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Ceci n'est pas une dose : building a bridge from the bench to the human dose

In a medicinal chemistry project, we optimize many endpoints in parallel: potency, metabolic stability, permeability, protein binding, solubility. These measurements are made at the bench, but the question that ultimately matters is: what dose will patients need?

Too often, the two sides are only connected at the candidate nomination. Until then, each endpoint is looked at separately, so it is easy to improve a parameter that barely changes the dose, or to miss the one that makes it unrealistic.

With ML models for ADME properties now good enough to support design decisions, we can build this bridge much earlier, even before a compound is made. Instead of predicting each endpoint on its own, the predictions can be combined through IVIVE, allometry and simple PK simulation into a predicted human dose. That gives the project one integrated design parameter.

In this talk, we will go through the methods behind this chain and the questions it raises for model builders:

- Which endpoints really drive the dose, and where should modelling effort go?
- How do model errors and applicability domain carry through to the dose?
- When is a predicted value good enough to replace a measurement, and when is it not?

We will also show why a single predicted number is not really the dose. Once the uncertainty is propagated, what we get is a dose distribution, and that is what should guide decisions. Using project-inspired examples, we will show how this changes everyday choices, such as ranking virtual analogues or identifying which parameters limits the dose.

Finally, we will present PKBridge, the web application and API we built to run this workflow (measured or predicted inputs -> human PK -> dose distribution)

Curriculum vitae of Dr. Stephane De Cesco



Stéphane De Cesco, PhD, is a computational drug discovery leader with over 10 years of experience spanning biotech and academia. He currently serves as Director of Computational Drug Design & Data Sciences at Coultreon Biopharma, following leadership roles at Galapagos and Confo Therapeutics, and research positions at the University of Oxford and McGill University. His expertise combines structure-based drug design, cheminformatics, and AI/machine learning to accelerate small-molecule discovery and optimization. He has contributed to drug discovery programs across multiple therapeutic areas, with a particular focus on integrating computational methods with medicinal chemistry. Stéphane holds a PhD in Chemistry from McGill University and is an author of 15 peer-reviewed publications and a co-inventor on three patent applications.

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