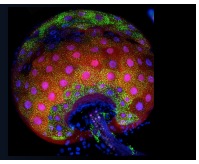
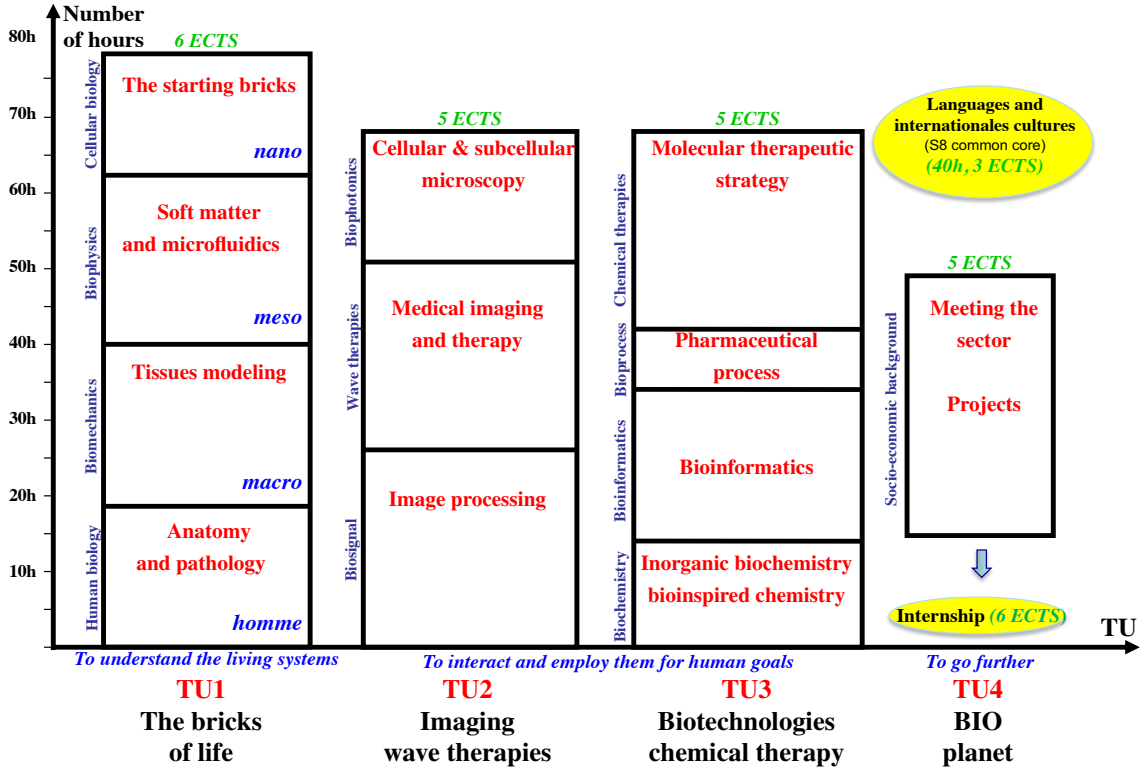
S8 BIOENGINEERING

CENTRALE MARSEILLE



In a context of life expectancy's increase, climate change and exhaustion of fossil resources, biotechnologies represents hope to answer these crucial stakes. By combining engineering and life sciences, bioengineering brings a new paradigme as well as innovative solutions for issues on health, sustainable production, reduction of the ecological footprint, innovative modes of power production. The one-semester bioengineering training program of École Centrale de Marseilles aims to broaden students horizon by interdisciplinary teachings in order to be able to approach life. Thus, the training's program is organized in four Teaching Units (TU). [1]



The first covers the multiscale description of the living matter, going from the molecule up to the human's body. The two next ones focus on the ways of interacting with it, especially for therapeutic purposes. The last one is an openning to the activity area with conferences and visits or a project.

It is an introduction to bioengineering that lets students the freedom to pursue any type of engineering studies but which allows also to continue in this field, abroad within the T.I.M.E. network or in France within the "Groupe des Ecoles Centrales". For instance, pursuing in biomechanics at Centrale Marseille is possible with the last year educational training program Materials and Structures Mechanical Modeling, in parallel with the "Tissues and Implants Bioengineering" program of the the Master in Engineering and ergonomics of physical activities of Aix-Marseille University. Moreover, Ecole Centrale of Marseille is a founder member of the Turing Center for living systems CenTuri, an ambitious interdisciplinary research project, gathering fifty research teams in Marseille in order to better understand the complexity of living systems. CenTuri offers to engineering students numerous perspectives of master internship and PhD within the various research laboratories involved, in varied disciplines : biology (neuroscience, immunology, biology of the development), physics, mathematics, biocomputing.

The members of the teaching staff of this one-semester bioengineering training program come from Centrale Marseille, Aix-Marseille University, CNRS and INSERM. Moreover, without directly intervening in teaching, several academic collaborators or economic actors take part in this educational program by proposing visits, conferences, internships and research projects.

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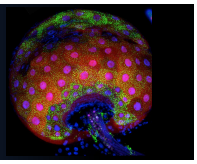
Intranet: Collaborative space for S8 BIOENGINEERING (Moodle: S8 BIOENGINEERING)

1. This document gives a description by TU and by subject. Scroll down the pages for a complete overview or **go directly to a TU or subject of your choice using the red hyperlinks in the table**. At the end of each part, an hyperlink will bring you back to this introductory page. The text written in pink corresponds to external hyperlinks (e-mail address, website).



THE BRICKS OF LIFE

The subject of this TU is the biological material in a multiscale vision, including the molecular and cellular nanoscale (The starting bricks), the biofluids flow mesoscale (Soft matter and Microfluidics) and tissus macroscale (Tissue modeling), until the full human scale (Anatomy and patholgy).

The complexity of the living matter comes from its multiscale organization. This TU gives a global vision of it through a multidisciplinary approach, which is believed to be essential for its understanding. Involved disciplines are chemistry, physics, mechanics, mathematics and numerical modeling. Studying a material or a system in a multidisciplinary vision shows the significance of a multidisciplinary education for new scientific, technological and social challenges.

This Teaching Unit completes others in material sciences. Nowadays, the living matter is recognized as a promising source of inspiration in the fields of biomimicry and bioinspired materials.

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Intranet: Collaborative space for TU1 (Moodle : THE BRICKS OF LIFE)

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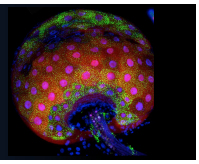

THE BRICKS OF LIFE

THE STARTING BRICKS

Karine ALVAREZ [1]
Anaïs BAUDOT [2]
Stéphane BETZI [3]
Stéphane CANAAN [4]
Alexandre MARTINEZ [5]

Composition of matter has a crucial impact on structure (through elementary physical interactions), which itself dictates the function of the object (it is therefore indispensable to become familiar with the building blocks constituting DNA before looking at a DNA chip, with amphiphilic objects before considering a lipidic drug carrier or with proteins before designing antibiotics). Analyzing the constituents of living matter is the indispensable prerequisite to the design of systems interacting with living objects, imitating or overcoming their properties.

Thus, this section focuses on the micro- to nano-world. A preliminary introduction to the basics of structures and functions of cells is proposed in a first chapter. The molecular building blocks of life will then be explored starting from elemental monomeric constituents (nucleotides, aminoacids, carbohydrates, lipids) in order to understand how their assembling can lead to the corresponding polymers and aggregates (namely nucleic acids, proteins, polysaccharides, membranes). A structural physical analysis will be conducted in order to explain how these building blocks and their connecting mode can lead to objects of high molecular masses, displaying remarkable structures and universally equipping the living world.

As a second step, structure-function determinisms will be deciphered on these objects. This analysis will consist in elucidating how the structure of these macromolecular objects has been optimized through ages by nature leading to molecular machines with remarkable functions. Concerning deoxyribonucleic acids, the analysis of the structural properties of the architecture should explain why this polymer is universally used for information storage and transmission in living organisms. Similarly, a large panel of examples will illustrate the diversity of functions lead by proteins, the structural versatility of polysaccharides as molecular cellular fingerprints and the drug action of protein-target complexes.

Cellular organization (S. Canaan)

Session 1 : The cell (2h)

Cells description and composition.
Function of all organites.

Session 2 : DNA and RNA (2h)

Properties of nucleic acids.
Transcription.
Traduction.

Genetics, heredity, evolution (A. Baudot) (2h)

Molecular bases : genes, RNA, proteins.
Heredity, mitosis, meiosis, reproduction, X-linked transmission, mitochondrial DNA.
Genetic variation, complex traits.
Mutations, natural selection, evolution, phylogenetic trees.

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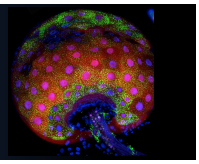

Carbohydrates and lipids (K. Alvarez) (2h)
Definition.
Importance and role in biology.
Classification.
Structure.
Properties.
Application : structure of biological membranes.

Amino acid and proteins (A. Martinez)

Session 1 : Amino acid (2h)
Amino acid's structure.
Physicochemical properties.
Reactivity.
Peptic synthesis.

Session 2 : Protéins (2h)
Protein's structure (primary, secondary, tertiary, quaternary).
Interactions involved.
Examples of proteins.

From the structure of protein-target complexes to the drug (S. Betzi)

Session 1 : Study of the structure of proteins by crystallography (2h)
X rays.
Crystals.
Diffraction.

Session 2 : Study of the protein/ligand's molecular contacts (drug) (2h)
Electronic density.
PDB file.
Co-crystallization and soakings.
Analysis of the action's mode and of the molecular contacts.
Drug optimization on the basis of structures of protein/ligand complexes.

Assessment test: continuous assessment (written examinations, practical exercise report).

Reference textbooks

B. Alberts, A. D. Johnson, J. Lewis, D. Morgan, M. Raff, K. Roberts, P. Walter : "Molecular Biology of the Cell", Garland Science.

D. Voet, J. G. Voet, C. W. Pratt : "Fundamentals of Biochemistry : Life at the Molecular Level", Wiley.

J. M. Berg, J. L. Tymoczko, L. Stryer : "Biochemistry", New York : W. H. Freeman.

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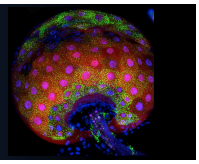

THE BRICKS OF LIFE

SOFT MATTER AND MICROFLUIDICS

Marc JAEGER [1]

The scale of observation corresponds to the mesoscopic one, between the molecular scale used by the chemist and the macroscopic one used by the mechanical engineer. So it is the physicist's one, which describes the structure of condensed matter in terms of physical bonds. It's the action of these cohesive forces that apply between two molecules and by addition between surfaces and colloids at the meso-scale, that is essential for micro-systems. These forces can explain a large number of specificities of the living matter, from self organized systems (surfactants, micelles, liposomes, cellular membranes) to the rheologic properties of complex fluids (as blood for example).

Soft matter

The usually amazing behavior of soft matter can only be understood by its bottom-up organization, starting at the molecular level. This organization is lead by the intermolecular forces, which playing together give the long-range interactions that organize the condensed matter. However, going from the molecular scale, where matter has a discret nature, to the macroscopic one, where the matter can be seen as a continuous medium, implies a too huge number of particles to allow a deterministic description. Like for a perfect gaz, these particles have a random motion induced by thermal agitation, which needs a statistical description. However, contrary to the perfect gaz case, interaction potentials cannot longer be ignored since they are responsible for the organization of condensed matter. The first part of this course will thus be devote to statistical physic's reminders, applying them to the perfect gaz case. Fundamental notions like entropy and chemical potential must bee deeply understood. We will then see how an interaction potential can be taken into account. The second part will focus on the nature of molecular interactions, leading finally to the VDW's interactions and to the paire interaction model of Lennard-Jones . The step toward the mesoscale will bring us to DLVO forces and the Hamaker constant to characterize VDW forces between mesoscopic objects, like colloïds. Lastly, the usefulness of the statistical approach to understand the living matter at the mesoscale will be shown on two examples of interest for biology : self-organization of amphiphilic molecules (fondamental for the organization of the living matter at the cell and subcell levels) and entropic elasticity.

Session 1 : Physics of liquids and soft matter (2h)
Place in material sciences of physic's of liquid and soft matter.
Reminder of the structure of solids, atomic packing factor.
Necessity of a statistical description of fluids.
Increasing importance of intermolecular and superficial forces, from simple liquids to complexe ones.

Session 2 : Reminders of the principles of statistical thermodynamics (self-paced study)

Session 3 : The ideal gas in the canonical ensemble (2h)

Session 4 : The ideal gas in the grand-canonical ensemble (2h)

Session 5 : Intermolecular forces modeling (2h)
The pair interaction.
The repulsive interaction and the structure of liquids.
The hard sphere's and Lennard-Jones models. Considering interactions in the statistical thermodynamic description of fluids.

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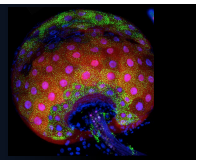


Session 6 : Nature of intermolecular forces (2h)
The electro-statistical origin of intermolecular forces.
Van Der Waal's forces in vacuum (London) and in a solvent (Mc Lachlan).

Session 7 : Chemical potential and self energy (2h)
Self energy in a cristatline solid.
Self energy in a liquid.
Chemical potential.

Session 8 : Chemical potential and cohesive energy (2h)
Chemical potential and connection to energy.
Titer of a solution.
Cohesive energy for a liquid, Trouton's rule.
Thermal energy as the measure unit for interactions.

Session 9 : Self organization, Critical Micellar Concentration (CMC) (2h)

Session 10 : Entropic elasticity (2h)

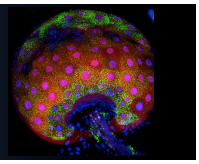
Microfluidics

In MEMS's (Micro Electro Mechanical Systems) capillaries, like in living matter, fluid flows presents typical small scale's properties. Therefore, specific theoretical and technological approaches are needed. The role of superficial forces, mostly ignored in fluid mechanics, becomes dominant and the mixing, omnipresent in the inertial regime, a challenge. The control of flows in MEMS requires to design small-scale adapted control systems like sluice gates, pumps, mixers, which necessitate specific manufacturing process often inspired by micro-electronics.

Session 1 : Specificities of microfluidics (2h)
Stokes flows.
Importances of surface forces.
Wall slip condition.
Encapsulation.

Session 2 : DLVO superficial forces (2h)
DLVO forces.
Van der Waal's forces between macroscopic objects, the Hamaker constant.
Electrostatic forces between macroscopic objects, the Debye length.
Electro-osmosis.

Assessment test: continuous assessment (written examinations, homework).



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R. Balian : "From microphysics to macrophysics - Methods and application to statistical Physics", Vol.1 and 2, Study Edition, Springer.

C. Ngo, H. Ngo : "Physique statistique - Introduction", Dunod.

J. N. Israelachvili : "Intermolecular and interface forces", Academic press.

B. J. Birky : “Micro- and Nanoscale Fluid Mechanics“, Cambridge University Press.

P. Tabeling : "Introduction à la microfluidique", Belin.

Additional bibliographic sources

J. P. Hansen, I. R. McDonald : "Theory of simple liquids", Elsevier Academic press.

J.-L. Barrat, J.-P. Hansen : "Basic concept for simple and complex liquids", Cambridge University Press (chap. 2).

J. Charvolin : "Architectures de la matière molle : des films de savons aux membranes biologiques", Belin.

P. G. DeGennes, D. Quere, F. Brochart-Wyart : “Gouttes, bulles, perles et ondes“, Belin.

E. Guyon, L. Petit, J.-P. Hulin : “Hydrodynamique physique“, EDP Sciences.

D. D. Joseph, T. Funada, J. Wang : “Potential flows of viscous and viscoelastic fluids“, Cambridge University Press.

J. Wolfe : "Cellular Thermodynamics", in "Encyclopedia of Life sciences".

E. Ben-Jacob, H. Levine : "The artistry of nature", Nature, 409, 985-486 (2001).

F. Huber et al. : "Emergent complexity of the cytoskeleton : from single filament to tissue", Adv. Phys., 62, 1-112 (2013).

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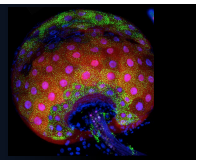

THE BRICKS OF LIFE

TISSUES MODELLING

Jean-Marie ROSSI [1]
Olivier BOIRON [2]
Stéphane BOURGEOIS [3]

The scale of observation corresponds to the engineer's macroscopic scale who considers the biological material as a continuous medium. Tissues are considered as heterogeneous media with more or less organized microstructures and within which fluids may flow. It is then imperative to find methods to change scales that make it possible to obtain macroscopic mean models of mechanical behavior.

Starting from a real clinical issue, the objective of this teaching is, thanks theoretical and numerical tools, mechanics and image analysis, to understand and model biological tissues at different scales : bones, tendons, cartilages, ligaments...

The following aspects are discussed :

- Fluid/structure coupling, porous media ;
- Homogenization of heterogeneous materials and structures in order to obtain mean models of mechanical behavior (rigidity, permeability...) ;
- Dynamic modeling of the evolution of living tissue (remodeling, cell differentiation, pathologies, treatments...) ;
- 3D reconstruction of anatomical finite element models at macro- or micro-scale from medical images (X-rays, micro-scan, MRI...) ;
- Design optimization of an implant or a biomaterial (dimensioning, link with 3D manufacturing, surgical practices...) ;
- Introduction to finite element modeling with software such as ABAQUS or COMSOL (practical exercises on machines).

Mechanical modeling of bone tissues (J.-M. ROSSI)

Session 1 : Introduction to Biomechanics (2h)

Main areas of analysis and application.
A short history of biomechanics.
Different approaches (in vivo, in vitro, in silico).

Session 2 : The bone tissue (2h)

Bones function.
Bones classification.
Components of bone tissue.
Bone tissues classification.
Cortical bone versus trabecular bone.

Session 3 : Bone remodeling process (2h)

Cellular mechanisms of bone remodeling.
Adaptation to mechanical stresses.
Adaptation to energy inputs.
Some bone diseases.

Session 4 : Mechanical behavior of bone tissues (2h)

At the macroscopic scale.
At the microscopic scale.
At the nanoscopic scale.
Different techniques of characterization and influence of biological parameters on the tissue's mechanical behavior.

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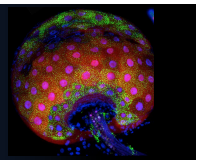

Modeling of flows in tissues (O. BOIRON)

Session 1 : Biological fluids (2h)
Biological characteristics of the main biological fluids.
Elements of rheology, non-Newtonian fluids.
Main physiological flows, effects of non-stationarity and rheology.

Session 2 : Transfers within tissues (2h)
Tissues as porous media.
Basic elements of porous media mechanics.

Session 3 : Physiological flows (practical exercise with COMSOL software) (2h)
Oscillating versus pulsed flows. Transfers of passive scalars to walls.

Tissue modeling with homogenization methods (S. BOURGEOIS)

Session 1 : Homogenization in the large (2h)
Objectives.
Notion of Representative Volume Element (RVE).
Homogenizabilty conditions.
Principle of mean stress and strains.

Session 2 : Methods in Elasticity (2h)
Full-field methods (homogeneous stress boundary conditions, affine displacement boundary conditions , periodic homogenization).
Computational homogenization.
Mean field methods for isotropic media (Voigt, Reuss, Hashin and Shtrikman estimates, Mori- Tanaka, self-consistent method, Walpole bounds).
Case of unidirectional long fiber tissues.
Permeability of periodic porous media.

Session 3 : Numerical estimates of elastic moduli of heterogeneous media with the Abaqus software (4h)
Periodic tissue made of unidirectional long fibers.
Comparison of different methods applied to bone tissue from a sample whose microstructure is obtained by micro-tomography.

Assessment test: continuous assessment (written examinations, practical exercise report).

Reference textbooks

S. C. Cowin : "Tissue mechanics", Springer.

S. De : "Computational modeling in biomechanics", Springer.

Additional bibliographic sources

C. Mattheck : "Design in nature : learning from trees", Springer.

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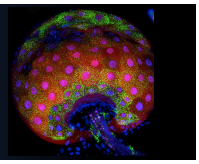

THE BRICKS OF LIFE

ANATOMY AND PATHOLOGY

Serge MESURE [1]

Bioengineering problematics, for instance the development of medical devices that can be implanted, raise problems that deal with the engineering and medical sciences. The ultimate goal is the improvement of the service provided to the patient with better functionalities, an improved durability and a reduction of secondary effects. These approaches imply the acquisition of knowledge on host tissues. To achieve this goal, this course will provide scientists with essential knowledge in that field.

Session 1 : Lower limb - Arthrology (study of anatomy and articulations)). (2h)
- Hip.
- Knee.
- Ankle and foot.
- Pathological orientation.
- Practical implication.

Session 2 : Lower limb - Myology (study of muscles). (2h)
- Thigh muscles.
- Leg muscles.
- Foot muscles.
- Pathological orientation.
- Practical implication.

Session 3 : Lower limb - kinesiology (study of the movement). (2h)
- Knowledge of movement range regarding lower limb.
- Stretching and tridimensional representations.
- Pathological orientation.
- Practical implication.

Session 4 : Upper limb - Arthology (study of anatomy and articulations). (2h)
- Shoulder.
- Elbow.
- Wrist and hand.
- Pathological orientation.
- Practical implication.

Session 5 : Upper limb - Myology (study of muscles). (2h)
- Arm muscles.
- Forearm muscles.
- Inherent hand muscles.
- Pathological orientation.
- Practical implication.

Session 6 : Upper limb - kinesiology (study of the movement). (2h)
- Mobility and movement range organisation in the upper limb.
- The finger clip.
- Pathological orientation.
- Practical implication.

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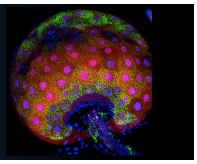

Session 7 : Trunk - Arthology (study of anatomy and articulations). (2h)
Cervical vertebrae.
Thoracic vertebrae.
Head.
Pathological orientation.
Practical implication.

Session 8 : Trunk - Myology (study of muscles). (2h)
Abdominal wall muscles.
Muscles of the back.
Respiratory muscles.
Pathological orientation.
Practical implication.

Session 9 : Trunk - kinesiology (study of the movement). (2h)
Spine mobility.
Respiratory mobility.
Occipital mobility.
Pathological orientation.
Practical implication.

Assessment test: audio-visual production.

Reference textbooks

A. I. Kapandji : "Anatomie fonctionnelle", Maloine.

F. Netter : "Atlas d'anatomie humaine", Elsevier Masson.

M. Dufour : "Anatomie de l'appareil locomoteur", Elsevier Masson.

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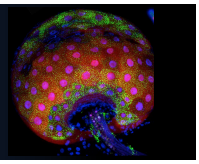

IMAGING AND WAVE THERAPY

Medical imaging is the subject of multiple challenges. In the area of health, non-invasive observation of the body provides morphological, metabolic and functional information, leading to significant progress in terms of public care and health (screening). From an industrial point of view, the development of new modalities has resulted in the manufacture of increasingly sophisticated and highly specified equipment. Browsing a wide range of scales (from cellular to macroscopic), we describe wave-tissue interaction and their use in imaging and therapy. The different imaging modalities, from the more conventional to the more advanced, and the associated therapies are put into perspective. Digital image processing is a key step for diagnostic assistance and therapeutic control. In particular, the following subjects are discussed : notions of image quality, data analysis, tracking of objects in sequences and decision support. The objective is to provide training on the most advanced imaging methods considering the physical foundations in order to be able to offer the best innovation potential in the medical care field.

This teaching deals with various aspects related to medical imaging and wave therapy. At the end of this Teaching Unit, students will have a good knowledge of fundamentals and potentiality of medical imaging :

- Physiological and metabolic properties targeted by the different imaging or therapy modalities ;
- Numerical techniques implemented in each techniques.

Therefore, different disciplines are involved : mechanics, physics and photonics, signal and image processing. In physics, this teaching unit allows to address and complete the aspects related to imaging systems (microscopic and macroscopic) and interaction of electromagnetic or mechanical waves with living matter (modeling and practical applications for imaging and therapy). In image processing, the notions of signal processing seen in the common core are completed by the notions specific to images and the notion of reconstruction is introduced.

This teaching allows to broaden the basic concepts of physics, mechanics or image processing to imaging and wave therapy (applied to the living). These techniques involve the analysis of information resulting from the interaction between waves and matter in order to obtain an image and/or an effect on matter useful for therapy and then the information processing useful for diagnosis, reconstruction or follow-up. Students will be able to analyze the socio-economic context related to medical imaging and therapy through the presentation of the stakes associated with each technique and thus be able to measure the potential for innovation (emerging technologies in development in the laboratories). Practical exercises will also make it possible to give concrete expression to these different notions (in particular experiments on standardized ghosts, practice applications of the techniques of image processing).

This teaching essentially presents multidisciplinary notions applied to living systems. More precisely, it will enable us to adopt a global vision of the complexity of imaging living matter, to use physical concepts to extract useful information for diagnosis or therapy, to recognize the specific elements related to the study of living beings for application to medical or biological imaging, to identify and understand the interactions between living matter and waves to derive morphological or functional information about matter, to draw from the interaction between living matter and waves an information to build and process an image, to take into account the uncertainty associated with all the complexity of the living being by taking, for example, into account the noises (electronic, acquisition ...), the movements of the human body, inhomogeneity between individuals... The methods of resolution will be illustrated in practical exercises and will highlight the contribution of the triptych biology/chemistry/physics for the development of optimal solutions (systems).

A large part of the scientific and technical dimensions related to the problem of imaging and therapy by going from the physical phenomenon to the image and then to the extraction of practical and useful information will be tackled. The goals of the imaging and image processing systems will be set according to the purpose (image contrast, information to be targeted...). Work methods in the specific field of the imaging life will be tackled (from acquisition to treatment, reflection on the adequacy of the means originating from physics research to medical needs, synthesis of the contribution of physics to medicine, measurement of potential for innovation (emerging technologies under development in laboratories)...).

At the end of this teaching unit, students will have a good knowledge of the foundations and possibilities offered by medical imaging (from waves-matter interaction to data processing). Comprehension, on the one hand, of the physiological properties and the metabolisms targeted by the different modalities, and on the other hand, of the numerical techniques implemented, specific to each modality. This skills base will allow students to respond effectively to diagnostic and therapeutic needs, with an appreciation of the medical constraints.

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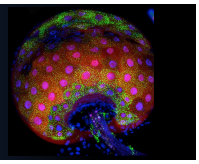

Intranet: Collaborative space for TU2 (Moodle: IMAGING AND WAVE THERAPY)

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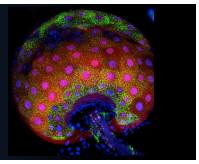

IMAGING AND WAVE THERAPY

CELLULAR AND SUB-CELLULAR MISCROCOPY

Gaëlle GEORGES [1], Hervé RIGNEAULT [2]

The subject is high resolution imaging which aims to probe and observe cells or molecules. The goal here is to find approaches which allow to see structures that are thin and small. Optical microscopy is a technique often used to watch cellular mechanism. Its main benefits are that it allows an imaging :

- that is non-invasive for living samples ;
- that as a good contrast, specific or not ;
- eventually in three dimension of living specimens ;
- in real time of temporal phenomenon.

Microscopy for the cellular observation (Gaëlle GEORGES)

Session 1 : basic techniques 1 (2h)
Introduction and history.
Structure of a simplified microscope.
Study of the components of an optical microscope.
Properties of microscope imaging (imaging under strong coverage)

Session 2 : basic techniques 2 (2h)
Properties of microscope imaging (resolution and coherence of lighting, depth of field).
Evolution of optical microscope.
Specific methods allowing to improve contrast or imaging properties.

Microscopy for the sub-cellular observation (Hervé RIGNEAULT)

Session 1 : advanced techniques 1 (2h)
Bioinformations (Cellular signaling and machinery).
Conventional contrast in optical imaging.
Fluorescence microscopy.

Session 2 : advanced techniques 2 (2h)
Non linear contrast in optical imaging.

Session 3 : advanced techniques 3 (2h)
Reduction of the observation volume

Session 4 : Practical work in biophotonics (6h) [3]
Samples preparation.
Handling of techniques seen in class.
Report in group on the different handles.

Assessment test: continuous assessment (written examinations,practical exercise report).

BACK

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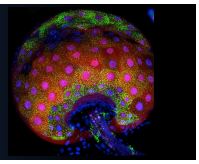

IMAGERIE ET THÉRAPIE PAR ONDES
MEDICAL IMAGING AND THERAPY

Caroline FOSSATI [1], Gaëlle GEORGES [2]
Philippe LASAYGUES [3], Serge MENSAH [4]
Carine GUIVIER-CURIEN [5]

The subject deals with the morphologic, therapeutic and functional imaging from distinct methods. In particular, it focuses on the modeling of the interactions between waves and tissues, in order to optimize the image quality and the therapeutic index.

Optical imaging (Gaëlle GEORGES)

This part takes first a closer look at the interaction between light wave and tissue. Then, it moves to the spread of this wave in biological tissue. According to the environment, distinct ways of transport of the light will be presented. Then, imaging systems (spatial, temporal...) and the use of polarized light for functional imaging will be covered. Finally, several laser therapies will be shown.

Session 1 : Light-material interaction (spread of the light in a biological tissue) (2h)
- Introduction to optical imaging techniques.
- Light-matter interaction.
- Optical parameters.
- Conclusion for the optical imaging.

Session 2 : Light propagation in tissue and tissue imaging (2h)
- Integrative formulation.
- Radiative transfer equation.
- Resolution of an inverse problem.
- Imaging techniques
- Applications

Session 3 : Use of other properties of the light (example of polarization) (2h)
- Light polarization and representation of a polarization state.
- Spread of a polarized light through an optic system. Tissue's polarimetric properties. Tissue's polarization imaging.

Session 4 : Optic-wave therapies and conclusion (2h)
- Laser-tissue interaction.
- Photochemical effect.
- Photothermal effect.
- Photomechanical effect.
- Photoablative effect.
- Conclusion and comparison between optical techniques and other techniques of medical imaging.

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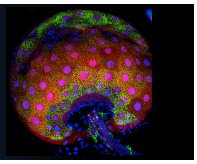


Imaging and electromagnetic therapy (Caroline FOSSATI)

Session 1 : MRI imaging (2h)
Principle (T1 and T2 relaxation, chemical move).
Techniques (spin echo, selective impulse).
Imaging (field gradient, tomography).
Functional (BOLD) and diffusion (neurology) MRI.
Constraints and risks.

Session 2 : X-ray imaging and therapy (2h)
Differential absorption.
Tomodensitometry (CT scan) and angiography.
Radiotherapy.

Session 3 : Nuclear imaging and therapy (2h)
α, β, γ radiations.
Gamma camera.
PET (Positron emission tomography) scan.
Brachytherapy and Proton therapy.

Imaging and ultrasonic therapies (Serge MENSAH)

Session 1 : Introduction, historical background and spread of medical ultrasounds (2h)
Specificity of the ultrasonic imaging (real-time and non-ionizing imaging)
Therapeutic potential (drug delivery, localized tissue destruction).
Piezoelectricity.
Evolution and miniaturization of ultrasound scanners.
Diagnosis and therapy.
Compressional and shear waves.
Specificity of compressional and shear modulus for the tissue characterization
Reflectivity.
Adaptative filtering.

Session 2 : Ultrasound scan A and B (2h)
Intensity (transmitted, reflected and dosimetry).
Time Gain Compensation (TGC).
Electronic focalization.
Logarithmic compression.
Speckle (origins and reducing).
Artefacts (nuisance or information source ?).

Session 3 : Ultrasound scan B and TM (2h)
Ultrasonic Semiology (application to senology).
Echocardiography.
Doppler.

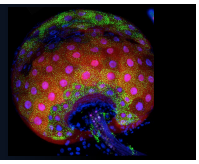
Session 4 : Other aspects (2h)
HIFU (high intensity focused ultrasound) waves and extra-corporeal shock waves (lithotripsy, histotripsy).
Contrast agents for ultrasound (microbubbles).
Sonoporation and vectorization.

Session 5 : Practical work on ultrasonic imaging (Carine GUIVIER-CURIEN, Philippe LASAYGUES) (3h) [6]
Handling of a sonographic instrument.
Measures on calibrated phantoms.

Assessment test: continuous assessment (written examinations).

BACK

6. Technical facilities of the licence Pro MTB de l'IUT d'Aix-Marseille à Saint Jérôme.



IMAGING AND WAVE THERAPY
IMAGE PROCESSING

Salah BOURENNANE [1], Caroline FOSSATI [2], Thierry GAIDON [3]

Digital image processing of images is a key step for diagnostic support and therapeutic control. In particular the subjects of imaging quality, data analysis, objects tracking in sequences and decision helping will be discussed. This course also introduces deep-learning and shows how it differs from usual machine-learning's algorithms. The main methods used by the artificial intelligences community will be presented, as well as the key families of models (convolutive networks, recurrent networks and generative models). Finally, examples in image processing will be considered in practice.

Basic of image processing (Salah BOURENNANE)

Session 1 : Introduction (1h)

Session 2 : Basic methods (2h)
- Organization of an image processing line.
- Acquiring, sampling and quantization.
- Pixels, neighborhood and connectedness.
- Image enhancement.
- Convolution filters.

Session 3 : Optimal method of image denoising (2h)
- Inverse filter.
- Frequency filtering.
- Wiener's filter.

Detection, classification and segmentation in image processing (Thierry GAIDON)

Session 4 : Methods of image detection and classification (2h)
- Introduction to classification.
- Statistical approaches.
- Neural networks.

Session 5 : Methods of image segmentation (2h)
- Region-growing methods.
- Histogram thresholding method.
- Clustering methods.
- Edge detection methods.

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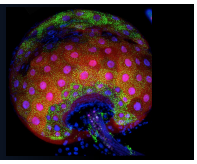


Deep-learning in image processing (Salah BOURENNANE)

Session 6 : Introduction to deep-learning (2h)
Fondamentals.
Relevance of deep-learning.
Big-data and deep-learning.

Session 7 : Learning optimization by deep-learning (2h)
Optimization technics for deep-learning.
Different models (deep architecture).

Session 8 : Deep-learning in image processing (2h)
Activation function and their use.
Application in image processing.

Basic of image reconstruction (Caroline FOSSATI)

Session 8 : Notions of image reconstruction (2h)
Tomographic reconstruction.

Session 9 : Methods of image reconstruction (2h)
Filtered backprojection method.

Image processing in practice (Caroline FOSSATI, Thierry GAIDON)

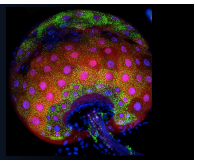
Session 10 : Using the main techniques of image denoising (4h) [4]

Session 11 : Using image segmentation algorithms (4h) [5]

Assessment test: continuous assessment (written examinations,practical exercise report).

BACK

4. Image processing facilities of Centrale Marseille.
5. Image processing facilities of Centrale Marseille.



BIOTECHNOLOGIES AND CHEMICAL THERAPY

This teaching unit is about biotechnology and pharmacology. So it makes sense to study the strategies used in the development of bioinspired systems and in the production of biologically active compounds, both natural and synthetic ones. In pharmacology, the industrial technologies and process of the traditional pharmaceutics are introduced, while in biotechnologies the progress based on basic modules of every living being (nucleic acids, proteins) are presented. Recently, the economic sector has developed new instruments (MEMS, DNA microarrays, bioinformatics etc.), which accelerate the research of new medication, to optimize their employment (vectorization), and revolutionize the process of biological analysis. In the past few years these promising technologies have boomed considerably, first in the academic world, then through the creation of a multiplicity of start-ups which are currently being integrated in the pharmaceutical industry. Today, the principles based on this new tools are sources of innovation in lots of other branches of industry.

This class involves knowledge about process engineering and chemistry for the pharmaceutical aspects and the bioinorganic studies of living systems, leading to a biomimetic chemistry. It also entails skills in discrete mathematics and in computer science for bioinformatics. The skills gained in these lessons complete those already attained by the students. Observation of the development and life-cycle of pharmaceutical products illustrates the multidisciplinary education required in this sector and shows to our students the interest in a general education for new scientific, technological and social challenges in the field of biotechnologies and health.

The development of a medicament is a procedure with multiple parameters, involving regulatory, temporal and social conditions, as well as an innovative component. Multiple guidelines must be respected (regarding efficiency, availability, harmlessness etc.). Thus, it is a sector in which, par excellence, the solutions emerge from the capacity to mobilize complementary competences and to approach a complex problem with multiple parameters. These required complexity and multidisciplinary approach are illustrated by the continuity and the complementarity of the dispensed education, by the case studies and by the variety of suggested professional reports.

Thus, the heart of this Teaching Unit hence concerns the creation and the commercial launch of new active molecules and biotechnological devices. It is about stimulation of ingenuity to invent creative and original solutions with the help of what has been produced in the past and of what is developed today. In addition, a great part of the teaching is dedicated to bioinformatics and to biotechnologies, which aim for using genomes, biomolecules, cells and tissues in order to create innovative tools to face human challenges of the future. The sector itself is conducive to stimulate the imagination as it is in direct contact with life, which due to its long creativity of several millions of years of evolution is the richest of all sources of inspiration for humans.

Responsible: Marc JAEGER (marc.jaeger@centrale-marseille.fr)

Intranet: Collaborative space for TU3 (Moodle: BIOTECHNOLOGIES AND CHEMICAL THERAPY)

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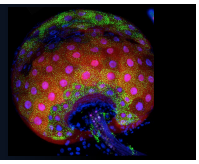

BIOTECHNOLOGIES AND CHEMICAL THERAPY

MOLECULAR THERAPEUTIC STRATEGY

Karine ALVAREZ [1]
Stéphane CANAAN [2], Jean-François CAVALIER [3],
Stéphane BETZI [4], Philippe ROCHE [5]

Healthcare Regulatory Affairs (RA), the different scales of production, the targeted molecule choice and the strategy of quick synthesis (structure activity relationships, test with large family of compounds, shipping optimization, screening technologies, drugs major targets, product life cycle...) are introduced. Protein biotechnologies are overviewed : new diagnosis tools and new drugs obtained by genetic engineering. Case studies are discussed and supplemented with a visit of a high throughput screening platform and with a lab work session on biologic activity assays for active molecules.

Therapeutic strategies (K. ALVAREZ)

Session 1 : Therapeutic strategies (2h)

Introduction to drugs.
Drug discovery and development.
Pharmaceutical Industry (some figures).
Concepts definition (epidemiology, epidemic, endemic, pandemic, prevalence).
Drugs contribution to mankind.
Dosage, indications, contraindications. The drug conception key steps are :

- Disease choice.
- Drug target choice.
- Structured biological activity development.
- Identification, isolation, purification, structure establishment of the “lead” molecule.
- Identification of the structure activity relationships and of the pharmacophore.
- Interactions with the target improvement.
- Pharmacokinetics properties study and improvement.
- Drug metabolism study and toxicity tests.
- Manufacturing processes development.
- Clinical trials.
- Commercialization.

Screening and protein structure (S. BETZI)

Session 2 : Screening and experimental validation (2h)

Active compounds identification, chemical libraries, robotization.
Experimental tests design.
Enzymatic screening.
Z factor.
Non enzymatic screening (ELISA, Double Hybrid, FRET, HTRF, BRET).
Screening development (miniaturization, screening for pharmaceutical industry, screening integration and robotization).
Orthogonal confirmation (micro-calorimetry, interferometry, various methods of co- purification, NMR confirmation).
Structure confirmation (NMR, crystallography).
Screening on cells and animals : High Content Screening (HCS).

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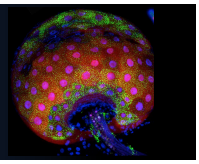


Session 3 : Structural method for the study of protein/drug interactions and molecules optimization (2h)

Experimental structural method reminder (EM, Saxs, NMR, X-Ray).
Crystallographic structure of protein/small molecule complex (co-crystallization, soaking, electron density, solution, alternative conformations, B-factor).
RCSB data base : PDB, *.pdf files, *.sdf files, *.mol2 files.
Structure Based Drug-Design and guided SAR with crystallographic data.
Water molecule and protein structures.
NMR for protein structure solving and protein/ligand interaction study.
Interaction strength and speed.
Intrinsically disordered proteins.
Protein/protein interactions (notions).

Session 4 : Macromolecule visualization and manipulation with PyMol software (6h)

Protein Data Bank.
Crystallographic structure.
3D molecule imaging.
Helix, beta sheet, random coil.
Active site.
Inhibitors.
Water molecule.
Hydrogen bond.
"Van der Walls" contacts.
Electron density.

Therapeutic targets, molecular modeling and drug design (P. ROCHE)

Therapeutic targets (2h)

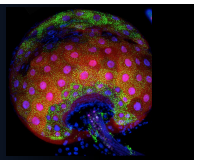
From the target to the drug.
Bioactive molecule conception strategies.
Therapeutic target large family.
Protein structure reminder.
Receptors :
— Definition and functional principle
— Example : GPCR.
Protein recognition modes.
Enzymes :
— Definition and functional principle.
— Example : protein kinase.

Session 6 : Molecular modeling and drug design (2h)

Modeling contribution to drug discovery processes.
Introduction to molecular modeling.
Protein structure prediction (homology modeling, ab initio, docking...).
Modeling applications.
Introduction to molecular mechanic.
Force fields definition.
Molecular dynamic principle.
Molecular dynamic application for drug design.

Session7 : Example of a biological target : protein-protein interaction (3h)

Protein-protein interactions as therapeutic targets.
Biologic concerns for protein-protein interactions.
Protein-protein interactions distinctives features.
Peptidomimetic compounds.
Example : Inhibitors development of the MDM2/P53 complex :
— Structure-based approach.
— Ligand-based approach.



Chemical library development for protein-protein interactions.
Study case (inhibitors development of the MDM2/P53 interaction).

Pharmacokinetics (K. ALVAREZ)

Session 8 : Pharmacokinetics (2h)

Study and improvement of pharmacokinetic properties in drug design.
Introduction to pharmacokinetics and pharmacodynamics for drugs.
Definition of the main concepts and issues.
Drug activity definition.
ADMETox (definitions).
Description of the different drug administration modes.
Concept definition (adsorption, distribution, metabolization, toxicity).
Chemical principles for the improvement of pharmacokinetics.

Screening in practice (K. ALVAREZ)

Session 9 : Example of a screening platform (1h30) [1]

Biological assay in practice (S. CANAAN, J.-F. CAVALIER)

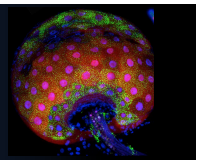
Session 10 : Lab Work on biologic activity assays for active compounds (4h) [2]

Understanding of a lab protocol.
Calculation of test sample (dilution ratio, moles of enzymes, molar excess of inhibitor...).
Enzyme activity measurements using the pH-stat technique.
Interpretation of kinetic curves with determination of enzyme specific activity.
Inhibition tests using Orlistat as reference inhibitor.
Plot of obtained inhibition curves.
Interpretation of results.
Writing a test report.

Assessment test: continuous assessment (written examinations, homework, practical exercise report).

BACK

1. AFMB lab on the campus of Luminy.
2. LISM's technical facility on CNRS Joseph Aiguiller campus.



BIOTECHNOLOGIES AND CHEMICAL THERAPY
PHARMACEUTICAL PROCESS

Nelson IBASETA [1]

This part is devoted to the Crystallization of active substances, which is a fondamental process for the production of drugs.

Session 1 : Polymorphism (2h)
- General introduction.
- Introduction to polymorphism.
- Characterization of polymorphic forms.

Session 2 : Thermodynamics (2h)

Session 3 : Kinetics (2h)

Session 4 : Using (2h)
- Approach and strategy.
- Case study.

Assessment test: continuous assessment (written examinations).

Reference textbooks

D. Ronze "Introduction au génie des procédés - Applications et développements“, Tec et Doc, Lavoisier, 2013.

A.J. Hickey, D. Ganderton, Dekker “Pharmaceutical Process engineering”, 2001.

B. Atkinson, F. Mavituna "Biochemical engineering and biotechnology handbook", Stockton Press, 1991.

J.E. Bailey, D.F. Ollis "Biochemical Engineering Fundamental", McGraw Hill, 1977.

D. J. Amende "Chemical Engineering in the Pharmaceutical Industry. R&D to Manufacturing".

H.-H. Tung, E. L. Paul, M. Midler, J.A. McCauley "Crystallization of Organic Compounds. An Industrial Perspective".

Additional bibliographic sources

J. W. Mullin "Crystallization".

A. S. Myerson "Handbook of Industrial Cristallization".

BACK

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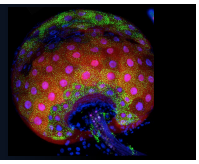

BIOTECHNOLOGIES AND CHEMICAL THERAPY
BIOINFORMATICS

Anaïs BAUDOT [1]
Léo LOPEZ [2], Elisabeth REMY [3]

The goal of the education in bioinformatics is to provide the students with general knowledge on what is commonly called bioinformatics, giving fundamentals on three distinct themes.

Introduction to bioinformatics and systems biology (A. BAUDOT)

The purpose is to give an overview of different technologies used nowadays in genomics and functional genomics, as well as a presentation of some applications, in particular as part of systems biology. Indeed, biology has known a significant evolution since the data production on a large scale and the resulting modifications in its approach. The objective of this course is to present the technological developments (sequencing, omics) that led to this evolution, together with the challenges, that biologists have to tackle currently. We will discuss particularly systems biology approaches for human health and notions of complex diseases and personalized medicine.

Session 1 : History (1h)
History of applied bioinformatics.
History of biology in the big data era.

Session 2 : Genome sequencing (2h)

Session 3 : Biological networks and systems biology (2h)

Session 4 : Clinical bioinformatics (2h)

Modeling and analysis of biological regulation networks (E. REMY)

At the heart of every living organism, genes play an essential role. Besides their existence and their capacity for expression or inhibition, it is more precisely their interactions over time which make organisms have a certain number of phenotypic properties, follow a certain morphogenetic process... These interactions are difficult to define experimentally and, even if we were able to explicate them point by point, their global effect would remain an impossible mystery to characterize with molecular biology methods, because of the inherent complexity of the studied systems. In this context, we will present computer and mathematical methods related to discrete dynamical systems and control networks, which allow us to abstract the biological reality in order to apprehend the essence of the interactions and their influence over real biological systems.

Session 1 : Introduction to modeling of complex systems (2h)

Session 2 : Dynamical systems (2h)
Discret dynamical systems.
Attractors.
Pools of attraction.
Updating modes.

Concrete applications to biology (2h)

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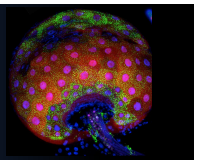

Artificial intelligence and deep learning (L. LOPEZ)

Artificial intelligence (AI) future seems full of promise. As the Russian President V. Poutine said, the leader in artificial intelligence will rule the world. It seems that AI is an area of strategic interest for industrialized countries and it is also ubiquitous given how it conquers all the fields of society and science (medicine, physics, intelligent robotics, connected objects, administration, etc...).
In this course, we will present a large view on AI through its concrete results, intelligent (cognitive) robotics and the nascent field of artificial general intelligence (AGI). We will show the links with neuroscience (when they exist). We will study more particularly a sub-domain of statistical learning : the deep learning. We will decipher its algorithms and will precise the interests and limits of this field. Finally, we will examine the applications of deep learning in biomedicine.

Session 1 : AI, robotics, cognition (2h)
- AI and cognitive science.
- Cognitive robotics.
- Artificial general intelligence : myths and realities.

Session 2 : A diving into the (deep) water of statistical learning (2h)
- Deep learning, short introduction.
- Deep neural networks, autoencoders, deep belief networks, convolutional networks.
- Links with neuroscience.

Session 3 : Deep learning : applications in biomedicine (2h)
- Networks analysis.
- Drug repurposing.
- Prediction of protein function.

Assessment test: continuous assessment (homework).

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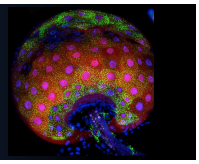

BIOTECHNOLOGIES AND CHEMICAL THERAPY

INORGANIC BIOCHEMISTRY AND BIOINSPIRED CHEMISTRY

Alexandre MARTINEZ [1]

This course deals with complex biological systems. Di-oxygen transport, electron transfer in living system, photosynthesis or catalases are presented in detail. This helps understanding how nature finds elegant answers to crucial problems. Biologically inspired strategies are also discussed in order to illustrate how and why Chemistry mimics this type of systems. For instance, the advantage of such an approach will be illustrated with the study of the mechanism of action of cis-platinum, a powerful anticancer drug. The mechanism of action of an anti malaria drug and fighting strategies against Alzheimer disease are also studied.

Session 2 : Transition elements in biological systems (2h)
- Transition elements properties.
- Biological ligands.
- Structure/properties relation.

Session 3 : the special case of Iron (2h)
- Iron's role.
- Siderophores.
- Ferritin.
- Hemoglobin.

Session 4 : Breathing and dioxygen transport (2h)
- Hemoglobin and myoglobin.
- Transport mechanism.
- Hemocyanin and "blue blood".

Session 5 : Photosynthesis (2h)
- Antenn.
- Photosystem I.
- Photosystem II.

Session 6 : Enzymatic catalysis (2h)
- Principle.
- CO2 Transport : carbonic anhydrase.
- Methane mono-oxygenase.

Session 7 : Study of cytochrome P-450 (2h)
- Role in living systems : oxydation and detoxifying of the cell.
- Structure.
- Mechanism.

Session 8 : Transition metals in medicine (2h)
- Anticancer therapy (cis-platinum).
- Antimalaria drug (artemisinin and quinine).
- Strategies to fight against Alzheimer disease.

Assessment test: continuous assessment (written examinations).

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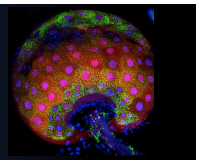

Reference textbooks

D. Voet, J.G. Voet : "Biochimie", De Boeck, seconde édition, 2005.

D.F. Shriver, P. W. Atkins : "Chimie inorganique", De Boeck, troisième édition.

J. E. Huhey, E. A. Keiter, R. L. Keiter : "Inorganique Chemistry", De Boeck, 2004.

S. J. Lippard, J. M. Berg : "Principe of bioinorganic chemistry", Wiley, 2006.

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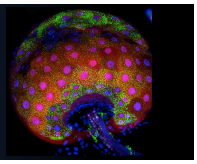

BIO PLANET

The objective of this Teaching Unit is to allow the students to go out of the school context in order to embrace more widely the biotechnological sector. The S8 BIOengineering offers them a large overview by meeting the biologist and health Aix-Marseilles community or eventually realising a project [1].

The object of this Teaching Unit is the opening to the socio-economic sector by giving students the possibility to interact with the professional environment. This is why its position is out of the regular academic boarders. Nevertheless, the multidisciplinary training of our students is the basis to build more complex competences of interpersonal skills.

The assessment mode is original as well. The aim is to produce a short audio-visual report (clip), a communication mode that gain more and more importance today. Support in this field will be offered at the beginning of the semester.

Responsible: Marc JAEGER (marc.jaeger@centrale-marseille.fr)

Intranet: Collaborative space for TU4 (Moodle: BIO PLANET)

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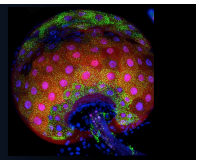
1. The project activity is possible as long as the student gets ready in advance with the subject to start with it at the beginning of the S8.



BIO PLANET

MEETING THE BIO-HEALTH SECTOR

Gaëlle GEORGES [1]
Marc JAEGER [2]
Jean-Marie ROSSI [3]

Bioengineering is the ultimate example of an emergent booming business sector, which increases continuously thanks to scientific and technological discoveries from public and private research laboratories. With an exceptional large number of researchers and hospital practitioners and an impressive quantity of laboratories, which cover a broad-spectrum of bioengineering research, the Aix-Marseille site offers an interesting opportunity to understand the challenges of this sector for the ones who accept to go out of the school walls. In order to invite the students to this trip, to this open-mindedness, a day of training a week is decentralized in the Luminy site (in the south of Marseille, at the heart of the national park of the Calanques). This site offers an environment recognized for its research activity in Biology, Biochemistry, Biophysics, Biomechanics, Bioinformatics, and generally Biotechnologies. Its economic business park dedicated to the establishment of biotechnological start-ups and companies has already attracted an important number of investors (see Grand Luminy Technopôle). Other Marseilles places offer many opportunities to meet the community as well, like the hospitals center of Saint Marguerite, of the Timone or of North hospitals. Moreover, the anatomy and pathology lectures will be given at the Institut du Mouvement et de l'appareil Locomoteur (IML) of l'hôpital Sainte Marguerite Many others opportunities to interact with the bioengineering sector are offered in the frame of this TU. A liste of all the activities proposed each year is available on intranet (Moodle: BIO PLANET). This liste can be elaborated in concertation with students to consider at best their interests, at the condition that they tall us largely before the start of the S8.

Assessment test: video report.

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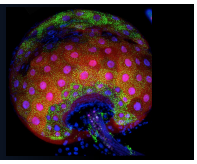

BIO PLANET
PROJECT

The recommended procedure for the project activity results from a double analysis :

1. The second year Internship is the golden opportunity to complete the discovery of the bioengineering sector thanks to a direct observation on the field.
2. The 8th semester lasts 4 months, which give a very comfortable timeframe to mature an internship subjects with the following actions (non-exhaustive list) :
   — To make contact with the internship team, and if possible to get familiar with them ;
   — To gather information on the problematic via a bibliographic study ;
   — To get accustomed to the useful tools/techniques for the internship.

It is the mission that is proposed to our students within the scope of their project activity. It also offers a guarantee for the potential internship supplier to have a student who is more operational from the first day of internship, which makes the 2nd year internship more attractive. However, it implies to be already decided on the internship subject before starting the semester and to be able to propose a project, that is in relation to Bioengineering, even if the internship subject can differ. A data base of our partners is available for the interested students to help them in their search (Moodle: BIO PLANET), contact data upon request.

A project activity, which is de-correlated of the second year internship, is also possible under the same conditions of tackling the issue before the start of the semester. Students can propose themselves a subject on Bioengineering, which matter to them, and find a teacher/researcher, who agrees to supervise and validate the project. They can also solicit them for a subject proposition.

In every instance, it is suitable to contact early the teaching team to validate the proposed project subject (content, assessment, supervisor).

Assessment test: video clip presentation (my project in 180 s).

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