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What drives copper isotope effects in the serum of cancer patients? Mechanistic insights from box modeling.

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In the past few decades, mass spectrometry advancements have enabled the isotopic characterization of metabolically significant metals (*e.g.*, Cu, Fe, Ca) in biological systems. In certain cases, biological materials (*e.g.*, blood, serum, urine, tissue) from individuals with specific diseases have been found to display distinct isotopic signatures relative to those from healthy individuals. In particular, Cu isotopes have been found to be isotopically lighter in the serum of breast cancer patients compared to healthy patients, and the shift from normal to light composition may precede shifts in other molecular biomarkers by 2-3 months [1]. These results have led to significant interest in potentially using Cu isotopes as a tracer for cancer progression. With the excitement of these results, it is important to assess the potential for these measurements to act as diagnostic tools.

Here, we aim to determine the feasibility of utilizing Cu isotopes as a diagnostic tool for cancer progression by performing a first-order analysis of Cu isotopic cycling in the body. To do this, we built a box model to simulate the kinetics of Cu flow throughout its significant reservoirs in the human body (*i.e.*, tumor, liver, blood, etc.). We then allowed isotopic fractionation to occur during Cu uptake into/release from these reservoirs before and during cancer progression (in which case Cu fluxes into/out of the tumor is also taken into account). This allows us to assess under which conditions the Cu isotopic composition of serum or tissue will reflect any cancer growth-related isotopic perturbation, at a level resolvable with modern mass spectrometry. Using predictions from *ab initio* calculations to constrain the magnitude of Cu isotope fractionation imparted by Cu transport processes, we find that tumor growth alone is unable to explain the light isotopic signature in serum. These findings allow us to make connections to previous mapping studies and begin to probe the mechanisms behind the measured isotopic compositions. At the conference, we will discuss the implications of these models on the diagnostic potential of Cu isotopes in cancer onset/progression/remission.

[1] Télouk, P. *et al.* (2015) *Metallomics* 7, 299–308.