Biological Diffusion and Brownian Dynamics Brainstorm 2

BDBDB2

11 – 12 – 13 October 2010

Heidelberg Institute for Theoretical Studies (HITS)

and

University of California, San Diego (UCSD)

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Monday 11 October 2010

Gary Pielak - Effects of proteins on protein diffusion

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Despite increased attention, little is known about how the crowded intracellular environment affects basic phenomena like protein diffusion. We used NMR to quantify the rotational and translational diffusion of a 7.4-kDa test protein, chymotrypsin inhibitor 2 (CI2), in solutions of glycerol, synthetic polymers, proteins, and cell lysates. As expected, translational diffusion and rotational diffusion decrease with increasing viscosity. In glycerol, for example, the decrease follows the Stokes-Einstein and Stokes-Einstein-Debye laws. Synthetic polymers cause negative deviation from the Stokes laws and affect translation more than rotation. Surprisingly, however, protein crowders have the opposite effect, causing positive deviation and reducing rotational diffusion more than translational diffusion. Indeed, bulk proteins severely attenuate the rotational diffusion of CI2 in crowded protein solutions. Similarly, CI2 diffusion in cell lysates is comparable to its diffusion in crowded protein solutions, supporting the biological relevance of the results. The rotational attenuation is independent of the size and total charge of the crowding protein, suggesting that the effect is general. The difference between the behavior of synthetic polymers and protein crowders suggests that synthetic polymers may not be suitable mimics of the intracellular environment. NMR relaxation data reveal that the source of the difference between synthetic polymers and proteins is the presence of weak interactions between the proteins and CI2. In summary, weak but nonspecific, noncovalent chemical interactions between proteins appear to fundamentally impact protein diffusion in cells.

Joerg Langowski - Multiscale Modeling of Chromatin Dynamics

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Chromatin is the fundamental structure responsible for packing DNA in the eukaryotic cell nucleus and for regulating access to genomic information. One focus of our research is to understand the structure and dynamics of chromatin on all its length scales, from the nucleosome to the folding of entire chromosomes, combining simulation techniques with biophysical experiments. Here I will present some new results of coarse-grained molecular dynamics simulations of mononucleosomes that show a plausible mechanism for DNA detachment from the histone core, and single-molecule spectroscopy experiments that give insight into the mechanism of nucleosome opening under physiological conditions.

Martin Held - Mechanisms of protein-ligand association and its modulation by protein mutations

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Protein-ligand interactions are important for virtually every biological information transfer, but the underlying biophysical association process remains poorly understood. Fundamental questions in this regard are for example which factors influence the formation of protein-ligand encounter complexes, or if designated association pathways exist. We present a new methodology which allows to study these questions by theoretical means. Considering Brownian dynamics for the binding of a phosphate ion to its carrier the phosphate binding protein (E. coli) transition path theory is applied to study this process. Various mutants of the phosphate binding protein are created and their effect on the change in free binding energy, association rate and association pathway distribution is investigated. Furthermore, we look at the binding of a phosphate ion to the phosphate binding protein when there is already a phosphate located close to the protein surface. The results reveal the existence of two regions at the protein surface that are likely to hold the phosphate in place. Residue mutations at the respective positions modulate their attraction strength and change the attraction pathways of the phosphate ligand.

James Weisshaar - Protein Diffusion in Live E. coli

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Fluorescence recovery after photobleaching (FRAP) has been used to study the diffusive motion of proteins in the cytoplasm and periplasm of E. coli. By varying osmotic conditions, we have characterized translational diffusion of cytoplasmic GFP for different degrees of crowding and immediately following moderate osmotic upshift. The seven-fold reduction of Dgfp from buffer to cytoplasm, the wide variation in Dgfp from cell to cell under identical conditions, and the 50-fold decrease in < Dgfp > after osmotic upshift are not well explained by simple hard-sphere crowding models. Fluorescence anisotropy measurements suggest an approximate three-fold increase in the rotational correlation time of GFP from buffer to cytoplasm at 0.28 Osm growth osmolality. On average, periplasmic GFP diffuses 1.5-3.5 times more slowly than cytoplasmic GFP, depending on growth osmolality. GFP-labeled RNA polymerase in the cytoplasm exhibits comparable mobile and immobile fractions on a 30-60 s timescale. For the mobile fraction, presumed to be engaged in “hopping” and “sliding”, <Drnap> = 0.24 um2-s-1. This is remarkably similar to measured 1D sliding diffusion coefficients of RNAP on ds-DNA in vitro. We suggest that the immobile fraction comprises RNAP copies that are actively transcribing or stalled at transcription initiation sites. Cell-to-cell heterogeneity in both Drnap and f(mobile) is substantial. Finally, recent single-molecule tracking studies of the protein Kaede in the E. coli cytoplasm reveal spatial heterogeneity in Dkaede, with faster diffusion in the nucleoid region. Time permitting, we will also present a statistical model that explains nucleoid-ribosome segregation in the E. coli cytoplasm.

Johannes Seibert - Spatiotemporal model of particle diffusion in the primary rod vision signal transduction

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Rod cell phototransduction is a prime example of a functional module whose properties may strongly depend on its specific spatial embedding. The rod outer segment has a highly regular layered geometry comprising disc membranes that are densely filled with the photon-collecting Rhodopsins and their G-proteins Transducin. Despite a wealth of functional studies on rod cell phototransduction and a rather complete knowledge of the proteins involved in the process, the spatiotemporal mechanism of the activation cascade is poorly understood. Since recently, the existence Rhodopsin patterns on the disc and their possible effects on functional properties of photoactivation are highly debated. In the present study we conduct spatiotemporal simulations of the two-dimensional reaction-diffusion photoactivation processes on the disc membrane with all protein copies explicitly resolved. We investigate the effects of crowding, the spatiotemporal evolution of the activation, and different settings of the reaction rates of the physicochemical events such as the dissociation of G-protein subunits. Finally, we compare free diffusion of the involved proteins with a situation where attractive interactions favor Rhodopsin-Rhodopsin aggregations. In order to compare our results to a well-defined experimental test system, the simulations are set up on a spherical membrane mimicking experimentally prepared disc membrane vesicles for which extensive kinetic studies exist. Our analyses yield insight into which space-time mechanisms in the phototransduction activation module are possible and allow a number of highly debated questions concerning pattern formation on the disc membrane to be reconsidered.

Matthias Weiss - Crowding and anomalous diffusion in vivo, in vitro, and in silico

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Diffusion is the basic means of intracellular transport. Due to macromolecular crowding and oligomerization processes, however, diffusion often becomes anomalous ('subdiffusion'). Using fluorescence correlation spectroscopy (FCS) in combination with computer simulations, we were able to determine and quantify the subdiffusive motion of transmembrane proteins and tracer particles in the cytoplasm and the nucleus of living cells. Subdiffusion in the cytoplasm and the nucleus is a consequence of the highly crowded state of the respective fluids and relates to the fluids' viscoelastic properties on the nanoscale. Indeed, all tested cell lines showed a strong viscoelastic characteristics for the cytoplasm and the nucleoplasm, with almost equal viscous and elastic moduli over a wide frequency range. Consequently, the particles' random walk is most consistent with the properties of a fractional Brownian motion. Based on the observation, that anomalous diffusion is indeed a fairly common phenomenon, we finally discuss how generic cellular processes (e.g. complex formation) are altered in the presence of subdiffusion.

J. Andrew McCammon - Gated diffusional binding of ligands to proteins

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The binding of a ligand to a protein often requires that the protein adopt an "open binding site" conformation. The kinetics of binding can therefore be coupled to the kinetics of the conformational transitions of the protein. This talk will outline a number of such situations that have been studied by computer simulation, including substrate and inhibitor (drug) binding to enzymes. More information, including images and animations, can be found at http://mccammon.ucsd.edu/

Adrian Elcock - Large-scale Brownian Dynamics Simulations of the Cytoplasm

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This talk will describe our BD simulation work aimed at developing a working molecular model of the bacterial cytoplasm. The results of the simulations will be discussed, as will the use of simulation snapshots for making quantitative predictions of protein stability in vivo. Some of the challenges that will need to be overcome in a future generation BD model will be outlined.

Tuesday 12 October 2010

Maxim Petoukhov - Modern methods for solution scattering data analysis from biological macromolecules

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Solution scattering (SAS) becomes a standard tool in modern structural molecular biology providing valuable information about overall structure and conformational changes of native individual proteins and functional complexes. Its ability of rapid analysis of structural changes in response to variations in external conditions makes SAS indispensable for studies of flexible macromolecules and assembly/dissociation processes. The variety of structural questions addressed by SAS ranges from evaluation of the overall geometrical parameters and low-resolution shape reconstruction in the absence of a priory structural information to structure validation, identification of biologically active oligomers and rigid body refinement if high-resolution atomic models are available. Novel methods to scattering data analysis exploiting efficient algorithms and promoting incorporation of complementary information from other methods (bioinformatics, electron microscopy, NMR, biochemistry), resulted in numerous practical applications. The details of the state-of-the-art data analysis approaches and highlights of the biological objects analysed with SAS will be presented.

Gideon Schreiber - Transient complexes along the association reaction of proteins in solution and in the crowd

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Rates of protein interactions are one to five orders of magnitude slower than the theoretically calculated collision rate of spheres of the same size. Recent studies have established that the association reaction proceeds through transient complexes, which may be specific or diffusive in nature. We have investigated the structural features of these encounters using a combination of simulations and experimental data on the hetero-dimerization of TEM1-ß-lactamase with ß-lactamase inhibitor protein (BLIP) and barnase with barstar. We have shown that some transient complexes are fruitful, while others are futile. Mutations that stabilize the fruitful encounters increase the rate of association, while alterations of the futile encounters have no effect on the binding rates. Next, we investigated the role of crowding on binding, as this may mimic the crowded environment inside living cells. It was shown that crowding enhances oligomerization and polymerization of macromolecules. Conversely, on transient

protein-protein interactions we have shown that crowding has only a small effect on the rate of association, dissociation and affinity of interaction. We suggest that the limited effect of crowders, which is much bellow the expected from the increased viscosity of the solutions, is a result of the occluded volume effect in high crowder concentrations. We suggest that this is a result of the stabilization of fruitful encounter complexes along the association reaction. We also contrasted these with the effect of crowding on the weak binding pair CyPET-YPET. On this pair, aggregation, and not enhanced dimerization, was detected in PEG solutions. The results suggest that typical crowding agents have only a small effect on specific protein-protein dimerization reactions while promoting aggregation.

Johan Elf - Probing Intracellular Kinetics at the level of Single Molecule

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I will present our resent advancements in tracking individual freely diffusing fluorescent protein molecules at high time resolution in the cytoplasm of bacterial cells. In vivo tracking of individual proteins molecules makes it possible to study kinetics high time resolution without synchronizing the population of molecules. For example by monitoring the kinetics of the response mediator RelA we have developed a single molecule assay to study stress response and starvation at the level of individual bacteria. The RelA protein binds to a small fraction of ribosomes, where it synthesizes the global transcriptional regulator ppGpp in response to amino acids deprivation. This the ppGpp molecule binds to the RNAP and rapidly reprograms the cell for the new environment, in what is called the stringent response. While E. coli contains on average about 100 RelA molecules and 10000 ribosomes, using a photo-activatable fluorescent probe we can activate only a few fluorescent molecules per cell at any given time and track them at high time resolution. When the cell grows exponentially, RelA trajectories closely resemble trajectories of fluorescently tagged ribosomal proteins (D~0.4 μm^2/sec as compared to D~0.3 μm^2/sec for ribsomes). After nutritional downshift, RelA binding kinetics changes rapidly and the protein diffuses very fast (D~3.5μm^2/sec) as if it only binds to ribosomes transiently. I will also discuss some recent advances in modeling stochastic reaction diffusion processes using the reaction diffusion master equation.

Daria Kokh - Brownian dynamics simulation of protein binding to solid surfaces

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The present study is aimed at building a computational model for understanding and predicting the chemical and physical properties of protein binding to solid surfaces. Recently we have developed a ProMetCS (Protein-Metal Continuum Solvent) [1] approach for modeling the interaction of a protein with an atomically flat gold surface in aqueous solvent. The computational algorithm is based on Brownian dynamics simulations with interaction described at the atomistic level while treating solvent as a continuum medium. The forces between the protein and the surface are due to the sum of a number of energetic terms that we have modelled and parameterized on the basis of quantum mechanical and molecular dynamics calculations. The ProMetCS approach has been tested for amino acid residues and shown a good agreement of computed free adsorption energies with those obtained in molecular dynamic simulations with water treated explicitly. The purpose of the presentation will be to show results of the ProMetCS approach validation using experimental binding properties of BLIP-homopeptides fusions to gold nanoparticals as well as the method application for calculation of adsorption constants and binding characteristics for several other proteins studied experimentally [2] .

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Maciej Dlugosz - From single molecules to dense biomolecular systems - Brownian dynamics simulations with the BD_BOX package

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With a growing interest in characterizing transport properties in the cell environment and the fact that most biological phenomena involve steps that are diffusion-mediated, there is a need for a tool that would allow to routinely perform multiscale Brownian dynamics simulations of systems containing significant numbers of different molecular species. I will present a novel, massively parallel Brownian dynamics package that we have recently developed - BD_BOX. Within the BD_BOX framework macromolecules are represented with flexible models. Each molecule consists of a various number of spherical subunits (beads) connected with FENE (finite extensible nonlinear elastic) or harmonic bonds. Bonded interactions resulting in deformations of planar and dihedral angles are also included. Direct, non-bonded interactions between molecules are evaluated using pairwise functions describing screened electrostatics in dielectric media with effective charges assigned to spherical subunits and Lennard-Jones potential types. The far-field hydrodynamic effects are modeled using the configuration dependent Rotne-Prager-Yamakawa mobility tensor or its Ewald-summed form applicable to periodic

systems (because the minimum image convention fails when applied to long-ranged hydrodynamic interactions, resulting in non-positive definite mobility tensors). Equations of motions are propagated using either the Ermak-McCammon scheme or the predictor-corrector IG-T algorithm by Iniesta and Garcia de la Torre. Hydrodynamically correlated random displacements are generated either via the Cholesky factorization of the configuration-dependent mobility tensor matrix or, optionally, using the TEA-HI approach proposed by Geyer and Winter. BD_BOX simulations can be performed without or with boundaries; in the latter case reflective or periodic boundary conditions can be used. With BD_BOX one can also simulate molecules in homogenous flows or external electric fields (direct, alternate or rotating fields). For efficient simulations of dense systems we implemented an algorithm preventing the overlapping of diffusing molecules. This numerical procedure applied at each step of the Brownian dynamics simulation locates time, collision partners and parameters for every collision occurring in the system in chronological order. BD_BOX uses modern computational technologies such as parallelization (MPI and OpenMP libraries), vectorization (SSE CPU extension) and GPU programming (NVIDIA CUDA), allowing the user to effectively simulate either single molecules or biomolecular systems composed of large numbers of different species with hydrodynamic interactions enabled. I will describe theories and models that BD_BOX is built upon and problems that we have encountered and solved during its development - particularly when dealing with dense systems. I will also present exemplary applications and future plans regarding extensions of BD_BOX functionality.

Gary Huber - Recent and future developments in the Browndye package

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An overview of the structure of the Browndye software package for Brownian dynamics will be given. Algorithms allowing the simulations to scale to large systems will be presented, such as charge lumping, collision detection, and trajectory propagation. Finally, work in progress will be discussed, such as generation of effective charges and addition of flexibility.

Joanna Trylska - On the structure and aggregation of N-terminal Huntingtin fragments

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Huntington's disease is a neurodegenerative disorder caused by a polyglutamine (polyQ) expansion in the N-terminal fragment of the Huntingtin (Htt) protein. The expansion exceeding ~35-40 glutamines leads to the formation of protein aggregates that are toxic to neurons. Structural properties of Htt N-terminal regions and the molecular mechanism leading to protein aggregation have not been fully explained yet and there exist conflicting hypotheses. A common view is that the expanded polyQ undergo a structural transition prior to their oligomerization, however, an aggregation model mediated by the polyQ flanking region was also proposed. We performed all-atom replica exchange molecular dynamics simulations to investigate the structures of Htt N-terminal parts with polyQ tracts of non-pathogenic and pathogenic lengths. The monomers were composed of the headpiece (17 N-terminal residues), a polyQ tract (polyQ(17) for native and polyQ(55) for pathogenic sequence), a polyP(11) region, followed by 17 amino acids of mixed sequence. We found that corresponding regions in both fragments fold to similar secondary structures; the headpiece and polyQ stretch adopt alpha-helical conformations and polyP(11) forms the PP II-type helix. In general, the native fragment is more compact and stabilized by hydrophobic interactions between the surface of polyP(11) and the amphipathic helix of the Htt headpiece. On the contrary, in the pathogenic fragment the headpiece is solvent exposed and does not interact with polyP(11). The predicted structure of the native N-terminal fragment agrees with the x-ray structure of the Htt first exon containing polyQ(17). The structure of the pathogenic fragment adheres to an aggregation model in which the initial nucleus is formed by the Htt headpieces that further incorporates the extended polyQ tracts.

Barry Grant - Electrostatically biased binding of kinesin to microtubules

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Kinesins are a large family of motor proteins responsible for ATP dependent unidirectional transport along microtubules. It has recently been established that twin-headed kinesin-1, the best-studied family member, moves using an alternating-hand-over-hand walking action. However, it is not clear to what extent unidirectional progress along the microtubule results from directionally biased binding events or directional conformational changes once bound. We report here, using atomistic BD simulations and mutational analysis, that conserved electrostatic interactions enhance association and enable kinesin heads to preferentially bind tubulin heterodimers lying ahead in the progress direction. Furthermore, we find that the tethering of two heads in a dimer reduces the search space for binding sites on the microtubule lattice and further biases binding to a single microtubule protofilament. Simulations with different subfamily representatives and selected charge neutralizing mutations suggest that different kinesin subfamilies have tailored their electrostatic properties to effectively modulate association rates and their directional bias along the microtubule. We conclude that the neck-linker region acts not as a force-generating element but rather as a rectifier of electrostatically biased diffusional association that is an intrinsic feature of the kinesin-microtubule system. We propose a model where a myosin-like power-stroke may not be the sole determinant of unidirectional kinesin motion.

Patricia Bauler - Channeling by Proximity : The Catalytic Advantages of Active Site Colocalization Using Brownian Dynamics

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Nature often co-localizes successive steps in a metabolic pathway. Such organization is predicted to increase the effective concentration of pathway intermediates near their recipient active sites and to enhance catalytic efficiency. Here, the pathway of a two-step reaction is modeled using a simple spherical approximation for the enzymes and substrate particles. Brownian dynamics are used to simulate the trajectory of a substrate particle as it diffuses between the active site zones of two different enzyme spheres. The results approximate distances for the most effective reaction pathways, indicating that the most effective reaction pathway is one in which the active sites are closely aligned. However, when the active sites are too close, the ability of the substrate to react with the first enzyme was hindered, suggesting that even the most efficient orientations can be improved for a system that is allowed to rotate or change orientation to optimize the likelihood of reaction at both sites.

Wednesday 13 October 2010

Gerhard Naegele - Dynamics in concentrated dispersions of colloids and biomolecules: Theory, simulation and experiment

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"Dispersions of charged colloidal particles and biomolecules undergoing correlated Brownian motion are of fundamental interest in chemical industry, biology and food science. We explore the short-time and long-time dynamics of well-characterized model systems using simulation methods and many-body theory in conjunction with dynamic scattering experiments. Transport properties are discussed including the effective shear viscosity, hydrodynamic function and various diffusion coefficients [1]. We scrutinize the validity of generalized Stokes-Einstein relations between diffusion and rheological properties [2]. A far-reaching dynamic scaling behavior relating long-time to short-time dynamics, and collective diffusion to self-diffusion, is shown to apply approximately to charged colloids [3]. The universality of the experimentally observed scaling behavior is analyzed theoretically by mode-coupling theory and Brownian dynamics simulations. Moreover, results of a novel simulation study on the dynamics in dense suspensions of solvent-permeable spheres are presented, with a high-precision account of many-body hydrodynamic interactions [4]. Our study gives new insights into the generic behavior of porous particle dispersions.

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Paolo Mereghetti - Brownian dynamics simulations of protein solutions

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The study of solutions of biomacromolecules provides an important basis for understanding the behaviour of many fundamental cellular processes, such as protein folding, self-assembly, biochemical reactions, and signal transduction. Here, we describe a Brownian dynamics simulation procedure and its validation for the study of the dynamic and structural properties of protein solutions. In the model used, the proteins are treated as atomically detailed rigid bodies moving in a continuum solvent. The protein-protein interaction forces are described by the sum of electrostatic interaction, electrostatic desolvation, non-polar desolvation and soft-core repulsion terms.
The linearized Poisson-Boltzmann equation is solved to compute electrostatic terms. Simulations of homogeneous solutions of three different proteins with varying concentrations, pH and ionic strength

were performed. The results were compared to experimental data and theoretical values in terms of long-time self-diffusion coefficients, second virial coefficients and structure factors. The results agree with the experimental trends and, in many cases, experimental values are reproduced quantitatively. There are no parameters specific to certain protein types in the interaction model, and hence the model should be applicable to the simulation of the behaviour of mixtures of macromolecules in cell-like crowded environments.

Jose Garcia de la Torre - Recent advances and applications in the prediction of dilute-solution properties of macromolecules and nanoparticles: hydrodynamic calculations and Brownian dynamics simulation

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The activity of our Group is mainly intended to develop methods for the prediction of dilute-solution properties of macromolecules and nanoparticles, including hydrodynamic coefficients, scattering-related properties, NMR and viscoelastic relaxation, and even single-molecule dynamic events of synthetic polymers, biological macromolecules and colloidal entities and nanoparticles. Most of these developments are of public domain [1]. The hydrodynamic predictions for rigid particles are done using bead models based on atomic or more coarse-grained structures. Several programs, comprising the HYDRO suite [1, 2], that we have devised for this task, will be mentioned. The requirement of rigorous consideration of the hydrodynamic interaction (HI) effect in these model calculations poses a problem of computational expense. Particularly in the matrix algebra required for the consideration of HI increases remarkably the computational requirements of the calculation. We have recently developed or implemented efficient procedures which reduce notably the CPU time for those calculations. Another advance is the development of graphical user interfaces, which may facilitate the work of some users. The prediction of dynamic and other solution properties of flexible macromolecule or particles, includes, in addition to the hydrodynamic computational problems mentioned above, the conformational variability caused by flexibility adds further difficulty. Monte Carlo procedures are adequate for conformational and some overall hydrodynamic coefficient, and a rigorous description of aspects based on internal motion, or single-molecule events require Brownian dynamics simulation with full HI. As for rigid particle, we have developed our own (and now public-domain) computer programs for those simulations: MonteHydro [3] for Monte Carlo and SIMUFLEX [4] for Brownian dynamics. Recently, we have made improvements in their performance. The main idea is that these simulation problems are well suited for distributed computing in multi-core platforms, with the help of public domains tools for load-balancing by batch queues. Now, we have adapted our computational protocols to high-performance computing in multi-processor machines and clusters by means of pre- and post- processing batch-programs, that split the simulated problem, and collect the multiple simulation results. Anoher relevant aspect is the level of detail that one considers in the macromolecular structure, which can range from fully atomic to very coarse-grained description, in which elements are large subunits or domains, including medium-grained models at the residue (aminoacid or nucleotide). Along with descriptions of the description of the new computational approaches, I shall present a variety of applications, including biological macromolecules: proteins and

DNA, with various levels of detail [4]), and complex synthetic polymers (dendrimers [5]). Aknowledgements: Funded by Ministerio de Ciencia e Innovación (CTQ-2006-06381) and Fundación Séneca de la Región de Murcia (Grupo de Excelencia 04531/GERM/06).

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Thiamer Geyer - Coarse-Grained Simulations of a Small Peptide: Effects of Finite Damping and Hydrodynamic Interactions

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In the coarse grained Brownian Dynamics simulation method the many solvent molecules are replaced by random thermal kicks and an effective friction acting on the particles of interest. For Brownian Dynamics the friction has to be so strong that the particles' velocities are damped much faster than the duration of an integration time step. Here we show that this conceptual limit can be dropped with an analytic integration of the equations of damped motion. In the resulting Langevin integration scheme our recently proposed approximate form of the hydrodynamic interactions between the particles [1] can be incorporated conveniently, leading to a fast multi-particle propagation scheme, which captures more of the short-time and short-range solvent effects than standard BD. Comparing the dynamics of a bead-spring model of a short peptide, we recommend to run simulations of small biological molecules with the Langevin type finite damping and to include the hydrodynamic interactions [2]. We also demonstrate our recently released “Brownmove” simulation package for coarse-grained many-particle simulations incorporating the above explained propagation techniques.

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Elfriede Friedmann - Spatio-temporal simulations of the JAK2/STAT5 pathway in CFU-E and NIH3T3 cells

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Cellular geometries can vary significantly, how they influence signaling remains largely unknown. Here, we investigate the influence of cell shape on the Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway by data-based mathematical modeling, numerical simulations and parameter identification. As cellular model systems we use spherical shaped erythroid progenitor cells at the colony-forming unit erythroid stage (CFU-E) and NIH3T3 fibroblast cells. The key components of the pathway are modeled with a system of ordinary differential equations (ODE) to estimate the parameters that can not be measured experimentally. The ODE model is then enlarged by the transport of STAT5 through the cytoplasm. A mixed system of differential equations (PDE + ODE) with Robin boundary conditions is obtained which is solved with the in-house software Gascoigne based on Finite Elements. Realistic cell geometries for the simulations are obtained by three-dimensional reconstruction of microscopy data. Numerical algorithms are explored to reduce the long computing time caused by the fine mesh and a small time step size necessary due to fast diffusion combined with slow activation and deactivation kinetics of STAT5. We use Implicit Euler, Crank-Nicholson time stepping method and discretization of the stationary equations by Q1, Q2 Finite Elements. The resulting linear system is solved with multigrid methods. We analyze the influence of the cell shape on the gene response to the activated pathway and do some in silico experiments. For similar linear models in signal transduction we can conclude which geometry and which diffusion coefficient is necessary so that diffusion plays a significant role in the dynamics of the observed pathway.

Yuji C. Sasaki - High-speed Observations of Intramolecular Brownian motions on Functional Proteins using X-rays and Electrons.

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Single molecular detection systems are very important methodologies in basic nanobiosciences and nanotechnologies. Recent technological progress in dynamical observations of individual functional single protein molecules in living cell has been achieved with several single molecular techniques and systems. Usually, these methods utilize visible lights. Important technical elements on above technologies are how to improve the accuracy and speed. In order to improve both monitoring super-precisions of internal conformational changes and stability of the super-high-speed dynamical signal intensity from single molecular units, we have proposed new single molecular techniques using more shorten wavelength, for example, X-rays, electrons, and neutron. Diffracted X-Ray Tracking (DXT) [1] has been developed for obtaining the information about the dynamics of single molecules. This method can observe the rotating Brownian motion of an individual nanocrystal, which is linked to specific sites

in single protein molecules, using a time-resolved Laue diffraction technique. Recently, we succeeded high-speed time-resolved (micro-second level) x-ray observations of dynamical Brownian motions of individual single potassium channel (KcsA) in aqueous solutions through the labeled nanocrystals[2]. The size of the observed rotational motions occurred with about 20-30 degrees during 100-300ms. In the next step, we may be able to control the rotational motions using magnetic nanocrystals. Until now, we are trying to observe Brownian motions of individual DNA molecules, myosin head molecules, denatured proteins, functional protein membranes (bacteriorhodopsin, AChBP, KvAP), antigen-antibody interactions [3], actin, and monitoring super-weak force (pN) [4]. This DXT method needs a very strong X-ray source, such as the SPring-8, so we began to develop a compact instrument for monitoring the rotations of the single protein molecules, using the electron beam instead of the X-rays. Instead of the Laue diffraction using white X-ray, the Electron Back-Scattered Diffraction Pattern (EBSP) is adopted to monitor the crystal orientation of the nanocrystals linked to the single protein molecules. We called Diffracted Electron Tracking (DET).

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Huan-Xiang Zhou - Theory and Simulation of Diffusion-Influenced Bimolecular Reactions

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"Molecular recognition is central to chemistry and biology. Recognition involves the binding of a receptor and a ligand. We have been developing theories and simulation methods for calculating receptor-ligand binding rate constants. Various realistic aspects are accounted for in order to accurately model biochemical reactions. These include stereospecificity of the receptor-ligand complexes, interactions of receptor and ligand molecules, conformational changes of the reactant molecules, and intracellular crowding [1-5]. In solutions, relative diffusion of reactant molecules brings them together to bind. In the Smoluchowski formalism, the kinetics of such diffusion-influenced bimolecular reactions is described by a time-dependent rate coefficient, k(t). This rate coefficient is determined by the pair distribution function. For rigid, anisotropic molecules, the pair distribution function can be written as $p(\mathbf{r},\mathbf{w}_1,\mathbf{w}_2, t)$, where $\mathbf{r}$ is the relative separation of the reactant molecules and $\mathbf{w}_1$ and $\mathbf{w}_2$ represent their orientations. We write ($\mathbf{r}$, $\mathbf{w}_1$, $\mathbf{w}_2$) collectively as $\mathbf{x}$. p($\mathbf{x}$, t) satisfies the Smoluchowski equation, i.e., the diffusion equation with the inter-molecular potential U($\mathbf{x}$) accounted for. In a certain "reaction" region, the reactant pair can form the complex; this step is modeled by an intrinsic rate constant $\kappa(\mathbf{x})$. The Smoluchowski equation is solved subjected to the initial condition $p(\mathbf{x}, 0) = \exp[-\beta U(\mathbf{x})]/(8\pi^2)^2$. The rate coefficient is given by $k(t) = \int d\mathbf{x}(\kappa(\mathbf{x})p(\mathbf{x},t))$. The initial value of the rate

coefficient is $k(0) = \int d\mathbf{x}\kappa(\mathbf{x})\exp[-\beta U(\mathbf{x})]/(8\pi^2)^2$.
We developed an efficient algorithm for calculating k(t) from simulating the translational and rotational diffusion of the reactant pair [1, 2]. The algorithm is based on the identity $p(\mathbf{x},t) = S(t|\mathbf{x})\exp[\beta U(\mathbf{x})]/(8\pi^2)^2$, where $S(t|\mathbf{x})$ is the survival probability of the reactant pair starting from configuration **x**. The rate coefficient can then be written as $k(t) = k(0)\langle S(t|\mathbf{x})\rangle_{\mathbf{x}}$, where $\langle ...\rangle_{\mathbf{x}}$ denotes averaging over an initial distribution proportional to $\kappa(\mathbf{x})\exp[-\beta U(\mathbf{x})]$. Of particular interest is the steady-state rate constant, kss. We have derived a very useful approximation for kss. When the reaction region is small, meaning that the binding is highly stereospecific, and the interaction potential is long-ranged, as in the case of electrostatic interactions, we showed that [2,6] $k_{ss} = k_{ss0}\langle \exp[-\beta U(x)\rangle_{\boldsymbol{r}}$, where k_{ss0} is the rate constant in the absence of the long-range interaction potential and $\langle ...\rangle_{\boldsymbol{r}}$; signifies averaging over the reaction region. k_{ss0} is the basal rate constant set by relative translational and rotational diffusion between the binding molecules. The above approximate formula, referred to as the transient-complex theory, has been used to calculate, with high accuracy, binding rate constants for a number of protein-protein and protein-RNA complexes [3]. The theory was used to dissect a record-setting rate constant, at $>10^{10}$ $M^{-1}s^{-1}$, of a ribotoxin binding to a biologically essential RNA loop on the ribosome [7]. We have also accounted for conformational changes of the binding molecules [5] and effects of macrmolecular crowding [3, 4]. These theories and simulations are allowing us to realistically model the kinetics of biochemical reactions.

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Olga Dudko - Biomolecules under mechanical stress: New insights from the hopping-over-a-barrier problem

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Single-molecule biophysical tools permit measurements of the mechanical response of individual biomolecules to external load, revealing details that are typically lost when studied by ensemble methods. An analytical theory of single-molecule force experiments based on Kramers picture of diffusive crossing of a barrier in one dimension will be reviewed. The theoretical procedure of interpreting experimental data will be illustrated with the unzipping of individual DNA hairpins by nanopores, unfolding of a riboswitch by optical tweezers and unfolding of a protein with an atomic force microscope. Next, effects of multidimensionality of the free energy landscape of the biomolecule on the nature of its response to force will be explored. The proposed minimal model reveals the

existence of a spectrum of unusual responses of the biomolecule to force and points out to a remarkably simple but largely overlooked mechanism of such unusual behavior. The theory is applicable to biological contexts ranging from protein folding to ligand-receptor interactions.

Joanna Sulkowska - Tightening of knots in proteins

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We perform theoretical studies of stretching of 20 proteins with knots within a coarse grained model. The knot's ends are found to jump to well defined sequential locations that are associated with sharp turns whereas in homopolymers they diffuse around and eventually slide off. The waiting times of the jumps are increasingly stochastic as the temperature is raised. Larger knots do not return to their native locations when a protein is released after stretching.

Gaurav Arya - Using force to interrogate single molecules

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I will describe in this talk our group's recent efforts in developing theoretical and computational models to reconstruct the free energy landscape of single molecules being stretched through pulling devices such as optical tweezers and AFM cantilevers. Specifically, I will describe the development of theoretical models to capture the effects of the pulling device stiffness [1] and connecting linkers [2] in extracting the height and location of free energy barriers and the associated rates from constant-force and constant-velocity measurements.

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Johan Hake - Modeling of Ca dynamics in the dyadic cleft: Mixing continuous description of the diffusive process with discrete channel dynamics

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Ca dynamics in the small volume between the sarcolemma and the sarcoplasmic reticulum (SR), called the dyadic cleft or dyad, controls the excitation contraction coupling in the heart cell. When a cell gets excited, the L-type Ca channel opens and Ca enters the cell. Ca diffuse across the cleft and trigger further Ca release from SR by activating the Ryanodin receptor, a large Ca channel residing on the SR membrane. This process is known as the Ca induced Ca release (CICR). The CICR in a single dyad is random due to the small number of participating channels, which open and close by stochastic conformational changes. A coupled continuous and discrete model of the Ca dynamics in the dyad will be presented. Ca diffusion is governed by a continuous diffusion equation, and the binding of single Ca ions and conformational changes in single channels are governed by discrete and stochastic Markov models. The stochastic equations are solved using a a modified Gillespie solver, which is coupled to the continuous Ca field. When a channel switch between an open and closed conformation, it will cause a change in the Ca flux in the continuous model. A time stepping scheme to handle the two way coupling between the discrete and continuous equation will be presented. The modified Gillespie solver is implemented in a GPL licensed software called gillstep. Gillstep comes with a Python and a C++ frontend together with a high level Markov model editor. The editor can generate efficient C++ code, which interface with the Gillespie solver. The combination of high level editor together with code generation makes the modeling process fast and easy. The gillstep software, the Gillespie solver and Markov model editor, will be demonstrated.

Map for reaching the Castle