Why FLASH Radiotherapy Is Efficient: A Possible Explanation

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1. What is radiotherapy: a brief reminder

- Radiotherapy is one of the most effective ways of fighting cancer, when radiation is applied to the tumor.
- Traditionally, each radiotherapy session lasts between 10 to 30 minutes.
- From the purely engineering viewpoint, it is possible to apply the same overall dose of radiation faster.
- However, traditionally, medical doctors were reluctant to bring this dose too fast.
- They were afraid of undesirable side effects of radiation-per-hour.

2. FLASH radiotherapy

- Recently, it turned out that not only these fears were unfounded; moreover:
  - a very fast session, when the whole dose of radiation is sent in a few seconds,
  - seems to work even better than the traditional radiotherapy.
- Specifically:
  - experiments on animals have shown that
  - such *FLASH* radiotherapy actually decreases the undesirable effects on the surrounding healthy cells.
- These results make FLASH radiotherapy a promising approach to cancer treatment.

3. Problem

- How can we explain these unexpected experimental results?
- In this talk, we provide a possible explanation for the success of FLASH radiotherapy.

4. Let us formulate the problem in precise terms

- The main objective of a radiotherapy session is to transmit the overall radiation dose D_0.
- How we do it can be characterized by a function $D(t)$ that describes:
  - how much radiation has been transmitted during this session
  - by time t (starting from the beginning of this section).
- We start at time $t = 0$, when the dose-so-far is 0: $D(0) = 0$.
- At each moment of time, we can only add more radiation.
- So this function is (non-strictly) increasing: if $t \le t'$ then

$$D(t) \le D(t').$$

- At the end of the session, we should have $D(t) = D_0$.
- This amount should remain the same until the next session.
- The time until the next session – usually, several weeks – is much larger than the session's duration.

5. Let us formulate the problem in precise terms (cont-d)

- Thus, it makes sense, when describing the current session:
  - to ignore this future session – which is too far away from now, and
  - to simply assume that the function $D(t)$ remains equal to D_0 for all non-negative value t.
- In these terms:
  - selecting an appropriate schedule means
  - selecting a (non-strictly) increasing function $D(t)$ for which $D(0) = 0$ and $\lim\limits_{t \to \infty} D(t) = D_0$.
- There are many such functions, which of them should we choose?
- Informally, we should select the best of these functions.
- The question is how we describe "the best" in precise terms.

6. How to describe "the best" in precise terms: general case

- Usually, "the best" means that some objective function attains the largest (or the smallest) possible value.
- However, this is not the most general way of describing optimality.
- For example:
  - if you have two different doses that have the same curing effect,
  - it is reasonable to use this non-uniqueness to optimize something else,
  - e.g., minimize the possibility of negative side effects.
- In this case:
  - instead of the original single objective function $f(a)$, we have a more complicated scheme,
  - when an alternative a is better than an alternative b:
    - if either $f(a) > f(b)$,
    - or if $f(a) = f(b)$ and $g(a) < g(b)$ for some other function $g(a)$.

7. How to describe "the best" in precise terms (cont-d)

- If this more complex scheme still selects several alternatives:
  - we can use this non-uniqueness to optimize something else, etc.,
  - until we reach the final optimality criterion in which we have only one optimal alternative.
- The only thing we can say about such more general optimization settings is that we should be able, for any two alternatives a and b, to decide:
  - whether a is better than b (we will denote it by $a > b$),
  - or b better than a ($b > a$),
  - or a and b have the same quality (we will denote it by $a \sim b$).
- These relations $a > b$ and $a \sim b$ should satisfy natural consistency requirements.
- E.g., if a is better than b and b is better than c, then a should be better than c. Thus, we arrive at the following definition.

8. Definition

- Let A be a set. Its elements will be called *alternatives*.
- By an *optimality criterion*, we mean a pair of binary relations $\langle >, \sim \rangle$ that satisfy the following conditions for all a, b, and c:
  - if $a > b$ and $b > c$, then $a > c$;
  - if $a > b$ and $b \sim c$, then $a > c$;
  - if $a \sim b$ and $b > c$, then $a > c$;
  - if $a \sim b$ and $b \sim c$, then $a \sim c$;
  - if $a > b$, then we cannot have $a \sim b$.
- We say that an alternative a_{opt} is *optimal* with respect to the optimality criterion $\langle >, \sim \rangle$ if for every $a \in A$, we have:
  - either $a_{\text{opt}} > a$
  - or $a_{\text{opt}} \sim a$.

9. Definition (cont-d)

- We say that the optimality criterion is *final* if there exists exactly one alternative which is optimal with respect to this criterion.
- In our case, alternatives are different (non-strictly) increasing functions $D(t)$ for which $D(0) = 0$ and $D(t) \to D_0$ as $t \to \infty$.
- We will call them D_0-*alternatives*.

10. Natural invariance

- There is no fixed unit of time relevant for this process.
- So it makes sense to require that the optimality criterion will not change if we use a different measuring unit to measure time.
- If we know the dependence $D(t)$ in the original scale, how will this dependence look like in the new scale?
- If we replace the original measuring unit by a one which is λ times larger, then:
  - moment t in the new scale corresponds to
  - moment $\lambda \cdot t$ in the original scale.
- For example:
  - if we replace second with minutes – which are 60 times larger,
  - then 2 minutes in the new scale is equivalent to $2 \cdot 60 = 120$ seconds.

11. Natural invariance (cont-d)

- In general:
  - the value $D_{\text{new}}(t)$ corresponding to moment t in the new scale
  - is thus equal to the value $D(\lambda \cdot t)$ when time is described in the original scale.
- Thus, $D_{\text{new}}(t) = D(\lambda \cdot t)$, and we arrive at the following definition.

12. Definition

- Let D_0 be a real number.
- For every $\lambda > 0$ and for every D_0-alternative $D(t)$, by a λ-*rescaling* $R_\lambda(D)$, we mean a D_0-alternative $D_{\text{new}}(t) \stackrel{\text{def}}{=} D(\lambda \cdot t)$.
- We say that the optimality criterion of the set of all D_0-alternatives is *scale-invariant* if:
  - for every $\lambda > 0$ and for every two D_0-alternatives a and b,
  - we have the following:
    - if $a > b$, then $R_\lambda(a) > R_\lambda(b)$, and
    - if $a \sim b$, then $R_\lambda(a) \sim R_\lambda(b)$.

13. Main result

- Now, we are ready to formulate our main result.
- **Proposition:**
  - *Let D_0 be a real number, let $(<, \sim)$ be a final scale-invariant optimality criterion on the set of all D_0-alternatives.*
  - *Then, the optimal D_0-alternative has the form $D(t) = D_0$ for all $t > 0$.*
- This result explains the empirical fact that an instantaneous ("flash") radiotherapy indeed leads to the best medical results.

14. Proof: Part 1

- Let us first prove that:
  - for every final scale-invariant optimality criterion on the set of all D_0-alternatives,
  - the optimal D_0-alternative D_{opt} is itself scale-invariant,
  - i.e., $R_\lambda(D_{\text{opt}}) = D_{\text{opt}}$ for all $\lambda > 0$.
- Indeed, by definition, the fact that D_{opt} is optimal means that:
  - for every D_0-alternative D,
  - we have either $D_{\text{opt}} > D$ or $D_{\text{opt}} \sim D$.
- This is true for every D_0-alternative D.
- Thus, this property holds for $R_{\lambda^{-1}}(D)$.
- So, we have either $D_{\text{opt}} > R_{\lambda^{-1}}(D)$ or $D_{\text{opt}} \sim R_{\lambda^{-1}}(D)$.

15. Proof: Part 1 (cont-d)

- Since the optimality criterion is scale-invariant, we can conclude that:
  - either $R_\lambda(D_{\text{opt}}) > R_\lambda(R_{\lambda^{-1}}(D)) = D$
  - or $R_\lambda(D_{\text{opt}}) \sim R_\lambda(R_{\lambda^{-1}}(D)) = D$.
- This is true for all D_0-alternatives D.
- Thus, by definition of optimality, this means that the D_0-alternative $R_\lambda(D_{\text{opt}})$ is also optimal.
- However, we assumed that our optimality criterion is final.
- This means that there is only one optimal D_0-alternative, and thus,

$$R_\lambda(D_{\text{opt}}) = D_{\text{opt}}.$$

- The statement is proven.

16. Proof: Part 2

- Let us now use the result from Part 1 to prove that the optimal D_0-alternative has the desired flash form.
- Indeed, the equality $R_\lambda(D_{\text{opt}}) = D_{\text{opt}}$ means that the values of these two functions coincide for all t.
- By definition of λ-rescaling, this means that for every t and every $\lambda > 0$, we have $D_{\text{opt}}(\lambda \cdot t) = D_{\text{opt}}(t)$.
- In particular, by taking $\lambda = s > 0$ and $t = 1$, we conclude that for every $s > 0$, we have $D_{\text{opt}}(s) = D_{\text{opt}}(1)$.
- Thus, the function $D_{\text{opt}}(s)$ attains the same constant value $D_{\text{opt}}(1)$ for all $s > 0$.
- In particular, for $s \to \infty$, we have $D_{\text{opt}}(s) \to D_{\text{opt}}(1)$.
- By definition of a D_0-alternative, this limit must be equal to D_0.
- Thus, $D_{\text{opt}}(1) = D_0$ and therefore, for all $s > 0$, we have $D_{\text{opt}}(s) = D_0$.

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