Supporting Information

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

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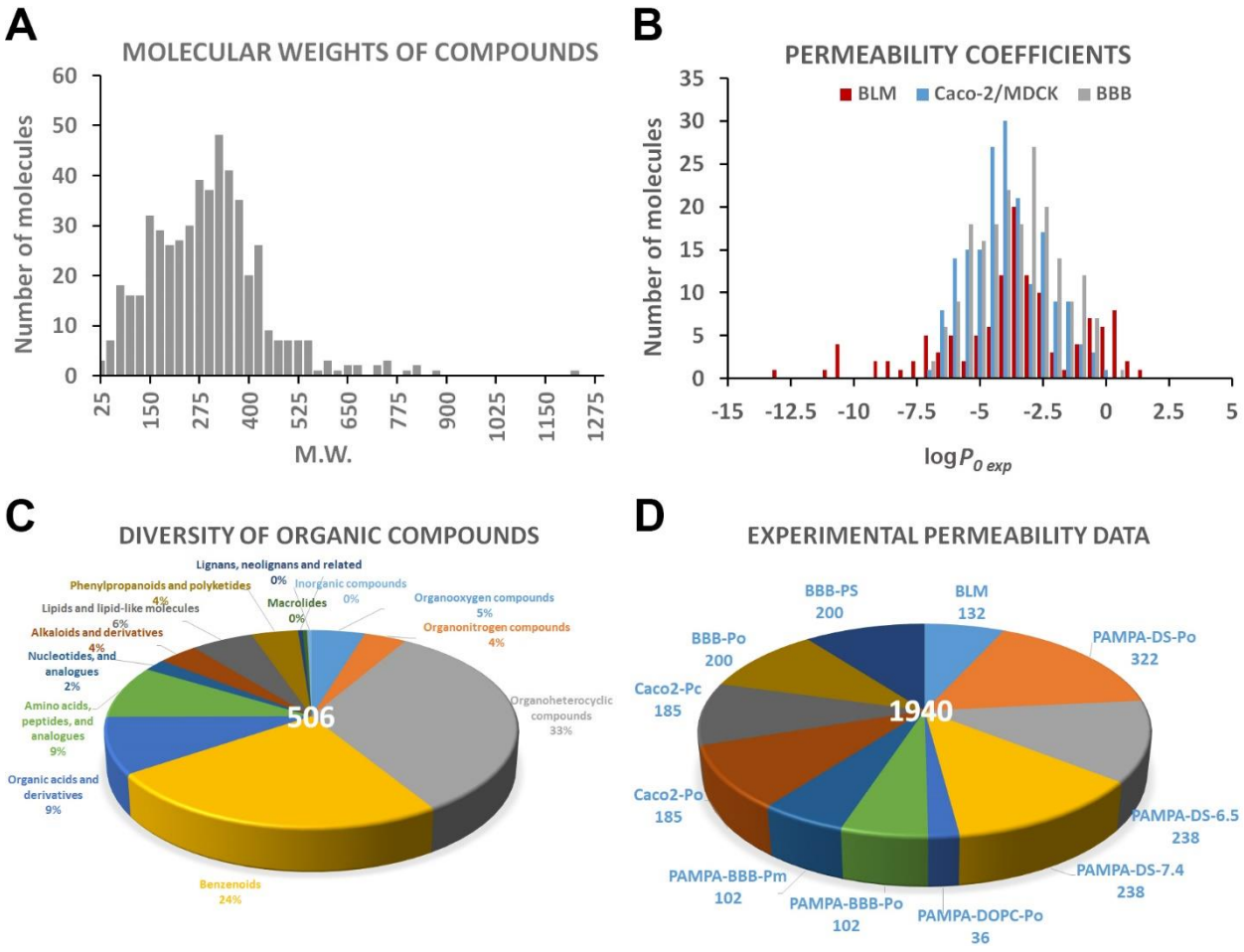

Figure S1. PerMM database statistics. (A) Sise distribution of compounds in the databases. (B) Distribution of values of experimentally measured permeability coefficients for BLM (red), Caco-2/MDCK cell-based assays (blue) and BBB membranes (gray). (C) Chemical diversity of molecules in the database.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

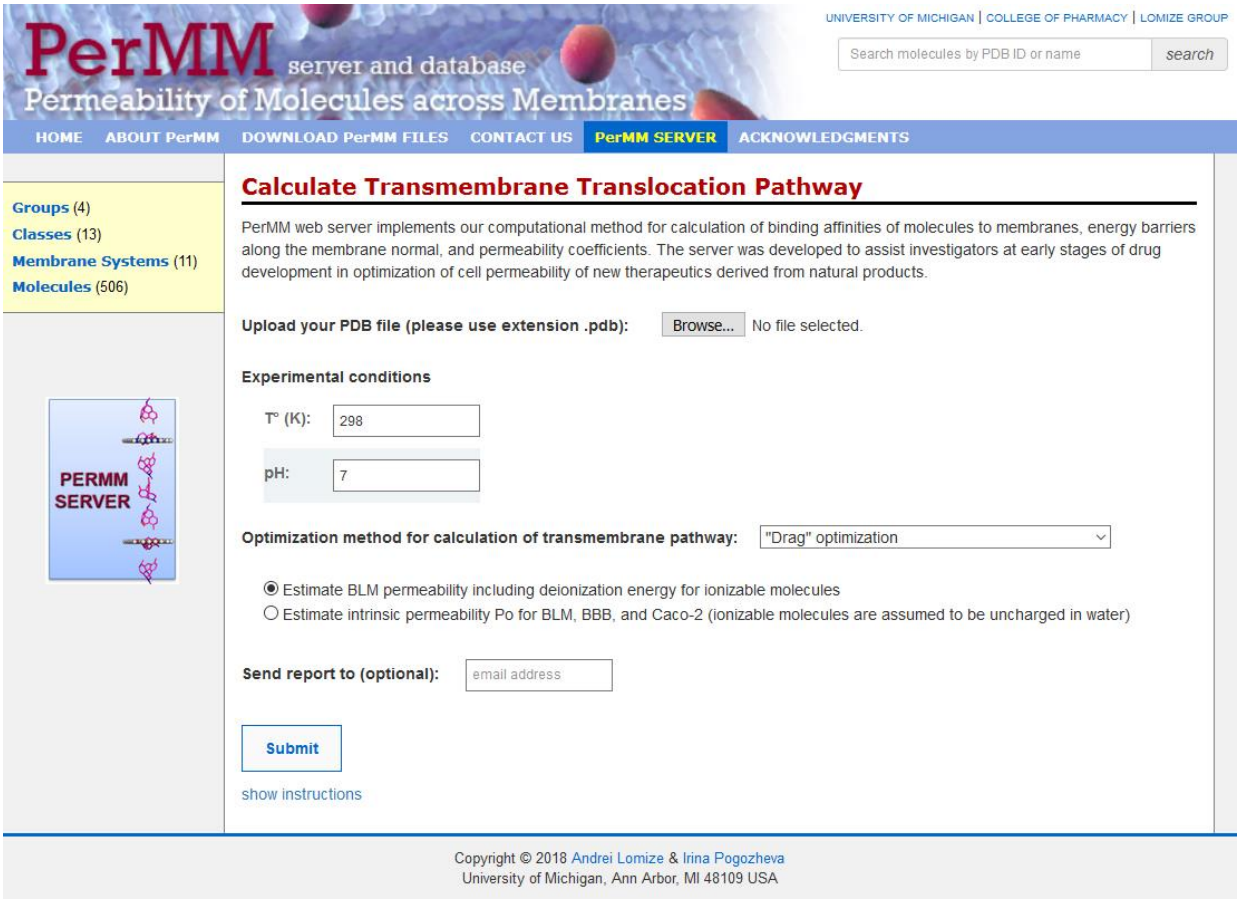

Figure S2. Interface of the PerMM web server for prediction of permeability coefficients of molecules through DOPC bilayer (BLM), Caco-2/MDCK cells, and BBB membranes.

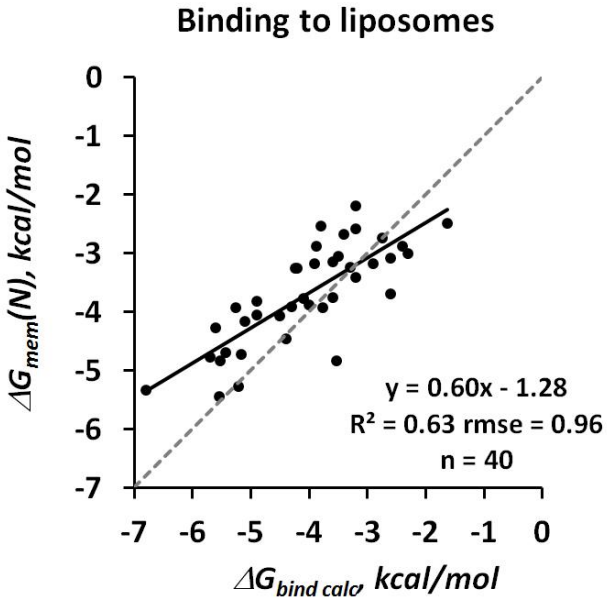

Figure S3. Comparison of experimental and calculated membrane binding energies for 40 compounds (organic molecules and FDA-approved drugs)**.** Experimental liposome-water partition coefficients of mostly uncharged compounds were taken from publications[5-9] and the Avdeef's collection.[10]

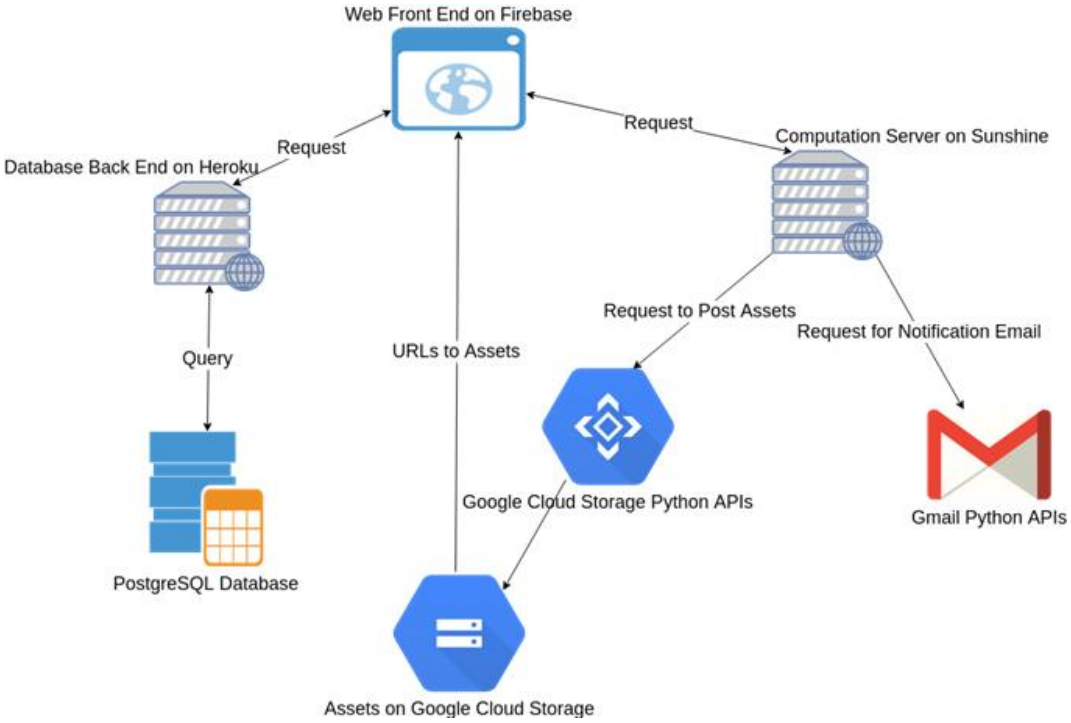

Figure S4. The PerMM database and server deployment diagram.

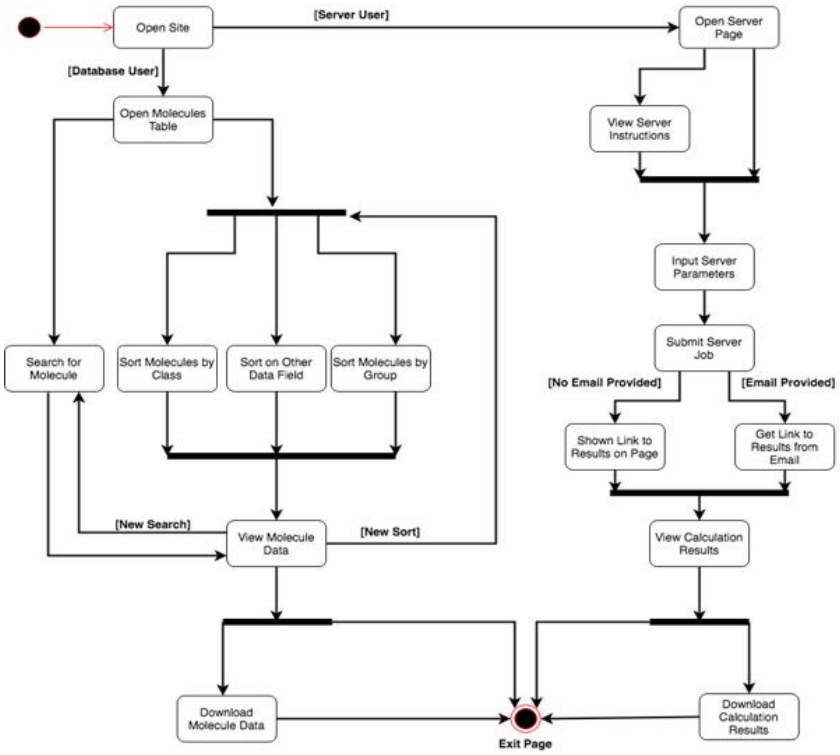

Figure S5. **Activity diagram of the PerMM web site, which includes the PerMM database and the PerMM web server**.

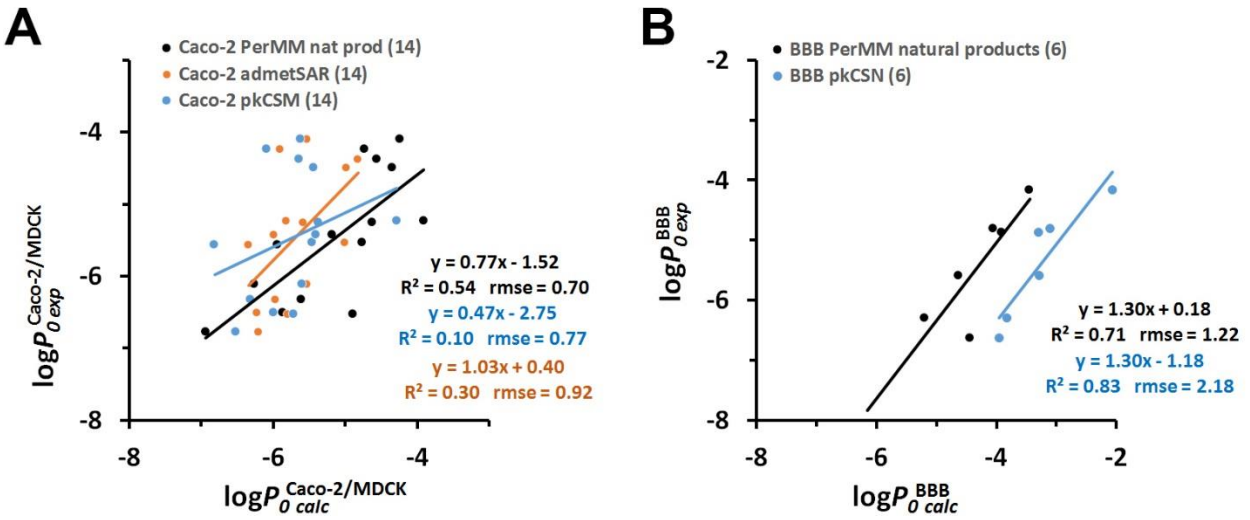

Figure S6. Performance of PerMM and other public web servers on natural product-derived drugs. Comparison of the accuracy of prediction of Caco-2 (A) and BBB (B) permeability coefficients by PerMM (black circles) and other public web servers: pkCSM (blue circles) and admetSAR (orange circles). Permeability 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.

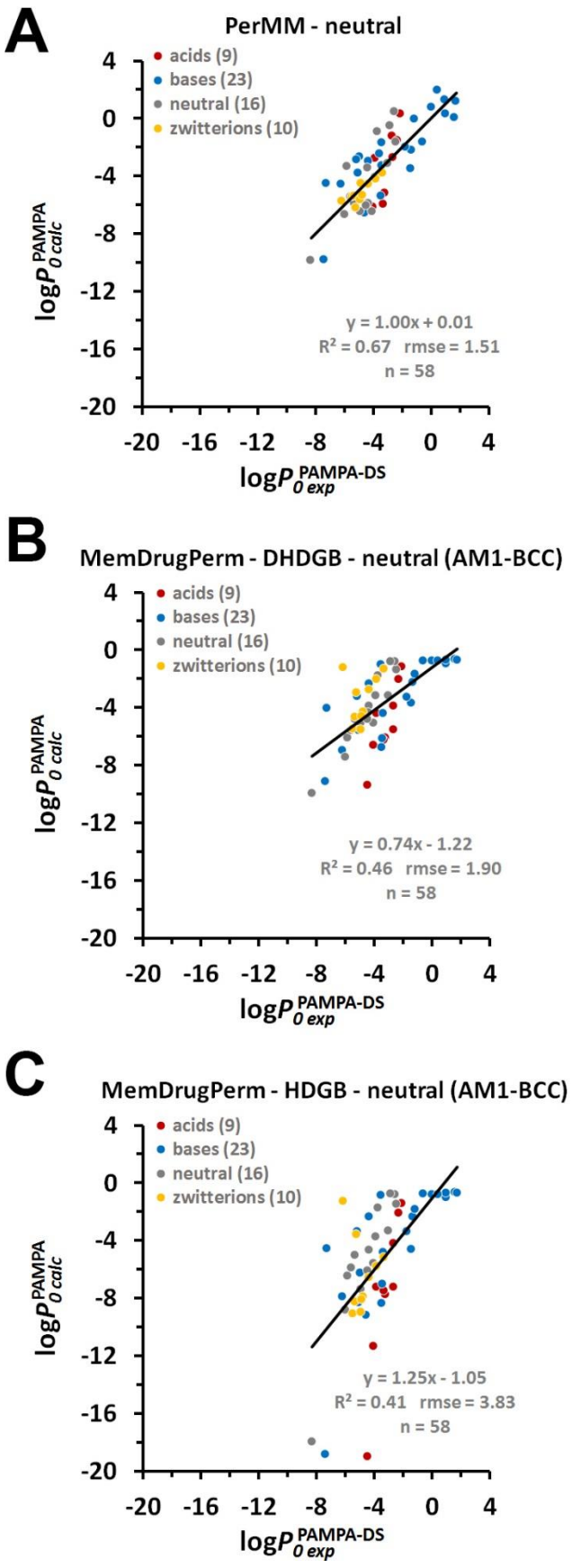

Figure S7. Comparison of the accuracy of prediction of PAMPA permebility coefficents by PerMM (A) and MemDrugPerm (B, C). Results for 58 common compounds (9 acids, 23 bases, 16 neutral molecules, 10 zwitterions) calculated by MemDrugPerm were taken from (Table S6: columns 2 and 3) in ref.[1] The predicted permeability coefficients were evaluated against the experimental logP_0 values for PAMPA-DS assays compiled by Avdeef.[2]

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