Large scale simulations to understand the evolution of COVID-19 and design effective therapies

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The current COVID-19 pandemic is an unprecedented health and economic emergency. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has already caused more than two million deaths all over the world. The unprecedented response of the scientific community allowed the development and approval in less than one year of a number of vaccines and several clinical trials are underway to test antiviral drugs and therapeutic antibodies. However, no effective therapy has emerged yet, while the rapid pace of viral mutation as well as the appearance of more infectious variants are a great concern. Indeed, the mutations might make it more infectious and cause resistance to vaccines and to the antiviral drugs being developed. A possible strategy to counter this serious threat is to develop combined therapies targeting different viral genes at the same time.
Since the beginning of the pandemic, my group has used large-scale computer simulations and free energy calculations combined with experiments to address various relevant questions and design new drugs. In particular, we studied the effects of the prevalent genetic variants on the conformational changes of the spike of COVID-19 to understand their effect on infectiousness.[1] We are also using computer aided drug discovery approaches to design new peptides that block the spike-receptor interactions and small molecules that bind non-structural protein 1, an important yet difficult-to-target viral protein. The designed peptides and ligands are currently being experimentally validated in the hope of using them in combined anti-COVID-19 therapies.

1. Ilmjärv, S; Abdul, F; Acosta-Gutiérrez, S; Estarellas, C; Galdadas, I; Casimir, M; Alessandrini, M; Gervasio, FL; Krause KH Epidemiologically most successful SARS-CoV-2 variant: concurrent mutations in RNA-dependent RNA polymerase and spike protein doi: https://doi.org/10.1101/2020.08.23.20180281

Bio

Francesco Luigi Gervasio (FLG) is currently professor of Chemistry, professor of Structural and Molecular Biology at University College London and full professor of pharmaceutical sciences at University of Geneva.
FLG got his PhD in Chemistry from University of Firenze, Italy at the end of 2001. He then joined the group of Prof. Parrinello at ETH Zurich first as a postdoc and the as Oberassistent (2002-2009).
At ETHZ he focused on the time-scale problem of molecular dynamics simulations and the calculation of free energies associated to complex biological events, contributing to the development of methods such as **Metadynamics, Parallel-Tempering Metadynamics (PT-MetaD) and the path-like collective variables method (PCV)**.

In 2009 he joined the Spanish National Cancer Research Center in Madrid- Spain as the leader of the Biophysics group. There he continued the development of computational methods, including a method to predict binding kinetics (PRL 2013). He also combined simulations with NMR experiments to better understand the mode of action of cancer-causing mutations and allosteric drugs.

In 2013 he joined **University College London as full professor**. Research highlights from this period include the development of a method to predict previously unknown **cryptic binding pocket,** which was used to design allosteric modulators of **FGFR** (Cancer Cell, JACS 2016); the development of a computational approach combining evolutionary principles with a physics-based coarse-grained model to predict protein structure and dynamics (PNAS 2015); the clarification of an unexpected moonlighting activity by Glutamine Synthetase (**Nature** 2018). In 2020 FLG also joined the **University of Geneva** as full professor of Pharmaceutical Sciences (while retaining his chairs at UCL). The current research focus of the group is the development of simulations-based methods to understand the regulation of drug targets and design new therapeutic agents. In this context, the group used enhanced sampling simulations to clarify the activation mechanism of the glucagon receptor (PNAS 2020).

FLG is the **editor in chief** of Frontiers in Biological Modeling and Simulation; **editor** of Nature's group Scientific Reports and a member of the **Faculty of 1000**.

He has an **h-index of 46**, more than 8400 citations (Google Scholar) and more than 110 peer-reviewed publications, including several in leading journals such as Nature, Cancer Cell, Chem. Rev., Acc. Chem. Res., Rep. Prog. Phys, Sci. Adv., Nat. Comm., Proc. Nat. Acad. USA, J. Am. Chem. Soc., Angew. Chem. and Phys. Rev. Lett. FLG organized several international conferences, workshops and tutorials on allosteric regulation and biomolecular simulations. His research group is supported by the EPSRC, EU H2020 (Marie Curie and Human Brain EU flagship project). He actively collaborates with AstraZeneca, GSK, EVOTEC, Heptares and UCB and he is a consultant for UCB and EVOTEC.