Brave new RNA world

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In 1995, you could still find, in the opening paragraphs of manuscripts and grant applications from my lab and others, the phrase “In the absence of a crystal structure for the ribosome....,” by way of rationalizing any number of biochemical studies aimed at figuring out the three-dimensional locations of things inside the ribosome, and ultimately its mechanism. We no longer have this excuse. Today, the Protein [sic] Data Bank, or PDB, lists *several dozen* high-resolution crystal structures of the ribosome. Needless to say, this has dramatically transformed the ribosome field. When the first ribosome crystal structures were announced at the meeting in Helsingør, Denmark, in June, 1999, I anticipated an occasion of great celebration; after all, we had waited some 40 years for this magical moment. Instead, the atmosphere was like that of a funeral, whose participants were paying their somber respects to the deaths of their careers. There was a widespread impression that all of the main questions concerning the mechanism of protein synthesis had been answered, and we would now put the ribosome to rest. Instead, we find that the ribosome continues to challenge and humble us. Although it is true that we could not expect to understand its mechanism at the molecular level in the absence of a crystal structure, the structure itself has raised more questions than it has answered. For example, confusion and controversy continue to haunt the study of aminoacyl-tRNA selection and translocation, two of the most fundamental steps of protein synthesis. But investigators of very different political and religious persuasions are at last able to agree that the mechanism of action of the ribosome is based fundamentally on its RNA, rather than its protein components.

In the 20 years since the founding of this journal, the practice of academic science itself has undergone profound changes, not all of which can be scored as improvements. Most notable has been the takeover of our lives and consciousnesses by computers and related devices. In 1995, you could still see faculty members working in their laboratories, or discussing experiments at the blackboard with students and postdocs. Now, as I stalk the hallways of my department, I find my colleagues in their offices staring

into screens, typing. Students and postdocs seem to spend more time logged into their laptops (further cut off from potential interaction with their bay-mates by ear-buds fed by MP3 players) than doing actual experiments. Nor has the proliferation of kits (which shield us from the distraction of actually knowing what we are doing) helped this situation. The simple presentation of one’s progress at group meeting devolves into a weeks-long adventure into the mysteries of Powerpoint, Photoshop, and font selection. Submission of a manuscript for publication has morphed from a couple of hours of Xeroxing into a mind-numbing marathon of file formatting and figure rendering, followed by endless automated responses from the journal with requests for pdf conversions, faxed legal documents, and the details of which authors handled which pipet. In spite of the Internet, e-mail, electronic submission, and electronically-generated figures and text documents, there continues to be a delay of months between submission and publication. It is sobering to remember that a paper by Watson and Crick, published in *Nature* on April 25, 1953, had only been submitted on April 2nd (!), long before the existence of personal computers, FedEx, or even fax machines. Note that the 23-day interval had to have included converting Odile Crick’s drawing of the DNA double helix into an engraving or lithograph that could be set and inked by the printers.

On the bright side, the emergence of the crystal structure of the ribosome almost exactly paralleled the development of the technology that was essential to solve it. The first crystallographic data that we collected from our weakly-diffracting ribosome crystals required an exposure time of several minutes per frame at the synchrotron, and an additional several minutes to read out the data from the imaging plate. Nowadays, much better data are collected with exposures of a fraction of a second and readout times of a few milliseconds. In the early 1980s, the fastest graphics computers struggled to rotate an all-atom representation of a small protein, and cost (including the enormous VAX 750 “minicomputer” and reel-to-reel tape recorder required to drive it) about \$250,000 in 1980 dollars. Perversely, the subsequent rapid development of computer graphics technology was not driven by the needs

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of physicists, engineers or molecular biologists, but by the video-game industry. By the time we needed to display whole ribosomes and their electron density maps in the late 1990s, the Silicon Graphics workstation had evolved to the point where the fastest SGI models could just handle it. (Eventually, of course, an undergraduate would show me an all-atom display of the complete ribosome structure on his iPhone.) Crystallographic computation took a similar path. With the need to refine the positions of hundreds of thousands of atoms against the amplitudes of millions of Bragg spots, we initially had to beg for days of time on supercomputers. These same calculations now run on a simple Linux box.

Part of the reason that we academics spend so much of our time typing is that the success rate of our grant applications is so low. Each grant application that falls below the pay-line (which currently hovers around the tenth percentile at NIH) sends us back to our keyboards for another try. Our need to publish our work creates yet more typing, compounded by the pressure from our institutions and granting agencies to publish in so-called “high-impact” journals—the “CNS” journals. With so many submissions crossing their desks, the sensibilities of the CNS editors are becoming dulled to the point of excluding all but the most (apparently) spectacular discoveries from consideration. This, in turn, drives investigators to exaggerate their findings with manuscripts bearing ever more hyperbolic titles and abstracts. A potential consequence is that manuscripts containing only modest descriptions of important discoveries risk rejection

without review, again sending us back to the keyboard. These kinds of concerns already worried the co-founders of the embryonic RNA Society more than 20 years ago, leading to creation of *RNA*, a sort of high-quality “people’s journal” for RNA enthusiasts, and a proud counterpoint to the CNS journals. The success of *RNA* has been in no small part due to its editor, Tim Nilsen, whom one can only imagine as an omnivorous yet critical and informed speed-reader. Congratulations and thanks, Tim!

What will we be typing (and Tim digesting) during the next 20 years? It seems as though a new class of RNA is discovered about once a year, so by 2035 there should be plenty of papers describing another 20 or more classes of yet undiscovered RNAs, along with their respective “omics.” Knowledge of the structure and function of spliceosomes will eventually catch up with ribosomes, with the interesting (and daunting) twist that the spliceosome is a moving target, morphing its way through the different steps of pre-mRNA splicing with major changes in its molecular composition and structure. An increased understanding of the principles of RNA structure and function will open the door to RNA engineering, allowing us to leap-frog in vitro selection to create novel RNAs of predicted function and specificity. CRISPR technology may turn guide RNAs into medicines that will be prescribed for patients with viral diseases, cancers and genetic disorders. Meanwhile, I am confident that the ribosome will continue to intrigue and baffle, endlessly provoking controversy among new generations of the RNA faithful.

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