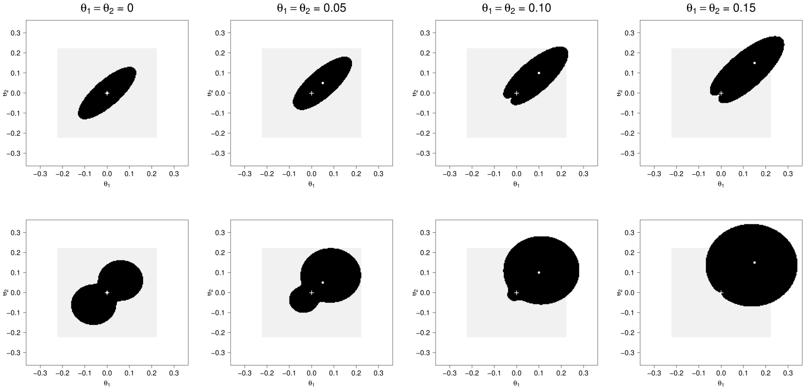
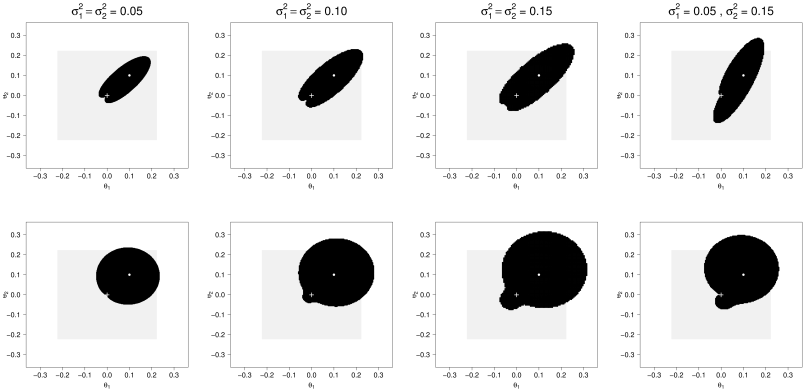
The Limaçon confidence region

90% confidence regions for $\boldsymbol{\theta}_0 = \mathbf{0}$, $\sigma_1 = \sigma_2 = 0.1$, $n = 10$ and $\rho = 0.8$ with varying $\theta_1 = \theta_2$



The Limaçon confidence region

90% confidence regions for $\boldsymbol{\theta_0 = 0}$, $\theta_1 = \theta_2 = 0.1$, $n = 10$ and $\rho = 0.8$ with varying σ_1 and σ_2



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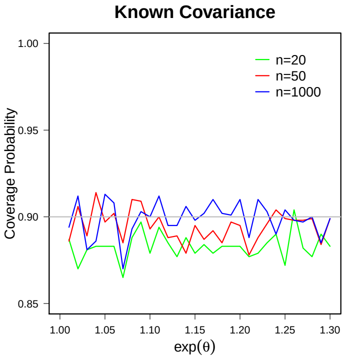
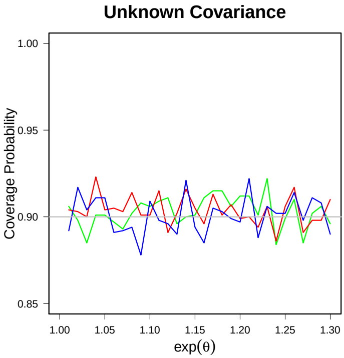
The Limaçon confidence region

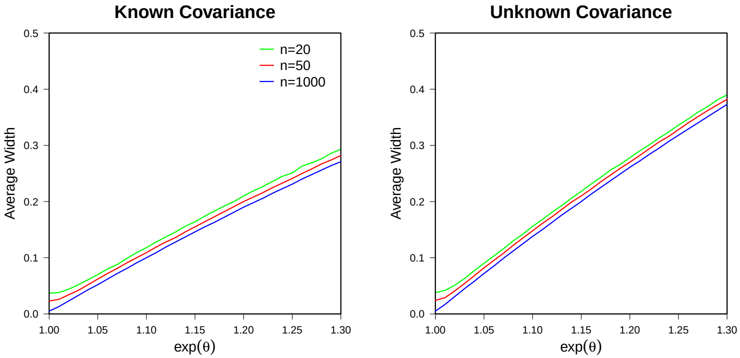
Simulated coverage probability for $\theta_0 = \mathbf{0}$, $\sigma^2 = 0.05$, $\rho = 0.9$ and target level 90% (1000 runs)





The Limaçon confidence region

Simulated average width for $\theta_0 = \mathbf{0}$, $\sigma^2 = 0.05$, $\rho = 0.9$ and target level 90% (1000 runs)



The Tseng confidence region

An alternative optimality criterion: minimum expected effective length at prespecified θ_0 (Tseng 2002)

Natural choice: $\boldsymbol{\theta}_0 = \mathbf{0}$

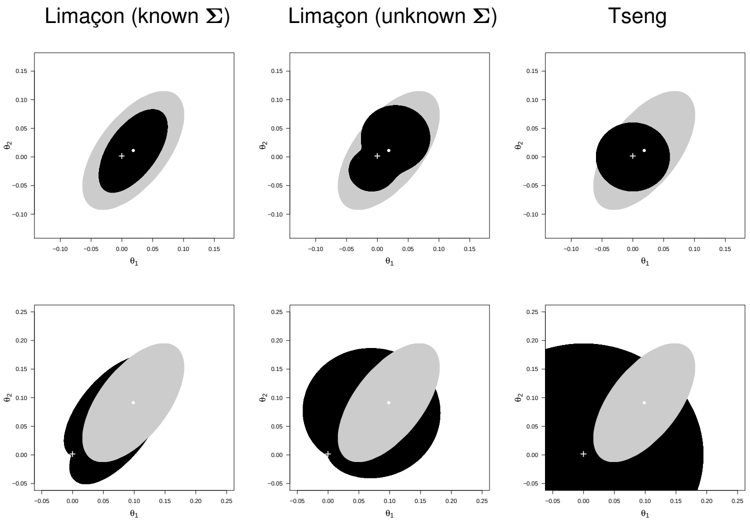
Approximation when $\boldsymbol{\Sigma} = \sigma^2\mathbf{I}$:

$$C^{Tse}(\mathbf{X}, s) = \left\{\boldsymbol{\theta}\colon \frac{||\mathbf{X}||^2}{ps^2} \geq F_{1-\alpha,p,\nu}\left(\frac{||\boldsymbol{\theta}||^2}{s^2}\right)\right\}$$

with σ^2 being estimated as s^2 where $\frac{\nu s^2}{\sigma^2} \sim \chi^2_\nu$ is independent of $\boldsymbol{\theta}$, $F_{1-\alpha,p,\nu}(\lambda)$ the $100(1-\alpha)\%$ quantile of the F-distribution with p and ν DF and noncentrality parameter λ, and $||\cdot||$ denoting the Euclidian norm

Can be an empty set

When are the “optimal” regions useful?



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An empirical Bayes confidence region

Centred at positive-part James-Stein estimator (shrinkage towards $\mathbf{0}$ for $p \geq 3$) (Casella & Hwang 1983)

$$C^{EB}(\mathbf{X}, s) = \left\{ \boldsymbol{\theta} \colon ||\boldsymbol{\theta} - \delta^{+}(\widehat{\boldsymbol{\theta}}, s)|| \leq \frac{s}{\sqrt{n}} v_E \left(\frac{n||\mathbf{X}||}{s} \right) \right\}$$

with

$$\delta^{+}(\widehat{\boldsymbol{\theta}}, s) = \left(1 - \frac{\nu(p-2)s^2}{(\nu+2)n||\widehat{\boldsymbol{\theta}}||^2} \right)^{+} \widehat{\boldsymbol{\theta}}$$

where $(x)^{+}$ indicates $\max(0, x)$, and

$$v_E^2 \left(\frac{n||\mathbf{X}||}{s} \right) = \begin{cases} \left(1 - \frac{a}{pF_{1-\alpha,p,\nu}}\right) \left[pF_{1-\alpha,p,\nu} - p \log \left(1 - \frac{a}{pF_{1-\alpha,p,\nu}} \right) \right] & \text{if } \frac{n||\mathbf{X}||^2}{s^2} \leq pF_{1-\alpha,p,\nu} \\ \left(1 - \frac{as^2}{n||\mathbf{X}||^2}\right) \left[pF_{1-\alpha,p,\nu} - p \log \left(1 - \frac{as^2}{n||\widehat{\boldsymbol{\theta}}||^2} \right) \right] & \text{if } \frac{n||\mathbf{X}||^2}{s^2} > pF_{1-\alpha,p,\nu} \end{cases}$$

where $a = \frac{\nu(p-2)}{\nu+2}$

Ellipse centred at ML estimator for $p = 2$

From regions to intervals

How can (simultaneous) intervals be derived from a joint region?

Preferable: direct computation rather than "regional detour" but this is only possible for "standard" intervals/ellipses and empirical Bayes intervals/regions (He 1992)

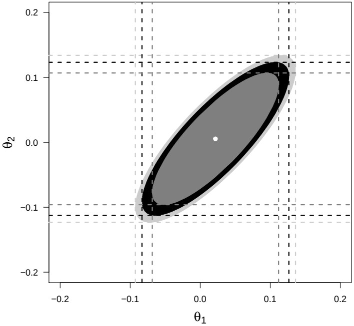
Otherwise: project boundary onto axes (very conservative)

How can a non-convex region like the Limaçon be translated into marginal intervals?

How can such a region even be (usefully) presented without a graph?

Digression: Confidence intervals generating ellipse

CIGEs generating 95% Scheffé/Bonferroni/unadjusted intervals



Example: the perpendicular shadows of a 86.03% confidence ellipse are marginal 95% confidence intervals (for $\nu = 20$)

The `R` package `jocre`

`R` implementation of joint confidence regions (Pallmann 2017)

Core function: `cset` for joint regions and (simultaneous) intervals around multivariate normal mean vectors

- `print` or `summary` to display parameter estimates and interval bounds (or projections of the region's boundary onto the axes)
- `plot` to generate a (2D) graph

Other functions:

- `csetMV`: joint confidence regions for the mean and variance of a normal distribution
- `iutsize`: how conservative is the "multivariate" TOST?
- `translate`: confidence levels of joint confidence ellipses and marginal intervals

Conclusions

Whenever the joint location of a parameter vector is of interest, a joint confidence region will be preferable to (simultaneous) confidence intervals

Using joint regions does not (usually) increase the power as compared to the TOST, nor do “optimal” regions necessarily perform well: “reduced volume by itself offers no guarantee of superior performance” (Efron 2006)

Challenges yet to be resolved:

- How should the boundary of a confidence region be summarised in a results table?
- How can a >3D hyperregion be displayed graphically?
- Are rectangular equivalence regions appropriate for joint confidence regions? (Munk & Pflüger 1999)
- Is shrinking the estimate more effective than shifting the confidence set in >2D? (Casella & Hwang 2012)
- Can the “optimal” regions be “optimised” with a prior?

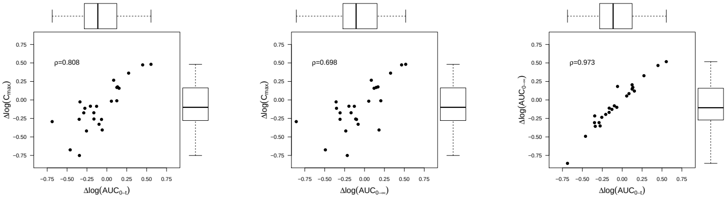
Case study

Single-dose ticlopidine hydrochloride (250mg active ingredient) administered as a tablet of commercial reference product Tiklid (R) or test formulation (T)

2 x 2 x 2 crossover study with 24 healthy male volunteers randomised to sequence RT or TR (Marzo *et al.* 2002)

AUC_{0-t}, $AUC_{0-\infty}$, C_{max} data in `R` package `jocre` (Pallmann 2017)

The PK parameters are correlated:



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Case study

Exercises:

1. Test whether formulations T and R are bioequivalent regarding all three PK parameters. Use the TOST procedure at $\alpha = 0.05$ with the conventional [80%, 125%] bioequivalence range.
2. Compute and plot the corresponding 90% confidence intervals as well as the 95% "expanded" intervals for AUC_{0-t} and C_{max}.
3. Compute and plot the 90% joint confidence ellipse, both Limaçon regions (assuming known and unknown $\mathbf{\Sigma}$, respectively) and the Tseng region for AUC_{0-t} and C_{max}.
4. Calculate the James-Stein estimates for all three PK parameters jointly and compare them to the ML estimates.
5. What is the confidence level of the Scheffé intervals obtained by projecting the 90% joint ellipse onto the axes? What confidence level of a joint ellipse would be needed for its perpendicular projections to yield 90% Scheffé intervals?

Case study: code & results

```r
### Dataset

library(jocre)
data(marzo)
head(marzo, 5)


##   Volunteer Sequence Cmax_T Cmax_R  AUC_T  AUC_R AUCinf_T AUCinf_R
## 1         1       TR  784.3  878.2 2021.7 2665.2   2131.4   3030.1
## 2         2       RT  304.2  211.7  901.7  685.9   1107.9    798.6
## 3         3       TR  307.3  259.6  741.4  654.0    806.2    696.1
## 4         4       TR  156.7  307.8  475.6  753.7    509.9    833.7
## 5         5       RT  745.6 1036.2 2521.4 2781.9   2784.0   3015.6
```

```r
### Differences of logarithms

marzo$logdiffAUC <- log(marzo$AUC_T) - log(marzo$AUC_R)
marzo$logdiffAUCinf <- log(marzo$AUCinf_T) - log(marzo$AUCinf_R)
marzo$logdiffCmax <- log(marzo$Cmax_T) - log(marzo$Cmax_R)
head(marzo, 5)


##   Volunteer Sequence Cmax_T Cmax_R  AUC_T  AUC_R AUCinf_T AUCinf_R
## 1         1       TR  784.3  878.2 2021.7 2665.2   2131.4   3030.1
## 2         2       RT  304.2  211.7  901.7  685.9   1107.9    798.6
## 3         3       TR  307.3  259.6  741.4  654.0    806.2    696.1
## 4         4       TR  156.7  307.8  475.6  753.7    509.9    833.7
## 5         5       RT  745.6 1036.2 2521.4 2781.9   2784.0   3015.6
##    logdiffAUC logdiffAUCinf logdiffCmax
## 1 -0.27634036   -0.35181658  -0.1130828
## 2  0.27355003    0.32736142   0.3625152
## 3  0.12543294    0.14683852   0.1686825
## 4 -0.46041725   -0.49165900  -0.6751171
## 5 -0.09831984   -0.07991007  -0.3291262
```

Case study: code & results

```r
### TOST p-values
t.test(x=marzo$logdiffAUC, alternative="greater", mu=log(0.8))$p.value

## [1] 0.01162843

t.test(x=marzo$logdiffAUC, alternative="less", mu=log(1.25))$p.value

## [1] 1.55846e-05

t.test(x=marzo$logdiffAUCinf, alternative="greater", mu=log(0.8))$p.value

## [1] 0.01184553

t.test(x=marzo$logdiffAUCinf, alternative="less", mu=log(1.25))$p.value

## [1] 7.135828e-05

t.test(x=marzo$logdiffCmax, alternative="greater", mu=log(0.8))$p.value

## [1] 0.03083552

t.test(x=marzo$logdiffCmax, alternative="less", mu=log(1.25))$p.value

## [1] 3.533647e-05
```

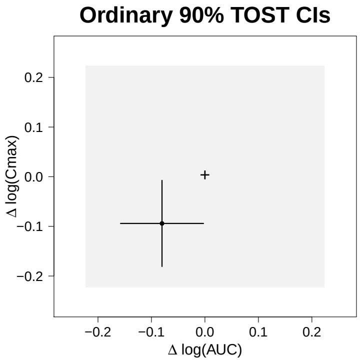
Case study: code & results

```
### 90% TOST intervals

tost <- cset(dat=marzo[, c(9, 11)], method="tost", alpha=0.1)
summary(tost)


## Parameter estimates and 90% simultaneous confidence intervals:
##
##              Estimate  Lower  Upper
## logdiffAUC     -0.080 -0.158 -0.003
## logdiffCmax    -0.094 -0.181 -0.008
```

```
ax <- c(expression(paste(Delta, " log(AUC)")), expression(paste(Delta, " log(Cmax)")))
plot(tost, equi=log(c(0.8, 1.25)), axnames=ax, main="Ordinary 90% TOST CIs")
```



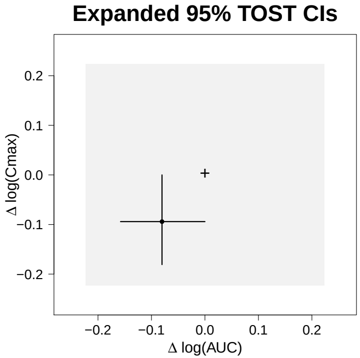
Case study: code & results

```
### 95% "expanded" TOST intervals

expanded <- cset(dat=marzo[, c(9, 11)], method="expanded", alpha=0.1)
summary(expanded)


## Parameter estimates and 90% simultaneous confidence intervals:
##
##               Estimate  Lower Upper
## logdiffAUC      -0.080 -0.158     0
## logdiffCmax     -0.094 -0.181     0
```

```
plot(expanded, equi=log(c(0.8, 1.25)), axnames=ax, main="Expanded 95% TOST CIs")
```



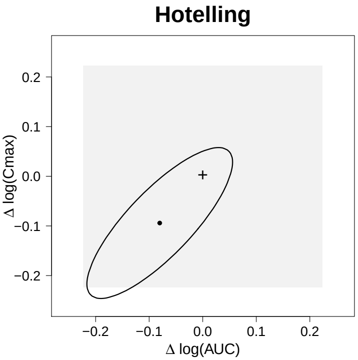
Case study: code & results

```r
### 90% standard ellipse

hotel <- cset(dat=marzo[, c(9, 11)], method="hotelling", alpha=0.1)
summary(hotel)


## Parameter estimates and projected boundaries of the 2-dimensional
## 90% simultaneous confidence region:
##
##              Estimate  Lower Upper
## logdiffAUC     -0.080 -0.216 0.056
## logdiffCmax    -0.094 -0.246 0.058
```

```r
plot(hotel, equi=log(c(0.8, 1.25)), axnames=ax, main="Hotelling")
```



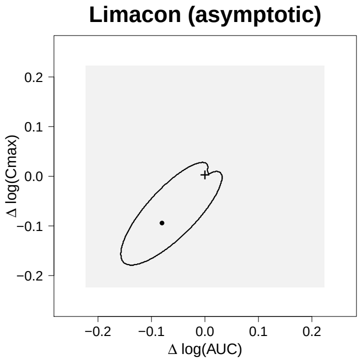
Case study: code & results

```
### 90% Limacon region (assuming known covariance)

limasy <- cset(dat=marzo[, c(9, 11)], method="limacon.asy", alpha=0.1)
summary(limasy)


## Parameter estimates and projected boundaries of the 2-dimensional
## 90% simultaneous confidence region:
##
##              Estimate  Lower Upper
## logdiffAUC    -0.080 -0.158 0.032
## logdiffCmax   -0.094 -0.179 0.029
```

```
plot(limasy, equi=log(c(0.8, 1.25)), axnames=ax, main="Limacon (asymptotic)")
```



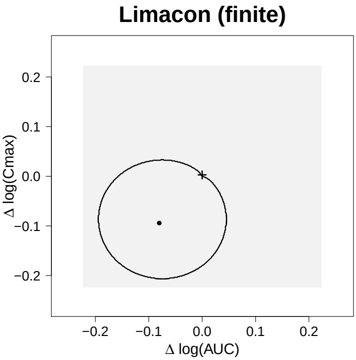
Case study: code & results

```r
### 90% Limacon region (assuming unknown covariance)

limfin <- cset(dat=marzo[, c(9, 11)], method="limacon.fin", alpha=0.1)
summary(limfin)


## Parameter estimates and projected boundaries of the 2-dimensional
## 90% simultaneous confidence region:
##
##              Estimate  Lower Upper
## logdiffAUC     -0.080 -0.195 0.046
## logdiffCmax    -0.094 -0.207 0.033
```

```r
plot(limfin, equi=log(c(0.8, 1.25)), axnames=ax, main="Limacon (finite)")
```



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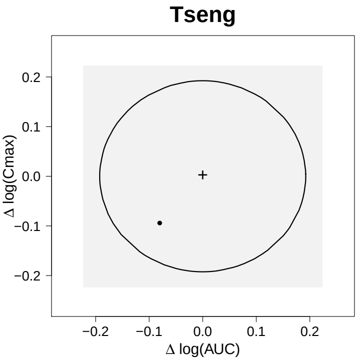
Case study: code & results

```
### 90% Tseng region

tseng <- cset(dat=marzo[, c(9, 11)], method="tseng", alpha=0.1)
summary(tseng)


## Parameter estimates and projected boundaries of the 2-dimensional
## 90% simultaneous confidence region:
##
##                Estimate  Lower Upper
## logdiffAUC       -0.080 -0.192 0.192
## logdiffCmax      -0.094 -0.192 0.192
```

```
plot(tseng, equi=log(c(0.8, 1.25)), axnames=ax, main="Tseng")
```



Case study: code & results

```
### ML and shrinkage estimates

cset(dat=marzo[, 9:11], method="hotelling", alpha=0.1)


## Parameter estimates and projected boundaries of the 3-dimensional
## 90% simultaneous confidence region:
##
##               Estimate  Lower Upper
## logdiffAUC      -0.080 -0.243 0.083
## logdiffAUCinf   -0.068 -0.246 0.109
## logdiffCmax     -0.094 -0.277 0.089


cset(dat=marzo[, 9:11], method="emp.bayes", alpha=0.1)


## Parameter estimates and projected boundaries of the 3-dimensional
## 90% simultaneous confidence region:
##
##               Estimate  Lower Upper
## logdiffAUC      -0.066 -0.224 0.092
## logdiffAUCinf   -0.056 -0.214 0.101
## logdiffCmax     -0.077 -0.235 0.080
```

Case study: code & results

```r
### Converting confidence levels

translate(0.9, ddf=22, "cr2ci")

## [1] 0.9661753

translate(0.9, ddf=22, "ci2cr")

## [1] 0.7493057
```

Literature

Berger RL (1982) Multiparameter hypothesis testing and acceptance sampling. *Technometrics*, **24**(4), 295–300.

Berger RL, Hsu JC (1996) Bioequivalence trials, intersection-union tests and equivalence confidence sets. *Statistical Science*, **11**(4), 283–319.

Brown LD, Casella G, Hwang JTG (1995) Optimal confidence sets, bioequivalence, and the Limaçon of Pascal. *Journal of the American Statistical Association*, **90**(431), 880–889.

Casella G, Hwang JT (1983) Empirical Bayes confidence sets for the mean of a multivariate normal distribution. *Journal of the American Statistical Association*, **78**(383), 688–698.

Casella G, Hwang JTG (2012) Shrinkage confidence procedures. *Statistical Science*, **27**(1), 51–60.

Draper NR, Smith H (1998) *Applied Regression Analysis.* 3rd Edition. John Wiley & Sons.

Efron B (2006) Minimum volume confidence regions for a multivariate normal mean vector. *JRSSB*, **68**(4), 655–670.

He K (1992) Parametric empirical Bayes confidence intervals based on James-Stein estimator. *Statistics & Decisions*, **10**(1–2), 121–132.

Munk A, Pflüger (1999) 1–α equivariant confidence rules for convex alternatives are $\alpha/2$-level tests—with applications to the multivariate assessment of bioequivalence. *Journal of the American Statistical Association*, **94**(448), 1311–1319.

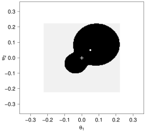
Pallmann P, Jaki T (2017) Simultaneous confidence regions for multivariate bioequivalence. *Statistics in Medicine*, **36**(29), 4585–4603.

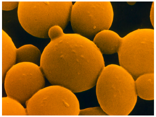
Pallmann P (2017) `jocre`: joint confidence regions. `R` package version 0.3.3. https://cran.r-project.org/package=jocre

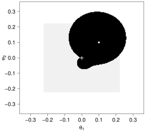
Tseng YL (2002) Optimal confidence sets for testing average bioequivalence. *Test*, **11**(1), 127–141.

Wang W, Hwang JTG, DasGupta A (1999) Statistical tests for multivariate bioequivalence. *Biometrika*, **86**(2), 395–402.

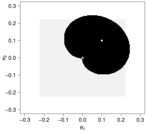
Thanks for your interest!

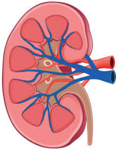


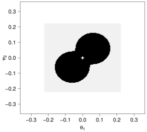




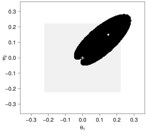
$\rho = 0$

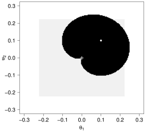






$\theta_1 = \theta_2 = 0.15$





Thanks for your interest!

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