while the metal strips remain superconducting. Josephson also calculated that the application of a magnetic field in the plane of the junction lowers the critical current. Matisoo's idea was to use the magnetic field generated by a current in an adjacent superconducting strip to switch the Josephson junction between its zero-voltage and nonzero-voltage states. Logic and memory circuits could be built upon this basic switching action.

In the 1970's, under Wilhelm Anacker, IBM researchers made considerable progress toward a Josephson junction computer. The high point of this effort was a so-called cross section model that served no explicit electronic function but nonetheless contained all the types of circuits a full-fledged computer would have. The module also demonstrated a packaging scheme for mounting all the logic and memory chips in a box about 10 centimeters on a side (*Science*, 1 January 1982, p. 42). No comparable achievement in high-speed semiconductor technologies has been reported.

About 2 years ago, a decisive shift in the IBM program took place. Joseph Logue replaced Anacker as Josephson junction manager. At the time, Logue told *Science* that his intention was to establish a pilot production line at IBM's East Fishkill, New York, plant. The idea was to make Josephson junction chips in a realistic pilot line atmosphere to test whether the fabrication processes developed in the laboratory could be made to yield large numbers of defect-free chips. A researcher who has seen the East Fishkill facility says it is "very large and filled with very expensive equipment."

At about the same time, IBM also made a materials switch. The Josephson junctions made with lead alloy were insufficiently mechanically stable to withstand extensive cycling between room temperature and 4 K. The company therefore adopted the refractory metal niobium for the bottom superconductor in the Josephson junction but kept a lead alloy as the top superconductor.

An additional wrinkle to keep up the switching speed of the niobium–lead alloy Josephson junctions was to make them as small as possible. IBM researchers accomplished this by covering the top of the niobium strip with a relatively thick layer of niobium oxide but with a much thinner layer on the edge of the strip. They then deposited the lead alloy on the oxide-covered niobium. Current flows only through the thin oxide on the edge. It is much easier to control the thickness of the niobium strip as it is deposited than it is to control its width by the photolithographic techniques

Editing mRNA Precursors

Ever since most genes of eukaryotic organisms were discovered in 1977 to be interrupted by noncoding sections, or introns, molecular biologists have puzzled over two major questions. First, what is the role of introns in the origin and functioning of such genes? And second, what are the mechanics of editing out the noncoding sections from RNA transcripts of these genes? No one is surprised that answers to the first question are slow in coming, as, by their nature, definitive tests are difficult to devise. The second question has been tougher to resolve than might have been expected, however, especially in view of the technical wizardry that prevails in any decent laboratory these days. But, at last, the problem is beginning to crack, as four laboratories in the United States and one in Germany are currently reporting various in vitro reaction systems from whole cell or nuclear extracts that faithfully perform the RNA-splicing function.

Only by establishing reliable test-tube reaction systems will biologists be able to both determine what components are involved in splicing messenger RNA precursors and define what specific nucleotide signals are required to ensure the fidelity of the process. The in vitro systems developed so far are still in relative infancy; nevertheless they have revealed several general points. For instance, splicing is not necessarily coupled to transcription: in vitro splicing has been achieved both in systems in which the RNA precursor is synthesized endogenously and in which it is added exogenously. The splicing apparatus almost certainly includes at least one form of small ribonucleoprotein particle (specifically a class known as U1 snRNP's), as antibodies that precipitate them in in vitro tests halt splicing. This result adds welcome support to data from intact cells.

One intriguing observation from several laboratories is a lag time of 1/2 to 1 hour between the addition of the pre–messenger RNA and the onset of splicing. Phillip Sharp of the Massachusetts Institute of Technology notes that the naïve interpretation is that a complex splicing apparatus has first to assemble itself, presumably involving the U1 snRNP's. Tom Maniatis and his colleagues at Harvard and Walter Keller and his colleagues at the German Cancer Research Center in Heidelberg see the same phenomenon and agree—in the absence of any direct data—on the general interpretation. By contrast, Carlos Goldenberg and co-workers at Washington University, St. Louis, and Ryszard Kole, formerly at Yale but now at the University of North Carolina, have not noticed a significant lag period preceding splicing.

It seems clear by now that splicing does not proceed by a simple "scanning" of the RNA precursor molecule from one end to the other by a splicing complex. An endogenous structural specificity of the splicing apparatus, including the long precursor RNA molecule, must therefore be responsible for the precise excision of introns and the ligation of coding regions in the correct order. The overall configuration might be conferred by the tertiary structure of sections of the introns or coding regions, with precise alignment between splice junctions being assured by their complementarity with a short sequence of the small RNA molecule in the U1 snRNP particle.

Efficiency of splicing in the in vitro systems varies somewhat between laboratories, though in all cases it is high enough to allow experimental dissection of the component parts. Sharp, for instance, using whole cell HeLa extracts, achieves around 15 percent splicing with added precursor, whereas Kole, using the same system, has not yet reached this level. Both the Keller and Maniatis laboratories are developing nuclear extracts from HeLa cells: Keller regularly achieves 15 percent efficiency, and sometimes much higher; the Maniatis system is consistently higher. Goldenberg reports an 80 to 90 percent splicing efficiency with a myeloma nuclear extract.—**ROGER LEWIN**

Additional Reading

B. Weingartner and W. Keller, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 4092 (1981); W. Keller and N. Hernandez, *Cell*, in press; R. Kole and S. M. Weissman, *Nucleic Acids Res.* **10**, 5429 (1982); R. A. Padgett, S. F. Hardy, P. H. Sharp, *Proc. Natl. Acad. Sci. U.S.A.* **80**, 5230 (1983); C. J. Goldenberg, *Nucleic Acids Res.* **11**, 1337 (1983).