Towards a framework to unify *in silico* methods for endocrine disruptors identification: the inhibition of thyroid peroxidase

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The recurrent daily exposure of human beings to different chemicals along with increasing evidence highlighting endocrine-related human diseases [1], has led to a growing interest in understanding how endocrine-disrupting chemicals (EDCs) can affect the human endocrine system. These EDCs can be present in the environment from different sources, e.g., plant protection products (PPPs), pharmaceuticals, or dietary components [2]. Recently, guidance to identify this class of compounds in the context of PPPs and biocidal products was issued by the European Chemical Agency (ECHA) and the European Food and Safety Agency (EFSA) [3] upon a request by the European Commission (EC). Considering this new guidance, the development of new *in silico* methodologies capable of identifying EDCs is of utmost importance, not only for drug discovery but also for chemical risk assessment campaigns. In this context, this project aims at maximizing the predictive performance of different in silico methodologies by combining ligand-based and structural-based techniques with machine learning algorithms, overcoming the limitation of each approach, and leveraging their individual strengths. In this communication, the initial steps of this project, which focused on thyroid pathways, more specifically on the inhibition of thyroid peroxidase (TPO), will be discussed. TPO catalyses the iodination as well as the coupling of tyrosine residues to thyroglobulin to generate T3 and T4 thyroid hormones, which are of utmost importance in the regulation of multiple physiological processes of the endocrine system. Preliminary results, highlighting the criteria for the curation of a dataset assembled from a high-throughput *in* vitro assay developed in the Endocrine Disruptor Screening Program by the United States Environmental Agency to predict TPO inhibition via the oxidation of Amplex UltraRed in the AUR-TPO assay [4] will be shown. These results will be compared with previously reported workflows [5,6] applied to the same dataset, and a discussion on the importance of the selected curation steps will be undertaken. These steps are of major importance not only to increase the quality of the dataset, but also to reduce the noise than non-relevant compounds could have in the performance of the predictive models that will be generated in the future.

[1] Bergman, A., *et al.*, World Health Organization, 2013
[2] Frye, C.A., *et al.*, J. Neuroendocrinol. 2012, 24, 144
[3] Andersson, N. et al., EFSA Journal 2018, 16, 5311
[4] Friedman, F.K., *et al.*, Tox. Sci., 2016, 151, 160
[5] Lomana, M. G., *et al.*, Chem. Res. Toxicol., 2021, 34, 396
[6] Gadaleta, D., *et al.*, , Front. Pharmacol., 2021, 12, 713037

Acknowledgements:
FCT for grants
PTDC/BIA-BFS/28419/2017 (B. L. Victor)
UIDB/04046/2020−UIDP/04046/2020 (BioISI)