Projecte de Treball Fi de Màster (TFM)

Màster en Modelització Computacional Atomística i Multiescala en Física, Química i Bioquímica
UB/UPC

Títol	**Disseny de polifàrmacs amb models generatius multitarget.**
Title	**Design of Polypharmacological Drugs with Multitarget Generative AI.**

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Departament	**Life Science**
Universitat	**Barcelona Supercomputing Center**
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Curs	**2023-24**

Summary[2]

Polypharmacology is dedicated to creating molecules targeting multiple disease pathways simultaneously. Generative AI models (GM) involve training models on extensive chemical databases to generate novel molecules with specific properties. The presented project aims to employ a multitarget GM workflow to design a polypharmacological drug. Leveraging the vast data collected during the COVID-19 pandemic and the comparatively straightforward nature of viruses, this project aims to utilize COVID-19 as its initial test case. Specifically, the project endeavors to simultaneously target both the MPRO and an RNA regulatory element of SARS-CoV-2. First, we will generate and select an optimal ensemble of RNA conformations for the RNA regulatory element using advanced molecular modeling techniques. Then, we will employ an in-house GM workflow that has demonstrated effectiveness in generating novel molecules with affinity for specific targets. This GM workflow will be utilized to generate molecules with affinity for both SARS-CoV-2 MPRO and the selected SARS-CoV-2 RNA regulatory element. Finally, a set of candidate molecules will be chosen for further in-depth analysis.

Keywords[3] Polypharmacology, Generative models, Drug Discovery, Molecular Modeling, SARS-CoV-2, RNA, MPRO

Breu descripció del projecte[4]

Polypharmacology aims to design molecules capable of simultaneously targeting multiple disease pathways, providing several advantages over traditional single-target molecules [1]. For instance, a molecule affecting multiple targets is presumably more effective, as it exhibits cumulative efficacy across all individual targets. This is particularly relevant in complex diseases such as cancer [2]. However, the inherent promiscuity of such molecules presents various challenges, including the need to prevent binding to antitargets, which could lead to off-target adverse effects.

Within Drug Discovery, Generative AI models (GM) involve models that undergo training using extensive databases of chemical structures and properties to learn patterns and relationships within them. Following this training, these models can generate new molecules, potentially with specific properties such as enhanced efficacy toward a particular target [3].

In this project, we aim to leverage a multitarget GM workflow to design a polypharmacological drug capable of simultaneously targeting multiple targets. As a test case, we aim to develop a polypharmacological drug tailored to COVID-19 by targeting both the MPRO and an RNA regulatory element of SARS-CoV-2. The selection of COVID-19 as the initial subject for our study is based on the straightforward nature of viruses and the vast amount of structural and inhibitory data available for SARS-CoV-2 after the pandemic. To begin with, we will generate and select an optimal ensemble of RNA conformations for the specified RNA regulatory elements. To do so, we will employ several molecular modeling approaches, including molecular dynamics simulations and an in-house all-atom Monte Carlo software named PELE, designed for simulating the docking of molecules to a given target [4]. Subsequently, we will utilize an in-house GM workflow that has already demonstrated its effectiveness in generating novel molecules with affinity towards specific targets [5]. This GM workflow will be applied to generate molecules with affinity for both SARS-CoV-2 MPRO and the chosen SARS-CoV-2 RNA element. Throughout this stage, we will utilize Glide, a well-established rigid docking software, in conjunction with various chemoinformatics metrics such as molecular similarity. Ultimately, we will select a final set of candidate molecules for further analysis.

[1] Kabir, A., & Muth, A. (2022). Pharmacological research, 176, 106055.
[2] Antolin, A. A., Workman, P., Mestres, J., & Al-Lazikani, B. (2016). Current pharmaceutical design, 22(46), 6935–6945.
[3] Ł. Maziarka, et al. J. Cheminformatics 12, 2 (2020).
[4] K. W. Borrelli, A. Vitalis, R. Alcantara, V. Guallar. J. Chem. Theory Comput. 1, 1304–1311 (2005).
[5] I Filella-Merce, et al. arXiv preprint arXiv:2305.06334

[1]Si el director no és un professor de la UB o e la UPC, caldrà assignar un tutor del TFM que designarà la Comissió Coordinadora del Màster.
[2]Aquest "summary" és el que apareixerà a la futura pàgina web dedicada al TFM. Procureu que sigui concís i entenedor (máx. 10 línies).
[3]Aquestes "keywords" no només són les que apareixeran al web sinó que ajudaran la Comissió Coordinadora del Màster a **assignar el projecte a un àrea concreta**.
[4]Procureu ser concisos però proporcioneu prou informació per tal que l'estudiant i la Comissió Coordinadora del Màster es facin una idea prou acurada de en què consistirà el treball. **Indiqueu 3-6 publicacions de referència en la descripció del projecte per donar una idea dels fonament, metodologia, objectius, etc.**

Competències addicionals[5] (opcional)

Tasques a desenvolupar[6]		Cronograma (setmanes)																	
Tasca	Descripció	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18
T01	Bibliographie (aprox. 75 h)	X	X	X											X	X			
T02	Data Gathering (aprox. 50h)	X	X	X															
T03	Preliminar Molecular Modeling tests (aprox. 75h)		X	X	X	X													
T04	RNA Ensemble Generation and Selection (MD and PELE) (aprox. 75h)				X	X	X	X											
T05	Multitarget Generative Modeling (aprox. 100h)							X	X	X	X	X					X	X	X
T06	Validation with Molecular Modeling approaches (aprox. 50h)											X	X	X					
T07	Manuscrit writting													X	X	X			
T08																			
T09																			
T10																			

Observacions i comentaris
Per a la realització del treball pròpiament dit es preveu una dedicació d'unes quatre hores diàries durant cinc dies a la setmana, amb la opció de modificació de l'horari per poder adaptar-se millor a l'horari acadèmic de l'estudiant.

Victor Guallar - DNI 4374250J (SIG)

Digitally signed by Victor Guallar - DNI 4374250J (SIG)
Date: 2024.02.05 15:41:44 +01'00'

Signatura (el director del TFM)

Signatura (el tutor del TFM, si s'escau)

[4] Enumereu breument qualsevol competència addicional a les competències genèriques enumerades en el Pla Docent del TFM (opcional).
[5] Feu servir només les línies que calgui. Escolliu-les de manera que donin una idea aproximada de en què consistirà el treball i la seva distribució temporal.