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PERSPECTIVE

Reflections on the past 25 years

Federico Gago

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If I were to name what has changed more drastically in the computational labs devoted to drug discovery and molecular simulations in the last 25 years, I would point my finger in three directions:

1. Availability of programs and servers that perform lots of different tasks, sometimes computationally expensive, usually for free. As a consequence, the number of commercial solutions and vendors has decreased substantially, and more and more specialists and non-specialists have broad access to molecular modeling tools, including the following:
   - 1.1. *Molecular graphics software*: vector graphics were rapidly superseded by raster graphics, and workstations and personal computers became more or less indistinguishable. Visualization of molecular structures on your own laptop has reached a level of quality and performance that was simply unimaginable at the end of the eighties, and essentially at no cost: programs and plugins such as RasMol, Chime, JMol, and PyMOL are probably the best known examples.
   - 1.2. *Building of small molecules*: writing Z-matrices by hand and manipulating real wireframe or ball-and-stick models was customary. Today Java molecular editors allow students and their mentors to draw literally any molecule on an electronic board and convert it to a 3D structure using programs such as CORINA. The former nightmare of formats interconversion appears to be history thanks to programs like OpenBabel and storage of chemical notations has been simplified with SMILES. The downside is that many users do not even know what is inside their files!
   - 1.3. Homology modeling of proteins, structural comparisons, cavity and tunnel detection, binding site characterization, ligand docking, in silico protein–protein complex formation, etc. are operations that can be easily (and many times reliably) done by any interested user.
2. Existence (and proliferation) of hyperlinked databases covering the known chemico-biological space and most of the existing bibliography. There is little excuse nowadays to miss the relevant reference or ignore the antecedents of your work. Parallel progress in so many areas, most notably in structural biology, has opened enormous possibilities for research. Navigation through the different electronic highways requires some expertise mostly to focus on the intended information and not to get entangled along the way.
3. Increased computer power, massively parallel calculations, and devoted special-purpose machines such as Anton have pushed the limit of what was theoretically possible only a few years back. The fact that quantum mechanics programs like Gaussian, which required mainframe computers or even supercomputers for some calculations, can be run on laptops and desktop computers, is considered by many as a real revolution.

Future advances in the next 25 years will go necessarily hand in hand with technological innovations, most of which we probably cannot even figure out at present, insofar as it is proven that we could not anticipate the current state of affairs 25 years ago. Thanks for reading.

F. Gago (✉)
Departamento de Farmacología, Universidad de Alcalá, 28871 Alcalá de Henares, Madrid, Spain
e-mail: federico.gago@uah.es