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Response to "Complexity vs. Simplicity: The Winner Is?" Mechanism-Based Classifiers Provide More Than Just Classification

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To the Editor:

We appreciate the interest in our recent publication in *Clinical Pharmacology & Therapeutics*,[1] and we welcome the opportunity to reply to Dr. Mistry letter (Complexity vs. Simplicity, the Winner Is?). The letter notes that our simulation-based drug classification method involves considerable complexity, and that simple, empirical approaches can often distinguish drug classes equally well. We agree with this general principle, as we noted when we cited the important study by Kramer *et al.*,[2] which used a simple, two-variable heuristic to distinguish between torsadogenic and nontorsadogenic drugs. We therefore believe the relevant issue is not to declare a particular type of approach "the winner," but instead to emphasize the potential advantages and disadvantages of empirical and mechanism-based strategies.

Drug classification approaches based on biological mechanism do indeed introduce complexity, but the advantage of these strategies is that they leverage prior knowledge about how drugs actually act, which offers the potential for future insight and improvements. Developing a method for drug classification was only one aim of our study[1]—through this work we also sought to generate novel mechanistic predictions and suggest strategies for improving drug development. Our results generated several such predictions, including:

- Drugs with isolated case reports of Torsades may reveal this risk only when these drugs reach excessively high concentrations in individual patients (our **Figure 4**).
- Combined measurements of how drugs influence both action potentials and intracellular calcium are more predictive of Torsades risk than action potential measurements only (our **Figure 3**).
- Ion transport pathways besides those routinely assessed may contribute to Torsades risk,[3] and the relative importance of the different pathways can be quantified (our **Figure 6** and **Supplementary Table S2**).

These predictions, which can be experimentally tested, are especially relevant in the context of the Comprehensive *in vitro* Proarrhythmia Assay, or CiPA.[4,5] This regulatory agency/academic/pharmaceutical industry partnership aims to replace current proarrhythmia tests

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with a fully *in vitro* assay involving ionic current measurements, mathematical modeling, and drug effects assessed in cells. Our study[1] shows how mechanism-based modeling can be useful not only for synthesizing results after experiments have been performed, but also for prioritizing the experiments that will be part of the CiPA.

Thus, although we agree with Dr. Mistry that simple classification systems can indeed be useful, it's important to emphasize that mechanism-based simulations, which account for the underlying biological complexity, can provide insight and actionable predictions that are generally not obtained from simple, empirical approaches.

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