Proton beam de-energisation and the Bragg Peak for cancer therapy via jump stochastic differential equations

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With thanks to team members: Emma Horton (Warwick), Ali Crossley (Warwick), Karen Haberman (Warwick), Sarah Osman (UCLH), Colin Baker (UCLH), Ana Lourenço (NPL), Tristan Pryer (Bath), Alex Cox (Bath), Veronika Chronholm (Bath)

Nuclear interactions of a proton beam

- Ionization (Coulomb effect)
- Coulomb interactions with atomic nucleus
- Nuclear interactions with atomic nucleus

These interactions govern how protons deposit their dose in patient

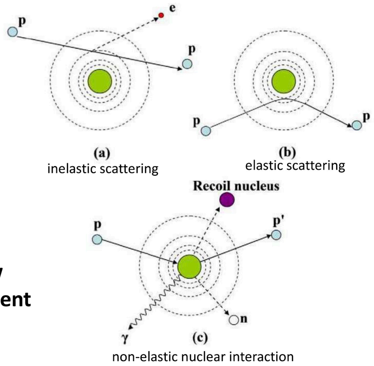
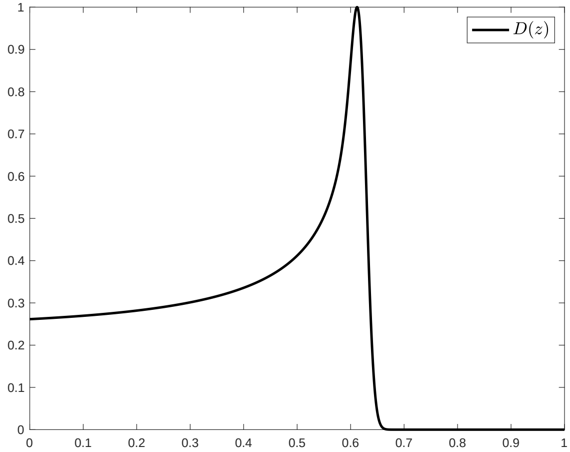
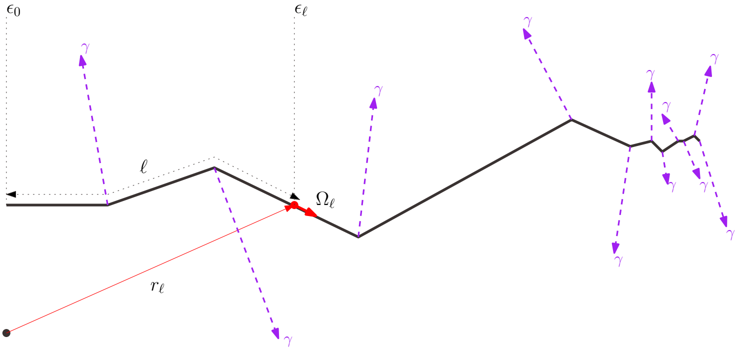


Figure: Diagram taken from: Newhauser and Zhang 2015 Phys. Med. Biol. 60 R155.

Bragg Peak



Schematic of sequential proton track



Proton beam SDE

A special kind of Stochastic Differential Equation models the energy deposition of individual proton streams: $Y_\ell = (\epsilon_\ell, r_\ell, \Omega_\ell) \in \mathcal{C} := [0,\infty) \times D \times \mathbb{S}_2$

- ϵ_ℓ is the energy of the proton stream after it has traversed a distance ℓ
- r_ℓ is the position of the proton stream after it covers a distance ℓ
- Ω_ℓ is the direction of travel of the proton after it covers a distance ℓ.

$$
\begin{aligned}
\epsilon_\ell &= \epsilon_0 - \int_0^\ell \varsigma(Y_{l-})\,\mathrm{d}\,l - \int_0^\ell \int_{(0,1]} \int_{\mathbb{S}_2} u\epsilon_{l-} N(Y_{l-}; \mathrm{d}\,l, \mathrm{d}\,\Omega', \mathrm{d}\,u) \\
r_\ell &= r_0 + \int_0^\ell \Omega_{l-}\,\mathrm{d}\,l \\
\Omega_\ell &= \Omega_0 - \int_0^\ell m(Y_l)^2 \Omega_{l-}\,\mathrm{d}\,l + \int_0^\ell m(Y_{l-})\Omega_{l-} \wedge \mathrm{d}\,B_l \\
&\qquad + \int_0^\ell \int_{(0,1]} \int_{\mathbb{S}_2} (\Omega' - \Omega_{l-}) N(Y_{l-}; \mathrm{d}\,l, \mathrm{d}\,\Omega', \mathrm{d}\,u)
\end{aligned}
$$

for $\ell < \Lambda := \inf\{\ell > 0 : \epsilon_\ell = 0 \text{ or } r_\ell \notin D\}$

SDE components

$$
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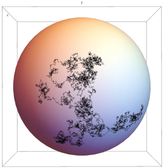
\end{aligned}
$$

$(B_\ell, \ell \geq 0)$ is a standard Brownian motion on $\mathbb{R}^3$ and

$$
\Omega_\ell = \Omega_0 - \int_0^\ell m^2 \Omega_{l-}\,\mathrm{d}\,l + \int_0^\ell m\Omega_{l-} \wedge \mathrm{d}\,B_l
$$

represents Brownian motion on a sphere with ‘speed’ m



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\end{aligned}
$$

- $\varsigma(x)$ is the configuration dependent continuous rate of loss of energy (due to inelastic Coulomb interaction and small elastic Coulomb interaction);
- For each $x \in [0,\epsilon_0] \times D \times \mathbb{S}_2, \ell \geq 0, \Omega' \in \mathbb{S}_2, u \in (0,1]$, $N(x;\mathrm{d}\,\ell,\mathrm{d}\,\Omega',\mathrm{d}\,u)$, is an optional random measure with previsible compensator $\sigma(x)\pi(x;\mathrm{d}\,\Omega',\mathrm{d}\,u)\,\mathrm{d}\,l$, so that $\sigma(x) = \sigma_{\mathrm{e}}(x) + \sigma_{\mathrm{ne}}(x)$ is a finite cross section and at each arrival, the incoming configuration $x = (\epsilon_{\ell-}, r_{\ell-}, \Omega_{\ell-})$ jumps to configuration $(\epsilon_{\ell-}(1-u), r_{\ell-}, \Omega')$ with probability distribution

$$
\pi(x;\mathrm{d}\,\Omega',\mathrm{d}\,u) := \frac{\sigma_{\mathrm{e}}(x)}{\sigma(x)}\pi_{\mathrm{e}}(x;\mathrm{d}\,\Omega') + \frac{\sigma_{\mathrm{ne}}(x)}{\sigma(x)}\pi_{\mathrm{ne}}(x;\mathrm{d}\,\Omega',\mathrm{d}\,u), \qquad u \in (0,1], \Omega' \in \mathbb{S}_2.
$$

Where's the math?

- Interrogating energy deposition: We can define for a test function f on $(0, \infty) \times D \times \mathbb{S}_2$ (the configuration space of the solution), the 'interrogation' potential of where (and how much) energy is deposited along its stochastic path:

$$\mathtt{U}[f](x) = -\mathbb{E}_x \left[\int_0^{\Lambda} f(Y_{\ell-}) \mathrm{d}\epsilon_\ell \right], \qquad x \in \mathcal{C}$$

  - Λ is the total distance covered by the proton stream and $Y_\ell = (\epsilon_\ell, r_\ell, \Omega_\ell)$
  - $x \in \mathcal{C}$ is the incoming configuration of the stream
  - A proton stream is one random physical sequence of radiative events; averaging over proton streams gives the behaviour of a proton **beam**
- Suppose there is an occupation density:

$$\mathbb{E}_x \left[\int_0^{\Lambda} 1_{(Y_\ell \in \mathrm{d}y)} \, \mathrm{d}\,\ell \right] = \mathtt{r}(x, y) \, \mathrm{d}\,y, \qquad y \in \mathcal{C},$$

- If **(and that's a big if!)** there is an occupation density: then we can write

$$\mathtt{U}[f](x) = \int_{\mathcal{C}} f(y) \mathtt{u}(x, y) \, \mathrm{d}\,y,$$

then, for $x, y \in \mathcal{C}$,

$$\mathtt{u}(x, y) = \left\{ \varsigma(\epsilon, r, \Omega) + \epsilon \sigma(y) \int_{(0,1]} u \pi((\epsilon, r, \Omega); \mathbb{S}_2, \mathrm{d}\,u) \right\} \mathtt{r}(x, y),$$

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then, for $x,y\in\mathcal{C}$, we see a higher-dimensional Bethe-Bloch formula emerging

$$\mathtt{u}(x,y) = -\left\langle\frac{\mathrm{d}\epsilon}{\mathrm{d}\ell}\right\rangle\mathtt{r}(x,y),$$

Where's the math?

- Now if we define

$$D[f](x) := -\lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\mathbb{E}_x\left[\int_0^{\Lambda}\Big(f(r_\ell+\varepsilon\Omega_\ell)-f(r_\ell)\Big)\,\mathrm{d}\,\epsilon_\ell\right]$$
$$=\int_{\Upsilon}\Omega\cdot\nabla_r f(r)\,\mathtt{u}(z)\,\mathrm{d}\,z,$$

  where $\mathtt{u}(x,z)$ is a density associated to $\mathtt{U}[f](x)$.
- Because of the existence of the density, we can appeal to duality to tell us that

$$D[f](x) = \langle \Omega\cdot\nabla_r f, \mathtt{u}(x,\cdot)\rangle = -\langle f, \Omega\cdot\nabla_r \mathtt{u}(x,\cdot)\rangle.$$

- Theorem (and the added value of this heavy mathematical perspective): the density exists!
  This carries the implication that:
  - $\mathtt{b}(x,y) := \Omega\cdot\nabla_r \mathtt{u}(x,y)$ is the natural notion of energy deposition that extends the Bethe–Bloch formula
  - Monte–Carlo simulation of $\varepsilon^{-1}\int_0^{\Lambda}\Big(\mathbb{1}_A(r_\ell+\varepsilon\Omega_\ell)-\mathbb{1}_A(r_\ell)\Big)\,\mathrm{d}\,\epsilon_\ell$ is a natural way to numerically simulate $\mathtt{b}(x,A)$
  - **Important:** the analytical structure of the theory developed here works whether the SDE is simulated using e.g. FLUKA/GEANT-4/etc or whether one uses ab in-line parametric family of rate functions and calibrates against experimental data - in 1D, 2D or 3D.

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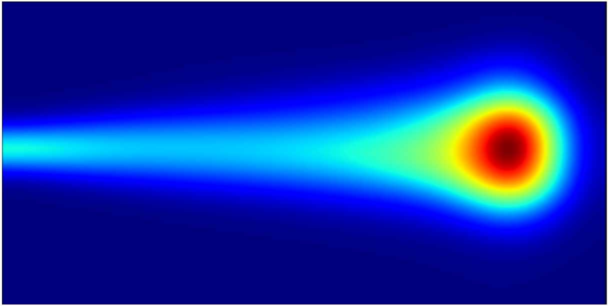
BRAGG MANIFOLD

We defined the *path Bragg manifold* to be the quantity

$$\boxed{\mathtt{b}(x, z) = -\Omega \cdot \nabla_r \mathtt{u}(x, z).}$$

As alluded to above, this is the average rate of directional energy deposition at configuration $z = (\epsilon, r, \Omega) \in \mathcal{C}$ in the sequential proton track for an initial configuration $x \in \mathcal{C}$.



3D

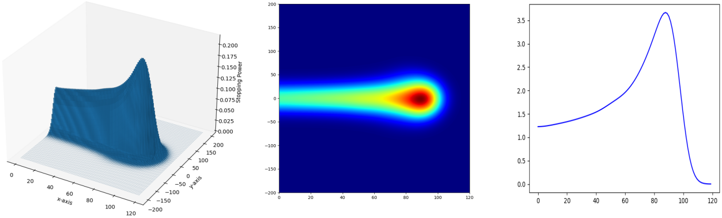


Figure: (L) Realisation of 1,000 proton paths in 3D plotted against stopping power giving a realisation of a Bragg surface $(x, y) \mapsto \mathtt{b}(x, y)$. (C) Two dimensional heat map of the stopping power $(x, y) \mapsto \mathtt{b}(x, y)$ for a simulated protons beam with heat added according to stopping power. (R) The projection of the Bragg surface $(x, y) \mapsto \mathtt{b}(x, y)$ onto the x-axis giving, $x \mapsto \mathtt{b}(x, (-20, 20))$ a classical Bragg peak.

3D

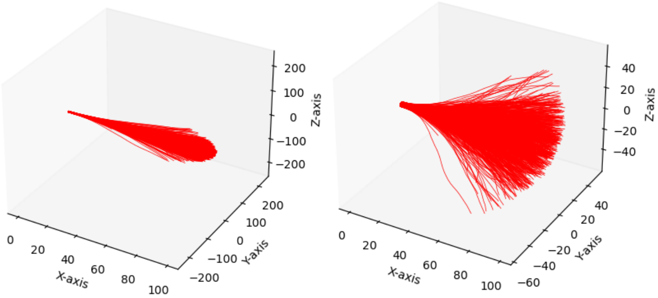


Figure: (R) 3D simulated proton beam. (L) Scaled 3D simulated proton beam.

2D

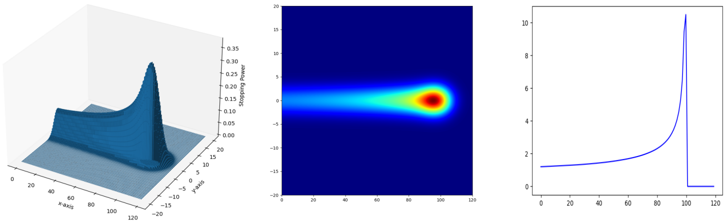


Figure: (L) Realisation of 10,000 proton paths in 2D plotted against stopping power giving a realisation of a Bragg surface $(x, y) \mapsto \mathtt{b}(x, y)$. (C) Two dimensional heat map of the stopping power $(x, y) \mapsto \mathtt{b}(x, y)$ for a simulated protons beam with heat added according to stopping power. (R) The projection of the Bragg surface $(x, y) \mapsto \mathtt{b}(x, y)$ onto the x-axis giving, $x \mapsto \mathtt{b}(x, (-20, 20))$ a classical Bragg peak.

Thank you!