The shape of things to come? Fractal dimensionality and its applications in deep-learning-driven ligand-receptor interaction prediction.

R. Byrne, (CH, SE), L. Friedrich, CH, G. Schneider, CH
I.P.W/Institute for Pharmaceutical Sciences, ETH Zürich, Vladimir-Prelog-Weg 4, CH-8093 Zürich, Switzerland
Discovery Sciences, Innovative Medicines and Early Development Biotech Unit, AstraZeneca R&D Gothenburg, 431 83 Mölndal, Sweden

Abstract:
Recent developments in the application of deep-learning methods in chemoinformatics have brought with them significant advances in our field, facilitating *de novo* compound suggestions, advanced target-prediction, and even the suggestion of synthetic routes [1,2]. All of these efforts share a common requirement: that we should have good representations of our entities in the first instance, whether small- or macro-molecule. Current representations are often dependent on features pertinent to one, but not the other, and rarely perform well over the entire range.

This study develops on the known importance of the geometric complementarity between ligands and their targets [3]. Specifically, we focus on the rapid generation and analysis of shape-based fingerprints which incorporate geometric information from the local atomic environment as described through the pseudofractal behaviour of the molecular surface[4], which can be calculated for any molecule type. This provides both an alignment-independent shape-based similarity search, and a molecular representation which is a natural, consistent, and easily-stored input for the bleeding-edge deep-learning methods employed today.

We examine the extent to which ligand-receptor interactions can be predicted by employing deep-learning methods trained purely on geometric information from ligands and targets, and discuss whether insights obtained from such models might be used to rapidly screen virtual libraries based on an inferred pattern of on-target-likeness, including in cases where the target has not yet been structurally resolved. We provide a case-study exemplifying the utility of such a system.

Literature:
[1] H. Chen, O. Engkvist, Y. Wang, M. Olivecrona, T. Blaschke, *Drug discov. today* **2018**, *23*, 1241–1250.
[2] E. Gawehn, J. A. Hiss, G. Schneider, *Mol. Inform.* **2016**, *35*, 3–14.
[3] A. Kahraman, R. J. Morris, R. A. Laskowski, J. M. Thornton, *J. Mol. Biol.* **2007**, *368*, 283–301.
[4] P. Grassberger, I. Procaccia, *Phys. Rev. Lett.* **1983**, *50*, 346–349.

Acknowledgements:
This project has received funding from the European Union's Framework Programme for Research and Innovation Horizon 2020 (2014-2020) under the Marie Skłodowska-Curie Grant Agreement No. 675555, Accelerated Early staGe drug dIScovery (AEGIS).