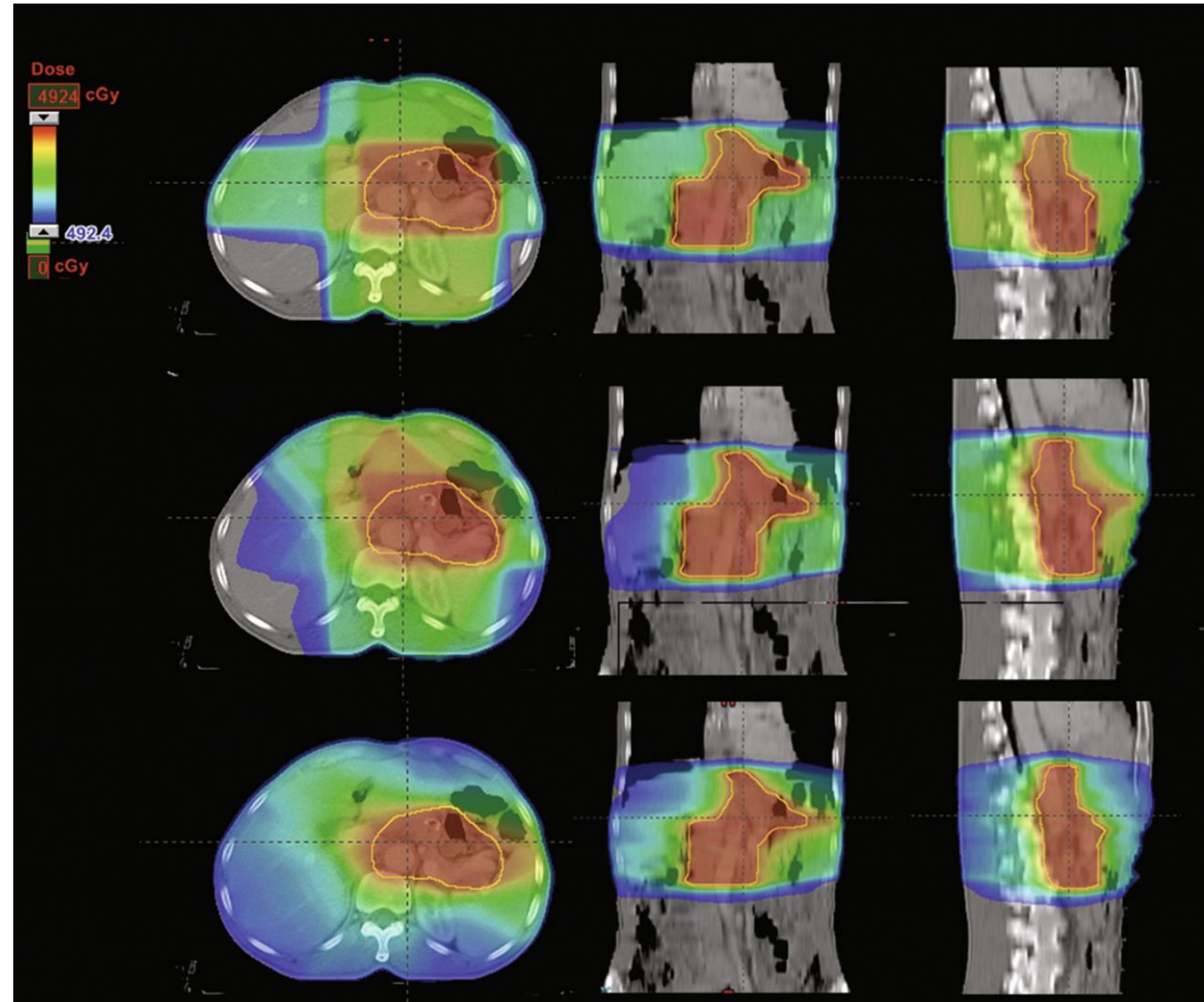


Simple Models of the Relative Biological Effectiveness

Maren Wagner
University of Edinburgh
Tutor: Dr. Thomas Friedrich
16.09.2026

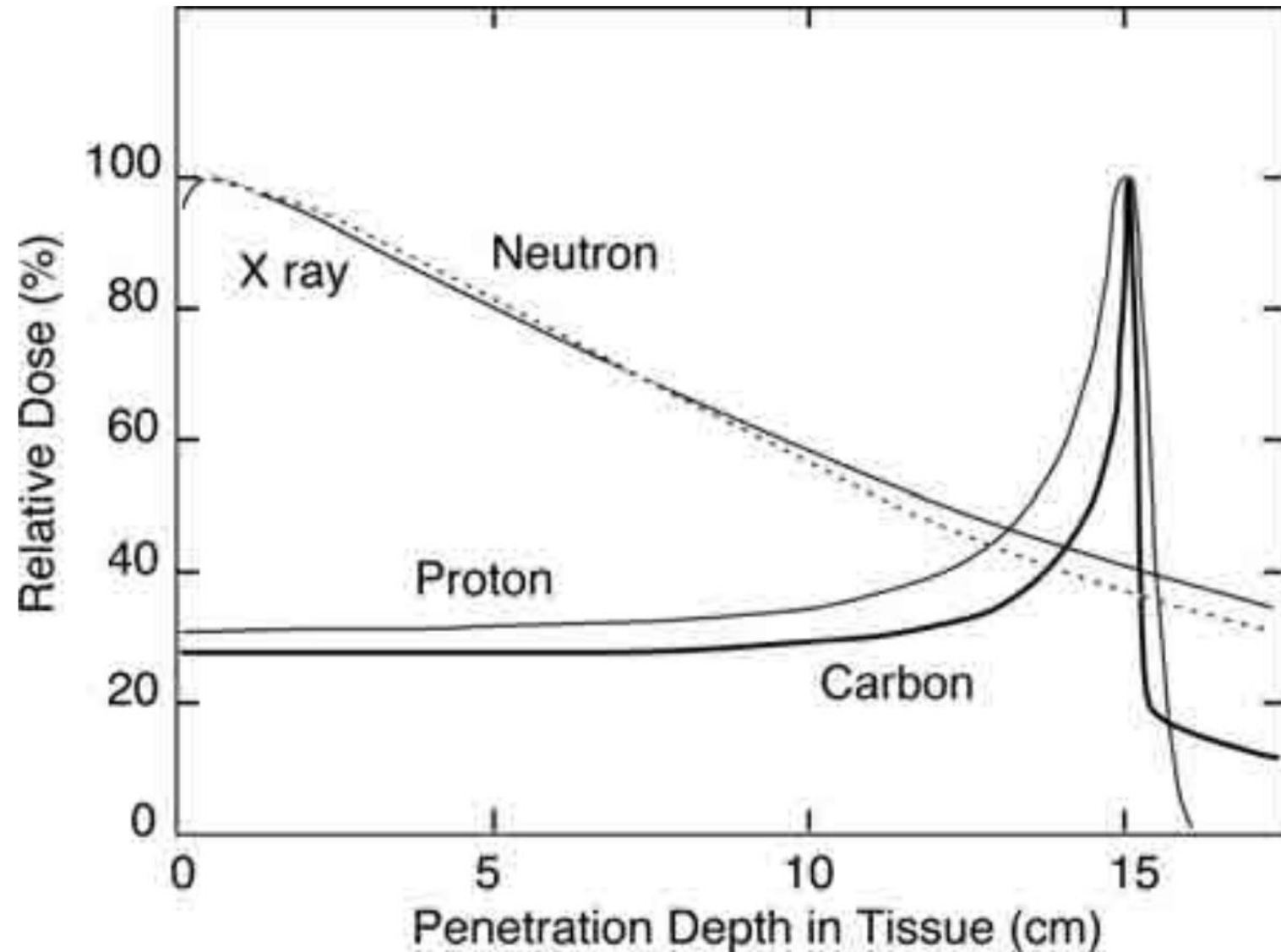
Radiotherapy

- Use ionizing radiation to kill cancer cells
- Conventionally using high energy photons
- radiation targeted at tumor
- Photons deposit energy slowly along their path
- Irradiating healthy tissues around the tumor causes unwanted side effects



Ion Radiotherapy

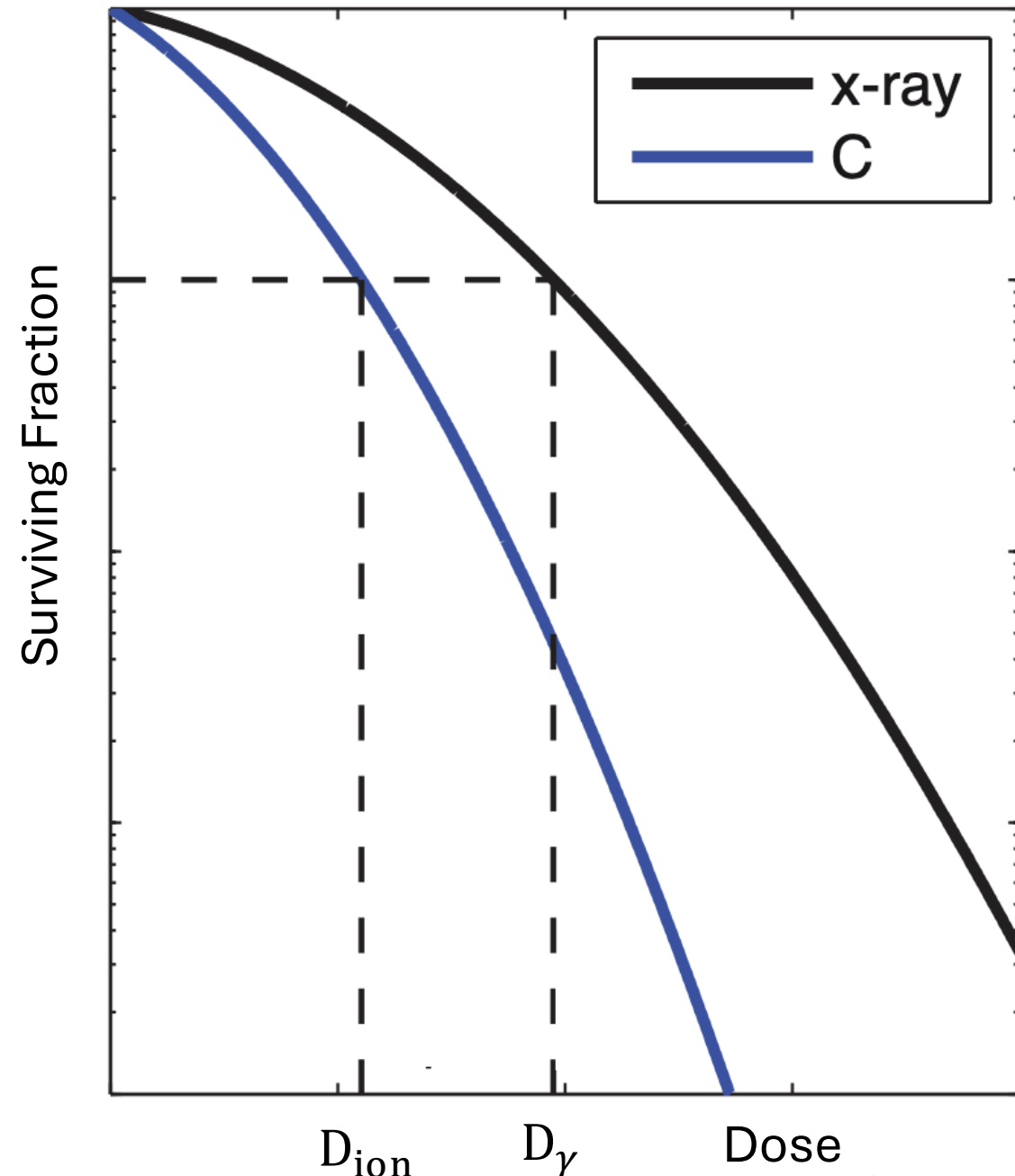
- Massive particles lose energy by interacting with atoms and electrons in the material
- Results in “Bragg Peak” energy deposition is sharply peaked before the particle stops
- Enables dosage to be targeted more precisely
- Linear Energy Transfer (LET): energy deposited into material per unit length ($\text{keV}\mu\text{m}^{-1}$)



(Alonso and Antaya, Rev. Accel. Sci. Technol., 2012)

Dose Response Curves

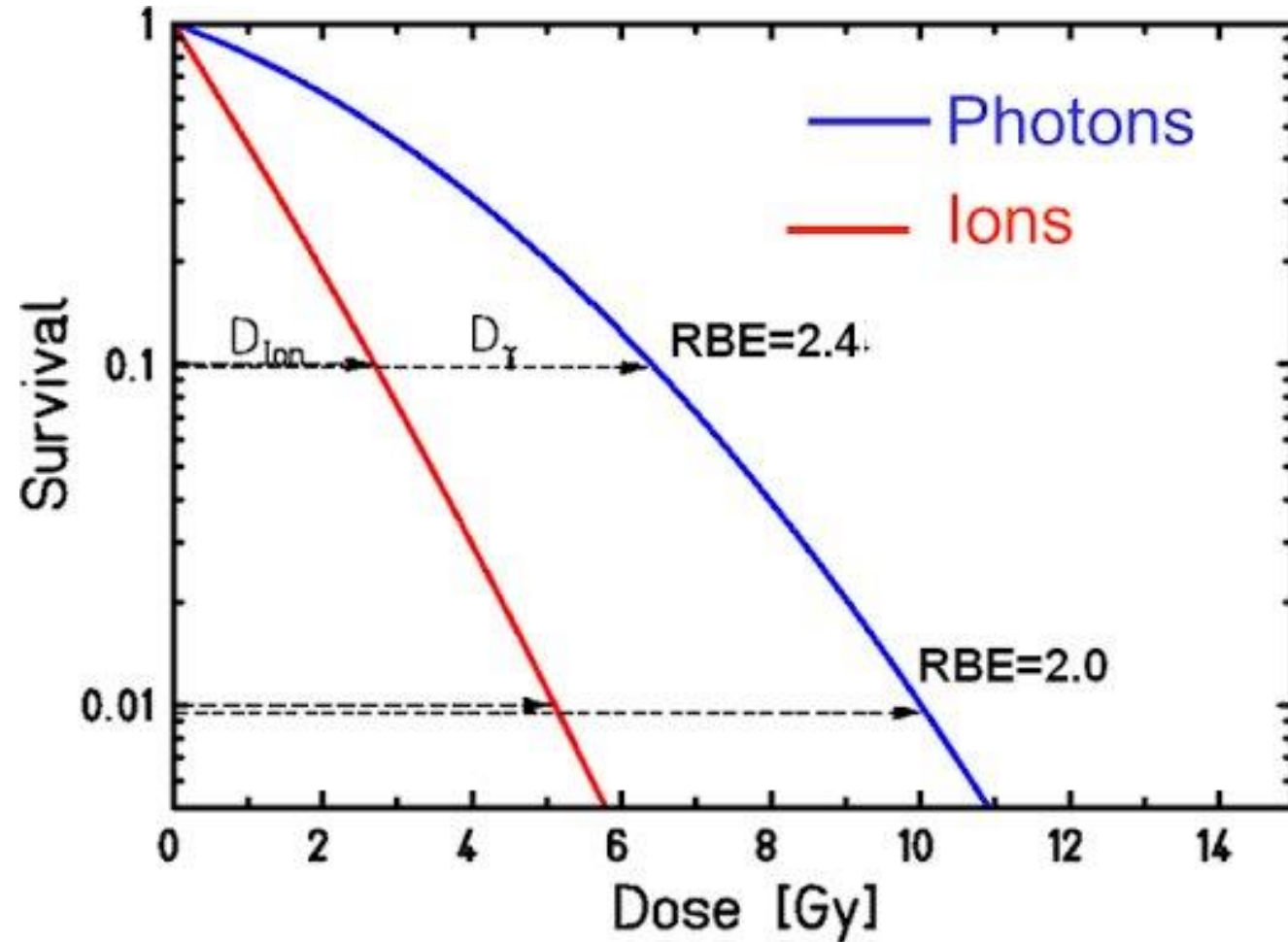
- Dosage of ionizing radiation absorbed by biological material
 - Units of *Gray* (Jkg^{-1})
- When cells are irradiated some die and others don't
- Fraction of surviving cells at a given dose
- Linear-quadratic model
- $S(D) = e^{-\alpha D - \beta D^2}$



Relative Biological Effectiveness (RBE)

- Quantify how different types of radiation cause different biological damage
- Ratio of dosage of reference radiation (photons) and test radiation
- Evaluated at the point where they produce the same biological effect (kill same fraction of cells)

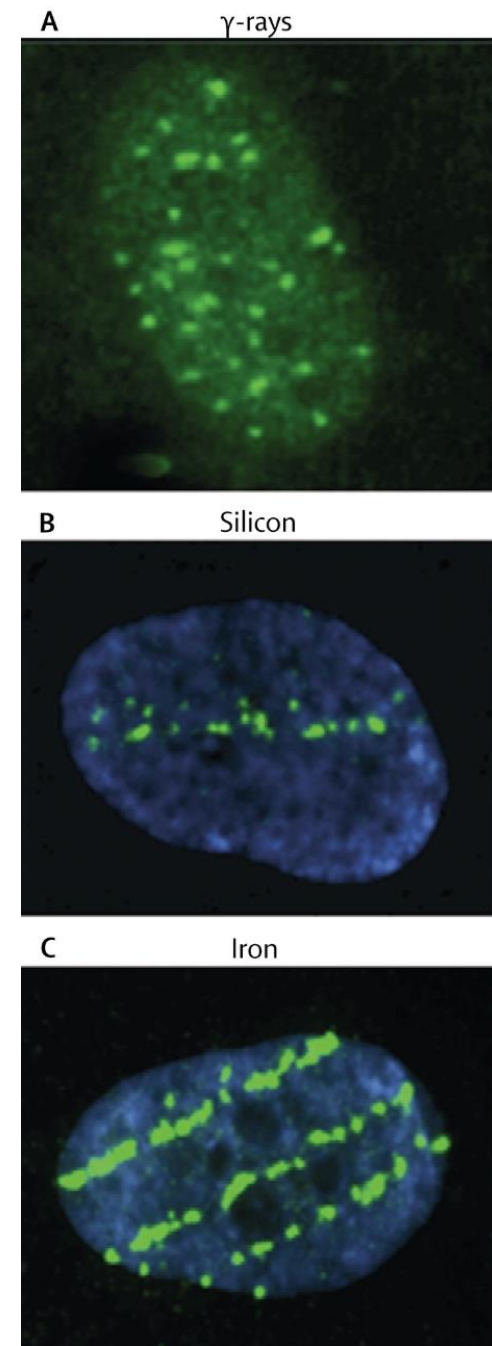
- $$\text{RBE} = \frac{D_{\gamma}}{D_{\text{ions}}} \Big|_{\text{isoeffective}}$$



(Myers et.al., Rev. Accel. Sci. Technol., 2019)

Low Dose Limits of RBE

- Ionising radiation kills cells in different ways
- To second order cells can:
 - Get hit by a particle directly $\rightarrow \alpha$
 - Get hit by a scattered particle $\rightarrow \beta$
 - $S(D) = e^{-\alpha D - \beta D^2}$
- Limit of low doses
 - $\ln(S) \approx -\alpha D$
 - $RBE_{\alpha} = \frac{\alpha_{\text{ions}}}{\alpha_{\gamma}}$
- RBE in the limit of low doses



Modelling RBE

- In clinical practice $RBE \approx 1.1$ for proton therapy
- There is evidence that using variable RBE improves treatment outcomes
- Seek simplest model that has more explanatory power than constant RBE
- **Can we use a simple model to capture variations in the RBE?**



(Image: GSI-Tumorthérapie, GSI)

Linear LET Models of RBE_α

- RBE increases with LET and decreases with α/β (Paganetti et al., Medical physics, 2019)
- Approximate to lowest order
 - $RBE_0 = k_1 + k_2 \cdot \frac{LET}{\alpha_\gamma/\beta_\gamma}$
- At high LET values the RBE should reach a saturation level
 - Exponential attenuation towards high doses
- At low LET ion radiation acts like photons
 - $\lim_{LET \rightarrow 0} RBE = \text{constant}$
- $d_1 = \frac{LET}{\rho \cdot A}$, ρ density of water, A cell nucleus cross sectional area

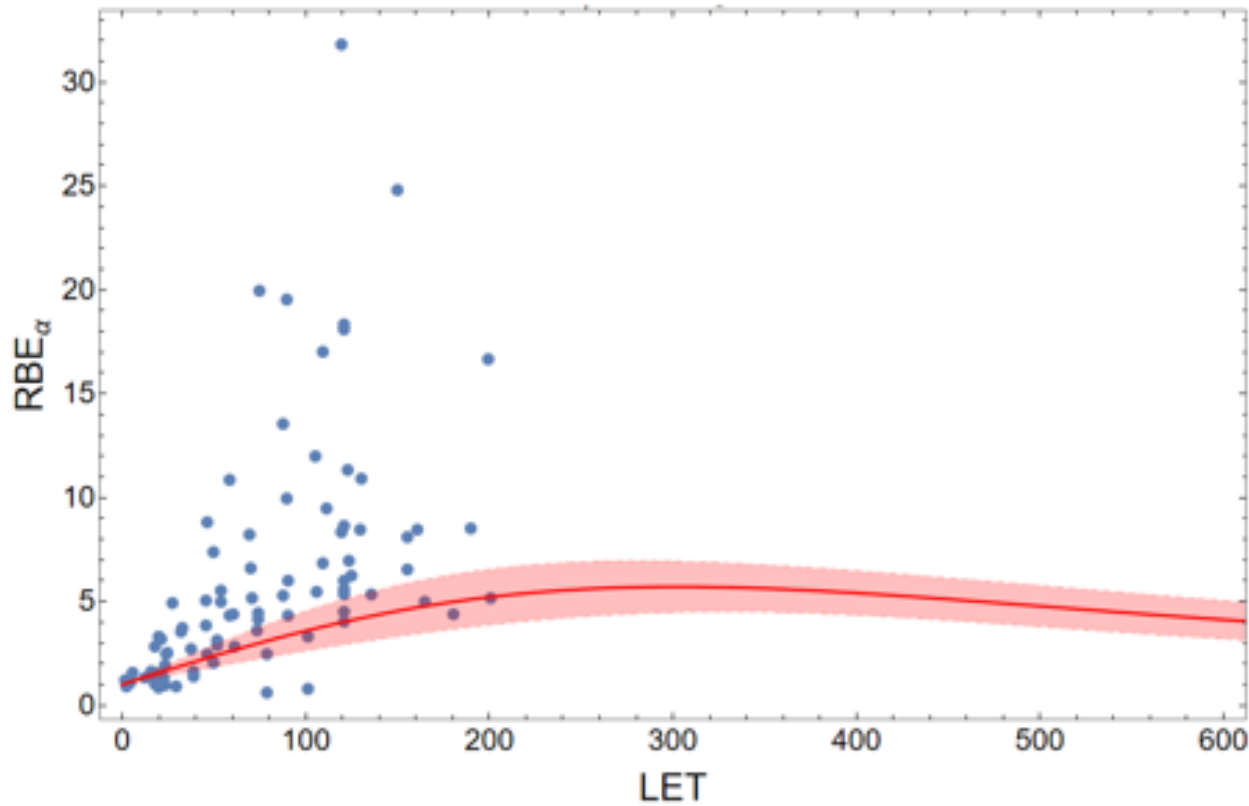
$$RBE_\alpha = \frac{1}{\alpha_\gamma \cdot d_1} \left[1 - e^{-\alpha_\gamma \cdot d_1 \cdot RBE_0} \right] = \frac{\alpha_{\text{ions}}}{\alpha_\gamma}$$

Fitting k_2

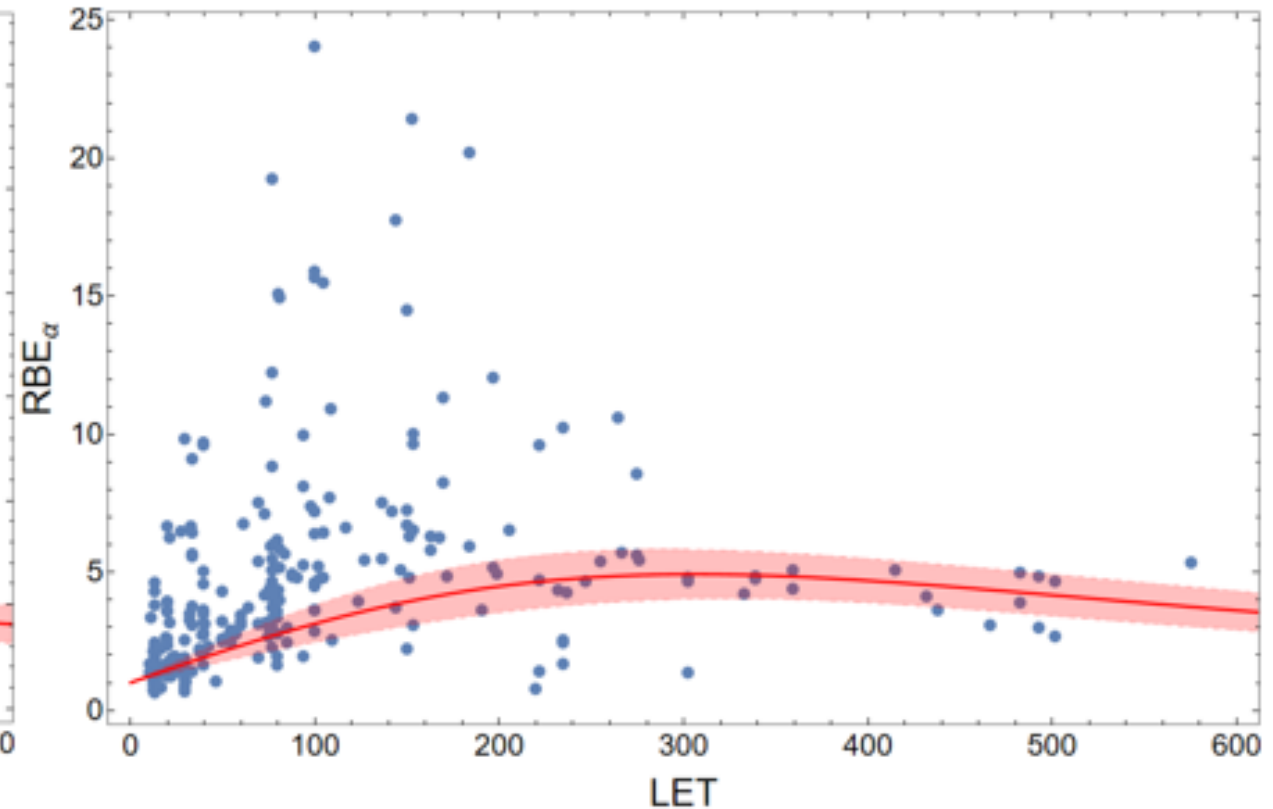
- Fit the k_2 parameter in the RBE_α equation
- Use database of experimental survival data for ions
 - $Z = 1, 2, 6, 8, 10, 14, 18, 26$ (Friedrich et al., Journal of Radiation Research, 2021)
- Take $\alpha_\gamma, \beta_\gamma, LET$ from the measured data
- Let $A = 80\mu\text{m}^2, k_1 = 1$
- Minimise sum of least squares to fit the k_2 parameter for each ion species
- Calculate 90% confidence interval

$$RBE_\alpha = \frac{1}{\alpha_\gamma \cdot d_1} \left[1 - e^{-\alpha_\gamma \cdot d_1 \cdot RBE_0} \right]$$

Plot of Fitted RBE_α against LET



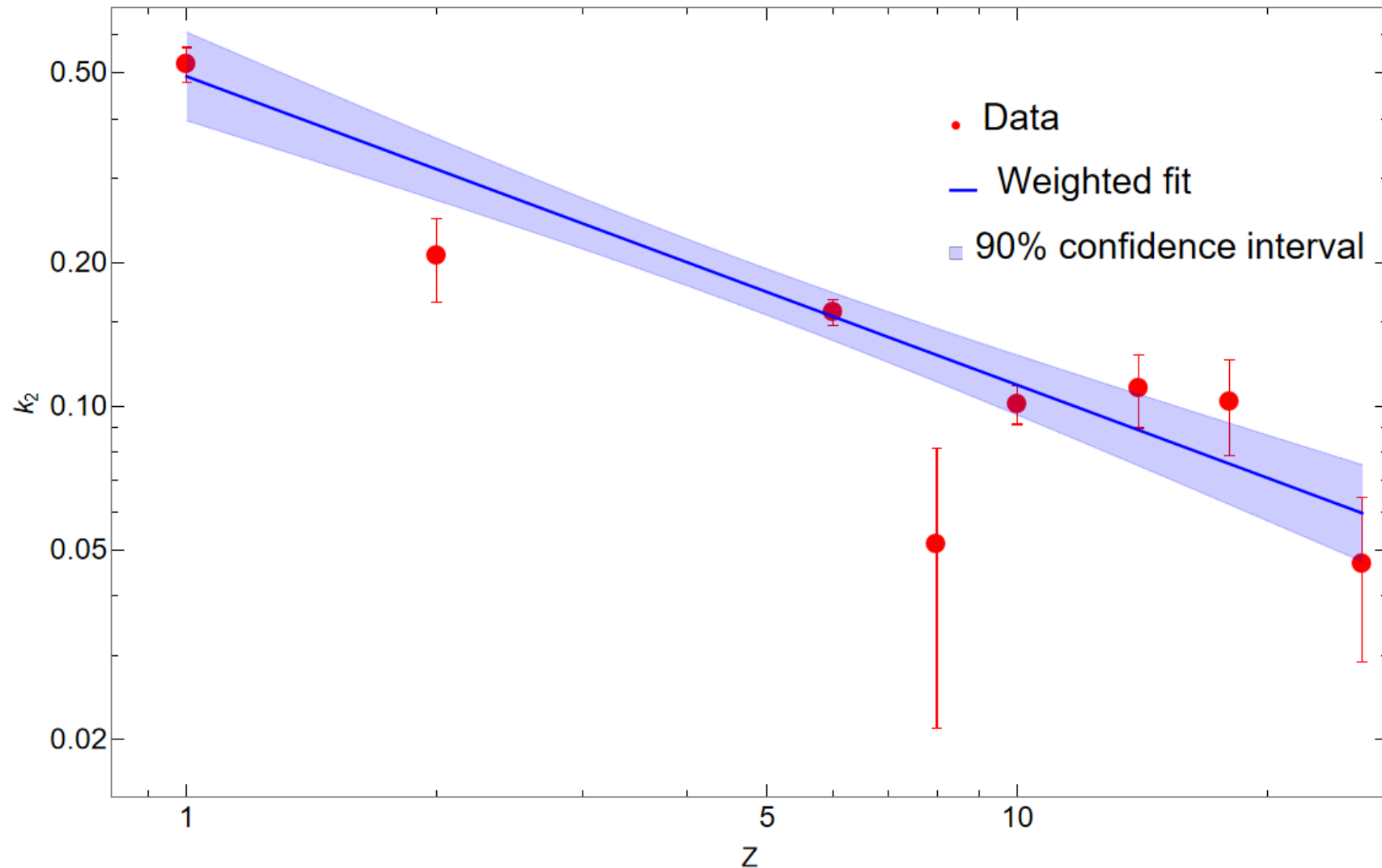
Helium radiation



Carbon radiation

Linearised Model

- Observe exponential relationship between k_2 and Z
 - $k_2 = C_1 e^{-C_2 Z}$
- Plot values on logarithmic plot
- Linear fit weighted by error bars
- Substitute into RBE_α equation



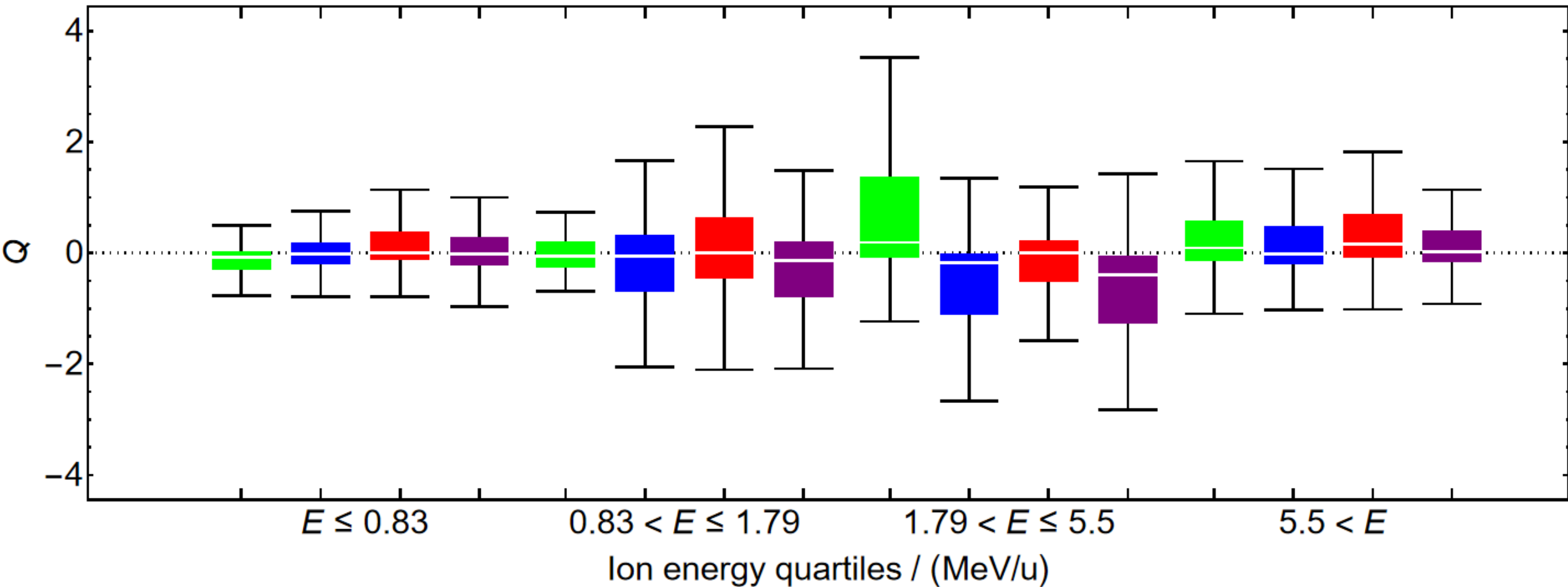
Expanding to full RBE

- Model gives RBE_α
 - Need full RBE to compare to experimental data
- Database gives survival data points for photons and ions
 - Fit $S(D) = e^{-\alpha D - \beta D^2}$
 - $D = \frac{-\alpha \pm \sqrt{\alpha^2 - 4\beta \ln S}}{2\beta}$
- Set $\beta_{\text{ion}} = 0.03 \text{ Gy}^{-2}$ and calculate
- $\text{RBE} = \frac{D_\gamma}{D_{\text{ions}}} \Big|_{\text{isoeffective}}$

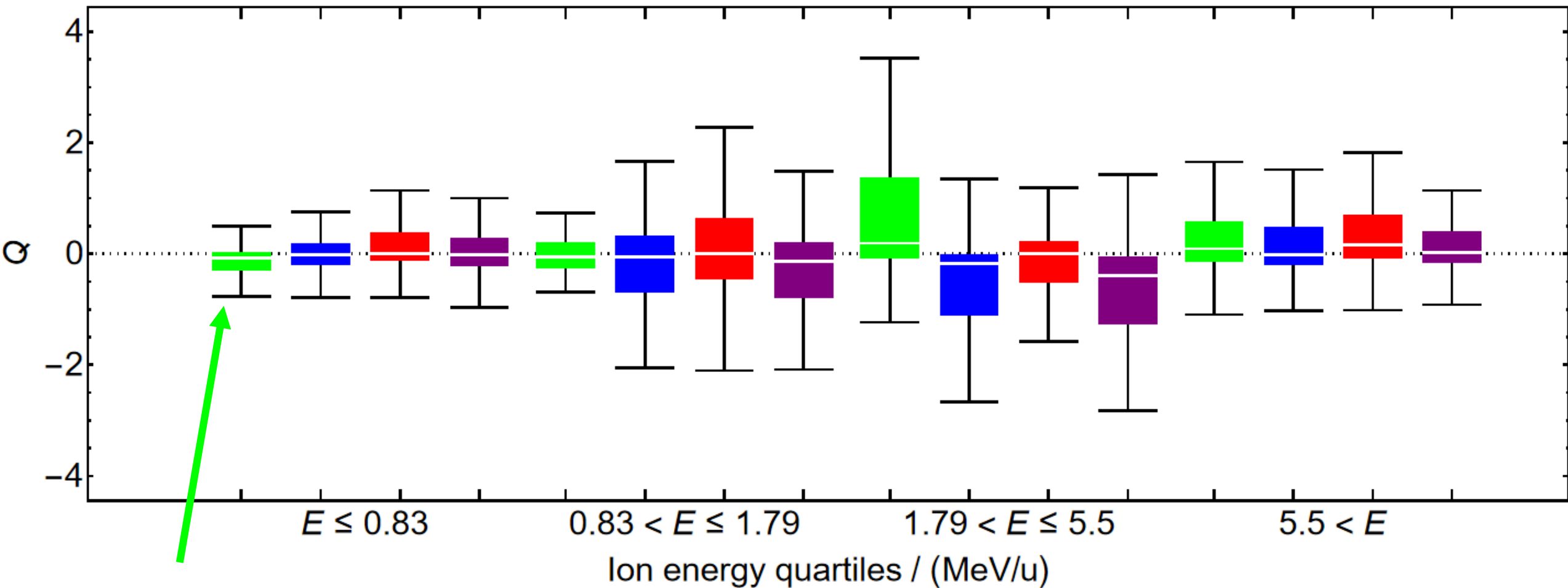
Comparison to Experimental Data

- Work of Deglow et al. *(Deglow et al., 2026)*
 - Assessing the effectiveness of different RBE models
 - Microdosimetric Kinetic Model (mMKM), Mayo Clinic Florida MKM (MCF MKM), Local Effect Model (LEM) IV
- Measure precision of RBE prediction
 - $Q = \frac{RBE_{\text{measured}} - RBE_{\text{predicted}}}{\sigma}$
 - Quantify size of deviations normalised by scale of fluctuations in the data
- σ is the 90% margin of error
 - Propagate variance in D_γ and D_{ion} data to calculate $\text{var}(RBE)$
 - $\sigma = \sqrt{\text{var}(RBE)} \cdot 1.645$

Model Comparison to Experimental Data for Helium



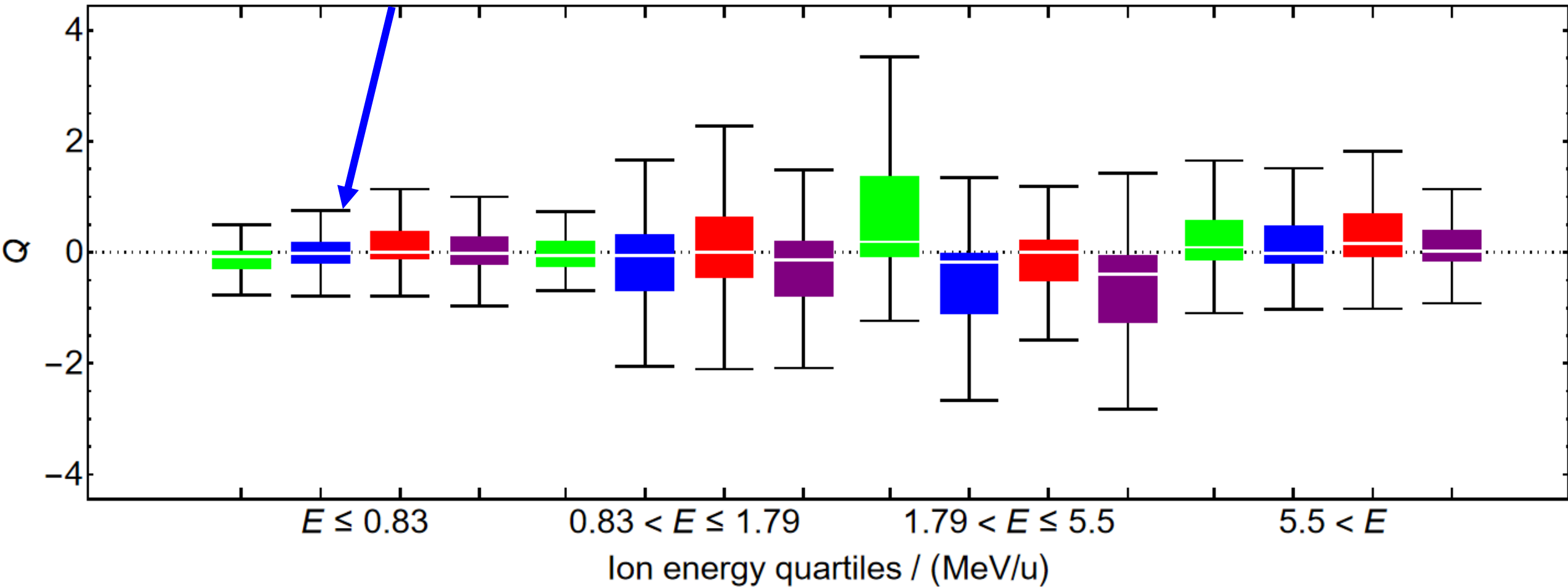
Model Comparison to Experimental Data for Helium



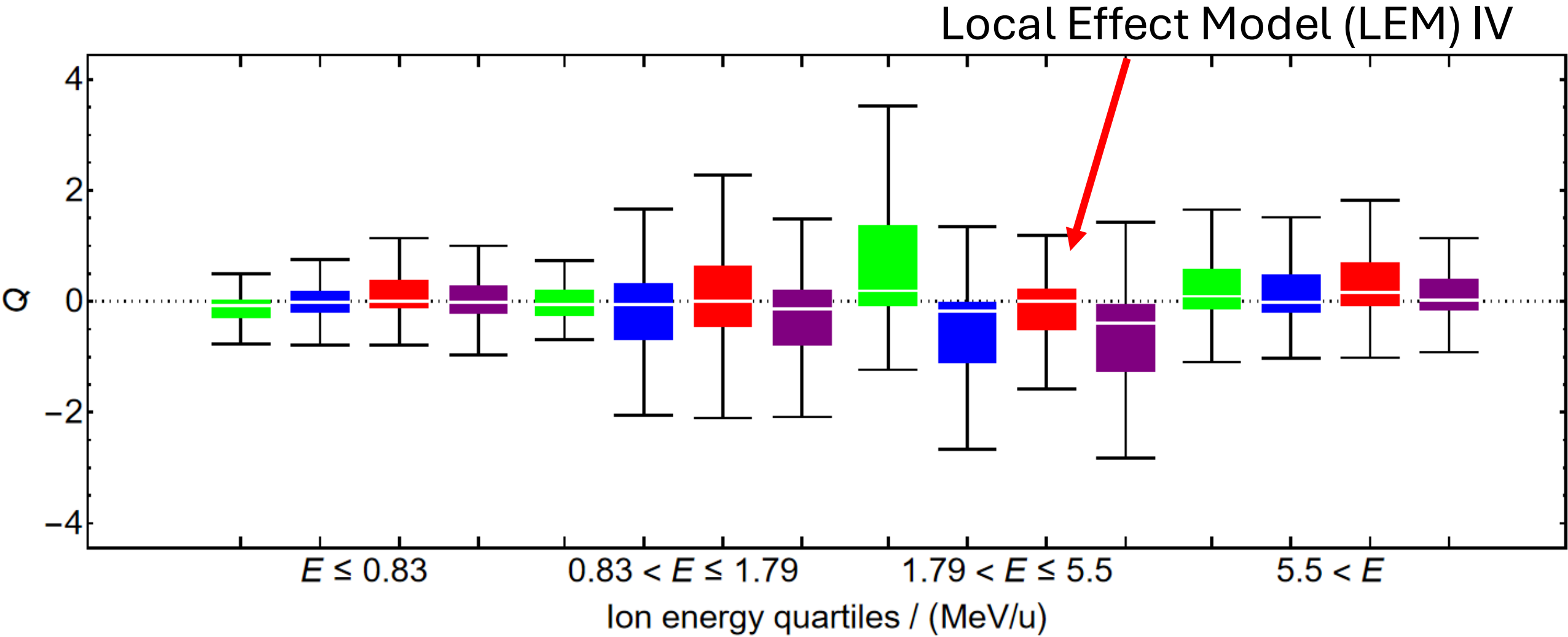
Microdosimetric Kinetic
Model (mMKM)

Model Comparison to Experimental Data for Helium

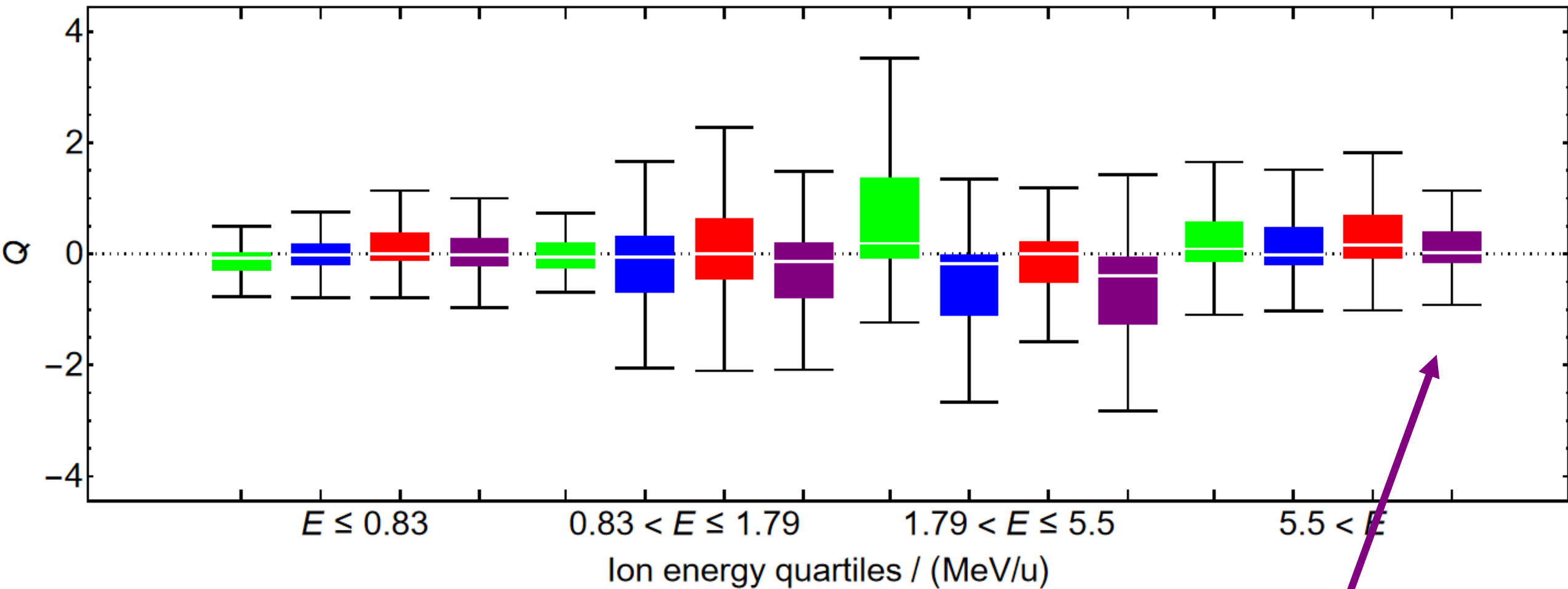
Mayo Clinic Florida MKM (MCF MKM)



Model Comparison to Experimental Data for Protons



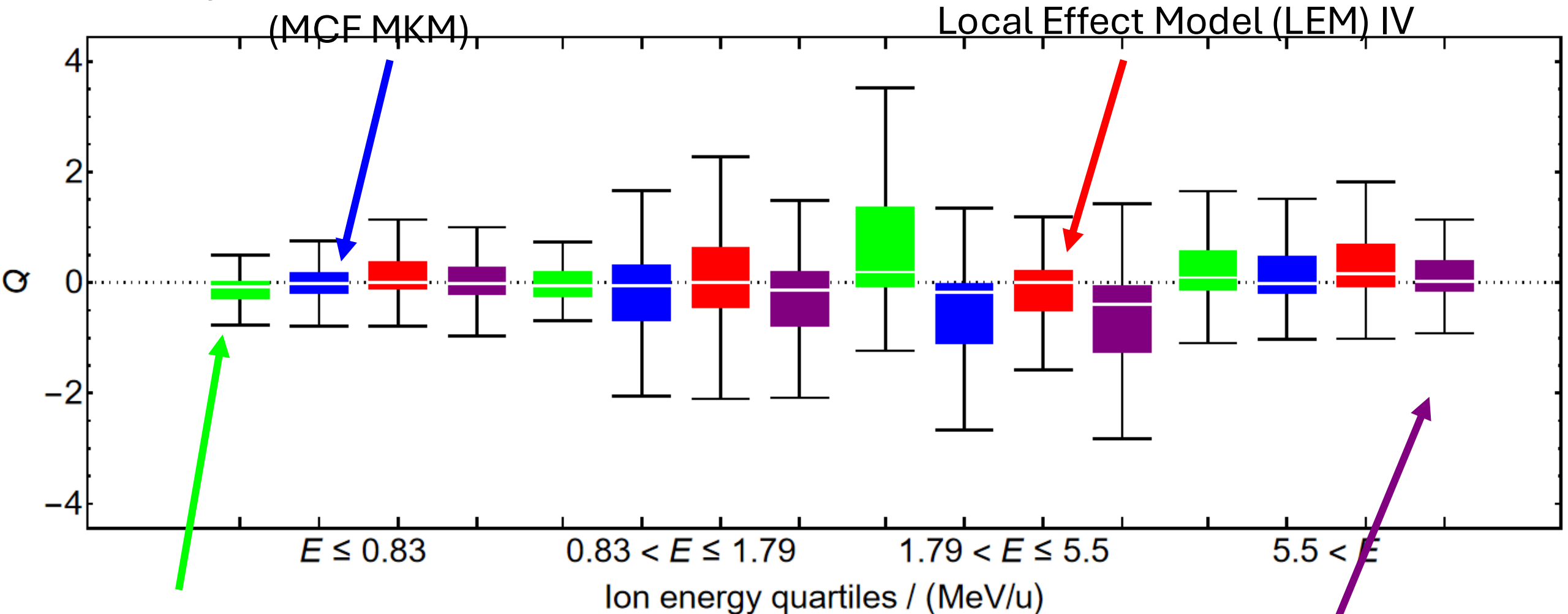
Model Comparison to Experimental Data for Helium



Simplified Model

Model Comparison to Experimental Data for Helium

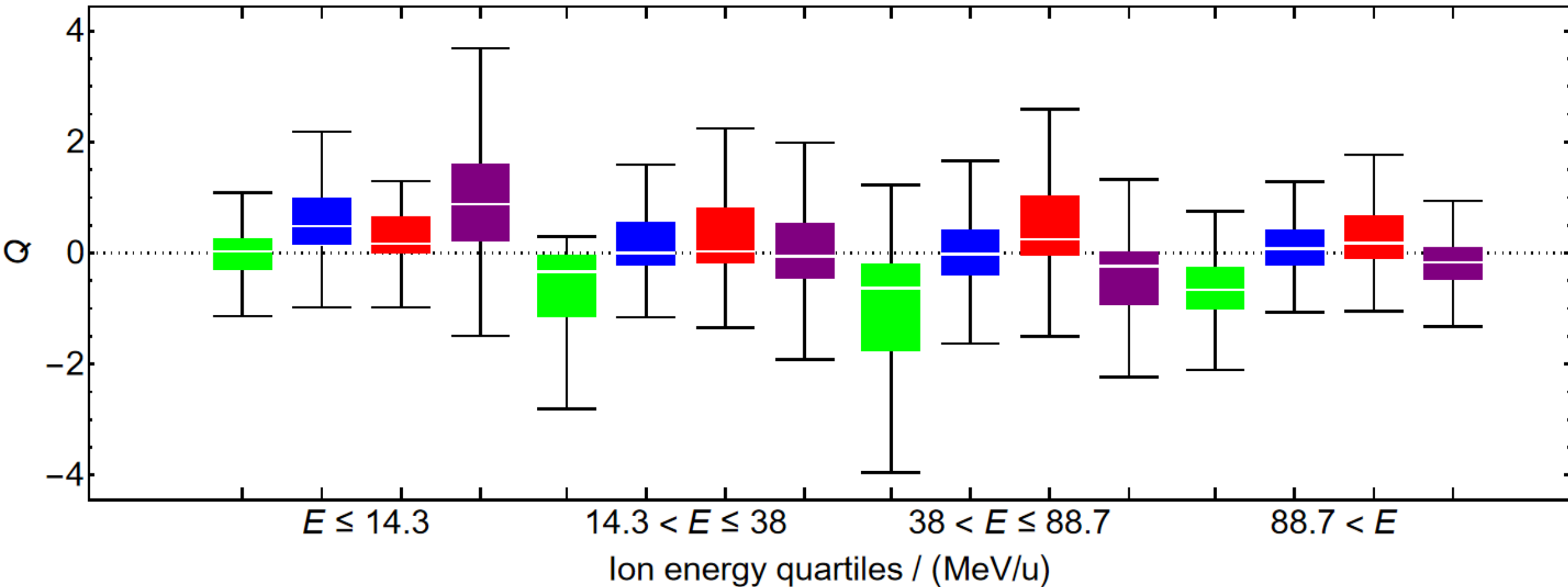
Mayo Clinic Florida MKM



Microdosimetric Kinetic
Model (mMKM)

Simplified Model

Model Comparison to Experimental Data for Neon



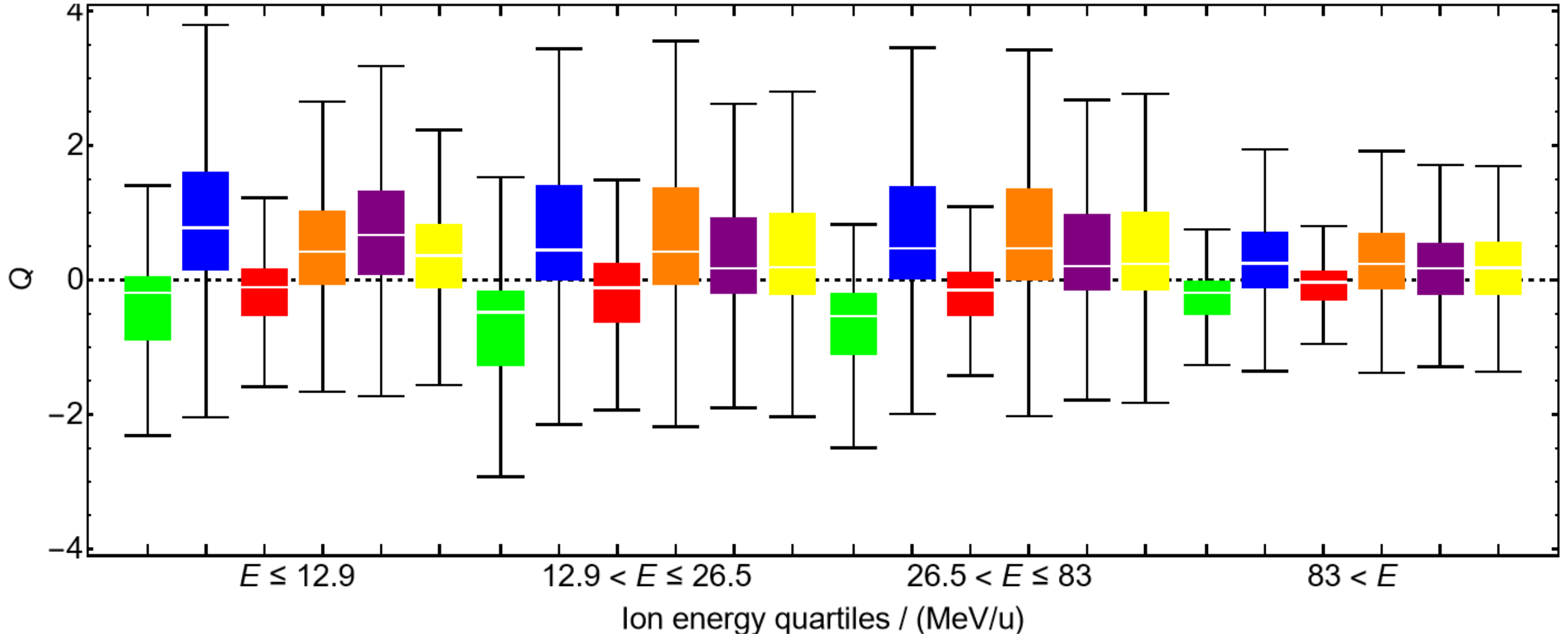
Model performance worse for higher Z ion species

Further Simplification

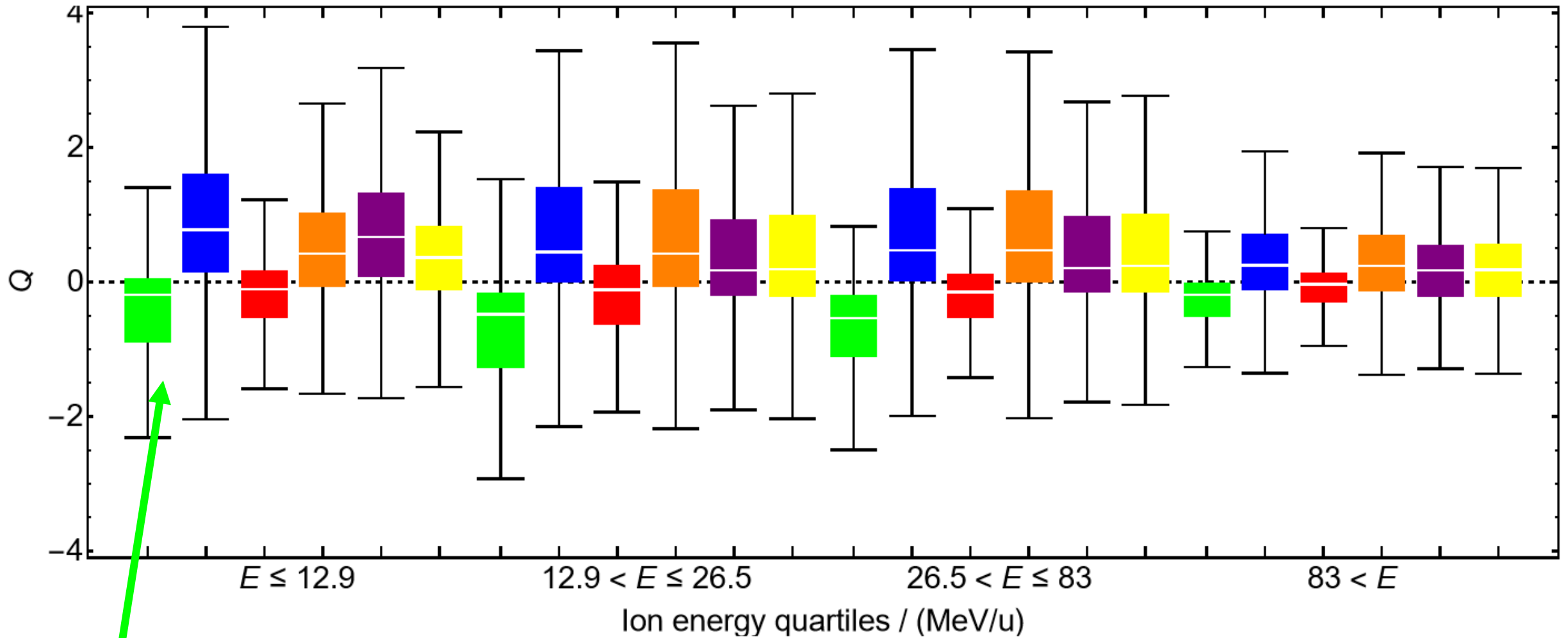
- Averaging parameter values over dataset for each ion species
 - α or α/β
- Take out α/β and absorb into k_2
 - $RBE_0 = 1 + k_2 \cdot LET$
 - Average α for each ion species
- Compare models to data using same method as Deglow et al. as discussed before

$$RBE_{\alpha} = \frac{1}{\alpha_{\gamma} \cdot d_1} \left[1 - e^{-\alpha_{\gamma} \cdot d_1 \cdot RBE_0} \right]$$

Further Simplified models for Carbon Data

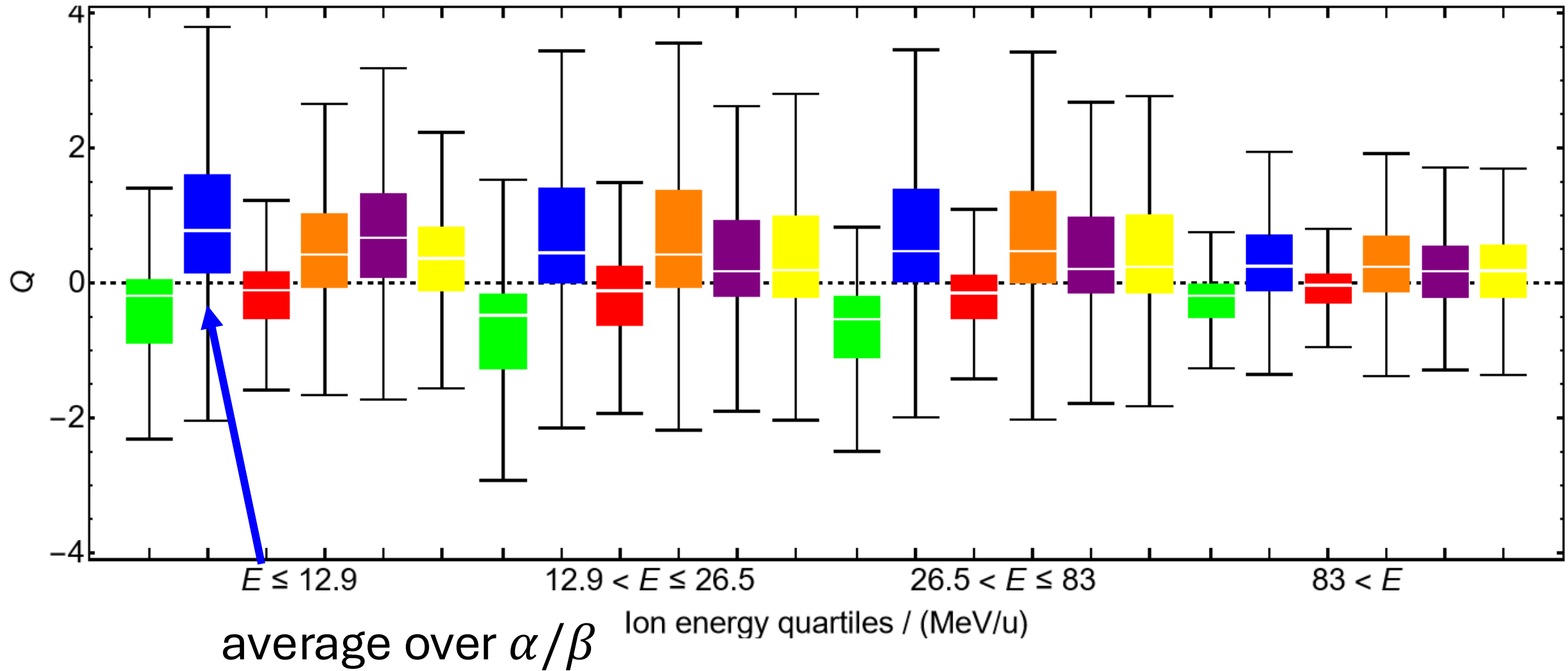


Further Simplified models for Carbon Data

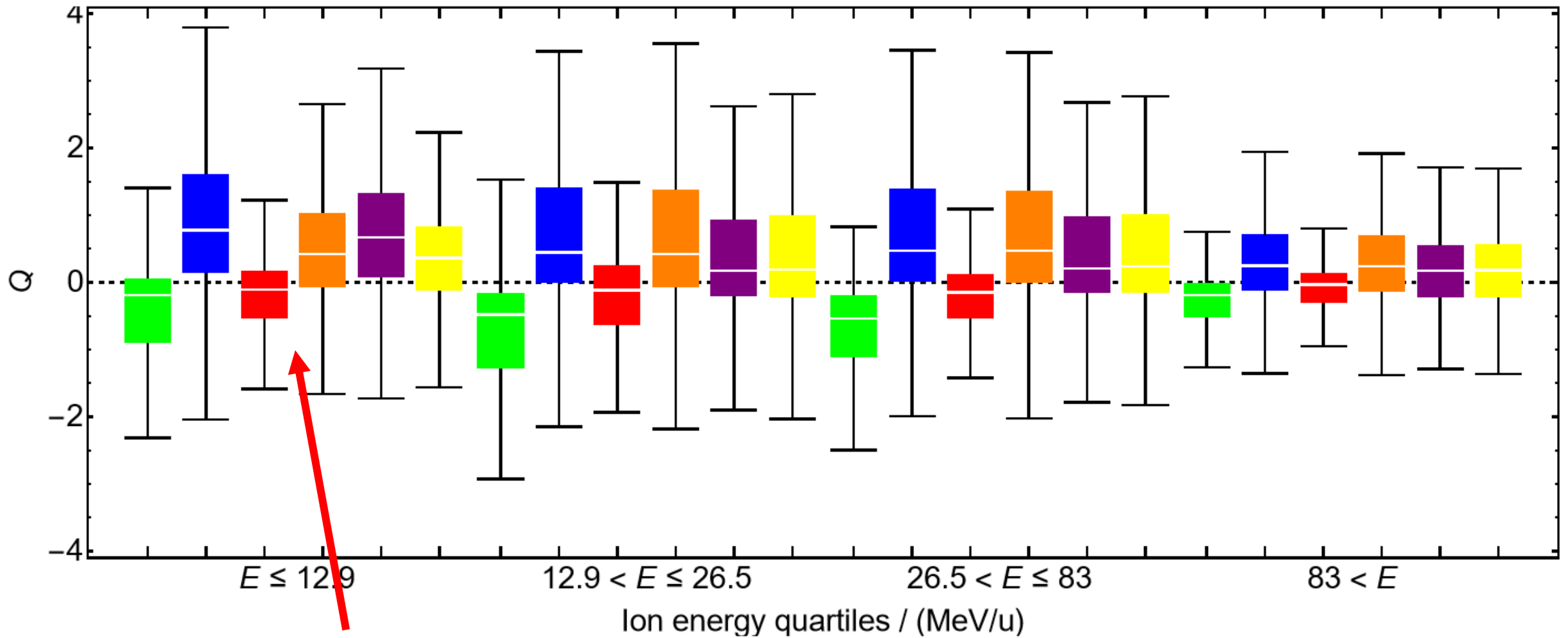


Full model

Further Simplified models for Carbon Data



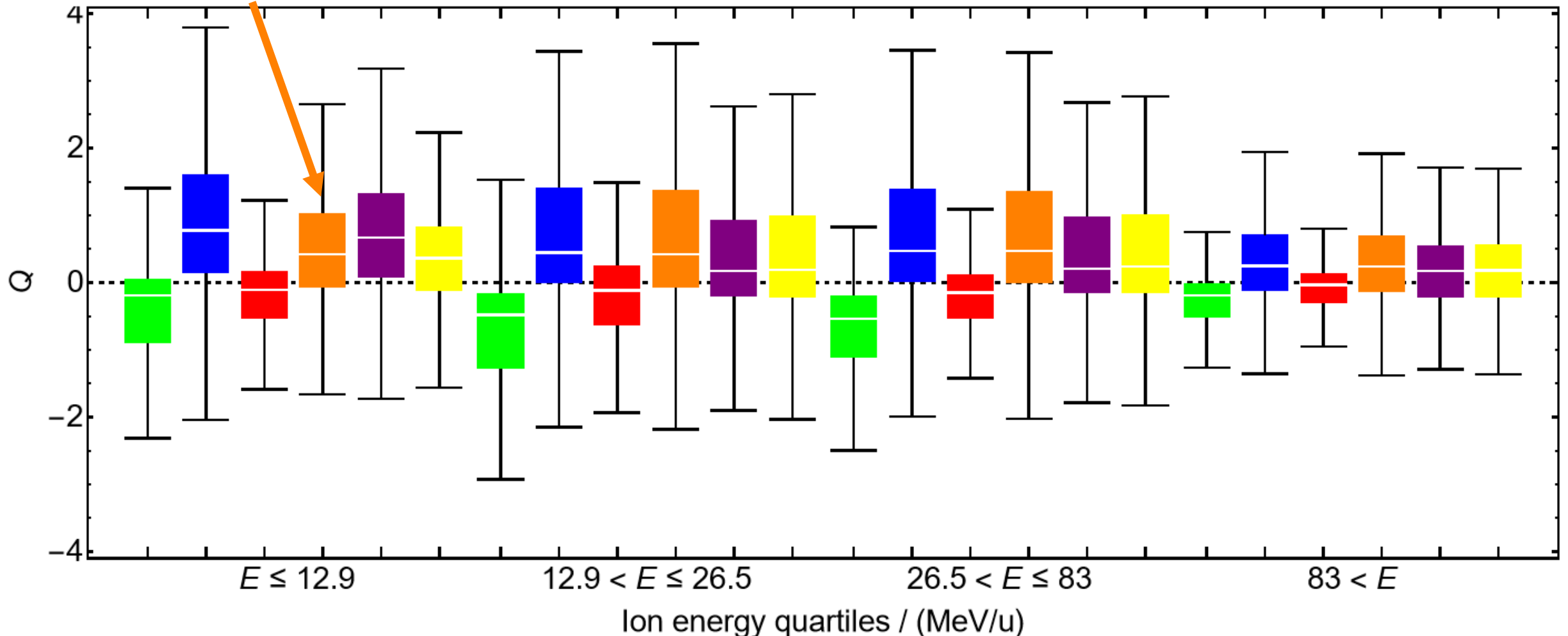
Further Simplified models for Carbon Data



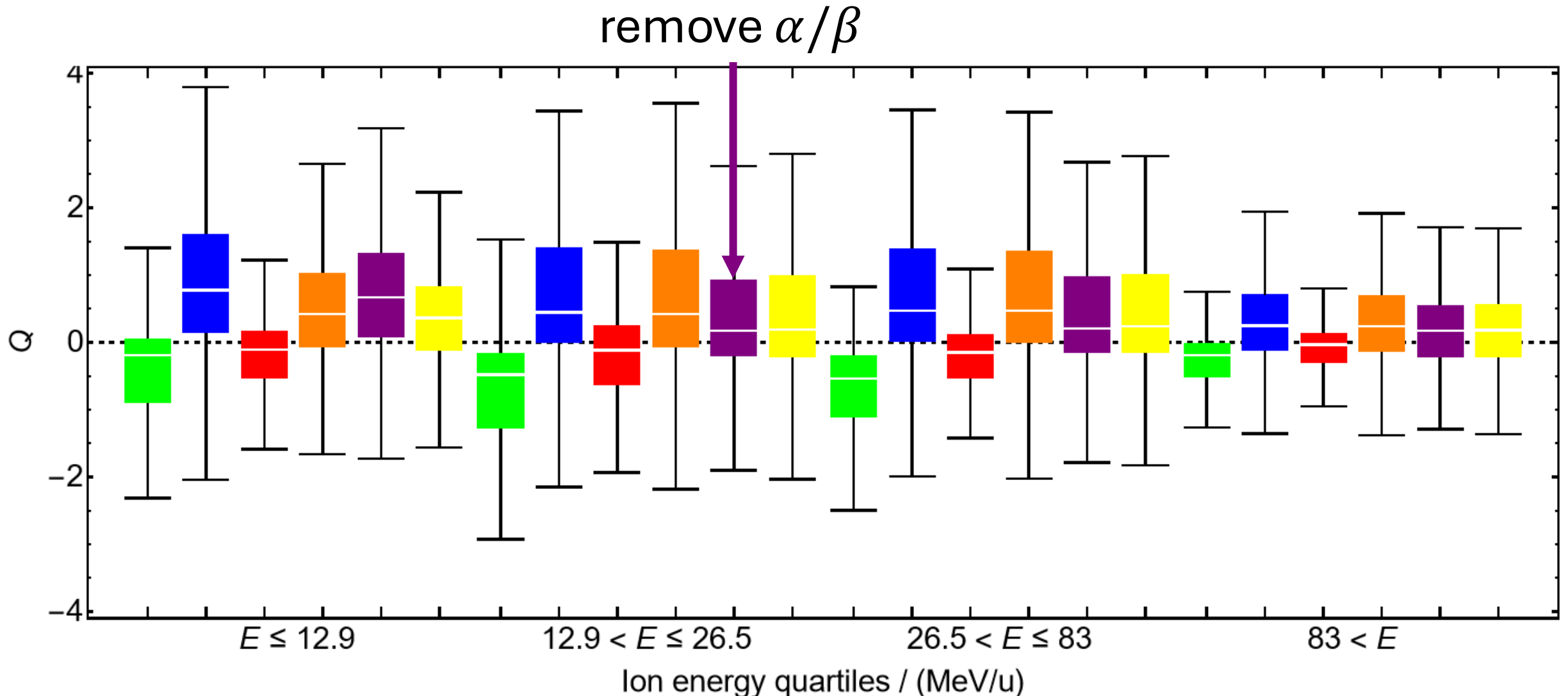
average over α

Further Simplified models for Carbon Data

average over both

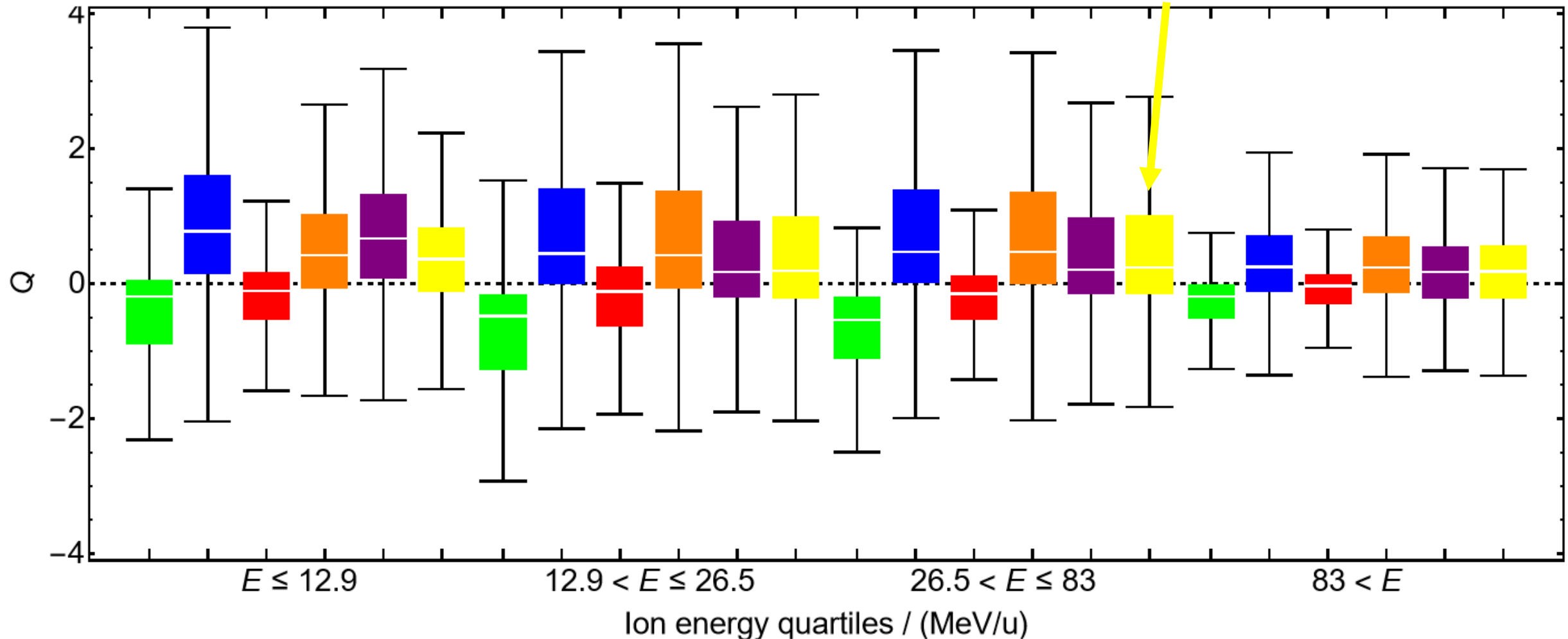


Further Simplified models for Carbon Data

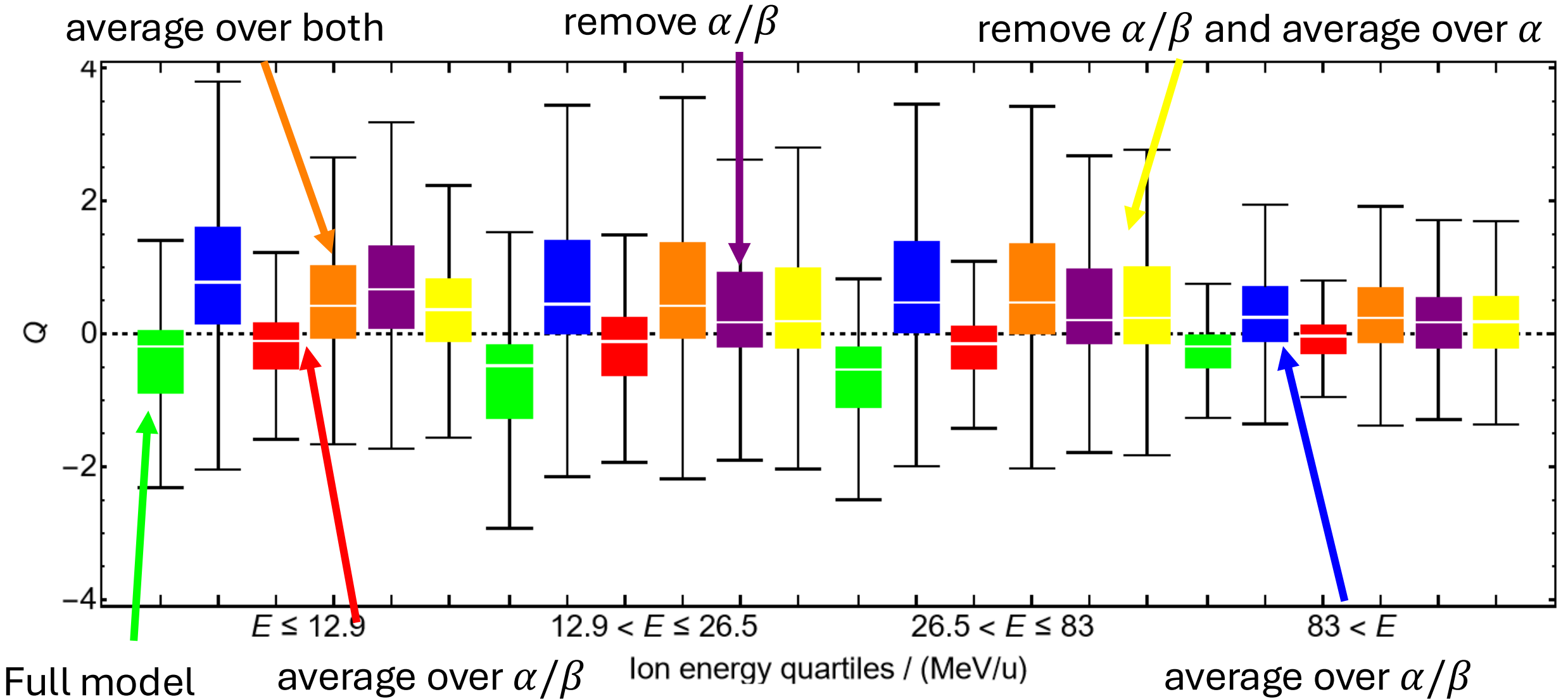


Further Simplified models for Carbon Data

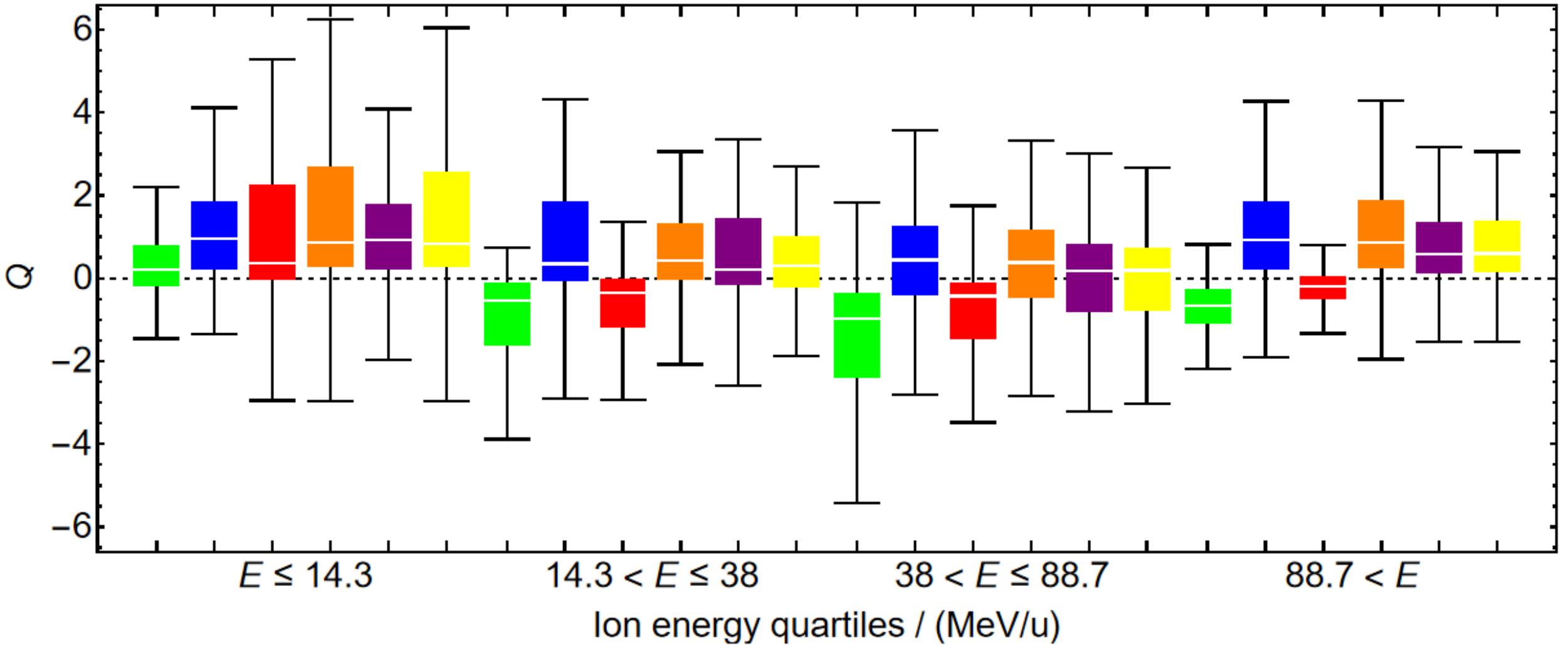
remove α/β and average over α



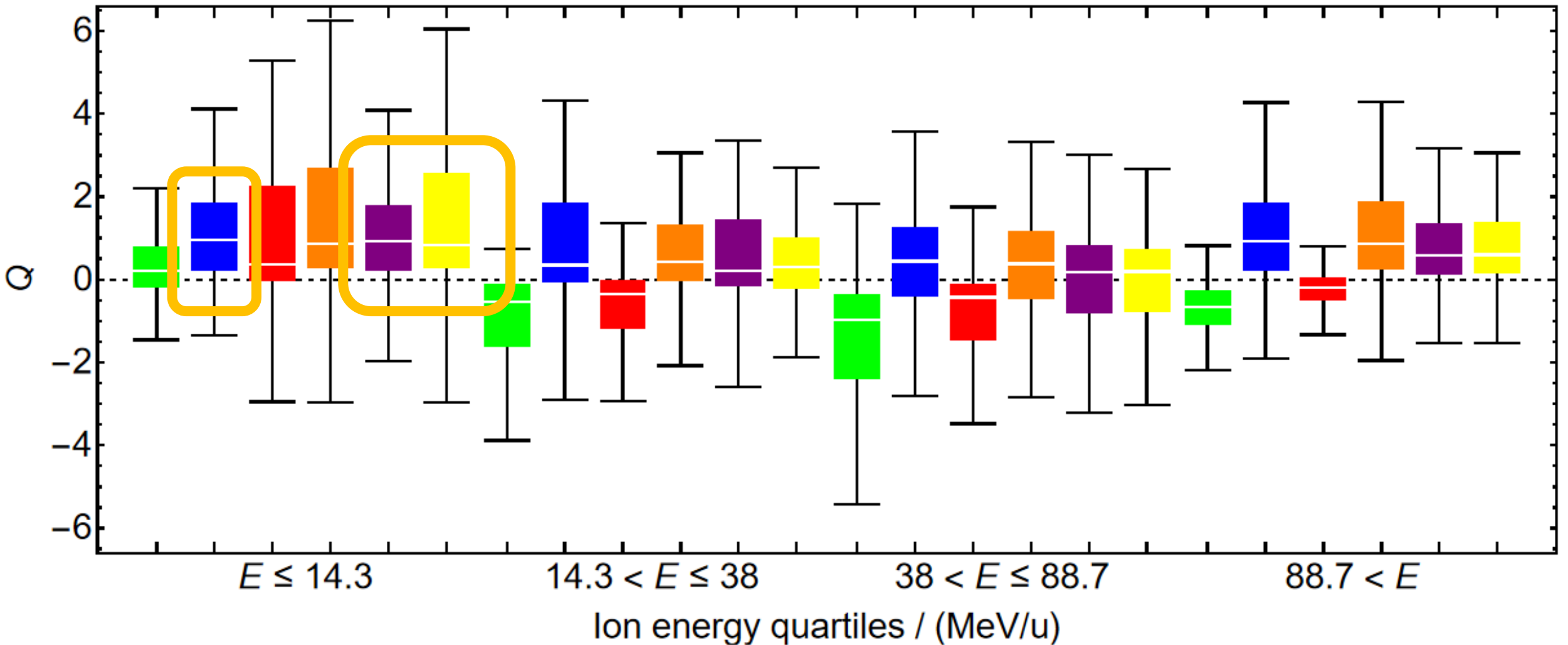
Further Simplified models for Carbon Data



Further Simplified models for Neon Data



Further Simplified models for Neon Data



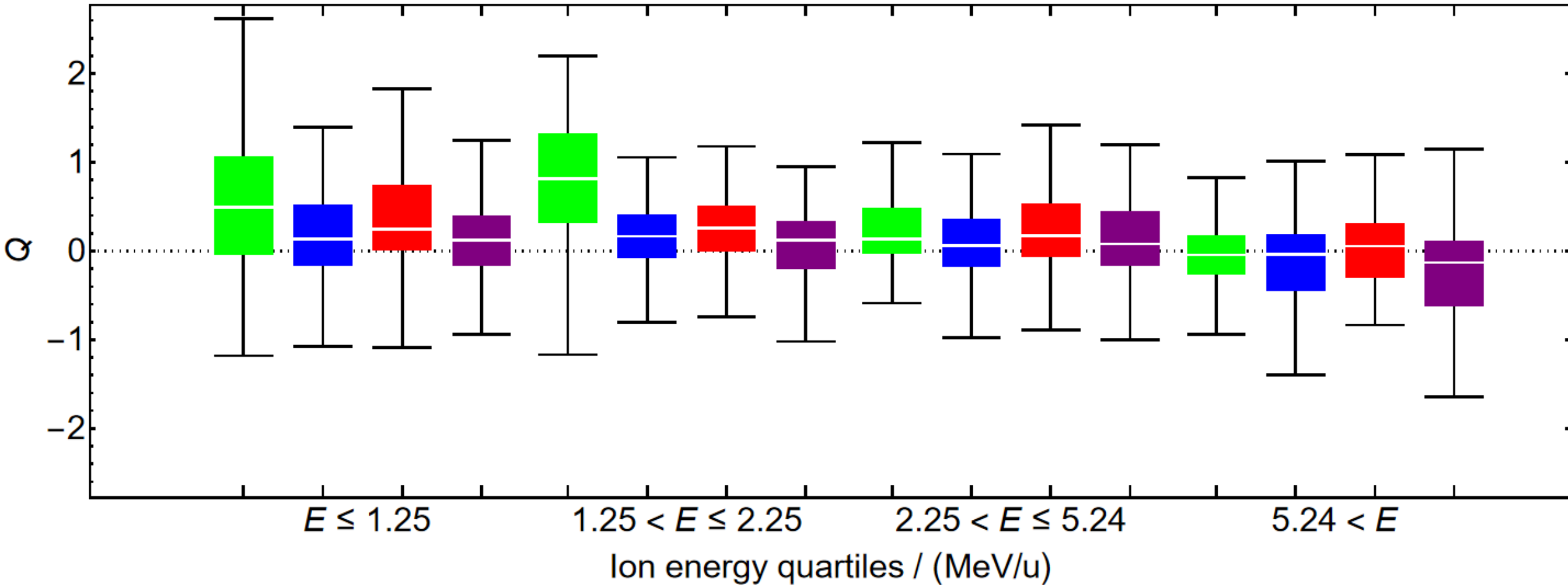
Disregarding the α/β ratio results in the worst model performance

Conclusion and Outlook

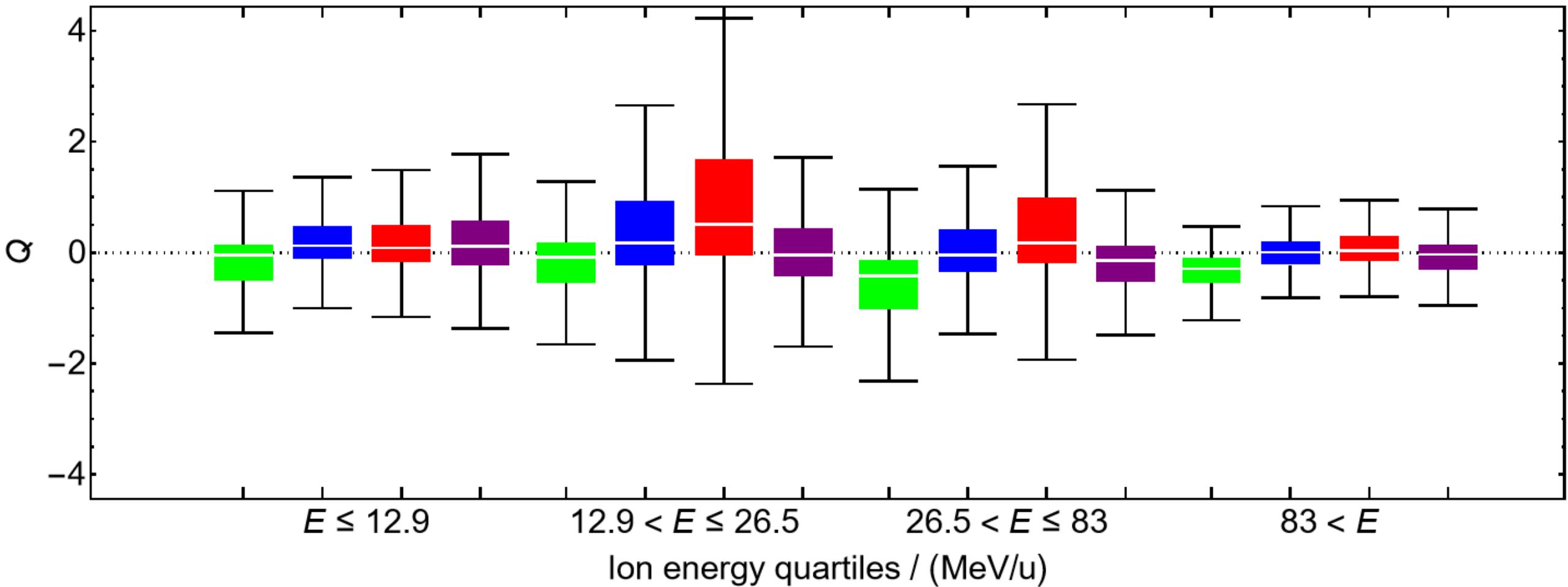
- Linear *LET* models work reasonably well with low Z ion species
- Less effective towards high charge numbers
- Simplifying the model further makes performance worse
- Removing the α/β parameter makes the model worse
 - Suggests that this term has some explanatory power
 - Interactions become more important for higher Z values
- Key limitation: model is (mostly) phenomenological
 - No first principles derivation
- Further work
 - Relax fitting assumptions
 - Derive model from first principles (Bloch equation?)

Thank You for your Attention!

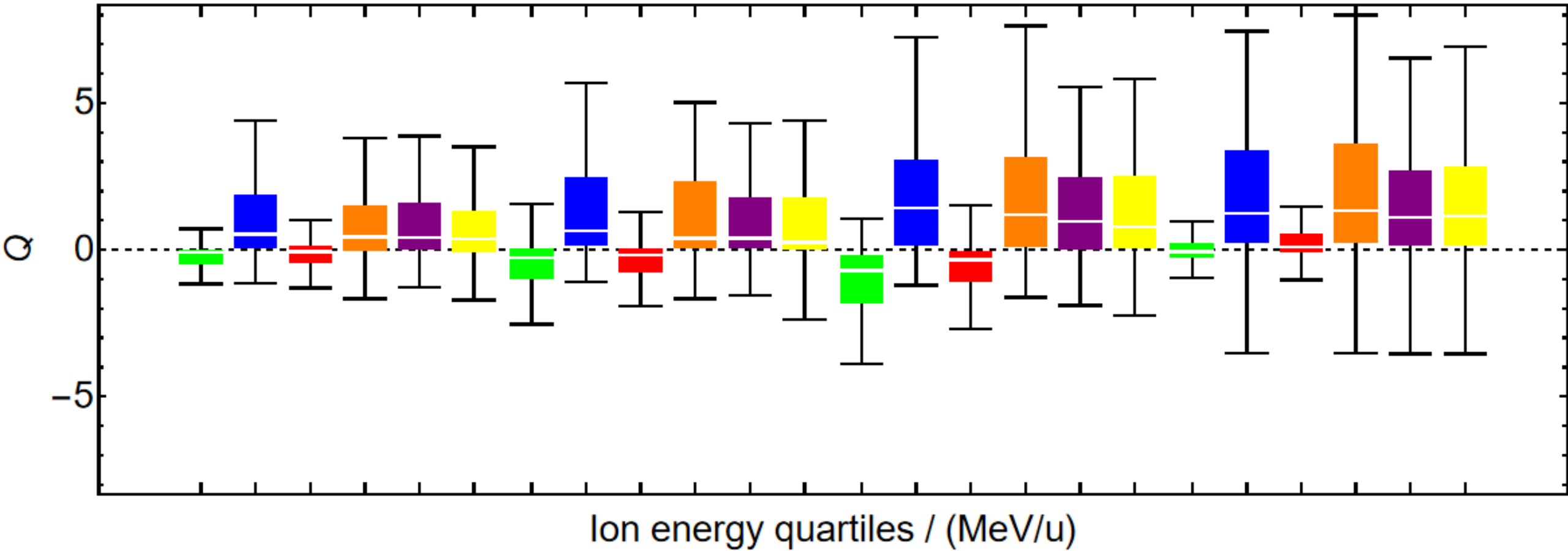
Model Comparison to Experimental Data for Protons



Model Comparison to Experimental Data for Carbon



Further Simplified models for Proton Data



Further Simplified models for Helium Data

