

Supporting Information

PerMM: a web tool and database for analysis of passive membrane permeability and translocation pathways of bioactive molecules

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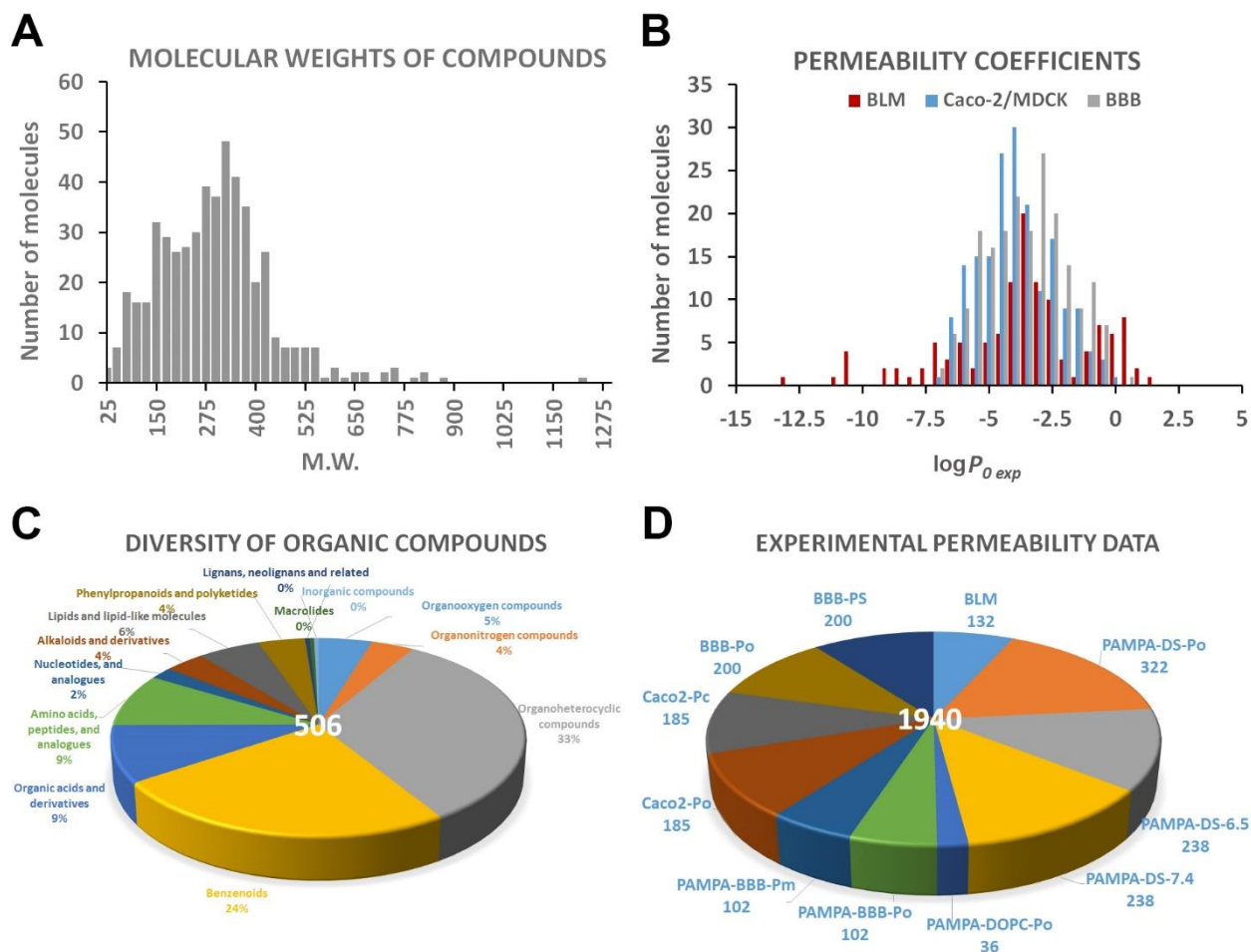


Figure S1. PerMM database statistics. (A) Size distribution of compounds in the databases. (B) Distribution of values of experimentally measured permeability coefficients for BLM (red), Caco-2/MDCK cell-based assays (blue) and BBB membranes (gray). (C) Chemical diversity of molecules in the database. Numbers of compounds are indicated for each chemical class. (D) Experimentally obtained permeability coefficients in different artificial and biological membrane systems. Numbers of measured permeability coefficients are indicated for each membrane system.

Notes: intrinsic BBB permeability coefficients were obtained from *in situ* rodent brain perfusion in efflux-minimized conditions referred to permeation from saline at pH 7.4 and corrected for ionization.³ Intrinsic permeability coefficients for intestinal cellular membranes were obtained in Caco-2/MDCK cell-based assays and corrected for all non-transcellular effects using the pCEL-X program (http://www.in-adme.com/pcel_x.html)⁴. Intrinsic permeability coefficients obtained in PAMPA-DS assay using the lecithin-based double sink (DS) model were corrected by Avdeef for permeability through the aqueous boundary layer adjacent to both sides of the membrane.²

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PerMM server and database
Permeability of Molecules across Membranes

Search molecules by PDB ID or name

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Groups (4)
Classes (13)
Membrane Systems (11)
Molecules (506)

PERMM SERVER

Calculate Transmembrane Translocation Pathway

PerMM web server implements our computational method for calculation of binding affinities of molecules to membranes, energy barriers along the membrane normal, and permeability coefficients. The server was developed to assist investigators at early stages of drug development in optimization of cell permeability of new therapeutics derived from natural products.

Upload your PDB file (please use extension .pdb): No file selected.

Experimental conditions

T° (K):

pH:

Optimization method for calculation of transmembrane pathway: "Drag" optimization

Estimate BLM permeability including deionization energy for ionizable molecules
 Estimate intrinsic permeability Po for BLM, BBB, and Caco-2 (ionizable molecules are assumed to be uncharged in water)

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Figure S2. Interface of the PerMM web server for prediction of permeability coefficients of molecules through DOPC bilayer (BLM), Caco-2/MDCK cells, and BBB membranes.

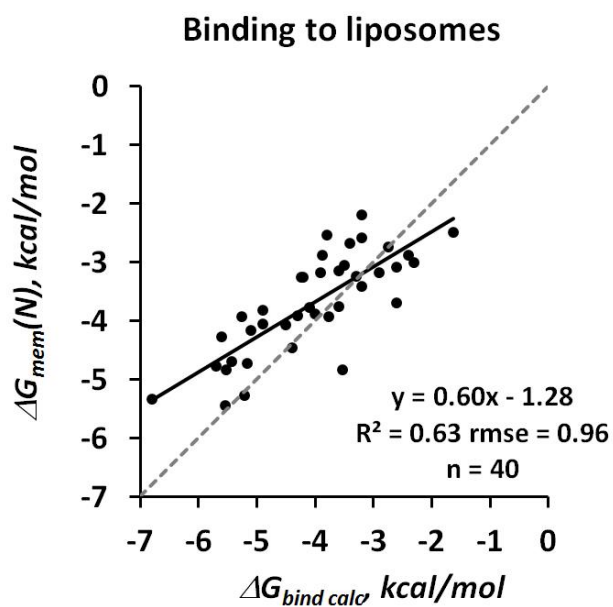


Figure S3. Comparison of experimental and calculated membrane binding energies for 40 compounds (organic molecules and FDA-approved drugs). Experimental liposome-water partition coefficients of mostly uncharged compounds were taken from publications⁵⁻⁹ and the Avdeef's collection.¹⁰

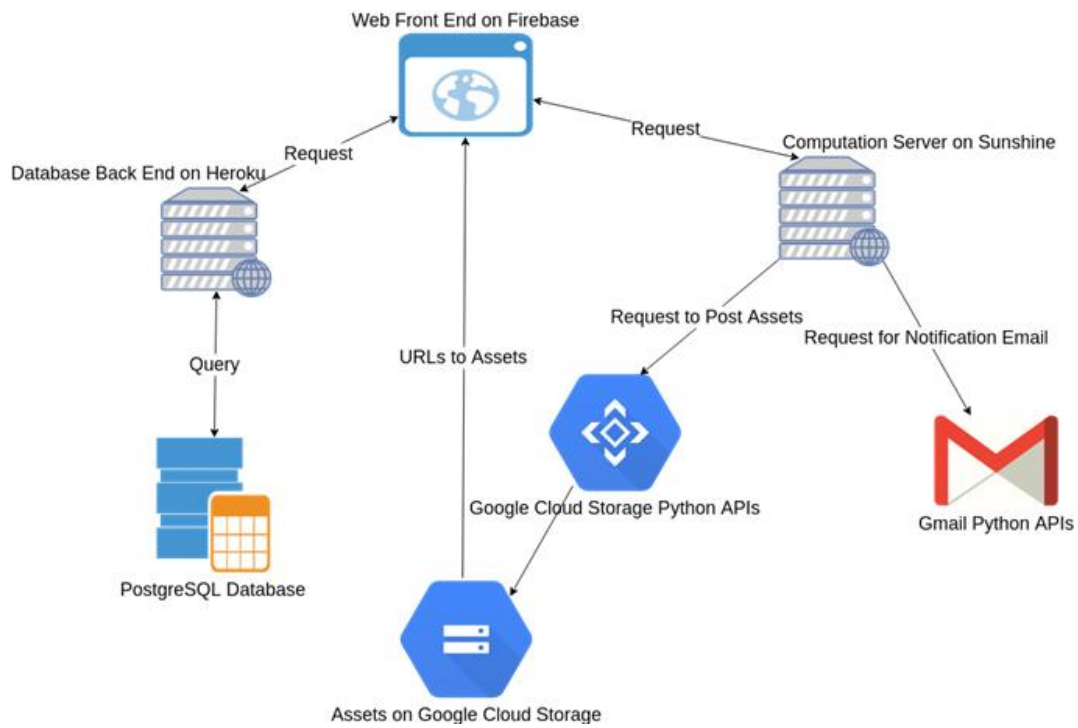


Figure S4. The PerMM database and server deployment diagram.

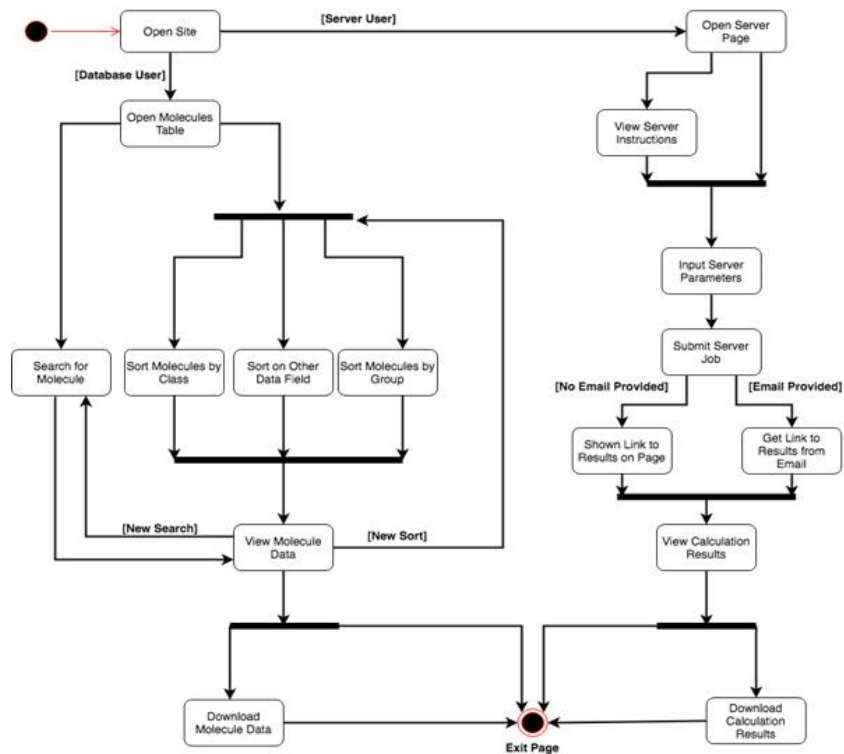


Figure S5. Activity diagram of the PerMM web site, which includes the PerMM database and the PerMM web server.

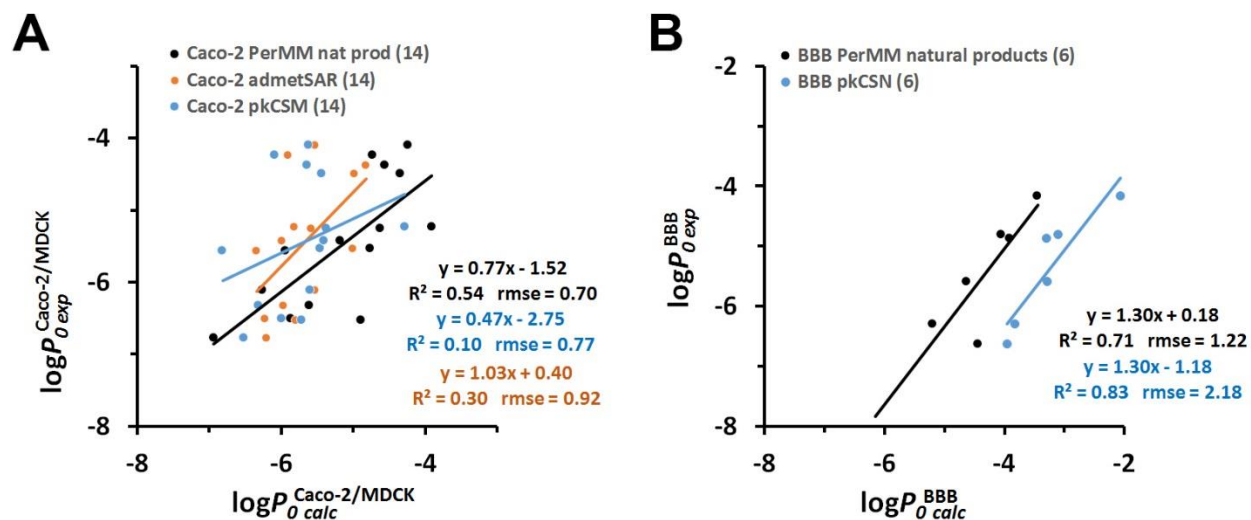


Figure S6. Performance of PerMM and other public web servers on natural product-derived drugs. Comparison of the accuracy of prediction of Caco-2 (A) and BBB (B) permeability coefficients by PerMM (black circles) and other public web servers: pkCSM (blue circles) and admetSAR (orange circles). Permeability coefficients were predicted for natural product-derived drugs with MW>400 Da. The BBB set includes 6 compounds: cyclosporin A, digoxin, paclitaxel, ritonavir, vinblastin, vincristin. The Caco-2 set includes 14 compounds: amprenavir, cefratizine, cefsulodine, cephaloglycin, cephaloridine, cyclosporin A, digoxin, erythromycin, etoposide, lincomycin, paclitaxel, ritonavir, vinblastin, vincristin. Numbers of compounds are indicated in parenthesis.

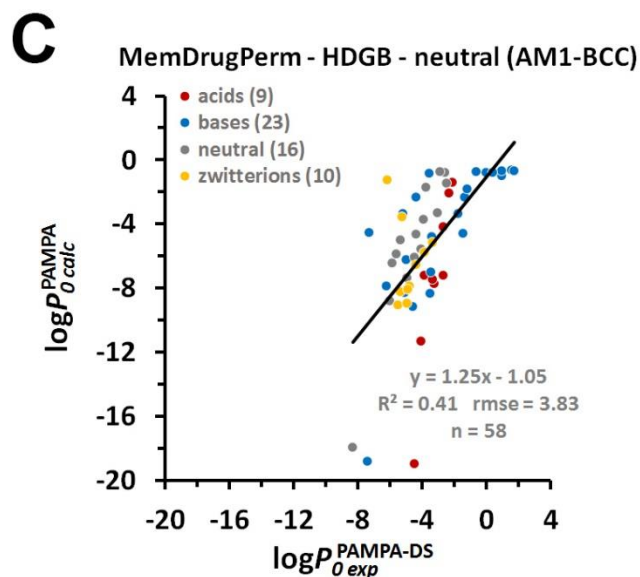
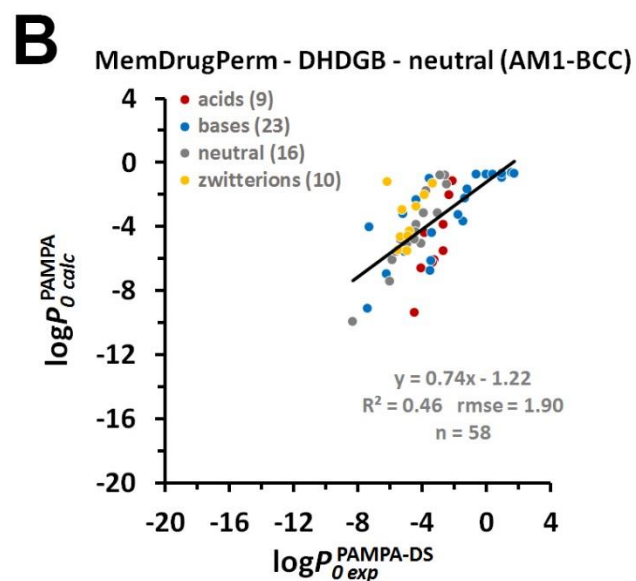
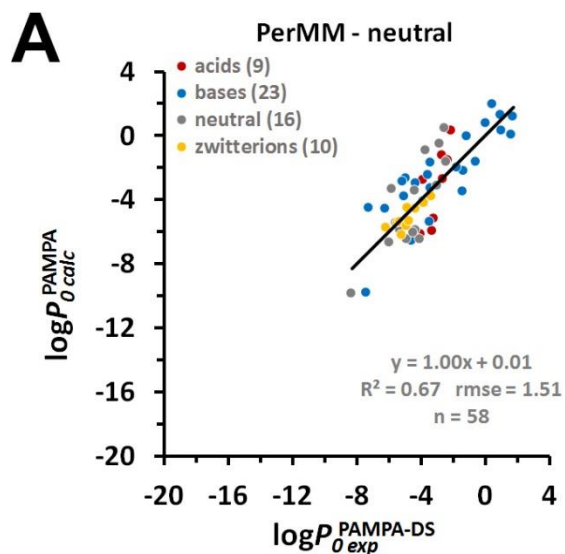


Figure S7. Comparison of the accuracy of prediction of PAMPA permeability coefficients by PerMM (A) and MemDrugPerm (B, C). Results for 58 common compounds (9 acids, 23 bases, 16 neutral molecules, 10 zwitterions) calculated by MemDrugPerm were taken from (Table S6: columns 2 and 3) in ref.¹ The predicted permeability coefficients were evaluated against the experimental $\log P_0$ values for PAMPA-DS assays compiled by Avdeef.²

REFERENCES

1. Brocke, S. A.; Degen, A.; MacKerell, A. D.; Dutagaci, B.; Feig, M., Prediction of membrane permeation of drug molecules by combining an implicit membrane model with machine learning. *J Chem Inf Model* **2018**, 59, 1147-1162.
2. Avdeef, A. Permeability—PAMPA. In *Absorption and Drug Development*; John Wiley & Sons, Inc.: 2012, pp 319-498.
3. Avdeef, A. Permeability: Blood–Brain Barrier. In *Absorption and Drug Development*; John Wiley & Sons, Inc.: 2012, pp 575-680.
4. Avdeef, A. Permeability: Caco-2/MDCK. In *Absorption and Drug Development*; John Wiley & Sons, Inc.: 2012, pp 499-574.
5. Seydel, J. K. Octanol-Water Partitioning versus Partitioning into Membranes. In *Drug-Membrane Interactions: Analysis, Drug Distribution, Modeling.*, Seydel, J. K.; Wiese, M., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: 2002; Chapter 2, pp 35-50.
6. Vaes, W. H. J.; Ramos, E. U.; Hamwijk, C.; vanHolsteijn, I.; Blaauboer, B. J.; Seinen, W.; Verhaar, H. J. M.; Hermens, J. L. M., Solid phase microextraction as a tool to determine membrane/water partition coefficients and bioavailable concentrations in in vitro systems. *Chem Res Toxicol* **1997**, 10, 1067-1072.
7. Escher, B. I.; Schwarzenbach, R. P.; Westall, J. C., Evaluation of liposome-water partitioning of organic acids and bases. 2. Comparison of experimental determination methods. *Environ Sci Technol* **2000**, 34, 3962-3968.
8. Lukacova, V.; Peng, M.; Fanucci, G.; Tandlich, R.; Hinderliter, A.; Maity, B.; Manivannan, E.; Cook, G. R.; Balaz, S., Drug-membrane interactions studied in phospholipid monolayers adsorbed on nonporous alkylated microspheres. *J Biomol Screen* **2007**, 12, 186-202.
9. Wimley, W. C.; White, S. H., Experimentally determined hydrophobicity scale for proteins at membrane interfaces. *Nat Struct Biol* **1996**, 3, 842-848.
10. Avdeef, A. Liposome–water partitioning. In *Absorption and Drug Development*; John Wiley & Sons, Inc.: 2012, pp 220-250.