Supplementary Material for

“Using *Situs* for the Integration of Multi-Resolution Structures” by Willy Wriggers

A. A Personal History of the Development of Situs

At the time of this writing, the *Situs* package has just passed the ten-year anniversary of its 1999 journal publication. Whereas the main article documents how *Situs* continues to be useful to the biophysical community, it may be worthwhile on this occasion to reflect on how the package came into existence.

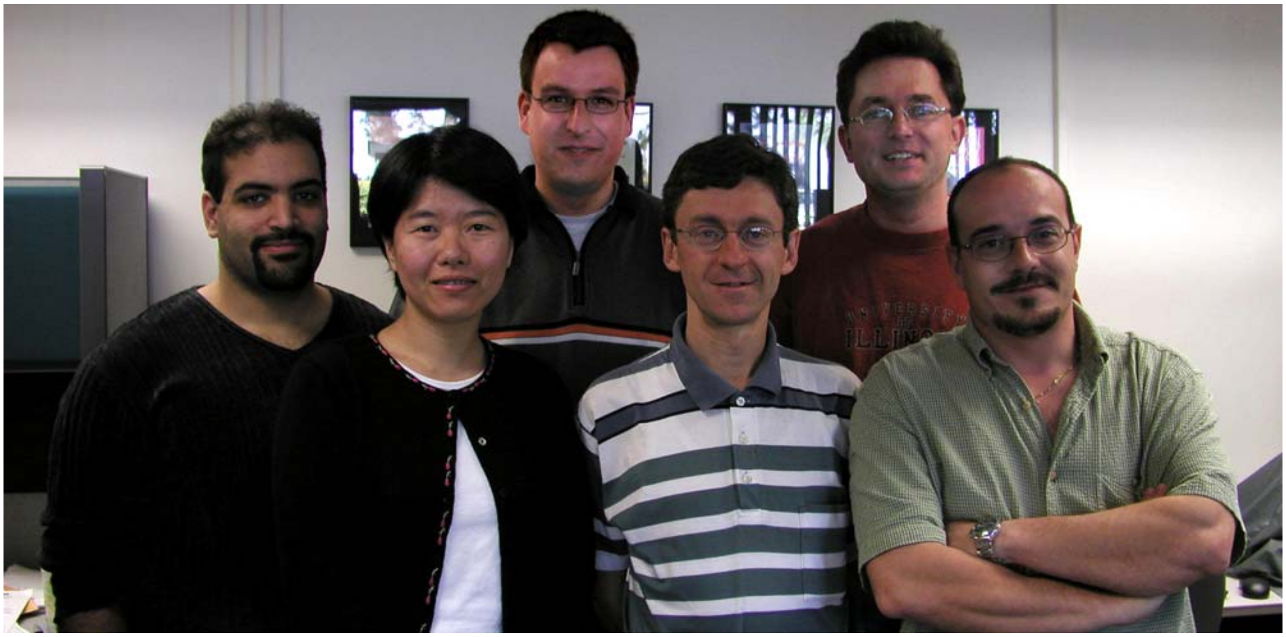
As a physics graduate student in Klaus Schulten's group at the University of Illinois at Urbana-Champaign (UIUC), I received rigorous training in biomolecular modeling and simulation. In the early 1990s, Schulten was still leading a formidable computational neuroscience program that he had built at Technical University Munich, Germany, and moved to Illinois in 1988. In particular, Schulten and visiting professor Annette Zippelius taught a course on the “Physics of Neural Networks” in the spring of 1993, which I attended as a graduate student at UIUC. For the term paper for this course, I studied the geometric properties of the Kohonen self-organizing map [1] and the “neural gas” algorithm that had been developed by Thomas Martinetz in the group [2,3]. The term paper and the corresponding programs proved valuable during the initial design of *Situs*. In the meantime, by the mid-1990s, Schulten decided to focus exclusively on biophysics. Consequently, I shifted my interests to molecular dynamics simulations of cell motility proteins and methods for simulating and mathematically characterizing large-scale conformational changes. In one resulting article, I predicted a conformational change of the kinesin motor when superimposed with a 2D projection of the microtubule density solved by the Milligan laboratory (Figure 12A in [4]). Although only in 2D, the figure proved inspirational during a visit to San Diego in the summer of 1997, and both Milligan and I saw a potential for extending this type of fitting to the third dimension.

In November 1997, I joined the McCammon group at UCSD for a postdoctoral tenure. J. Andrew McCammon, a power house in physical chemistry and biomolecular simulation, actively encouraged my growing interactions with Milligan, whose laboratory at The Scripps Research Institute (TSRI) was within walking distance. Given the freedom to chose suitable methodologies, I decided to continue the work on neural networks started with Schulten five years earlier. In January 1998, it became clear that the Martinetz neural gas algorithm would be highly valuable for biomolecular docking in that it could provide a coarse-grained representation of 3D data. McCammon suggested that I bring in my own funding for a joint postdoctoral research project and, together with Milligan, we were successful in securing a *La Jolla Interfaces in Science* (LJIS) postdoctoral fellowship. LJIS was an interdisciplinary and multi-institutional training program supported by the Burroughs Wellcome Fund that encouraged dual mentorship of postdocs in the La Jolla community. The fellows gained wide visibility in San Diego, which later proved important. In

August 1998, I also became formally affiliated with the Milligan laboratory at TSRI. This arrangement proved very productive; the underlying methods were tested in the McCammon group at UCSD and applied to experimental data at TSRI. To this end, I received instruction in electron microscopy (EM) theory and practice from Milligan and his friendly (and patient) coworkers. The first article resulting from the LJIS collaboration was published the same year [5].

The idea of developing *Situs* as a software package first took shape in the summer of 1998, mainly through interactions with professor Gina Sosinsky at UCSD. In late August, Sosinsky alerted me to an upcoming issue on molecular visualization software in the *Journal of Structural Biology*. These special issues are widely read in the EM community. A first version of the package was written, and the article [6] submitted less than eight weeks later, in retrospect an incredibly short time. *Situs* would be the first designated fitting package for EM, but I soon became aware of a competing article in the same journal issue. I realized that I could legally distribute my code freely on the web in open source form. Eager to be the first to roll out a package publicly, I created a tutorial and user guide and used McCammon's web server for their dissemination. Some early adopters heard about the web site and the first documented download of *Situs* before its official release occurred on November 10, 1998. Version 1.0 was officially announced on six mailing lists on February 1, 1999. The *Situs* paper [6] made the journal cover and appeared in April 1999. At around the same time, I received a phone call from Charles L. Brooks III (TSRI). Brooks was about to renew his NIH Resource grant and indicated that he could utilize some of the ideas; he asked if I would like to join TSRI as an assistant professor in his domain. At the time I was only 17 months into my postdoctoral tenure, but I saw an opportunity to continue my work seamlessly at a prestigious institution, and accepted. I remain indebted to Andy McCammon, who allowed me to move *Situs* to TSRI. A few weeks later I attended the Gordon Research Conference on 3D EM in Henniker, New Hampshire, June 20-25, 1999. The special journal issue with our cover figure was widely distributed at that meeting and I met many leading electron microscopists for the first time. The conference chair, Bridget Carragher, invited me to give a talk, and I gave the first public demonstration of *Situs* in a session organized by Gina Sosinsky and Michael Schatz (Image Science, Berlin, Germany). The events of 1999 were a highlight of my early career, and I enjoyed the sudden attention my work received.

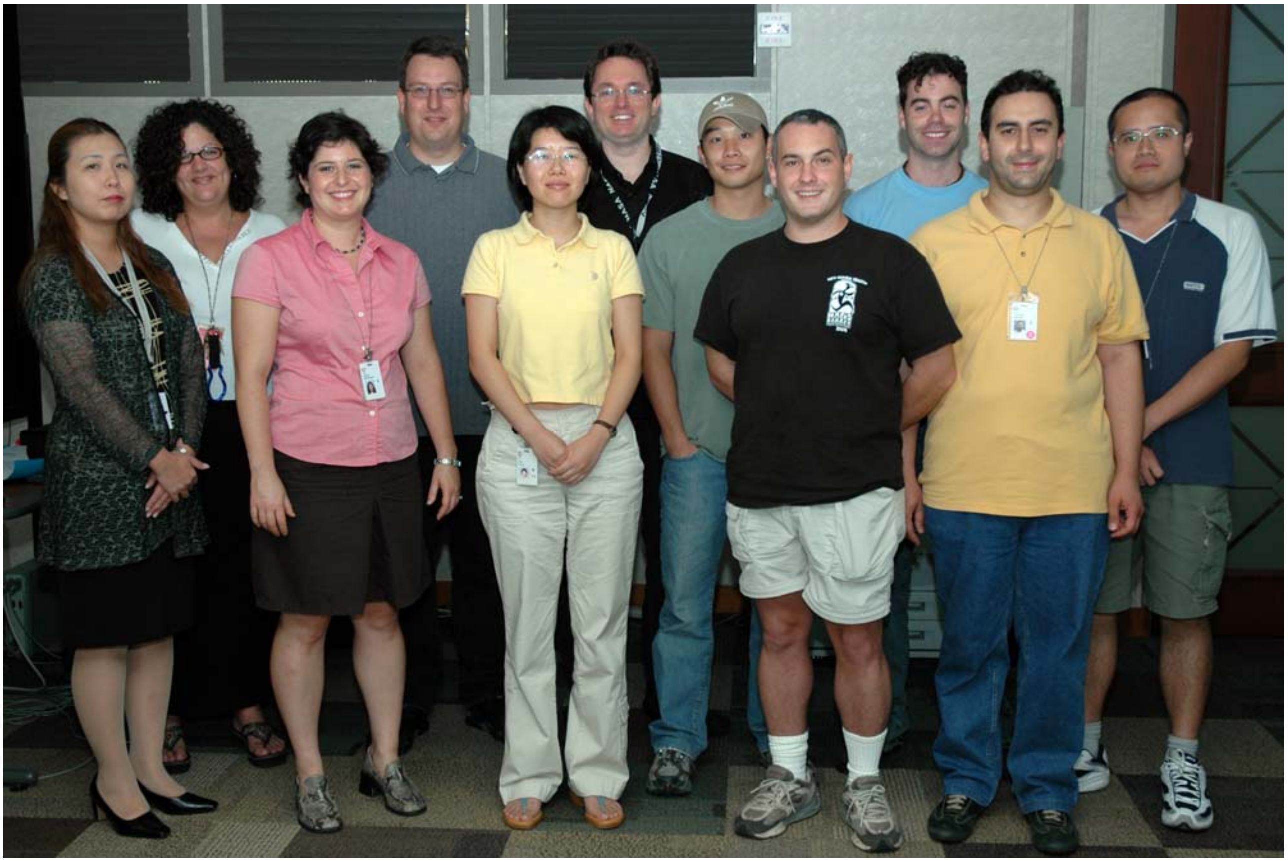
What happened in the decade after the first distribution of the code? The original manuscript [6] was later recognized with the *Journal of Structural Biology* Paper of the Year Award [7]. Among several grants, I secured an NIH grant in 2001 (R01GM62968, renewed in 2006) that was directly based on the development of *Situs* and supported a growing group of coworkers. Supplementary Figure 1 shows the TSRI group in 2002.



Supplementary Figure 1. Computational Structural Biology Group (TSRI), 2002. From Left: Essam Metwally, Yao Cong, Stefan Birmanns, Julio Kovacs, Willy Wriggers, and Pablo Chacón.

I cannot comment here on every one of my 30 coworkers over the years (for more information, see our alumni pages at URL http://wriggers.biomachina.org/people/alumni.html), but I'd like to state that attracting a good postdoc right away makes a big difference in productivity. I was fortunate to have Pablo Chacón contact me in 2000, shortly after I entered my position at TSRI. Pablo was well trained in biophysics and his experience fit the project perfectly. Brooks kindly provided the initial funding for Pablo's position until fellowships and grants were secured. At the time, my small team was still closely interacting with Ron Milligan's laboratory at TSRI. An amusing fact is that we mostly met to discuss science during Milligan's cigarette breaks (both Pablo and Milligan were smokers). Consequently, I almost ended up smoking myself (it was for a good cause; our collaborator was otherwise very busy!). Inspired in part by Pablo's background in scattering, we broadened the application of the *Situs* tools to other areas of biophysics such as small angle X-ray scattering [8]. The coarse graining that we initially used for rigid-body docking [9] also laid the groundwork for the later development of a flexible docking technique and elastic network models [10-12]. In a series of papers, we took advantage of Fourier correlation theory to rapidly scan the six translational and rotational degrees of freedom of a probe molecule relative to a (fixed) target density map [13-15].

After our move to Houston in 2003, my group at the University of Texas Health Science Center (UTHSCH) doubled in size (Supplementary Figure 2), and I found myself busy teaching courses. A trusted postdoctoral teaching assistant in my “Computational Structural Biology” course was Sugoto Chakravarty, who co-authored a review article on biomolecular linkers based in part on *Situs* calculations [16]. We were also fortunate to have Stefan Birmanns, a computer scientist who had collaborated with the group over the years while completing his Ph.D. in Jülich, Germany, join us as a postdoc to coordinate the group's hardware and software development. Although Stefan primarily developed his own visualization software, *Sculptor* (http://sculptor.biomachina.org), he made substantial contributions to *Situs* tools with next-generation algorithms [9,12]. Although many more of my group members deserve praise, the above three postdoctoral coworkers (Chacón, Chakravarty, and Birmanns) stand out because they each moved on to academic faculty positions.



Supplementary Figure 2. Laboratories for Biocomputing and Imaging (UTHSCH), 2004. From Left: Namiko Burleson, Joan Zuñiga, Hilary Wriggers, Stefan Birmanns, Yao Cong, Willy Wriggers, Char Hu, Chance Coble, Paul Boyle, Valerio Mariani, and Zhiyong Zhang.

Here, I would also like to honor the memory of UTHSCH graduate student Paul C. Boyle from Killibegs, Ireland, who died in a tragic car accident on November 29, 2004. Paul was a bright and cheerful coworker, and made many contributions in my group in Houston (Supplementary Figure 2). Paul was working on a new release of *Situs* and carried out molecular dynamics simulations to simulate Epidermal Growth Factor [17]. He also contributed a software program (now in *Sculptor*) that allows for the inspection of volumetric maps. Paul was posthumously awarded an M.S. degree, and UTHSCH has established an annual student achievement award in his name.

Like most scientists, software developers are judged by the quality of scientific work in peer-reviewed publications. On the other hand, to gain acceptance in the user community, it is important to offer support and hands-on outreach programs. Consequently, a balance is needed between the two modes of communication. Although we participate in meetings and symposia by other groups, we have also found it useful to organize our own seminars and workshops to connect more directly with our user community (programs, lecture materials, and video recordings of the following events are available at URL http://wriggers.biomachina.org/events):

In 2001 we organized an afternoon workshop, “Docking Do's and Don'ts,” that was attended by more than 100 participants at the Gordon Research Conference on 3D Electron Microscopy, Bristol, RI, June 24-29. In San Diego in 2003, we organized a “*Situs* EM/X-tal Fitting and Modeling Workshop,” February 3-5, with 29 participants from the US, Europe, and Japan. In addition to a lectureship series of external speakers that took place in Houston approximately every second month, we also organized a complementary Houston town meeting every other month for local speakers. Overall, we hosted 27 visiting scientists on site and trained them in the usage of our software.

Our greatest venture to date was a six-day international workshop in late April 2006 on “Innovations in Nanoscale Modeling and Imaging of Biological Systems” in Houston (Supplementary Figure 3). The workshop featured 21 invited speakers and 50 invited participants from as far away as Germany, Israel, Singapore, South Africa, Spain, and the United Kingdom. In addition, about 30 Houston-area scientists attended the public lectures. Hands-on computer sessions trained participants in the use of software developed by selected speakers and by our group. The speakers were mainly early-career software developers at other institutions that I knew from my research and from international conferences. Many new collaborations were fostered during this time, and we were able to connect with the users of our software, who presented their own work on posters. As an organizer, I found it to be an incredibly motivating experience to meet with the enthusiastic users in person.

Supplementary Figure 3. “Innovations in Nanoscale Modeling and Imaging of Biological Systems” in Houston, April 17-23, 2006. (Left) Opening speakers (from left): Robert Glaeser, Willy Wriggers, Jack Smith, and Zhiyong Zhang. (Right) Group picture of late night participants at Cabo MixMex Grill, downtown Houston.

Ron Milligan once commented that I was “clever or lucky, it doesn't much matter which” in getting into computational biophysics at this particular time. In 2006 I was awarded tenure at UTHSCH, in part based on the success of the *Situs* package and the organizational and grantsmanship milestones we achieved. I went from student to associate professor in nine years and had my share of tragedy and triumph along the way. What would be the next challenge in this personal journey? After some soul searching I found I was happiest when I had the opportunity to be personally involved in science, and I wanted to free myself form administrative responsibilities as much as possible so that I could focus more on research and learning. I knew that such a rejuvenation would require either a longer sabbatical or a permanent relocation. I was fortunate in being selected to join the privately funded laboratory, D. E. Shaw Research, in Manhattan (http://www.DEShawResearch.com). Stefan Birmanns took the helm in Houston, so I was able to leave my coworkers in good hands while exploring a new phase in my career.

Although my research interests have diversified, *Situs* continues to be useful to many researchers in biophysics. Over the years, more than 2,000 users have registered the download, and a growing number of research groups use the software (about 100 research projects and more than 1,000 citations refer to our work). With the assistance of collaborators, alumni, and enthusiasts in the community, I hope to continue the development of the package in the next decade and beyond.

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