Master of Science in Computational Biology
Nice Sophia Antipolis University

Programme for 2015/2016

The Master of Science in Computational Biology is a one-year program of second year Master level. This document describes the courses of the first period (October, 4, 2015 – February 26, 2016) which will correspond to 24 ECTS (+6 ECTS for PFE project). The second period will correspond to an internship in a research lab or a company.

Contents

(*) Each UE (Unite d'Enseignement) will be completed by 2 elective courses
♣This course is shared with another specialization stream from the Master in Computer Science
★This course is shared with the MathMods Erasmus Mundus MSc Course

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Course list

Basics in Mathematics and Biology

2 weeks of intensive course to learn the basics (second-half of september)

[1 ECTS] Basics in biology, K. Robbe-Sermesant

Faculty: F. Duprat (CNRS, IPMC), F. Brau (CNRS, IPMC), F. Dayan (CNRS, LJAD), D Zugaj (Galderma), G Baudin (CHU Nice)

Summary

This module gives the basics needed to understand the enormous complexity of a living organism. Following these courses, students will comprehend the present and future challenges in designing, performing, analyzing, and interpreting experimental results in biology. First, the main concepts that organise life and future directions for research are exposed. The major components and structures of life are studied at diverse levels starting from biomolecules (proteins and others) up to whole organisms (small animals and humans). A special emphasis is placed on the physiology of some crucial organs from the nervous and cardiovascular systems, and on tumors formation in cancer. Second, courses on the experimental procedures used in clinical, industrial R&D and in academical research show the numerous needs for advanced technologies and mathematical modeling of biological systems.

Prerequisites

None

Content

1. Introduction, basics in biology (6h)
   (a) Scales in biology
      - Notions of population, organism, system, organ, tissue, cell, organelle and cellular compartment, molecule
      - Cellular biology : structure of eucaryotic cells, division,
      - Time scales in biology
   (b) The molecules of life
      - Water, lipids, glucids, ions, nucleic acids, proteins (structures I-IV)
   (c) Coding information
      - Genetic, DNA-RNA-proteins axis, chromosomes, genes, alleles, transcription, traduction, maturation
   (d) Cell-cell interaction
      - Tight, gap junctions, integrins
   (e) Protein-protein interaction
      - Agonists and receptors, conformation, folding, docking, protein domains, affinity, specificity, signal transduction
2. Focus on the nervous systems (6h)
   (a) Central and peripheral Nervous Systems
   (b) Anatomy of the SNC
      - Brain,ventricules, cortex (neocortex, columns), areas, nuclei, brain stem, dorsal chord,)
   (c) Cellular components
      - Neurons (dendrites, cell body, axons, synapses, grey and white matter, various types), glial cells (schwann, astrocytes, microglial), ion channels.
   (d) Vascularisation (artery, vein, capillary, blood brain barrier)
   (e) How information is processed by neurons ?
      - Action potential, chemical and electrical synapses, post-synaptic potential
   (f) Neural networks
3. Focus on cancer (2h): Tumor and cancer (basics of formation, various types, gliome,)

4. Focus on the heart (3h)
   (a) Anatomy of the heart
      - Ventricles, atriums, auricles, valves, myocytes, nodal tissue (sinoatrial node, His, Purkinje,), coronary circulation
   (b) How is working the beating heart ?
      - Pacemaker, action potential, myocyte contraction.
5. Imaging techniques in biology and medicine
   (a) Techniques & applications in academical research
      - Bright-field and phase microscopy, Fluorescence microscopy, Confocal, two-photons microscopy, FRAP, FCS, Electron microscopy, Single molecule detection, Cellular and molecular imaging, cell shape and mobility, live-cell microscopic imaging,
   (b) Techniques & applications in pharmaceutical research (2h)
      - Examples of image analysis, high-throughput imaging and screening in dermatological research & development.
   (c) Techniques & applications in medicine (2h)
      - Example of use of MRI, fMRI, PET SCAN, ... in Nice hospital imaging facility.
6. Final evaluation (1h)

[1 ECTS] Basics in mathematics★

Faculty: F. Delarue, L. Michel and J. Vtois (LJAD)

Summary

This refresher course will provide background in applied mathematics, in conjunction with topics developed in the Computational Biology program. Core notions from multivariate analysis and optimization, geometry, probability theory and data analysis, as well as dynamical systems will be surveyed, and pointers to detailed mathematical treatments will be provided along the way.

Content

1. Multivariate analysis and optimization (5h)
   (a) Multivariate Taylor formula; critical points and their index.
   (b) Introduction to optimization.
   (c) Lagrange multipliers.
   (d) Basic numerical algorithms in optimization: Newton's method, gradient descent—and its analysis in the convex case.
2. Geometry (5h)
   (a) Study of the height function $z = f(x, y)$: local form, principal curvatures, mean and Gauss curvatures, Euler's formula.
   (b) Introduction to affine geometry : affine and vector spaces, simplices and simplicial complexes, barycentric coordinates.
3. Rudiments of probability theory and data analysis (5h)
   (a) Elementary notions in probability theory: conditional probability, Bayes' formula, etc.
   (b) Elementary notion in statistics: law of large numbers, central limit theorem, binomial law, etc.
   (c) (Weighted) Least Squares, Kalman filtering.
   (d) Data analysis : SVD, PCA, ICA, Digital Signal Processing and Filter Theory (e.g. FIR, IIR, Adaptive Filters, Moments Cumulants - HOS).
4. Dynamical systems (6h)
   (a) The Morse lemma.
   (b) Differential equations and the Cauchy-Lipschitz theorem.
   (c) Elementary methods in dynamical systems theory, stability analysis.
   (d) Example analysis in bifurcation theory.

[1 ECTS] Basics in computer Science, E. De Maria

Faculty: E. De Maria (UNS, CNRS-I3S)

Summary

This small module is concerned with the revision, implementation, and deep investigation of some classical algorithms to solve simple problems.

Prerequisites

None

Content

- Algorithm and pseudo-code
- Notion of complexity
- Sorting Algorithms
- Primitive data structures (lists, stacks, heaps, etc.)
- Algorithms and data structures to manage sets (hash tables, binary search trees, etc.)
- Algorithms on graphs and trees (depth-first visit, breadth-first visit, computation of strongly connected components)

Bioinformatics

[2 ECTS] Algorithmic problems in computational structural biology; Understanding proteins and protein interactions, F. Cazals

Faculty: F. Cazals (INRIA-ABS)

ECTS: 2

Summary

Understanding the structure-to-function relationship as well as biomolecular interactions are major challenges in current structural biology. This course aims at providing an advanced introduction to the computational tools which are instrumental in investigating these challenges.

The first part will consist of getting familiar with proteins, protein complexes and their biochemistry. The fundamental notions will be discussed while manipulating static and dynamic macro-molecular structures—using VMD and Gromacs, and a number of modeling problems will be presented.

The second part, which may be entitled "Mathematical morphology for molecular shapes", will consist of developing the mathematical tools which are best suited to manipulate Van der Walls models, with applications to the analysis of the packing properties of atoms, the description of molecular surfaces, volumes and interfaces, as well as the investigation of voids and cavities. The classes will revolve around Voronoi diagrams and related constructions, which offer a unique setting to get exposed to fundamental mathematical concepts such as Morse theory and homology calculations, in a combinatorial and algorithmic setting.

Content

1. Practical Computational Structural Biology (6h)
   (a) Proteins and protein complexes (3h)
      - Notions of biochemistry
      - The Protein Data Bank
      - Protein complexes

   (b) Force fields and Molecular Dynamics (MD) simulations (3h)
      - Force Fields
      - Molecular dynamics simulations with Gromacs
      - Analysis of MD simulations

2. Mathematical morphology for molecular shapes (15h)
   (a) Voronoi and Delaunay diagrams (6h)
      - The space of spheres and applications
      - Affine Voronoi diagrams
      - The duality Delaunay - Voronoi

   (b) Union of growing balls and alpha-shapes (3h)
      - The alpha-complex
      - Applications to molecular shapes

   (c) Modeling interfaces and binding patches (3h)
      - Elements of Morse theory
      - Macro-molecular interfaces
      - Shelling macro-molecular models

   (d) Elements of simplicial homology (3h)
      - Chains and homology groups
      - Application: counting tunnels and voids for unions of balls

References

- C. Branden and J. Tooze , Introduction to Protein Structure, Garland, 1999.
- A. Lesk, Introduction to Bioinformatics, Oxford, 2002.
- A. Tramontano and A. Lesk , Protein Structure Prediction: Concepts and Applications, Wiley, 2006.
- D. Voet, J. Voet and C.W. Pratt, Fundamentals of Biochemistry: life at the molecular level, 3rd ed., 2008.
- JD. Boissonnat and M. Yvinec, Algorithmic Geometry, Cambridge, 1998.
- M. Henle, A Combinatorial Introduction to Topology, Dover, 1994.
- A.T. Fomenko and T.L. Kunii, Topological Modeling for visualization, Springer, 1997.
- A. Zomorodian, Topology for computing, Cambridge, 2005.

[2 ECTS] Discrete and continuous approaches to model gene regulatory networks, J.L. Gouze

Faculty: J.L. Gouze (INRIA-Comore), M. Chaves (INRIA-Comore) and A. Richard (CNRS-I3S)

ECTS: 2

Summary

The first part of the course will develop the basic modelling approach introduced by Ren Thomas (Brussels). The space of possible gene expression levels can be decomposed into several intervals leading to a discrete approach which can be formalized (according to formal methods of computer science). We will show how to use formal logic in order to extract unknown parameter values from the observed behaviours. We will also explain how some of the current software testing methods can be used in order to generate interesting "wet biology" experiments, starting from the formal descriptions of the interaction graph and the biological hypotheses under consideration. The second part of the course will develop the basics of the use of ODE to model gene regulatory networks with more precise dynamic predictions. For each considered gene, the production rate is defined as a combination of the various contributions of the interacting genes and of the degradation rate. Some examples will be used to illustrate the notions defined during the course. In particular the simple model of mucus production in Pseudomonas aeruginosa will be fully studied. Pseudomonas aeruginosa is a opportunistic bacteria which infects the lungs of patients of cystic fibrosis.

Prerequisites

Basic knowledge in discrete mathematics and ODE

Content

1. Discrete approaches of Ren Thomas to model gene networks (G. Bernot, J.-P. Comet)
   (a) Gene regulatory networks as directed labelled graphs
   (b) Discrete parameters, focal points, resource table and asynchronous state graph
   (c) Reverse engineering: inference of parameters
   (d) Classical results on positive and negative regulatory loops
   (e) Temporal logics applied to Thomas' networks
   (f) Simple example of the mucus production in P. aeruginosa
   (g) Singular states and applications
2. Part 2: Continuous approaches to model gene networks (J.-L. Gouze, M. Chaves)
   (a) Some models of gene networks
   (b) Example: the bistable switch
   (c) Example: the negative loop, oscillators (2 and 3 genes)
   (d) Recalls: state space analysis for non linear ordinary differential equations
   (e) Asymptotic analysis (equilibriums, limit cycles), qualitative analysis
   (f) The continuous formalism for gene networks models
   (g) The Piecewise Linear formalism for gene networks models
   (h) Examples: study of models of the carbon starvation genetic network for E. coli.

References

- R. Thomas, M. Kaufman. Multistationarity, the basis of cell differentiation and memory. II. Logical analysis of regulatory networks in terms of feedback circuits. Chaos 11, 180-195, 2001.
- G. Bernot, J-P. Comet, A. Richard, J. Guespin. Application of formal methods to biological regulatory networks: Extending Thomas' asynchronous logical approach with temporal logic. J. of Theoretical Biology (JTB), Vol.229, Issue 3, p.339-347, 2004.
- E. Klipp, R. Herwig, A. Howald, C. Wierling, and H. Lehrach. Systems Biology in practice. Wiley-VCH, Weinheim, 2005.

[- ECTS] Introduction to Metabolic Networks, J.A. Sepulchre

Faculty: J-A Sepulchre (UNSA)

ECTS: -

Summary

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Prerequisites

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Content

1. The basic concepts
   (a) A survey of metabolism (catabolism, anabolism)
   (b) The concept of metabolic pathways.
   (c) A central pathway : glycolysis
2. Some mathematical analysis of metabolic networks
   (a) The stoichiometric matrix
   (b) Subspaces associated with the S matrix (and biochemical interpretation)
   (c) Stationary metabolic fluxes
3. Coupling metabolic and genetic networks
   (a) Biochemical regulatory networks
   (b) An example of metabolico-genetic network

Biomedical signal and image analysis

[2 ECTS] Variational methods and geometric flows for brain imaging, R. Deriche

Faculty: Rachid Deriche (INRIA, Odyssée)

ECTS: 2

Summary

This course is concerned with the presentation of advanced tools and algorithms for studying and modeling brain anatomy. It relies on state-of-the-art variational methods and geometric flows developed in computer vision and image processing for curves and surfaces and include methods of image regularization through Partial Differential Equations as well as methods of active image segmentation based on the geodesic active contours and regions framework, implemented via the level-set technique. Applied to the images of biological tissues, such as the white matter in the brain, produced in vivo and non-invasively by Diffusion Magnetic Resonance Imaging, the tools and algorithms studied in this course open the possibility of recovering a detailed geometric description of the anatomical connectivity between brain areas and distinguish the anatomical structures of the cerebral white matter. Various applications to Brain Imaging will be presented and discussed including the estimation, regularization and segmentation of diffusion images as well as the tracking, the reconstruction and the clustering of the bundles of white matter fibers.. The well-known Diffusion Tensor Model will be presented and discussed as well more advanced models recently proposed to overcome its weaknesses.

Prerequisites

The prerequisites for the course include basic knowledge in image processing, mathematics and differential geometry at bachelor level.

Content

1. PDE and Variational methods in Image Processing
   (a) A variational framework for scalar and Vector valued image processing
   (b) Constrained Vector Valued Image Processing with application to regularization
   (c) Non Flat Image Processing and Regularization in Manifold
2. Geometric flows for curves evolution and level-sets
   (a) On snakes and classical active contours : A historical point of view
   (b) From Geodesic Active Contours to Geodesic Active Regions Segmentation
   (c) The level-set technique and its applications to Geodesic flows
   (d) Geometric flows for multi-valued image active segmentation
3. Computational Brain Imaging
   (a) On Diffusion Magnetic Resonance Imaging
   (b) Diffusion Tensor Imaging : Estimation, Regularization and Segmentation
   (c) From Diffusion Weighted Images to White Matter Fibers through tractography
   (d) White Matter Fibers reconstruction, segmentation and clustering
   (e) Beyond the tensor model : High order Diffusion Tensor and High Angular Resolution Diffusion MRI
   (f) On some Clinical Applications
4. Implementation
   A set of articles will be proposed for lecture, implementation and presentation and a written exam will be given at the end of the module.

References

- G. Sapiro : Geometric Partial Differential Equations and Image Processing . Cambridge University Press, January 2001.
- J. Sethian : Level Set Methods and Fast Marching Methods Evolving Interfaces in Computational Geometry, Fluid Mechanics, Computer Vision, and Materials Science . Cambridge University Press, 1999
- D. Tschumperl and R. Deriche : Vector-valued image regularization with pde's : A common framework for different applications. IEEE Transactions on Pattern Analysis and Machine Intelligence. 27(4):506-517, April 2005. ftp://ftp-sop.inria.fr/odyssee/Publications/2003/tschumperle-deriche:03.pdf
- N. Paragios and R. Deriche : Geodesic active regions: a new paradigm to deal with frame partition problems in computer vision. Journal of Visual Communication and Image Representation, Special Issue on Partial Differential Equations in Image Processing, Computer Vision and Computer Graphics, 13(1/2):249-268, march/june 2002. ftp://ftp-sop.inria.fr/odyssee/Publications/2002/paragios-deriche:02b.pdf
- D. Tschumperl and R. Deriche. Diffusion PDE's on Vector-Valued images. IEEE Signal Processing Magazine, 19(5):16-25, 2002. ftp://ftp-sop.inria.fr/odyssee/Publications/2002/tschumperle-deriche:02b.pdf
- C. Lenglet, M. Rousson, R. Deriche, O. Faugeras. Statistics on the Manifold of Multivariate Normal Distributions: Theory and Application to Diffusion Tensor MRI Processing, Journal of Mathematical Imaging and Vision, 25(3), 423-444, October 2006
- M. Descoteaux and R. Deriche. High Angular Resolution Diffusion MRI Segmentation Using Region-Based Statistical Surface Evolution. Journal of Mathetical Imaging in Vision, special issue on Mathematics in Image Analysis , Volume 33, Number 2, Feburary 2009, Pages 239-252 ftp://ftp-sop.inria.fr/odyssee/Publications/2008/descoteaux-deriche:08.pdf
- M. Descoteaux, E. Angelino, S. Fitzgibbons, R. Deriche Regularized, Fast and Robust Analytical Q-Ball Imaging, Magnetic Resonance in Medicine, Volume 58, Issue 3. Pages 497-510. ftp://ftp-sop.inria.fr/odyssee/Publications/2007/descoteaux-angelino-etal:07.pdf
- C. Lenglet, J.S.W. Campbell, M. Descoteaux, G. Haro, P. Savadjiev, D. Wassermann, A. Anwander, R.Deriche, G.B. Pike, G. Sapiro, K. Siddiqi and P. Thompson. Mathematical Methods for Diffusion MRI Processing. NeuroImage . special issue on Mathematics in Brain Imaging, Volume 45, Issue 1, Supplement 1, March 2009, Pages S111-S122. ftp://ftp-sop.inria.fr/odyssee/Publications/2008/lenglet-campbell-etal:08.pdf

[2 ECTS] Deconvolution and denoising for confocal microscopy, J. Zerubia

Faculty: J. Zerubia (INRIA-Ariana) and Laure Blanc-Feraud (CNRS-Ariana)

ECTS: 2

Summary

This course is concerned with the presentation of basic and advanced models and algorithms for confocal microscopy. First an introduction to confocal microscopes will be done, including the description of the various types of noises and point spread functions (PSF). Then, a brief overview about sampling theory, convolution and inverse filtering will be conducted, followed by the description of the basic restoration and deconvolution techniques proposed in the literature using either variational or Markovian models. Various confocal microscopy deconvolution methods will be introduced (using the L1 or L2 norm, blind or not). Wavelets and Wavelet packets for confocal microscopy image restoration and deconvolution will be presented. Finally an invited talk of a well know researcher in the field will be given (the speaker will change every year, coming from INRA, Pasteur Institute, Curie Institute, Weizmann Institute, EPFL or ETHZ).

Prerequisites

Basic course in image processing and in optimization

Content

1. Confocal microscopy: PSF, noise and Signal processing tools for image restoration (deconvolution, denoising): Fourier transform, sampling, convolution, filtering, introduction to inverse problems.
2. Markov Random Field for image restoration.
3. Variational approach for image restorartion.
4. Regularized restoration of confocal microscopy images (Richardson Lucy algorithm, L2 and L1 regularization, PSF estimation).
5. Wavelet transform, complex wavelet Packets, application to restoration of confocal images.
6. Parameter estimation with complete or incomplete data.

References

- Handbook of Biological Confocal Microscopy. James Pawley. Springer-Verlag, Revised edition, 2006.
- Mathematical Problems in Image Processing, Aubert, Kornprobst, Springer Verlag, Applied Mathematical Sciences , Vol. 147, 2006.
- Markov Random Field Modeling in Image Analysis, Stan Z. Li, Springer Verlag, Revised edition, 2009.
- A Wavelet Tour of Signal Processing: The Sparse Way, Stephane Mallat, Academic Press, Revised edition 2008.
- On blind deconvoltion for thin layered confocal imaging. P. Pankajakshan and B. Zhang and L. Blanc-Fraud and Z. Kam and J.C. Olivo-Marin and J. Zerubia. Applied Optics, 48(21), July 2009.
- Richardson-Lucy Algorithm with Total Variation Regularization for 3D Confocal Microscope Deconvolution. N. Dey and L. Blanc-Fraud and C. Zimmer and Z. Kam and P. Roux and J.C. Olivo-Marin and J. Zerubia. Microscopy Research Technique, 69: pages 260-266, 2006.

[2 ECTS] Digital signal processing for the analysis and modeling of electrophysiological records, O. Meste ♣

Faculty: O. Meste, P. Comon and V. Zarzoso (UNS-CNRS-I3S)

ECTS: 2

Summary

The course begins by presenting the genesis of bioelectrical activity from the cell to the sensor. Understanding the different types of action potentials helps explain the global electrophysiological behavior of body organs such as the heart, the brain and the skeletal muscle, giving rise to the bioelectrical signals most commonly recorded in clinical practice: the electrocardiogram (ECG), the electroencephalogram (EEG) and the electromyogram (EMG). Moreover, the modeling of bioelectrical signal generation justifies the signal processing methods that can be proposed to solve a particular biomedical problem. Recent approaches in the domain of time delay estimation are introduced for the modeling and analysis of ECG and EMG recordings, in which the property of signal quasi-periodicity can be advantageously exploited. Classical approaches to signal extraction such as optimal Wiener filtering are based on prior temporal or spectral knowledge of the signals of interest. More modern techniques referred to as blind or semi-blind reduce the amount of prior information required to perform signal estimation. Among them, the principal component analysis (PCA) and independent component analysis (ICA) techniques are reviewed in the biomedical signal processing context. Recent applications such as brain computer interfaces and atrial fibrillation analysis illustrate these modern signal analysis tools.

Content

(27h)

1. Genesis of biomedical signals
   (a) From the cell to the organ: basics of human electrophysiology
   (b) Biomedical signal acquisition
      - the electroencephalogram (EEG)
      - the electrocardiogram (ECG)
      - the electromyogram (EMG)
   (c) Preprocessing of biomedical signals
      - baseline wander removal
      - noise removal, interference cancellation
      - time filtering, spatial filtering
   (d) Time-delay analysis
      - interval estimation
      - synchronization
      - averaging
2. Blind techniques
   (a) Statistical tools
   (b) Principal component analysis (PCA)
   (c) Independent component analysis (ICA)
   (d) Blind signal extraction
   (e) Blind identification
   (f) Performance analysis
3. Applications
   (a) ECG

- non-invasive fetal ECG extraction
- atrial activity extraction in atrial fibrillation
- time-delay estimation, averaging, shape analysis

(b) EEG

(c) EMG

Prerequisites

Basics of linear algebra and probability theory.

References

- V. Zarzoso, R. Phlypo, O. Meste, and P. Comon, Signal extraction in multisensor biomedical recordings, in: P. Verdonck (Ed.), Advances in Biomedical Engineering, Elsevier, Amsterdam, 2008, chapter 3, pp. 95-143.
- L. Srnmo, and P. Laguna, Bioelectrical Signal Processing in Cardiac and Neurological Applications, Elsevier, Amsterdam, 2005.

Course shared with the TNS option from Dept of Elec. Engineering

[2 ECTS] Computational anatomy and physiology of the human body, X. Pennec

Faculty: X. Pennec, H. Delingette, G. Malandain and N. Ayache (INRIA-Asclepios)

ECTS: 2

Summary

For many centuries, anatomy and physiology was based on the description of few specimens through dissections. In-vivo and in-situ imaging is radically renewing the field since the 1980ies. An ever growing number of imaging modalities allows to observe both the anatomy and the function at many spatial scales (from cells to the whole body) and at multiple time scales: milliseconds (e.g. beating heart), years (growth or ageing), or even ages (evolution of species). The non-invasive aspect allows repeating the observations along time and on multiple subjects. This has a strong impact on the goals of the anatomy and physiology which are changing from the description of representative individuals to the description of the structure organization and functioning of organs at the population level, with a gradual evolution from descriptive atlases to interactive and generative models allowing the simulation of virtual subjects. This course will cover the mathematical methods needed to perform statistics on anatomical objects, with a specific focus on image registration and atlases. From the physiological point of view, we will focus on the macroscopic modelling of the growth of tumour cells and the electromechanical modelling of the heart. The main applications are in medicine and biology, where computational anatomy and physiology can be used to better understand the basic processes leading to the apparition of pathology, to model its probable evolution and to plan, simulate, and monitor its therapy.

Content

1. Introduction to Medical Image Analysis [NA]
   (a) Context
   (b) Registration
   (c) Segmentation
   (d) Modeling
   (e) Computational anatomy
   (f) Computational physiology
   (g) Example applications
2. Statistics on Riemannian manifolds and Lie groups [XP]
   (a) Charts, parameterizations & atlases
   (b) Tangent vectors & tangent spaces
   (c) Riemannian metrics
   (d) Geodesics, exponential map
   (e) Riemannian distance, completeness, Cut locus
   (f) Practical Example on rotations
   (g) Riemannian measure
   (h) Definitions of mean / median / variance
   (i) Algorithm to compute the mean
   (j) Covariance, Parametric distributions / tests
   (k) Statistical Analysis of the Scoliotic Spine
   (l) Evaluation of rigid registration performances
3. Manifold valued image processing: the tensor example [XP]
   (a) Diffusion tensor imaging & DMRI

(b) An affine-invariant metric on tensors
(c) Interpolating, filtering and smoothing tensor images
(d) Log Euclidean and other metrics
(e) A MAP estimate of tensor images with Rician noise
(f) Morphometry of the Cortex from Sucal Lines

4. Non-linear registration and statistics on deformations [XP]
   (a) Demons, Pasha,
   (b) Notions of diffeomorphisms (LDDMM)
   (c) Geometric constraints
   (d) Non-linear Registration of DTI Images
   (e) Non-homogeneous regularization
   (f) Image morphing
   (g) Riemannian elasticity
   (h) Statistics on one parameter subgroups of diffeos
   (i) Symmetric diffeomorphic demons
   (j) Polyrigids and polyaffine transformations
   (k) Courants for curves, surfaces and fiber bundles
5. Building Atlases [GM]
   (a) The EM segmentation framework
   (b) Averaging intensities vs deformations
   (c) Groupwise registration
   (d) Multimodal atlases (closest neighbor techniques).
6. Biomechanical Registration and Tumour Modelling [HD]
   (a) Soft Tissue Rheologie and Linear Elasticity
   (b) Real-Time Simulation of Surgical procedures
   (c) Propagation based on Fast marching and Reaction Diffusion Equations
   (d) Mechanical coupling of tumor growth and tissues
   (e) Inverse problems
7. Cardiac Modelling [HD]
   (a) Electrophysiology of the heart
   (b) Heart muscle fibers
   (c) Heart muscle mechanics
   (d) Inverse problems

Modeling in neuroscience

[2 ECTS] Inverse problems in functional brain imaging, M. Clerc

Faculty: Maureen Clerc and Théo Papadopoulo (INRIA-Odyssée)

Summary

This course deals with functional brain imaging by non-invasive devices such as Magneto- and Electro-encephalography (MEG,EEG). EEG and MEG measure passively the electromagnetic field created by cortical electrical activity. They have a high temporal resolution (millisecond), but the spatial localization of cortical activity is challenging, requiring to solve ill-posed inverse problems. This course presents the state of the art in physical, numerical, and statistical models related to these functional brain imaging devices. The field of Brain Computer Interfaces will also be briefly presented.

Prerequisites

Basic linear algebra, Basic probability theory, Notions of electromagnetism

Content

1. Introduction
   (a) Source models of cortical activity
   (b) Maxwell's equations
   (c) Specificities of MEG and EEG
2. Forward Problem
   (a) Conductivity models
   (b) Numerical Methods
      - Analytical
      - Boundary Element Methods
      - Finite Element Methods
3. Inverse Problem
   (a) Ill-posedness
      - Uniqueness
      - Stability
   (b) Regularization strategies
   (c) Validation issues
4. Pre- and post-processing data
   (a) Signal processing
      - Power spectrum, periodogram
      - Time-frequency analysis, wavelets
      - Single-trial analysis
   (b) Statistical methods
      - Hypothesis testing
      - Common test statistics
      - Permutation tests
5. Towards Brain Computer Interfaces
   (a) Communicating through brain activity
   (b) Feature extraction
   (c) Feature classification
   (d) Role of feedback

References

- Magnetoencephalography: theory, instrumentation, and applications to noninvasive studies of the working human brain, M. Hmlinen, R. Hari, et al, Rev. Mod. Phys. 65, 413 - 497 (1993)
- Rank-deficient and Discrete Ill-Posed Problems, P.C. Hansen, SIAM
- A Wavelet Tour of Signal Processing, S. Mallat, Academic Press

[2 ECTS] Neuron dynamics, B. Cessac

Faculty: B. Cessac (LJAD and INRIA-NeuroMathComp) and O. Faugeras (INRIA-NeuroMathComp)

ECTS: 2

Summary

The nervous system is characterized by the parallel interaction on many sub-systems with scales from molecules to brain as a whole where, the state of each subsystem is permanently evolving in space and time. Understanding these systems requires to develop new mathematical tools. This lecture is devoted to give skills in this domain, where both biological and mathematical aspects will be considered, with the aim of giving a concrete and operational perspective. The lecture is organised according to the different characteristic scales in the central nervous system: Neurons and synapses, neuronal networks and neural masses

Prerequisites

Good skill in mathematics (ODE, probability theory), basic knowledge in statistical physics

Content

1. Neurons and synapses. The neuron activity depends on the integration of synaptic activities which evolve in real time in non linear and plastic way. In this context the analysis of neuron dynamics will be presented using methods from dynamical systems theory (stability, bifurcations, asymptotic dynamics).

2. Neuronal networks. At this scale, the dynamical evolution is characterized by non-linear systems with a large number of degree of freedom. We shall present methods allowing to obtain the evolution equations of mesoscopic fields generated by neuronal activity.

3. Neural masses. At a mesoscopic scale the neuronal substrate can represented by a continuum where points represent neuronal populations. In this setting one can relate the model-behaviour to experimental observations obtained with specific recording techniques. Several examples will be considered.

Elective courses

Mathematical biology

[2 ECTS] From dynamical systems to complex systems, J.M. Gambaudo ★

Faculty: J.M. Gambaudo (Universit Nice Sophia Antipolis, LJAD)

ECTS: 2

Summary

Time evolution of phenomena either in physics, hydrodynamics, celestial mechanics or in biology or ecology involves tools issued from dynamical systems theory: stability, bifurcations, attractor, complexity, phase transition, transition to chaos, emergent properties of collective systems....

Content

In this series of lectures we will be concerned but several different aspects of this theory:

1. Dynamics of ODE's and maps;
2. Coupled systems lattice;
3. Cellular automata;
4. Systems of particles and lattice gas.

Each of these themes will be illustrate by concrete examples in physics and biology.

[2 ECTS] Transport equations in biology, T. Goudon ★

Faculty: T. Goudon, R. Masson (Universit Nice Sophia Antipolis, LJAD)

ECTS: 2

Summary

Elementary examples of population dynamics. Populations structured by size or age and transport equations. Modeling of simple biological phenomena like births, deaths, mutations. Elements for the analysis of integro-differential systems : entropy, definition of the first eigenvalue. Numerical implementation.

Content

1. 1st class :
   (a) Quick presentation.
   (b) section 1.1 : Invasion and space structure.
   (c) section 1.2.1 : The 2 by 2 Lotka-Volterra system.
   (d) section 1.2.3 : Chemostat.
   (e) section 1.6 : Ecological model of competition for resources.
2. 2nd Class : Chapter 3, Population balance equations: the renewal equation
   (a) section 3.1 : The renewal equation
   (b) section 3.2 : Eigenelements
   (c) section 3.3 : Existence theory
3. 3rd class : Part of Chapter 6, General mathematical tools
   (a) section 6.3.1 : Generalized relative entropy, The Perron-Frobenius theorem
   (b) section 6.4.1 : Generalized relative entropy, parabolic and integral PDEs
   (c) section 6.6 : The Krein-Rutman theorem
4. 4th class : End of Chapter 3, Population balance equations: the renewal equation
   (a) section 3.5 : Generalized relative entropy
   (b) section 3.6 : Long time asymptotic, entropy method
   (c) section 3.7 : Long time asymptotic, exponential decay
5. 5th class : Chapter 4
   (a) section 4.1 : Equal mitosis
   (b) section 4.2 : Size structured model for asymmetric cell division

   6th-8th class
   (a) Chapter 5 and section 6.1

References

- B. Perthame : Transport Equations in Biology, Birkhuser, Frontiers in Mathematics 2007

Other possibilities

[2 ECTS] Automata in biosciences, E. Formenti ♣

Faculty: Enrico Formenti, Faculty of Sciences, University of Nice-Sophia Antipolis

Summary

Automata theory and automata based models have acquired a central position in the formal studies of many biological phenomena. In this course, we give an excerpt of three big classes of automata models and of their application to bioinformatics and biology.

Prerequisites

Standard courses from Applied Mathematics B.Sc. or Computer Science B.Sc.

Content

1. Cellular Automata (7h)
   (a) Basic definitions (1h)
   (b) Example of Dynamics (1h)
   (c) Basic ideas and results for Dynamics (1h)
   (d) From CA to ODE and back (2h)
   (e) Cellular modeling (1h)
   (f) Example: tissue and tumor development (1h)
2. P systems (5h)
   (a) Basic definitions (1h)
   (b) P systems as models for chemical reactions (1h)
   (c) Basic results (1h)
   (d) P systems as computing systems (2h)
3. Stochastic automata (15h)
   (a) Quick review of probability theory (3h)
   (b) Stochastic processes (discrete time) (4h)
   (c) Stochastic processes (continuous time) (3h)
   (d) Queuing systems (2h)
   (e) Applications to gene regulatory networks (3h)

References

1 P. Kůrka. *Topological and symbolic dynamics*, Cours spécialisés Vol. 11, SMF, 2003.

2 A. Deutsch, S. Dormann. *Cellular Automaton Modeling of Biological Pattern Formation: Characterization, Applications, and Analysis* . Birkhauser Boston, 2004.

3 G. Păun and G. Rozenberg. *A Guide to Membrane Computing.* TCS 287(1):73–100, 2002.

4 S. Taati, E. Formenti, J.-P. Comet and G. Bernot.

- On the impact of the distance between two genes on their interaction curve. Submitted, 2009.

[2 ECTS] Large scale distributed systems, J. Montagnat ♣

Faculty: Johan Montagnat (CNRS)

Summary

Large scale distributed infrastructures leverage the high performance networks to federate computing, data and scientific resources from multiple institutions interconnected through the Internet. Distributed computing technologies have undergone a very fast evolution these last years and the infrastructure deployed have become a critical tool in many scientific disciplines. This lecture describes the foundation of distributed computing infrastructures. It introduces the main computing models exploited in Grids and Clouds to evolve from cluster computing towards more virtualized resources and across-institutional user communities. The main problems encountered when deploying such very large scale infrastructures are discussed: users identification and authorization, security of data and computations, heterogeneity of resources, redundancy and fault tolerance, deployment, management, and computation flow control The most wide spread technologies and their associated middlewares are reviewed. Several examples illustrate the concepts introduced.

Prerequisites

Basic remote/distribtued computing knowledge

Content

1. Grid models
   (a) clusters and grid computing
   (b) global/meta computing, web computing
   (c) security, trust infrastructure
   (d) information systems
   (e) redundancy
   (f) large scale distribution, fault reliance
2. Services infrastructures
   (a) Services, interoperability and platform independence
   (b) Open Grid Service Infrastructure / Architecture
   (c) Web Services / WS-RF
3. Infrastructures and deployment
   (a) Production grids
   (b) Deployment models
   (c) Information systems
   (d) Infrastructure examples
4. Authentication, Authorization, security
   (a) Certificates and authentication
   (b) Virtual organizations
   (c) Authorization, access control
   (d) Security, logging, privacy protection
   (e) Network issues, firewalls
5. Distributed data management
   (a) Distributed data management systems

(b) Peer-to-peer
(c) Replication, data redundancy
(d) Storage Managers and File Catalogs

6. Workflows
   (a) Expressiveness of workflow and data flows
   (b) Computational dependencies
   (c) Flow of tasks and services
   (d) Scheduling

7. Applications
   (a) Scientific domains
   (b) Embarassingly parallel applications
   (c) Parallelism models
   (d) Application deployment and scientific computing

8. Grid middlewares
   (a) global computing examples: GLOBUS, gLite, OAR...
   (b) meta computing examples: Web Services, GridRPC (DIET / Ninf / Netsolve)
   (c) practicals

Course shared with the MSc in Ubiquitous Computing

[2 ECTS] Introduction to inverse problems. Application in medical imaging and astronomy, E. Debreuve ♣

Faculty: Eric Debreuve (UNS-CNRS-I3S, Sophia Antipolis), Sandrine Anthoine (LATP, Marseille)

ECTS: 2

Summary

An inverse problem refers to the computation of a "hidden" or unobservable information at the origin of some experimental observations. For example, one observes a picture that has been blurred as a result of an imperfect optical system, and wants to compute the original, unblurred image. This course deals with the modeling and resolution of such problems. Three classes of problems will be studied: model identification, inversion, and source separation.

We will rely on both basic mathematical problems (for example, resolution of a linear system of equations or sample interpolation using a smooth curve) and classical problems in image processing (denoising, volume reconstruction...) to study difficulties such as the non-linearity of the model and the presence of noise. These considerations will lead us to the notion of ill-posed inverse problem, i.e., a problem which cannot be solved from the observations alone. Imposing constraints on the solution, a.k.a. regularization, will be presented as a way to overcome this obstacle. Half-quadratic regularization and regularization using sparsity constraints will be detailed.

The principal stochastic and deterministic resolution methods will be apprehended by tackling real-world problems in medical imaging and astronomy such as the Expectation-Maximization (EM) algorithm in nuclear medecine emission and transmission imaging, the method of weighted residuals and the finite element piecewise approximation in electro-/magnetocardiography, or a variational approach of reconstruction from multifrequency data in astrophysics.

Content

1. Introduction (3h)
   (a) Definitions and examples
   (b) Forward problem modeling
   (c) Ill-posed inverse problem
   (d) Regularization
2. Some classical methods of resolution (6h)
3. Application to image restoration (3h - Problem solving class on computer)
4. Detailed study of a couple of problems in medical imaging (3h)
5. Detailed study of a couple of problems in astronomy (3h)
6. Application to image analysis (3h - Problem solving class on computer)

Planning

2015/2016 program will start on September 14, 2015 .

The program is organized as follows:

- September 14, 2015 – October 2nd, 2015 : A 2 week-period of intensive course will be proposed at the beginning of the program to help students learn the basics in biology, mathematics and computer sciences on how to follow the Computational Biology program in a better way.
- October, 4, 2015 – February 26, 2016: M2S1(30 ECTS). A 16 week course of half day lectures (24 ECTS). 8 required courses (16 ECTS) will be complemented by 4 elective courses (8 ECTS) chosen from the MSc panel with the assistance of the coordinator to form a coherent plan of study. There will be two periods[1]. Schedule is presented on next page. During those periods, you will also work on a project to specialize yourself (6 ECTS) ( ).
- March 1, 2016 – September 14, 2016: M2S2 (30 ECTS). Fulltime internship in research lab or industry (minimal duration: 5 months)

[1] **Period 1** = October, 4, 2015 – December 11, 2015
Period 2 = December 14, 2015 – February 26, 2016

2015/2016 Computational Biology Schedule

Period 0 = September 14, 2015 – October 2nd, 2015
Except if stated otherwise Biology classes and Mathematics classes are given in "Salle PV1 of Petit Valrose, Parc Valrose" (Nice) (just 100m outside the main campus, the room is on the ground floor). Room CB is under the auditorium in the building called "Amphiteatre de Chimie" and Room C2/1 is in the building named "Travaux Pratique Chimie" `http://portail.unice.fr/jahia/page1652.html`. Details on the Biology classes can be found here. Courses DE MARIA hours are 15:00–18:00 and are located at Salle 216, in Petit Valrose in Nice. Except if noticed otherwise the lectures hours are 9:00–12:00 and 14:00–17:00.

Period 0	Sept. 14	Sept. 15	Sept. 16	Sept. 17	Sept. 18
Morning					ROBBE–SERMESANT, Basics in Biology 1, Sophia IMPC B22
Afternoon		DE MARIA: Basics in Computer Sciences	DE MARIA: Basics in Computer Sciences		

Period 0	Sept. 21	Sept. 22	Sept. 23	Sept. 24	Sept. 25
Morning	ROBBE–SERMESANT, Basics in Biology 2, Sophia IMPC B07	MIENVILLE: Focus on the nervous system, Nice Room Risso	BRAU: Techniques in fluorescence imaging Nice Room Risso		DAYAN: Focus on cancer Sophia IPMC B22
Afternoon	BRONSARD: Human Anatomy, Sophia IPMC B22, 13:30–16:30	DESCHAUX: Focus on the brain anatomy, Nice 615 Grande BA	PhysBio Workshop: Nice Valrose, IBV Salle des sminaires	DE MARIA: Basics in Computer Sciences	MARTIS: Medical Semiotics Sophia IPMC B07

Period 0	Sept. 28	Sept. 29	Sept. 30	Oct. 1	Oct. 2
Morning					
Afternoon				DE MARIA: Basics in Computer Sciences	

Period 1 = October, 4, 2015 – December 11, 2015
Period 2 = December 14, 2015 – February 26, 2016
Christmas holidays: December 19, 2015 – January 3, 2016
Required courses: 8 courses
Elective courses: 4 courses

Period 1	Monday	Tuesday	Wednesday	Thursday	Friday
Morning	CESSAC: Neuron dynamics	PENNEC: Comp. anat. & physio.			CAZALS: Comp. Structural biology
Afternoon	DERICHE: PDEs for brain imaging		**FLE: French courses**	FORMENTI: Automata in biosciences	ZERUBIA: Confocal microscopy

Period 2	Monday	Tuesday	Wednesday	Thursday	Friday
Morning	GOUZE: Gene regulatory network	CLERC: Inv. pbs brain imaging			
Afternoon	MESTE: DSP electrophy. records	MONTAGNAT: Large scale dist. syst. / DEBREUVE: Intro to inverse probs	**FLE: French courses**		

Four UEs (teaching units)

UE1 PFE (6 ECTS)

UE2 de parcours (12 ECTS)

- [2 ECTS] Basics in mathematics, Computer Scienec and biology, E. De Maria and K. Robbe-Sermesant ★ [label: Basics in math & bio]
- [2 ECTS] Algorithmic problems in computational structural biology; Understanding proteins and protein interactions, F. Cazals [label: Comp. Structural biology]
- [2 ECTS] Discrete and continuous approaches to model gene regulatory networks, J.L. Gouze [label: Gene regulatory network]
- [2 ECTS] Deconvolution and denoising for confocal microscopy, J. Zerubia [label: Confocal microscopy]
- [2 ECTS] Digital signal processing for the analysis and modeling of electrophysiological records, O. Meste ♣ [label: DSP electrophy. records]
- [2 ECTS] Neuron dynamics, B. Cessac [label: Neuron dynamics]

UE3 de déclinaison (12 ECTS)
Modules imposés (6 ECTS)

- [2 ECTS] Variational methods and geometric flows for brain imaging, R. Deriche [label: PDEs for brain imaging]
- [2 ECTS] Computational anatomy and physiology of the human body, X. Pennec [label: Comp. anat. & physio.]
- [2 ECTS] Inverse problems in functional brain imaging, M. Clerc [label: Inv. pbs brain imaging]

Modules au choix (6 ECTS à choisir parmi:)

- [2 ECTS] From dynamical systems to complex systems, J.M. Gambaudo ★ [label: From dyn to cplx systems]
- [2 ECTS] Transport equations in biology, T. Goudon ★ [label: Transport eq. in bio.]
- [2 ECTS] Automata in biosciences, E. Formenti ♣ [label: Automata in biosciences]
- [2 ECTS] Large scale distributed systems, J. Montagnat ♣ [label: Large scale dist. syst.]
- [2 ECTS] Introduction to inverse problems. Application in medical imaging and astronomy, E. Debreuve ♣ [label: Intro to inverse probs]

UE4 stage de 6 mois (internship) (30 ECTS)

Condition to have the diploma is to have more than 10/20 on each UE

♣This course is shared with another specialization stream from the Master in Computer Science
★This course is shared with the MathMods Erasmus Mundus MSc Course