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Progress in Physics (74)

What physics in Switzerland is doing to meet the COVID-19 challenge

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Selected International Studies

Progress in Physics (74)

The corona crisis hit the world completely unprepared, and this although one could have expected it. The unanimous worldwide political measures of reducing all social contacts and economic processes on the one hand, and of raising gigantic funds on the other hand, are methods without any sustainability and reflect the helplessness of public decision makers. Since pandemics are also to be expected in the future, science is challenged in three ways: in explaining the causes, in providing real-time measurement methods that can be applied universally and without social acceptance problems, and in physically proved modelling of the propagation of the pandemic. Therefore many institutes but also big research facilities have started initiatives to support involved health institutions with the necessary scientific and technical expertise of physicists.
The first article summarises a selection of running activities at PSI in cooperation with Swiss universities. Following this one we mention some research studies performed by and/or coordinated at large international research institutions, The random selection should underline the broad scientific field that physicists have to cover in cooperation with colleagues from other disciplines in order to understand the pandemic. https://www.interactions.org/interactions-members-fight-covid-19 and https://naturalsciences.ch/organisations/chipp/activities/covid_19_task_force .

BB, HPB

What physics in Switzerland is doing to meet the COVID-19 challenge

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The COVID-19 pandemic is redefining the political and economic landscape of the world and also challenges physicists to contribute to its resolution. We describe here how as in physics, the identification, measurement and management of key features and variables allows progress towards a solution of the problem presented. The features and variables range from the structures of the implicated proteins through the lung damage caused by the disease to the infection rates at the core of the epidemiology of the pandemic. The problems to which solutions are needed include that of low-cost and reliable testing for both the virus itself as well as antibodies, the development of vaccines and other pharmacological countermeasures, medical imaging, and optimal timing of control measures imposed on the general population. It should come as no surprise to the general readership of this journal that physical scientists in Switzerland are contributing on all of these fronts, and the purpose of this article is to provide an overview of activities.

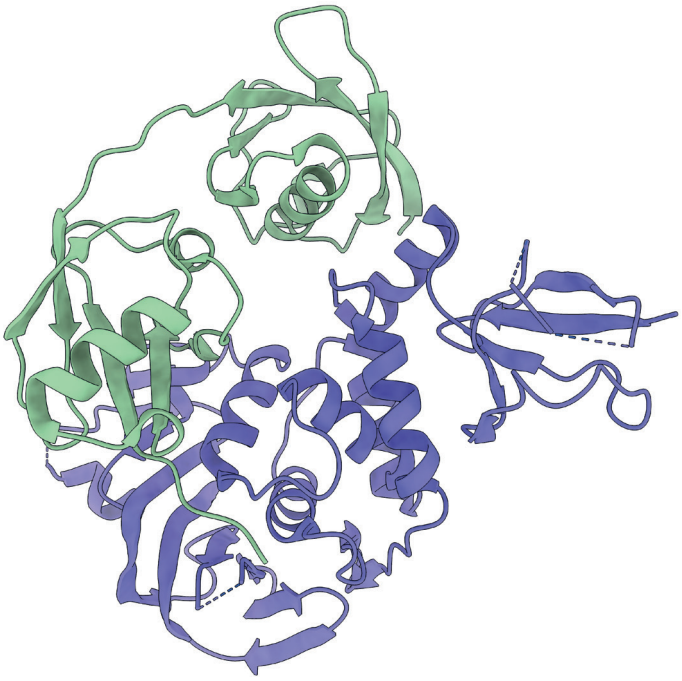

Fig. 1: Crystal structure of SARS-CoV-2 papain-like protease PLpro (violet) in complex with ubiquitin-like protein ISG15 (green) presented as cartoon model (PDB ID 6YVA).

We start with the underpinning molecular biology, where the reproduction of the virus in mammalian cells is an elaborately choreographed sequence of protein interactions, whose success and kinetics depend on structural matches during docking events. For this reason, determining the

atomic-level structure of the relevant proteins when docked and released opens the door to fundamental understanding. In addition, candidate drug molecules can be introduced to frustrate docking. A key probe here is X-ray diffraction, where atomic positions, for both the proteins as well as drug molecules, can be determined with exquisite precision. In response to the current pandemic, the Swiss Light Source of the Paul Scherrer Institute has already contributed several new COVID-19-related structures to the Protein Data Base which is the standard repository. Among them is the crystal structure (Fig. 1) of SARS-CoV-2 papain-like protease PLpro in complex with ubiquitin-like protein ISG15 from the Dikic's group at the Goethe University in Frankfurt am Main, Germany [1]. Required for the assembly of new viral particles, PLpro represents an important drug target to block the virus spread within human cells.

X-rays are useful not just for imaging atoms via diffraction, but are also a powerful tool for tomographic microscopy of biomedical samples. A particular challenge though is to go well beyond clinical routines, and to perform high-sensitivity tomographic (3D) imaging at the micro- and nanoscale. In a recent article [2] published by the TOMCAT team lead by Prof. Marco Stampanoni from ETHZ and PSI, multi-scale tomographic microscopy has been used to generate a high-precision map of the inner structure of an entire rat lung, as shown in Fig. 2. This imaging technique will allow detecting COVID19-induced damages to the alveolar structure and will provide a quantitative assessment of its impact on pulmonary performance.

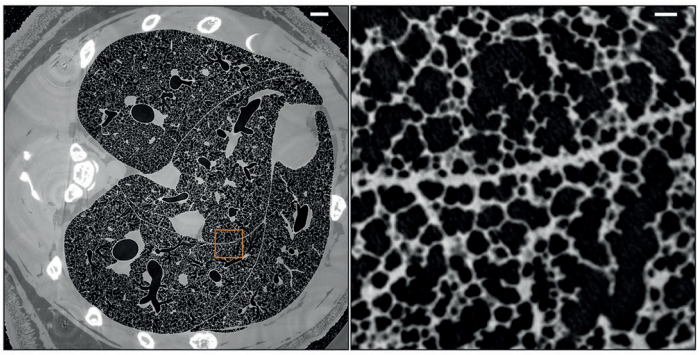

Fig. 2: Left: A 20 × 20 mm² horizontal slice through a rat lung under immediate post-mortem conditions. The full volume contains the entire pulmonary structure from the trachea down to the parenchyma in a single dataset. The isotropic voxel size is 2.5 µm³, which allows to clearly distinguish single alveoli, as shown on the right panel. Scale bars: 1 mm (left), 100 µm (right). Full dataset available at https://doi.org/10.16907/7eb141d3-11f1-47a6-9d0e-76f8832ed1b2 .

Let us now turn to epidemiology and economics. The systems of equations characterizing population dynamics or the evolution of epidemics are very familiar to physicists, and indeed many epidemiologists started their careers by studying mathematics and physics. Out of the many parameters that enter epidemiological evolution equations, a key quantity, the reproduction number *R*, is often referred to in the media. It captures the average number of additional infections that each infected person induces.

The value of *R* is affected by the boundary conditions implemented by policies. The number *R* has to be determined from fitting observables such as the number of reported cases, hospitalizations, or deaths to a given epidemiological model. Theorists at PSI are exploring how the acquisition of different data, namely the prevalence of asymptomatic but infectious persons in a random sample or specific subgroups of the population, may help to measure the value of *R* more rapidly and/or more reliably.

In the absence of a vaccine or a cure, two strategies have been used to limit the scope of a pandemic such as the one that we are currently facing with COVID-19. One strategy consists in imposing socio-economic restrictions, as were put in place in Switzerland from March until May of 2020. What is accomplished here is a tuning of *R* from a dangerous value well above unity (estimated to be 3 for a typical developed country with no social distancing or mask regime), to a value which is hoped to lie below unity. Because of their severe economic consequences, such lock-downs must almost inevitably end before the virus has completely disappeared.

If relaxed too quickly, *R* can grow back to a value above unity, entailing a "second wave". The "management" of the pandemic thus reduces to managing *R* in such a way that no waves of infection numbers become too large to challenge the capacity of the health care system to cope with the fraction of infected people with severe symptoms. The interested reader can visit www.covidsim.org (created in a collaboration between Imperial College and a company co-founded by one of the authors of this article) to play the policymaker who modulates disease transmission rates over time in an effort to minimize mortality and prevent overloading of hospitals.

Another strategy, which is effective if infection numbers are sufficiently low, consists in tracking transmission pathways and isolating the infected people detected via contact tracing. This has been done successfully in South Korea and could also be a model for countries such as Switzerland where prevalence has been sufficiently reduced by physical distancing. Unfortunately, this approach requires symptomatic individuals to already have emerged, which delays the response to sudden growths in prevalence.

The authors of this contribution have produced a manuscript [3] which details how sampling the population or specific subgroups for active virus could function as an efficient "thermometer" with a shorter delay time than standard approaches. This allows to regulate physical distancing measures during the lengthy lead time until a vaccine is produced in sufficient quantity to administer to an entire population. A shorter delay time, will allow to react more rapidly if the reproduction number happens to increase relatively suddenly to a higher value upon a release of restrictive measures. This in turn reduces the increase of the prevalence and the ensuing health damage, including the death rate. To illustrate the economic benefit of shortening the delay time, let us estimate the economic cost of detecting a jump of *R* to a value 1.3 with an extra delay of 4 days (during which the prevalence increases by a factor of *R*). This undoes a reduction by 30 % of the case numbers that had been achieved over about 3 days during the lock-down. The latter has been estimated to amount to about 1.5 billion CHF in lost economic value generation. Thus gaining even just a few days

in measuring the value of *R* may have a large effect, both for public health and for the economy.

In summary, physicists in Switzerland are making various important contributions to meet the challenge of COVID-19. In particular, the Swiss Light Source is contributing crucial structural information on length scales from centimeters to Ångstroms, while the type of thinking about time-dependent collective phenomena that physicists have developed over centuries is producing useful insights into epidemiology and pandemic management.

[1] D. Shin et al., To be published, http://doi.org/10.21203/rs.3.rs-27134/v1
[2] E. Borisova et al., Histochemistry and Cell Biology (2020), https://link.springer.com/article/10.1007/s00418-020-01868-8
[3] Using random testing to manage a safe exit from the COVID-19 lockdown. M. Müller, P. M. Derlet, Ch. Mudry, and G. Aeppli, *arXiv:2004.04614*.

Selected International Studies

1 Argonne National Laboratory

New drug target found for COVID-19 *(March 20, 2020)*

Scientists discover critical protein that lets virus hide from immune system. A new potential drug target has been identified in SARS CoV-2 — the virus that causes COVID-19 — by scientists who say multiple drugs will be needed to treat the pandemic. Scientists from Northwestern University Feinberg School of Medicine have mapped the atomic structure of two critical proteins in a complex, nsp10/16. These proteins modify the genetic material of the virus to make it look more like the host (human) cell RNA. This allows the virus to hide from the cells, giving it time to multiply. If a drug can be developed to inhibit nsp10/nsp16, the immune system should be able to detect the virus and eradicate it faster. (https://www.anl.gov/article/new-drug-target-found-for-covid19en)

2 Brookhaven National Laboratory

Researchers Working on Computational Models to Design Ways to Treat COVID-19 *(April 6, 2020)*

Project will sift through 1 billion drug-like molecules and 60 sites on virus to find most promising options for targeted drug development. A team of Stony Brook University (SBU) researchers is working on computer models that could help speed the discovery of drugs to combat the novel coronavirus responsible for COVID-19. They are doing this work in collaboration with scientists at the U.S. Department of Energy's (DOE) Brookhaven National Laboratory and Argonne National Laboratory, and will be leveraging those laboratories' computational resources and expertise. The researchers are working on models to better understand how the "spike" protein on the surface of the COVID-19 virus interacts with the cells it infects. (https://www.bnl.gov/newsroom/news.php?a=117161)

3 CERN

CERN established the ***CERN against COVID-19*** task force to collect and coordinate ideas and contributions from the CERN community of over 18 000 people worldwide. These initiatives draw on scientific and technical expertise and facilities at CERN, in the Member State countries and beyond, and in close contact with the medical community and the WHO.

These include the high-energy physics community ventilator, **HEV** (https://arxiv.org/pdf/2004.00534.pdf), the **Mechanical Ventilator Milano**, MVM (https://arxiv.org/abs/2003.10405) project spearheaded by the INFN in Italy and involving physicists from around the world, and **Openbreath** (https://www.openbreath.it/en/) to develop and produce scalable low-cost lung ventilators. The designs will be published using the CERN Open Hardware License, so that they can be reproduced wherever there is a need and freely adapted to comply with local regulatory frameworks.
CERN is the hub of a vast global computing resource, the Worldwide LHC Computing Grid, WLCG, and is also home to the CERN openlab collaboration with key players in the IT industry. This represents a considerable potential resource for fighting the pandemic, with potential applications ranging from the support of therapy and vaccine research, to the deployment of the data-sharing platform Zenodo, and epidemic modelling.

4 GSI Darmstadt

In order to develop vaccines, inactivated viruses are needed with as little damage to the virus' structure as possible. In past years, the inactivation of viruses for vaccine development has been carried out with gamma radiation. In a new project at GSI influenza and SARS-CoV-2 viruses are irradiated with high-energy heavy ions. Energetic ions are able to inactivate the virus by inducing breaks in the viral RNA with only a few passages in the envelope, thus minimizing membrane damage. The resulting viruses will then be examined at the HZI in Braunschweig for their ability to promote the formation of virus-binding and neutralizing antibodies after vaccination.
Pneumonia caused by SARS-CoV-2 may be treated with low-dose radiation. The anti-inflammatory effects in the lung are studied and compared in cases where a low-dose X-ray radiation is applied or an increased radon activity is administered.
Polymer foils are irradiated with individual ions for chemical etching to create single nanopores whose geometry and diameter can be adjusted very precisely. The nanopores are specifically functionalized to monitor the transport of specific particles, molecules or even viruses, which opens opportunities the detection of viruses such as SARS-CoV-2.
https://www.gsi.de/en/start/news/details/2020/04/16/gsi_fair_forschung_unterstuetzt_den_kampf_gegen_corona0.htm