

Comment

The slide rule and the calculator

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Now that the race to sequence the human genome is over, with both sides engaging in the most patently phony display of amity since the negotiations that ended the Vietnam War, we can put aside petty political considerations and try to answer the most profound question that this monumental achievement raises: who won?

It's exactly the same question that I found myself asking at the conclusion of the first cricket match I ever saw, but is a lot easier to answer. The obvious answer, and the one offered by most pundits, is that we all won. We have the sequence, and we can go ahead with all the exciting science it will enable us to do. We have it faster and at a lower cost than if the private competition had not stepped in and made use of the public project's data and, because of newer technology, forced the public initiative to change its strategy and accelerate its pace. This argument has considerable merit. Celera Genomics, the private company, acknowledges that it made use of the publicly available sequence data from the Human Genome Project in assembling the fragments of sequence produced by its whole-genome shotgun-sequencing strategy. The Human Genome Project acknowledges that the arrival of Celera on the scene caused it to abandon its original goal of producing a complete, highly accurate sequence slowly and drove it instead to generate a draft sequence of lower quality as rapidly as possible. From these facts, it is possible to conclude that each side needed the other and, since they ended up publishing simultaneously, the race could be considered to have ended in a dead heat.

But when other facts are taken into account, this conclusion - which is the one the public project would dearly like accepted - seems simplistic. The private effort did not really need the public data. Celera has shown repeatedly that its whole-genome shotgun-sequencing method is capable of assembling an accurate draft sequence entirely on its own, even for multi-chromosomal genomes far larger than those of bacteria. Craig Venter and Ham Smith, the inventors of this approach, clearly devised a superior strategy to that

used by all of the public initiatives. The slowness of the public projects to recognize this superiority is, in retrospect, hard to understand. Celera's technology was also superior. By assembling huge banks of automated sequencing machines and employing massive computational resources to assemble fragments of the genome into their proper order on each chromosome, the private initiative was - and is - able to sequence any genome many times faster, and at least an order of magnitude cheaper, than by traditional methods.

The power of the technology has not yet made its full impact felt, but it will. If Celera were to turn the full force of its sequencing capabilities on a single problem, it could sequence the entire yeast genome in less than a day. Genomes the size of mouse, chimpanzee or human can be done in draft form in at most a few months. This is transforming technology. It changes our entire perspective on data-gathering in biology. It is so fast, and potentially so cheap (less than a million dollars for yeast), that it demands that we start to ask which genomes we would like to have sequenced, not which ones we can afford to have sequenced. It frees us to consider the use of genome sequencing as a routine tool in basic medical science and evolutionary and developmental biology. As we contemplate this power, it becomes clear that Celera only used the human project's published data because it would have been stupid not to.

None of this is intended to minimize the considerable contributions of the public effort. After all, the publicly funded researchers started the whole thing. They mobilized the support of governments and the public as a whole for the effort, gathered the resources needed, mapped the genome, and developed many important early-stage technologies. Now they want to finish the job they originally started: to produce a high-quality, complete genome sequence for the human genome. They have earned the right to do so. But it's unclear that they should ever do another genome by the same methods. Celera's technology is clearly the way to go in the future, and the best use of public funds would be to

contract companies like Celera to produce desired genome sequences with a condition of the contract being immediate public availability of the data. As a for-profit entity responsible to its shareholders, a company like Celera would probably find such a revenue stream attractive. My recommendation would be for the Human Genome project to set aside a large sum for such contracts and then convene a panel of biologists to establish priorities for which genomes to sequence.

What, then, should the public project do with itself after it finishes the complete human sequence? Gathering data on single-nucleotide polymorphisms (SNPs) and other individual genetic characteristics may make some sense, but I think most of the interesting work in this area will probably be done more rapidly in the private sector because of possible commercializable medical applications. A better goal for the human initiative would be to produce and make available the cDNA clones of all human genes for research use. They could do the same for other important higher organisms such as the mouse, the fly, the worm and the dog, and for important microbial organisms as well. I think it would also be a good idea for them to turn their attention to proteomics and functional genomics. They can develop techniques for both of these efforts, and can - and should - carry out analysis of protein structure and function for organisms of no medical or commercial importance, as these are unlikely to be investigated privately. But if they try to compete with the private sector for genome-wide analysis of medically related and industrially useful organisms, they are likely to find themselves once again losing the race. The public programs will, of course, do something. It would be unreasonable to expect them to do what Senator Aiken of Vermont urged the US to do in the middle of the Vietnam War (and what the US should clearly have done) - declare victory and go home.

In retrospect, it would have been very smart for the public sequencing initiative to have done just that when Celera announced its intention to compete. But the public effort had too much pride invested, and I think also greatly underestimated the power of the Celera technology. My guess is, however, that the real reason it made what I consider the wrong response to the challenge of the private initiative is that it saw its mission in too narrow terms. The researchers viewed their objective as simply to sequence the human genome. In much the same way, the makers of slide rules saw their function as simply to manufacture slide rules. Had they seen their mission more broadly - say, to facilitate calculations - they would have developed the electronic calculator themselves, or at least marketed it when it was developed by others. But they didn't, and now they and their product are primarily historical artifacts. Had the public effort seen its mission as the provision of tools and data that would enable the human genome sequence to be obtained, no matter by whom, they would have stepped aside for Celera at the appropriate time or truly joined forces with it. Their best

hope for escaping irrelevance now is to take the widest possible view of their future goals.

Perhaps it would not have mattered had they judged things correctly. No organization willingly contributes to its own demise. (This is why the police are unlikely to completely eradicate crime.) Organizations are like organisms: they do whatever they can to survive. Public genome projects, and the big-science philosophy they have spawned, will be with us for a long time to come. We can't expect them to put themselves out of business. But we can demand that they do not stick to that business when they should get out, and that they become as adaptable in this age of genomics as we individual biologists have had to become.

Editor's note: The author has declared that he has no financial or commercial interest in Celera Genomics.