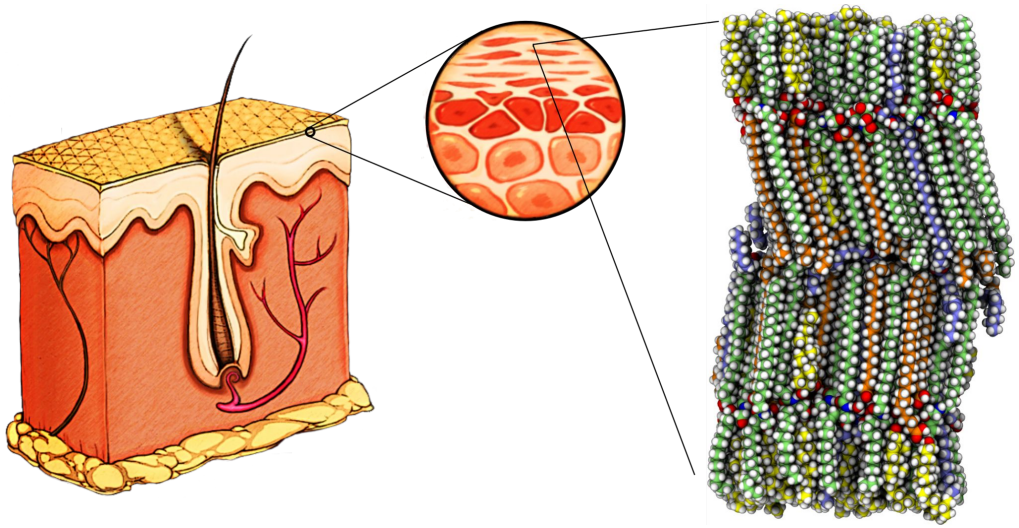
# Predicting Skin Permeability Using Molecular Dynamics Simulations

Experiences from HPC systems and local clusters

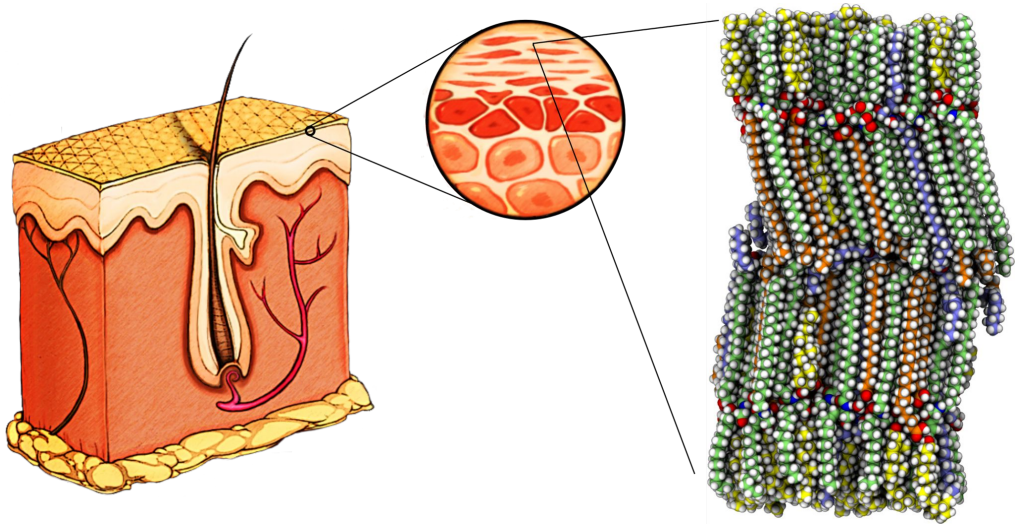
# Background

- Transdermal drug administration
  - Avoid first pass metabolism
    - Fewer side effects
  - Continuous delivery
    - Stable dosage levels
- Relatively few drugs can be administered through skin
  - Effective barrier



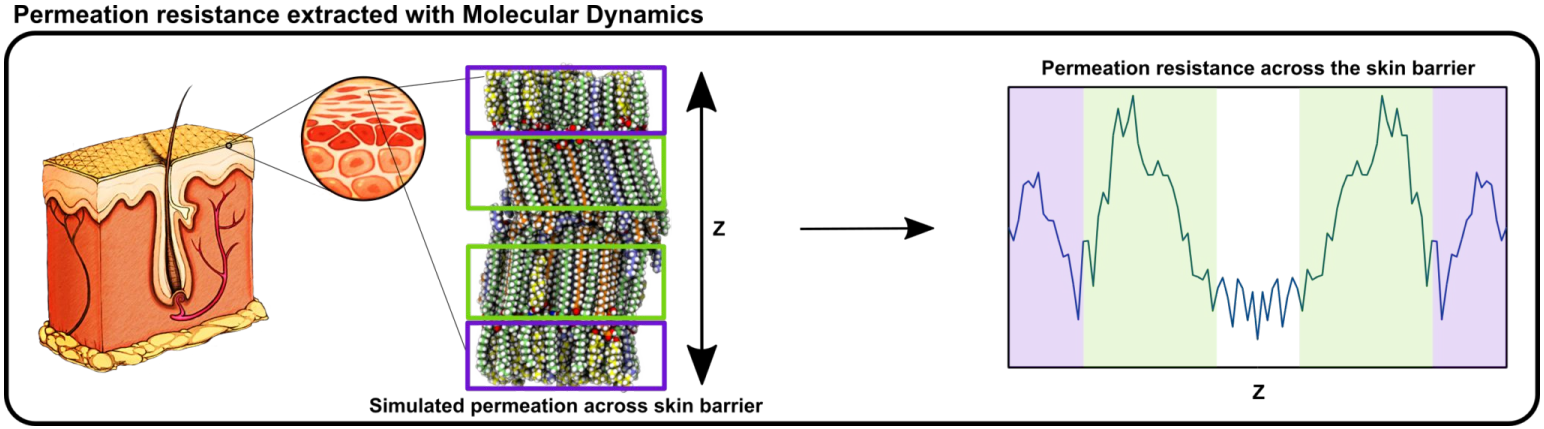
# Background

- Atomistic model of the lipid barrier in stratum corneum.
  - Based on cryo-EM images and molecular dynamics (MD) simulations.
  - Developed together with Prof. Lars Norlén at Karolinska Institutet.
- MD simulations allow explanations of processes at a level of detail difficult to access *in vitro* or *in vivo*.

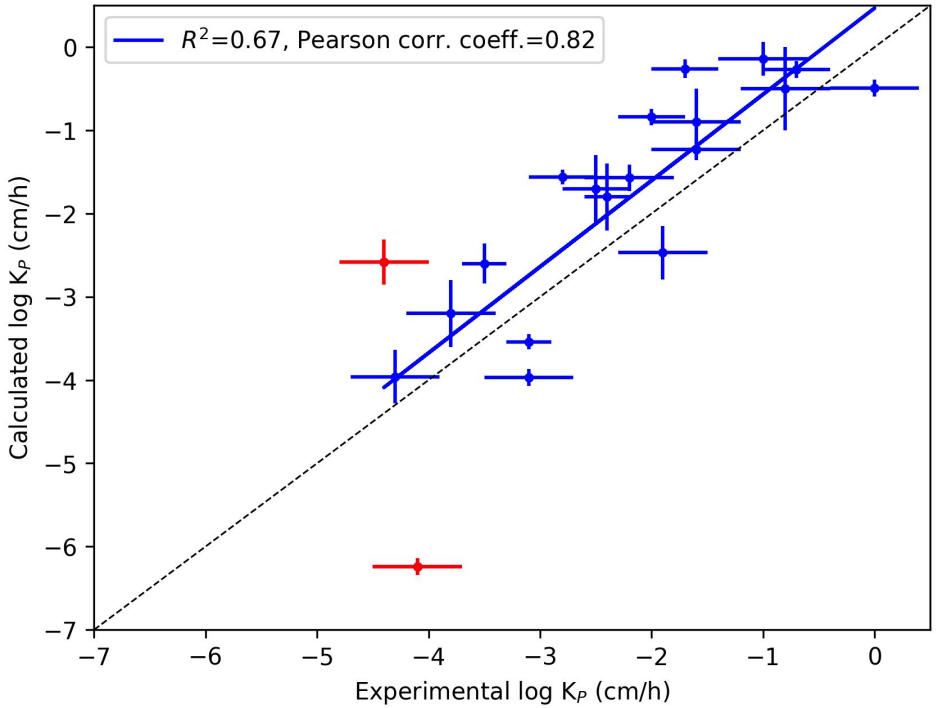


# Skin permeability calculations

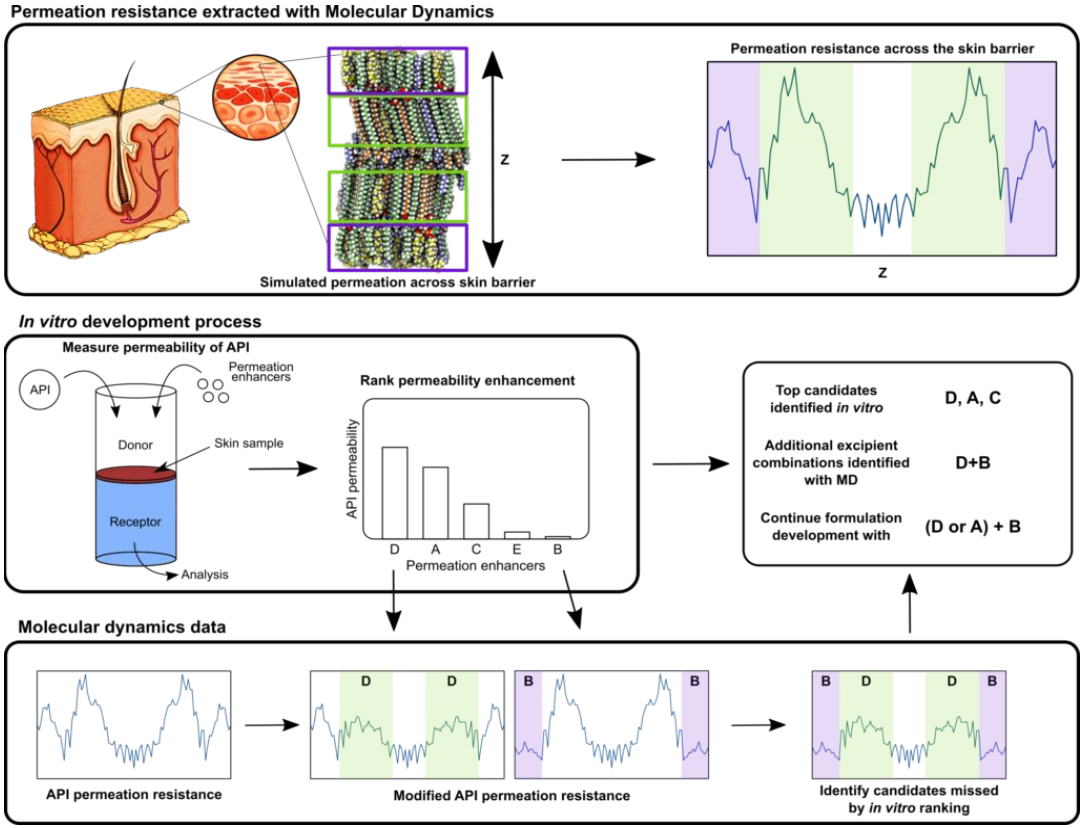
- Understanding which regions of the skin barrier affect permeability the most.
- Where do excipients in transdermal drug formulations go in the skin barrier?
- Improved understanding how excipients can be combined for complementary, or synergistic, effects.
- What ingredients permeate the skin?



# Skin permeability calculations

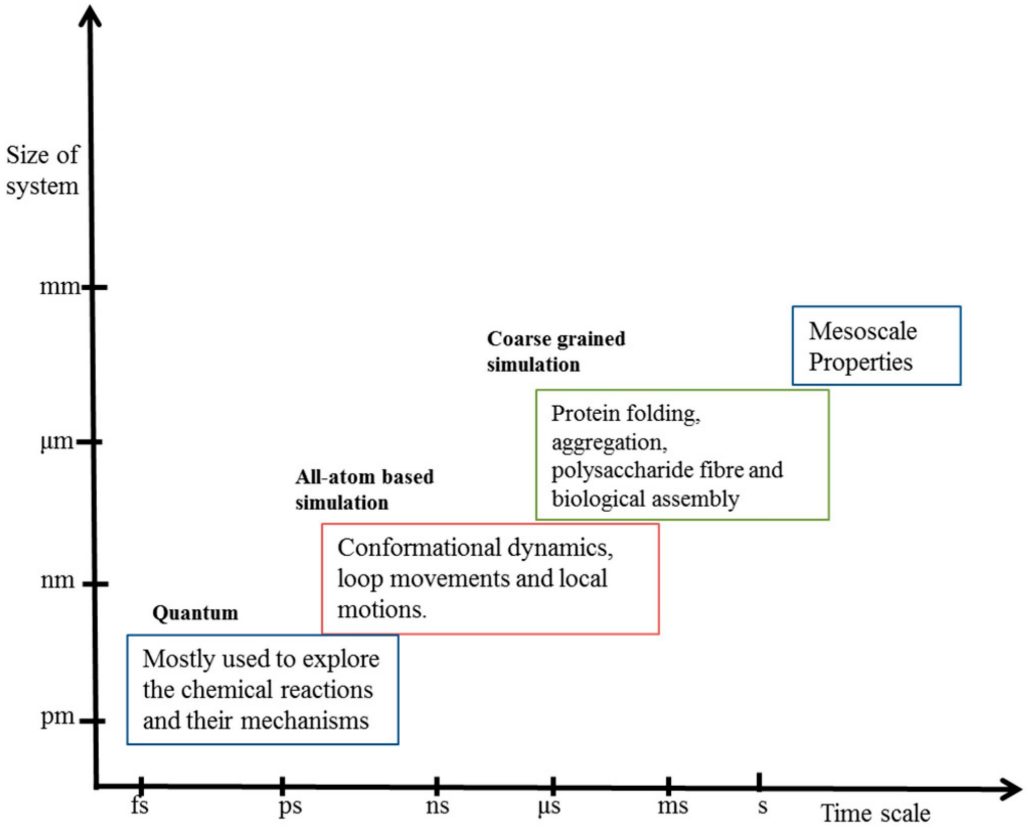



Lundborg, M. et al. Sampling Spatial and Alchemical Reaction Coordinates. *Biophys. J.* In Press.


Permeation resistance extracted with Molecular Dynamics
Permeation resistance across the skin barrier
z
z
Simulated permeation across skin barrier
In vitro development process
Measure permeability of API
API
Permeation enhancers
Donor
Skin sample
Receptor
Analysis
Rank permeability enhancement
API permeability
D A C E B
Permeation enhancers
Top candidates identified in vitro
D, A, C
Additional excipient combinations identified with MD
D+B
Continue formulation development with
(D or A) + B
Molecular dynamics data
D D
B B
B D D B
API permeation resistance
Modified API permeation resistance
Identify candidates missed by in vitro ranking

# Software used

- GROMACS
  - Open source MD simulation software
    - Major development group at KTH and Stockholm University, located at Scilifelab, Solna
    - ERCO Pharma is actively involved in the development team
  - High performance compared to similar software
    - Efficient use of CPU and GPU resources
      - SIMD for CPUs
      - CUDA, OpenCL and SYCL for GPUs
  - Sophisticated algorithms for accelerating the sampling of the molecular system




Singh, N.; Li, W. Recent Advances in Coarse-Grained Models for Biomolecules and Their Applications. *Int. J. Mol. Sci.* 2019, **20**, 3774.

# Local Hardware Resources

- Company cluster, 18 servers
  - Dual 12 core Intel Broadwell CPUs
  - 4 Nvidia GPUs (GTX 1080 Ti and RTX 2080)
- Access to academic cluster, ~30 servers
  - Intel (Skylake) and AMD (Naples) CPUs
  - 4 Nvidia GPUs (RTX 2080 or RTX A5000)

# HPC resources

- Vega (Maribor, Slovenia)
  - 960 CPU nodes:
    - Dual AMD Epyc 7H12 (64 cores/CPU)
  - 60 GPU nodes:
    - Dual AMD Epyc 7H12 (64 cores/CPU)
    - 4 NVidia A100 GPUs

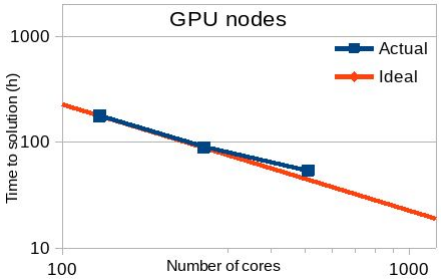
ENCCS
EuroCC National Competence Centre Sweden

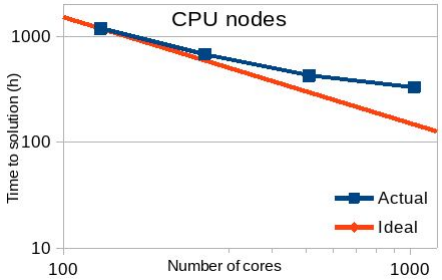
# Previous HPC allocations

- Tetralith, NSC, Linköping, Sweden
- Dardel, PDC, Stockholm, Sweden
- Beskow, PDC, Stockholm, Sweden

# HPC Resource Usage (Vega)

- Full node CPU allocation.
- Low RAM requirements.




# Performance

| System | Approximate time to solution (days) |
|---|---|
| Local cluster 1 GPU node | 14 |
| Local cluster 3 GPU nodes | 5 |
| Vega 3 CPU nodes | 18 |
| Vega 3 GPU nodes | 2.5 |

# Observations

- Good help from ENCCS when applying for allocations.
- EuroHPC Joint Undertaking can be valuable for European industry.
- Vague communication regarding publication of results.
  - From EUROHPC-JU-Decision: “Requirements: … Commit to publish the results of their project.”
  - From Vega Terms of Use: “Unless otherwise agreed or specified, e.g., in a contract for industrial or other commercial use, research results must be released publicly, preferably for peer review.”
  - From ENCCS “... you do not need to publish details.”