Our long-term objective is to explain the behaviour of living organisms by means of theoretical models, the roots of which are anchored in the basic principles of physics and chemistry. With this general aim, we work with several methodologies, from the mining of biological databases to classical dynamics and quantum chemistry calculations. The use of such diverse techniques allows us to explore a wide range of problems, from drug design to genome analysis. Special emphasis is placed on connecting basic interactions with the global properties of biological systems. In general terms, our work centres on the following three major areas: (i) the study of small model systems, (ii) the analysis of stressed or unusual nucleic acids, and (iii) the dynamics of proteins.

Figure 1. Example of a classical 2D output of DNAAlive. Top figures correspond to physical properties derived from quasi-harmonic mesoscopic simulations of DNA (parameters obtained from MD simulations). Figures at the bottom correspond to biological annotations on the same genome fragment. Marked in red is a region of unusual physical properties, which is later found to correspond to a transcription start site.
Small model systems

Our group has a long trajectory in the study of small model systems of biological relevance (nucleobase complexes, drugs, isolated complexes of amino acids, stacked or hydrogen bonded complexes, etc.). The study of these simple systems can shed light on the behaviour of much more complex biological molecules. Almost a decade ago, we realised that such studies were simple in the gas phase but very difficult in aqueous solution, thereby hampering the true application of the information obtained to the biological scenario. This led us to develop methods to describe solvent systems, some of which are considered the current state of the art in the field, and to develop approaches for accurate representation of molecular interactions.

As planned, during 2008 we have advanced in the development of methods for the efficient representation of polarisation effects (Soteras et al., 2008a; Soteras et al., 2008b). We have also considerably improved our MST continuum model, which has now been adapted to provide complete thermodynamics of solvation with high accuracy (Bidon-Chanal et al., 2008; Klamtz et al., 2008).

In collaboration with colleagues at Minnesota (Xie et al., 2008), we have developed a novel method to perform full quantum mechanical calculations in proteins. The method is based on the partition of the entire system in inner (treated as QM clusters) and external (treated classically) fragments. We are now parallelising the code to allow extension of these quantum mechanical/molecular dynamics (QM-MD) calculations to the nanosecond time scale. The potential use of all these new methodologies in the context of drug development and nucleobase design have been explored in detail (Cozzini et al., 2008; Vázquez-Mayogoita, 2008) during 2008.

Principal Investigator  Modesto Orozco  Research Associates  Xavier de la Cruz, Agustí Emperador, Josep Lluís Gelpí  Postdoctoral Fellows  Montse Barbany, Oliver Carrillo, Chiara Catellazzi, Marco d’Abramo, Rebeca Garcia, Agnes Noy, Alberto Pérez, Guillem Portella, Nadine Utz  PhD Students  Annalisa Arcella, Ozgen Deniz, Ignacio Faustino, Carles Fenollosa, Josep Ramon Goñi, Adam Hospital, Sergio Lois, Tim Meyer, Jordi Morata, Laura Orellana, Antonella Paladino, David Piedra, David Talavera  Research Assistants  José Antonio Alcántara, Jordi Camps, Chiara Castellazzi, Damjan Cicin  Lab Technician  Mª Luz Ruiz  Administrative Assistants  Margarita Pedro, Cristina Villanueva  Visiting Scientists  Andrea Amadei (Italy), Sarah Harris (United Kingdom)  Visiting Students  Ariadna Giró (Spain), Venu Kurella (India), Eva Novoa (Spain), Francesco Raimondi (Italy)
Analysis of stressed or unusual nucleic acids

Major breakthroughs in the field of nucleic acid simulations emerged from the work performed by our group in 2007 related to the development of PARMBS0 force-field, which, after additional tests (Svozil et al., 2008), has become the default force-field for nucleic acid simulations (Orozco et al., 2008). Thanks to this refined force-field and to the mass computer power of MareNostrum, we have deciphered the mechanism by which RNAase H differentiates between hybrids to be degraded and homopolymers that must be resistant to the enzyme (Noy et al., 2008). Using the same force-field, we have successfully designed modified nucleobases that display a unique effect on G-DNAs, stabilising or destabilising them depending on the position where they are inserted (Gross et al., 2008).

Considerable effort has been focused on the characterisation of the equilibrium sequence-dependent stiffness of duplex DNA through PARMBS0-powered molecular dynamics simulations (Pérez et al., 2008). These studies have allowed us to derive a full mesoscopic model of the flexibility of DNA, which can be used to study chromatin deformability (Perez et al., 2008, Goñi et al., 2008). In this context, the development of DNAime (Goñi et al., 2008) has been a major landmark since it has allowed us for the first time to obtain an integrated view of chromatin by including physical information and biological annotations in a single tool. DNAime is the perfect link between DNA simulation and genomics (Figures 1-2). We are currently using DNAime intensively to study several aspects of chromatin structure and dynamics and during 2009 we plan to extend it to account for epigenetic changes.

Protein dynamics

The creation of the MODEL (Molecular Dynamics Extended Library) database has been the focus of a massive amount of work by the group. During 2008 we have finished the first draft of the database and started to work on the derivation of complementary databases, such as that of proteins of pharmacological interest, kinases and protein complexes. We have also almost completed the analysis of the trajectories to decipher the patterns of protein flexibility and their association with solvent structure (Figure 3).
Using our μMODEL reduced set, we have examined the impact of environmental changes on protein structure. Multi-microsecond-long simulations on urea have been performed during 2008 (they will finish in 2009) to illustrate the atomistic mechanism of chemo-thermal unfolding. This year we have completed the mapping of the gas phase proteome (Meyer et al, 2008), again using the reduced μMODEL database. This study has provided surprising evidence of the stability of proteins under electrospray-like conditions, thereby opening up the possibility to use gas phase structural information derived from x-free electron laser microscopy to obtain the protein structure in solution (Figure 4).

The availability of several terabytes of trajectories in μMODEL has opened up many possibilities for proteome-scale analysis, including systematic exploration of essential dynamic movements in proteins and their connection with function and evolution (Velázquez-Muriel et al, 2008). It has also provided the opportunity to study protein channels following the MDGRID methodology developed by our group (Carrillo et al, 2008) and to perform genome-scale ensemble docking experiments to identify new drugs.

MD trajectories deposited in μMODEL have helped us to derive new coarse-grained models designed to obtain a fast first-order approximation to protein flexibility using very simple potential functions. During 2008 we have developed and optimised pseudo-harmonic methods based on normal model analysis and Brownian MD (Emperador, 2008a). We have explored the use of ballistic equations for recovering dynamics trajectories using either residue or atom-resolution representations of proteins (Emperador, 2008b). Given their speed, these methods are expected to allow a full-proteome representation of protein flexibility, even in protein mixtures. We are currently finishing the development of an entire platform (named FlexServ) that will automatise these types of studies.

Finally, we should remark that dynamic information, obtained from either MD, coarse-grained methods or even evolutionary methods (Velázquez-Muriel et al, 2008) can help to improve the structural representation of proteins obtained for ensemble techniques such as NMR, as demonstrated in the COCO web server developed by our group, in collaboration with colleagues in Nottingham and at the European Bioinformatics Institute (Laughton et al, 2008).

**Figure 3.** Examples of dynamic analysis of protein flexibility derived from our MODEL database.

**Figure 4.** Structures of 3 ultra-representative proteins in solution (start) and upon ideal (NC) and normal (ESIC) electrospray vaporisation.

---

**Publications**


Research networks and grants

Estudio de formas inusuales o tensionadas del DNA. Implicaciones biotecnológicas y biomédicas
Spanish Ministry of Science and Innovation, BIO2006-01602 (2006-2009)
Principal investigator: Modesto Orozco

European Life Science Infrastructure for Biological Information (ELIXIR)
European Commission, 211601 (2007-2010)
Principal investigator: Modesto Orozco

Molecular recognition
Marcelino Botin Foundation
Principal investigator: Modesto Orozco

Proyecto CONSOLIDER Supercomputación y eCiencia
Principal investigator: Modesto Orozco

Reconeximent molecular
Principal investigator: Modesto Orozco

Other funding sources

Collaboration contracts with Salvat Laboratories, Neuropharma and Palau Pharma-Grupo Uriach

Collaborations

Design of nucleobase derivatives for stabilization of anomalous DNAs
Ramon Eritja, IRB Barcelona-CSIC (Barcelona, Spain)

Development of new tools for computer assisted drug design
Francisco Javier Luque, Faculty of Pharmacy, University of Barcelona (Barcelona, Spain)

Development of strategies for improvement of NMR-samplings
Charles A Laughton, Nottingham University (Nottingham, UK), Williams Vranken, European Bioinformatics Institute, EBI-EMBL (Cambridge, UK)

Force-field refinement for nucleic acid simulations
Thomas Cheatham, University of Utah (Salt Lake City, USA), Jiri Sponer (Brno University (Brno, Czech Republic) and Filip Lankas, Lausanne University (Lausanne, Switzerland)

Introduction of polarisation effects in force-field calculations
Cristophe Chipot, Nancy University (Nancy, France) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Mixed QM-MM methods for protein simulations
Donald Truhlar and J Gao, University of Minnesota (Minnesota, USA)

New algorithms for drug design
Paolo Cozzini, Perugia University (Perugia, Italy) and Robert Soliva, PalauPharma-Uriach Group (Barcelona, Spain)

Physical properties of DNA
David Torrents, Barcelona Supercomputing Center (Barcelona, Spain)

SCRF solvation methods
Jacopo Tomasi, Pisa University (Pisa, Italy), Andreas Klamtz, CosmoLogic Inc. (Leverkusen, Germany) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Study of DNA-metal complexes
Miguel Fuentes-Cabrera, Oak Ridge National Laboratory (Oak Ridge, USA) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Awards and honours

Distinguished fellow of the Marcelino Botin Foundation
Awardee: Modesto Orozco

Red temática de investigación cooperativa en biomedicina computacional (COMBIOMED)
Instituto de Salud Carlos III, COMBIOMED RD07/0067/0009 (2008-2012)
Principal investigator: Modesto Orozco

Structural bioinformatics
Genoma España, GN4 (2007-2009)
Principal investigator: Modesto Orozco

Other collaborators

Charles A Laughton, Nottingham University (Nottingham, UK), Williams Vranken, European Bioinformatics Institute, EBI-EMBL (Cambridge, UK)

Introduction of polarisation effects in force-field calculations
Cristophe Chipot, Nancy University (Nancy, France) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Mixed QM-MM methods for protein simulations
Donald Truhlar and J Gao, University of Minnesota (Minnesota, USA)

New algorithms for drug design
Paolo Cozzini, Perugia University (Perugia, Italy) and Robert Soliva, PalauPharma-Uriach Group (Barcelona, Spain)

Physical properties of DNA
David Torrents, Barcelona Supercomputing Center (Barcelona, Spain)

SCRF solvation methods
Jacopo Tomasi, Pisa University (Pisa, Italy), Andreas Klamtz, CosmoLogic Inc. (Leverkusen, Germany) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Study of DNA-metal complexes
Miguel Fuentes-Cabrera, Oak Ridge National Laboratory (Oak Ridge, USA) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Awards and honours

Distinguished fellow of the Marcelino Botin Foundation
Awardee: Modesto Orozco

Other funding sources

Collaboration contracts with Salvat Laboratories, Neuropharma and Palau Pharma-Grupo Uriach

Collaborations

Design of nucleobase derivatives for stabilization of anomalous DNAs
Ramon Eritja, IRB Barcelona-CSIC (Barcelona, Spain)

Development of new tools for computer assisted drug design
Francisco Javier Luque, Faculty of Pharmacy, University of Barcelona (Barcelona, Spain)

Development of strategies for improvement of NMR-samplings
Charles A Laughton, Nottingham University (Nottingham, UK), Williams Vranken, European Bioinformatics Institute, EBI-EMBL (Cambridge, UK)

Force-field refinement for nucleic acid simulations
Thomas Cheatham, University of Utah (Salt Lake City, USA), Jiri Sponer (Brno University (Brno, Czech Republic) and Filip Lankas, Lausanne University (Lausanne, Switzerland)

Introduction of polarisation effects in force-field calculations
Cristophe Chipot, Nancy University (Nancy, France) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Mixed QM-MM methods for protein simulations
Donald Truhlar and J Gao, University of Minnesota (Minnesota, USA)

New algorithms for drug design
Paolo Cozzini, Perugia University (Perugia, Italy) and Robert Soliva, PalauPharma-Uriach Group (Barcelona, Spain)

Physical properties of DNA
David Torrents, Barcelona Supercomputing Center (Barcelona, Spain)

SCRF solvation methods
Jacopo Tomasi, Pisa University (Pisa, Italy), Andreas Klamtz, CosmoLogic Inc. (Leverkusen, Germany) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Study of DNA-metal complexes
Miguel Fuentes-Cabrera, Oak Ridge National Laboratory (Oak Ridge, USA) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Awards and honours

Distinguished fellow of the Marcelino Botin Foundation
Awardee: Modesto Orozco

Other collaborators

Charles A Laughton, Nottingham University (Nottingham, UK), Williams Vranken, European Bioinformatics Institute, EBI-EMBL (Cambridge, UK)

Introduction of polarisation effects in force-field calculations
Cristophe Chipot, Nancy University (Nancy, France) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Mixed QM-MM methods for protein simulations
Donald Truhlar and J Gao, University of Minnesota (Minnesota, USA)

New algorithms for drug design
Paolo Cozzini, Perugia University (Perugia, Italy) and Robert Soliva, PalauPharma-Uriach Group (Barcelona, Spain)

Physical properties of DNA
David Torrents, Barcelona Supercomputing Center (Barcelona, Spain)

SCRF solvation methods
Jacopo Tomasi, Pisa University (Pisa, Italy), Andreas Klamtz, CosmoLogic Inc. (Leverkusen, Germany) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Study of DNA-metal complexes
Miguel Fuentes-Cabrera, Oak Ridge National Laboratory (Oak Ridge, USA) and Francisco Javier Luque, University of Barcelona (Barcelona, Spain)

Awards and honours

Distinguished fellow of the Marcelino Botin Foundation
Awardee: Modesto Orozco