From structure to function: Influx and efflux systems
Cagliari 6-8 May 2009

Organizers:
Dr. Matteo Ceccarelli (Università degli Studi di Cagliari)
Prof. Paolo Ruggerone (Università degli Studi di Cagliari)
Prof. Ulrich Kleinekathofer (Jacobs University, Bremen)

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Summary

The meeting was attended by 60 participants, representing different countries in Europe incl. Italy, France, Germany, Spain, Portugal, UK, Austria, and Switzerland. Additionally, three speakers arrived from US universities (although being native Japanese, Iranian and French). Among the speakers were Prof. Roland Benz and Prof. Hiroshi Nikaido, two pioneers and founders of the field, which are still active as researchers. Furthermore, to widen the spectrum of point of view of the research in the field a researcher from a pharmaceutical company participated. The second invited representative of an important pharmaceutical company had to cancel her arrival at the last moment. Local researchers from different Departments, Toxicology, Microbiology, Biochemistry, Chemistry and Physics attended the workshop. Some students of the medical school in microbiology were also present during the first day of the meeting.

The meeting was divided in 6 sessions over three days, with 25 speakers, 17 invited, and 8 contributed; among them 5 PhD students, two of them Marie Curie fellows. One of the main characteristics of the meeting was the high multidisciplinarity of the participants, biochemists, microbiologists, physicists, biophysicists, crystallographers, and bioinformaticians. The meeting was also animated by many discussions both during and after the talks, and continued during coffee breaks, lunches and dinners, organized to keep all participants together. The different background of the participants also helped to make these discussions lively and very fruitful.

On the local newspaper an article appeared to announce the event and an interview to the organizers has been published to present the main purposes of the workshop. The funding organizations were cited as fundamental for their support to this workshop. A booklet was also prepared to collect the program together with useful information on how to reach the city and important addresses.

Given the importance of the arguments touched and discussed it would be worth to organize this workshop again in 2/3 years, provided that fundings will be available. The impression the organizers had at the end of the workshop was positive from all points of view. The participants appreciated the organization. Guests were accommodated mainly in bed&breakfast located downtown, allowing an important save of money (the organizers took care of reserving and paying). The location for the conference, the Aula Magna of the Faculty of Architecture with his patio for coffee-breaks and lunches, was an excellent choice to maintain all participants together at any moment. Other rooms have been available for discussions. Finally, the atmosphere of the workshop and its location has probably contributed to the establishing of future collaborations among several participants.

Description of the Scientific Content and Discussions

The first day was devoted to the experimental problem, with the introduction of Prof. Benz (*40 years of research on porins*) and Prof. Nikaido (*The major multidrug efflux system of E. coli, AcrAB-TolC*) as wells as the point of view of Dr. Dreier (*Detection of Drug Efflux in Whole Cells*), group leader of an European pharmaceutical company active in the field of research and production of anti-infective, Basilea Pharmaceutica. In his contribution, Prof. Benz gave a partially historical overview over the research on porins, i.e. the influx of substances into bacteria. He described the experimental progress over the year and which conclusions can be drawn especially from single-pore measurements. Also Prof. Nikaido was involved in the early research on porins but in his presentation he concentrated on the more recent work on efflux pumps and on the mechanisms by which bacteria protect themselves from the attack of antibiotics. The antibiotics efflux is the major source of resistances of certain bacteria against particular classes of antibiotics. Starting with an overview of the problem, he illustrated the most recent techniques in the field of biophysics and biochemistry used to investigate the physico-chemical parameters controlling the behaviour of bacterial porins and efflux pumps. A first important point raised is that of a necessity of redundancy of results: it is recommended to use more techniques before drawing conclusions, due to the complexity of proteins involved and the response of the background. Prof. Nikaido proposed also a new technique by which it is possible to mutate a homo-trimeric protein differently in each monomer. The representative of the company Basilea, Dr. Dreier, presented techniques used in his company to quantify the efflux of drugs through efflux proteins, pointing out the necessity to interact with researchers at universities. It was very interesting to see how different the same problem is tackled in an industrial environment. Of course, the research in a pharmaceutical company is much more result-driven and still relies on a trial and error strategy, due to the current lack of understanding of the processes involved. It became directly clear how, for example, this company and antibiotics research in a whole would benefit from a molecular level understanding of influx, but especially efflux of drugs in bacteria.

The second experimental session was devoted to the structure of efflux proteins and properties of both porins and efflux pumps. Two crystallographers, Dr. Luisi and Dr. Seeger, from the University of Cambridge and the University of Zurich respectively, presented their work on TolC and AcrB, two important components of the major efflux pump in E. coli. TolC is a protein located in the outer membrane and it is not only involved in one type of efflux pumps. Using simulations, some mutations have been proposed to be able to make TolC more open, experimentally this was confirmed by crystallizing the mutants.

AcrB represents the protein that uses energy from a proton gradient to move drugs from the inner membrane towards the outer membrane although it is not even completely clear where the substrates enter the protein. Results of different crystal structure were shown and discussed. A possible pumping mechanism was proposed and discussed with the participants. The stucture of the third component of this tripartite efflux pump, AcrA, is lacking about one third of the amino acid sequence in the crystal structure. Furthermore, there were some discussions on the number of AcrA proteins needed to make the efflux pump functioning. This is an issue currently heavily discussed in the community. It was interesting to note that people from different communities (biophysics, biochemistry, crystallography, bioinformatics) have different perspectives on the complicated problem and that everybody recognized the necessity to combine all these expertises and methods to ultimately understand the structure-function relationship of this complicated machine. In addition, a recently proposed complete model of the tripartite efflux pump was discussed in detail among several participants. A further point of discussion has been the possible conformational changes of the components upon formation of the tripartite system.

Two microbiologists from University of Marseille presented their research on efflux pumps, focusing on the role of efflux pumps in bacterial resistance. Multi drug resistance bacteria show a clear involvement of efflux pumps in resistance (Dr. Davin-Regli). The search for inhibitors of efflux pumps represents a challenge for pharmaceutical companies. Dr. Bolla presented some interesting studies on natural products that show some activity against bacteria, and in particular seem to be able to block efflux pumps. PhD G. Duret from University of Houston closed the session presenting some results on two porins extracted from vibro cholerae, OmpT and OmpU, using electrophysiology techniques. The structure of these porins is not yet available and electrophysiology is used to obtain some structural parameters, such as pore radius, and functional properties, such as selectivity.

On the next day, the focus shifted more towards the possibilities of simulations in helping to understand biological systems. Prof. Dellago detailed the transport of water through narrow pores and how this can be used to test fundamental theoretical statements of transport theory. The forces and conformational dynamics in biomolecular nanomachines was the topic of the talk by Prof. Grubmüller. He reported on impressive simulations of biomolecular processes incl. transport phenomenona through membrane proteins and activity of muscular proteins. Free energy calculations were at the center of the talks by Dr. Branduardi and Dr. Gervasio, this latter being more focused on the binding of molecules in proteins and the former on new methods. In the context of influx/efflux systems these potential landscapes are of paramount importance since from them one can understand the binding and transport properties through the pores. Simulations on active transporters were reported by Prof. Tajkhorshid and Prof. Kandt. From these impressive simulations in the 100 ns time range, molecular level understanding of active transport can be drawn. However, many problems remain unresolved due to the still limited time scale possibly reached by coarse-grained simulations, which were discussed later in the meeting. The microscopic details of ion permeation through the K^+ channel were elucidated by Prof. Domene who pointed out many questions still open despite the efforts of theory and experiment on this issue over the last years. The talk of the PhD student A. Kumar on the results extracted from the metadynamics simulations of the translocation of antibiotics through OmpF raised a very lively discussion on the possible connection between the computational outputs and pharmacologically relevant information. At the end of the second day the PhD student C. Aponte presented a thorough studies on the mechanism of gating in aquaporin.

During the third and last day, Prof. Giorgetti discussed the potentiality of genetic bioinformatics in helping to gain insights into the function of membrane transporters. So far, this potentiality has not been exploited very deeply and extensively and one can envision more collaborations and applications on the issue of the workshop. Ion transport through OmpF was the topic of the talk by Prof. Arzo. He pointed out the advantages of having atomic level resolution to interpret experimental results. Afterwards, Prof. Ha-Duong presented a new approach to coarse-grain biological systems including different implicit solvent solutions. In the last talk of the morning section, the PhD student R. Schulz described an interesting approach to simulate the conformational changes of the RND transporter AcrB and their effects on a possible substrate. Using this scheme, it is possible to validate or rule out previously proposed models to explain the substrate extrusion in term of a peristaltic process.

In the last session of the workshop, Prof. Zacharias explained methods for flexible docking and showed the impressive performance in world-wide contests, presenting some results of his participation to the program CAPRI. Then, Prof. C. Chipot introduced new algorithms within NAMD to explore free-energy landscapes using different bias techniques. Finally, the meeting was closed by a presentation about coarse-grained potentials by Prof. M. Cascella, who introduced a recent method by which it is possible to include electrostatic interactions using an amino-acid type

approach. The workshop was closed by a general discussion.

Impact for future directions in the field

Today simulations can be used to investigate important processes in biology in detail, but we need to improve further their predictivity. It is time to compare simulations with a wide spectrum of experiments, since more than one set of experimental data is necessary to confirm or refute a physical picture, due to the complexity of biological systems and processes. A close and intensive collaboration with experimentalists can represent a sure advantage in order to extend the predictivity of simulations.

In details, more collaborations between experimentalist and theoreticians are needed to get the whole picture of influx/efflux processes. This has already been successfully demonstrated in the cases of OmpF and TolC where fruitful collaborations between crystallographers and simulators have been established.
Efflux systems are important systems not only in bacteria, but also in human cells. There, for example, they are also responsible for the efflux of chemotherapy drugs from tumour cells. Furthermore, MDR-like proteins can also be found at the 'blood-brain barrier' where they regulate the exchange of nutrients and chemicals that could affect the functions of the brain.

Another important and mainly unexplored field is that of mycobacteria, in particular tuberculosis. Here, we expect the identification and characterization of new channels for influx in the next years. For this challenging goal, bioinformatics may be extremely supporting, as it is now considered a powerful tool to identify sequences of new proteins in the genome of microrganisms. Additionally, some tools exist to get native structure by homology and by modelling. However, to date these tools (rosetta program developed by Prof. Baker) are exploited mainly for solvated proteins and only few examples exist for membrane proteins. In this context, modelling using coarse-grained description can be used to manage proteins in different environments and to complement the bioinformatic studies.

New computers and new algorithms are pushing all-atom MD simulations toward the microsecond time-scale. As a mater of fact, Prof. Tajkhorshid announced during the workshop that his university, Urbana-Champaign in Illinois, will host the next generation of supercomputers, a machine that will carry over 600.000 processors. In this context bias simulations can be slowly abandoned and replaced by standard techniques.

An application of bias simulations that can help in providing details of many processes is that of free-reaction coordinates methods. Without identifying some special reaction coordinates, that represent already an approximation and some time a strong bias per se, they are able to unravel the microsopic mechanisms underlying processes of biological interests, such as the protein-protein interactions presented by Dr. F. Gervasio and D. Branduardi. Here collaborations with informaticians and mathematicians are expected to provide new algorithms for simulating and representing results in a multidimensional space.

International Workshop

From Structure to Function: Influx and Efflux Systems

6-8 May 2009, Cagliari (IT)

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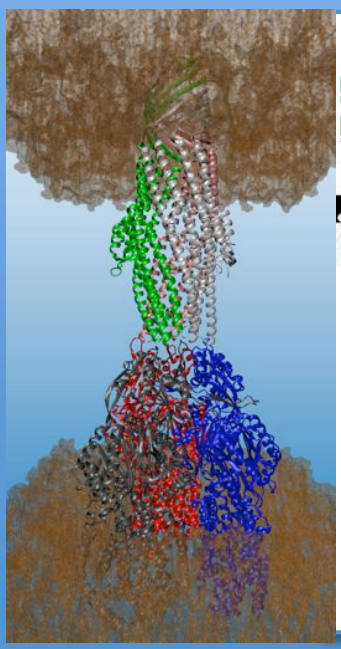

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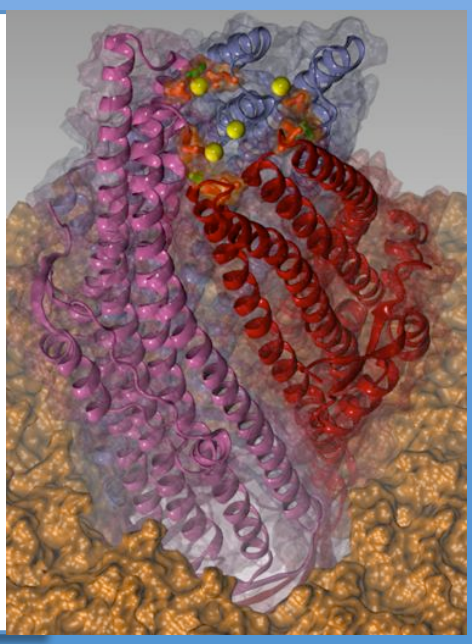

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Organizers:

M. Ceccarelli (Università degli Studi di Cagliari)
P. Ruggerone (Università degli Studi di Cagliari)
U. Kleinekathöfer (Jacobs University Bremen)

I) PROGRAM of the Workshop 06th, 07th, 08th of May 2009

Wednesday 6th May

Session 1 The experimental situation – Chair M. Winterhalter

9.30 – Welcome
10.00 - **R. Benz** – University of Würzburg – Opening and introduction to influx systems

11.00 Coffee Break

11.30 **H. Nikaido** – University of Berkeley - "The major multidrug efflux system of E. coli, AcrAB-TolC"

12.15 - **J. Dreier** - Basilea Pharmaceutica - "Detection of Drug Efflux in Whole Cells"

13.00 Lunch Break Food and drinks buffet will be served in the patio

Session 2 From Structure to Function – Chair J.-M. Pagès

14.30 **B. Luisi** – University of Cambridge - "A model for TolC opening and engagement in an efflux pump"

15.15 **A. Davin-Regli** – Universitée de la Mediterranee - "AcrAB-TolC involvement in clinical MDR Enterobacter aerogenes and Klebsiella pneumoniae isolates"

16.00 Coffee break

16.30 **M. A. Seeger** - University of Zurich - "Efflux by peristaltis: Structural and functional investigations on multidrug transporter AcrB"

17.15 **J.M. Bolla** -Université de la Mediterranée- "Natural products as chemosensitizer of resistant clinical-strains"

17.45 **G. Duret** - University of Houston- "Dynamics and modulation of the Vibrio cholerae porins OmpU and OmpT"

Thursday 7th May

Session 3 Role of Simulations and Free-energy methods – Chair M. Ceccarelli

9.30 **C. Dellago** – University of Vienna - "Water in narrow pores"

10.15 **H. Grubmüller** – Max-Planck-Institute Göttingen - "On Forces and Conformational Dynamics in Biomolecular Nanomachines"

11.00 Coffee Break

11.30 **D. Branduardi** - Italian Institute of Technology - "Free energy calculations with path collective variables"

12.15 **F. Gervasio** - Centro Nacional de Investigaciones Oncológicas - "Free-energy methods to study conformational transitions and ligand binding to flexible targets"

12.45 **F. Marinelli** - SISSA - "Insight on protein structure and dynamics from multiple biased molecular dynamics simulation"

13.15 Lunch Break Food and drinks buffet will be served in the patio

Session 4 Simulations of Channels – Chair A. Vargiu

14.45. **E. Tajkhorshid** – University of Illinois - "Visualizing the Art of Active Transport Across Cellular Membranes at Sub-Angstrom Resolution"

15.30 **C. Domene** – University of Oxford -"Ion permeation in K+-channels"

16.15 Coffee Break

16.45 **C. Kandt** - University of Bonn - "Opening, Closing & Substrate Sensitivity - Docking & Simulation Studies of the ABC Transporter BtuCD-F"

17.15 **A. Kumar** - Universita di Cagliari - " Determinants of Ampicillin diffusion through OmpF"

17.45 **C. Aponte** - Max Planck Institute for Biophysical Chemistry - "The gating mechanism of yeast aquaporin studied by MD simulations"

Friday 8th May

Session 5 Coarse grained simulations and bioinformatics – Chair E. Hajjar

9.30 **A. Giorgetti** – University of Verona - "Membrane Transporters: Insights from Bioinformatics"

10.15 **M. A. Arzo** - University of Castellon - "Divalent cation binding in the OmpF channel: experimental evidence and simulation"

11.00 Coffee Break

11.30 **T. Ha-Duong** – Universite d'Evry -"Modeling proteins and their interactions with solvent at a coarse-grained scale"

12.15 **R. Schulz** - Jacobs University - "Efflux pumps studied by MD simulations"

13.00 Lunch Break Food and drinks buffet will be served in the patio

Session 6 -Chair U. Kleinekathoefer

14.30 **M. Zacharias** – Jacobs University Bremen - "Efficient modeling of protein conformational changes during docking and structure formation"

15.15 **C. Chipot** – CNRS Nancy - "From modeling reaction coordinates to exploring free-energy landscapes using an adaptive biasing force"

16.00 Coffee Break

16.30 **M. Cascella** – University of Bern - "Development of new coarse grained potentials for the study of protein assembly and dynamics"

17.15 Closing / Discussions

II) Practical Information

For this event, we chose to locate everything near the very particular « Castello » - old medieval town district of Cagliari. It is tightly packed with churches, townhouses, a well-kept Roman amphitheatre, fine restaurants and breathtaking views to beaches/mountains surrounding Cagliari.
Below you will find: A) Directions to/from airport, conference hall, social meeting points; B) Accommodation information; C) Getting around; D) Facts about Sardinia, Cagliari, Castello; E) Climate; F) Food and Drinks.

A) Important Directions

Conference Room: **located in the Faculty of** Architecture, Via Corte d'Appello, 87, labeled "M" on the given map.
From the airport:
You can take a taxi from the airport to the hotel. The cost is less than 40 Euro and the trip takes about 15 minutes.
Alternatively, shuttle buses conveniently connect the airport (100m left from just outside the arrival hall) to the center of Cagliari (the only stop takes you to Piazza Matteotti). The ride takes 10minutes. The bus leaves every 30 minutes, with the following timetable: 08:45 09:15 09:45 10:15 10:45 11:15 11:45 12:15 12:45 13:15 13:45 14:15 14:45 15:15 15:45 16:15 16:45 17:15 17:45 18:15 18:45 19:15 19:45 20:15 20:45 21:15 21:45 22:15 22:45 23:30.
Tickets can be either bought from the automatic machine present in the arrival hall of the airport or cost 2 Euro (you need the exact change). Sometimes, the bus driver accept to sell you a ticket…
From the Piazza Matteotti: you can (depending on where your accommodation is located and how you feel like) walk or take another bus to reach your accommodation.
Buses number 8 will take you from Piazza Matteotti to the old part of town/Castello

B) Accommodations

GUEST NAMES	ACCOMODATIONS NAME/-ADDRESS-PHONE	IDENTIFIER ON MAP
Duret	Darija Ritter, via Lanusei 3 tel: 0039-347-4187510	Pink Arrow
Aponte	Darija Ritter, via Lanusei 3 tel: 0039-347-4187510	Pink Arrow
Marinelli	Darija Ritter, via Lanusei 3 tel: 0039-347-4187510	Pink Arrow
Alakbarov	a Casa di Giulia di Simona Granelli; via Pola, 5 , tel. + 39 346 5356859	Red Arrow
Raunest	a Casa di Giulia di Simona Granelli; via Pola,	Red Arrow
Kandt	B&B Via Sonnino n° 161 tel. (0039) 349 5090675	Blue Arrow
Fischer	B&B Via Sonnino n° 161 tel. (0039) 349 5090675	Blue Arrow
Chipot	hotel 2 colonne - via Sardegna 4 (+39070658710)	Dark Green Arrow
Giorgetti	hotel 2 colonne - via Sardegna 4 (+39070658710)	Dark Green Arrow
Cascella	hotel 2 colonne - via Sardegna 4 (+39070658710)	Dark Green Arrow
Seeger	hotel 2 colonne - via Sardegna 4 (+39070658710)	Dark Green Arrow
Zacharias	hotel 2 colonne - via Sardegna 4 (+39070658710)	Dark Green Arrow
Aguilella (Arzo)	hotel 2 colonne - via Sardegna 4 (+39070658710)	Dark Green Arrow
Luisi	affittacamere Sa Domu Cheta - via Portoscalas, 30 (+39070655002)	Dark Orange Arrow
Dellago	b&b Il Giardino Segreto - viale Sant' Ignazio 16 (+393394784575)	Light Orange Arrow
Ha-Duong	b&b Il Giardino Segreto - viale Sant' Ignazio 16 (+393394784575)	Light Orange Arrow
Branduardi	b&b Rose Rosse - via Lamarmora 116 (+393920469732)	Light Green Arrow
Domene	b&b Rose Rosse - via Lamarmora 116 (+393920469732)	Light Green Arrow
Masetti	b&b Rose Rosse - via Lamarmora 116 (+393920469732)	Light Green Arrow
Ceccarini	b&b Rose Rosse - via Lamarmora 116 (+393920469732)	Light Green Arrow
Masetti	b&b Rose Rosse - via Lamarmora 116 (+393920469732)	Light Green Arrow
Ceccarini	b&b Rose Rosse - via Lamarmora 116 (+393920469732)	Light Green Arrow
Pezeshki/Schulz	b&b Antico Palazzo Crisaripa - via Canelles 104 (+393479230287)	Purple Arrow
Gervasio	Karel - via Genovesi 12 (+393495220315)	Red Arrow
Tajkhorshid	Hotel Regina Margherita	Yellow Arrow

If you need anything at any point: you can contact:
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C) Getting Around

Electricity in Italy is 220 volts.
Most establishments will accept major credit cards (ATM are called here Bancomat).
Internet: there should be free internet (wi-fii) in (most/all) accommodations and in the meeting/conference room.
Telephone: The area code and the telephone number must be dialed in all Italy, even if you call someone within the same city. Italy's country code is 39, and Cagliari's area code is 070.
Pre-paid telephone cards can be bought at electronics shops, tobacconists' (tabacchi), newsstands and bars.
Busses cover the whole city:

- -The ones going from the main station by the port (piazza Matteoti) to the old-medieval town: (**Quartiere di castello) are number-**8 (stop at Viale Buon Cammino), or number-7 (stop at "Piazza Indipendenza" or "Via Lamarmora"), number 10(stop at Piazza Costituzione: and then take the stairs up to reach the old-town main door: **Bastione Saint Remy)**
- -The ones going to the Poetto beach nearby Cagliari are numbered "PQ" or "PF" and leave also from the port/ Piazza Matteoti.

Bus tickets cost 1euro for 90min of service and should be bought in kiosk or cafés: press/tobacco sellers.
Radio taxi in Cagliari: +39 070 400101 - +39 070 657070

D) Facts about Sardinia, Cagliari, Castello

Situated in the middle of the Mediterranean Sea, Sardinia with its app. 1,800 km of coastline, is one of the most popular destinations for people who love aquatic sports and seaside holidays, not only for its natural beauty and geographical position but also for its history. The sea around this large Mediterranean Island (second only to Sicily in size among all Mediterranean Islands) is among the most beautiful and transparent in the world. Note that the main beach of Cagliari, called "Poetto", is a short (10min bus) ride. However, for obvious practical reasons (to keep the serious/scientific content) we could not organize the meeting/conference "on the beach". In fact, although it is common to think of Sardinia as a land of "beach-and-sand", it is wrong. You would be surprised by the amount of history, nature and culture that the island has to offer!
Thus, to give you a "piece of this" we will try to give you a taste of food & drinks specialties along this meeting.
Furthermore, we decided to set both your accommodations and the conference room in the medieval old part of town of the capital of Sardegna: Cagliari.
Here's a quick description of **Quartiere di Castello:**
It is Cagliari's oldest quarter and the one which has maintained the vestiges of its past better than all the others. It was probably already the site of a trading post by the 12th century, then purchased by the Pisan authorities in 1217 and then fortified. Civil and religious authorities found a safe haven and the aristocratic families soon began to build their palaces and residences here. Its appearance today dates back to the 17th and 18th centuries. Although at the end of the 19th century did the quarter begin to lose its hegemonic role and slowly declined through abandon and neglect, in recent times, restoration works and enhancement projects are attempting to give lustre to the quarter once again. Recently, three different lifts have been installed to provide access to the Castello from the rest of the town. For visitors who enjoy strolling, it is possible, starting from Piazza Martiri, to arrive through the Porta del Leone and enter through the portico of the Boyl Residence into the narrow streets. Finally, those coming from the upper Stampace quarter, after reaching the Civil Hospital, can continue up Via Porcell bordering on the trench of San Guglielmo and enter the Castello directly in Via dei Genovesi starting from the Villa Pietrangeli. At the end of in Via dei Genovesi, at number 114, we find the Palazzo Siotto, formerly Palazzo Floris Thorel.

E) Climate

The climate in Sardinia is typically Mediterranean and the influences of the sea are present all around the island. It is characterized by long, warm summers and short, mild winters, accompanied by the blowing of the north-west wind
The average temperature in May is >20 degrees Celsius, and while you should normally expect clear blue sky, the strong wind can bring fast and drastic changes. Still, white skins=do not forget sun cream!

F) Food

Sardinia is an amazing destination for its rich gastronomy based on ancient recipes, influences from Africa, Middle-East, and of course Italy and the rest of Europe. Its vegetation has stimulating scents: saffron, rosemary (you see/smell it everywhere!), bay leaf and mint among others.

-Breakfast: a quick note here to warn you that there is no culture for breakfast in the island! What they call breakfast is basically a coffee, and maybe a "sort of" croissant! For this reason we will serve some (light) food during the organized coffee breaks of the meeting (see program).
-Bread: the traditional breads of Sardinia tend to be hard and dry. "Pane carasau", a crisp, thin bread is made from durum wheat semolina and wheat flour. It was the bread that shepherds and herdsmen could carry with them during their months in the mountains.
-Bottarga, also known as Sardinian caviar, is made from fish eggs (mullet or tuna) Bottarga is a real delicates, often served in fine slices or used as a dry powder in spaghettis for example.
-Pasta: the more traditional pasta of Sardegna is malloreddus, a small gnocchi made from durum wheat semolina, salt, water and saffron. There is also the type called "Fregola": a close relative to couscous, is a beads of semolina pasta. Both are usually served with complicated sauces, ragu, or with butter and grated percorino cheese. Finally, I must mention Culingiones: a typical potato/ravioli with a pecorino-chard filling.
-Meat: "Porchetto" (roasted pork) is typical of all Sardinian cuisine. They are strong also with Agnello (lamb) that can be served "con finocchietti": stewed with onion, tomato and wild fennel. Other specialty in the island includes horse meat ("Cavallo") and even more interesting: Donkey ("Asino").
-Fish: Of course the island has a rich seafood cuisine: and this goes far beyond the obvious "sardines". The best dishes you can get are based on "polpo" (octopus), "seppia". If you're unsure, you can also ask for the mixed grilled seafood plate: "fritura mista" and fresh calamari. Finally Tuna or Spada (Swordfish) steacks are a must!
-**Vegetables**: usually the salads come as a "Do It Yourself" pot, but you can have great dishes based on the fresh vegetables: mushrooms "funghi", artichokes "carcioffi" or "fava beans "Favata".
-Desserts: Sebadas or seadas: sweet focaccia baked with pecorino and bitter honey from blossoms of corbezzolo (the strawberry tree).
-Wines: the most renowned wines are: Cannonau, red wine, good with typical meat dishes; Carignano, red or rosé, excellent with starters, roast meat, and aged cheese; Vermentino, white wine, excellent with fish dishes; Vernaccia, classic aperitif/dessert wine.
-**Liquor**: After a "typically lengthy and massive Sardinian dinner", you will particularly appreciate the large range of digestive that the town has to offer: Mirto: a sweet liquor based on the blue and typical "mirto" berries that grow everywhere in the mountain areas of Sardegna. Limoncello: still sweet and strong and good (this one is more famous as it is based on lemons that grow everywhere, and not only in Sardegna). Filu 'e Ferru: this is like pure alcohol: equivalent to "grappa" or "aquavite", be careful as it looks like water, however it is a much better digestive than water, ask also for the nice story that gave the name to this "grappa".

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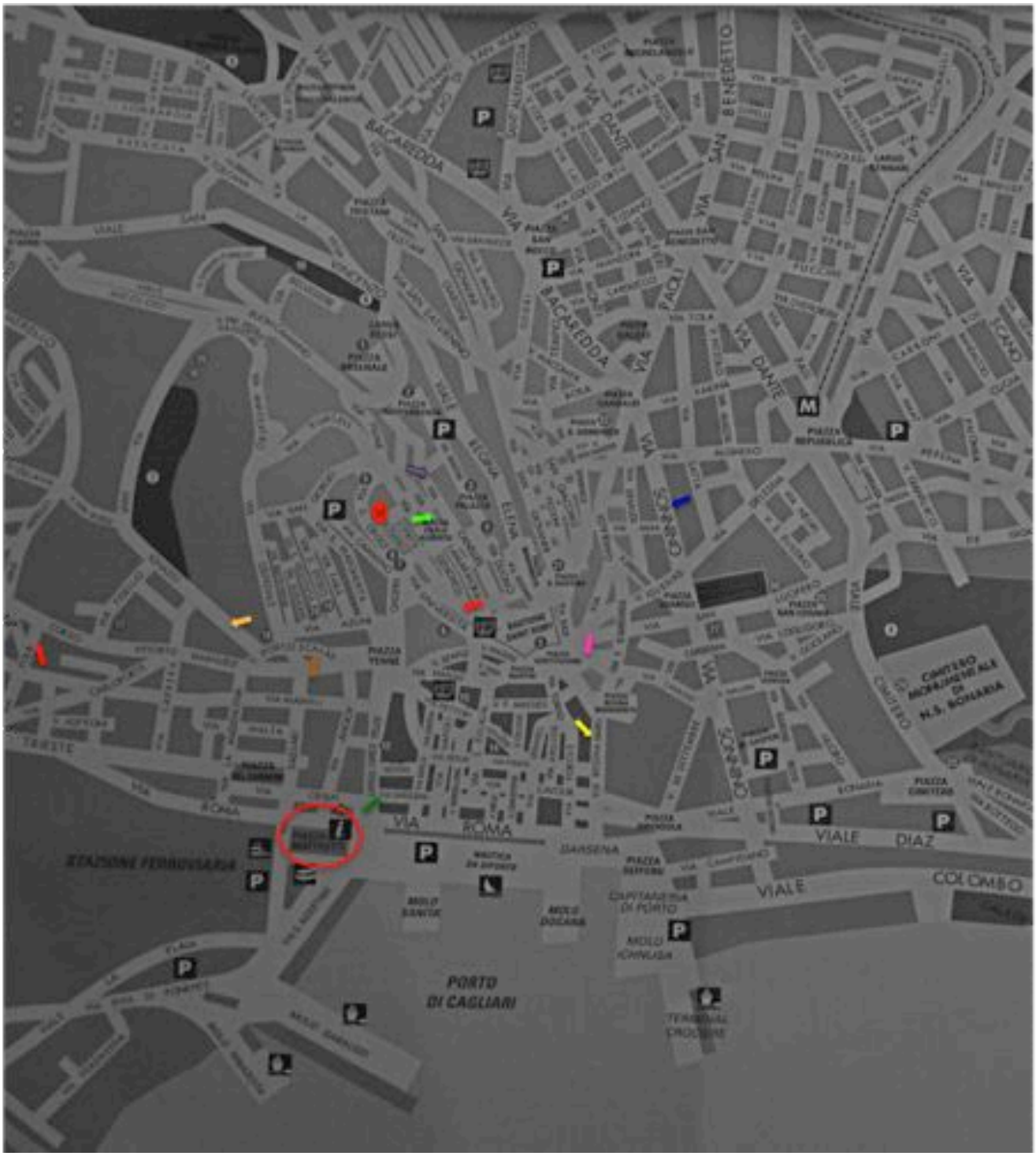

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Il racconto della moglie Mina, a Cagliari per un interessante incontro su "Pane amore e libertà (scientifica)", associazione Orizzonti Nuovi

Piergiorgio Welby

Ho detto addio a Welby un mercoledì dopo i pacchi

Mercoledì sera, dopo i pacchi. I pacchi di "Affari tuoi". Li conduceva Flavio Insinna, quel 21 dicembre del 2006, quando Piergiorgio Welby, da anni paralizzato dalla Sla, scelse di morire. «Non avevamo mai seguito quei programmi, ma negli ultimi tempi vedevamo di tutto: Maria De Filippi, "L'isola dei famosi", "Il Grande Fratello". Era un modo per avviarci alla fine». Parla con ironica tenerezza, Mina Welby. Il tono di voce basso, lo sguardo di chi ha condiviso tutto con l'uomo che ha amato: la vita e la morte. «*Adesso spegni*, mi ha detto dopo i pacchi. Solo allora il dottor Mario Riccio, che aveva accettato di aiutarlo a morire, lo ha sedato. Ha voluto salutare tutti gli amici presenti, uno per uno, poi mi ha chiesto di fargli sentire la *Primavera* di Vivaldi. Il cd era lì, era lì da sempre, e io non lo trovavo. Ero disperata. *Allora metti Bob Dylan*. E sa quale era la canzone che casualmente lo ha accompagnato verso la fine? *Tonight I'll Be Stayin' Here With You*, stanotte sarò qui con te».

Mina Welby ieri era a Cagliari, invitata alla Casa dello studente dall'associazione studentesca Orizzonti Nuovi. Il tema, *Pane amore e ... libertà (scientifica)*. Con lei, Michele Pipia che ha coordinato il dibattito, e due medici: Paolo Moi, genetista. E Salvatore Pisu, docente di bioetica. Il primo a sottolineare l'estrema importanza della libertà della ricerca scientifica, il secondo a ribadire che il problema al centro del dibattito parlamentare (la legge sul testamento biologico è al vaglio della Camera) non riguarda la libertà dell'individuo, ma la validità dello strumento. Temi delicati, che aprono la strada a dubbi angosciosi. Argomenti di scontro e di dibattito, che dividono opinione pubblica e classe politica, affrontati ieri con grande serietà.

Impegnata nell'Associazione Luca Coscioni, Mina Welby ha lanciato anche a Cagliari l'appello per istituire un registro provinciale del testamento biologico. Lo ha fatto in mattinata nel'incontro con il presidente del Consiglio provinciale Roberto Pili, la vice presidente Laura Pulga e il consigliere Sandro Cancedda (Idv), lo ha ripetuto alla Casa dello Studente. «Stiamo lavorando per sensibilizzare le amministrazioni sui grandi temi etici legati alla fine della vita, sulla possibilità che anche a livello provinciale, così come è già successo in una decina di comuni, possa essere istituito il registro del testamento biologico». Ora le preme «che si faccia una buona legge. Il testo approvato in Senato non ci piace, e secondo me è anticostituzionale, va contro il diritto della persona di decidere di se stessa. Mio marito si è sempre battuto per questa libertà. Ricordo le sue conversazioni con Francesco D'Agostino su una possibile legge, la sua angoscia nel vedersi in condizioni sempre più avvilenti. Già allora sognava di poter staccare la spina, invidiava chi poteva stordirsi con la morfina. *A me non succederà*. E di una decisione finale affidata al medico e non al paziente diceva con amarezza: *sarà come i cani che abbaiano alla luna*. Aveva ragione. Questa legge non ci piace. Le cattiverie sul caso Englaro neppure. Ma io ho fiducia. Spero che qualcosa cambi, confido nei giovani. Negli ultimi tempi ho ricevuto tre tesi di laureati in giurisprudenza, dedicate a Welby e a Eluana. Questo mi sostiene moltissimo, credo che gli uomini civili capiranno che si tratta di un diritto inalienabile della persona. Abbiamo il diritto alla salute ma nessuno è obbligato a sottoporsi a terapie che non vuole. Lo dice la nostra Costituzione, che fu scritta da laici e da cattolici. Io dico che la vita è indisponibile, ma per chi mi vuole uccidere! Per me però può essere violenza anche allungare i tempi di una sofferenza indicibile». «Io non ho imparato niente, io ho vissuto», precisa. «Ed è la mia storia che racconto a tutti. In trent'anni io e Piero non avevamo mai litigato. Ma io l'ho accusato di essere egoista. Non volevo che mi lasciasse. E lui non voleva la sedazione, temeva di non farsi trovare lucido dalla morte. Quel mercoledì dopo i pacchi, prima che gli iniettassero la fiala, gli chiesi se volesse davvero andarsene, disse sì. E allora anch'io dissi sì. Mi ha sorriso. Quando si è addormentato mi sono rilassata....».

MARIA PAOLA MASALA

Appuntamenti. Mostre di Podda e Pettinau. Parte il Festival della Scienza

A Cagliari "Riflessi d'arte" dal mondo

Si inaugura stasera alle 19, Espace S&P in via Savoia 19 a Cagliari, la mostra internazionale di 20 artisti *Riflessi d'arte attraverso Paesi*. Al vernissage, ore 20, concerto della pianista Irma Toudjian. Un appuntamento di spicco reso possibile dall'associazione francese "Ariane-Essor". Dal lunedì al venerdì dalle 19 alle 21 fino al 24.

GIORGIO PODDA. Tre partecipi presenti e un endecasillabo, per dare un titolo curioso alla sua mostra. Li ha scelti Giorgio Podda, che da oggi (alle 19) al 23 maggio espone nello Spazio (in)visibile di via Barcellona 75 a Cagliari. *Andante Venente Ritornante, d'Omero l'Odissea con l'acquerello* è visitabile dalle 10 alle 13 e dalle 17 alle 21.

LABORATORIO 168. Stasera alle 18,30 al Laboratorio 168 in via Mameli a Cagliari si inaugura la personale di Giuseppe Pettinau. Un'antologica che comprende 26 dipinti e 16 disegni realizzati tra il 1984 e il 2006. Sino al 21 tutti i giorni dalle 18,30 alle 20,30, tranne domenica e lunedì.

LABORATORIO DELLA CRISI. *Laboratorio della crisi* è il titolo della mostra allestita a Porto Torres da Az.Namusn.Art. Curata da Maurizio Coccia, si inaugura stasera alle 19,30 nell'Ex Consorzio Agrario, via Sassari 102, e resterà aperta sino al 31. Az.Namusn.Art è un gruppo attivo sulla scena artistica da più di due anni.

FUTURISMO. Stasera alle 18, Sala convegni di piazza del Carmine 4 a Cagliari, incontro sul futurismo con Giorgio Pellegrini e Angelo Abis

MACOMER. Da oggi a domenica a Macomer si svolge il campo regionale di orientamento per i ragazzi che partiranno all'estero con Intercultura. Ottanta studenti e una decina di volontari si ritroveranno a Sant'Antonio per una tre giorni di preparazione all'esperienza.

TINTI A SARROCH. Alla Biblioteca comunale di Sarroch verrà presentato stasera alle 18 il libro di Bruno Tinti "La questione immorale". Con l'autore parteciperanno Salvatore Mattana e Mauro Mura.

ORGOSOLO. Festival della Scienza di Orgosolo da oggi al 10 maggio: incontri, animazioni, spettacoli, seminari, esposizioni sull'alimentazione. Spazio per la cultura locale con la realizzazione di un murale e la cena scientifica.

CONVEGNI

Un simposio a Cagliari

La Fisica in campo contro i batteri: efficacia e risparmio

A partire dalla metà del secolo scorso gli antibiotici hanno rivoluzionato il trattamento delle malattie infettive, contribuendo in maniera determinante all'incremento dell'aspettativa di vita. I trattamenti antimicrobici sono impiegati anche nei vegetali e negli alimenti, per esempio sotto forma di biocidi contro i microbi patogeni, alcuni dei quali responsabili di tossinfezioni alimentari, come la Salmonella e la Listeria. Purtroppo, da circa vent'anni, i batteri hanno iniziato a sviluppare raffinate strategie per eludere i farmaci, facendo elevare la resistenza agli antibiotici al rango di priorità sanitaria di assoluto rilievo. Oggi la ricerca ha attivato numerose linee di studio per individuare nuove strategie di sviluppo di farmaci più efficaci. Sotto questi auspici si chiude oggi a Cagliari (aula magna della facoltà di Architettura dell'Università, in via Corte d'Appello 87) il congresso internazionale "From Structure to Function: Influx and Efflux Systems".

Il congresso è organizzato dall'Università di Cagliari, dal Cecam, dal Sardinian Laboratory for Computational Materials Science, dall'European Science Foundation e dall'Unione Europea nell'ambito del progetto "Translocation" (finanziato con tre milioni di euro dal Sesto programma Quadro con i fondi Marie Curie dedicati alla mobilità dei ricercatori).

Il fisico cagliaritano Matteo Ceccarelli, coordinatore del progetto "Translocation", spiega perché oggi anche i fisici si occupano di questi temi: «I meccanismi di resistenza non sono altro che interazioni molecolari fra gli antibiotici e le proteine, per questo noi siamo coinvolti in prima persona. In particolare ci occupiamo dei meccanismi di trasporto attraverso simulazioni al computer e in questo modo possiamo affrontare il problema dal microscopico al macroscopico, il cosiddetto bottom-up approach. Siamo al livello di ricerca di base. Una ricerca che sta cambiando la maniera di sviluppare gli antibiotici.».

Chi partecipa al simposio?

«Trattandosi di una ricerca multisciplinare abbiamo invitato 20 relatori di varie discipline: fisica, chimica, biologia, medicina. Tra questi, due biochimici che da 40 anni studiano le proprietà di trasporto attraverso i batteri: Hiroshi Nikaido dell'Università di Berkeley e Roland Benz della Jacobs University. I partecipanti sono attualmente una sessantina, anch'essi di varia provenienza disciplinare e geografica: Germania, Francia, Portogallo, Spagna, Inghilterra, Stati Uniti e Italia».

Qual è il vostro ruolo?

«Il dipartimento di Fisica è coinvolto nella ricerca attraverso una rete europea che coinvolge sette istituzioni scientifiche, due case farmaceutiche e cinque dipartimenti universitari, con lo scopo di far crescere studenti multidisciplinari».

Che tipo di sviluppi sono attesi per il futuro?

«Disegnare gli antibiotici al computer, allo scopo di selezionare meglio gli esperimenti da compiere per la fase pre-clinica risparmando tempo e soldi. Arriveremo a progettare nuovi antibiotici che oltre ad avere una buona capacità di legarsi hanno anche una mira migliore: riusciranno a penetrare facilmente la barriera esterna che protegge i batteri. C'è ancora molto da imparare dai batteri per come evolvono e quali tecniche adottano per difendersi dai nostri antibiotici».

ANDREA MAMELI

LA RICERCA

Parla Matteo Ceccarelli: progettare nuovi antibiotici attraverso il computer