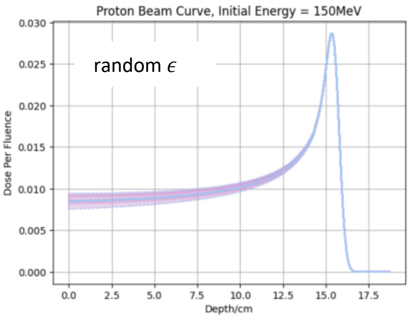
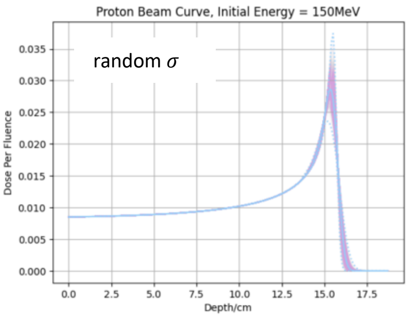
Sensitivity Analysis of Bortfeld's model of the Bragg curve

Thomas Bortfeld has derived an analytical approximation of the Bragg Peak curve for proton energies between 10 and 200 MeV[1]. He mentions that the parameters R_0 (range), ϵ (fraction of primary fluence contributing to the "tail" of the energy spectrum) and σ (width of Gaussian range straggling and energy spectrum) can be varied since not much is known about the energy spectra of proton beams.

$$D(z)=\Phi_0 \frac{e^{-\zeta^2/4}\sigma^{1/p}\Gamma(1/p)}{\sqrt{2\pi}\varrho p \alpha^{1/p}(1+\beta R_0)}\left[\frac{1}{\sigma}\mathscr{D}_{-1/p}(-\zeta) + \left(\frac{\beta}{p}+\gamma\beta+\frac{\epsilon}{R_0}\right)\mathscr{D}_{-1/p-1}(-\zeta)\right].$$

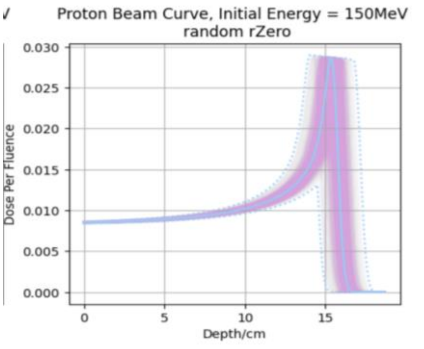




I have decided to treat these 3 parameters as random variables to see their effect on the shape of the curve when the initial energy is 150MeV. We have assumed they have the following distributions:

- $\epsilon \sim U(0,0.2)$
- $\sigma \sim N(0.3181, 0.05^2)$
- $R_0 \sim N(15.64, 0.469^2)$

The mean for the two Gaussian distributions were chosen to match the values Bortfeld estimated. We chose the standard deviation for the range to be 0.03%[2].



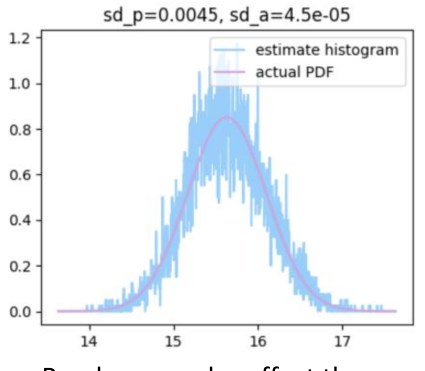
Varying ϵ only effects the tail of the curve, varying σ effects the height of the peak of the curve and varying R_0 effects the depth (z) where the peak occurs.
The range-energy relationship tells us that:

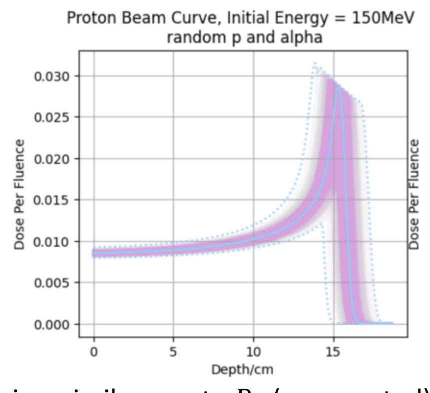
$$R_0 = \alpha E_0^p$$

where E_0 is the initial energy. The dose function also depends on these values of p and α, so we decided to treat those as random variables.

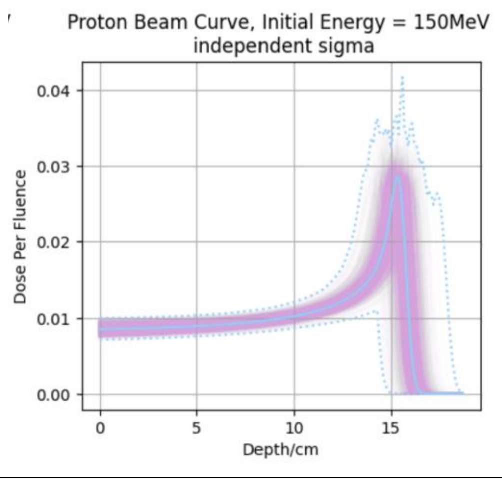
We need to find the distributions of α and p such that R_0 still follows the correct distribution. We assumed that both α and p followed Gaussian distributions and varied the values of the standard deviations until the histogram of R_0 using random α and p matched the pdf of R_0. We used the following distributions:

- $\alpha \sim N(0.0022, 0.000045)$
- $p \sim N(1.77, 0.0045)$





Random p and α effect the curve in a similar way to R_0 (as expected) but it also effects the curve at z = 0 and the height of the peak.

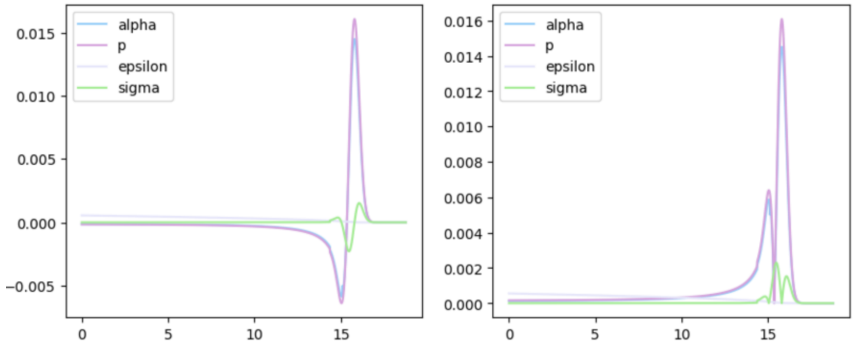


On the left we see the effect of the all the random variables on the curve. These random variables effect the whole curve. We want to see which variables effect the curve most at certain depths by performing a sensitivity analysis. Based on the plots above at z = 0 we would expect ϵ to have the greatest effect, then α and p, and then σ (which has barely any effect). At the peak, its hard to tell which variable has the greatest effect. To figure this out we will compare the absolute value of the partial derivatives with respect to the random variables and we will calculate the active subspaces at different depths. For this we will have to treat σ as though its independent from p and α by using their averages to calculate σ.

1. Bortfeld, T., *An analytical approximation of the Bragg curve for therapeutic proton beams.* Medical Physics, 1997. **24**(12): p. 2024-2033.
2. Hofmaier, J., *Variance-based sensitivity analysis for uncertainties in proton therapy:A framework to assess the effect of simultaneous uncertainties in range,positioning, and RBE model predictions on RBE-weighted dose distributions.* Medical Physics, 2020. **48**(2): p. 805-818.

Partial Derivatives

The partial derivatives will give us the rate of change of the dose function with respect to the random variables. The larger the absolute value of the partial derivative, the larger the effect on the curve. This compares the variables assuming they all have the same standard deviation, so we have scaled them so that we can compare them with the correct distributions. Below we have estimated the partial derivatives using difference quotients:



As expected, epsilon has the greatest effect at z = 0. At around z = 10 (just before the peak), α and p start to have a greater effect than ϵ. The effect increases until the Bragg peak (z=15.35) where it goes to 0 and then it increases again. σ starts to have a greater effect than ϵ at z=14.362. It has its greatest effect just after the Bragg peak, and then has a large effect again after the peak.

Active Subspaces

Active subspaces measure the global sensitivity (which is the average sensitivity of D to variations of α, p, σ and ϵ across the domain) and can be used to identify the important parameters. The active subspace method seeks to identify a collection of important directions[3]. We will look at the directions of the active subspace at z=0, z=14.362 (just before the peak), z=15.35 (the peak) and z=16.061 (just after the peak).

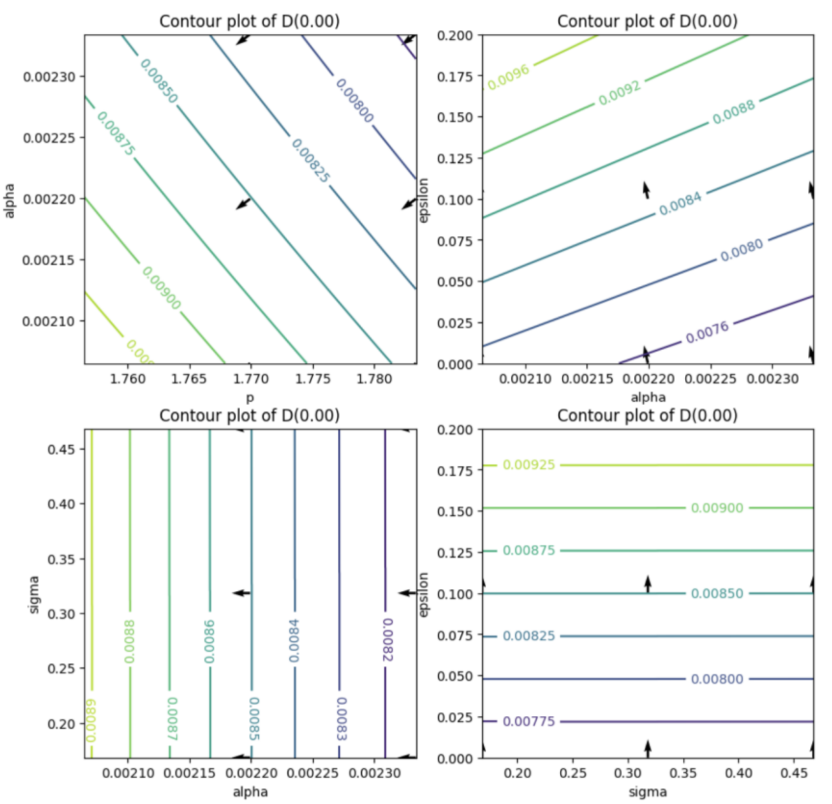
At z = 0, the direction of the active subspace is (-7.499e-02,-9.447e-02,-5.926e-05,3.288e-01). This suggests that ϵ has the greatest effect, then p and α and then σ. This matches what we saw in the plots on the previous page and what we saw when looking at the partial derivatives. At the bottom of the page, there are some contour plots that match this conclusion. The effect of α is very similar to p since the contour lines are diagonal. ϵ has a greater effect than α but only slightly since the lines are close to horizontal. α has a greater effect than σ since the contour lines are vertical, and ϵ has a greater effect than σ since the contour lines are horizontal. The direction of the active subspace is perpendicular to the lines on all the contour plots as expected.

At z = 14.362, the direction of the active subspace is (0.0749, 0.0461, 0.0397, -0.0093). This suggests that α, p and σ have a similar effect then ϵ has a smaller effect. σ has a larger effect than expected when comparing to the plots on the previous page but this direction matches what we saw in the partial derivatives

At z = 15.35, the direction of the active subspace is (-0.0749 -0.0504, -0.0299, 0.0067). This suggests that α and p have the greatest effect then σ and then ϵ. This matches what we see from the plots on the previous page, but based on the partial derivatives we would expect α and p to have barely any effect since they go to 0 at the peak.

At z = 16.061, the direction of the active subspace is (-0.0749, -0.0490, -0.0280, 0.005). This suggests that α and p have the greatest effect then σ and then ϵ. This matches what we saw in the plots on the page before and what we say in the partial derivatives.

To conclude, ϵ has the greatest effect at small z; then p and α have the greatest effect around the peak.



3. Sullivan, T.J., *Introduction to Uncertainty Quantification (Texts in Applied Mathematics 63)*. 2015: Springer.