Article 10 - Controlled mutation in the replication of synthetic oligomers

Núñez-Villanueva, D.; Hunter, C. A. Controlled Mutation in the Replication of Synthetic Oligomers. Chemical Science 2021, 12 (11), 4063–4068. https://doi.org/10.1039/d0sc06770a.

Figure 4:

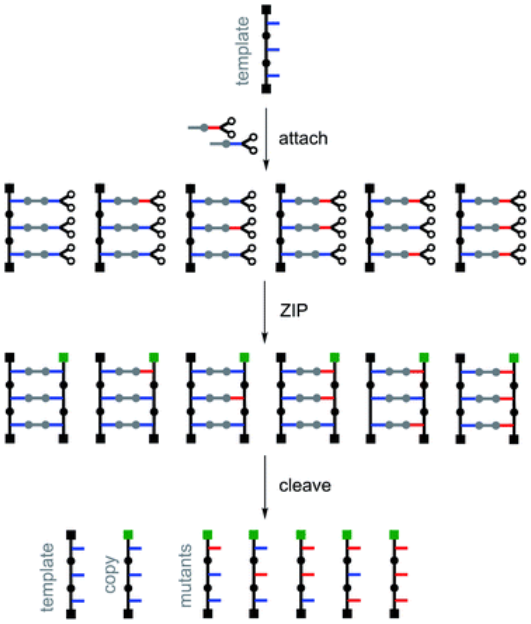

Figure 4 illustrates the principle of replication with a controlled mutation in a homo-oligomer system. During the attaching step, a mixture of two different monomers generates symmetric and unsymmetric base pairs in the pre-ZIP intermediate. The subsequent ZIP and cleave steps regenerate the template while producing an identical copy and all possible mutant sequences. The mutation rate is adjustable by varying the relative amounts of the two monomers used in the attached step. The isosteric base-pairing system, depicted in Figure 3, facilitates this error-prone replication process, with products distinguishable from the template by distinct end-capping groups introduced during the ZIP step.

Synopsis:

In the 2021 study "Controlled Mutation in the Replication of Synthetic Oligomers," researchers Diego Núñez-Villanueva and Christopher A. Hunter explored a method to introduce mutations at controlled rates during the replication of synthetic oligomers—short chains of monomer units. This work represents a significant step toward developing synthetic systems capable of evolution, which requires replication with variation.

In natural biological systems, evolution depends on the replication of genetic material with occasional mutations, leading to diversity and the potential for adaptation. Mimicking this process in synthetic systems has been a longstanding goal in chemistry, aiming to create materials that can evolve and adapt similarly to biological entities. Achieving controlled mutation rates in synthetic replicators is essential for this endeavor, as it allows for the deliberate introduction of variability while maintaining overall fidelity in replication.

The researchers employed a covalent template-directed synthesis approach, where a template strand guides the formation of a complementary oligomer. They utilized two distinct covalent base-pairing systems that are isosteric—having the same spatial arrangement—allowing them

to be used interchangeably without disrupting the overall structure. This interchangeability enabled both direct and reciprocal copying processes to occur simultaneously on the same template strand.

By introducing a mixture of monomers corresponding to the two base-pairing systems during the replication process, the researchers could control the mutation rate precisely. The proportion of each monomer type determined the likelihood of incorporating a different monomer than the original during replication, effectively introducing a mutation. This method allowed for fine-tuning the mutation rate by adjusting the relative concentrations of the monomers used.

Key Figure 4 in the article illustrates this process:

1. Template Strand: Shows the original oligomer sequence serving as the template for replication.

2. Monomer Mixture: Depicts the introduction of two types of monomers corresponding to the different base-pairing systems.

3. Replication Process: Illustrates the assembly of a new oligomer strand complementary to the template, with the possibility of incorporating different monomers, leading to mutations.

4. Resulting Oligomers: Shows the replicated oligomers, some identical to the template and others with mutations, depending on the monomer incorporation during replication.

This visual representation underscores the method's ability to introduce controlled mutations during the replication of synthetic oligomers.

The study's findings demonstrate that by carefully managing the monomer composition during template-directed synthesis, it is possible to achieve replication with a predetermined mutation rate. This capability is crucial for developing synthetic polymers that can undergo evolution, as it introduces variability while maintaining the integrity of the replication process. Such advancements could lead to the creation of adaptive materials with properties that evolve, opening new avenues in materials science and molecular engineering.

In summary, Núñez-Villanueva and Hunter's research provides a foundational strategy for introducing controlled mutations in synthetic oligomer replication. By leveraging isosteric covalent base-pairing systems and precise monomer mixing, they have paved the way for synthetic systems capable of evolution, mirroring the fundamental processes that drive diversity and adaptation in natural biological systems.