Double DSB Inventory (DDI) Models

The fruitless search for the Correct rad harm model

Jack Devanney

This post is aimed at the choir's scientist section, perhaps the choir's most fractious fraction. Others need only read the first couple of paragraphs. Non-scientists don't need this sermon.

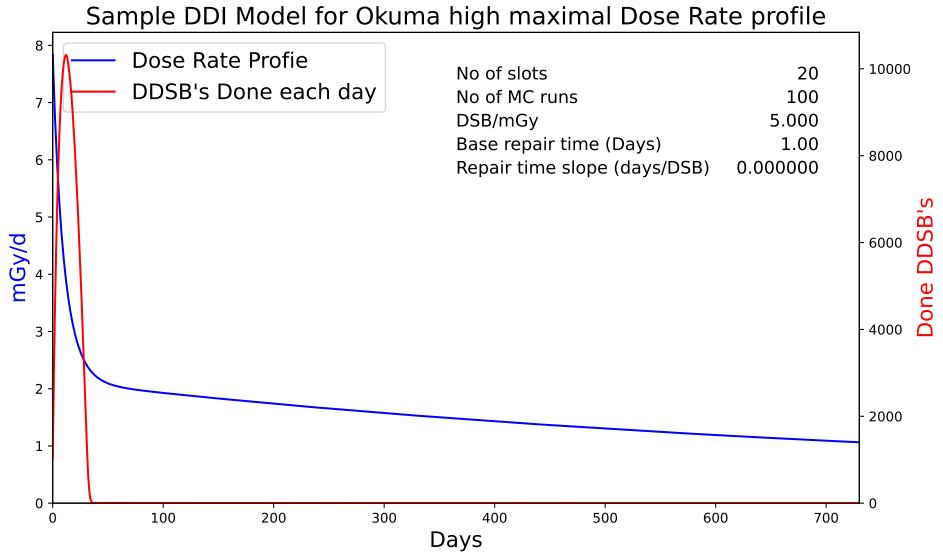

Figure 1: DDI Model response to Okuma high maximal DRP with fixed repair period. A Done DDSB is a DDSB that is either correctly repaired, misrepaired by rejoining the wrong ends, or not rejoined in which case the cell cannot replicate and cause cancer. It simply dies.

Non-technical people tend to lump engineers and scientists. They are both geeky types. The both have this nasty habit of lapsing into an unintelligible tongue written in undecipherable glyphs. There's not much difference. Nothing could be further from the truth.

Engineers are taught from day one that everything's a tradeoff. Your job is to come up with a good balance of performance, cost, reliability, and safety. The key question is: how well does it work? In modern parlance, they are non-binary.

Scientists on the other hand are very binary. They are on a search for "truth". A theory is either right or its wrong.

When it comes to radiation harm models, SNT is multiple orders of magnitude more realistic than LNT when the dose rate profile is spread more or less evenly over a long period. If implemented, it would result in reasonable radiation regulation. The engineer says "Wow. Big improvement. What are we waiting for?"

The scientist is not impressed. As far as she is concerned, both models are wrong. LNT denies our indisputable ability to repair DNA.[1] SNT claims that what's going on in the cell today has zero impact on what happens in the next day. (LNT makes the same assumption.) That's almost certainly wrong. There's no real reason to switch from one wrong model to another wrong model. We need more research to find the correct model. My grant application is in the mail.

So what can we do to mollify this bunch, and still remain simple enough to be implemented? One possibility is a Double DSB Inventory (DDI) model. The basic premise of a DDI model is: for cancer the key problem is closely spaced Double Strand Breaks in our DNA. Two closely spaced DSB's can be viably misrepaired, by rejoining the wrong ends, leading to mutations which can lead to cancer. There's quite a bit of experimental data that supports this hypothesis. So what we need to do is keep track of how many currently unrepaired DSB's the cell is dealing with and where they are on the DNA.

As long as the cell's repair processes are able to keep the current inventory of DSB's near normal levels, the likelihood of cancer will remain near normal levels. But if the dose rate is high enough, the repair processes won't be able to keep up with the damage. The inventory of unrepaired DSB's will start to grow, and the probability of another DSB very close to an existing DSB will climb steeply, and with it the probability of a viable misrepair. If the damage rate if high enough, this process would lead to a very rapid increase in the probability of cancer.

To implement this concept, a DDI model divides the DNA into a large number, M, of slots. It then steps thru time. For now we will assume a time increment of a day. Going into day n, we have b_m DSBs in the mth slot. The probability of repairing or otherwise safely disposing of each existing DSB will depend on the repair period t_{rep}. If the repair period is 1 day, then the number of DSB's in each slot will reduce by 1 each day, with a floor of zero. The probability of a new DSB in each slot will depend on the dose rate in day n. If each mGy produces k DSB's. then 1 mGy will produce k new DSB's, randomly spread over the M slots.[2] Keep track of the total number of *done DDSB*'s — DDSB's that are either rejoined or disposed of by not rejoining and allowing the cell to die — and assume cancer is proportional to that figure.

[1] This is LNT's foundational premise. Modern versions sometimes invoke proportional repair. But if Double DSB's are important to cancer incidence proportional repair contradicts LNT.

[2] We could model localized damage such as that produced by alpha particles with a two step process:

1. Randomly pick a target *region*, where each region is say 100 contiguous slots.
2. Randomly distribute all the new DSB's within that region. The distributions need not be uniform. This process would allow us to dispense with the bogus sievert unit.

This line of thinking results in a *Markov chain*. What happen in day n depends on the inventory of DSB's in the cell in day $n-1$. Repair periods are no longer independent. They are chained together.

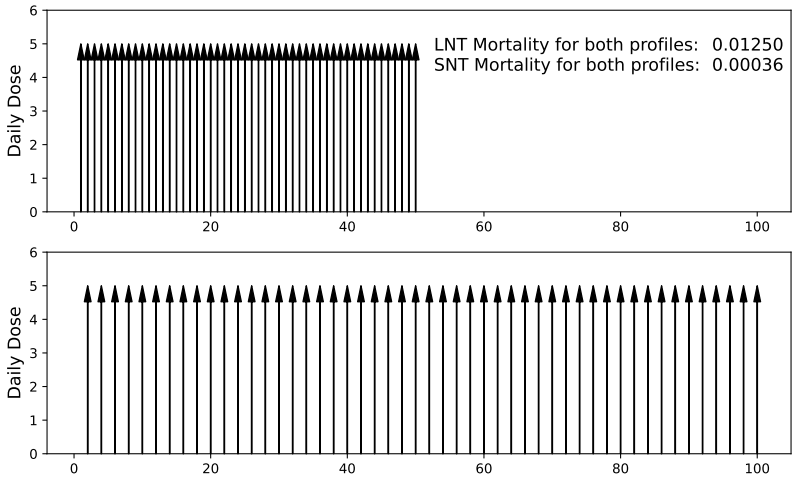

Figure 2: Two Dose Rate Profile's of 50 acute daily doses of 5 mGy. Both LNT and SNT claim these two DRP's result in the same cancer incidence. SNT is conservative for the top profile. It's still more conservative (less accurate) for the bottom.

Such a model has some attractive properties. SNT (and LNT) thinks the two dose rate profiles shown in Figure 2 have the same cancer mortality. That's almost certainly not true. The damage may be the same; but in the bottom profile, the cell has twice as long to repair the damage. A DDI model can distinguish between two such profiles.

The simplest DDI model assumes a fixed repair period. In an earlier post, for a constant dose rate profile, we found that the number of DDSB's was close to quadratic in the dose rate if the repair time did not depend on the dose rate or the current number of DSB's. But what happens when you give a DDI model the kind of dose rate profile that would be incurred in a big release.

Figure 1 shows the DDI response to the GKG's worst possible public dose rate profile at Fukushima. Ignore the numbers. All the DDI parameters here have been picked out of the air. We are just trying to get a qualitative feel for how DDI models work. For these parameters, early in the release, the repair processes can't keep up with the damage. The number of DDSB's soars. As the dose rate falls, the repair systems halt the climb, and then pull the DDSB's down.

Once the dose rate is low enough, the system is able to keep the DDSB's at nearly background levels. Nearly back ground is not at background. If you look very closely at the flat portion of the DDSB curve, there is a Monte Carlo ripple; but any increase in cancer incidence will be undetectable.

The repair period is almost certainly not independent of the dose rate or number of currently unrepaired DSB's. Bissell et found, that the DNA repair period depends on the number of Double Strand Breaks (DSB) which the cell has to deal with, which in turn depends on the dose rate.[1][Figure 3] The effect is not subtle. A factor of 20 increase in the dose pulse increases the repair period by a factor of 10.

In A Better SNT we found that, if the repair period increases linearly with the dose rate, then for a constant dose rate profile, the number of DDSB's is slightly more than cubic in the dose rate. This matches Rowland's best fit to the dial painter data.

> Here the numerical value of the exponent has to be in the range 2.7 to 4.1, with the value 3.15 for the exponent appearing to be the best fit to the [dial painter] data. Needless to say, it is difficult to find any physical meaning for such a dose response function.[2][page 3]

Turns out it is not difficult at all, if you focus on how our bodies repair DNA damage.

Figure 3 shows the DDI response to the Okuma high maximal profile, under the assumption that repair times increase with the number of currently unrepaired DSB's. The response is qualitatively the same as Figure 1; but it takes a lot longer for the body to get thing under control. But once it does, it can keep the number of DDSB's at very close to background levels.

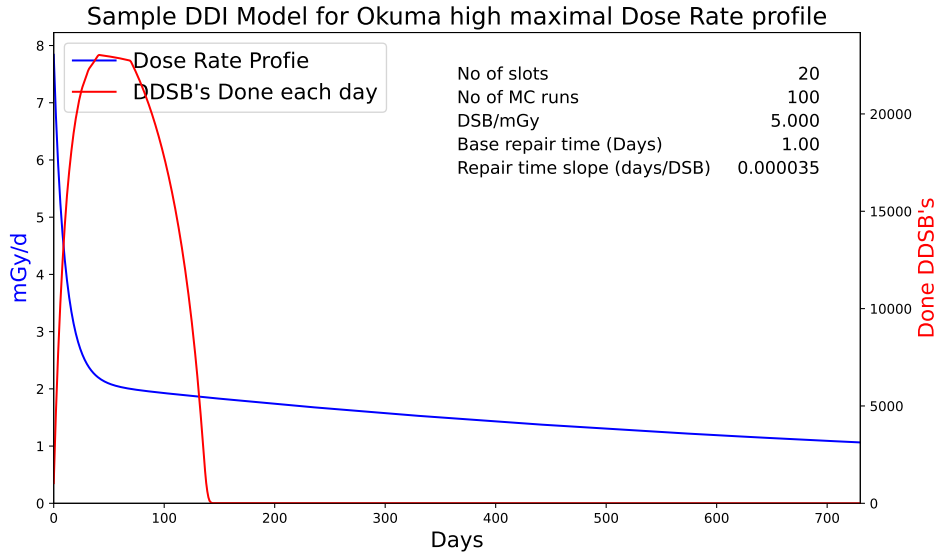

Figure 3: DDI Model response to Okuma high maximal DRP with mild increase in repair period with increasing number of DSB's. Vertical DDSB axis different from Figure 1

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But it was near thing. If you increase the slope of the repair time increase with the number of DSB's to a slightly larger number, then things get totally out of control. Figure 4 shows that DDI models can runaway. We can get ourselves into a situation where the number of DDSB's just keep increasing, even tho the dose rate is decreasing.

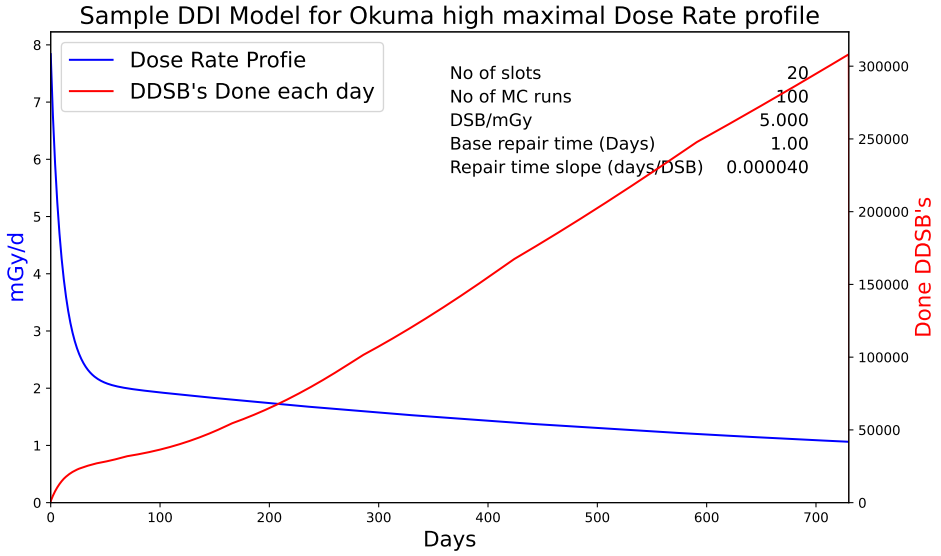

Figure 4: DDI Model response to Okuma high maximal DRP where the increase in repair time results in an explosion of DDSB's. Vertical DDSB axis totally different from Figure 3

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I find all of this mildly interesting; but DDI and similar models (perhaps DDI with an initial hormetian period) are a dead end policy wise. There are at least three problems;

1. Full Definition.
2. Calibration.
3. Building a Consensus.

Full Definition

How do you turn the above handwaving into an actually usable model? For just one example, what does a *slot* mean? I've made it sound like DNA is a 2-D object, just a long string. In fact DNA lives in a 3-D world. Most of the time the molecule is wound into a tight coil around spools called histones. What does *contiguous* mean for such a structure? How close do two DSB's have to be before they become a Double DSB capable of misrejoining? I could easily see august committees debating such issues for decades.

/nfs/TC/hazard/snt/ddi˙models/v1/

Calibration

Suppose you could somehow get agreement on all these issues. The next step would be calibrating the model to get it to match real world cancer incidence. The more complex the model, the more parameters you must choose. One of LNT's big practical advantages is it's a one parameter model. Once the establishment decided to go LNT, they only had to pick ***the*** slope. It turns out one parameter is not enough to even qualitatively model how our bodies work. SNT needs three. But to go to more, opens up all sorts of opportunities for endless debate.

Consensation

Here's the sad fact. For complex processes such as DNA damage and repair, there is no "correct" model. You can find a fault with any model. And for every fault, there will be a number of possible fixes. This leads to a fractal process in which the number of competing models grows exponentially. And since scientists are humans, just about every such model will find a group of supporters. Building a political consensus behind a single model in such an environment is impossible.

The Plea

So here's my plea to the choir's science section. There is no correct radiation harm model. Fortunately, for the purposes of regulation and compensation, we don't need one. We just need a model that's good enough, one that leads to reasonable radiation protection regulation and a generous but not socially destructive compensation for radiation exposure. LNT fails miserably to meet this low bar. SNT meets it. Get behind SNT for regulatory purposes. After we replace LNT with SNT, you may return to to the lab, and bitch about how SNT isn't really right all you want to.

References

[1] T. Neumaier, J. Swenson, and C. Pham. Evidence for formation of dna repair centers and dose-response nonlinearity in human cells. *PNAS Early Edition*, 2011.

[2] R. Rowland. Bone sarcoma in humans induced by radium: A threshold response? Technical report, Argonne National Laboratory, August 1996. ANL/ER/CP-90343.