



How a “weak” interaction shapes the structure of peptides

Tiina Autio

Folding and unfolding processes play an important role in the function of proteins, which consist of amino acid chains of various lengths. Short amino acid sequences (some tens) are called (poly)peptides. Citing an often used example, the FHI research group notes that if a protein folds into a non-native conformation and this misfolded form is replicated over and over again, diseases such as mad cow disease and some forms of diabetes can result – and that understanding the structure and dynamics of proteins could lead to a better understanding of these diseases.

The amino acid sequence formally defines a given protein, but the actual three-dimensional structure and function of a protein is the result of a complicated interplay of many variables – including both environment variables and those intrinsic to the molecule itself. According to the research group, in principle, the underlying mathematical theory determining any chemical system, including the structure of proteins, is well known: quantum mechanics as embodied in the Schrödinger equation is often referred to as the scientific “first principles” on which our understanding of the chemical bond-

is founded. The research group attempted to extend the reach of this ‘first-principles’ accuracy to a peptide of a meaningful size (16 amino acids) with present methods.

In any practical treatment of Schrödinger’s equation for real molecules, approximations must be made. The particular method used by the group to reach the necessary system sizes and times for molecular dynamics is known as density functional theory. The crux is that density functional theory as it is normally employed provides very good accuracy for bonded struc-

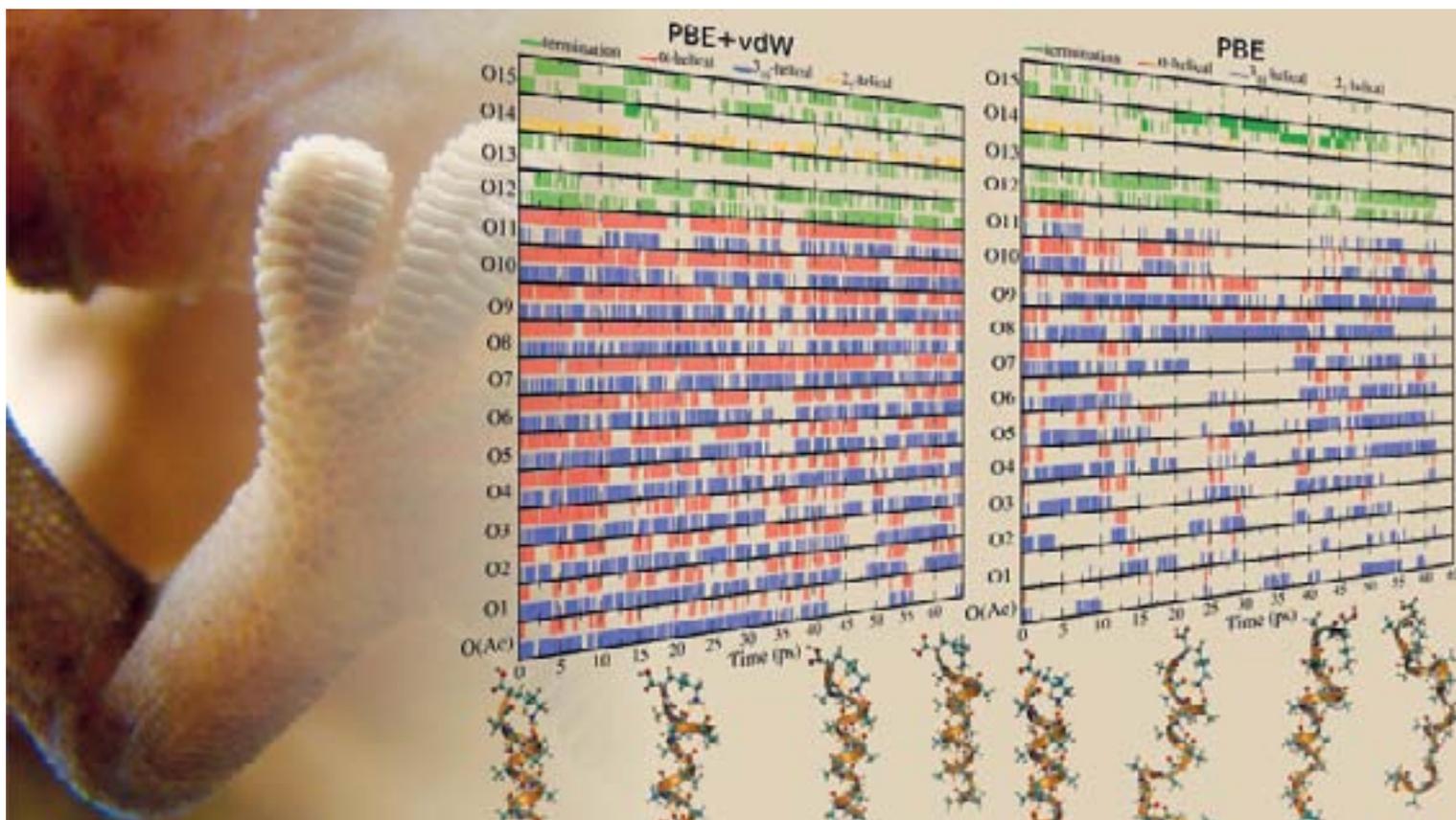


Figure 1 . Van der Waals forces are ubiquitous in nature. Although often called “weak” in a chemical sense (covalent or ionic bonds are individually much stronger, for example), the combined effect of van der Waals interactions in biology can be significant. One of the most striking examples in popular science is the ability of a Gecko’s foot to attach to a pane of glass. At the molecular scale, the group has demonstrated that a proper account of van der Waals interactions is essential for the formation of so-called “secondary structure” in peptide and protein molecules. Here, also, other interactions (hydrogen bonds or electrostatics) are often thought to constitute the main forces that stabilize the structure. However, the helical structure known from experiment for the molecule shown (Ac-Ala15-LysH+) is stable in theory over a few tens of picoseconds only if vdW interactions are properly accounted for, but not otherwise. The plots visualize the type of hydrogen bond formed during our simulations, separate for each C-O group in the peptide residue [O(Ac)-O(15)]. © The data and viewgraphs: Volker Blum, Mariana Rossi, Alex Tkatchenko and Matthias Scheffler. © Gecko’s foot: Wikimedia Commons. Author: Bjørn Christian Tørrissen.

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Deisa resources

The researchers used altogether 3 000 000 computational hours on their Deisa project named BioMolQM. The simulations were run with the following supercomputers: Huygens at SARA in the Netherlands, Vip at the Rechenzentrum Garching (RZG) of the Max Planck Society and the IPP in Germany, HECToR at EPCC in the United Kingdom, Louhi at CSC – the IT Center for Science in Finland and HLRB at the LRZ computer centre in Germany. Approximately 500 individual runs were made.

tures, but fails altogether to capture a weak, distant (non-local) class of interactions within molecules. These intramolecular forces are known as van der Waals (vdW) dispersion forces.

To achieve the necessary accuracy, the group included a carefully benchmarked correction for vdW interactions into its first-principles molecular dynamics simulations. “Inclusion of van der Waals interactions is essential - if there were no van der Waals interactions in the world, the structure formed by any peptide or protein could be completely different from what it is in reality. This would in turn change the function of the peptide or protein fundamentally”, the group says. A direct comparison to gas-phase experiments by other groups confirms the need for this correction.

“We picked a series of peptide molecules for which a very good model for the structure exists. Gas phase experiments are the basis for this model, i.e., the molecule is essentially completely isolated. These experiments provide an ideal reference to which theory can connect”, the group says. “Our attempt was to probe the structure and stability of the helical secondary structure in peptides, specifically a polyaniline peptide called Ac-Ala15-LysH+, by direct simulations with the full accuracy of a first principles calculation. A particular goal was to examine the various interaction contributions such as the Hydrogen bond strength with peptide length, the role of the termination and van der Waals interactions. This helix is known to be stable in a vacuum up to temperatures of ~700 K, far above the normal, biological stability range. Verifying

this remarkable stability was one of our primary questions”.

Weak interactions stabilize the structure of peptides

The study of the research group revealed the remarkably influential role that van der Waals interactions play as intramolecular forces stabilizing the structure of the investigated peptide up to the extreme temperatures observed in experiments.

“By using state-of-the-art electronic structure calculations on cutting edge supercomputers, we show that the extreme thermal stability of gas-phase peptides stems from the so-called “weak” van der Waals (vdW) interactions. Van der Waals interactions are crucial for the weak interlayer binding in graphite, and they can be influential in protein–protein and drug–protein binding inside our bodies”, the group explains. However, their role in protein secondary structure has not been fully established. “Our work clearly demonstrates that “weak” vdW interactions are even more ubiquitous than is generally appreciated”, the group says.

“What is remarkable is that we could not only verify and quantify the impact of intramolecular van der Waals interactions for protein structure stability indirectly, by static benchmark calculations. We were also able to verify and visualize the impact of van der Waals interactions directly in first-principles molecular dynamics. On a time scale of ~50 ps in multiple, temperature depend-

ent molecular dynamics simulations across several temperatures, we could show directly how the secondary structure is stable up to ~700 K when vdW interactions are appropriately included. In contrast, the same secondary structure clearly falls apart on the same short time scale when the standard theory neglecting van der Waals was applied”, the group explains.

The group’s present calculations show that it is possible to realize the potential of treating such molecules with the accuracy of quantum-mechanical “first principles” if all the relevant interactions are included. By considering van der Waals forces in the density-functional theory they were able to perform direct first-principles simulations of the structure and dynamics of peptides with several hundred atoms with an essentially converged energy landscape.

“The theory used by us is a parameter free way to describe the structure and structure changes of any molecule. If the environment is treated correctly and with sufficient computer power, this can lead to a reliable “screening” of molecules for many purposes, including medication. The same exact theory covers almost all materials and molecules known to us with great accuracy, and allows materials predictions as well as understanding”, the group notes.

For more information:

<http://www.deisa.eu/science/decision/projects2008-2009/BioMolQM>

DEISA Digest 2011 Published

DEISA has regularly reported on science projects through DEISA Newsletters and Digest magazines. After the DEISA Digest 2008, the DEISA video in 2009, and the DEISA Digest 2010, now the last DEISA Digest 2011 has been published and was already distributed during the recent DEISA PRACE Symposium in Helsinki.

This DEISA Digest 2011 magazine focuses on recent key results of the DEISA Extreme Computing Initiative and Extreme Computing projects from Science Communities in Life and Space sciences, covering major science areas ranging from Astro to Earth Sciences, to Engineering, to Life and Materials Sciences, and to Plasma Physics.

The DEISA Digest 2011 is available from all DEISA sites and can also be downloaded soon from the DEISA web site.

For more information:

<http://www.deisa.eu/publications>

DEISA PRACE Symposium 2011 attracted over 200 participants from 26 Countries

The DEISA PRACE Symposium 2011 was once again held as a big European HPC (High Performance Computing) event. The symposium featured speakers from different scientific communities as well as decision makers in science. The symposium was of major interest to a broad audience: from scientific users, HPC technology experts and vendors, government representatives, EC representatives to industry partners. The event gathered more than 200 participants from 26 countries. This symposium was held from April 13 to April 14 in Helsinki, at the National Museum of Finland, and was hosted by CSC – IT Center for Science Ltd.

Prominent keynote speakers from all over the world presented extreme computing technologies and challenges in computational science. Speakers on the first day included Zoran Stancic of the European Commission, Leena Vestala of the Ministry of Education, Culture and Science (Finland) Achim Bachem, Coordinator of PRACE (Germany), Thom Dunning from the University of Illinois at Urbana-Champaign (USA), Xuebin Chi from the Chinese Academy of Sciences (China), and David Keyes from the King Abdulah University of Science and Technology (Saudi Arabia).

During the sessions on 'Challenges in Computational Science', speakers from different scientific communities which are supported by DEISA and are planning to use the services provided by the PRACE Research Infrastructure presented their recent findings using HPC. The scientific fields covered were astrophysics, quantum computing, space research, engineering, climate research, materials science, biophysics, life sciences, turbulence, nuclear physics, chemistry, and bio-engineering. Speakers from the DEISA project presented highlights of the DEISA project, which ends in April 2011. Tier-1 services as provided by DEISA will be integrated in the PRACE Research Infrastructure (RI). The first call for combined Tier-0 and Tier-1 resources, starting on May 2, 2011, was also announced during the symposium.

The symposium also included the first PRACE User Forum. In this session PRACE representatives presented the services the PRACE RI offers to European scientists. The session ended with a panel discussion where HPC users expressed their opinions about the services of PRACE RI and the future of the PRACE User Forum. A group of HPC users from different scientific areas was established in order to facilitate fruitful PRACE User

Forums in the future. The activities for the creation of a sustainable User Forum will be followed up by PRACE together with the group of users established during the first User Forum and other users from various scientific fields that have HPC needs for advancing their research work.

The Symposia series was carried out as DEISA Symposia in 2005 in Paris, 2006 in Bologna, 2007 in Munich, 2008 in Edinburgh, and was continued as DEISA PRACE Symposia 2009 in Amsterdam, 2010 in Barcelona and 2011 in Helsinki. All presentations from the symposium are available at the DEISA and PRACE websites.

In continuation of the successful DEISA PRACE Symposia series, the PRACE Day 2012 is scheduled to be held during ISC'12 in Hamburg, Germany.

For more information:

http://www.deisa.eu/news_press/symposium/Helsinki2011

<http://www.prace-ri.eu/DEISA-PRACE-Symposium-2011>

Second EU/US Summer School on HPC Challenges in Computational Sciences August 7-12, 2011—Embassy Suites, Lake Tahoe, California

The US National Science Foundation's TeraGrid, the European Union Seventh Framework Program's Distributed European Infrastructure for Supercomputing Applications (DEISA), and the Partnership for Advanced Computing in Europe (PRACE) are pleased to announce the second joint EU-US summer school on High Performance Computing (HPC) Challenges in Computational Science, August 7-12, 2011 at Embassy Suites Lake Tahoe Hotel and Resort, Lake Tahoe, California.

Sweeping views of the Sierra Nevada Mountains frame the setting for an educational experience designed to foster international and multidisciplinary research collaborations. Sixty US and European graduate and postdoctoral scholars will

be selected to participate in a six-day educational and team-building program. Leading American and European computational scientists and HPC technologists will present a variety of topics, including:

- An overview of EU and US cyberinfrastructure
- HPC challenges by discipline (e.g., bioinformatics, computer science, chemistry, and physics).
- HPC Programming Proficiencies
- Performance Analysis & Profiling
- Algorithmic Approaches & Numerical Libraries
- Data Intensive Computing
- Scientific Visualization

The expense-paid program* will benefit advanced scholars from EU and US institutions who currently use HPC to conduct research. Applications from qualified candidates were accepted through April 25, 2011. More than 230 applications were received. Participants will be selected and notified via email by May 9, 2011.

For more information:

<http://www.ncsa.illinois.edu/Conferences/EUS-summerschool/>

*Pending final approval of funding by sponsoring agencies.

DECI – next call opens May 2, 2011

DECI – the DEISA Extreme Computing Initiative – was started in 2005. Six annual calls for proposals were done, leading to a support of more than 450 computational science projects.

During the DEISA PRACE Symposium 2011 in Helsinki, it was announced that PRACE is continuing DECI (what in future stands for “Distributed European Computing Initiative”) with a call opening already on May 2, 2011. All DEISA

“ex-customers” and computational scientists are kindly invited to participate after the official opening of the call by PRACE.

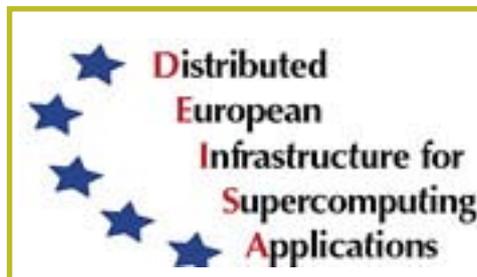
DEISA – a continuing success?!

Hermann Lederer

The DEISA-2 project indeed ends in April 2011. DEISA-2 is (or was) an EU FP7 co-funded project to further evolve and realize the DEISA idea. The DEISA idea originates back in April 2002 when a consortium was starting to form with the vision to create a Distributed European Infrastructure for Supercomputing Applications, in short DEISA. Here is an excerpt from the summary of the Expression of interest for an Integrated Project, submitted to the European Commission on June 4, 2002: “Leading European scientific organisations propose to build a Distributed European Infrastructure for Supercomputing Applications (DEISA) for science and technology. The aim is to provide a seamless and easy to use high performance computing facility, transparently accessible in a standardised way by end users across Europe. DEISA focuses on wide range of distributed general and potential applications (bioinformatics, environmental sciences, etc.)... “

This vision was started to be realized with EU FP6 support from May 2004 to April 2008 for the DEISA project, EC grant RI-508830. The enlargement of the consortium from eight to eleven partners and especially application enabling tasks for the “DEISA Extreme Computing Initiative”, DECI, which was started in spring 2005, was co-funded through the EU FP6 project eDEISA, grant RI-031513, from 2006 to 2009. DEISA services developed with the support of the EC grants were then seamlessly continued, further developed and expanded through the EU FP7 project DEISA-2 as of May 2008, EC grant RI-222919, until April 2011.

As already mentioned, DECI – the DEISA Extreme Computing Initiative – was introduced in 2005 to enhance the impact of the DEISA infrastructure for the advancement of science in Eu-



rope. From the very beginning, DECI has proven to be an extremely useful instrument in several aspects, and DECI has taken over an effective role as attractor for the computationally most challenging science projects in Europe. From 2005 to 2011, six DECI calls were realized. More than 180 European research institutes and universities have so far benefited from DECI. This initiative has been a catalyzing instrument to enhance the fraction of collaborative, multi-national projects. It has also stimulated to create and establish new science communities.

DECI has succeeded in attracting leading researchers to participate in DEISA with challenging projects. DEISA has contributed to the popularity of HPC simulations to address important problems in science and technology. The world’s top research projects have seen DEISA not only as an excellent infrastructure for HPC simulations, but also as a source of prestige due to the intense competition for DECI/DEISA projects. More than 450 challenging projects from major areas of computational sciences were hosted for scientist teams from 37 countries, including researchers from the Americas, Asia and Australia. Expert teams for application and infrastructure services have provided support for a persistent European HPC infrastructure.

In addition to DECI, direct support for whole science communities with a critical mass in their fields of science with a broad basis in sev-

eral European countries was initiated and established. Communities from Life Sciences, Climate Research, Astro Science and Fusion Energy Research showed an ongoing demand for DEISA resources related to HPC cycles, application support, and access to different state-of-the-art supercomputer architectures.

Through the twofold support strategy, DECI and support for Science Communities, European multi-national scientific collaborations have been further strengthened.

DEISA has enabled European computational scientists to obtain access to the most powerful national computing resources in Europe regardless of their country of origin or work, and also smaller countries are enabled to participate in cutting-edge research through internationally competitive computational science. Insight into the differences between usage of national and European resources and facilities gained by DECI also facilitates the understanding of requirements of users of European leadership-class supercomputers installed by PRACE, the Partnership for Advanced Computing in Europe.

After the formal end of the DEISA-2 project, DECI and the essential DEISA infrastructure services on top of national supercomputers, the so-called Tier-1 level, will be continued under the umbrella of PRACE. PRACE is not only deploying leadership-class Tier-0 supercomputers in Europe, but also integrating the Tier-0 and the Tier-1 services through the EU FP7 project PRACE 2IP starting in summer 2011.

For a seamless continuation of DECI, the next DECI call will be opened by PRACE already on May 2, 2011, as an excellent opportunity for the huge DECI customer basis gathered through DEISA.