

Dear Thomas,

Thanks to Norwid awardeness of the toxicity risk criteria option to the old DW updates at the end of the "Build Evolutionary Library"(EL) Add Criterion, I am experimenting with different protein/ligand pairs by adding it to my usual DW docking score, molecular weight and logP criteria that I called "evolutionary dockings".

I focus my comments now to preliminary results predicted with one model previously described for the ratVKORC1 protein/brodifacoum ligand complex (Coll, 2023 vs2 <https://chemrxiv.org/engage/chemrxiv/article-details/64c8ddd1ce23211b20ee37e3>).

1) PRELIMINARY EXPERIMENTS

I first made some preliminary experiments with different \pm toxicity risk values. The EL version was the most recent Windows update of 10/08/2023 which included the toxicity risk in an e9 of 47 CPU provided with 64Gb of RAM. Additional criteria included, DW docking score to the VKORC1/brodifacoum complex (Coll, 2023vs2) weight x4, molecular weight <400 x2, logP <3 x1 and \pm toxicity risk values x4. Other running variables were: cycle: automatic, total run count=1, compounds per cycle=128, compounds survive a cycle =16 , Create compounds like=Approved drugs. Results in Table and graphic:

- 1) Numbers of raw children. There were similar numbers of randomly generated raw children (13033-15827) for toxic risks 0, 0.3, 1 and 2. The lowest numbers were those obtained at the highest toxic risk=4. Maximal fitting to the set criteria were very similar for all cases (>0.89). Maximal docking affinities of the nontoxi-macro children were all higher than 114 DW docking-score unitless. Norwid Behrnd discovered that the number of raw children divided by the number of cycles was nearly constant ~ 100 (now confirmed in 6 other protein/ligand models). Norwid sugested that "there seems to be a compensation by DW, it keeps generating new molecules until enough spots per generation are allocated". It remains unclear whether or how that is accomplished by EL.
- 2) Numbers of fitted children. The numbers of raw children fitting the targeted criteria were between 1393 and 2691, except for those that were lower at the maximal toxic risk=4 (977).
- 3) Numbers after nontoxi-macro. The percentages of children fitting all the criteria which remained toxic (nontoxi-macro) as detected by the NorwidJulio's macro after EL, were minimal at risks 0.01, 0.1, 0.3, and 1 (100% may be expected if the criteria were not a preference). It looks like the risk option=0 doesn't work as expected. Is that because is a prefernce or because trouble interpreting the " $<=0$ risk?". Surprisingly, the toxic risk option =4 did not generated any nontoxic-macro children (?).
- 4) Main conclusions: With the above mentioned model and criteria, the toxic risk value =1 generated the highest number of nontoxi-macro children (2330). An ~ 2.6 fold higher than that obtained without using any toxic risk criteria (893). The recently introduced toxicity risk criteria seem to perform as expected during individual molecular docking evolution (confirmed in 6 differn protein/ligand published pairs). The final/manual Norwith/julio's macro serves to detect any toxic "survivors" that may remain after the EL with toxicity risk criteria. Their residual presence may be

explained because the toxicity risk criteria is a preference rather than a threshold. These are preliminary results because i) only one protein/ligand model was analysed, b) stochastic variations may be expected when more than 1 run would be applied, and c) all the EL criteria are defined at DW as preferences rather than as thresholds.

File Attachments

1) [Thomas Tables Agosto toxicityRisks.docx](#), downloaded 423 times
