

Muscular Dystrophy treatment: a population approach

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BACKGROUND.

- Limited treatment options are currently available for Duchenne Muscular Dystrophy (DMD).
- With quantitative clinical endpoints, such as muscle fibers cross sectional area (CSA), it is possible to objectively assess the efficacy of possible new treatments.
- Fiber CSAs are measured via skeletal muscle biopsies, once before and (at least) once after treatment (**Figure 1**).
- Being biopsy a destructive procedure, the measured tissue specimen changes on each occasion: pre- and post-treatment fiber CSAs cannot be paired.
- A particular data analysis problem arises: CSA empirical distributions need to be compared.

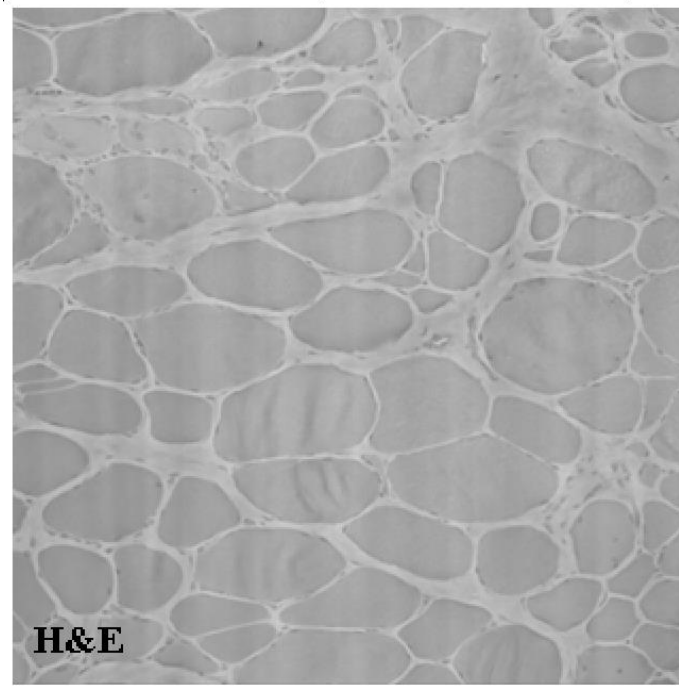


Figure 1: Bioptic sample stained with haematoxylin and eosin (H&E).

OBJECTIVES.

Here, CSA distributional data are analysed within a population approach framework, exploiting a hierarchical statistical method. In particular, the histological effects of the HDAC1 inhibitor Givinostat, a compound under study for DMD treatment, are assessed, based on data collected in a clinical trial [2] (**Figure 2**).

METHODS.

The DMD clinical trial [2]

- Two-part Phase II study by Italfarmaco S.p.A; 20 boys from 7 to <11 yrs old were enrolled to participate to both study parts.
- Study Part 1: the maximum tolerated dose (MTD, 37.5 mg BID) was identified.
- Study Part 2: the MTD was selected; in 63% of the patients the dose was reduced to 25 mg BID to maintain platelets within the normal range.
- Fiber CSAs and muscle composition data (i.e. muscle fiber area fraction, necrosis, fatty replacement and fibrosis) were obtained via biopsies once before and once after ≥ 12 months of treatment.

Hierarchical statistical approach in a population framework

- Lower level (intra-patient):** each fiber is considered a sample drawn from a population of fibers.
- Based on data inspection (**Figure 2**):
- the pre- and post-treatment distributions of log-transformed CSAs (logCSAs) are modelled as two-component Gaussian mixtures;
 - drug effect on logCSAs is described by a shift, corresponding to a multiplicative factor on CSAs (drug potency parameter, K)

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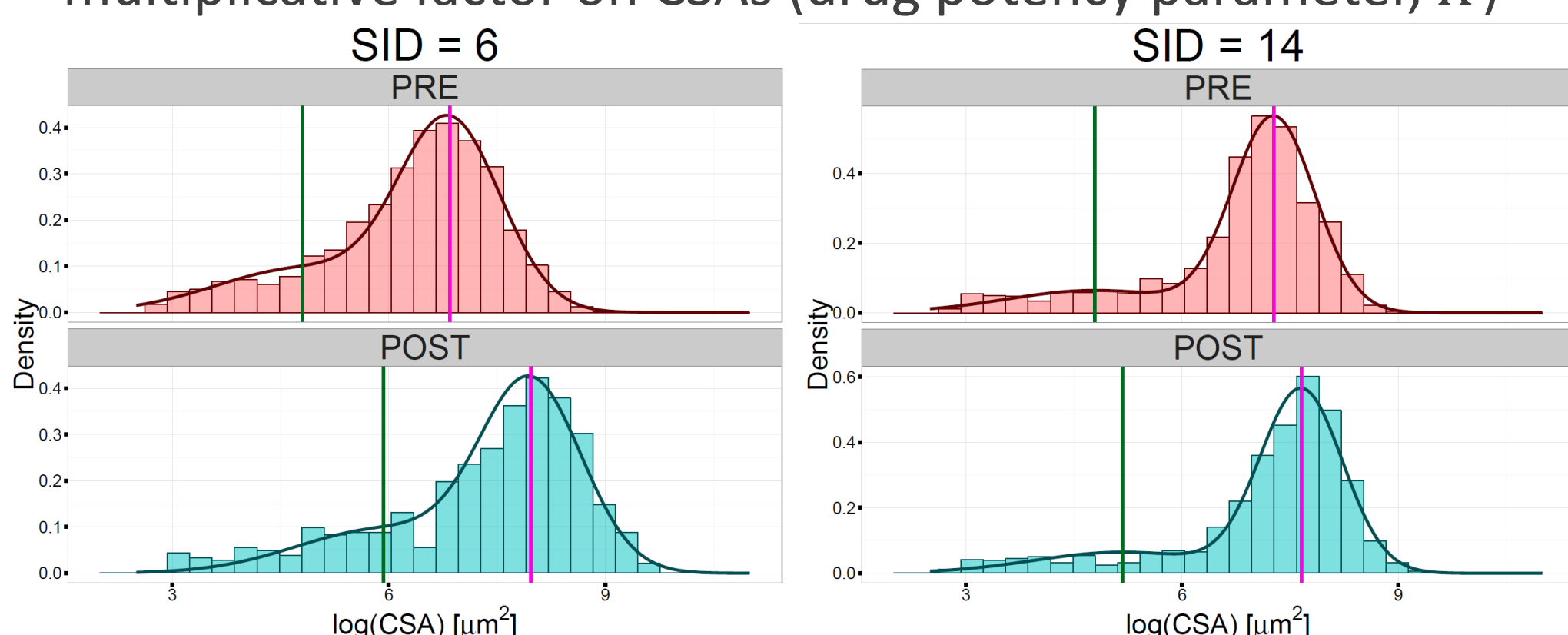


Figure 2: Observed data (histograms), pre- (red) and post-treatment (blue), for two subjects. Gaussian mixtures (dark lines), with means in evidence (m_1 : green line, m_2 : magenta line), are super-imposed to support the modeling hypotheses.

Hence model equations are:

$$f_{pre} = \lambda \phi(m_1, \sigma_1^2) + (1 - \lambda) \phi(m_2, \sigma_2^2)$$

$$f_{post} = \lambda \phi(m_1 + b, \sigma_1^2) + (1 - \lambda) \phi(m_2 + b, \sigma_2^2)$$

- Higher level (inter-patient):** typical values and inter-patient variabilities are computed via Global Two Stage (GTS) and their uncertainty evaluated via bootstrap.

Model validation

Model-predicted and observed post-treatment muscle composition data are compared.

RESULTS.

Hierarchical statistical approach in a population framework



Figure 3: Gaussian mixtures identified on patients' data, both before (red) and after treatment (blue).

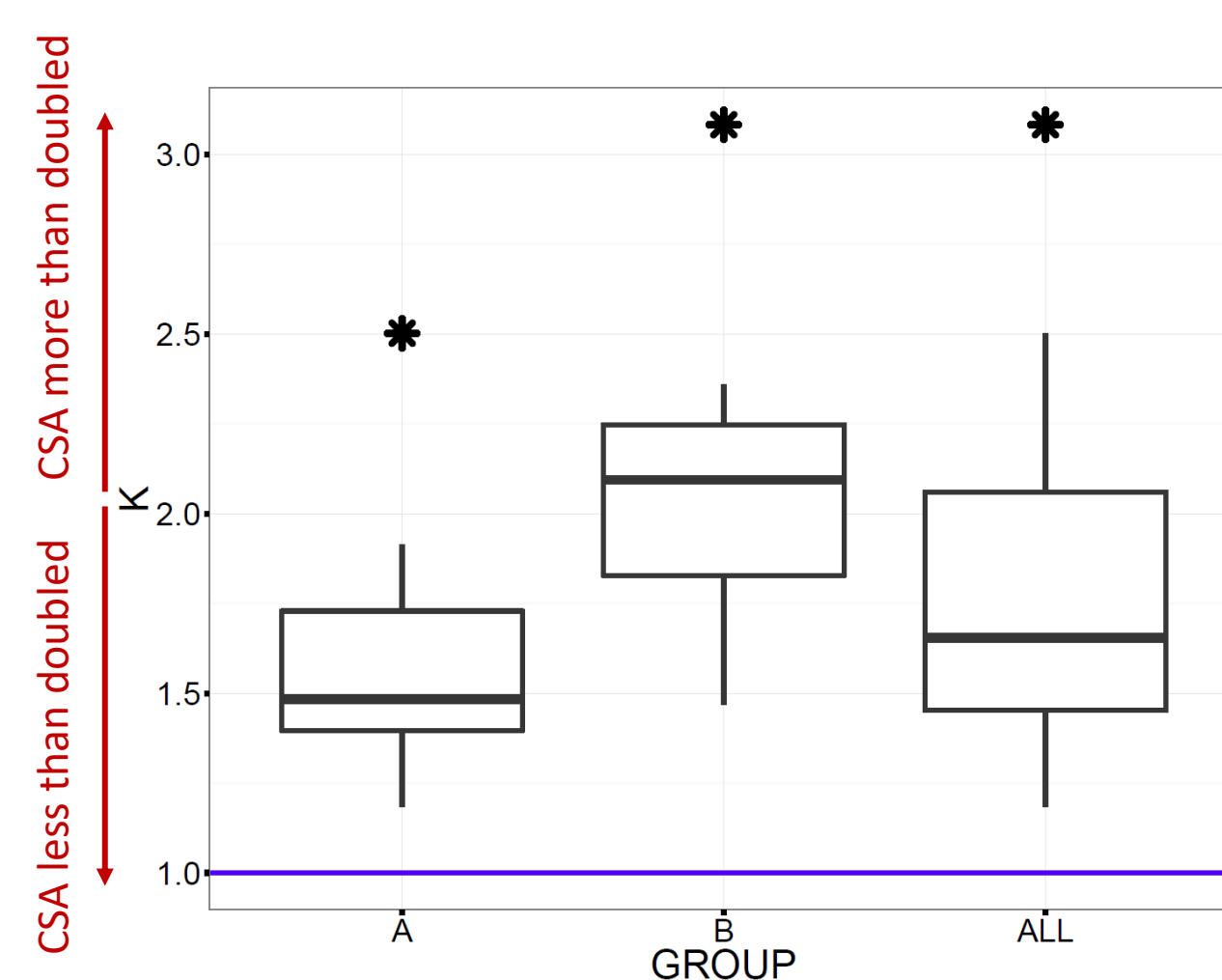


Figure 4: Boxplots of drug potency parameter K , in group A (dose=25 mg BID) and group B (dose=37.5 mg BID), and in patients all together (ALL).

Model validation

- $\log CSA_{post} = \log CSA_{pre} + b$
 $\Rightarrow CSA_{post} = K CSA_{pre}$
- Muscular Fiber Area: $MFA = \sum CSA$
- Total Muscle Area: $TMA = MFA + FIBR + NECR + FAT$;
 $MFA\% = (MFA/TMA)\%$

$$MFA\%_{post} = \frac{K MFA\%_{pre}}{\frac{(K-1)}{100} MFA\%_{pre} + 1}$$

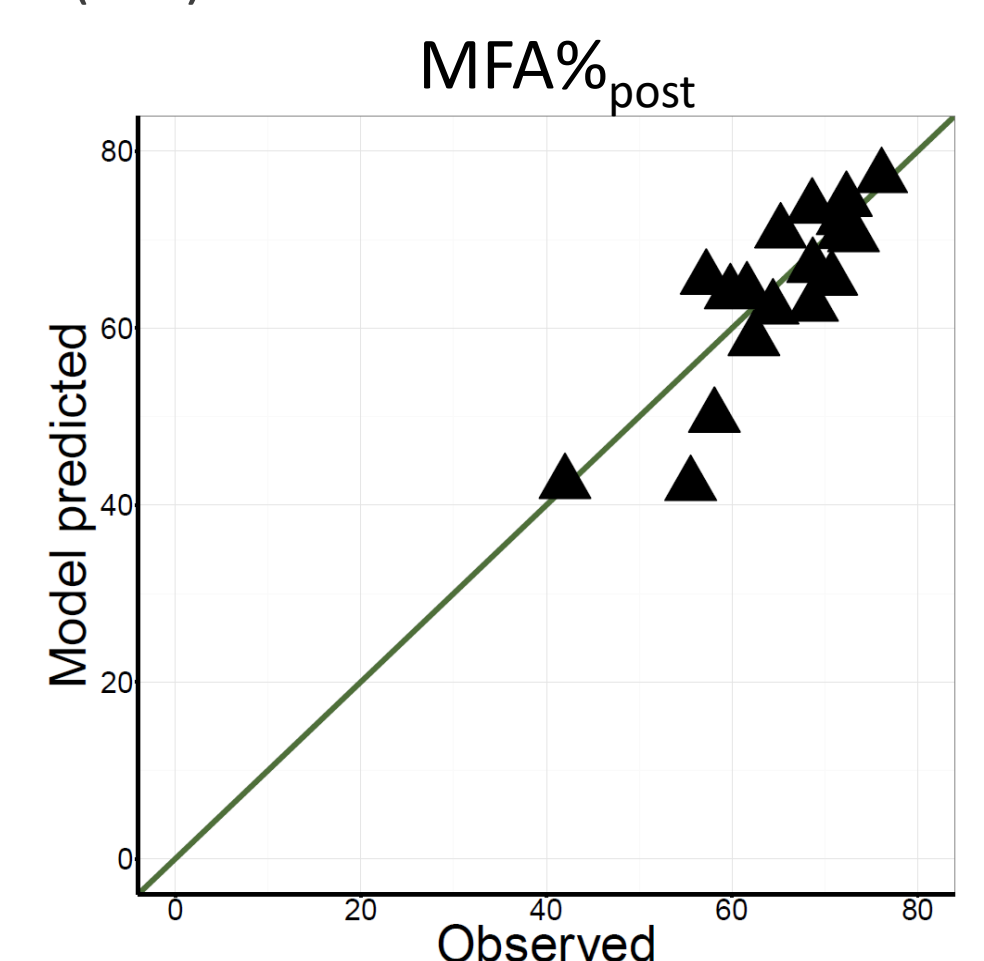


Figure 5: Post-treatment MFA%, predicted vs observed.

CONCLUSIONS.

- Muscular distributional data were analysed via a hierarchical statistical approach.
- The population approach was applied to each patient's muscle fibers.
- Distribution of fiber CSA and drug potency have been characterized.
- Givinostat has positive and dose-dependent histological effects.
- Model predictivity was confirmed by muscle composition data.
- The methodological approach might be applied to distributional data also in other contexts (other diseases, drugs, or endpoints).

REFERENCES.

- [1] Mah JK et al (2014) A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. Neuromuscul Disord 24:482-491
- [2] Bettica P et al (2016) Histological effects of givinostat in boys with Duchenne muscular dystrophy. Neuromuscul Disord 26:643-649