# Atomistic and Coarse-Grained Modelling of Gene Delivery Polymers

**Titus Adrian Beu, Alexandra Farcaş, Andrada-Elena Ailenei**

University Babeş-Bolyai, Faculty of Physics, Department of Biomolecular Physics, Cluj-Napoca, 400084, Romania

titus.beu@phys.ubbcluj.ro

Gene therapy has a remarkable potential to cure diverse inherited or acquired diseases. Essentially, it implies condensing the useful genetic material (typically, DNA) through the use of "delivery vectors" (often, cationic polymers) to sizes susceptible to penetrate the cellular membrane by endocytosis. One of the widely used gene delivery vectors is polyethylenimine (PEI). Its effectiveness is attributed to particular patterns of its protonated NH-groups, which can optimally couple to the negative phosphate groups of DNA.

Revising a previously published version [1], we have developed an accurate all-atom CHARMM [2] force-field for PEI, based on symmetric residues (with -C-N-C- backbone) and high-quality ab initio calculations on model polymers. The CHARMM force field is validated through massive molecular dynamics (MD) simulations of solvated PEI chains of various sizes and protonation patterns. We synthetically characterize the dynamic behavior of the PEI chains by the size and protonation dependence of the gyration radius, end-to-end distance, and diffusion coefficient. The simulated diffusion coefficients fairly agree with experimental findings.

The large ensembles of atomistic trajectories are used to construct probability distributions for the distances, angles, and dihedrals formed by the center-of-masses of the residues, regarded as coarse-graining (CG) beads. The probability distributions are then employed to derive stretching, angle bending, and torsion force field parameters for the CG beads, compliant with the MARTINI standard [3], by Boltzmann inversion techniques. Extensive MD simulations using the MARTINI force field evidence fair agreement of the CG structural parameters with the atomistic counterparts.

While CG modeling allows for the reduction of the number of atomic constituents by more than an order of magnitude, it also enables simulations with ten-fold time steps, which are essential prerequisites for performing realistic gene delivery simulations on realistic space and time scales.

## References

[1] T. A. Beu and A Farcaș, Journal of Computational Chemistry, 2017, **38**, 2335.

[2] K. Vanommeslaeghe, E. Hatcher, C. Acharya, S. Kundu, S. Zhong, J. Shim, E. Darian, O. Guvench, P. Lopes, I. Vorobyov and A. D. MacKerell Jr., Journal of Computational Chemistry, 2010, **31**, 671.

[3] S. J. Marrink, H. J. Risselada, S. Yefimov, D. P. Tieleman and A. H. de Vries, Journal of Physical Chemistry B, 2007, **111**, 7812.