SCIENCES & BIOENGINEERING SCIENCES

The Research Group
Structural Biology Brussels

has the honor to invite you to the public defence of the PhD thesis of

Joel Roca Martínez

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:

Exploring the RNA Recognition Motif: A computational analysis of RRM-RNA recognition and the interplay between multiple RRM domains

Promotor:
Prof. dr. Wim Vranken

The defence will take place on
Tuesday, October 31, 2023 at 16h in auditorium D.2.01

The defence can also be followed through a live stream on Microsoft Teams.

Members of the jury

Prof. dr. Peter Tompa (VUB, chair)
Prof. dr. Sophie de Buyl (VUB, secretary)
Prof. dr. Joris Messens (VUB)
Prof. dr. Tom Lenaerts (VUB)
Prof. dr. Olga Kalinina (Saarbrücken University)
Prof. dr. Rachid Tahzima (Université de Liège)

Curriculum vitae

Joel Roca was born in Mequinensa in 1995, a small village in the northeast of Spain. He moved to Tarragona to study biochemistry and biotechnology in 2013, then to Barcelona for a Bioinformatics Master in 2017. After working one year in Valencia as bioinformatician, he moved back to academia and started his PhD at the VUB in 2019, in the context of the EU ITN project RNAct. During his PhD, he completed two stays abroad, in the University of Florence and in the Helmholtz Zentrum in Munich, where he learned more practical aspects of structural biology to complement with his computational studies.

Abstract of the PhD research

The RNA recognition motif (RRM) is the most prevalent RNA-binding protein domain in eukaryotes and is involved in most of RNA metabolism processes. Their RNA binding preferences have been investigated for almost two decades, but their RNA recognition code has remained elusive. In addition, RRMs are often accompanied by other RNA-binding domains to achieve higher specificities and affinities, but their interplay is not very well understood either. On such arrangements the inter-domain linker plays a key role, but its highly dynamic nature and predominant conformational ambiguity makes it challenging to study. The goal of this thesis is to help fill these gaps by providing novel insights on the RRM-RNA recognition preferences, explore the relative orientations of tandem RRMs, and help elucidate the role of the inter-connecting linker and proteins with a conformational ambiguous behaviour in general.

We gathered all the available structural information on experimental RRMs and RRM-RNA complexes to develop RRMScorer, a computational scoring method to estimate canonical RRM-RNA binding. Our tool was reliable across several experimental sets and test-cases, and proved particularly useful when identifying single mutations to modify the RRM's specificity. We then focused on tandem RRMs, where two RRM domains are adjacent, to investigate their relative domain orientation in multi-domain proteins using inter-domain vectors referenced to a stable secondary structure element. By extending our analysis to AlphaFold2 (AF2) predicted structures, we demonstrate that inter-domain RRM orientations seem to be constrained.

According to our analysis, and in agreement with current literature, the linker region plays an important role in regulating many aspects of the tandem RRM's interplay while sometimes participating directly on RNA binding. We highlighted the challenges that surround capturing the behavior of conformationally ambiguous regions, which are still not well-captured by AF2 and require a probabilistic approach rather than the classic ordered/disordered vision. By connecting these findings, this thesis helps to enhance our understanding of RRM-containing proteins and their dynamic behaviour, illuminating a field with potential applications in therapeutics and biotechnological settings.