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Modelling biometal stable isotopes cycles in biological systems using the isobxr R package

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The strength of stable isotope metallomics (SIM) lies in its ability to finely detect the alterations of metal cycling in organisms, from systemic to sub-cellular scales, in pathologically active entities (e.g., diseased organs) as well as peripheral reservoirs (e.g., blood). Rooted in the principles of mass conservation, SIM offers the possibility to quantitatively assess the alteration of metal trafficking in health and disease. Building on this principle, we can develop numerical models of the dynamic metal isotopic cycles to infer the nature and extent of these alterations. Such approaches are formalized in stable isotope box-modelling (SIBM) to bridge the gaps between observed physio-pathological effects, mechanistic models, and quantitatively constrained estimates of metal cycles. The systematic use of SIBM approaches is however hampered by the lack of open-source, versatile and user-friendly numerical tools adapted to complex biological systems, composed of networks of numerous interconnected reservoirs.

Here, we present the *isobxr* R package (available on CRAN) dedicated to SIBM of open or closed systems for the calculation of the distribution of metal stable isotopes at steady-state or in reaction to a variety of perturbations. We will first shortly present the *isobxr* workflow allowing to initiate models (shiny user interface, definition of boxes, fluxes, isotopic fractionations), as well as the mathematical methods used to solve the systems of differential equations, either numerically or analytically. Taking real-life examples, we will introduce a multi-dimensional parameter fitting method based on the comparison of measured steady-state isotope compositions with simulations from a systematized exploration of the space of parameters. This n-dimensions sweeping approach allows to easily determine the parameter values (e.g., fractionation coefficients) that best explain the observed isotopic compositions. Finally, we will show how *isobxr* allows to build scenarios and quantify the response of systems to physio-pathological perturbations (e.g., pathological imbalance), taking real-life examples in health and disease.

The routine implementation of open-source numerical modelling of metal isotopes cycles in SIM bears the potential to foster the identification of the roles of metals in pathogenesis as well as the use of isotopic quantitative clinical biomarkers.