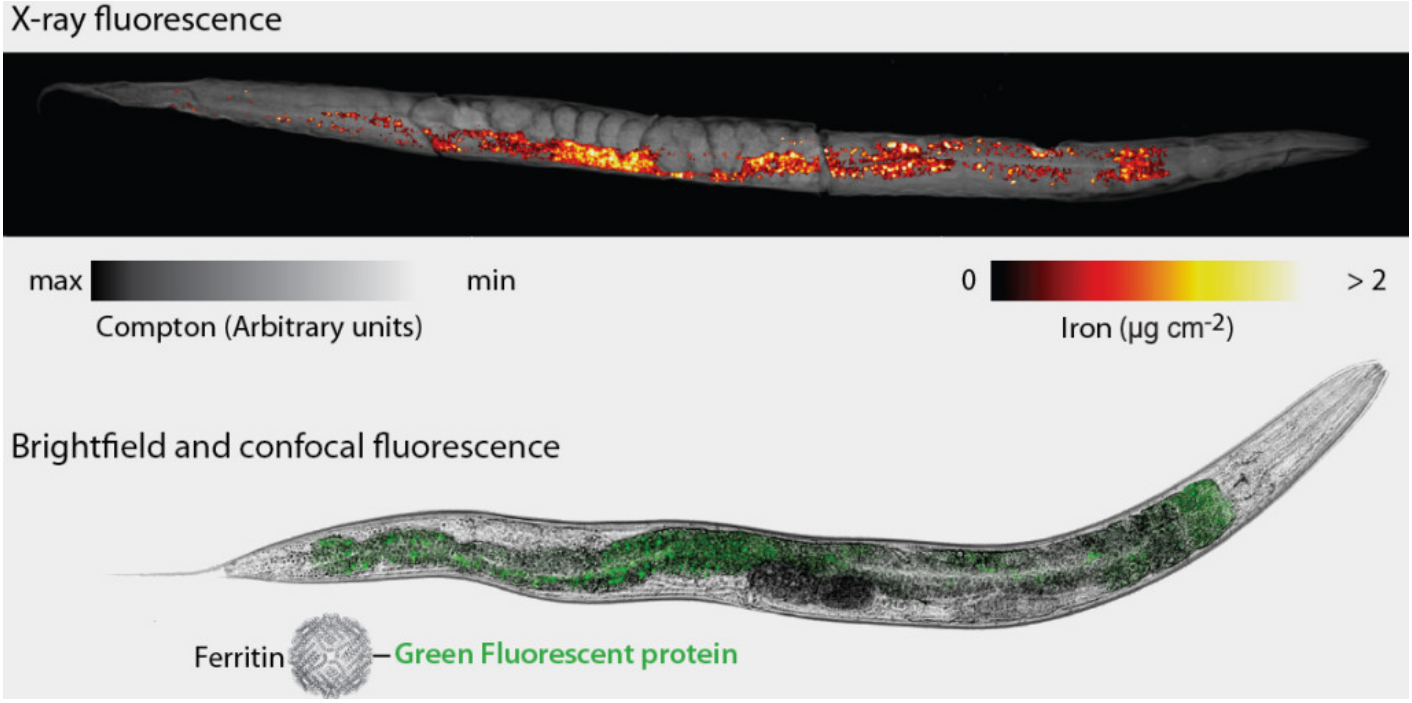
Combining a range of different imaging techniques to better understand the roles metals play in biology

Microscopes in various forms have helped identify disease-causing bacteria, miniaturize microprocessors and engineer superior metal alloys. However, in biology some things remain very difficult to see even at the highest levels of magnification. Metal ions (e.g. calcium, manganese, iron, etc) are essential for living cells to develop and function but can't be seen with normal light. Nearly a third of all proteins in an organism (including bacteria, worms and humans) require a metal partner, or co-factor, to function correctly. These co-factors often help move electrons around for essential chemical reactions and help proteins to adopt a correct structure. Tissues and organs are also comprised of lighter elements such as sulfur, chlorine and potassium, not to mention the building blocks of organic molecules, carbon, nitrogen and oxygen. Being able to see metals ions would greatly help our understanding of the roles that metal ions play in important and fundamental biology. Knowing where and how much of these elements are located in organs and cells will help us better understand their role in health and disease.



Schematic of a multiple imaging approach used to assess and map total element levels (e.g. iron), chemical state and associated protein binding partner(s). In this case we have imaged iron and then ferritin, a protein complex that binds and stored iron, engineered to be linked to green fluorescent protein allowing it to be seen within these nematodes via light microscopy.

In this study we used an intensely bright source of x-rays (at the Australian Synchrotron) to make atoms fluoresce (shine), giving us a finely detailed map in a simple microscopic roundworm, called Caenorhabditis elegans. This work involved collaboration across several disciplines of science, including biology, chemistry and physics. We were able to see elements, from relatively common phosphorous found in nearly all tissues to strontium, a rare element that in vertebrates (animals with back bones) is often incorporated in place of calcium in bones. The image resolution of the elemental maps produced was very fine, less than one-thousandth of a millimeter. This allowed us to compare our images against a centuries old technique for imaging iron. Perls' staining, also called Prussian blue, stains iron on biopsy specimens. Perls' staining, named after its inventor Max Perls (1843-1881, a pathologist from Giessen, Germany), involves a series of chemical reactions and has been a true workhorse for biology and medicine for more than a century. However, this technique only works for iron. Other chemical stains, often using toxic chemicals, are required for different metals, and no single stain can detect as many elements as an x-ray approach.

Equipped with these maps we are now ready to begin new kinds of research to explore what changes in biological metals occur at the very early stages of development through to the gradual process of ageing. We have previously seen that normal ageing in these nematodes is associated with dramatic changes in iron; a process that mirrors changes in the ageing human brain. This change in brain iron is thought to be a significant contributor to several age-related neurodegenerative diseases like Parkinson's disease. We believe that the elemental imaging approach described in this study will be used to help us understand the role biological metals play in development, life and death.

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