Modelling Nanoparticle-Radiation Interactions: Current Status and Outstanding Questions

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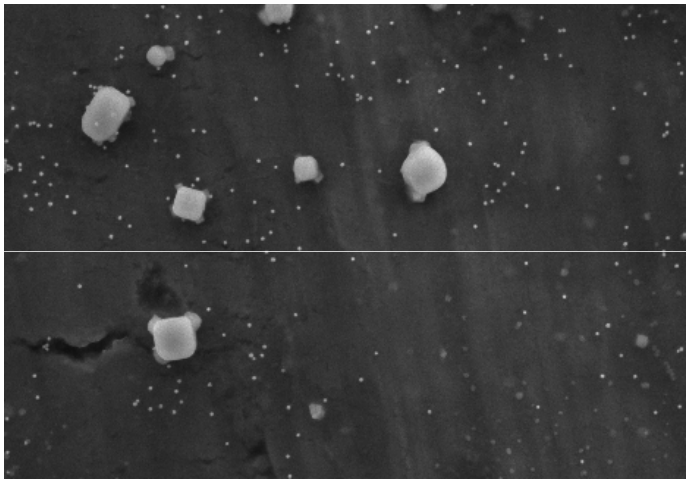
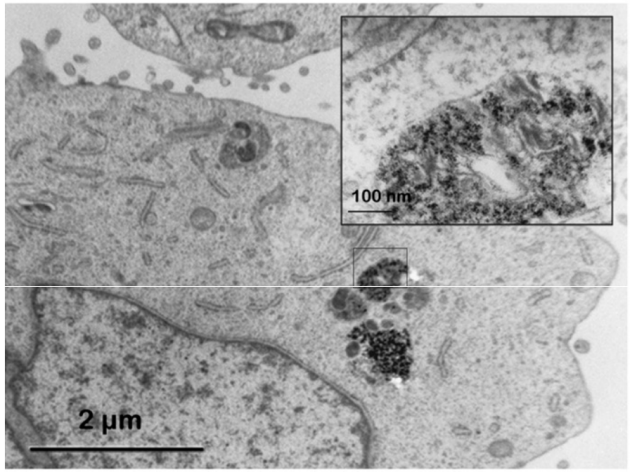
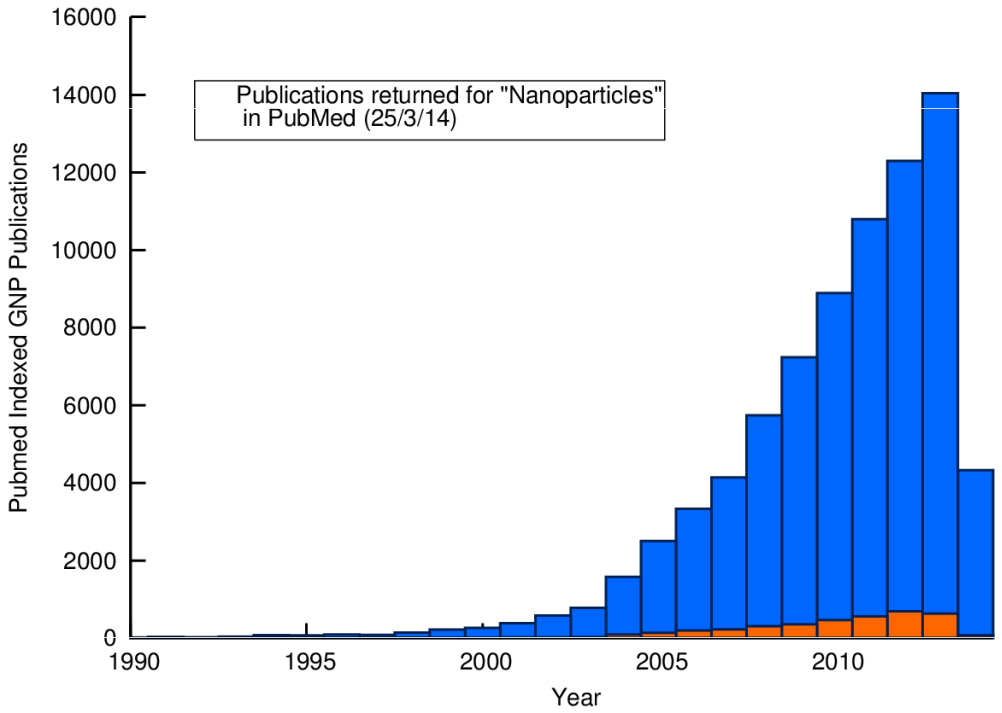
Nanoparticles







There is a considerable interest in nanoparticles in a wide range of areas, due to their advantageous physical properties in a number of applications.

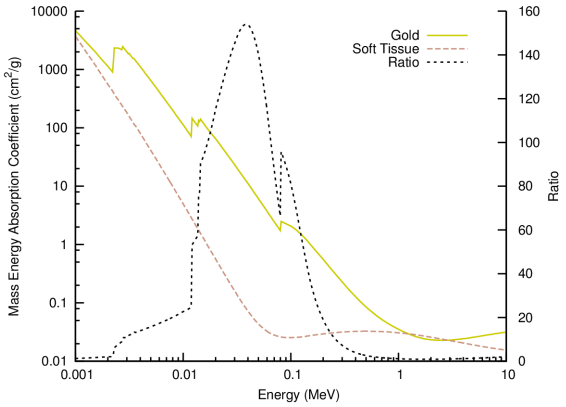
Nanoparticles and Radiation – 'The Basics'

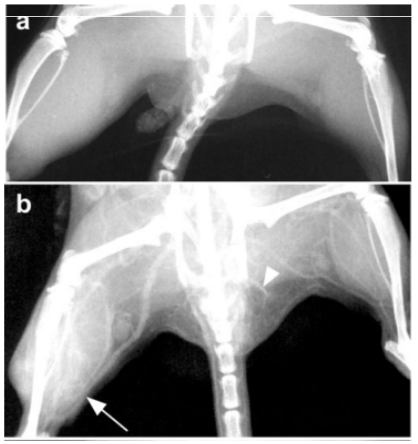
Most investigations of radiation-nanoparticle interactions are driven by three key properties:

1) High Atomic Number

2) Biocompatibility

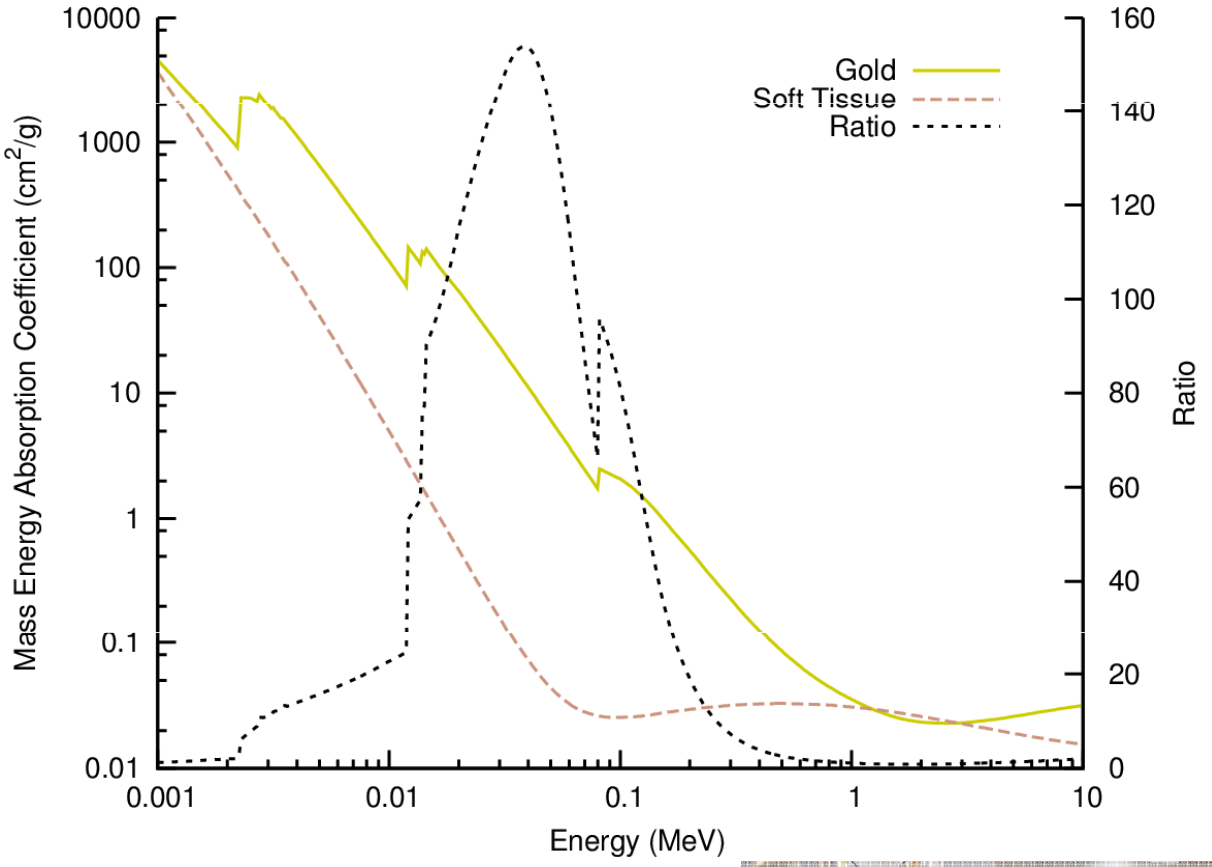
3) Preferential Tumour Uptake



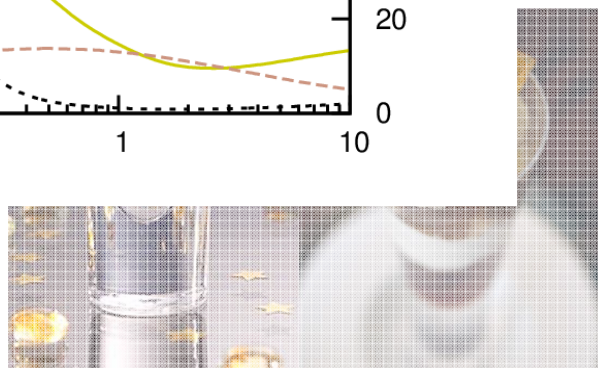


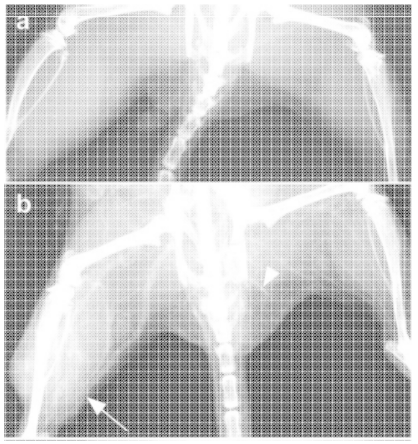
Nanoparticles and Radiation – 'The Basics'

1) High Atomic Number



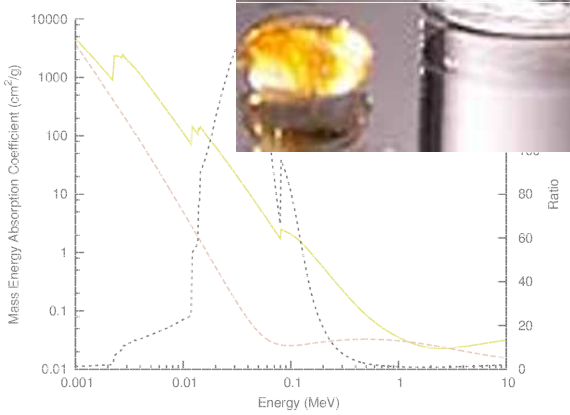
Large photoelectric cross-section ($\mu \propto Z^3$) drives significantly higher absorption in high-Z nanoparticles (e.g. gold) than soft tissue.

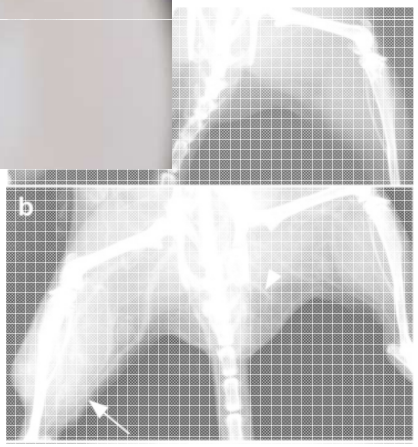




Nanoparticles and Radiation – 'The Basics'

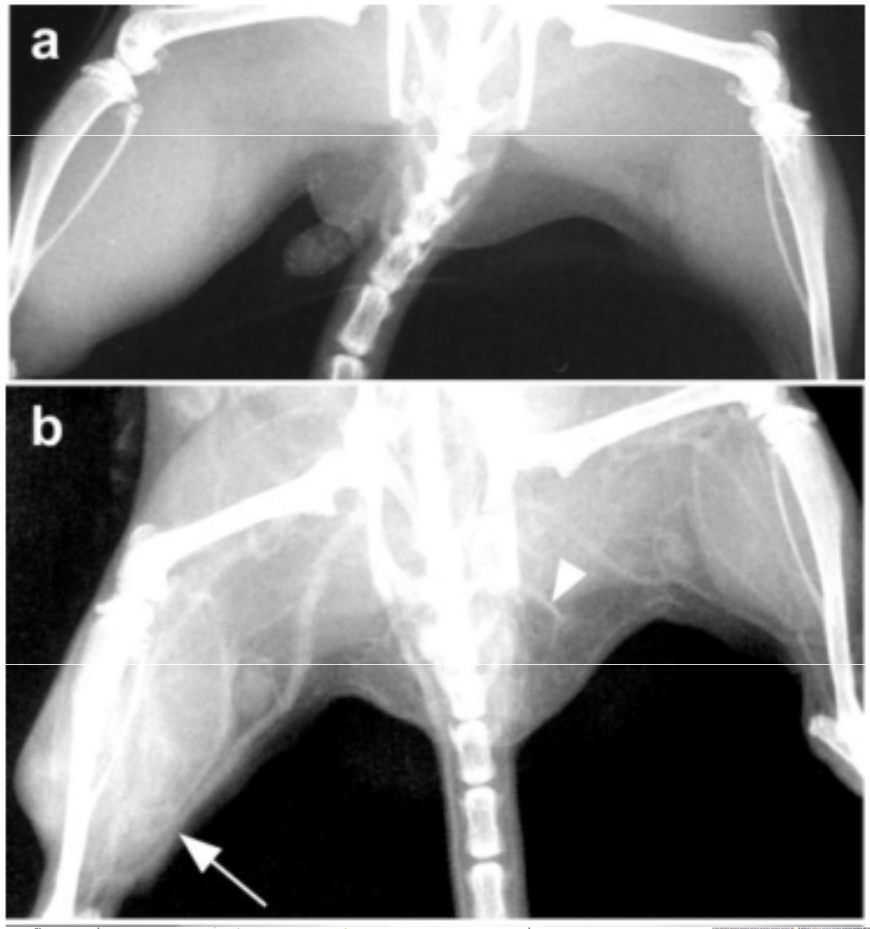
2) Biocompatibility

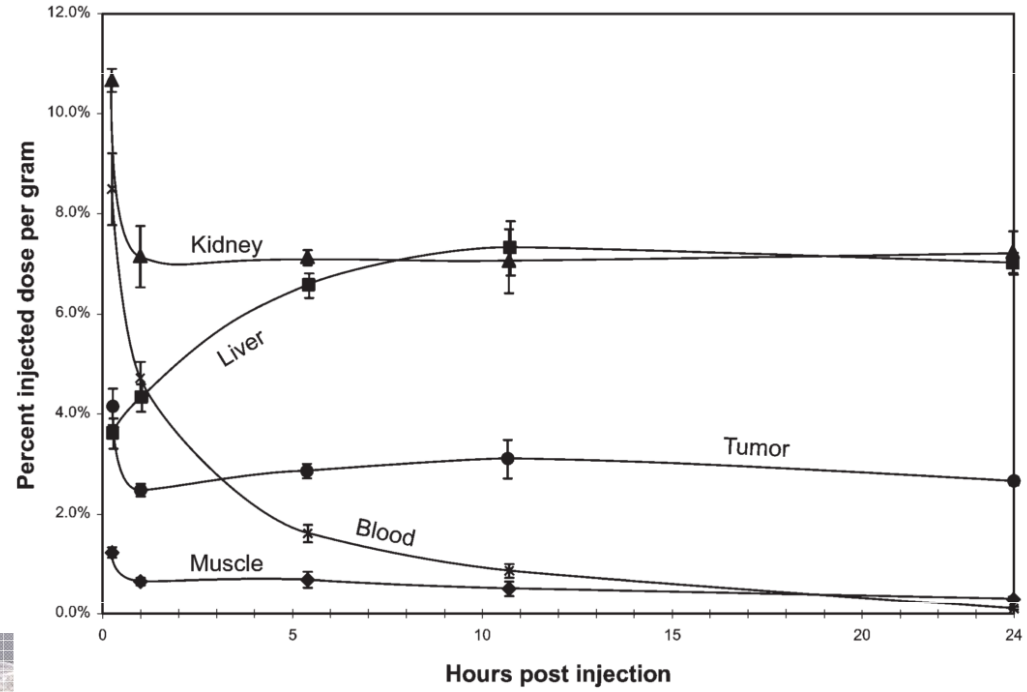


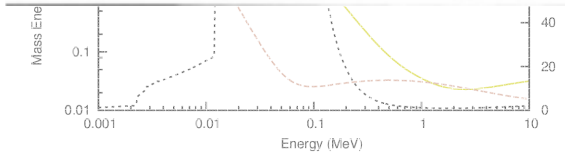


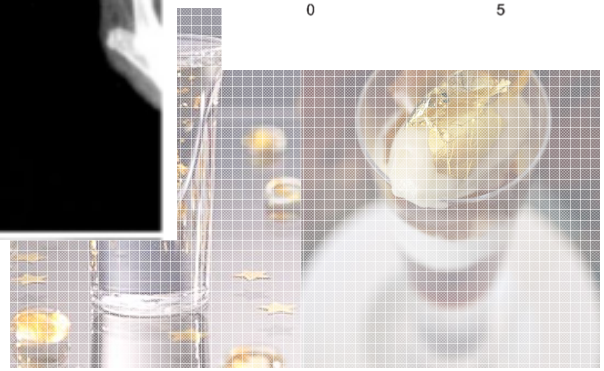
Nanoparticles and Radiation – 'The Basics'

3) Preferential Tumour Uptake



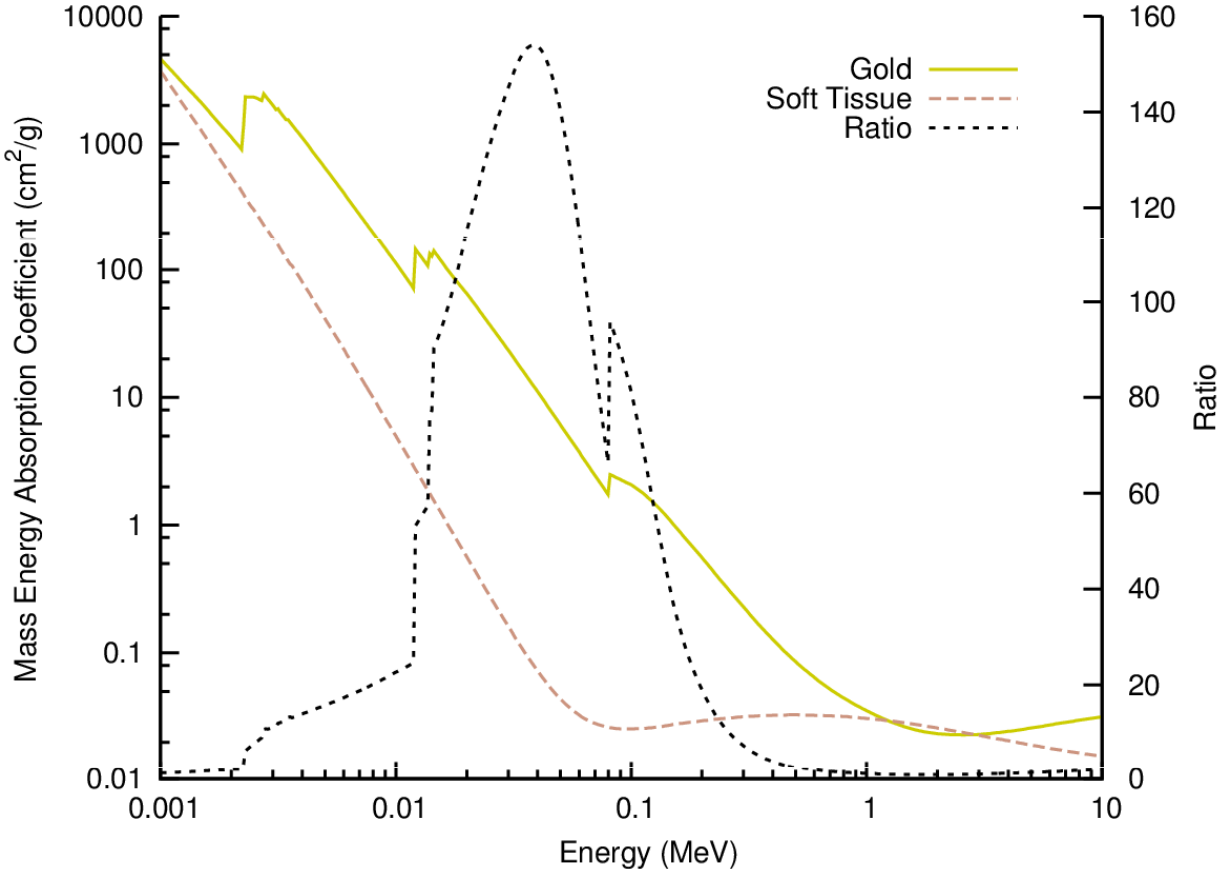






Hainfeld, J. F., et al. "Gold nanoparticles: a new X-ray contrast agent." *British Journal of Radiology* 79.939 (2006): 248-253.

Nanoparticle/Radiation Modelling – Macroscopic Dose

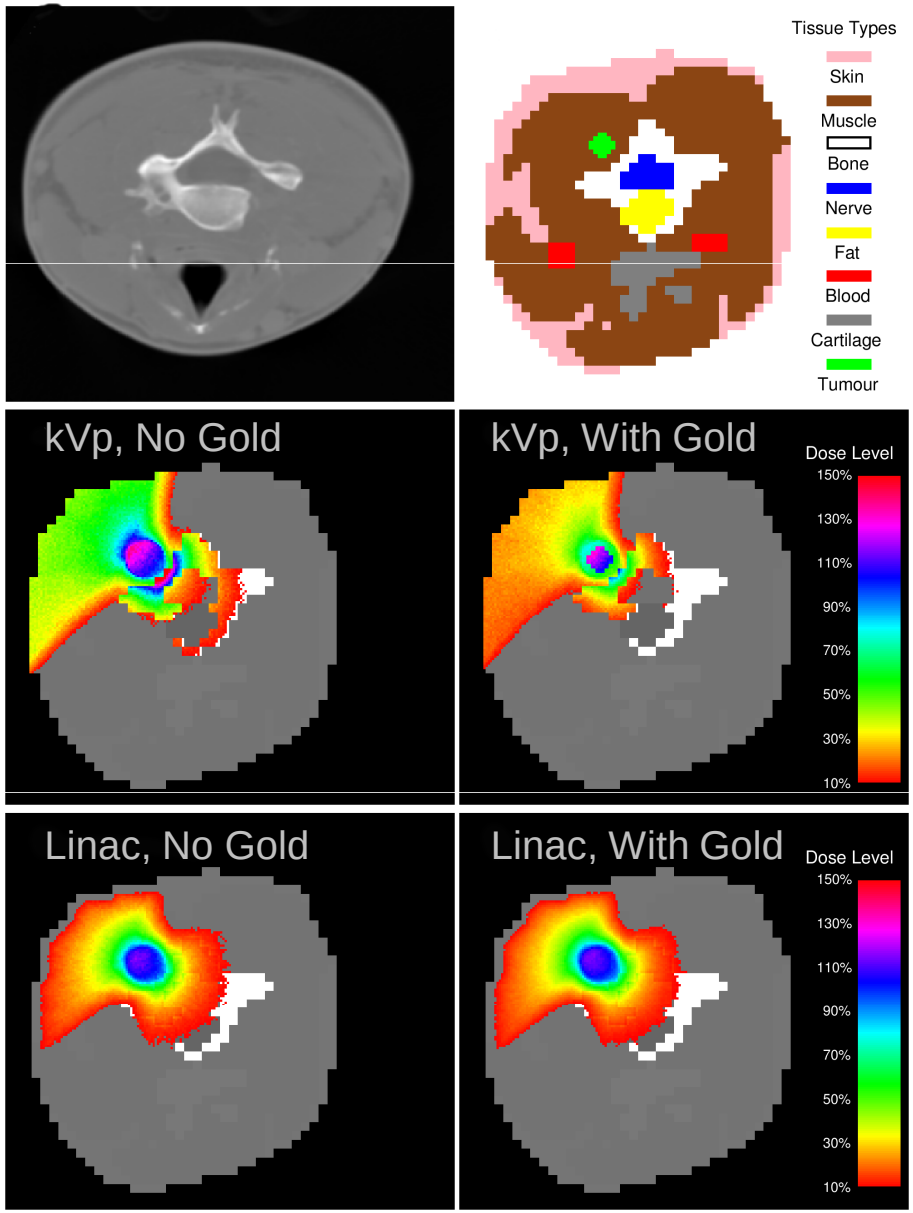


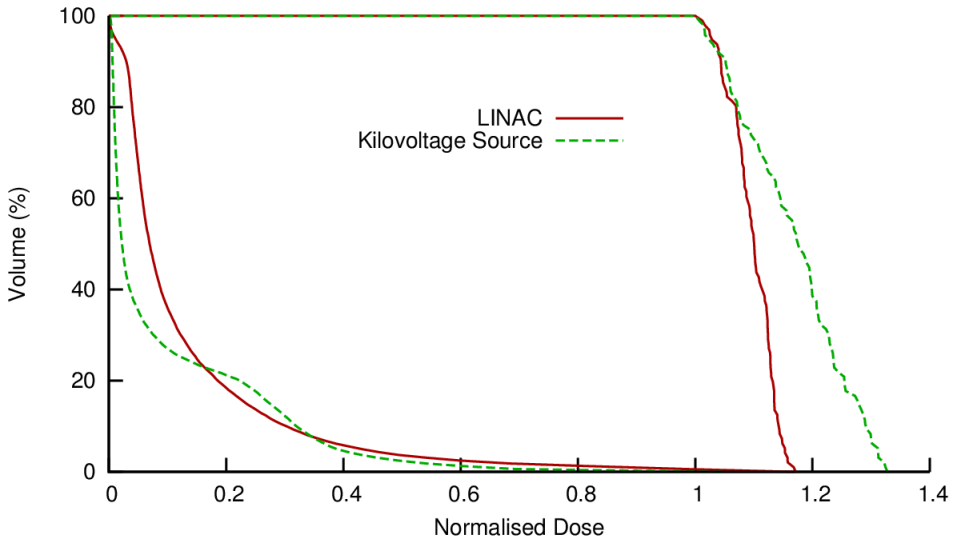
"Back of the envelope"

Assume contrast agent (e.g. gold) is homogeneously distributed throughout target volume. Then, dose enhancement is:

$$DEF = \frac{D_{Tissue+Au}}{D_{Tissue}} \approx \frac{\mu_{Tissue+Au}}{\mu_{Tissue}}$$

Nanoparticle/Radiation Modelling – Macroscopic Dose





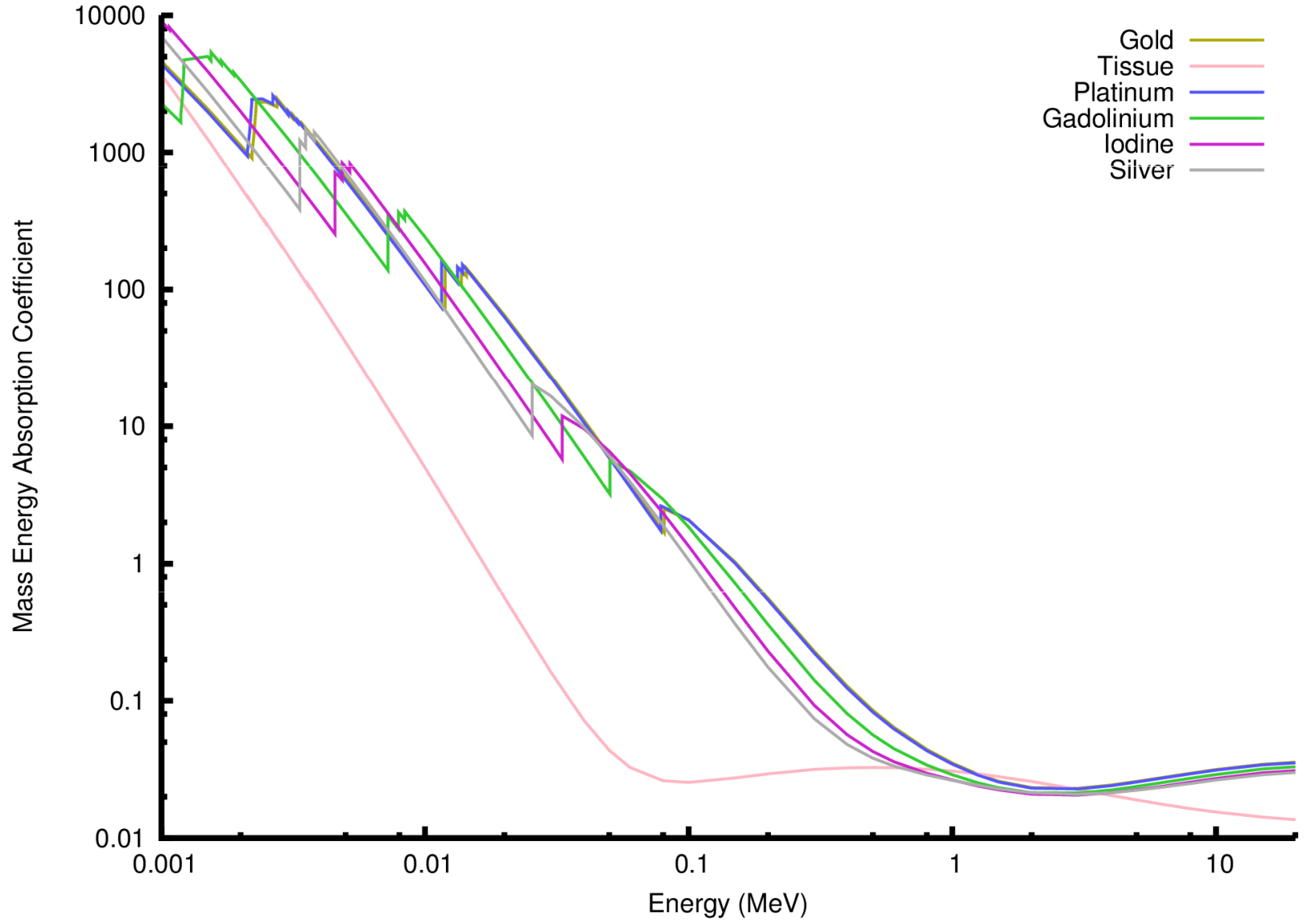
McMahon, S. J., Mendenhall, M. H., Jain, S., & Currell, F. (2008). Radiotherapy in the presence of contrast agents: a general figure of merit and its application to gold nanoparticles. *Physics in medicine and biology,* 53(20), 5635.

Material Optimisation

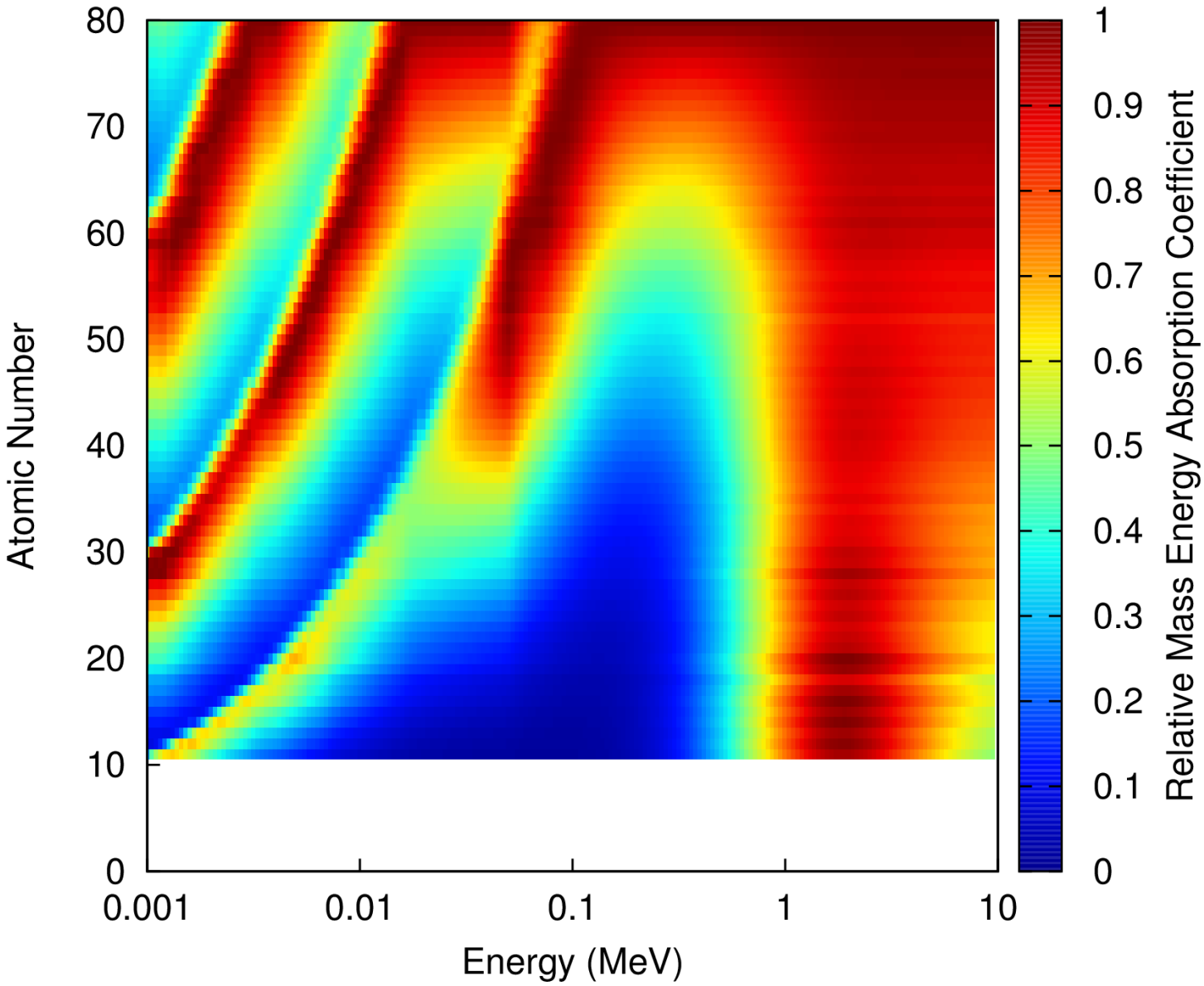
Basic models clearly show that high-Z elements can yield significant improvements in dose deposition, driven by high mass energy absorption coefficients. However, an obvious question:

What Element is Best?

Material Optimisation



Material Optimisation - Photons

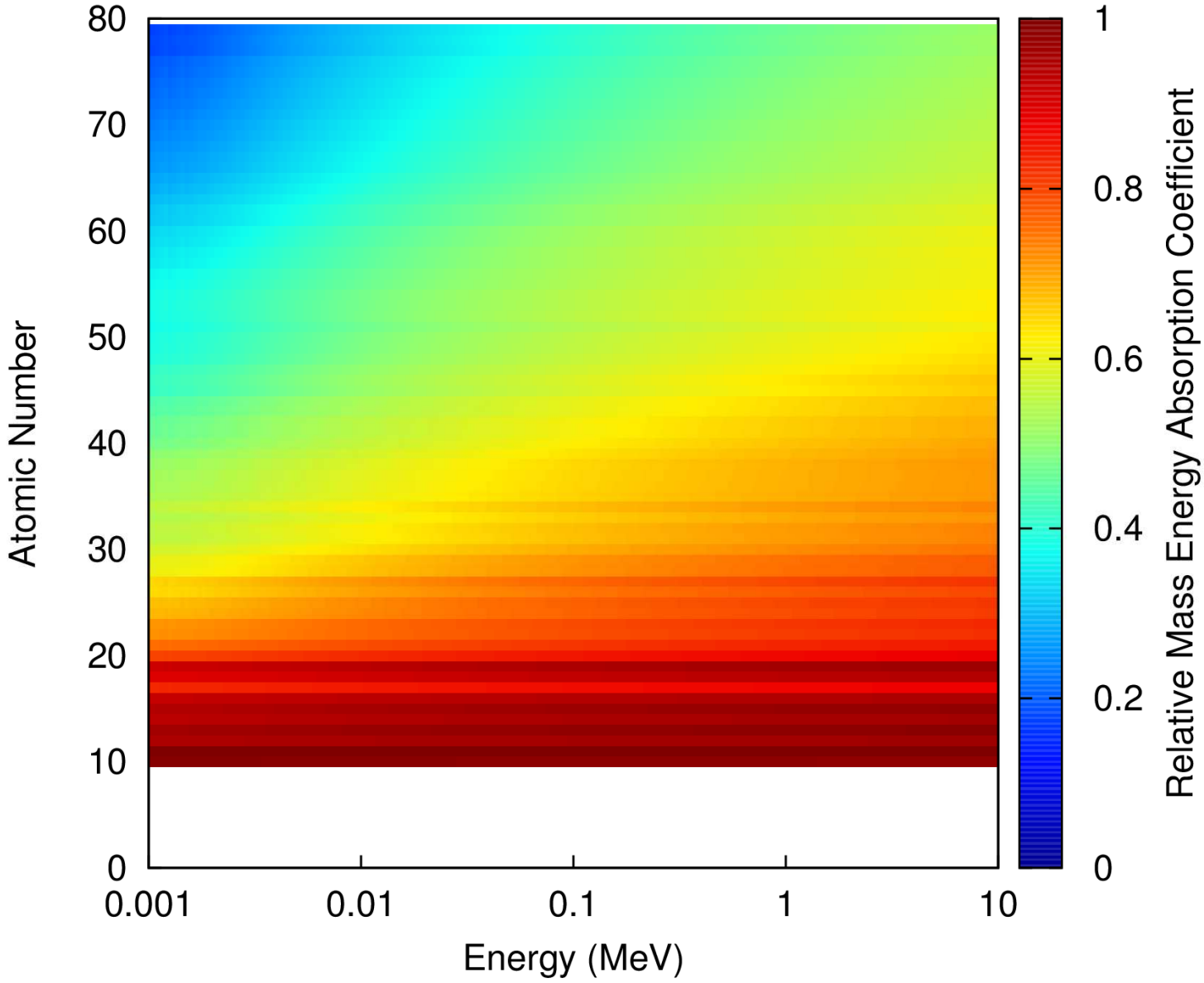


Material Analysis

At each energy, normalise mass energy absorption coefficients to maximum element at that value, investigate distribution.

At most energies, above Z~50, less than a factor of 2 difference in absorption ratios – easily outweighted by other biological or physical factors.

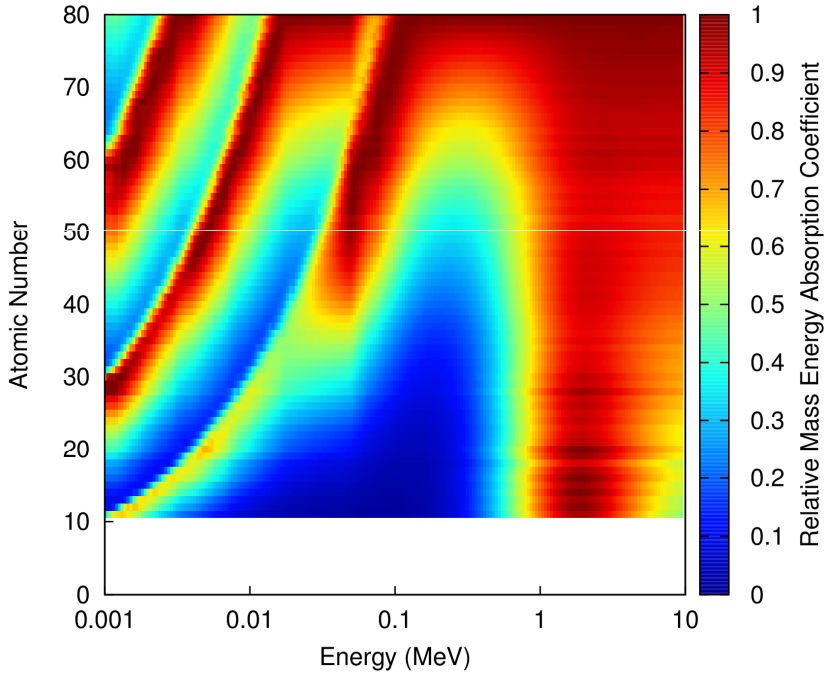
Material Optimisation - Electrons

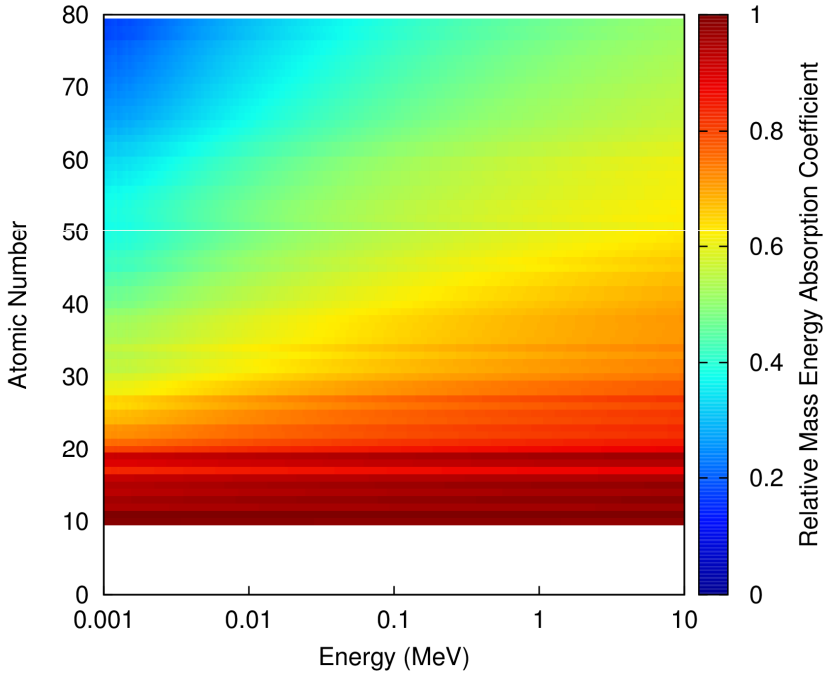


Material Analysis

Even more striking for electrons – while lower Z materials have a better stopping power than higher Z, this is never greater than a factor of 2 except at the very lowest energies and highest atomic numbers.

Macroscopic Dose Summary





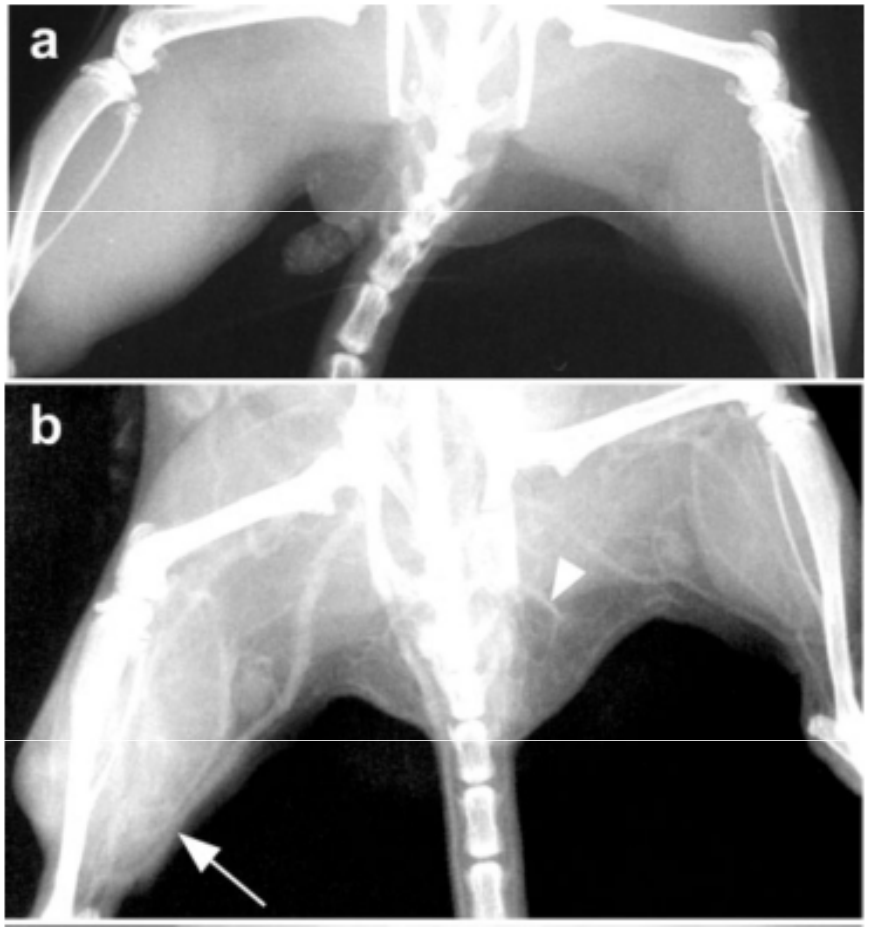
Simple models of high-Z atomic number contrast through increased absorption suggest good results may be achieved through the use of a range of contrast agents with Z>~50, but that optimisation above this is limited, and overall effect is small at megavoltage energies.

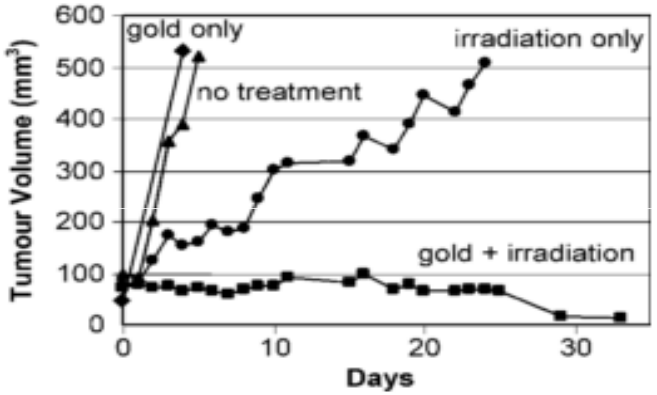
Biological Comparisons

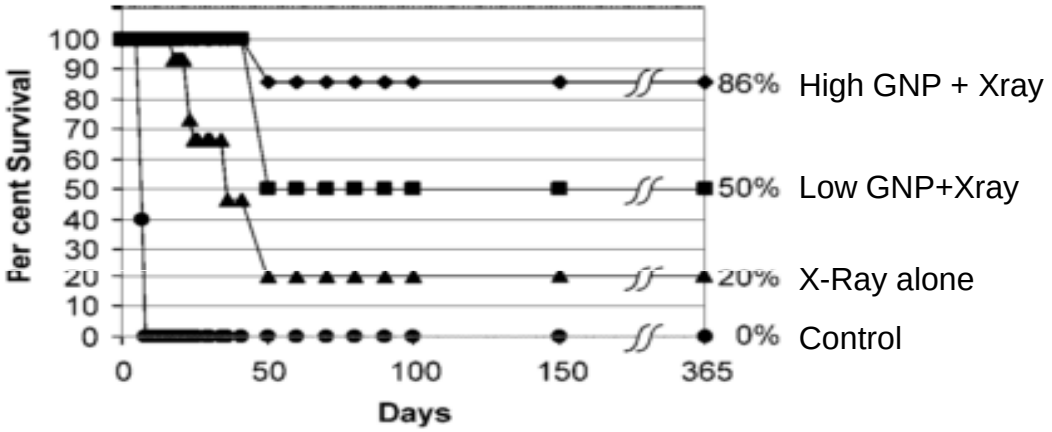
Material attenuation-based analysis suggests that there is significant potential for enhancement in cases where high-Z nanoparticles are combined with exposure to ionising radiation.

But: Does this actually translate into biological effects?

in vivo Validation



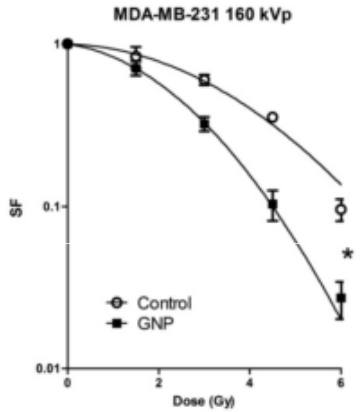


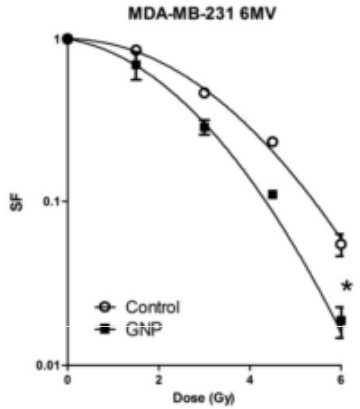


Combination of 0.7% by mass GNPs with 26 Gy of 250 kVp irradiation in mice produced dramatic improvements in tumour control.

Hainfeld, J. F., Slatkin, D. N., & Smilowitz, H. M. (2004). The use of gold nanoparticles to enhance radiotherapy in mice. *Physics in medicine and biology,* 49(18), N309.

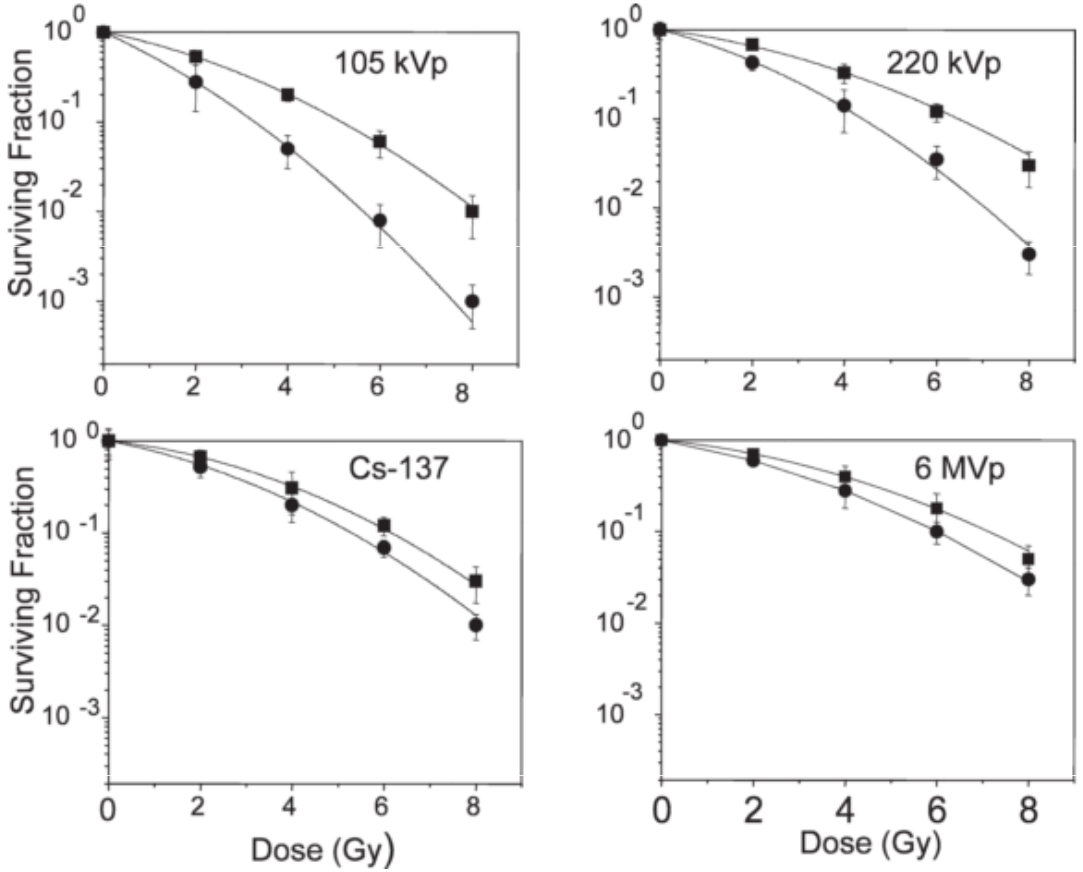
in vitro Sensitisation





Sensitisation by 500 ug/mL of 1.9 nm GNPs in MDA-231 cells.

Jain, S., et al, (2011). Cell-specific radiosensitization by gold nanoparticles at megavoltage radiation energies. *International Journal of Radiation Oncology* Biology* Physics,* 79(2), 531-539.



Sensitisation by exposure to ~10 ug/mL of 50 nm GNPs in HeLa cells.

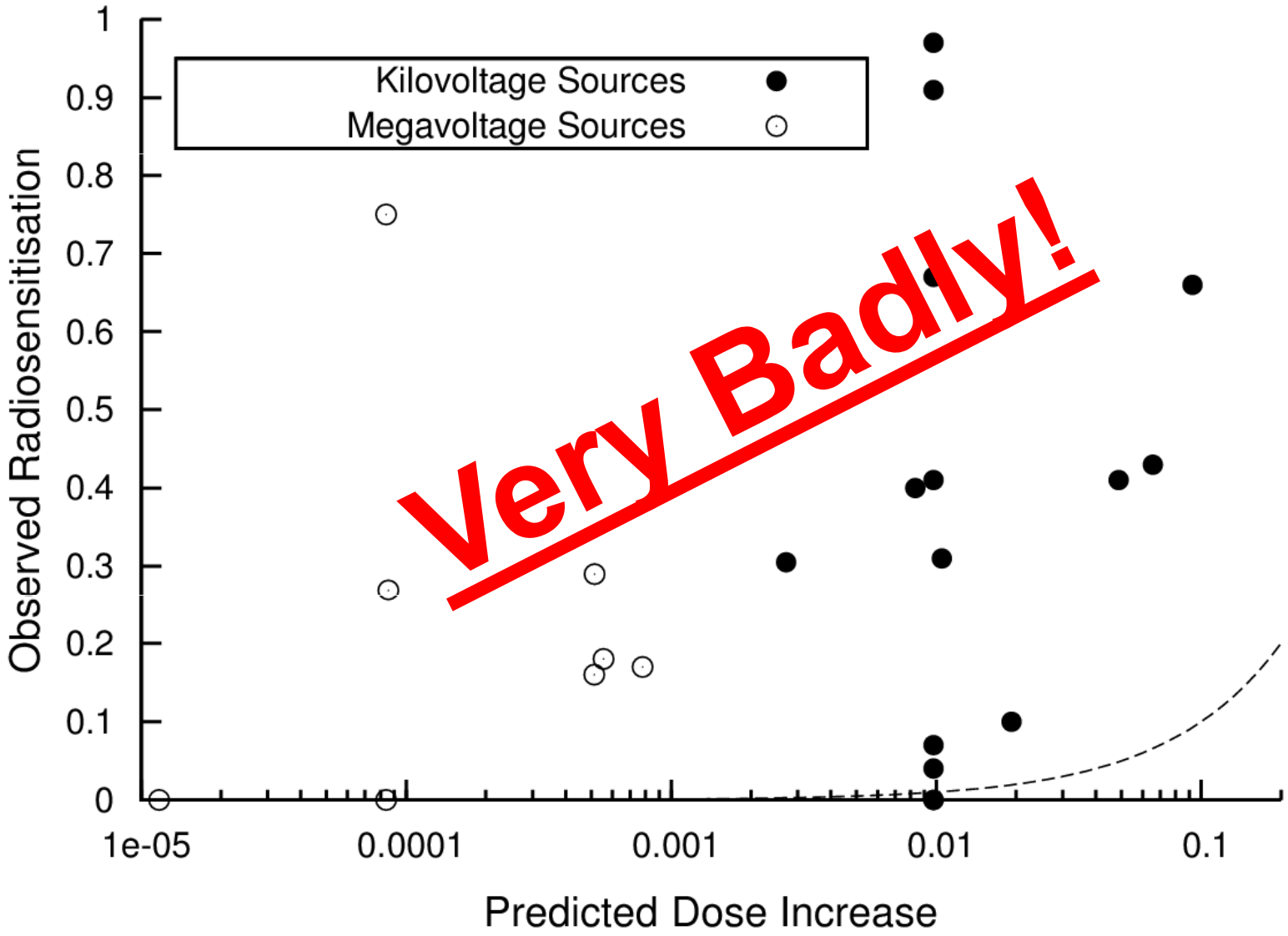
Chithrani, D. B. et al, (2010). Gold nanoparticles as radiation sensitizers in cancer therapy. *Radiation research*, 173(6), 719-728.

in vitro Quantification

Author	Size (nm)	Concentration	Surface coating	Cell model	Source energy	Observed SE
Geng *et al.*	14	5 nM	Glu	SK-OV-3	90 kVp	1.3
					6 MV	1.2
Jain *et al.*	1.9	12 μM	Thiol	DU-145	160 kVp	<1.41
				MDA-231MB	6 MV	<1.29
				L132	15 MV	1.16
					6 MeV e^-	<1.12
					16 MeV e^-	1.35
Chithrani *et al.*	14	1 nM	Citrate	HeLa	220 kVp	1.17–1.6
	74				6 MV e^-	
	50				662 keV	
Lui *et al.*	6.1	>1 mM	PEG	CT-26	6 keV e^-	2
				EMT-6	160 kVp	1.1
					6 MV	1
Butterworth *et al.*	1.9	2.4 μM	Thiol	DU-145	160 kVp	<1
		0.24 μM		MDA231MB		<1.67
				AG0-1522		<1.97
				Astro		<1.04
				L132		<1
				T98G		<1.91
				MCF-7		<1.41
				PC-3		<1.07
Kong *et al.*	10.8	15 nM	Glu	MCF-7	200 kVp	1.3
			AET	MCF-10A	662 keV	1.6
					1.2 MV	
Rahman *et al.*	1.9	<1 mM	Thiol	BAEC	80 kV	20
					150 kV	1.4
					6 MV e^-	2.9
					12 MV e^-	3.7
Roa *et al.*	10.8	15 nM	Glu	DU-145	662 keV	>1.5
Zhang *et al.*	30	15 nM	Glu	DU-145	200 kVp	>1.3
			TGS			>1.5
Chang *et al.*	13	11 nM	Citrate	B16F10	6 MV e^-	1
Chien *et al.*	20	<2 mM	Citrate	CT-26	6 MV e^-	1.19

Butterworth, K. T., McMahon, S. J., Currell, F. J., & Prise, K. M. (2012). Physical basis and biological mechanisms of gold nanoparticle radiosensitization. *Nanoscale*, 4(16), 4830-4838.

How well does absorption explain these effects?



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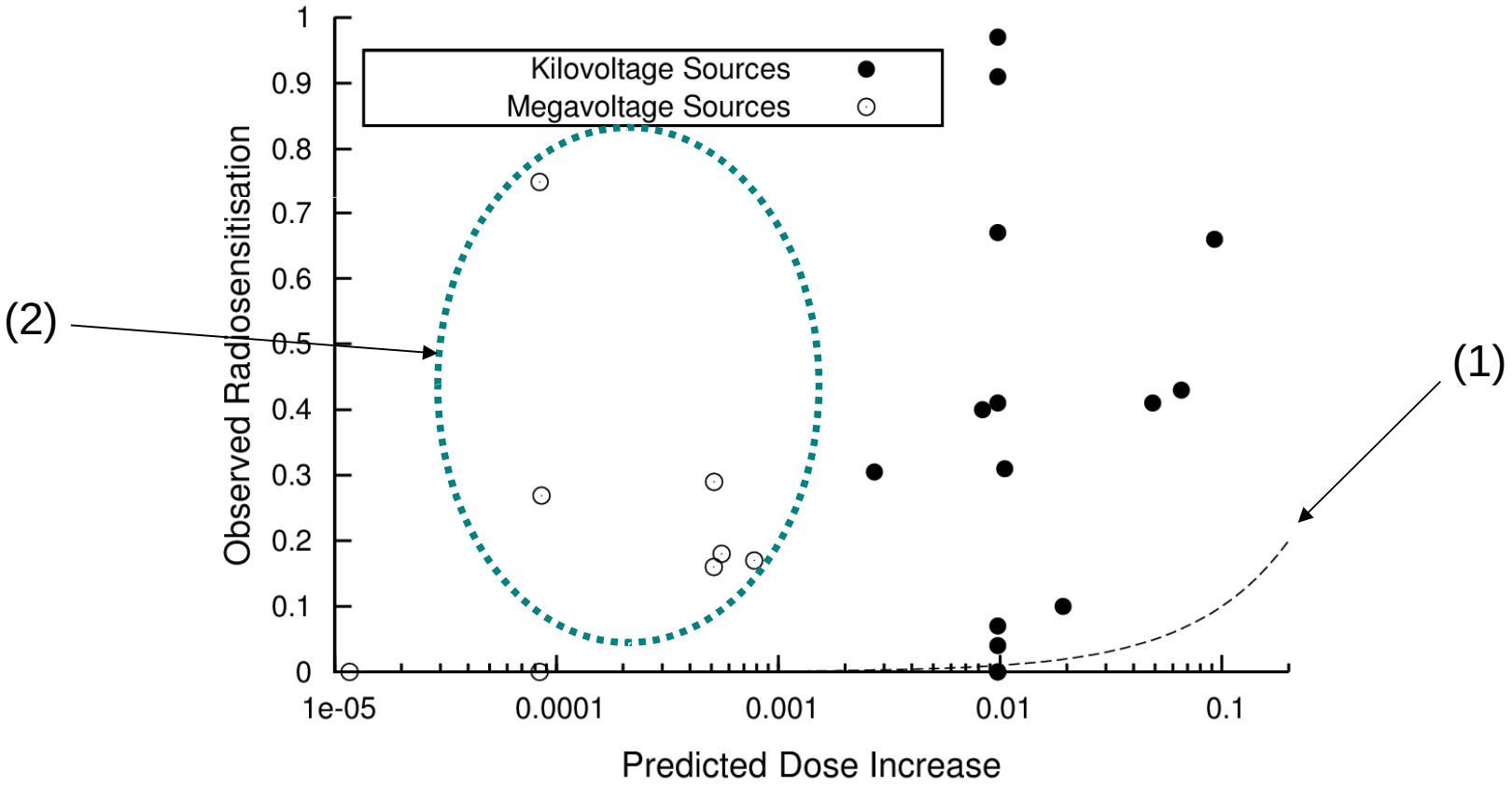


Two key discrepancies in this data:
1) Observed sensitisation is significantly higher than predicted, in almost all cases;
2) Significant sensitisation is observed even at MeV energies;
Clearly, simple macroscopic dose model does not fully describe this system.

Sources of Disagreement

From a macroscopic mass attenuation point of view, different sources of high-Z material are relatively interchangeable. But in reality, numerous experimental characteristics differ:

- Nanoparticle size (~2-100 nm)
- Concentration
- Elemental Chemistry
- Surface Coating
- Cell Type
- Beam Energy

Clearly, some or all of these characteristics are impacting on observed biological outcomes, suggesting additional mechanisms not included by macroscopic dosimetry.

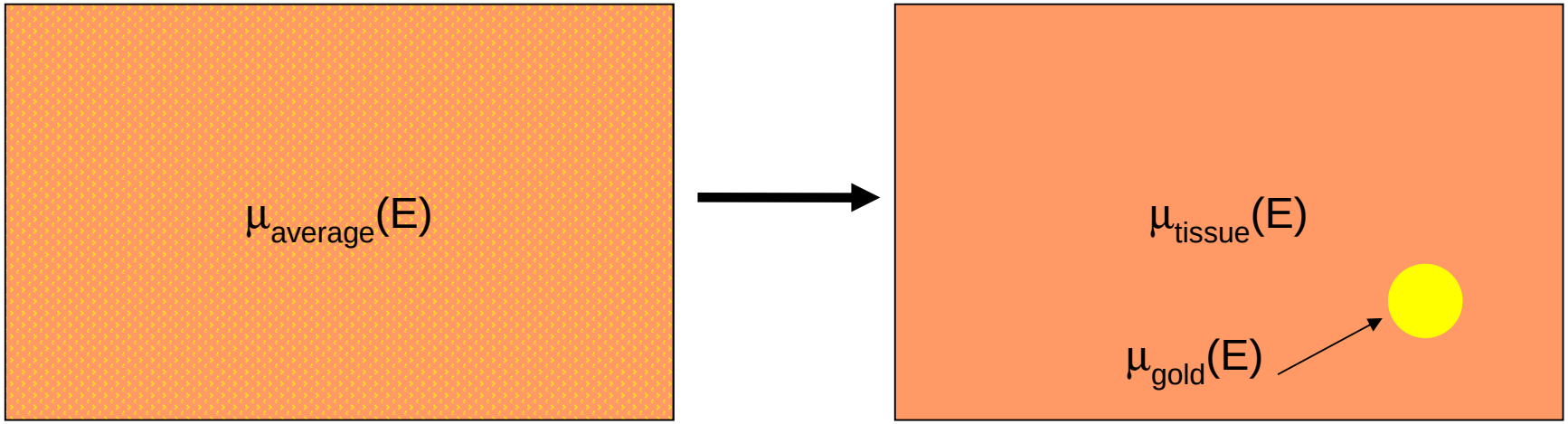
Potential Mechanisms

Macroscopic dosimetry is clearly insufficient to describe these effects, so some other factors must be involved, such as:

- The physical impact of nanoparticles on the dose distribution is not well-reflected by the average dose description;
- High-Z nanoparticles modify the down-stream effects which follow exposure to ionising radiation;
- Some nanoparticle preparations are not chemically inert and act as an additional source of biological stress;
- Nanoparticles are not as biocompatible as originally predicted, and alter cell's function in some fashion which leads to sensitisation.

(Or: All of the above, to some degree?)

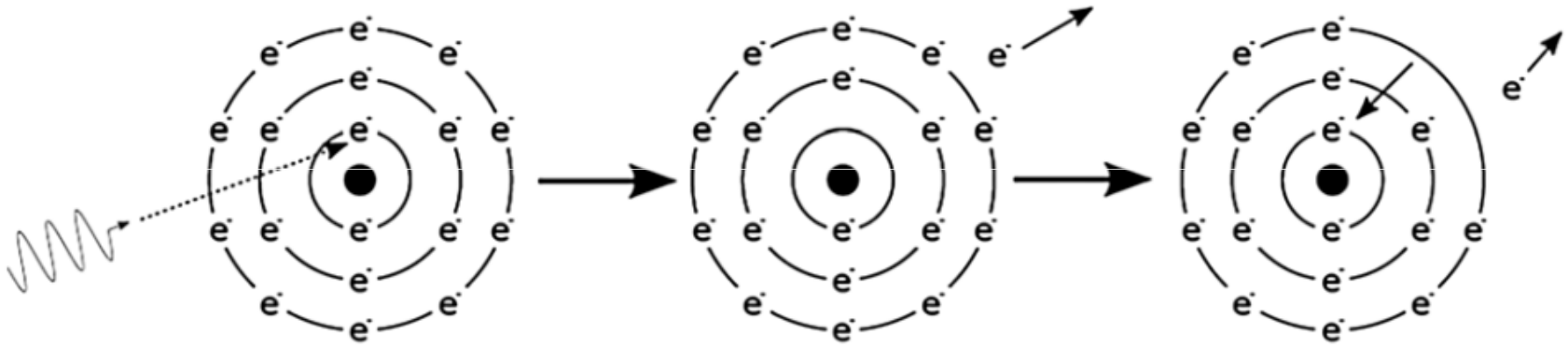
Physical Differences



Macroscopic dose models implicitly assume that atoms are uniformly distributed throughout the volume, giving uniformly escalated dose enhancement. However, nanoparticles give discrete regions containing very large numbers of a high-Z atom, embedded within surrounding tissue volumes.

This would be expected to significantly change their dosimetric impact.

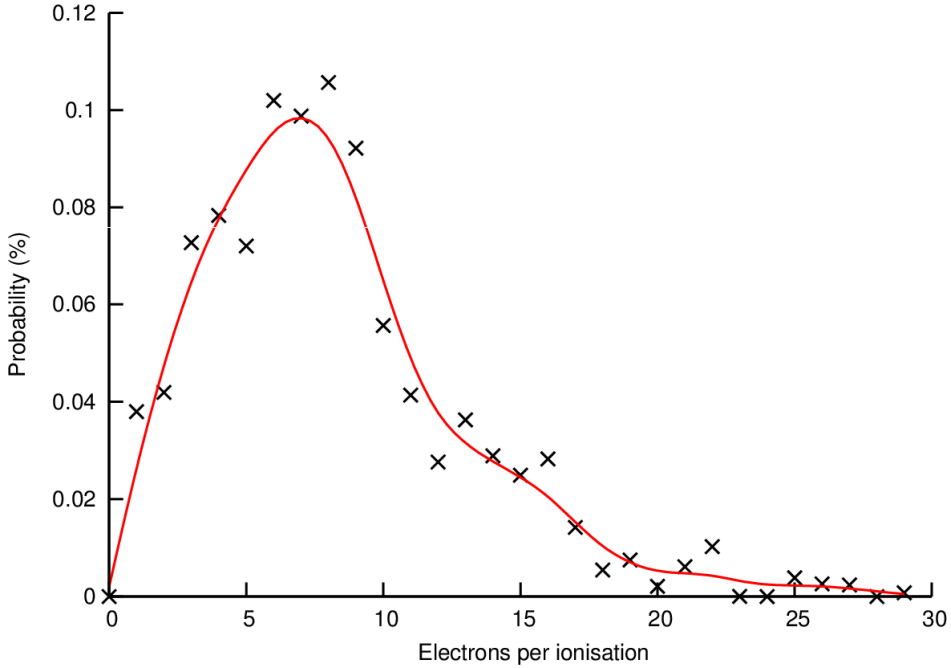
Auger Cascades



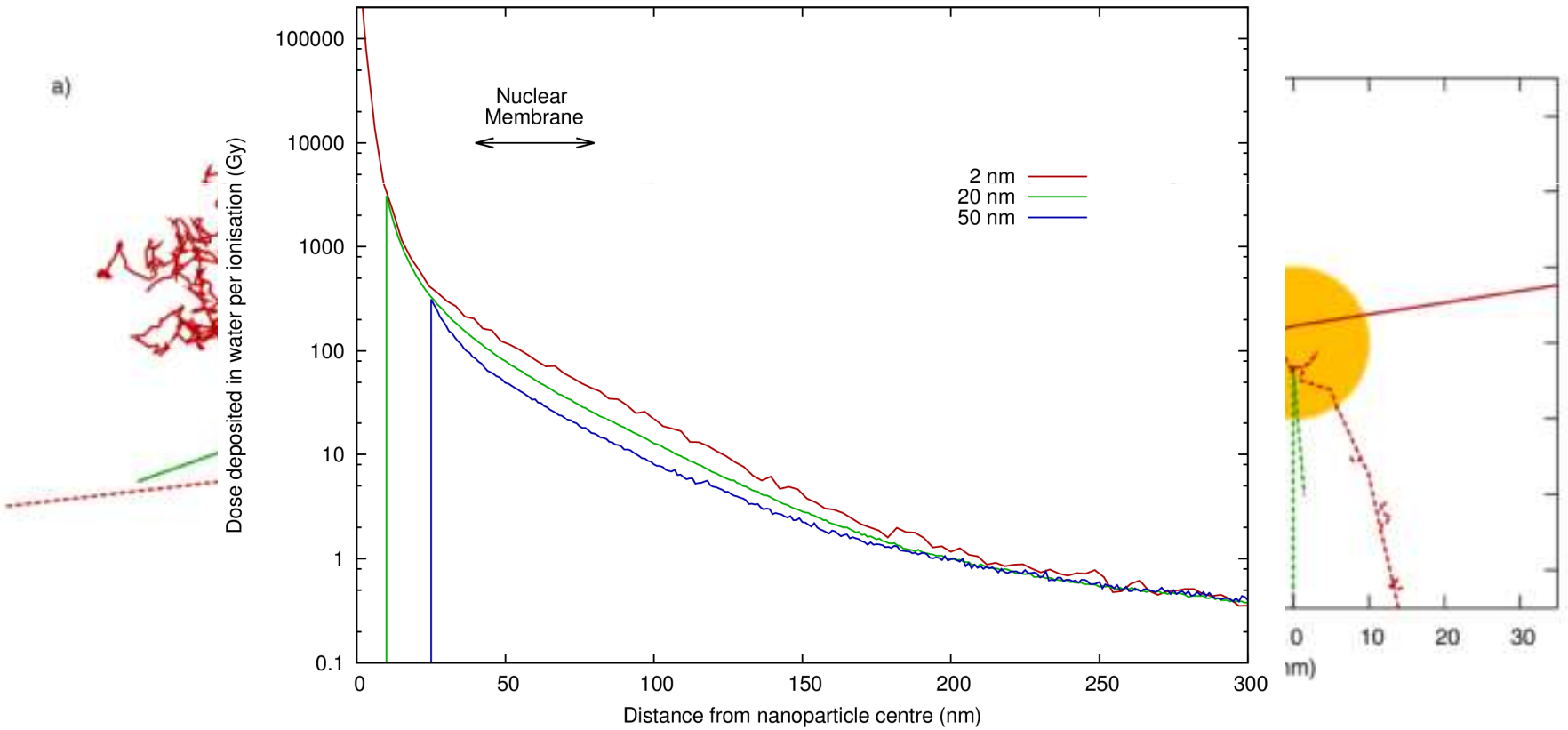
Photoionisation

Auger

For high-Z atoms, this is further exacerbated by Auger cascades, where large numbers of low-energy secondary electrons can be generated following a single ionisation, yielding high, localised doses.

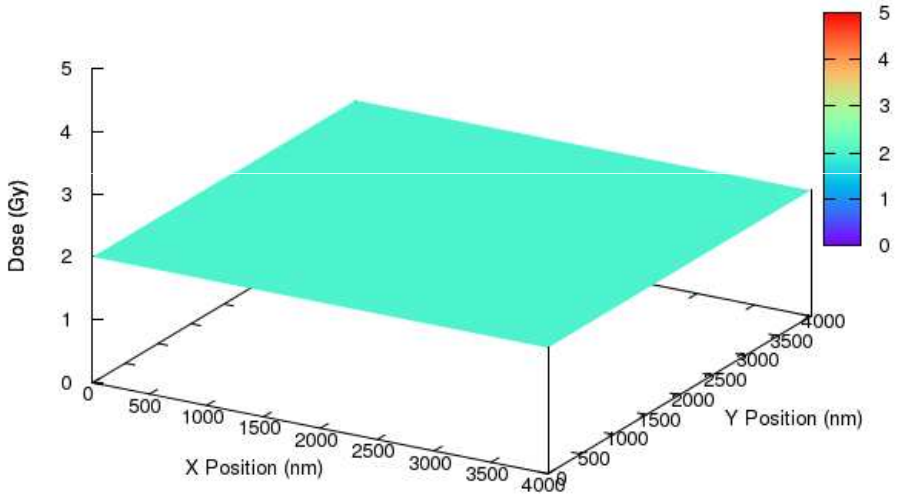


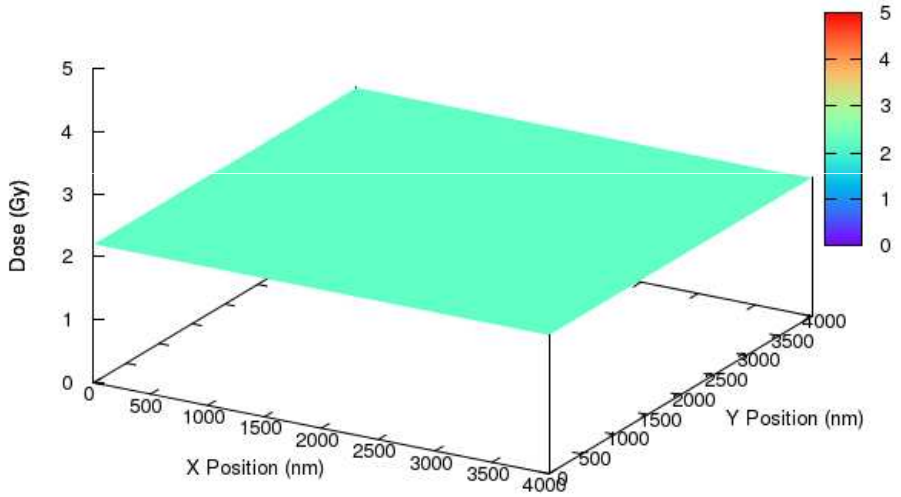
Dose Localisation



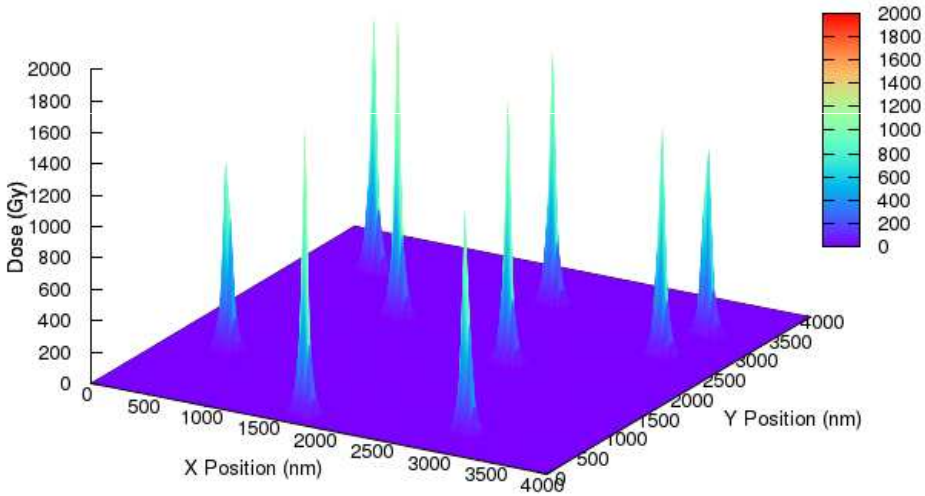
Together, these effects mean that nanoparticles tend to act as highly localised sources of dose within a cell, rather than the sparsely distributed ionisations typically seen in X-ray based therapies.

Dose Localisation





This leads to sharp dose discrepancies which are very different to uniform dose escalation in X-rays, and much more similar to the addition of an ion-like dose distribution.

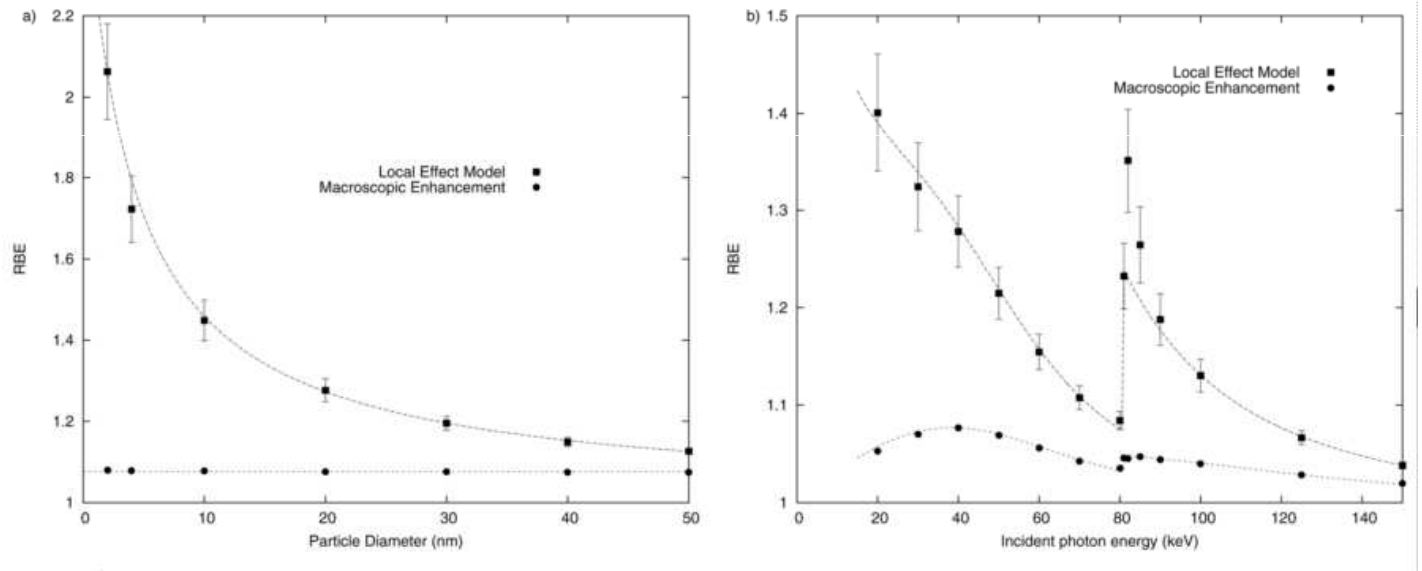


Local Effect Model (LEM)

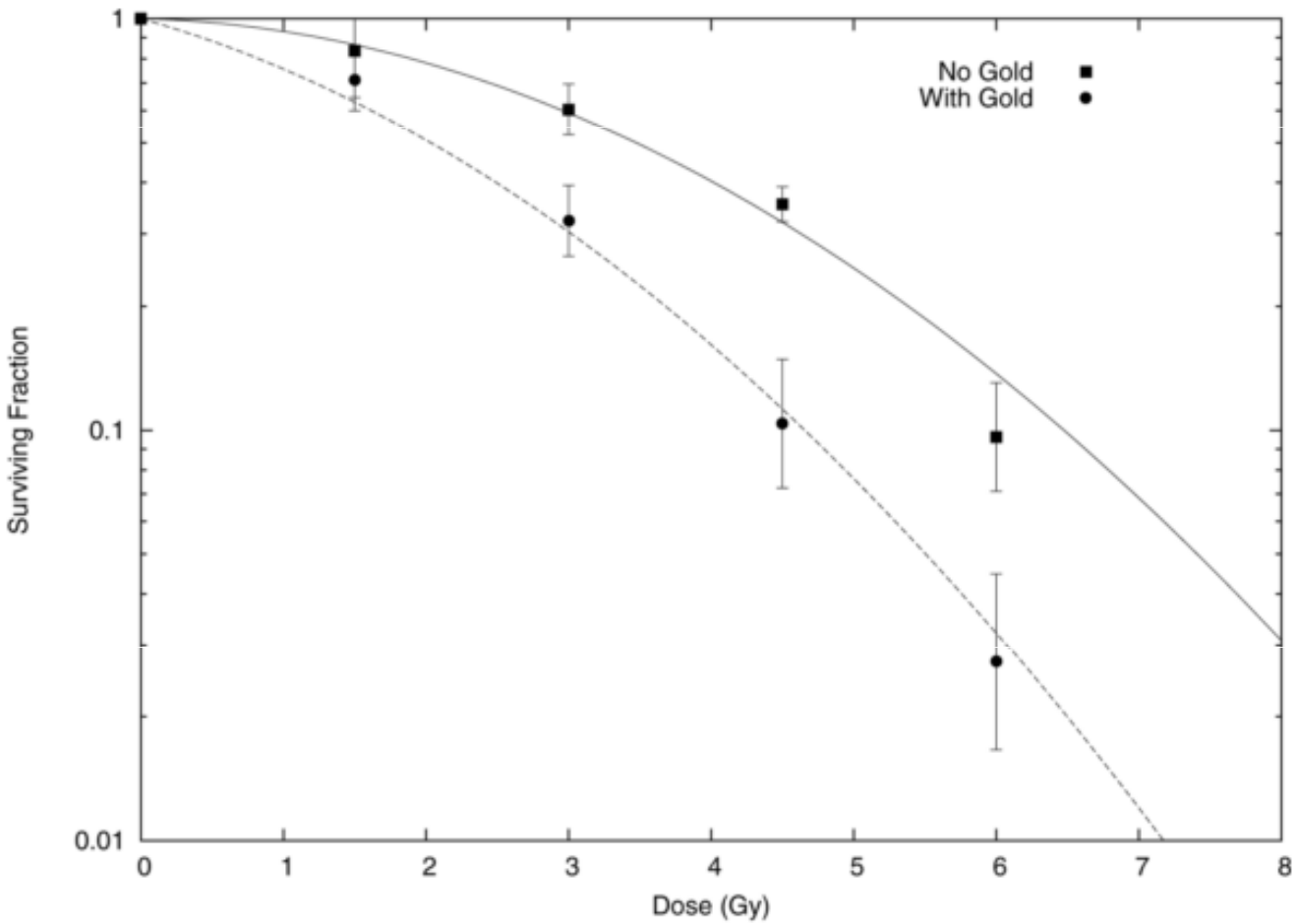
These doses are very similar to those deposited around ion tracks, which are known to have a high RBE. This suggests that models applied to describe ion's high RBE may be applicable here.

$$S_x(D) = e^{-N_x(D)}, \qquad v_x(D) = \frac{N_x(D)}{V},$$

$$N_{\text{ion}} = \int_{V_{\text{nucleus}}} dV\, v_{\text{ion}}[d(x,\ y,\ z)], \qquad N_{\text{ion}} = -\int_V dV\, \frac{\ln S_x[d(x,\ y,\ z)]}{V}.$$



Local Effect Model (LEM)



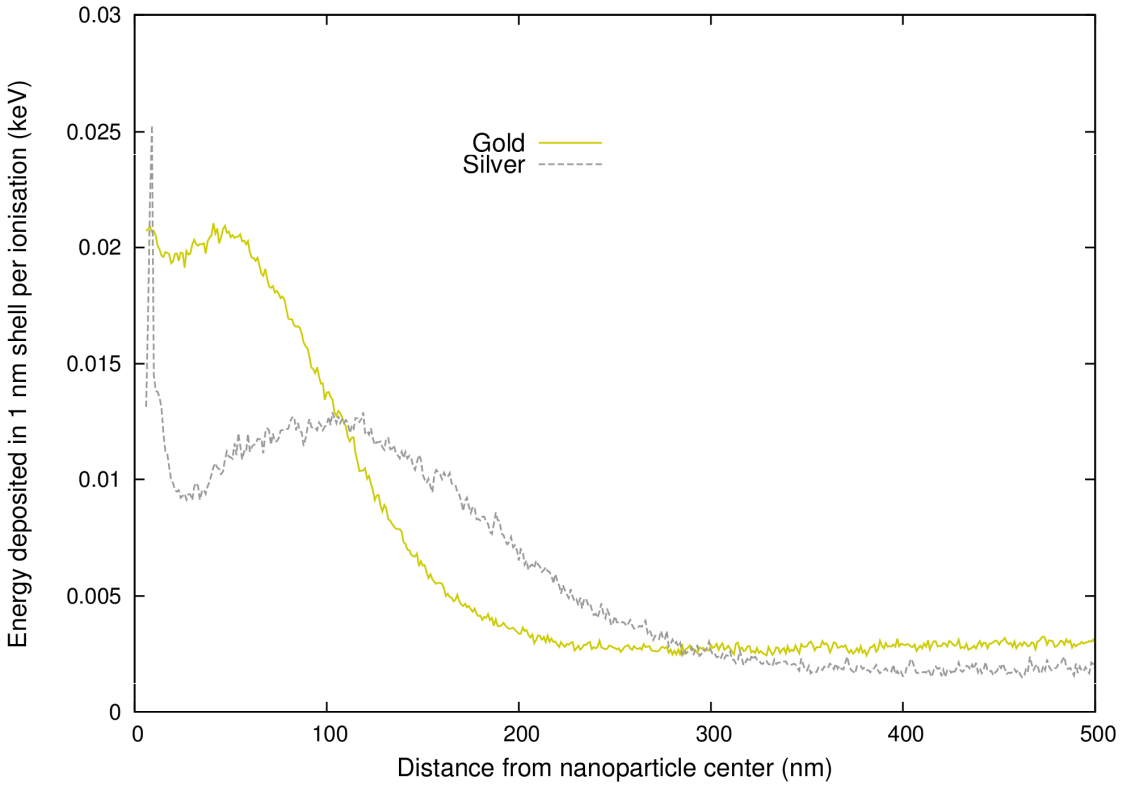
In some cell lines, this appears to resolve the discrepancy between experimentally observed sensitisation and theoretical predictions.

Left: Radio-sensitising effect of 1.9 nm GNPs in MDA-231 cells under 160 kVp exposure, compared to LEM theoretical predictions.

Does not fully rule out contributions from other effects, however.

McMahon, S. J., et al. (2011). Biological consequences of nanoscale energy deposition near irradiated heavy atom nanoparticles. *Scientific reports*, 1.

Atomic Number and Nanodosimitery



While mass energy attenuation coefficients may be controlled for, nanodosimetric effects add a further degree of complication.

Despite large differences in atomic number, gold and silver both deposit roughly the same energy (~20 keV) in short-range ionisations, with different distributions.

Currently very little investigation in this area, which may prove important depending on different localisation characteristics.

Outstanding Questions

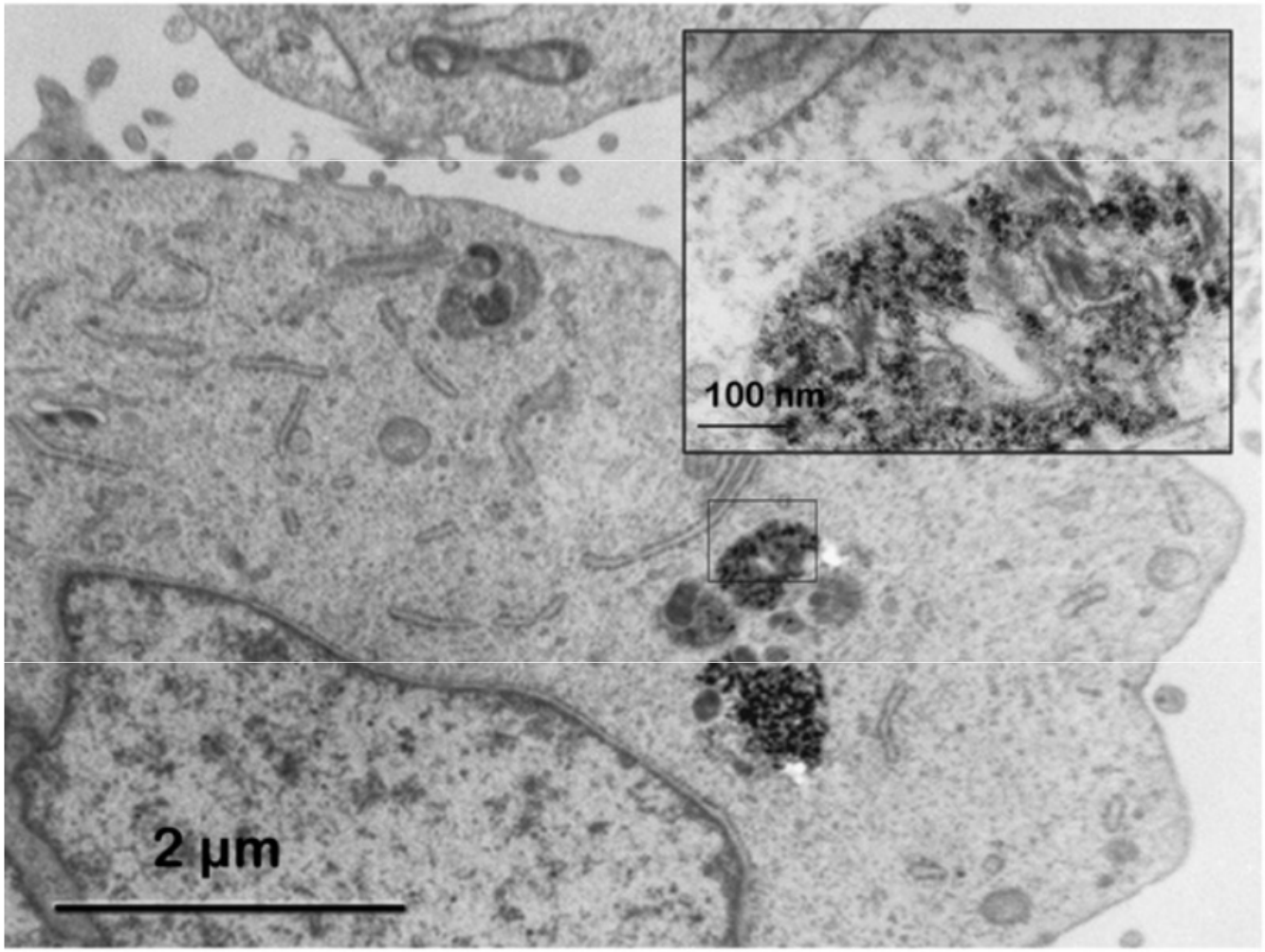
Nanoparticle effects, both in gold and other elements, are very poorly described by macroscopic dose models.

While nanodosimetric models may contribute in part to explaining these effects, a number of questions must be addressed before they can be fully validated and understood.

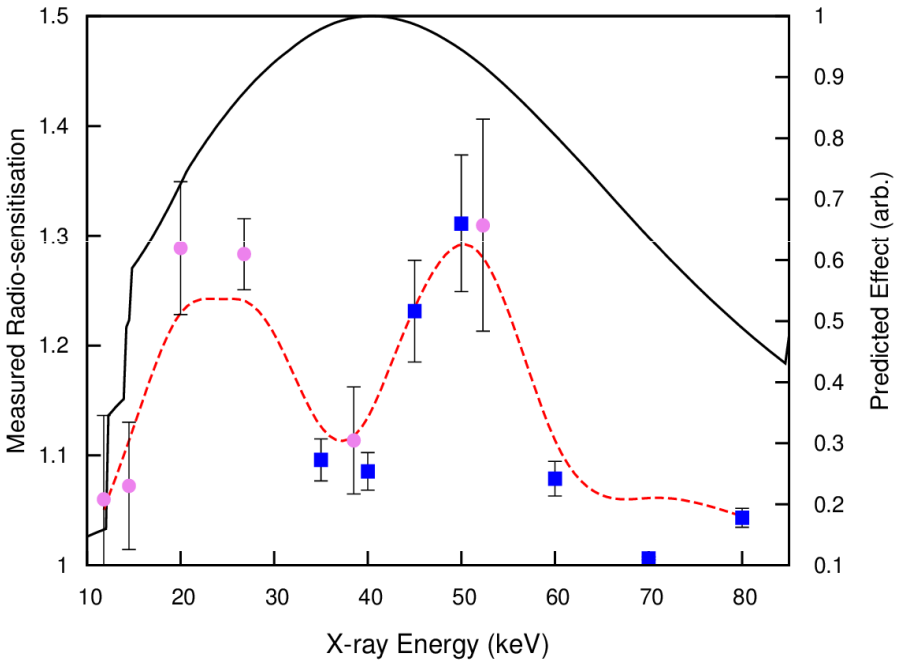
Uptake & Localisation

Nanoparticle uptake is also a very complex issue. Uptake in both tumour and cells depend on particle type, coating and size, and may have conflicting requirements.

Sub-cellular localisation may also need to be optimised, as many nanoparticle preparations are localised in sub-cellular compartments, which may affect their resulting effects.



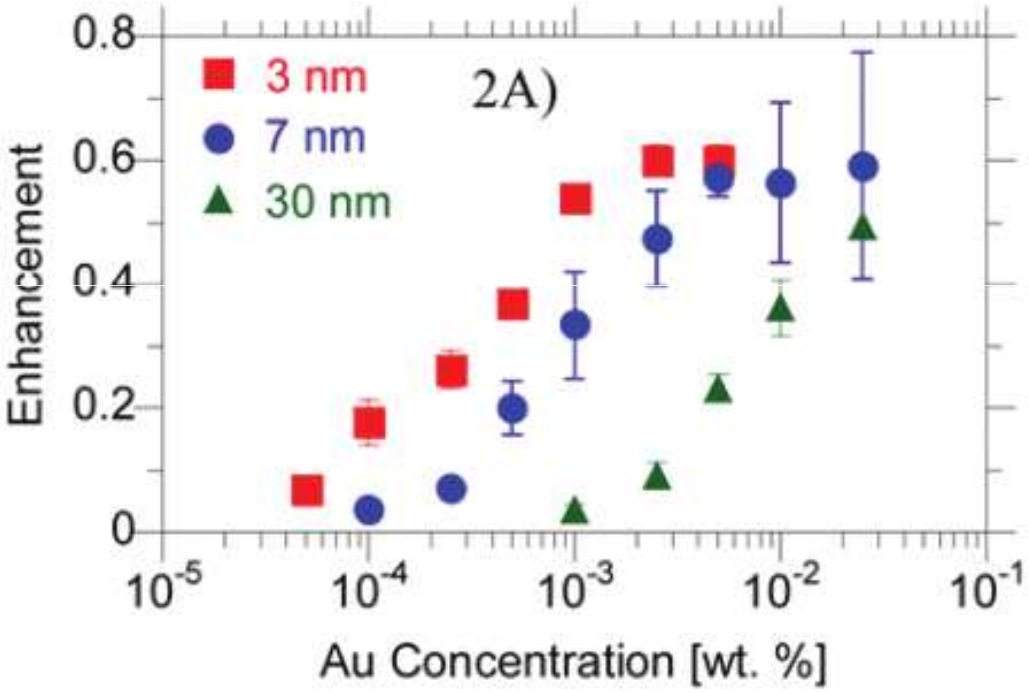
Impact on Radiochemistry



Above: Impact of GNPs on damage in plasmid DNA when exposed to monoenergetic X-rays *(See: Poster M44)*

McMahon, S. J., et al. (2011). Energy dependence of gold nanoparticle radiosensitization in plasmid DNA. *The Journal of Physical Chemistry C*, 115(41), 20160-20167.

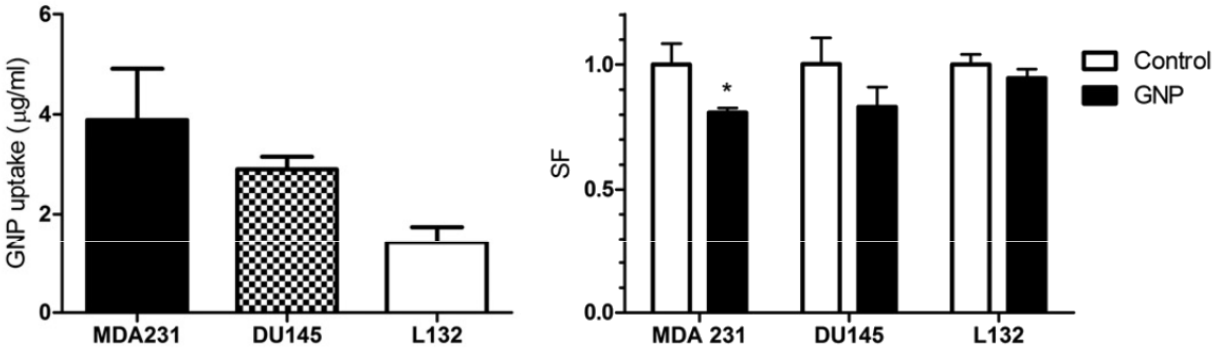
Nanoparticles are known to have complex chemical effects not seen on the macroscale. This may cause significant shifts in downstream radio-chemistry, e.g. hydroxyl radical production.



Right: Impact of GNPs on OH radical production following X-ray exposure.

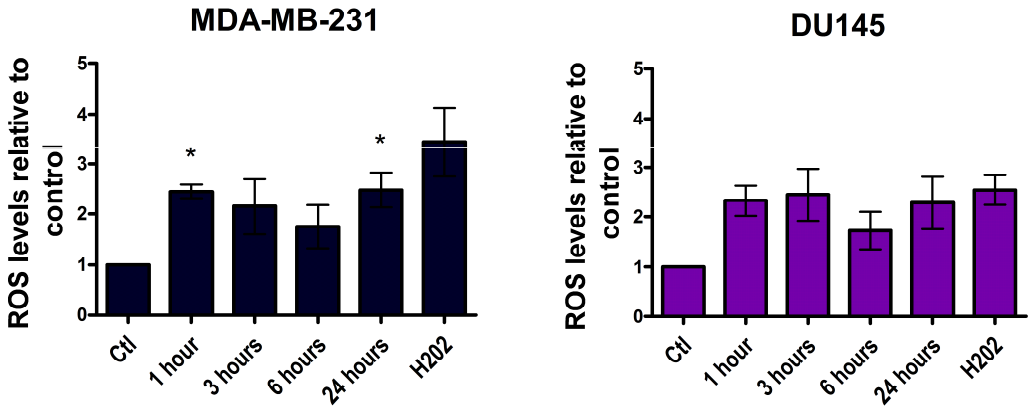
Cheng, N. N., et al, (2012). Chemical Enhancement by Nanomaterials under X-ray Irradiation. *Journal of the American Chemical Society,* 134(4), 1950-1953.

Toxicity & Altered Biology



Reduction in clonogenic survival induced by 500 ug/mL of 1.9 nm GNPs, in the absence of radiation.

Jain, S., et al, (2011). Cell-specific radiosensitization by gold nanoparticles at megavoltage radiation energies. *International Journal of Radiation Oncology* Biology* Physics,* 79(2), 531-539.



Persistent induction of Reactive Oxygen Species by the addition of 500 ug/mL of 1.9 nm GNPs.

(See Poster W31)

There is also good evidence that even simple metallic nanoparticles are not biologically inert. Alone, some particles have been shown to induce DNA damage and oxidative stress, which may cause apparent radiosensitisation.

Conclusions

It is becoming increasingly clear that many of the fundamental assumptions which promoted the early study of nanoparticle-radiation interactions are, at best, incomplete.

However, in many cases this appears to be a positive factor, as the observed degree of sensitisation appears to be in many cases greater than predicted by simple models, particularly in clinically-relevant MeV exposures.

While this means that nanoparticles may be viable radio-sensitisers in a wider range of contexts, it leaves many open questions which must be answered before a robustly optimised nanoparticle-bsed clinical protocol could be developed.

Questions...

- How significant is the inhomogeneous nature of physical dose deposition, and how does this impact on clinical applicability at varying energies?
- In light of increasing evidence that nanoparticles have complex chemical and biological activity, what are the underlying mechanisms of these effects?
- How can nanoparticles be optimised in terms of composition, size and coating to maximize the achieved sensitisation by these mechanisms?
- What is the best delivery mechanism, and can uptake be optimised to mitigate costs associated with the therapy?
- What are the clinical implications for these agents in a protracted, fractionated treatment, often in combination with other chemical agents?

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