

Pre-clinical and clinical research

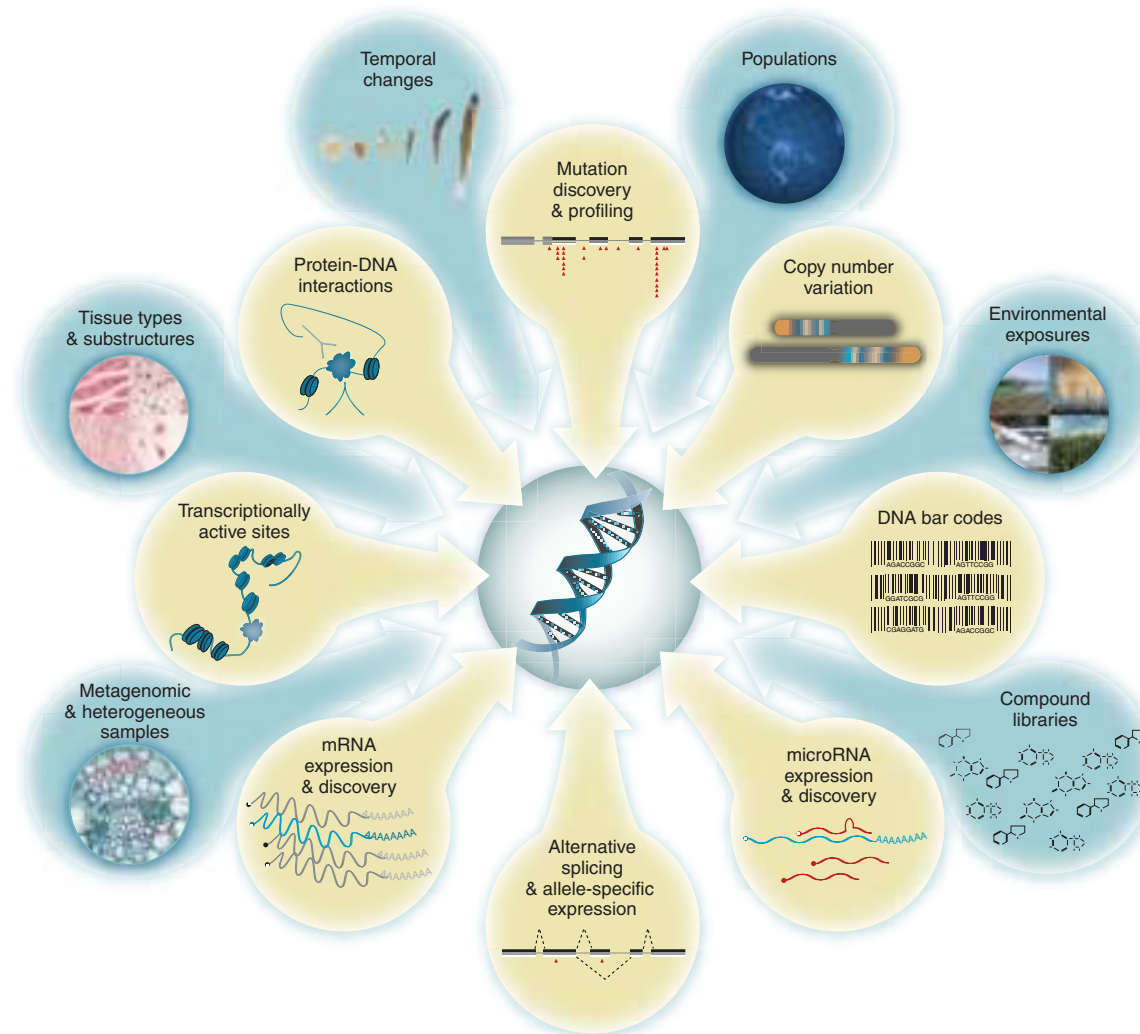
14:20	14:30	Sviluppo di algoritmi per la medicina personalizzata	<i>Francesca Cordero</i>
14:30	14:40	Modelli computazionali per lo studio di sistemi biologici	<i>Marco Beccuti</i>
14:40	14:50	Immagini digitali biomediche: simulazione ed elaborazione	<i>Marco Grangetto/ Nello Balossino</i>
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Sviluppo di algoritmi per la medicina personalizzata

Francesca Cordero
fcordero@di.unito.it

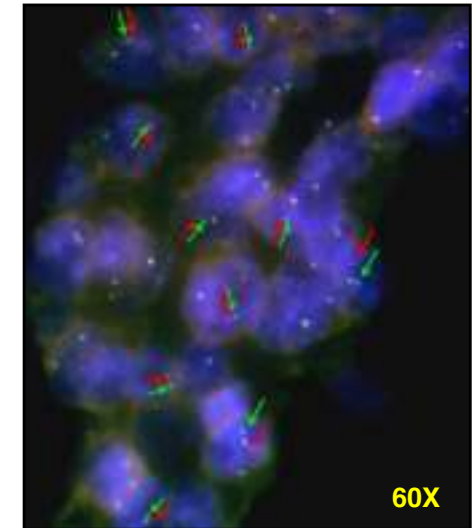
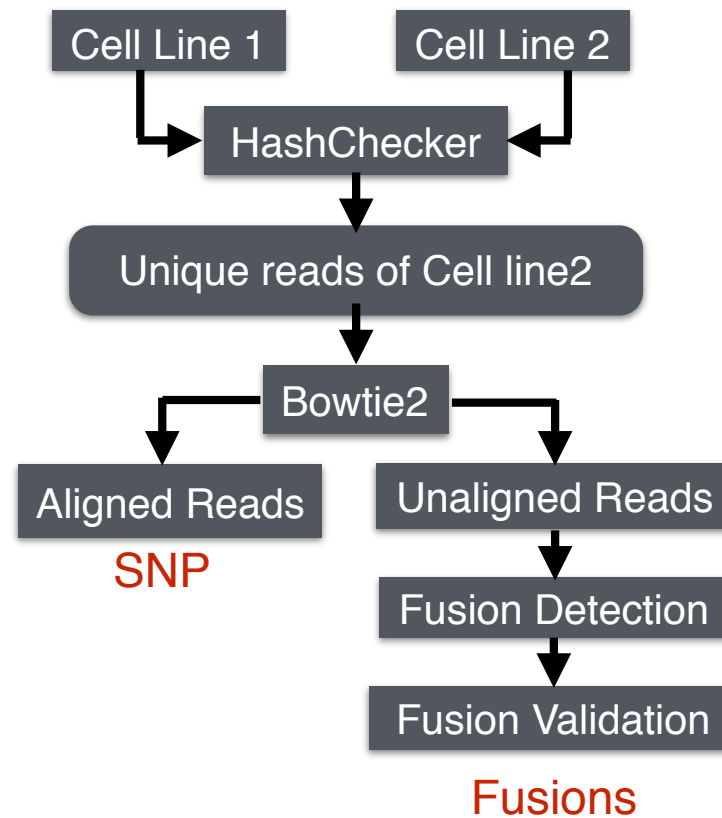
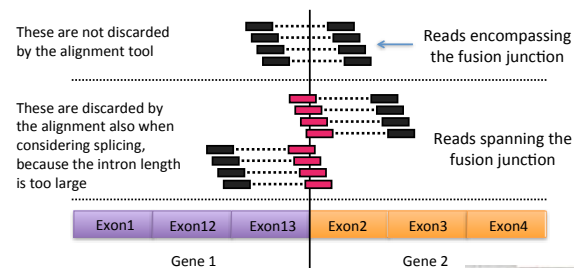
Deep sequencing technologies



Kahvejian A., et al. Nature Biotech 2008

Data Analysis - New insights: fusion genes

The molecular landscape of colorectal cancer cell lines
unveils clinically actionable kinase targets.



Medico E, et al., *Nature communication*, 2015

Beccuti M, et al., *Journal of OA Bioinformatics*, 2013

Carrara M, et al. *BioMed Research International*, 2013

Carrara M, et al., *BMC Bioinformatics*, 2013

M. Beccuti, et al., *Bioinformatics*, 2014

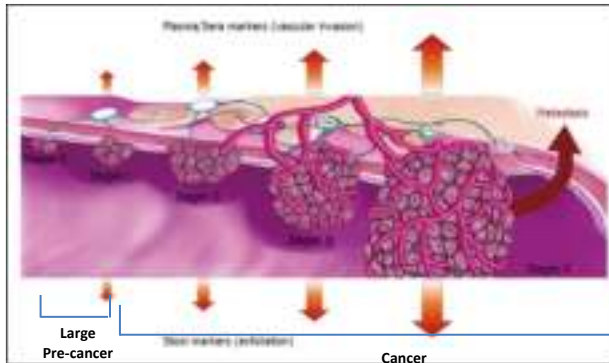
Prof. Alberto Bardelli

Prof. Enzo Medico



Clinical Biomarker discovery

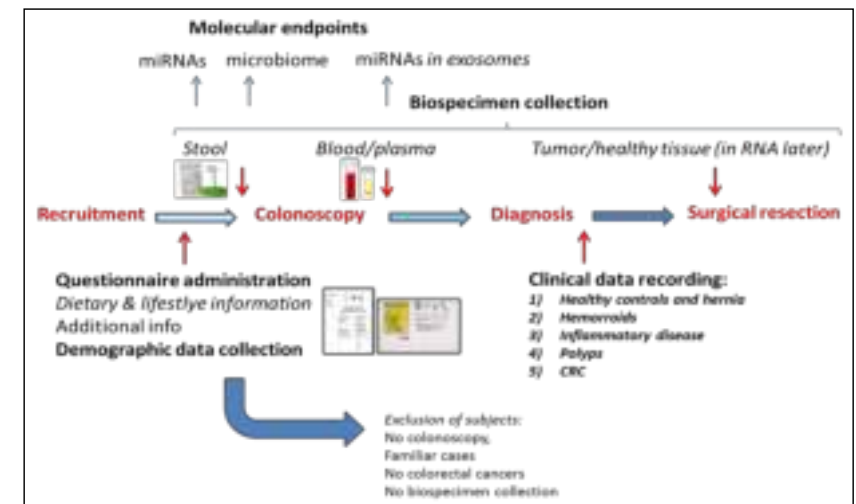
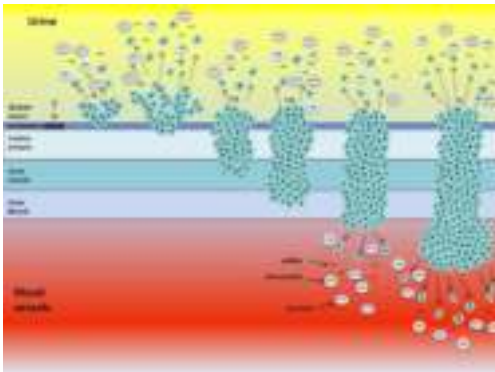
Colorectal Cancer



Tumor cells show:

- Altered expression levels of several miRNAs
- Loss of tumour-suppressor miRNAs
- Accumulation of oncomiRNAs

Bladder Cancer



Ferrero G, et al., **Oncotarget**, 2018
Pardini B, et al., **Oncotarget**, 2018
Cordero F, et al. **Plos One**, 2012
Kulkarni N, et al. **BMC Bioinformatics**, 2018

Dr Alessio Naccarati
Dr Barbara Pardini
Dr Mario Trompetto
Dr Carlo Senore

Clinical Biomarker discovery - New frontiers: The Microbiome



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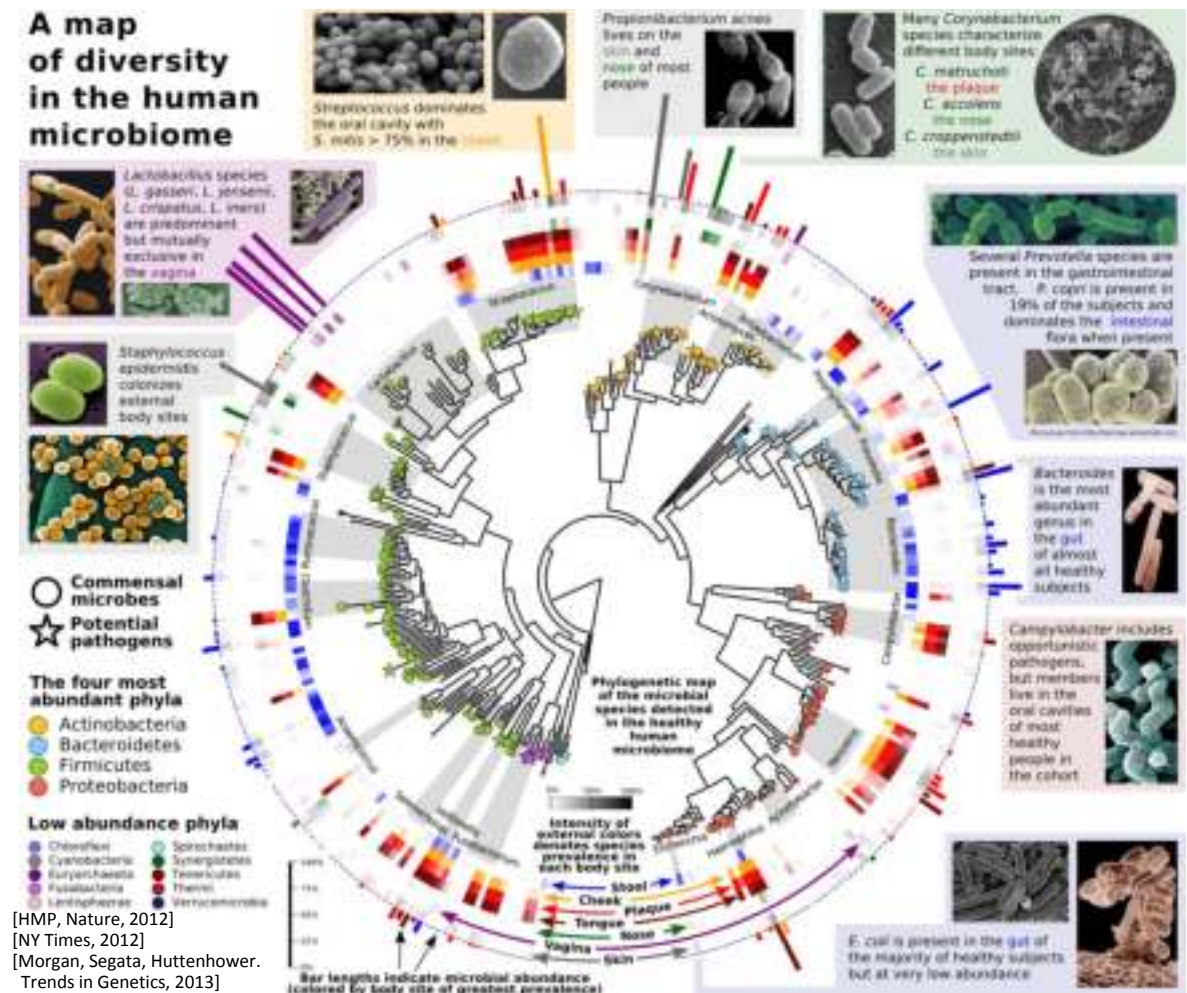


10x more microbial than human cells

1M times as many microbes inside
each of us than humans on earth

100x more microbial than human genes

Who is there?
What are they doing?



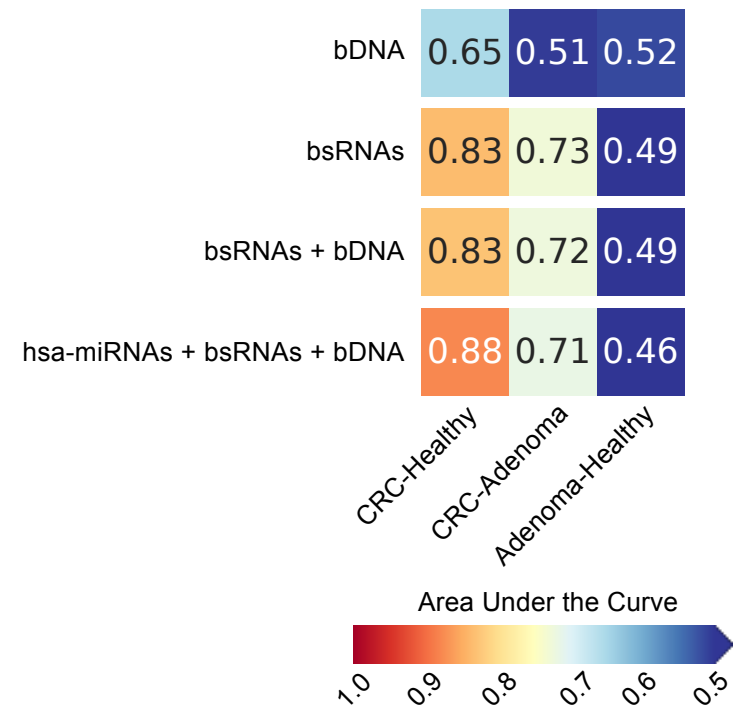
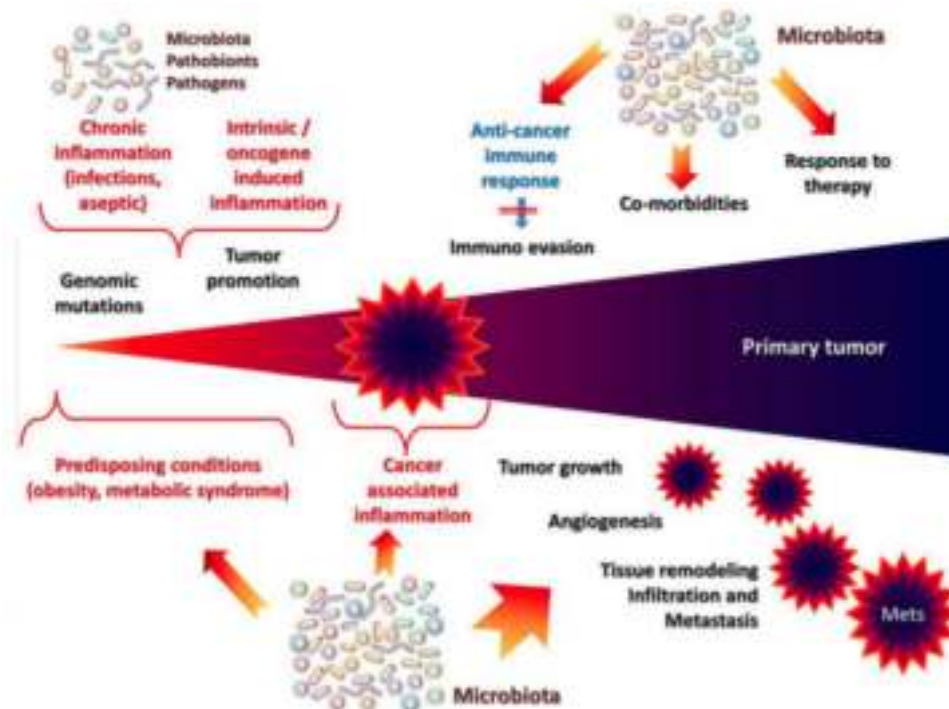
Clinical Biomarker discovery - New frontiers: The Microbiome



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Oncobiome: the study of the interplay between the human microbiome and cancer development



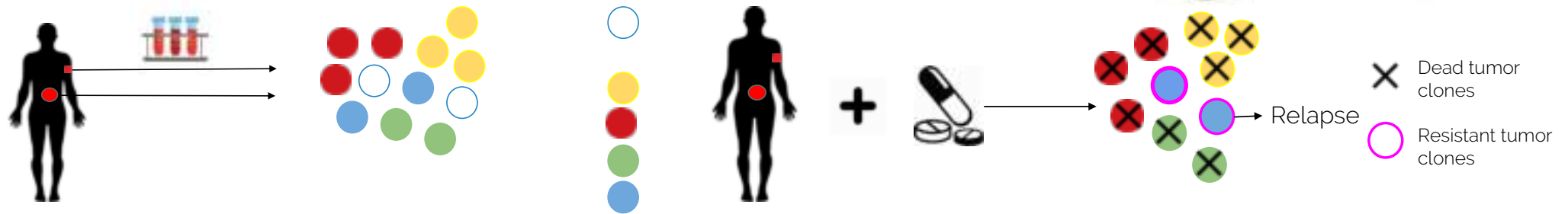
Tarallo S, et al. , *ISME* , 2018 - Under Review

Thomas A et al., *Nature Medicine*, 2018 - Under Review

Prof Nicola Segata

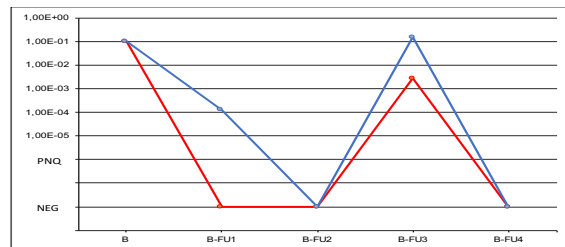
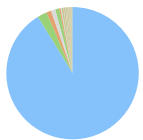


Cancer clones identification

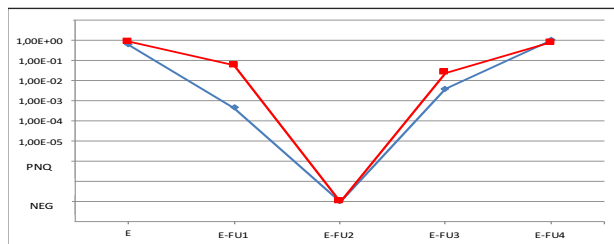
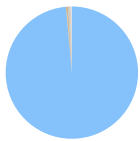


Leukemia - Minimal Residual Disease Analysis
ImmunoGlobulin Heavy chain (IGH) rearrangement as molecular marker of clonality

Pat A



Pat B

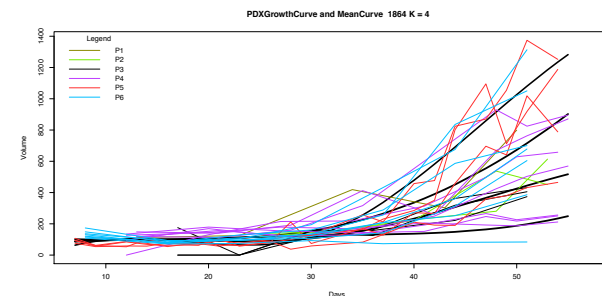
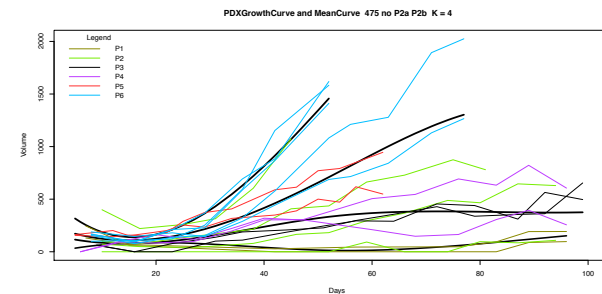


Dr Mario Boccardo
Dr Simone Ferrero

Beccuti M, et al., *BMC Bioinfo*, 2017



An high level of ITH affects the high-grade serous epithelial **ovarian cancer**



Prof. Flavia Di Renzo

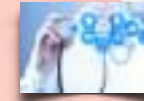


Biology Science



Giulio Ferrero
Laura Follia
Greta Romano
Giulia Piaggieschi
Raffaele Calogero

Medical Science



Niccolò Totis

Team

Francesca
Cordero

Mathematics



Simone Pernice

Computer Science



Gianfranco Balbo
Marco Beccuti
Susanna Donatelli

Collaborations





Pre-clinical and clinical research

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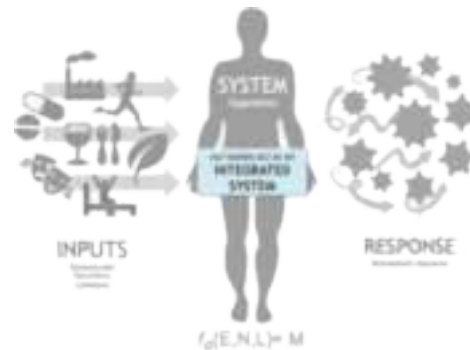
Computational models to study biological systems

Marco Beccuti

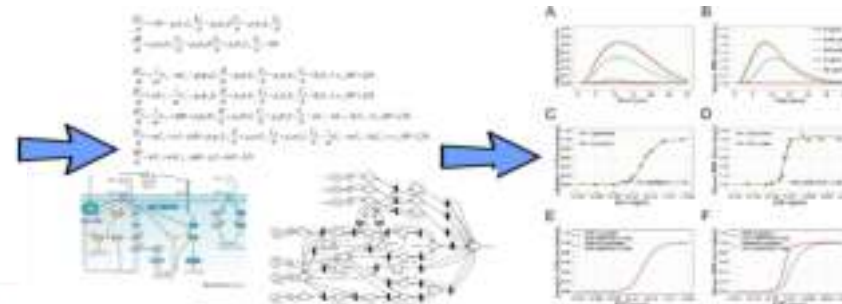
beccuti@di.unito.it

Computational models to study biological systems

- ◆ A biological system is a **complex network of biologically relevant entities**

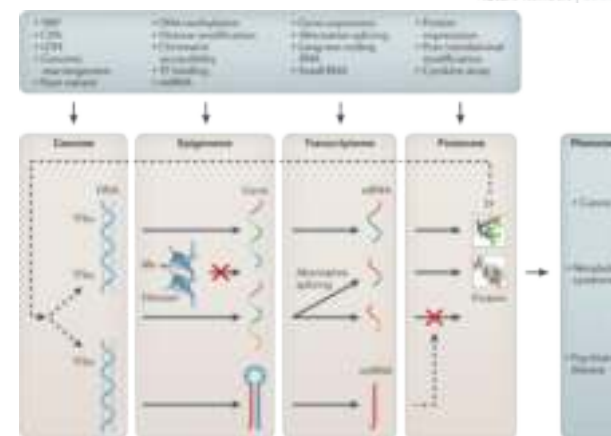
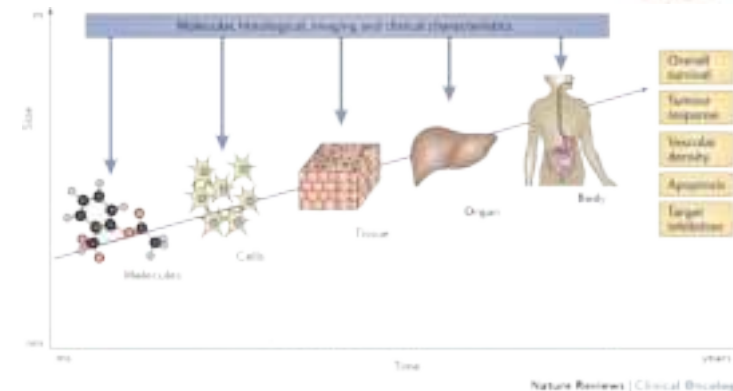


- ◆ In Systems Biology **mathematical and computational modeling** can help scientists in the study of biological systems



Computational models to study biological systems

- ◆ A biological system as a composition of sub-models with **different time and space scales**
- ◆ Sub-models can be parameterized using **different input data**.



Reichart MD et al. Nat Rev Genet 2015

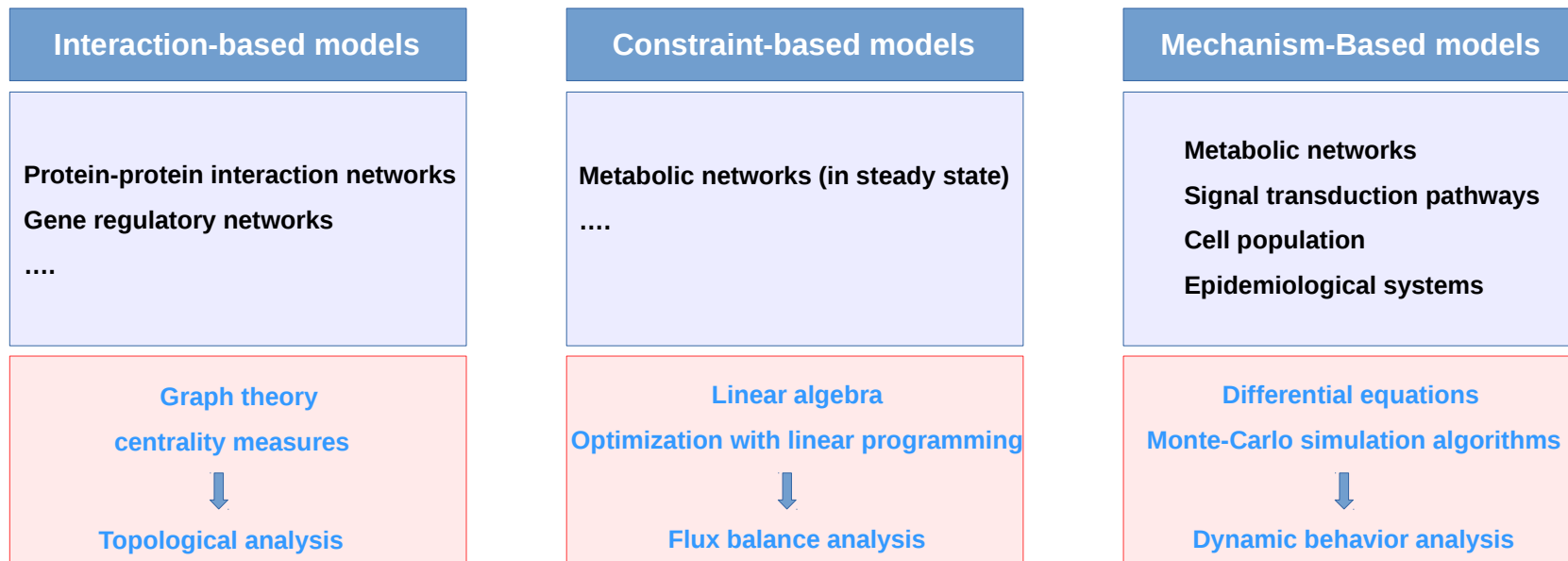
Challenge

How to efficiently model and study biological systems

Computational models to study biological systems



- ◆ **Different modeling approaches** can be exploited according to the specific biological question and system

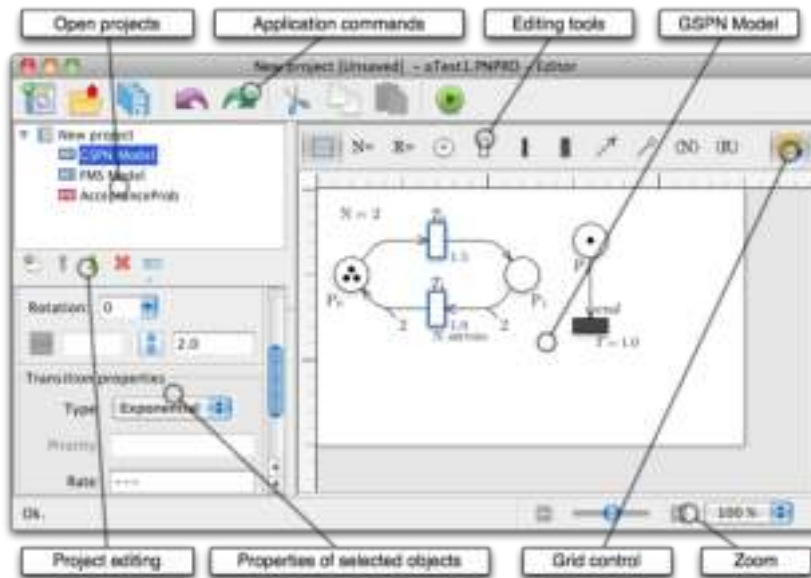


Computational models to study biological systems

◆ Our tools and methodologies:



A modeling framework based on **graphical formalism** which provides **different analysis techniques**



- **interaction-based approaches**
 - ✓ linear algebra;
 - ✓ CTL model checking.
- **constraint-based approaches**
 - ✓ Flux balance analysis;
- **mechanism-based approaches**
 - ✓ numerical techniques;
 - ✓ Ordinary Differential Equation (ODE) approximation;
 - ✓ Stochastic Differential Equation (SDE) approximation;
 - ✓ Monte-Carlo simulation.

✓ A. Angius, G. Balbo, M. Beccuti, E. Bibbona, A. Horvath, R. Sirovich. Approximate analysis of biological systems by hybrid switching jump diffusion. *Theoretical Computer Science*, Elsevier Press., Volume 587, July 2015, Pages 49-72.

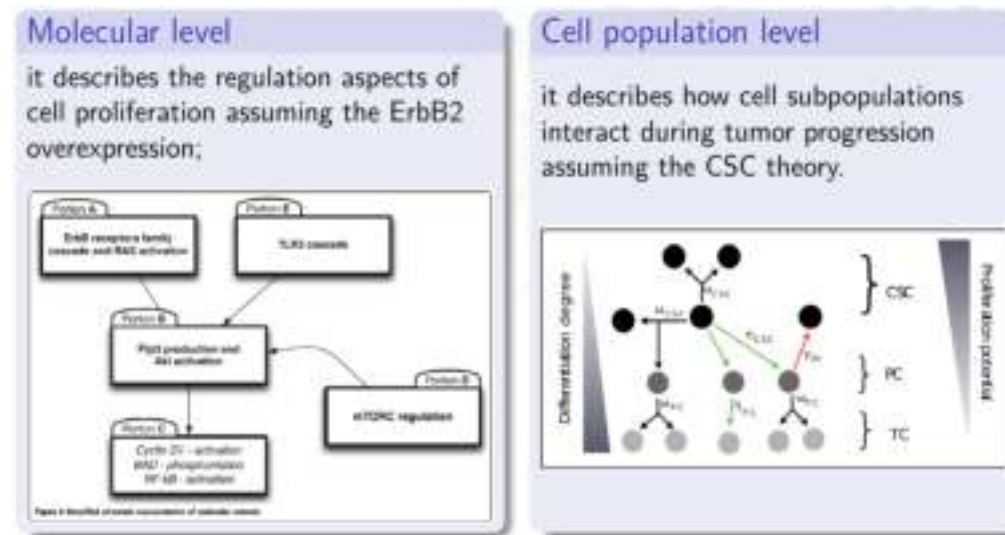
✓ M. Beccuti, C. Fornari, G. Franceschinis, S. M. Halawani, O. Barukab, A. Ahmad, G. Balbo. From Symmetric Nets to Differential Equations exploiting Model Symmetries. *The Computer Journal*, Oxford Univ. Press., Volume 58, Issue 1, Jan.2015, Pages 23-39.

Computational models to study biological systems

- ◆ **Application on breast ErbB2 cancer** in collaboration with Cavallo's group (Dip. di Biotecnologie Molecolari e Scienze per la Salute – Univ. di Torino).
- ◆ **Goal:** to exploit the model to study different vaccination therapies of ErbB2 and TLR2.

- ◆ A 2-level model to study **ErbB2 breast cancer progression:**

- ◆ ErbB2 is a **transmembrane protein**;
- ◆ 20% of breast cancers **overexpresses ErbB2**;
- ◆ ErbB2 is an appropriate **target for therapies**.

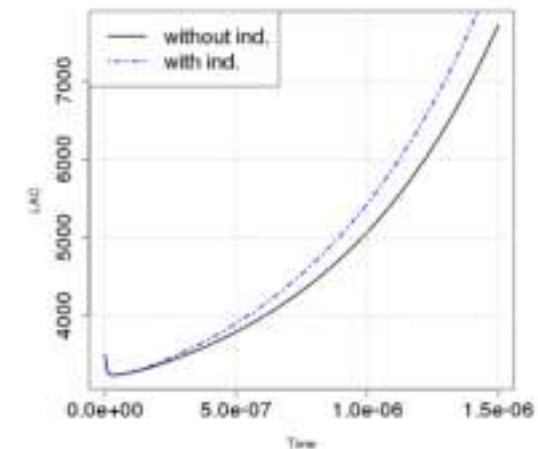
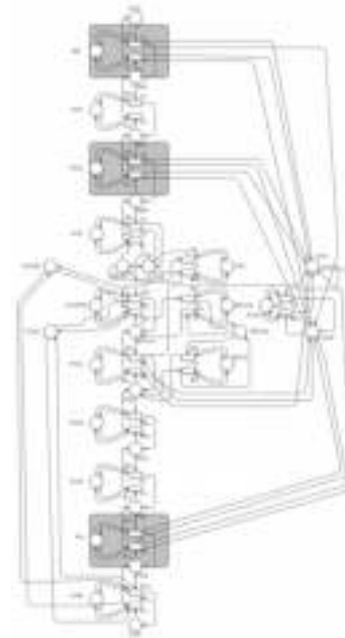


- F. Cordero, M. Beccuti, C. Fornari, S. Lanzardo, L. Conti, F. Cavallo, G. Balbo and R. Calogero. Multi-level model for the investigation of oncoantigen-driven vaccination effect. International Journal **BMC Bioinformatics**, Volume 14, Suppl. 6, 2013

Computational models to study biological systems

- ◆ **Application on cancer metabolism** in collaboration with Novelli's group (Dip. di Biotechnologie Molecolari e Scienze per la Salute – Univ. di Torino).
- ◆ **Goal:** To develop a new modeling approach to dealing with indetermination in biochemical networks.

We investigate the **Warburg Effect** in **PDAC patients**

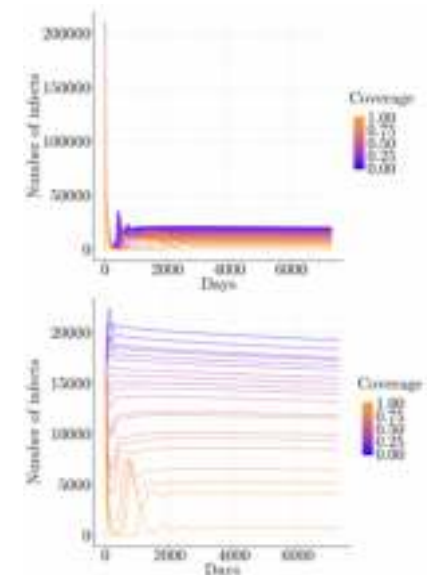
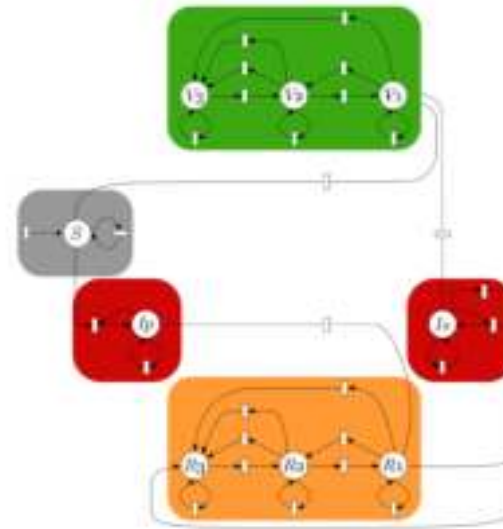


- N. Totis, L. Follia, F. Cordero, C. Riganti, F. Novelli, G. Balbo and M. Beccuti. Overcoming the lack of kinetic information in biochemical reactions networks. **ACM SIGMETRICS Performance Evaluation Review**. Volume 44 Issue 4, March 2017, Pages 91-102. ACM New York, NY, USA

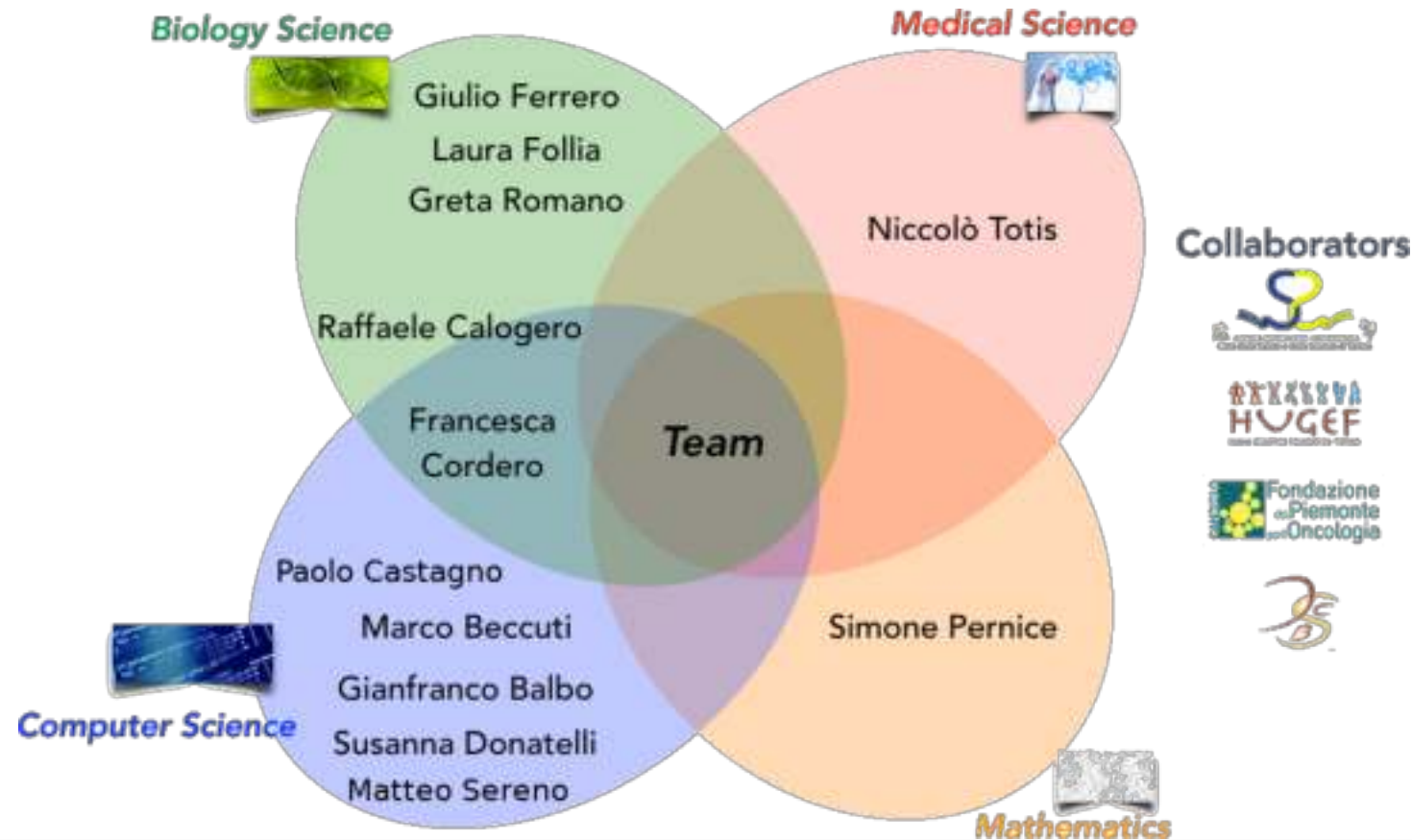
Computational models to study biological systems

- ◆ **Application on Computational Epidemiology:** in collaboration Paolotti's group (ISI foundation), Tozzi's group (Area di ricerca Malattie Multifattoriali e Malattie Complesse - Ospedale Bambin Gesù) and Ghetti's group (Adres srl).
- ◆ **Goal:** To develop a model to study the effects of different vaccine policies on pertussis epidemiology.

An extension of **classical SIRS** infection model was developed to include the **peculiarities of the pertussis infection** and the relative **vaccination cycle**



Computational models to study biological systems





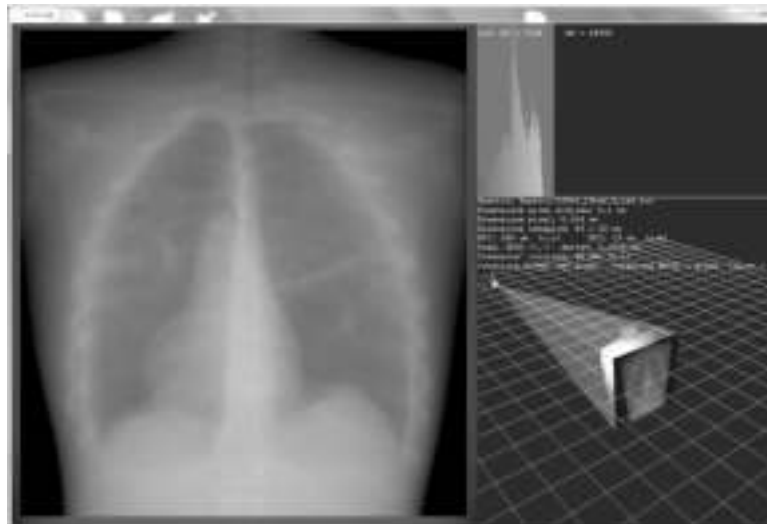
Pre-clinical and clinical research

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Digital image processing @ di.unito.it

- **Who?** <http://di.unito.it/EidosLab> founded in 1985
- **What?**

Biomedical Image processing



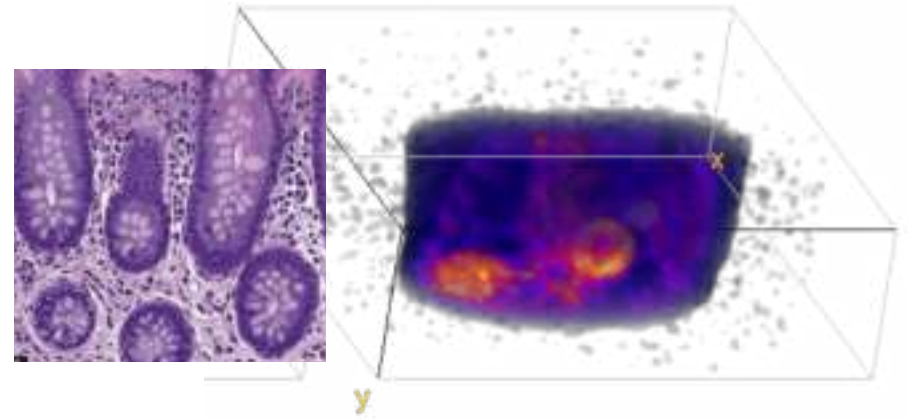
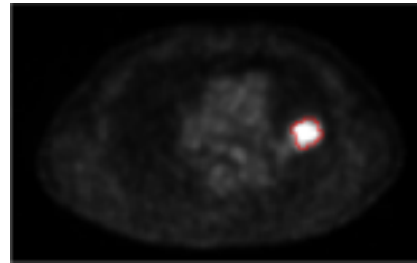
Simulations and virtual reality



Medical data integrity

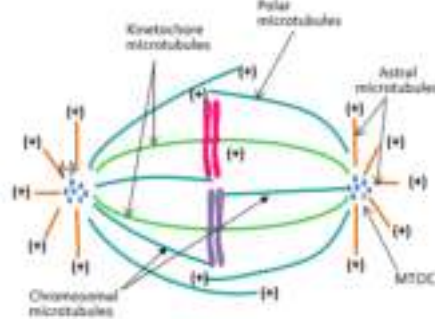
Biomedical image processing

- Usage of standard tools and design of novel methods for
 - Detection
 - Segmentation
 - Classification
 - Tracking
 - Enhancement
- Applications areas:
 - Clinical diagnosis support
 - Preclinical research



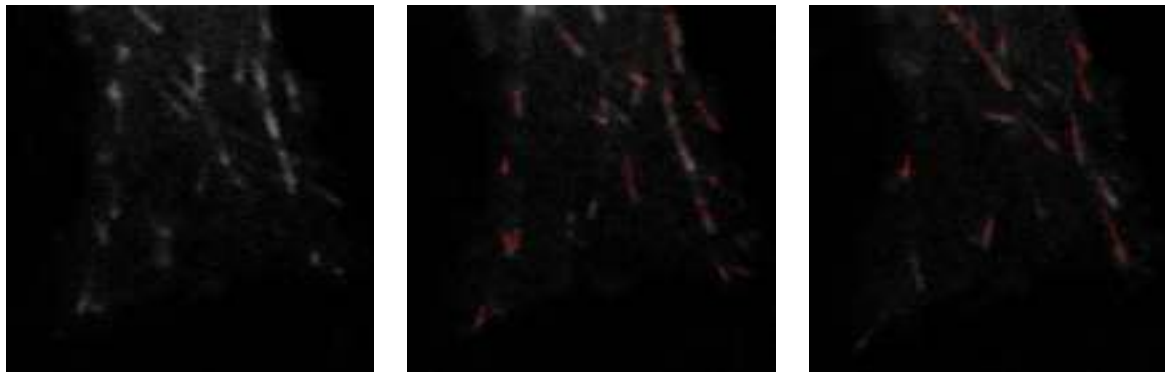
Recent & ongoing activities

- Automatic microtubule tracking in fluorescence images
- Eidos+MBC+POLITO



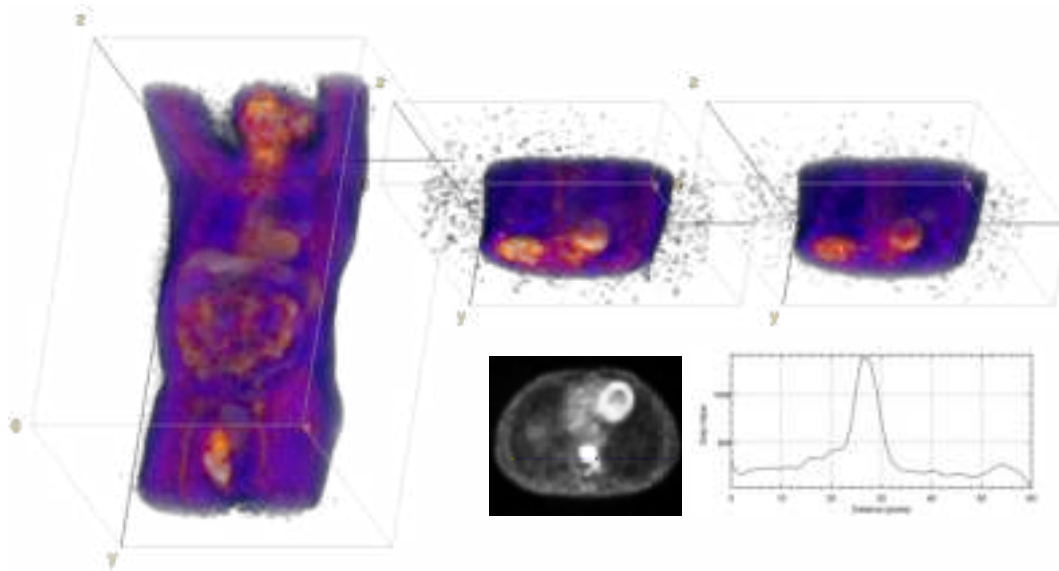
Levine, J., Grangetto M., Varrecchia, M., Olmo, G. 2018, September. Global and local anomaly detectors for tumor segmentation in dynamic PET acquisitions. In Image Processing (ICIP), 2018 IEEE International Conference

Varrecchia, M., Olmo, G., Levine, J., Grangetto, M., Gai, M. and Di Cunto, F., 2018. Automatic microtubule tracking in fluorescence images of cells doped with increasing concentrations of taxol and nocodazole. arXiv preprint.



Recent & ongoing activities

- Tumor segmentation from dynamic PET acquisitions
- Eidos + IRCCS Candiolo (Medical Physics department)

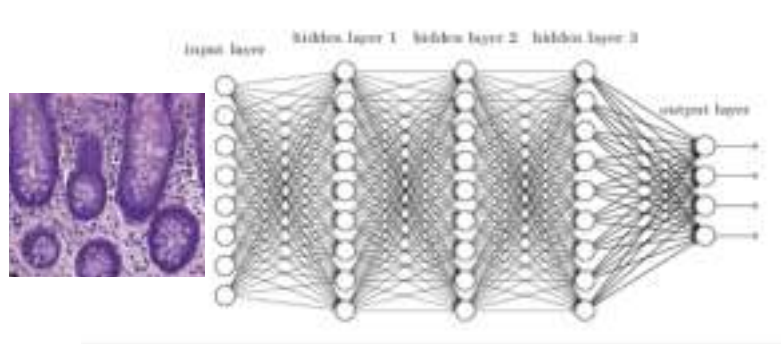


Verdoja, F., Bonafè, B., Cavagnino, D., Grangetto, M., Bracco, C., Varetto, T., Racca, M. and Stasi, M., 2016, September. Global and local anomaly detectors for tumor segmentation in dynamic PET acquisitions. In Image Processing (ICIP), 2016 IEEE International Conference on (pp. 4131-4135). IEEE.

Verdoja, F., Grangetto, M., Bracco, C., Varetto, T., Racca, M. and Stasi, M., 2014, October. Automatic method for tumor segmentation from 3-points dynamic PET acquisitions. In Image Processing (ICIP), 2014 IEEE International Conference on (pp. 937-941). IEEE.

Recent & ongoing activities

- Deep learning for histopathological characterization of colorectal polyps (Eidos+ prof. Paola Cassoni)



- Estimation of Ph maps from MRI images (Eidos + prof. Dario Longo)

Future works

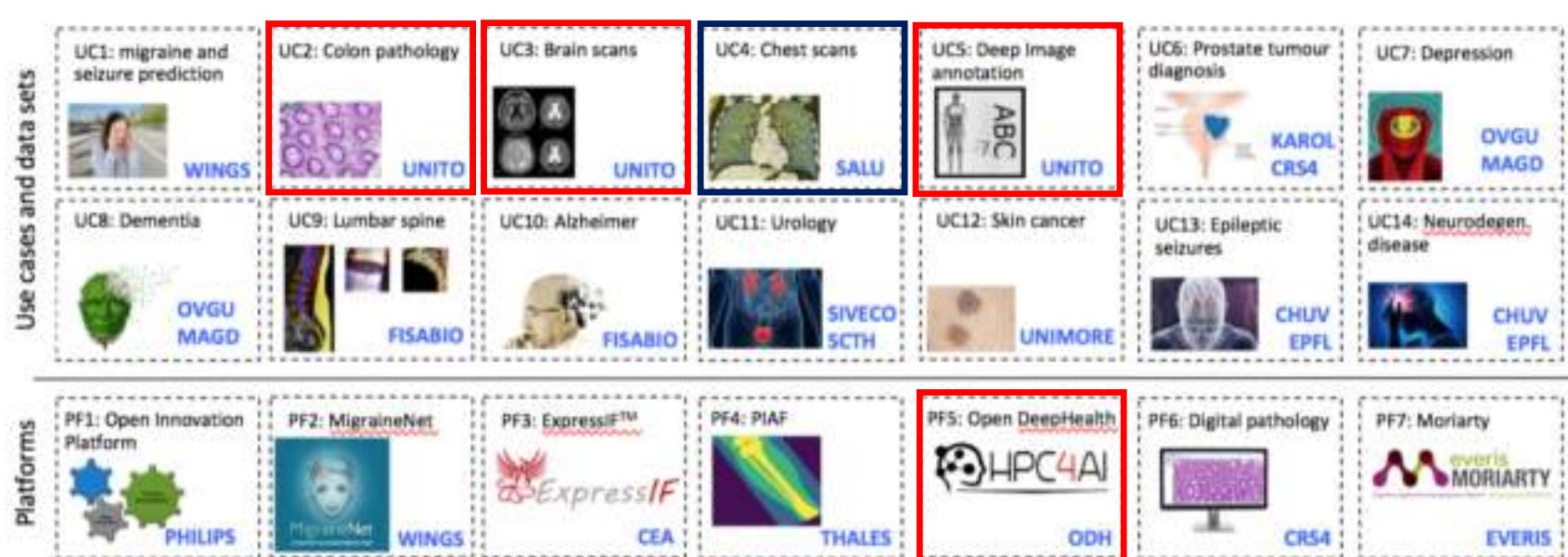
- Since 2012 **DeepLearning** is fostering a lot of interests in the area of automatic image interpretation: tremendous potential impact on imaging based diagnosis (needs of interdisciplinary research+large and well engineered datasets)

DeepHealth: Deep-Learning and HPC to Boost Biomedical Applications for Health

- H2020 proposal (IA call ICT-11-2018-2019)
- Involves 21 partners (Spain, Italy, Netherlands, Germany, Sweden, Switzerland, Romania, Greece) including **Unito** e **Città della Salute**

*The main goal of the DeepHealth project is to put **HPC computing** power at the service of **biomedical applications** with DL needs and, through an interdisciplinary approach, apply DL techniques on large and complex biomedical datasets to support diagnosis and to generate insights into complex diseases in a scalable and efficient way.*

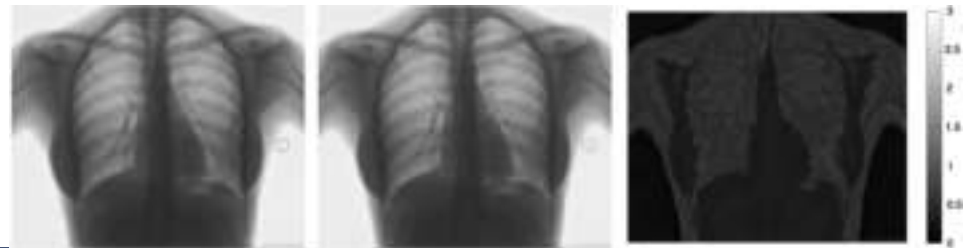
DeepHealth at a glance



Medical image integrity

- Verification of medical image integrity by using invisible and reversible watermarking (content validation, secure diagnosis and metadata handling)

Eidos + AOU Città della Salute
+ ASL CN2 Alba Bra

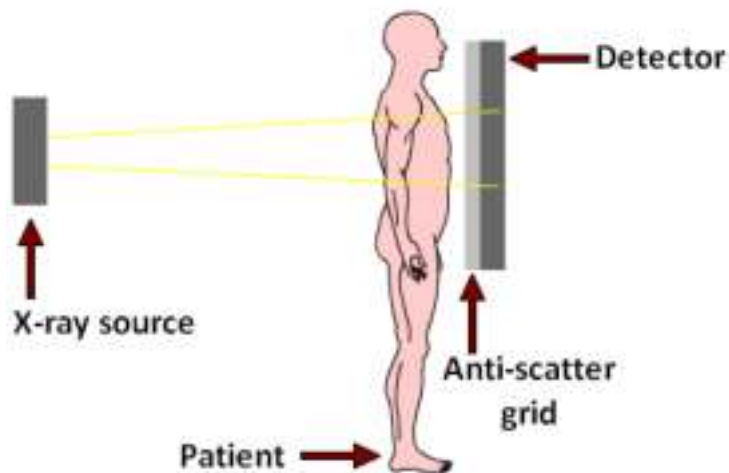


- Brevetto italiano nr. 0001419815: Procedimento e sistema per marcare immagini mediche tramite una tecnica di "watermarking" fragile e reversibile utilizzando un metodo statistico e firma digitale
- M. Botta, D. Cavagnino, V. Pomponiu. A modular framework for color image watermarking, Signal Processing, Elsevier, February 2016, Vol. 119, pages 102-114, ISSN 0165-1684
- D. Cavagnino, M. Lucenteforte, M. Grangetto. High capacity reversible data hiding and content protection for radiographic images, Signal Processing, Elsevier, December 2015, Vol. 117, pages 258-269, ISSN 0165-1684
- M. Botta, D. Cavagnino, V. Pomponiu. Fragile watermarking using Karhunen-Loève transform: the KLT-F approach. Soft Computing, vol. 19, n. 7, ISSN 1432-7643, pages 1905-1919, Springer Berlin Heidelberg (2015)
- M. Botta, D. Cavagnino, V. Pomponiu. Protecting the Content Integrity of Digital Imagery with Fidelity Preservation: An Improved Version. ACM Trans. Multimedia Comput. Commun. Appl. vol 10, no. 3, pp. 29:1-29:5, April 2014, ACM, New York, NY, USA, doi: 10.1145/2568224

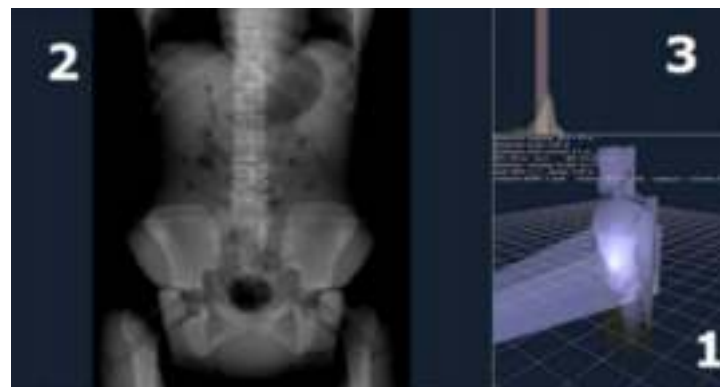
Virtual training for radiologist

- Simulation of the RX image acquisition for training in collaboration with **Città della Salute**

Real scenario



The simulation



1. Virtual radiological room
2. Radiography preview
3. Image histogram

Gallio, E., Rampado, O., Gianaria, E., Bianchi, S.D. and Ropolo, R., 2015. A GPU simulation tool for training and optimisation in 2D digital x-ray imaging. PloS one, 10(11), p.e0141497.

Coriasco, M., Rampado, O., Balossino, N. and Rabellino, S., 2014. L'immagine digitale in diagnostica per immagini: Tecniche e applicazioni. Springer.

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The Turin's centre on High-Performance Computing for Artificial Intelligence

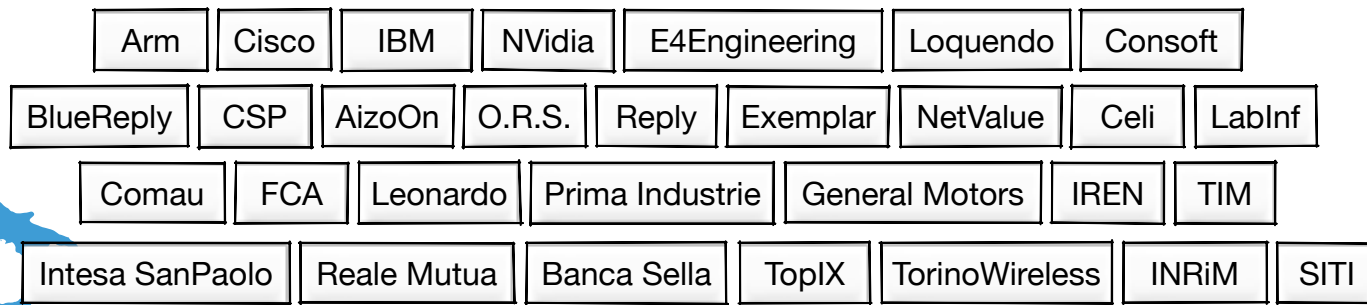
Prof. Marco Aldinucci

Computer Science Department, University of Torino

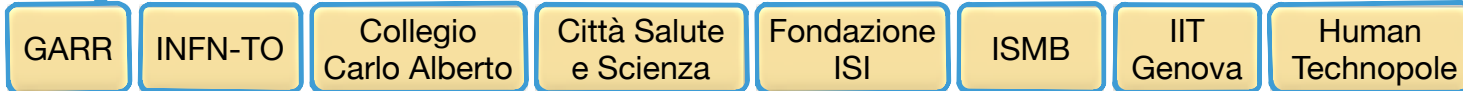


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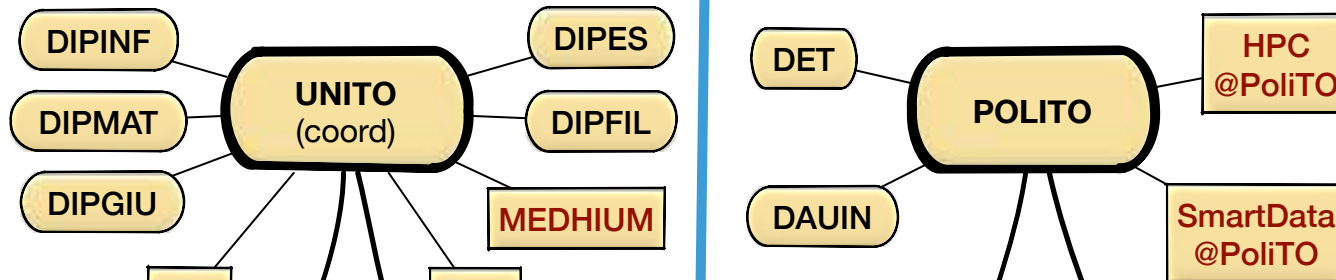
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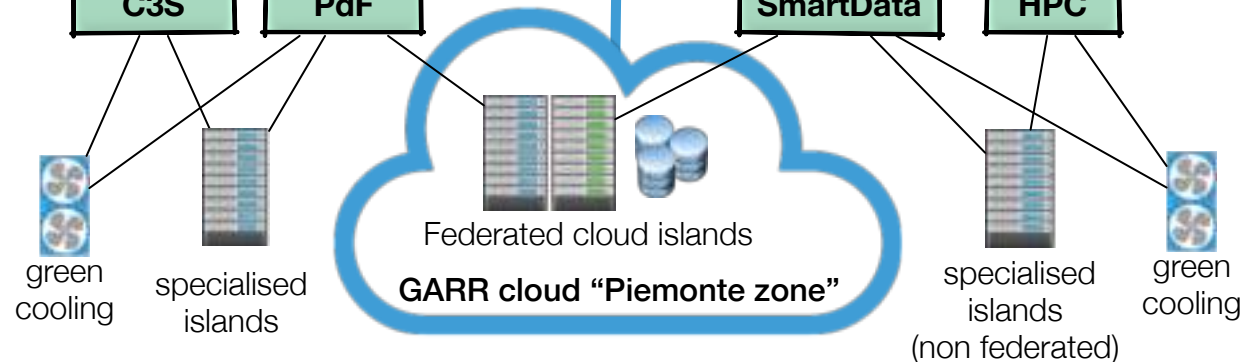
Universities
and
Departments



Data Centers



Hardware



HPC4AI: AI-on-demand platform

Regione Piemonte INFRA-P call Nov. 2017 - 4.5M€ total cost - Coord. M. Aldinucci
2 funded partners - 8 associated partners - Many industrial stakeholders

Turin's HPC4AI centre

A one-stop-shop for AI and BDA

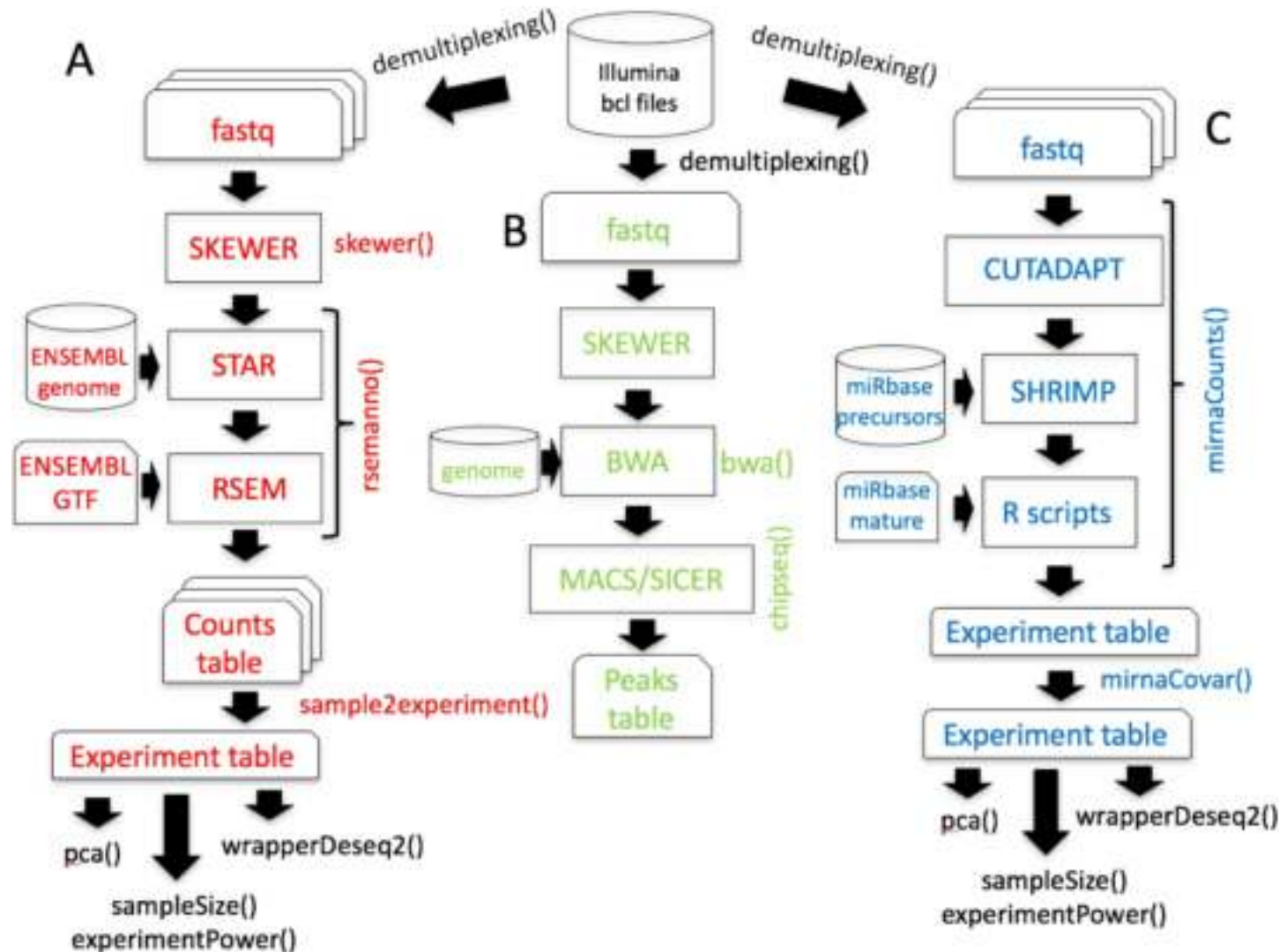
- **Data** - to store data & datasets
 - Securely, preserving ownership, always available
- **Processes** - to develop new protocols
 - Cross-pollinating computer and life sciences
 - Automation and continuous improvement of processes
- **Performance** - to ease the access to HPC
 - For Machine Learning and BigData on-demand

Data: Storage for life science research

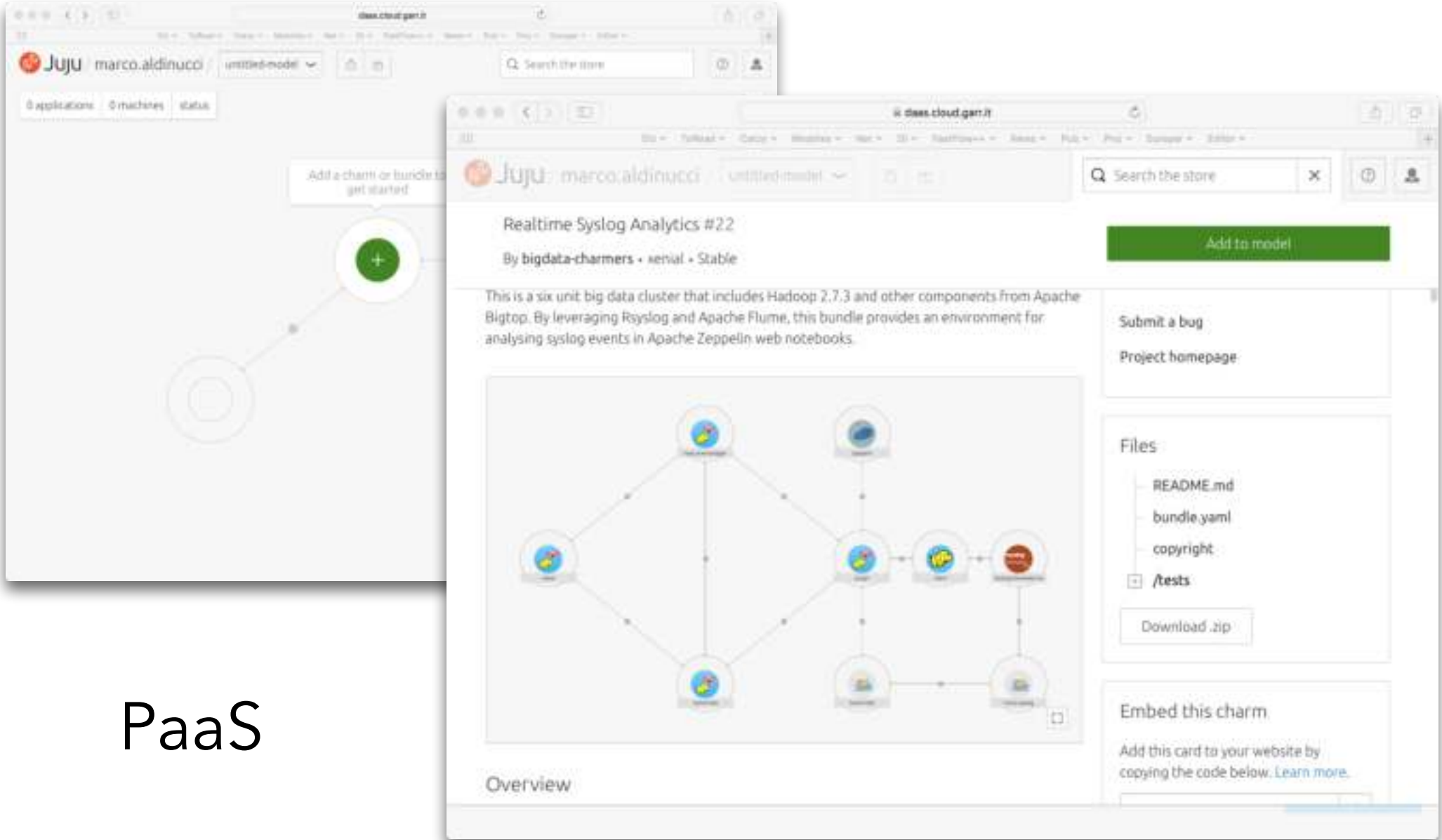


- Large, highly accessible, robust space
 - >5PB of space with 20Gb/s PoP on GARR backbone
 - Backup, encryption (on-demand)
- Federated cloud access
 - Preserving ownership and full control on accesses
 - Ease sharing on-demand (by way of the federation)
- Compute available on-site
 - Move TB for each data analysis is not really handy
- A marketplace of high-quality datasets
 - E.g. UNESCO software heritage
 - E.g. as imagined in ICT11a “Deepheath” with Cassoni (pathology) & Bergui (radiology)

Processes: Automate existing processes and protocols and improve them



Processes: Automatisé existing processes and protocols and improve them

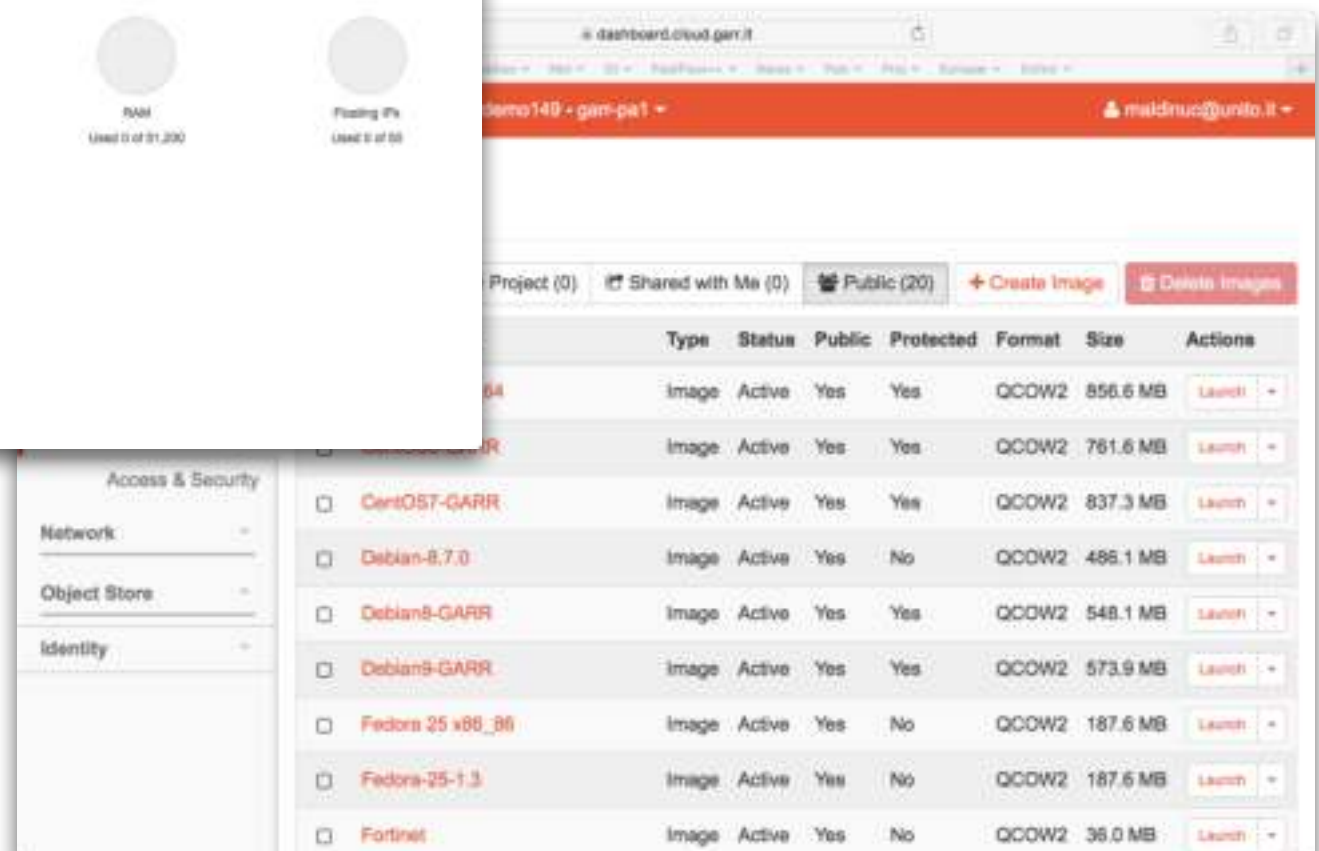
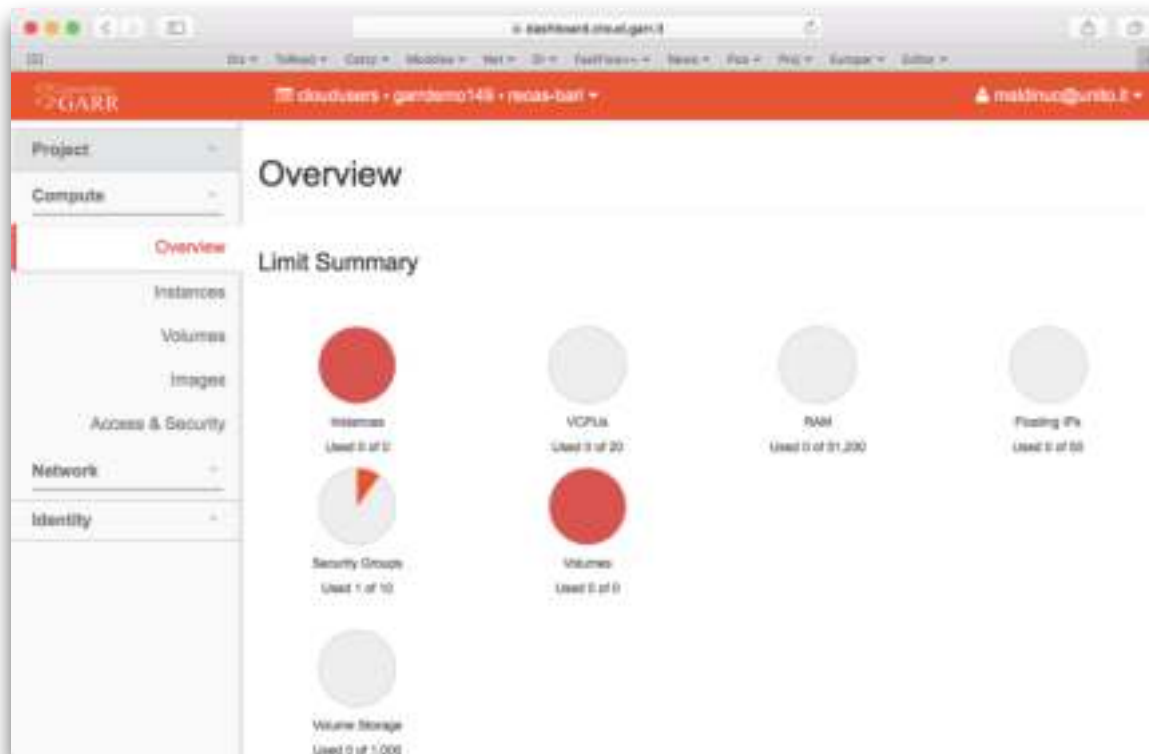


The image displays the Juju web interface, which is used for managing cloud infrastructure. The interface is shown in two overlapping windows. The background window shows a 'Juju' dashboard with a search bar and a 'Add a charm or bundle to get started' button. The foreground window shows the details of a charm named 'Realtime Syslog Analytics #22' by 'bigdata-charmers'. The charm is described as a six-unit big data cluster including Hadoop 2.7.3 and other components from Apache Bigtop. A diagram illustrates the cluster topology with six units connected in a diamond shape. The right sidebar contains links to 'Submit a bug', 'Project homepage', 'Files' (including README.md, bundle.yaml, copyright, and /tests), and 'Embed this charm'.

PaaS

Processes: Automate existing processes and protocols and improve them

IaaS



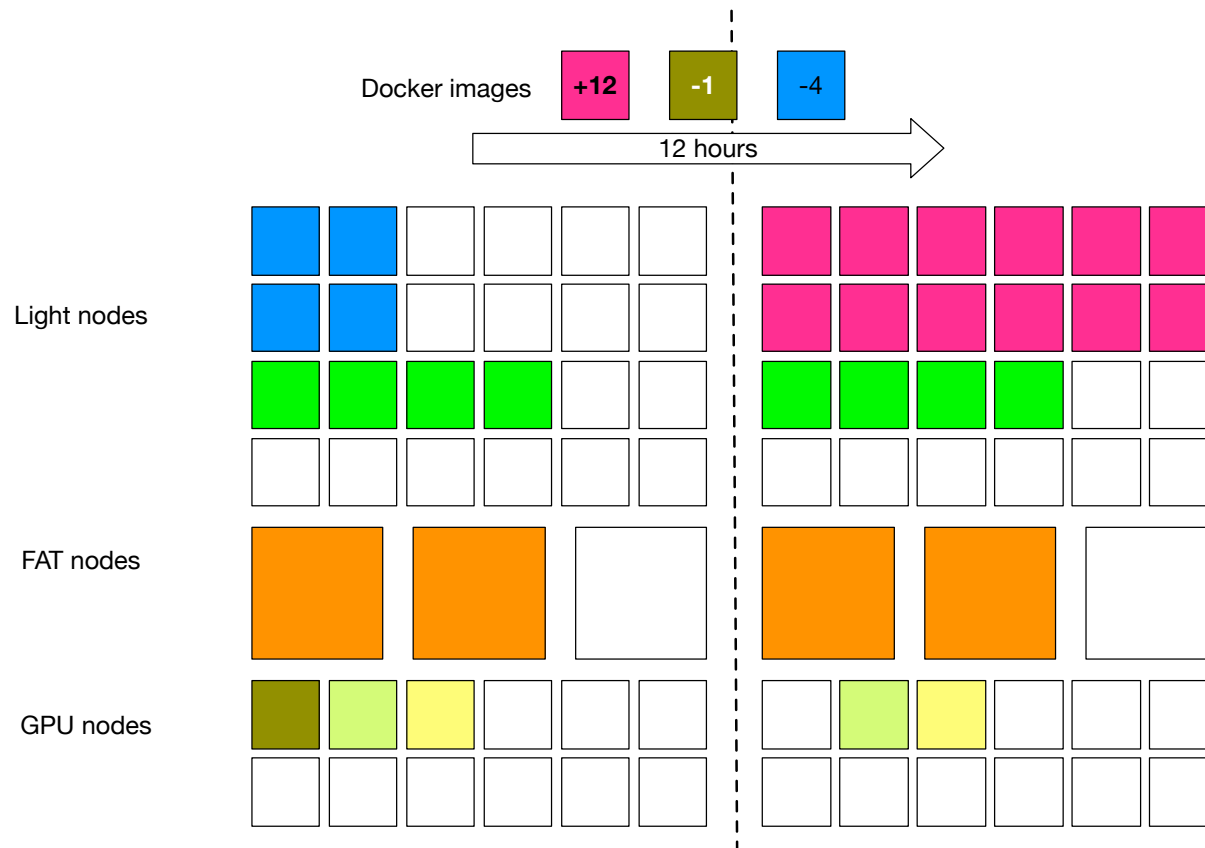
The screenshot shows the GARR cloud dashboard, specifically the 'Images' page. The left sidebar contains a navigation menu with 'Access & Security' and 'Object Store' sections. The main area displays a table of available images with columns for Type, Status, Public, Protected, Format, Size, and Actions. The table lists several images, including CentOS7-GARR, Debian-8.7.0, Debian8-GARR, Debian8-GARR, Fedora 25 x86_64, Fedora-25-1.3, and Fortinet.

Type	Status	Public	Protected	Format	Size	Actions
Image	Active	Yes	Yes	QCOW2	856.6 MB	Launch
Image	Active	Yes	Yes	QCOW2	761.6 MB	Launch
Image	Active	Yes	Yes	QCOW2	837.3 MB	Launch
Image	Active	Yes	No	QCOW2	486.1 MB	Launch
Image	Active	Yes	Yes	QCOW2	548.1 MB	Launch
Image	Active	Yes	Yes	QCOW2	573.9 MB	Launch
Image	Active	Yes	No	QCOW2	187.6 MB	Launch
Image	Active	Yes	No	QCOW2	187.6 MB	Launch
Image	Active	Yes	No	QCOW2	36.0 MB	Launch

Users	Kind of service	Services	Artifacts
Domain experts with no skills on ML and BDA. Training set not required. Off-the-shelf algorithms/networks.	Service-as-a-Service (SaaS)	SaaS for ML and BDA designed within HPC4AI partners	Market place for ML and BDA services: Dashboards, trained models in several domains (NLP, Vision, ...)
Domain experts skilled on ML and BDA. Not expert in parallel computing. New networks or pipelines; training set required.	Platform-as-a-Service (PaaS)	PaaS solutions for ML and BDA directly designed within HPC4AI or companion projects	Market place of VMs and Platforms realising software stacks for ML and BDA. Solutions for data ingestion, data lake, etc.
Researchers, cloud engineering, ML and BDA framework designers, cloud engineers, stack and automation designers.	Infrastructure-as-a-Service (IaaS)	GARR/other cloud able to support federation	Openstack, docker, VM, object storage, file storage, kubernetes, etc.
Researchers, run-time designers.	Hardware	Bare Metal	Multicore, GPU, storage, network, switch, UPS, cooling, etc.

Compute: VMs, HPC queues and much more

- 5000+ cores, 40+ GPUs (200K cuda cores), 1TB RAM per node (on some nodes), ...





Imagine next generation data management for life science

1. Start from existing data

- Store, share, sell: under the full control of owner

2. Imagine AI support

- For scoring, support and automation - not for diagnosis

3. Evaluate annotation, improve the process

- Imagine how to improve protocols/processes and annotation to be better automatised and AI-supported

4. Develop novel analysis techniques and GOTO 3

- Continuous improving of processes by cross-pollinating computer and life science



Pre-clinical and clinical research

14:20	14:30	Sviluppo di algoritmi per la medicina personalizzata	<i>Francesca Cordero</i>
14:30	14:40	Modelli computazionali per lo studio di sistemi biologici	<i>Marco Beccuti</i>
14:40	14:50	Immagini digitali biomediche: simulazione ed elaborazione	<i>Marco Grangetto/ Nello Balossino</i>
14:50	15:00	HPC4AI: Centro servizi e calcolo per AI and edge computing	<i>Marco Aldinucci e Giorgio Audrito</i>

Aggregate Computing @ di.unito.it

Who? System Modelling, Verification and Reuse (<http://di.unito.it/movere>)

Why? In the context of Working Group 4 (Application areas outside “pure” software reliability) of the EU COST Action IC1402 ARVI (Runtime Verification beyond Monitoring, <https://www.cost-arvi.eu>)

What? Edge computing technology for monitoring:

- medical devices
- hospital wards
- operating rooms
- laboratories
- ...



