Gegory Linshiz

Recursive construction of perfect DNA molecules from imperfect building blocks

Making faultless complex objects from potentially faulty building blocks is a fundamental challenge in computer engineering, nanotechnology and synthetic biology. Here, we show for the first time how recursion can be used to address this challenge and demonstrate a recursive procedure that constructs error-free DNA molecules and their libraries from error-prone oligonucleotides. Divide and Conquer (D&C), the quintessential recursive problem-solving technique, is applied in silico to divide the target DNA sequence into overlapping oligonucleotides short enough to be synthesized directly, albeit with errors; error-prone oligonucleotides are recursively combined in vitro, forming error-prone DNA molecules; error-free fragments of these molecules are then identified, extracted and used as new, typically longer and more accurate, inputs to another iteration of the recursive construction procedure; the entire process repeats until an error-free target molecule is formed. Our recursive construction procedure surpasses existing methods for de novo DNA synthesis in speed, precision, amenability to automation, ease of combining synthetic and natural DNA fragments, and ability to construct designer DNA libraries. It thus provides a novel and robust foundation for the design and construction of synthetic biological molecules and organisms.