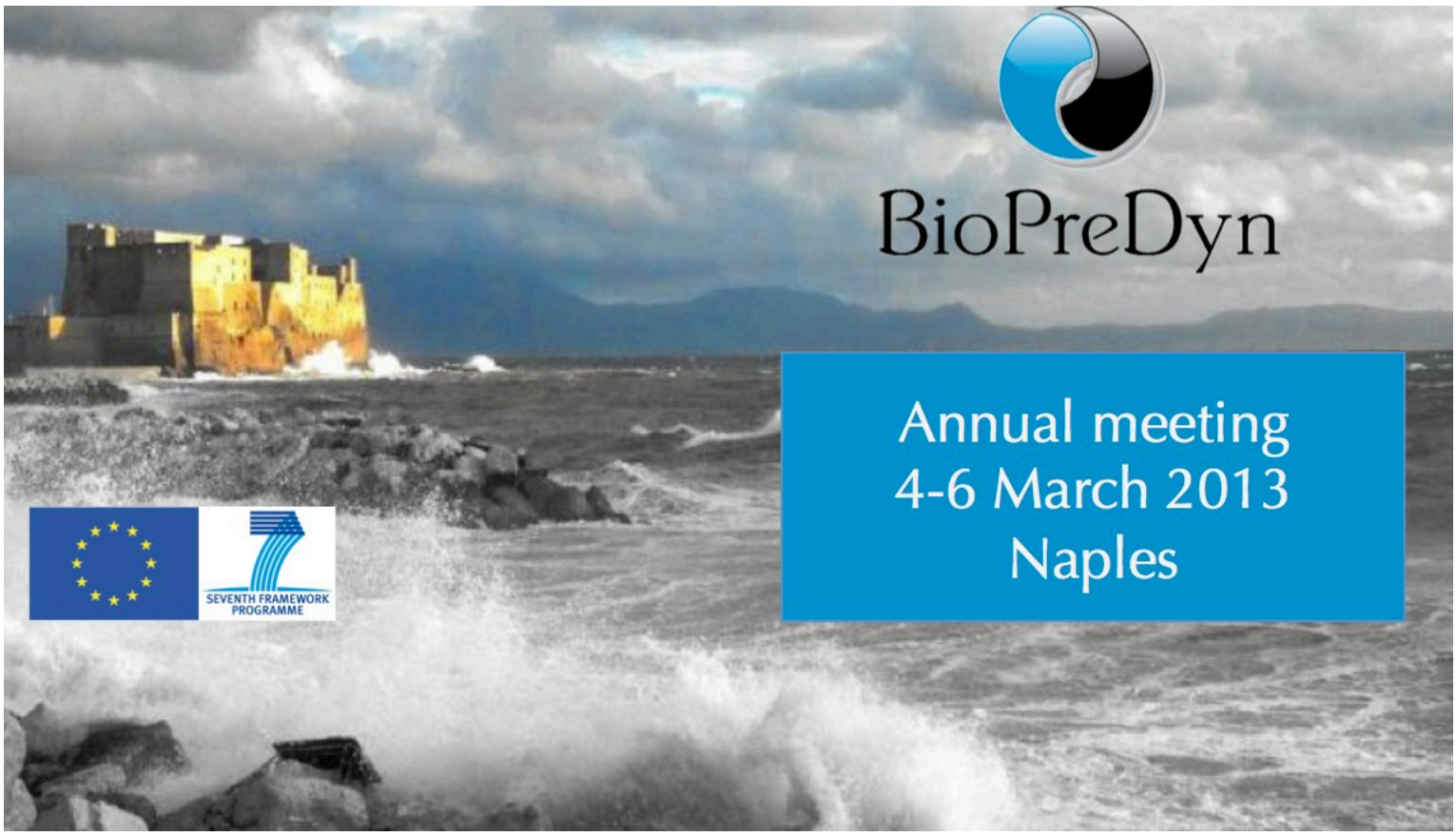


Agenda

Monday, 4 March

Participant arrival, hotel check-in (*Hotel Majestic,* Largo Vasto a Chiaia 68)

18:00	Meet for tour of Naples city center with Paola Cormio at the *Piazza Plebiscito*, in front of the Gambrinus café (we will leave at 18:15); please tell Veronica if you plan to join.
20:30	Networking dinner *Ristorante Pizzeria Hache'* (via Partenope, 6/D)

Tuesday, 5 March

Scientific talks in the *Aula Magna* (Via Partenope 26)

9:00	Diego	Welcome
9:20	Yogi/ Julio B.	Work packages: Overview and progress
9:50	Roberto (TIGEM)	*Developing a mathematical modeling framework for linking signaling, regulation, and metabolism: metabolic processes under the influence of hormones and genetic disorders as case studies*
10:15	Emanuel (EMBL)	*Linking models of signalling and metabolic networks*
10:40		coffee break
11:20	Maria (CWI)	*UQ in BioPreDyn*
11:45	Kieran (Manchester)	*Genome-scale metabolic models: from reconstructions to ODEs*

BioPreDyn is a Collaborative Project (project number 289434), funded by the Framework Programme 7 of the European Commission.

12:10	Nicolas (Sheffield)	*Detecting periodically expressed genes with Gaussian processes*
12:35	Julio B. (CSIC)	*Parameter estimation tools and related tasks*
13:00		Lunch
14:15		walk around *Castel dell'Ovo* (outside: bring rain coat or umbrella!)
15:30	Eva/Yogi (CSIC/CRG)	*Structural identifiability analysis*
16:05	Anton (CRG)	*11 ways to maltreat your data and still get the same results*
16:35		coffee break
17:05	Besray (CRG)	*Reverse engineering in a minimal bacterium: Mycoplasma pneumonia*
17:30	Sophia/Alex (Insilico/CSIC)	*A consensus approach for high quality predictions in CHO cell kinetic modelling*
18:05	Jaap (UvA)	*Parameter estimation for spatio-temporal models of gene regulatory networks in the sea anemone Nematostella vectensis*
18:30		End of talks
19:15		meet in front of venue for seaside walking tour with Paola
21:00		networking dinner *La Bersagliera* (Borgo Marinari 10/11)

Wednesday, 5 March

Discussion and talks in the *Aula Magna* (Via Partenope 26)

9:00	Veronica	Overview: project management
9:20	Yogi/ Julio B.	Overview: task progress (for task deliverables due at 18/24 months: 1.1-1.5, 2.1-2.3, 3.1, 3.2, 4.1-4.4, 5.1, 6.1, 7.2, 8.2)
10:30		coffee break
11:00	Betrand/Eric (CSM)	Software integration progress and issues
12:30	Lunch	
13:30	Yogi/Julio B.	**General assembly**: future scientific direction, collaborative efforts, additional issues
15:30		End of official meeting

Note that: 1. the general assembly meeting is **open for all** but not mandatory (except for the PIs)

2. the meeting will continue "unofficially" the afternoon and evening of the 6th with everyone who is staying due to flight arrangements

3. be aware of the potential for theft- it's better not to carry your computer around with you, for example, when you go for dinners or on walking tours.

Abstracts for talks

Tuesday, 5 March

Roberto Pagliarini (FTELE.IGM)

Developing a mathematical modeling framework for linking signaling, regulation, and metabolism: metabolic processes under the influence of hormones and genetic disorders as case studies

Developing a functional model combining signaling, regulation, and metabolism is one of the BioPreDyn project aims. The major focus of this talk lays in developing and establishing a mathematical modeling framework, which can be a valuable tool to study metabolic scenarious resulting from regulative mechanisms. For this goal, we propose an innovative computational workflow to describe the changes of metabolism under the influence of hormones or caused by mutations in enzymes or transporters affecting specific metabolic reactions, known as inborn errors of metabolism (IEM).

Our workflow exploits a genome-scale network model of human hepatocyte metabolism to predict compounds and reactions that are affected by genetic mutations or by hormone regulations. It allows the identification of metabolites that accumulate in hepatocytes via an innovative ”differential flux analysis”, while a variant of the Gene Set Enrichment Analysis, that we called ”Metabolic Enrichment Analysis”, is applied to infer if the compounds that change the most are enriched in disease-associated compound sets.

In case studies, we first simulated 38 IEM in liver. In about half of the cases, our workflow correctly identified the metabolites known to accumulate in the blood and urine of IEM patients. After that, we tested the workflow ability for representing scenarios describing metabolic processes under the influence of the hormones insulin and glucagon.

Emanuel Gonçalves (EMBL)

Linking models of signalling and metabolic networks

Mathematical modelling is increasingly becoming an indispensable tool for the study of cellular processes, allowing their analysis in a systematic and comprehensive manner. In the vast majority of the cases, models focus on specific subsystems, and in particular describe either metabolism, gene expression or signal transduction. Integrated models that are able to span and interconnect these layers are, by contrast, rare as their construction and analysis face multiple challenges. Such methods, however, would represent extremely useful tools to understand cell behaviour, with application in distinct fields of biological and medical research. In particular, they could be useful tools to study genotype-phenotype mappings, and the way they are affected by specific conditions or perturbations. Here, we review existing computational approaches that integrate signalling, gene regulation and/or metabolism. We describe

existing challenges and available methods and point out potentially useful strategies. We also illustrate this process by proposing a method to combine a signalling/gene regulatory network, initially represented in a Boolean formalism, with a kinetic metabolic model, which results in a single integrated dynamical system. We illustrate this approach with a model describing the hepatic glucose metabolism hormonally controlled by insulin and glucagon.

Maria Navarro (CWI)

UQ in BioPreDyn

The utilization of computer simulation modeling for real-world processes requires addressing Uncertainty Quantification (UQ). Using UQ could help us to draw flexible conclusions from a model that could differ from the deterministic version. We are thus working on this line and are developing a methodology to incorporate uncertainty into the models. At the same time, we are trying to apply this methodology to well-known models, like the classical Hodgkin-Huxley and even to more complex models, like CHO-S.

Kieran Smallbone (Manchester)

Genome-scale metabolic models: from reconstructions to ODEs

Two genome-scale metabolic reconstructions have been developed in Manchester: for E. coli (http://ecoli.sf.net/) and for yeast (http://yeast.sf.net/). These are highly-annotated metabolic maps, reconstructed from the genome sequence and from literature, and are periodically updated by a team of collaborators from various research groups. We will discuss a pipeline for automatic generation of first-pass kinetic models from these networks. We analyse some properties of these genome-scale models and show how the semantic annotations may be used to populate them with known kinetics.

Nicolas Durrande (Sheffield)

Detecting periodically expressed genes with Gaussian processes

The 24-hour cycle of days can be observed at many scales in the oscillations of biological mechanisms. This phenomenon, called circadian rhythm, can be seen for example at a microscopic level on gene expressions. It is believed that the genes involved in the oscillatory mechanism have themselves a cyclic expression, so that the detection of periodically-expressed genes is of great interest for completing current models.

We will present a new method for the detection of periodical phenomenon based on the decomposition of Gaussian processes. This approach allows to estimate and extract the periodic part of a signal that is observed at a limited number of points and it benefits from all the features of the Gaussian Process

framework.

We illustrate the method with gene expression data from the literature based on Arabidopsis. The comparison shows that the proposed method allows some new interesting genes with a strong periodic behaviour to be detected.

Julio Banga (CSIC)

Parameter estimation tools and related tasks

This talk will describe the work that CSIC has carried out regarding a new parameter estimation strategy. This new strategy is based on a parallel (cooperative) enhanced scatter search (CeSS) method which belongs to the class of stochastic global optimisation algorithms. This technique makes use of diversification (global search) and intensification (local search) methods, so it can be considered to be an advanced hybrid strategy. Currently it can handle non-linear programming (NLP) and, to some extent, mixed-integer nonlinear programming (MINLP) problems. Several innovative mechanisms have been implemented in CeSS in order to enhance its efficiency and robustness when solving large-scale optimization problems. CSIC has also implemented another stochastic method for integer programming (combinatorial optimization) based on extensions of the variable neighbourhood search (VNS) metaheuristic.

These methods were initially implemented in Matlab, and later, in collaboration with EMBL, have also been implemented in R. CSIC has tested this novel method with benchmark problems, including parameter estimation in large-scale models of E. coli.

Further, CSIC and EMBL have collaborated implementing these methods in a software toolbox (MEIGO, metaheuristics for global optimization in bioinformatics and systems biology), which allow users to choose among a wide range of powerful global search methods, taking advantage of parallel high-performance computers. The MEIGO toolbox offers Matlab and R implementations, thus facilitating its use with many existing packages in bioinformatics. EBI has also developed a Python interface to the R version.

Eva Balsa/Canto (CSIC) **/Yogi Jaeger** (CRG)

Structural identifiability analysis

We are studying the dynamics of pattern formation in the fruit fly, *Drosophila melanogaster*, using a data-driven modeling (reverse-engineering) approach. Our model system is the gap gene network, involved in segment determination during early embryogensis. While most of our research focuses on the pattern-forming potential encoded in transcriptional regulatory interactions among gap genes, whether post-

transcriptional mechanisms, such as regulated translation and protein degradation, contribute to the function and regulatory dynamics of the network is still an open question. I will present a model of gap gene translational regulation that shows that the correct positioning of expression-domain boundaries in space and time does not require translational regulation. The model is based on the assumption that translation can be treated as a delay-linear process, such that gap protein patterns resemble those of mRNAs a few minutes earlier. This model was obtained using a rigorous reverse-engineering process, including parameter estimation by global non-linear model fitting, plus a priori and a posteriori parameter identifiability analysis. No such analysis has been performed in a complex, multicellular context before. We demonstrate how it can be used to get precise estimations of production, diffusion, and decay rates for gap proteins, and to assess the mechanism and relative importance of post-translational regulation in pattern formation.

Anton Crombach (CRG)

11 ways to maltreat your data and still get the same results

We are performing a comparative systems-level study of the gap gene network, involved in patterning in the early embryo, across three species of Diptera: the vinegar fly *Drosophila melanogaster*, the scuttle fly *Megaselia abdita*, and the moth midge *Clogmia albipunctata*. Here I would like to focus on the methodology we have developed to elucidate multiple gene network architectures in a relatively short amount of time.

We apply a reverse engineering approach, also known as the gene circuit method, which is used to infer regulatory interactions from mRNA-based, spatial, gene expression data. Originally, it was developed for protein expression data, and we adapted the approach to work with whole-mount enzymatic mRNA in *in situ* hybridization. In this manner, we avoid various labor-intensive stages of the experimental protocol and are able to simplify the image processing of the fly embryos substantially. Importantly, the method works correctly, as shown with Drosophila as a test case: we extracted the boundaries of gap gene mRNA expression domains from embryos in the late blastoderm stages C10–C14A. We show that the gene regulatory network of the gap genes can be reliably interred from this mRNA boundary data and explore the minimal requirements of a data set in order to successfully perform the reverse engineering. Thus, we have developed a general method for the reverse engineering of gene regulatory networks. We are convinced that this reverse engineering method of gene regulatory networks has wider applicablity, potentially opening it to researchers from various fields for larger-scale analyses of their favorite gene networks.

Besray Unal (CRG)

Reverse engineering in a minimal bacterium: Mycoplasma pneumonia

Mycoplasma pneumoniae, a bacterium which leads to atypical pneumonia, is amongst the smallest self-replicating organisms. The small genome and various metabolomic and proteomic data of the bacteria offer a basis for understanding the minimal-cell concept and for characterizing the structure, function and dynamics of this organism. Despite its tiny genome, the regulatory networks of this bacteria are surprisingly complex. We aim to gain insight into the gene regulatory network via the reverse engineering approach.

For this, we are employing the genome-wide RNA and protein concentrations as time-series measurements different growth conditions, obtained from the Luis Serrano laboratory (CRG). As a novel approach over previous studies, protein and RNA data are being used together for gene-regulatory network determination. Our approach makes use of the following tools: 1) biclustering genes/proteins by cMonkey; 2) classical hard and fuzzy clustering; 3) mutual information via CLR (context likelihood relatedness); and 4) network inference by inferelator.

Alex Villaverde (CSIC) **/Sophia Bongard** (Insilico)

A consensus approach for high quality predictions in CHO cell kinetic modelling

Introduction: Constructing mathematical models that describe and predict the behaviour of complex dynamic networks is a fundamental goal in systems biology and provides an important basis for cell line engineering and synthetic biotechnology. Challenges in identifying of network kinetics are (i) to detect sensitive parameters and (ii) to evaluate their practical identifiability from time-series metabolite data. The confidence in predictions resulting from dynamic networks is constrained by various uncertainties that appear at different stages of the process.

Objective: Developing a methodology for high confidence predictions from time-series metabolite data.

Methods: In this contribution, we first classify sets of parameters. These parameter sets are obtained from correlations between concentrations and rates; those that manipulate the dynamics of a phenotypic property are grouped into a module. Next, we adopt an ensemble approach, where models with different parameterizations are constructed. Parameter values are estimated by calibrating the models in the ensemble. Due to lack of identifiability, different sets of parameter values fit the data similarly well, and different optimization runs find different solutions. The ensemble of models is then used for estimating the reliability of the predictions as follows: A new experimental condition is defined, under which the behaviour of each model is simulated. Convergence of model outputs (consensus) is used as an indicator of the confidence in the prediction.

Results: Tests were carried out on a metabolic model of Chinese Hamster Ovary (CHO) cells, which are used for protein production by fermentation. The model comprises 35 metabolites, 32 reactions, and 117 parameters. Ensemble predictions were found to be more accurate than individual predictions; furthermore, predictions that elicited consensus were more accurate than the others.

Conclusions: Preliminary results using simulated data show the application potential of the new methodology, which must be further validated with experimental data. Potential applications include optimization of host cell lines as well as optimization of media for CHO cell cultures.

Jaap A. Kaandorp (UvA)

Parameter estimation for spatio-temporal models of gene regulatory networks in the sea anemone Nematostella vectensis

We have developed a method to analyze spatio-temporal gene expression patterns (in situ hybridizations) and morphological data (based on confocal light microscopy images) of *Nematostella* during early embryonal development. The gene expression images are processed with two-dimensional geometry extraction methods and cell-layer decomposition methods to consistently compare and model the expression patterns. Moreover, a three-dimensional tool has been developed for geometry extraction and decomposition and to model expression patterns that are not radially symmetric about the main body axis. The model parameters and the gene network are inferred from the expression data using an optimization algorithm (e.g evolutionary algorithms and scatter search).

Wednesday, 6 March

Bertrand Moreau (CSM)**/ Eric Boix** (CSM)

Update and progress of software pipeline being developed together with the partners

Overall progress

CSM main task is the development of the BioPreDyn software suite (deliverable 3.4). As a consequence, CSM is currently working on the architecture of this deliverable, using the information gathered during group visits. In parallel, work is done on the pipelines used by BioPreDyn partners in order to integrate them in the final product; this task involves detailed understanding of the behavior of each tool used in the pipeline, and interfacing them with each other. In addition to these pipelines, the example workflow provided by CWI will be used as a test case for the software suite, and is currently studied by CSM.

Software suite: gathering requirements

Visits were made to different partners in order to define the requirements and specifications of the software suite to be developed by CSM. This effort will continue until all the required information is known to CSM. Three partners were visited so far:

- CSIC: specifications of the AMIGO toolbox, discussion about its integration in the consortium workflows, first draft of architecture;
- CRG: specifications for the fly developmental GRN pipeline, detailed analysis of the tools used by CRG, hands-on session;
- UNIMAN: specifications of the Copasi software, discussion about its integration in the consortium workflow, discussion about the software suite architecture.

Development tools

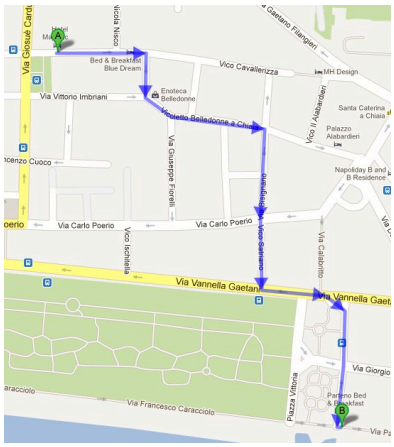
In addition to the BioPreDyn internal wiki, a second wiki was recently put online; it only contains information related to the development of the software suite, and will be used to make the source code of the suite available to all partners. This wiki is entirely populated and maintained by CSM so far. It will be made available to all BioPreDyn partners after the Naples annual meeting.

Participants

Bertrand Moreau	bertrand.moreau@thecosmocompany.com	CoSMO
Eric Boix	eric.boix@thecosmocompany.com	CoSMO
Anton Crombach	anton.crombach@crg.es	CRG
Yogi Jaeger	yogi.jaeger@crg.eu	CRG
Damjan Cicin Sain	damjan.cicin@crg.es	CRG
Evrim Besray Unal	besray.unal@crg.es	CRG
Veronica Raker	veronica.raker@crg.es	CRG
Alejandro Fernández Villaverde	afvillaverde@iim.csic.es	CSIC
Julio Rodriguez Banga	JULIO@IIM.CSIC.ES	CSIC
Eva Balsa-Canto	ebalsa@iim.csic.es	CSIC
Joke Blom	joke.blom@cwi.nl	CWI
Maria Navarro Jimenez	maria.navarro@cwi.nl	CWI
Emanuel Gonçalves	emanuel@ebi.ac.uk	EMBL-EBI
Julio Saez-Rodriguez	saezrodriguez@ebi.ac.uk	EMBL-EBI
Sophia Bongard	sophia.bongard@insilico-biotechnology.com	Insilico
Diego di Bernardo	dibernardo@tigem.it	TIGEM
Paola Cormio	p.cormio@tigem.it	TIGEM
Roberto Pagliarini	r.pagliarini@tigem.it	TIGEM
Jacobus Kaandorp	J.A.Kaandorp@uva.nl	Universiteit van Amsterdam
Pedro Mendes	pedro.mendes@manchester.ac.uk	Man
Marco Manca	marco.manca@postgrad.manchester.ac.uk	Man
Kieran Smallbone	kieran.smallbone@manchester.ac.uk	Man
Neil Lawrence	N.Lawrence@sheffield.ac.uk	Sheffield
Nicolas Durrande	n.durrande@sheffield.ac.uk	Sheffield
Markus Schwab	markuss@evolva.com	Evolva
Jane Dannow Dyekjær	janed@evolva.com	Evolva
Mara Sangiovanni	mara.sangiovanni@unina.it	Federico II University, Naples

Dinner 4 March 20:30

Ristorante Pizzeria Hache' (via Partenope, 6/D)



walking from hotel

MENU: First:

• Misto di bocconcini di pizza ripieni di provola e friarielli, scarole, o melenzane (mixed stuffed pizzas with provola cheese and broccoli, endives, or eggplant)

• Margherite spicchiate (margerite pizza)
• Bocconcini di mozzarella di bufala (bite-sized buffalo mozzarella)

• Parmigiana di melanzane (eggplant parmigiana)

• Julienne seppie e zucchine con cozze (cuttlefish and zucchini with mussels)

Second: choice of

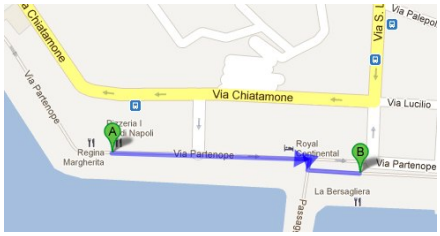
• Tris di hache alla griglia: manzo e vitello/pollo e tacchino/maiale e peperoni (Trio of meatball specialties: beef and veal/chicken and turkey/pork and bell peppers)
OR
• Hache di pesce spada in padella con pomodorini, ulive, capperi e pinoli (meatball of swordfish with tomatoes, olives, capers, and pine nuts)

patate al forno (baked potatoes)

dessert or fruit
water, wine (red or white)

Dinner 5 March 21:00

La Bersagliera (Borgo Marinari 10/11)



walking from venue

Prosecco

Coppetta di fritturine di mare (seafood cocktial)

Trenette, zucchine, fiori di zucca e lupini (pasta trenette with zucchini, zucchini flowers and lupini (type of bean)

Filetto di orata al forno o gratinato con verdurine di stagione (seabream fillet, baked or broiled, with seasonal vegetables)

Panna cotta al cioccolato (panna cotta with chocolate)

coffee, mineral water, wine

Castel dell'Ovo

Our venue is in front of the Castel dell'Ovo, and we will visit it briefly after lunch on the 5th.

From Wikipedia: **Castel dell'Ovo** (*Egg Castle*) is located on the former island of *Megaride*, now a penninsula, on the gulf of Naples. The castle's name comes from a legend about the Roman poet Virgil, who had a reputation in medieval times as a great sorcerer. In the legend, Virgil put a magical egg into the foundations to support the fortifications.