



Thesis (B.Sc. / M.Sc.)

Virtual Evolution: Biological Evaluation and Refinement of a Diffusion-Based SELEX Simulator

Background: Systematic Evolution of Ligands by Exponential Enrichment (SELEX) is a powerful experimental strategy to discover nucleic-acid ligands (aptamers) with high affinity and specificity for a target molecule. While highly effective, SELEX campaigns are time-consuming and sensitive to experimental design choices (library composition, selection stringency, amplification bias, number of rounds, etc.). As a result, computational tools that can *simulate* and *analyze* SELEX dynamics are valuable for accelerating ligand discovery and for understanding which mechanisms drive enrichment.

In our group, we have already developed a diffusion-based generative model that produces RNA sequence candidates and supports a first version of an *in-silico SELEX simulator*. The next critical step is to assess whether the generated sequences and simulated enrichment trajectories are *biologically plausible* and to refine the simulator accordingly. This thesis focuses on establishing biologically grounded evaluation criteria, performing systematic analyses, and improving the simulator to better reflect real SELEX behavior.

Department 18
Electrical Engineering and
Information Technology
Self-Organizing Systems Lab

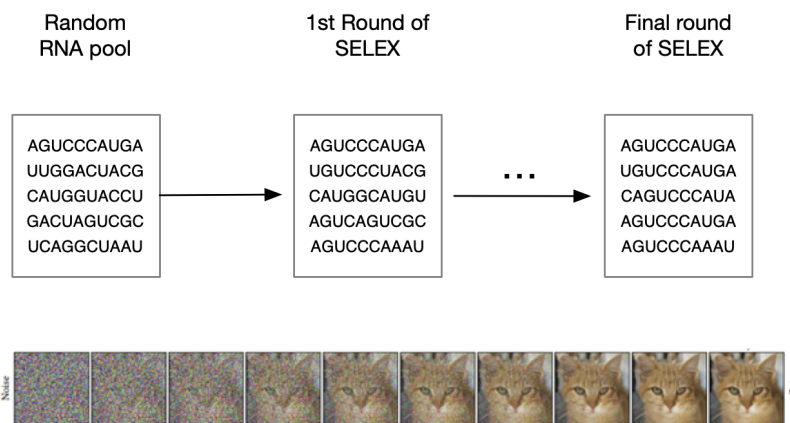
Prof. Dr. Heinz Koeppel
Head of lab

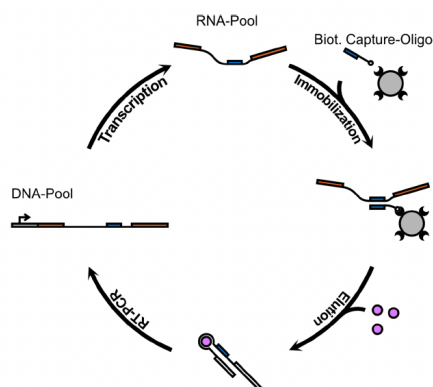
Philipp Froehlich
Project supervisor

S3|06 206
Merckstrasse 25
64283 Darmstadt

philipp.froehlich@tu-
darmstadt.de
<https://www.bcs.tu-darmstadt.de>

December 22, 2025





Schematic representation of the SELEX process for aptamer selection. Starting from a random RNA library, iterative rounds of selection, binding, and amplification enrich high-affinity aptamers for a target molecule. Image from [1].

Objective: The goal of this thesis is to *biologically evaluate and refine* our existing diffusion-based SELEX simulator. You will work with a ready-to-use generative model and focus on (i) defining meaningful biological metrics, (ii) identifying gaps between simulation and real SELEX outcomes, and (iii) implementing targeted improvements that increase realism and usefulness for virtual screening.

Key tasks (adaptable to B.Sc./M.Sc. scope):

- **Biological plausibility evaluation:** Develop evaluation criteria for generated RNA libraries and simulated enrichment, e.g., sequence diversity, motif emergence, GC-content distribution, structural diversity, predicted folding stability, and enrichment of recurring structural/sequence patterns across rounds.
- **Benchmarking against experimental evidence:** Compare simulator outputs to properties observed in real SELEX campaigns (e.g., enrichment dynamics, convergence behavior, diversity collapse, amplification bias signatures). Where available, use published datasets or internal experimental results as reference.
- **Refinement of the simulator:** Improve the simulator by incorporating biologically motivated components such as selection stringency schedules, PCR/amplification bias, mutation/error models, and structure-aware constraints (e.g., filtering or conditioning on predicted secondary structure features).
- **Virtual screening workflow:** Use the refined simulator to propose candidate aptamers and rank them using computational proxies (e.g., motif/structure scores, stability, similarity clustering), producing a short list suitable for downstream experimental validation.

Prerequisites:

- Background in medical engineering, electrical engineering, computer science, (computational) biology, mathematics, physics, or related fields.
- Solid Python skills; experience with machine learning frameworks (PyTorch preferred).
- Interest in interdisciplinary work at the interface of machine learning and molecular biology. Prior biology knowledge is helpful but not required; we provide onboarding to SELEX and aptamer fundamentals.

The Self-Organizing-Systems Lab combines practical biological applications of machine learning with strong theoretical foundations. The project is embedded in an interdisciplinary research team and offers the opportunity to



contribute to publication-oriented work.

For further information, please contact Philipp Froehlich.

[1] Kramat, J., Kraus, L., Gunawan, V. J., Smyej, E., Froehlich, P., Weber, T. E., Spiehl, D., Koepl, H., Blaese, A., & Suess, B. (2024). *Sensing Levofloxacin with an RNA Aptamer as a Bioreceptor*. *Biosensors*, 14(1), 56. <https://doi.org/10.3390/bios14010056>