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A comprehensive functional force velocity endurance (FoVE) model reveals unsuspected muscle properties affected by the expression of DUX4

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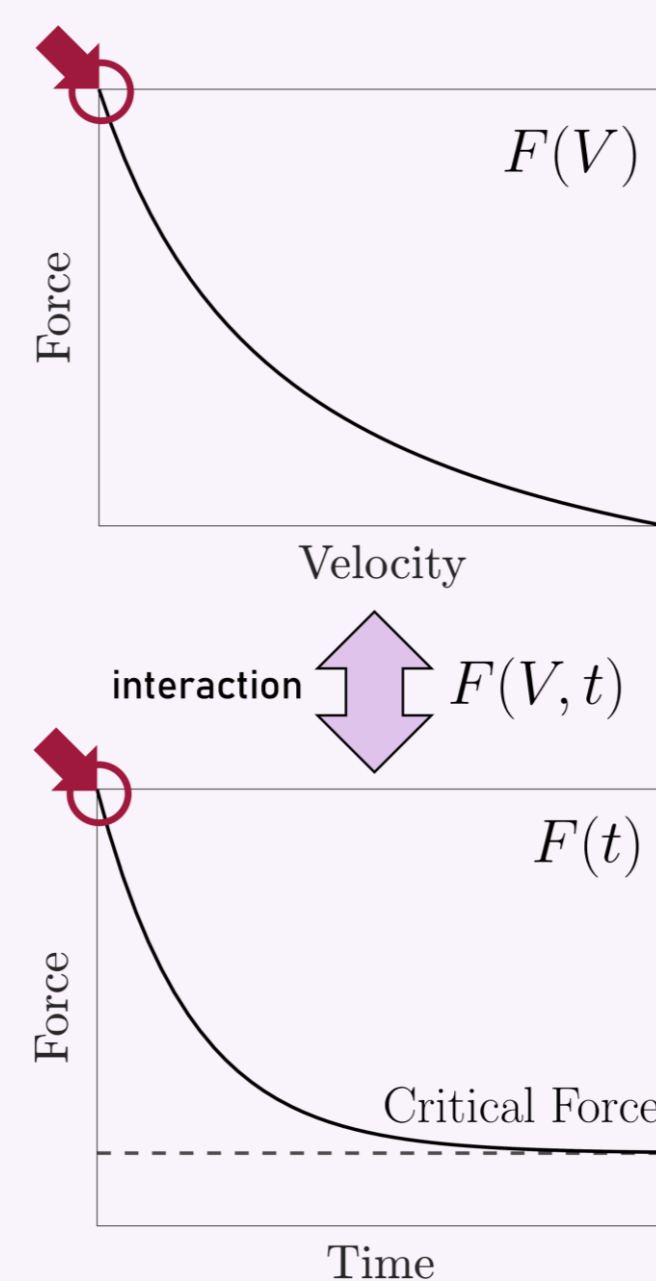
ABSTRACT

Measurements of muscle function is crucial to the assessment of potential treatments for muscular diseases. To date, several force tests have been proposed in the literature such as the grip strength test and in situ measure of maximum muscle force-producing capacity. These experiments are realized under isometric conditions at null velocity, which does not reflect what happens in everyday life. Here, we developed a Force-Velocity-Endurance (FoVE) model to *in situ* compare the muscle functional capacities of the ACTA1-MCM/+ (Cre+) and ACTA1-MCM/FLEXDUX4 (CD-Cre+) transgenic mice. The integrative FoVE model describes the evolution of the muscle force capacity simultaneously as a function of the contraction velocity and the time (i.e. fatigue). Experimentally, FoVE capacities were assessed during a fatiguing 180-s exercise by repeating maximal (100 Hz stimulation) shortening contractions performed at different velocities (2 to 15 mm.s⁻¹). This test provides a complete mapping of muscular function by describing the force production capacities at all velocity and fatigue levels. This comprehensive functional force-velocity-endurance model reveals muscle properties affected by the expression of DUX4, leading to a weaker, less powerful muscle but less quickly fatigable muscle.

Introduction

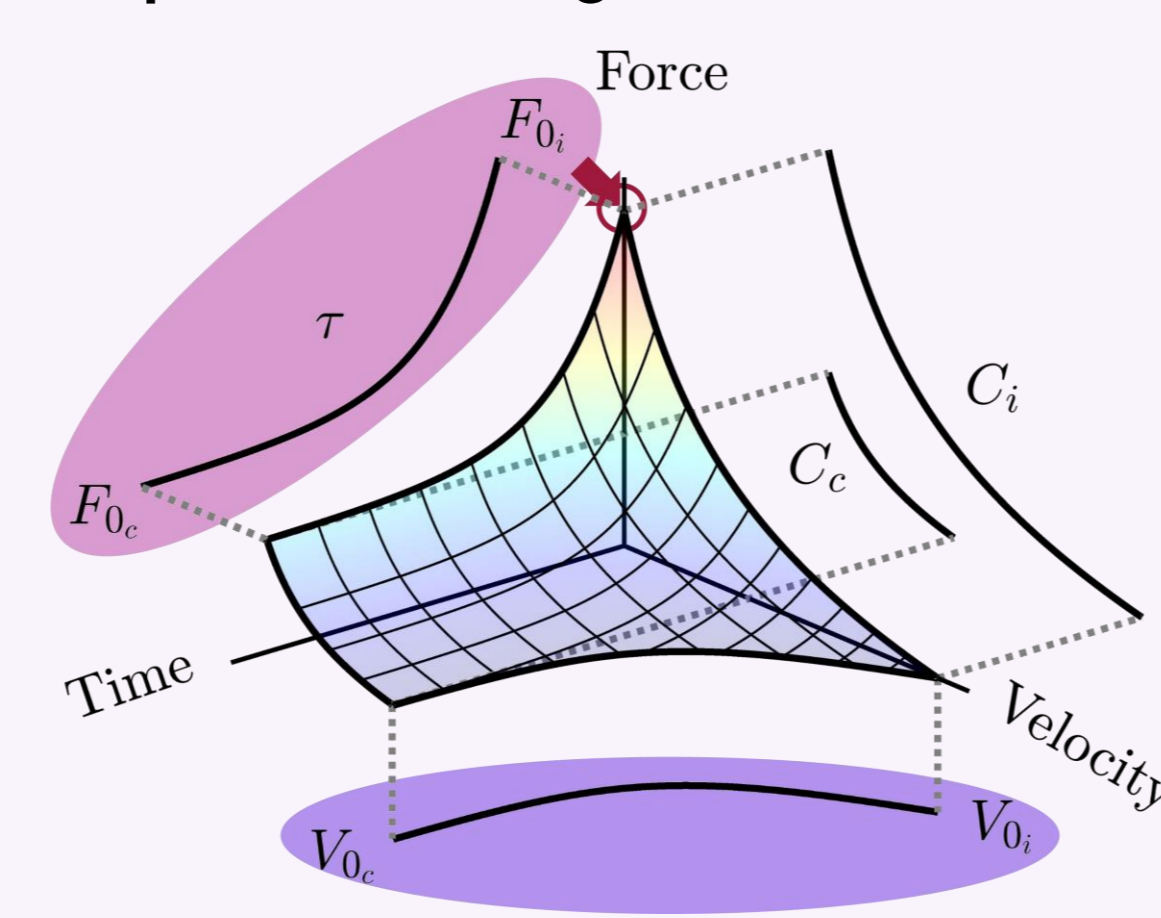
In murine models, muscle evaluation is traditionally based on muscle mass or force capacity under isometric conditions at null velocity.

Maximal isometric force (○) is a specific condition of two relationships: the Force-Velocity $F(V)$ [1] at $V=0$ and Force-Time $F(t)$ [2] at $t=0$ (without fatigue).



Mathematical Model

$F(V)$ and $F(t)$ have been studied separately, while interactions exist. Muscle functional capacities can be explored using a Force-Velocity-Endurance Model $F(V,t)$.



7 FoVE parameters:

- F_{0i} : Initial Isometric Force
- F_{0c} : Critical Isometric Force
- V_{0i} : Initial Maximal Velocity
- V_{0c} : Critical Maximal Velocity
- C_i : Curvature of $F_i(V)$
- C_c : Curvature of $F_c(V)$
- τ : Typical decay time

Protocol

Isolated Muscles (M)

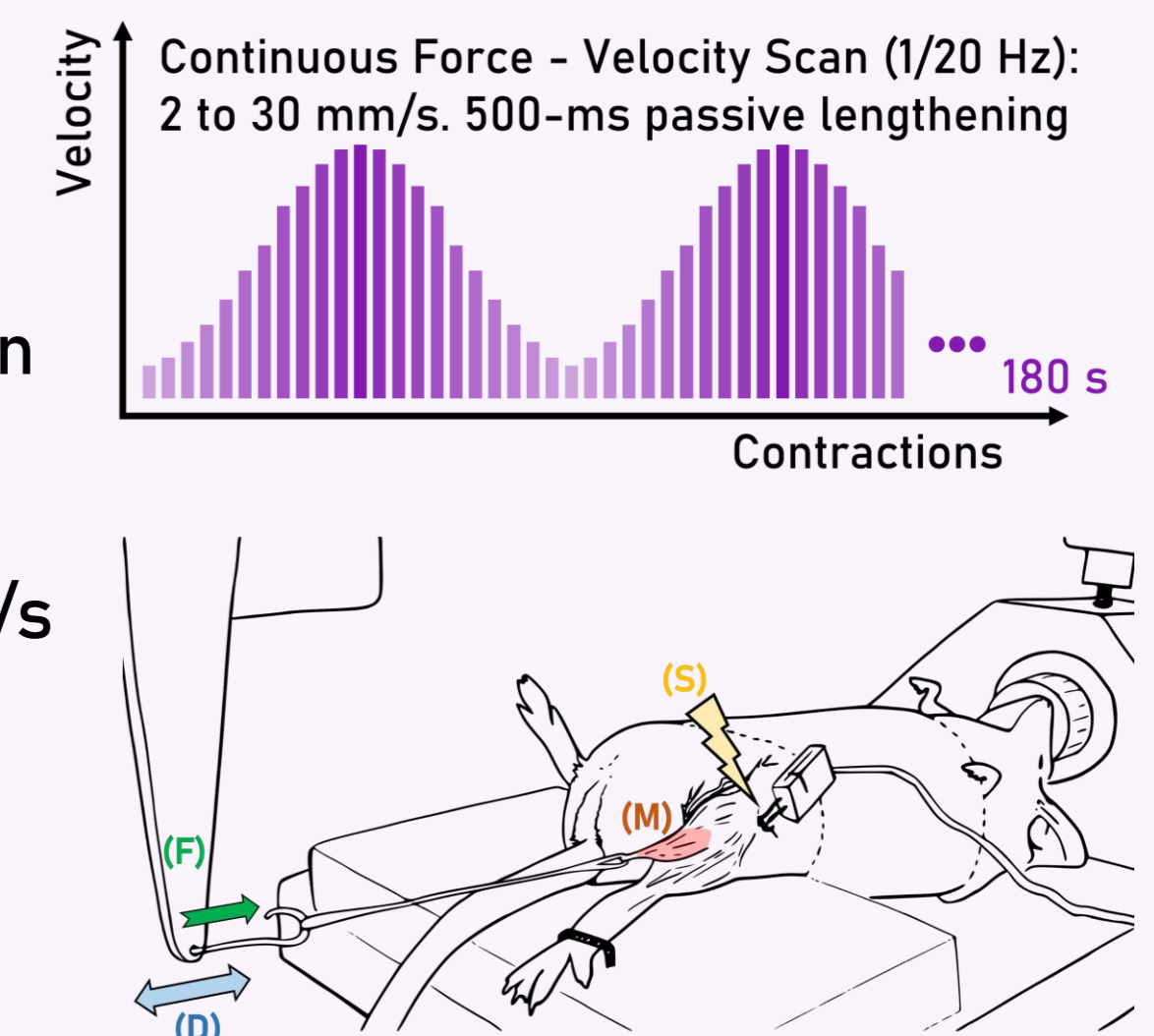
- Tibialis Anterior TA
- Electrical Stimulation (S)
- Tetanic nerve stimulation
- Frequency: 100Hz

Isokinetic displacement (D)

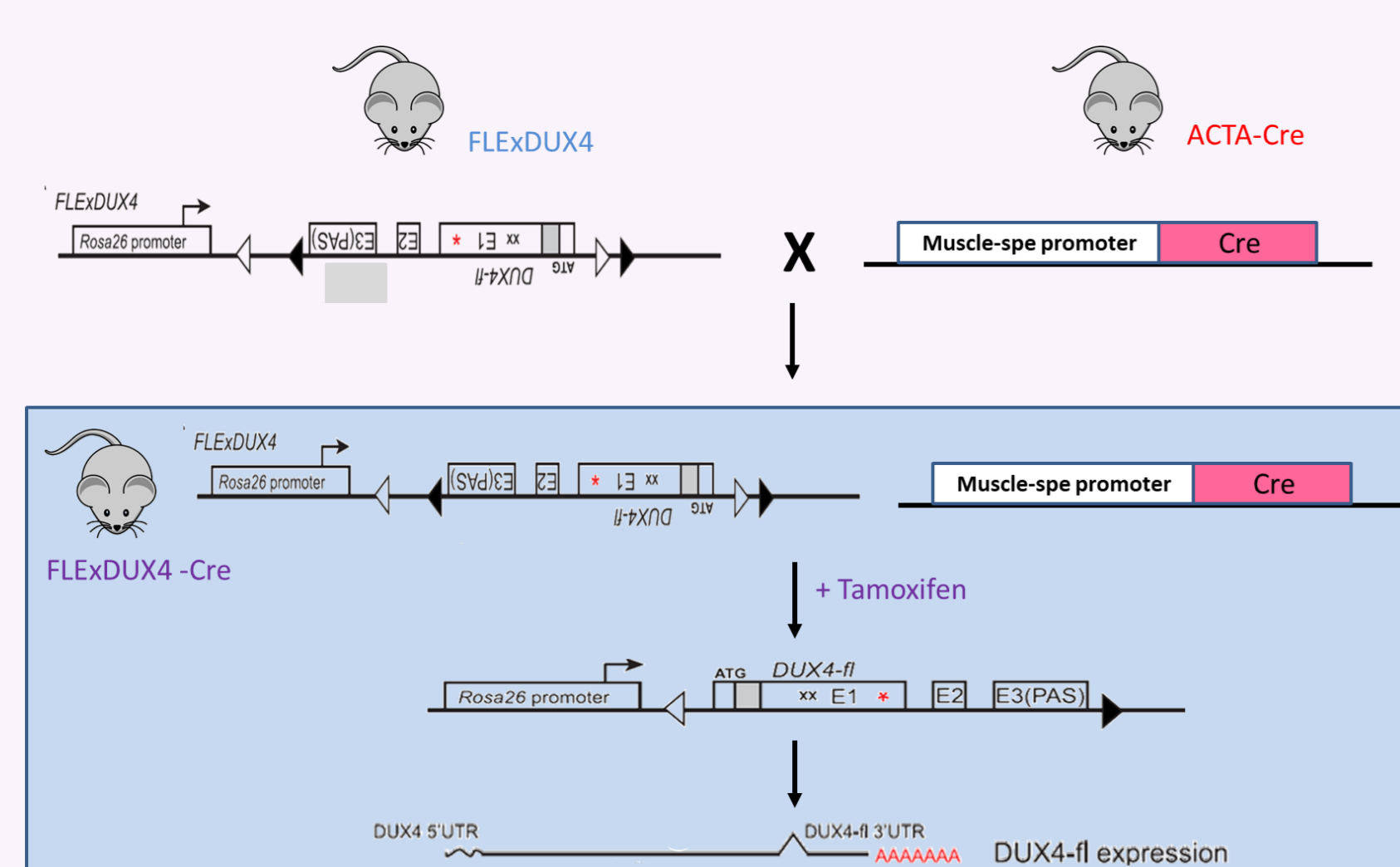
- Range: 2mm/s to 30mm/s
- Shortening: 1.5mm

Force Measurement (F)

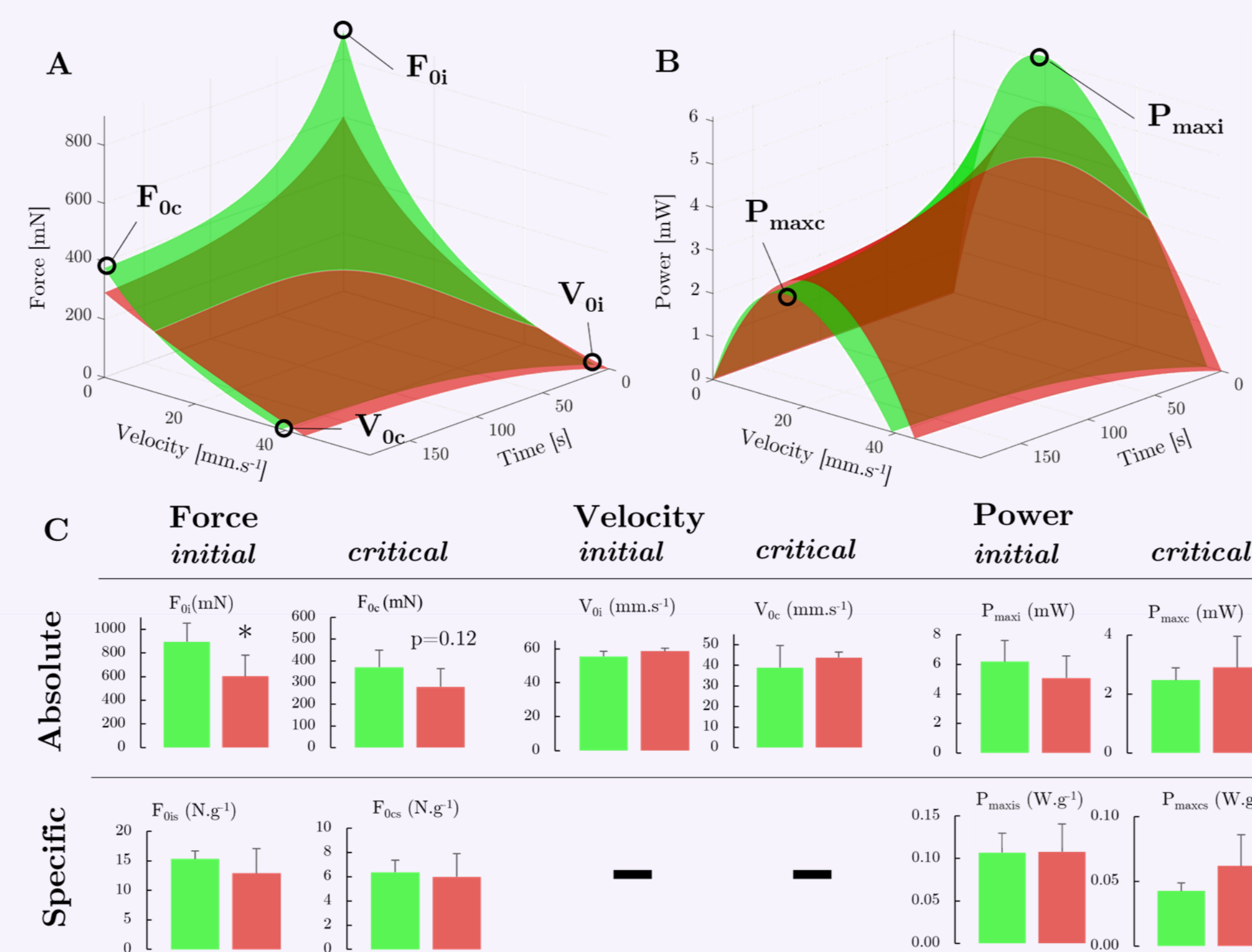
- Maximal force
- Concentric phase



Mouse model - Acta1-MCM;FLEXDUX4/+ Jones, PlosOne 2018



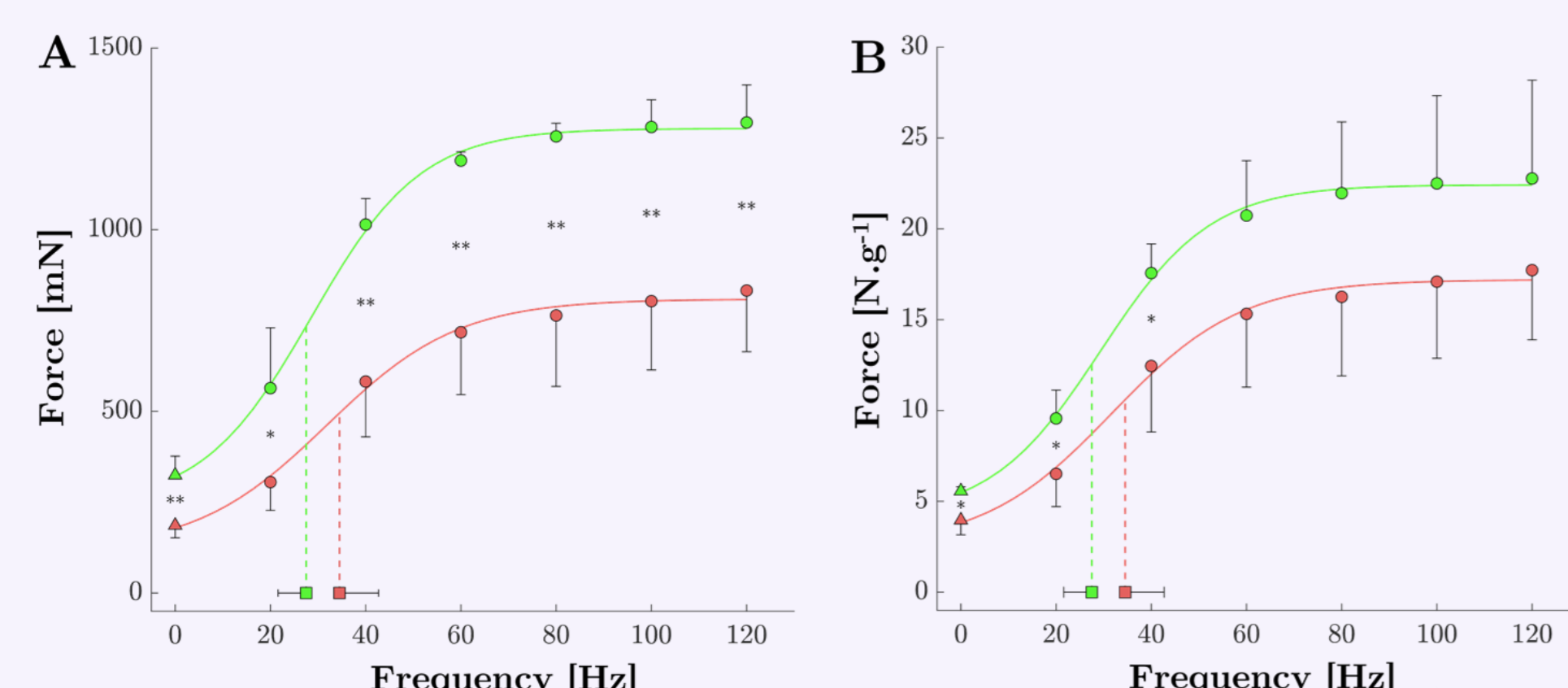
Acta1-MCM;FLEXDUX4/+ Force-Velocity-Endurance (FoVE) properties



Force-Velocity-Endurance (FoVE) evaluation in ACTA1-MCM/+ (Red) and Acta1-MCM;FLEXDUX4/+ mice (Green). The 3D graphical representation is presented for the relationship of the Force as a function of the contraction velocity and time (A) and Power as a function of contraction velocity and time (B). The main indices are represented graphically; F_0 : muscle maximal force in isometric condition (i.e. static, null velocity); V_0 : muscle maximum contraction velocity; P_{max} : muscle maximal power production capacity. Indices i and c , represent respectively the initial condition on a fresh state end in extreme fatigue, at the end of the test. Statistical comparison of FoVE indices expressed in absolute and specific, i.e. normalized to muscle mass (C).

FoVE 2-Dimensional absolute Force and Power projections on the Velocity and time axis in ACTA1-MCM/+ (Red) and Acta1-MCM;FLEXDUX4/+ mice (Green). (A) initial force-velocity; (B) critical force-velocity; (C) maximal force-time; (D) initial power-velocity; (E) critical power-velocity; (F) maximal power-time. When significant, indices are represented graphically on 2D projections: F_{0i} : initial muscle maximal force in isometric condition (i.e. static, null velocity); V_{optc} : critical optimal contraction velocity (i.e. maximizing power production); τ : characteristic decay time (at τ seconds $\approx 63\%$ of the final decay is reached).

Absolute and specific tetanic force



Tibialis anterior muscle force evaluation in FLEXDUX4/+ (Green) and ACTA1-MCM;FLEXDUX4/+ mice (Red). Peak Twitch (Pt; Frequency = 0 Hz) and maximum tetanic force (P0) for stimulation from 20 to 120 Hz expressed in absolute force (mN; A) and relatively to muscle mass (in N.g⁻¹; B); Squares represent ϕ i.e. frequency at which 63% of the maximum force is reached;

p values were calculated using Graphpad Prism9: 2-way ANOVA followed by a Fisher's LSD post hoc were performed. **p* < 0.05; ***p* < 0.01

Conclusion

- FoVE evaluation provides a complete mapping of muscular function by describing the force production capacities at all velocity and fatigue level
- The expression of DUX4 led to a decreased absolute in-situ force capacity for the tibialis anterior muscle partly due to loss of muscle mass
- ACTA1-MCM;FLEXDUX4/+ mice showed greater fatigue, albeit at a slower rate of onset
- ACTA1-MCM;FLEXDUX4/+ muscles have less force capacity but are able to maintain its power capacity both in a fresh and fatigued state.