Practical summer course:
Modeling for Systems Biology

June 14 – 19, 2015
Centre for Genomic Regulation
Barcelona

- Schedule -

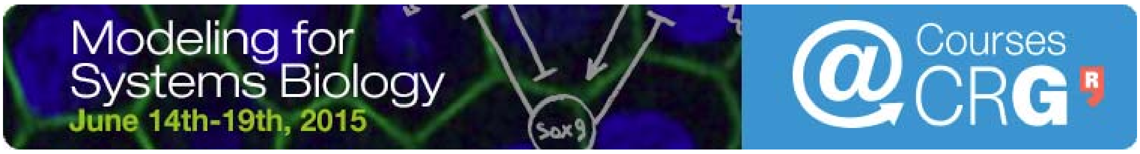
Activity Organized by:

CRG Centre for Genomic Regulation

SystemsX.ch
The Swiss Initiative in Systems Biology

Supported by:

EXCELENCIA SEVERO OCHOA



- Day 0, Sunday June 14th, 2015-

"Basic mathematical concepts & Introduction to MatLab" (Optional)

Hosts: James Sharpe & Andreea Munteanu

Instructors: Marco Musy, Andreea Munteanu & Xavier Diego

When	What	Topic	Where
11:00am – 01:00pm	LECTURE	Linear Algebra	Room 468
	Lunch		5th Floor Terrace
02:00pm – 04:00pm	LECTURE	Ordinary Differential Equations	Room 468
	Break		5th Floor Terrace
04:30pm – 6:30pm	LECTURE & PRACTICAL	Introduction to Matlab	Room 468
8:30pm	**Dinner**		Restaurant Arenal

Restaurant Arenal

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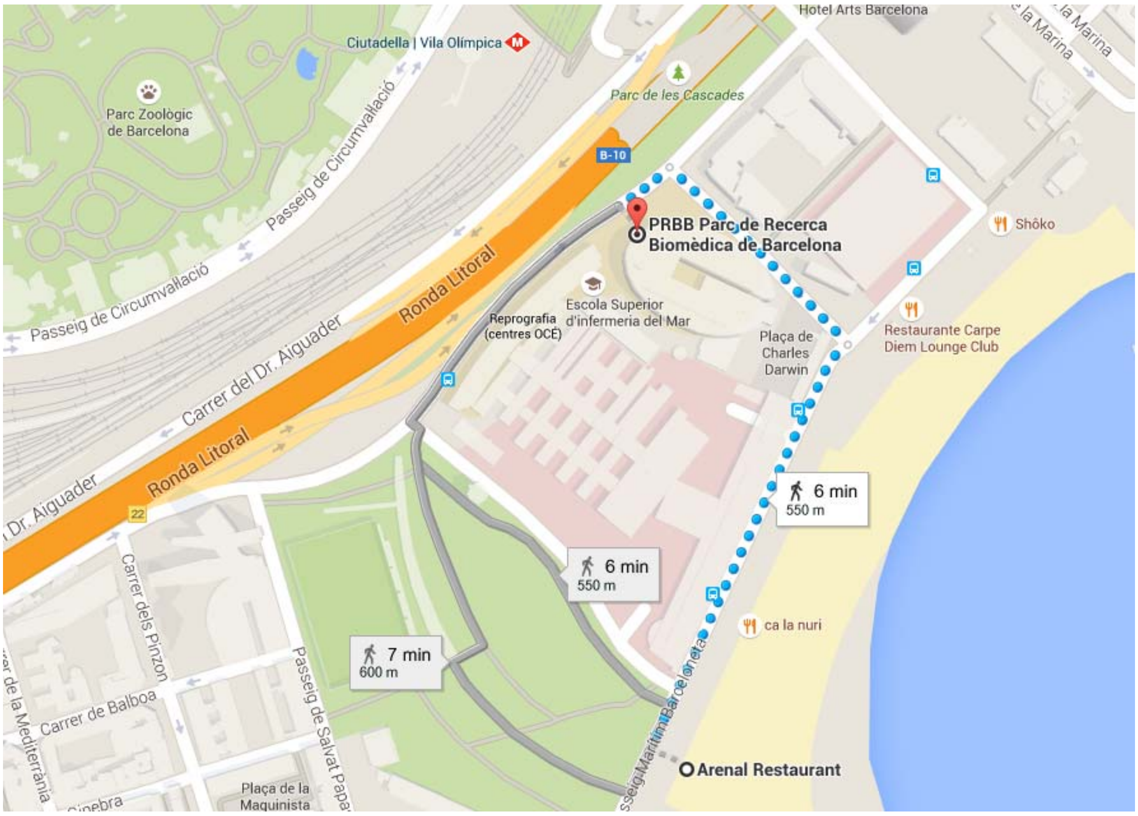


- Day 1, Monday June 15th, 2015-

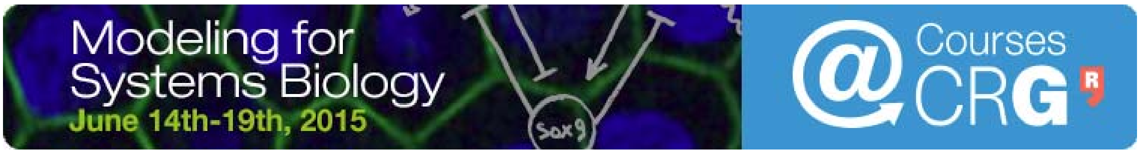
“Dynamical systems theory & networks”

Host: James Sharpe

Teacher: Marta Ibañes

Assistants: Jennifer Semple, Juan Jose Fraire and Tommaso Andreani

When	What	Topic	Where
09:00am – 09:30am	WELCOME	(BY JAMES SHARPE)	Room 468
09:30am – 10:30am	LECTURE	Models of gene regulation	
	Break		5th Floor Terrace
11:00am – 12:00am	PRACTICAL	Negative feedback	Room 468
12:00am – 1:00pm	LECTURE	Dynamical systems tools	
	Lunch		5th Floor Terrace
02:00pm – 03:00pm	PRACTICAL	Toggle switch	Room 468
03:00pm – 04:00pm	LECTURE	Analysis of small genetic circuits	
	Break		5th Floor Terrace
04:30pm – 05:30pm	PRACTICAL	Activator-repressor oscillator	Room 468
05:30pm – 06:00pm	DISCUSSION		



-Day 2, Tuesday June 16th, 2015-

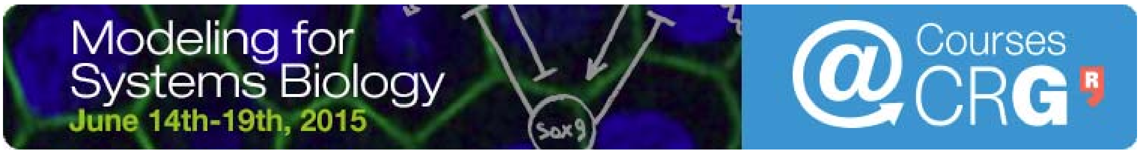
"Stochastic systems"

Host: Andreea Munteanu

Teacher: Jordi Garcia Ojalvo

Assistants: German Patterson, David Hayes and Dina Cramer

When	What	Topic	Where
09:00am – 10:00am	LECTURE	Evidences of noise in biochemical reactions	Room 468
	Break		5th Floor Terrace
10:30am – 11:30am	LECTURE	Modeling stochastic processes in cells	Room 468
11:30pm – 1:00pm	PRACTICAL	Adding noise to a deterministic model	
	Lunch		5th Floor Terrace
02:00pm – 03:00pm	LECTURE	Consequences of cellular noise	Room 468
	Break		5th Floor Terrace
03:30pm – 05:00pm	PRACTICAL	Controlling noise in stochastic simulations	Room 468
05:00pm – 05:30pm	DISCUSSION		



-Day 3, Wednesday June 17th, 2015-

"Multivariant and multidimensional data analysis"

Host: Andreea Munteanu

Teacher: Fernando Amat

Assistants: Ivica Slavkov, Natalia Bogatyreva and Cecilia Coimbra

When	What	Topic	Where
09:00am – 10:00am	LECTURE	Multivariate analysis and dimensionality reduction techniques	Room 468
	Break		5th Floor Terrace
10:30am – 11:30am	PRACTICAL	Dimensionality reduction techniques	Room 468
11:30pm – 1:00pm	LECTURE	Unsupervised pattern recognition methods	
	Lunch		PRBB Canteen
02:00pm – 03:00pm	PRACTICAL	Clustering methods	Room 468
03:00pm – 04:00pm	LECTURE	Supervised pattern recognition methods	
	Break		5th Floor Terrace
04:30pm – 05:30pm	PRACTICAL	Supervised learning techniques	Room 468
05:30pm – 06:00pm	DISCUSSION		
6.30pm	**Group Picture**		5th floor Terrace
07:00pm – 09:00pm	**Guided Tour Barcelona**		Casa Batlló

-Day 4, Thursday June 18th, 2015-

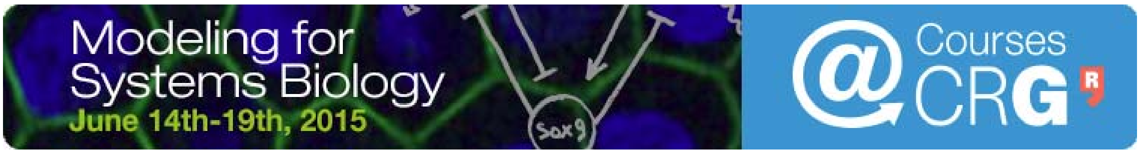
"Parameter inference, reverse engineering and optimization"

Host: James Sharpe

Teacher: Julio Rodríguez Banga

Assistants: Marco Musy and Thomas Pujol

When	What	Topic	Where
09:00am – 10:00am	LECTURE	Inference of static networks	Room 468
	Break		5th Floor Terrace
10:30am – 11:30am	PRACTICAL	Information-theoretic methods	Room 468
11:30pm – 1:00pm	LECTURE	Inference of dynamic models	
	Lunch		PRBB Canteen
02:00pm – 03:00pm	PRACTICAL	Parameter estimation in kinetic models	Room 468
03:00pm – 04:00pm	LECTURE	Optimal control and design of biosystems	
	Break		5th Floor Terrace
04:30pm – 05:30pm	PRACTICAL	Optimization examples in synthetic biology	Room 468
05:30pm – 06:00pm	DISCUSSION		



-Day 5, Friday June 19th, 2015-

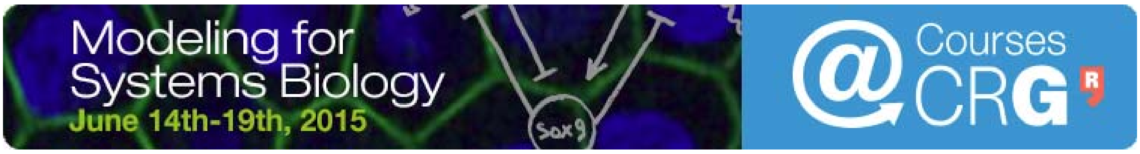
"Simulating tissue morphogenesis and signaling"

Host: James Sharpe

Teacher: Arthur Lander

Assistants: Alba Jiménez and Kai Dierkes

When	What	Topic	Where
09:00am – 10:00am	LECTURE	Basic concepts of spatial dynamics	Room 468
	Break		5th Floor Terrace
10:15am – 11:15am	PRACTICAL	Diffusion and reaction	Room 468
11:30pm – 12:30pm	LECTURE	Morphogen gradients	
	Lunch		5th Floor Terrace
02:00pm – 03:00pm	PRACTICAL	Robustness and noise	Room 468
04:00pm – 5:00pm	LECTURE	Advanced topics in morphogenesis	
	Break		5th Floor Terrace
04:30pm – 05:30pm	PRACTICAL	Gradient dynamics, self-organization and scaling	Room 468
05:30pm – 06:00pm	DISCUSSION & CLOSURE		
06:30pm	**Goodbye Drink**		5th Floor Terrace



Practical summer course:
Modeling for Systems Biology

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Barcelona

- Outlines lectures -

- Day 0, Sunday June 14th, 2015 -

"Basic mathematical concepts & Introduction to Matlab"

Instructors: Marco Musy, Andreea Munteanu & Xavier Diego

Overview

The objective of these introductory lectures is to familiarize the participants with the main concepts, keywords and tools that will be employed throughout the week. The topics covered are extremely broad, including fundamentals of linear algebra, defining and solving ordinary differential equations. Obviously, this broad introduction will be of a graphical and intuitive nature, minimizing the algebraic content, when possible. In addition, a short presentation of Matlab's main commands will provide the starting point for the practical sessions of the week.

Lecture Linear Algebra

Quantitative biology often aims at capturing the state of biological systems, e.g. of cells, in terms of sets of numbers, e.g. protein concentrations. Interpreting these lists of numbers as spatial coordinates, the different states of a system can be conceptualized as corresponding to distinct points within a space of suitable dimension, also referred to as state space. Linear algebra provides concepts and tools to describe and analyze the structure, the geometry, and the transformations of such abstract spaces. Within this lecture, we will introduce some of the important notions and techniques that will be used during the rest of this summer school.

Topics: State space; vector space; scalar vs vector; operations on vectors; orthogonality; basis and linear independence; linear transformations and matrices. Elements of statistics: revisiting the concepts of probability and types of distributions.

Lecture Ordinary Differential Equations

This lecture will define the main vocabulary associated to ordinary differential equations (ODEs), from their definition and necessity for modeling, to (conceptual) solving and subsequent graphical representation of the solutions. It will present an intuitive approach for transforming the information we can measure into a system of differential equations, and how to understand the output of such systems. Beyond and in contrast to ODEs, fundamental definitions on discrete systems and probability theory will be briefly mentioned.

Topics: Differential equation, ordinary vs partial; derivative & integral; analytic vs numerical; parameters & variables (dependent & independent); linearity vs nonlinearity; steady states, phase plane (portrait); eigenvalues. Deterministic vs stochastic; probability distributions.

Lecture Introduction to Matlab

This lecture introduces students to the scientific programming language MATLAB. Prior computer programming experience is not required.

The lectures begin with a presentation of variables within Matlab workspace like vectors, matrices, and arrays. Students are introduced to basic commands in MATLAB, as well as built-in functions that provide useful shortcuts.

Then we will focus on the differences between MATLAB scripts and MATLAB functions and describe when one method of programming organization might be preferable to the other.

The principles are illustrated through different examples and exercises that make it more interactive.

Because of its introductory nature, students who have prior programming experience may find these lectures to be essentially a review. For students without this experience, these lectures are a prerequisite to using MATLAB.

<u>Topics:</u> Variables in Matlab: vectors and matrices; defining functions and using m-filles; write and load data; control structures; data visualization.

- Day 1, Monday June 15th, 2015 -

"Dynamical systems theory, networks"

Teacher: Marta Ibañes

Overview:

One aim of Systems Biology is to understand the collective behavior of many interacting components in living organisms. These interactions occur at many different levels: between organisms, between cells and between molecular components inside cells. Mathematical and computational modeling of these interactions is a powerful tool to predict outcomes and provide understanding. In this first day of the course, we will focus on the process of gene regulation, which involves the interaction between molecular components. We will see how we can model it deterministically, considering continuous time dynamics and using molecular concentrations as variables. The basic concepts and tools for the analysis of such dynamics will be presented together with practical exercises.

Lecture: Models of gene regulation

Models based on reaction kinetics for the dynamics of gene regulation: Michaelis-Menten and Hill function; Separation of time scales; Feedback; Network motifs.

Practical: Negative feedback (whiteboard and laptop)

Comparison constitutive vs non-constitutive cases; Analysis of properties such as homeostasis.

Lecture: Dynamical system tools

Introduction to basic tools for the analysis of the dynamics of genetic circuits such as phase space, phase portrait, linear stability analysis, attractors, manifolds, bifurcations.

Practical: Toggle switch (whiteboard and laptop)

Bistability and hysteresis.

Lecture: Analysis of small genetic circuits

Brief overview of different genetic circuits: to analyse their properties by applying the tools from the previous lrecture. Genetic circuits excibiting oscillations and excitability.

Practical: Activator-repressor oscillator (whiteboard and laptop)

Phase portrait, period and amplitude.

- Day 2, Tuesday June 16th, 2015 -

“Stochastic systems”

Teacher: Jordi Garcia Ojalvo

Overview: Stochastic systems

Dynamic mathematical models in the form of ordinary differential equations approximate reasonably well the behavior of biochemical networks under many conditions. However, the underlying kinetics of cellular processes is fundamentally stochastic, as a result of the random occurrence of biochemical reactions in the cell. This randomness manifests itself in fluctuating, or “noisy”, levels of proteins and other biomolecules. Depending on the circuit of interest, this noise will affect not only quantitatively, but also qualitatively the operation of a circuit, resulting in some cases in behaviors that are not possible under a purely deterministic regime.

This part of the course focuses on the fundamental bases for describing noise in biochemical networks, starting from conceptual aspects (e.g., how to measure and detect noise) and fundamentals of chemical kinetics that allow for a quantitative description of random cellular processes, both from a continuous and a discrete perspective. Applications to prototypic circuits will reveal that stochastic noise can be detrimental –for instance, by deteriorating cellular decision processes– or advantageous –for example, by creating cellular diversity–.

Lecture: Evidences of noise in genetic circuits

Noise and heterogeneity; noise in monostable, bistable and excitable circuits. Birth-death process; chemical master equation; Poisson distribution. Sources of noise: white vs. colored noise.

Lecture: Modeling stochastic processes in cells

Brief overview of stochastic processes: Fokker-Planck equation, Langevin equation, additive vs. multiplicative noise. The stochastic simulation algorithm (SSA): computationally efficient variants of SSA; deterministic limit of the SSA; relation between the stochastic and deterministic approaches.

Practical: Adding noise to a deterministic biochemical circuit

From concentrations to molecule numbers; heterogeneity of a constitutively expressed gene; noise-induced switching in a bistable circuit; noise in a genetic oscillator.

Lecture: The effects of cellular noise

Controlling noise: global and local control; noise control at the circuit level. Effects of stochasticity: noise-induced transitions; noise-induced bistability; noise resistance of genetic oscillators; noise-induced stabilization of unstable states.

Practical: Controlling noise in stochastic simulations

Simulation of positive feedback regulation; controlling noise levels by balancing transcription and translation; controlling noise levels by tuning cell size; noise-induced bistability.

- Day 3, Wednesday June 17th, 2015 -

"*Multivariant and multidimensional data analysis*"

Teacher: Fernando Amat

Overview

The current trend in science, and systems biology in particular, is to acquire an increasing amount of data from different sources. For a human observer is very difficult to extract all the patterns and information contained in this raw data due to its size and the large number of variables involved (high dimensionality). The objective of the lectures on day 4 is to familiarize the students with the concepts involved in visualizing, analyzing, comparing and classifying multivariate signals (e.g. microarray expression data) in order to transform the data into meaningful representations where key insights can be obtained and explained. Each lecture will have a follow-up Matlab session with exercises drawn from the topics discussed in the lectures, where the students can apply the techniques to real-world datasets.

Lecture: Multivariate analysis and dimensionality reduction techniques

We will introduce the notation for multivariate analysis with different examples that will be used in throughout the day (in the lectures and the practical sessions) and discuss problems associated with high-dimensional signals such as the "curse of dimensionality" or data visualization. In this context, we will present various dimensionality reduction techniques, such as principal components analysis, multidimensional scaling, locally linear embedding or t-distributed stochastic neighbor embedding (t-SNE), to handle the complexity of high-dimensional feature spaces.

Topics: Curse of dimensionality, data visualization, model selection, dimensionality reduction, kernel methods.

Practical: Dimensionality reduction techniques

Principal component analysis; multidimensional scaling; locally linear embedding; t-SNE applied to micro-array data.

Lecture: Unsupervised pattern recognition methods

We will learn how the techniques of Lecture 7 fit into the paradigm of unsupervised learning. In particular, we will present different clustering techniques, such as k-means, spectral clustering and hierarchical clustering, in order to recognize patterns in the multivariate data when we do not have a label associated with it. We will also discuss different approaches to validate clustering results and to estimate the right number of clusters.

Topics: Clustering, K-means, hierarchical clustering, spectral clustering, GAP statistics, silhouette.

Practical: Clustering methods

K-means; hierarchical clustering, spectral clustering; GAP statistics applied to micro-array data.

Lecture: Supervised pattern recognition methods

We will learn how the techniques of Lecture 7 fit into the paradigm of supervised learning. In particular, we will present different classification and regression techniques, such as support vector machines and boosting trees, in order to recognize patterns in the multivariate data when we do have labels associated with it. We will also discuss different approaches to validate the trained model in order to avoid overfitting.

Topics: Training and test set, cross-validation, linear discriminant analysis, logistic regression, support vector machines, classification and regression trees, boosting.

Practical: Supervised Learning Techniques

Support vector machines; classification trees; boosting applied to fly behavior data.

- Day 4, Thursday June 18th, 2015 -

"*Parameter inference, reverse engineering*"

Teacher: Julio Rodríguez Banga

Overview

The interplay of mathematical modeling with experiments is one of the central elements in systems biology. The aim of *reverse engineering* is to infer, analyze and understand, through this interplay, the functional and regulatory mechanisms of biological systems. Reverse engineering is not exclusive of systems biology and has been studied in different areas, such as statistics, inverse problem theory, machine learning, nonlinear physics, (bio)chemical kinetics, control theory and optimization, among others. We will review the different perspectives and the main contributions from these fields, and their application to biological systems. We will make special emphasis on the possible pitfalls and challenges that can lead us to wrong results. In the practical sessions, we will illustrate, using examples of increasing complexity, the use of selected methods and tools to avoid such pitfalls.

Lecture: Inference of static networks

We will consider the problem of reverse engineering systems modeled as static interaction networks. We will present an overview of methods from three different perspectives: classical correlation, information theory and Bayesian inference.

Practical : Static network inference using information-theoretic methods

Mutual information; ARACNE; MIDER; examples with gene regulatory, metabolic and signalling networks.

Lecture: Inference of dynamic models

We will consider the reverse engineering of dynamic (kinetic) models of biological systems from time-series data, also known as the inverse problem in dynamic systems. These kinetic models typically consist of systems of nonlinear differential equations. We will discuss key concepts and issues which explain why these problems are so hard: multimodality, ill- posedness and ill-conditioning, identifiability, distinguishability, and over-fitting. We will present an overview of state of the art methods to handle these difficulties, including frequentist and Bayesian approaches.

Practical: Parameter estimation in kinetic models

Local and global optimization methods; identifiability analysis; over-fitting; cross-validation; examples with biochemical pathways of increasing complexity.

Lecture: Optimal control and design of biosystems

We now focus on the use of optimal control (optimization of dynamic systems with possible time-dependent decision variables) in biological systems, considering two classes of problems: (i) optimal dynamic experimental design, and (ii) (re-)design in metabolic engineering and synthetic biology.

Practical: Dynamic optimization examples in systems and synthetic biology

Basic optimal experimental design; metabolic engineering; design of synthetic oscillators and switches

- Day 5, Friday June 19th, 2015 -

"Simulating Tissue Morphogenesis and Signalling"

Teacher: Arthur Lander

Overview

Biology doesn't happen in a test tube – it plays out in space. The locations of molecules, cells, and tissues matter a great deal, yet are ignored by most modeling approaches. We will discuss how to extend the tools and insights of dynamical modeling into the spatial world. Lectures and practicals will focus both on developing an intuitive understanding of spatial phenomena, and on building the skills to create spatial models. Several models of pattern formation will be introduced and analyzed at different levels.

Lecture: Basic concepts of spatial dynamics

Compartment models, diffusion, Fick's equations, steady and non-steady solutions to PDE models, dimensionality, viscosity, tortuosity, diffusion with reaction, "decay lengths".

Practical: Diffusion and reaction

Fitting gradient shapes to models. Measuring transport *in vivo.*

Lecture: Morphogen gradients

Modeling the formation and shapes of morphogen gradients, taking into account realistic phenomena such as finite production regions, saturable receptors, non-receptor binding sites, and feedback regulation of receptor expression and/or function, and interacting diffusing species. Introduction to pre-steady state dynamics.

Practical: Robustness and noise

Sensitivity analysis. Robustness to parameter perturbations. Sources and influence of noise.

Lecture: Advanced topics in morphogenesis

Pre-steady state dynamics (transient phenomena in morphogen gradient formation). Interaction between gradient dynamics and dynamics of downstream phenomena (e.g. gene-regulatory networks). Self-organizing pattern (Turing patterns). Growing domains and scaling effects.

Practical: Gradient dynamics, self-organization and scaling

Writing down complex models. Simulating non- and pre-steady state behaviors.

Exploring Turing patterns.

- Teachers & Coordinators -

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