Premeltons are examples of emergent structures (i.e., structural solitons) that arise spontaneously in DNA due to the presence of nonlinear excitations in its structure. They are of two kinds: B-B (or A-A) premeltons form at specific DNA-regions to nucleate site-specific DNA melting. These are stationary and, being globally non-topological, undergo breather motions that allow drugs and dyes to intercalate into DNA. B-A (or A-B) premeltons, on the other hand, are mobile, and being globally topological, act as phaseboundaries transforming B- into A- DNA during the structural phase-transition. They are not expected to undergo breather-motions. A key feature of both types of premeltons is the presence of an intermediate structural-form in their central regions (proposed as being a transition-state intermediate in DNA-melting and in the B- to A- transition), which differs from either A- or B- DNA. Called beta-DNA, this is both metastable and hyperflexible – and contains an alternating sugar-puckering pattern along the polymer-backbone combined with the partial-unstacking (in its lower energy-forms) of every other base-pair. Beta-DNA is connected to either B- or A- DNA on either side by boundaries possessing a gradation of nonlinear structural-change, these being called the kink and the antikink regions. The presence of premeltons in DNA leads to a unifying theory to understand much of DNA physical-chemistry and molecular biology. In particular, premeltons are predicted to define the ends of genes in naked-DNA and DNA in active-chromatin, this having important implications for understanding physical aspects of the initiation, elongation and termination of RNA-synthesis during transcription. For these and other reasons, the model will be of broader interest to the general audience working in these areas. The model explains a wide variety of data, and carries within it a number of experimental predictions — all readily testable — as will be described in my talk Ultimately, one wishes to determine how genes—and the proteins they encode — function in the intact organism. Although it may sound counterintuitive, one of the most direct ways to find out what a gene does is to see what happens to the organism when that gene is missing. Studying mutant organisms that have acquired changes or deletions in their nucleotide sequences is a time-honored practice in biology. Because mutations can interrupt cellular processes, mutants often hold the key to understanding gene function. In the classical approach to the important field of genetics, one begins by isolating mutants that have an interesting or unusual appearance: fruit flies with white eyes or curly wings, for example. Working backward from the phenotype—the appearance or behavior of the individual—one then determines the organism's genotype, the form of the gene responsible for that characteristic. Today, with numerous genome projects adding tens of thousands of nucleotide sequences to the public databases each day, the exploration of gene function often begins with a DNA sequence. Here the challenge is to translate sequence into function. One approach, discussed earlier in the chapter, is to search databases for well-characterized proteins that have similar amino acid sequences to the protein encoded by a new gene, and from there employ some of the methods described in the previous section to explore the gene's function further. But to tackle directly the problem of how a gene functions in a cell or organism, the most effective approach involves studying mutant organisms that either lack the gene or express an altered version of it. Determining which cellular processes have been disrupted or compromised in such mutants will then frequently provide a window to a gene's biological role. In this section, we describe several different approaches to determining a gene's function, whether one starts from a DNA sequence or from an organism with an interesting phenotype. We begin with the classical genetic approach to studying genes and gene function. These studies start with a genetic screen for isolating mutants of interest, and then proceed toward identification of the gene or genes responsible for the observed phenotype. We then review the collection of techniques that fall under the umbrella of reverse genetics, in which one begins with a gene or gene sequence and attempts to determine its function. This approach often involves some intelligent guesswork—searching for homologous sequences and determining when and where a gene is expressed—as well as generating mutant organisms and characterizing their phenotype. Before the advent of gene cloning technology, most genes were identified by the processes disrupted when the gene was mutated. This classical genetic approach—identifying the genes responsible for mutant phenotypes—is most easily performed in organisms that reproduce rapidly and are amenable to genetic manipulation, such as bacteria, yeasts, nematode worms, and fruit flies. Although spontaneous mutants can sometimes be found by examining extremely large populations—thousands or tens of thousands of individual organisms—the process of isolating mutants can be made much more efficient by generating mutations with agents that damage DNA. An alternative approach to chemical or radiation mutagenesis is called insertional mutagenesis. This method relies on the fact that exogenous DNA inserted randomly into the genome can produce mutations if the inserted fragment interrupts a gene or its regulatory sequences. The inserted DNA, whose sequence is known, then serves as a molecular tag that aids in the subsequent identification and cloning of the disrupted gene. In Drosophila, the use of the transposable P element to inactivate genes has revolutionized the study of gene function in the fruit fly. Transposable elements have also been used to generate mutants in bacteria, yeast, and in the flowering plant Arabidopsis. Retroviruses, which copy themselves into the host genome, have been used to disrupt genes in zebrafish and in mice.

**Bottom Note:** This work is partly presented at EuroSciCon conference on Protein, Proteomics and Computational Biology

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