How To Make the Most of Future Supercomputing Resources

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COMPUTER SIMULATIONS STARTING FROM THE 1950s



ENIAC was able to carry out ~10⁴ operations/second

COMPUTER SIMULATIONS TODAY



ENIAC was able to carry out ~ 10^4 operations/second. Today, the leading supercomputers do close to 10^{18} operations/second.



REACHING PRE-EXASCALE COMPUTING LUMI STARTING TO OPERATE IN 2021 PERFORMANCE ~200 PETAFLOP/S (2 x 10¹⁷) https://datacenter.csc.fi/wp/about-eurohpc/



TIMELY SAMPLE: SARS-COV-2 & ITS MAIN PROTEASE5(3CLPRO)

16.000

18.000



After viral entry, an enzyme known as the main protease of SARS-COV-2 is needed for its replication. If the function of main protease is blocked, the replication of the virus is inhibited.

22.000

24.000

26.000

28,000

20.000



TIMELY SAMPLE: SARS-COV-2 & ITS MAIN PROTEASE



- Main protease has no human analogue, so it is an ideal antiviral drug target
- How to block the main protease?
- The enzyme's active form is a dimer, therefore block its dimerization
- CSC's COVID-19 project work in progress – about
 0.5 ms atomistic simulations in a month

S. Kaptan, M. Girych, G. Enkavi, W. Kulig, T. Rog, V. Sharma, IV (2020)

DIMERIZATION OF HOMODIMERIC CLASS I CYTOKINERECEPTORS & DISEASE ("easy")



- If these receptors associated with Janus kinases are too active, the outcome can be disease, such as leukemia
- Typical cause are mutations, but the mechanism of action?
- Experiments & simulations showed that the mechanism of activation is the dimerization of two related monomer proteins
- Certain mutations induce dimerization without cytokine binding

TACHYCARDIA – BETA BLOCKERS AND LIPIDS8CONTROL THE BEATING OF THE HEART ("harder")

β.-adrenergio

The activation of receptors such as β_2 AR that control the heart beating takes place on time scales in the range of milliseconds.

However, until now the simulations have reached 10-100 microseconds.



CHOLESTEROL MODULATES β₂AR





- Cholesterol binds allosterically to β₂AR.
- Cholesterol modulates its activation.
- Full activation cycle remains unclear: Computing resources should increase by a factor of ~10

DRY EYE SYNDROME – DES ("tough")





Tear Fluid Lipid Layer (TFLL): ~20-100 nm thick

10

- One of the most common ophthalmological diseases
- Typically caused by excessive evaporation of tear fluid from the ocular surface
- Current eye drop treatments help only a couple of hours – some key content is missing
- Lipidomics data show that DES patients have reduced wax ester profiles in the tear fluid lipid layer

ATOMISTIC SIMULATIONS FOR WAX ESTER LAYERS AT FIXED SURFACE PRESSURE



- Wax esters reduce water evaporation significantly
- Surprisingly, wax esters are not included in tear drops
- How about multi-component tear fluid lipids layers under blinking?



HOW IMPAIRMENT OF INSULIN RECEPTOR ACTIVATION LEADS TO TYPE 2 DIABETES ("tough")







dependent half-maps

Structure of the active-state insulin receptor fitted to the cryo-EM density map

However, activation process of the insulin receptor?





REACHING PRE-EXASCALE COMPUTING LUMI (FINLAND) STARTING TO OPERATE IN 2020-2021 PERFORMANCE ~200 PETAFLOP/S (2 x 10¹⁷) https://datacenter.csc.fi/wp/about-eurohpc/



SISU (decommissioned) + TAITO (decommissioned)

1.7 petaflop/s + 0.5 petaflop/s

PUHTI & PUHTI-AI & MAHTI

1.8 & 2.7 & 7.5 petaflop/s

INCREASES COMPUTING CAPACITY BY A FACTOR OF ABOUT **5-6**

LUMI & 20% share for Finland

200 petaflop/s & 40 petaflop/s

INCREASES COMPUTING CAPACITY BY A FACTOR OF ABOUT **18**

ALTOGETHER, THE TOTAL INCREASE IN COMPUTING POWER IS ABOUT A FACTOR OF **20**, COMPARED TO THE SITUATION IN JANUARY **2019** 15

With previous supercomputer acquisitions, during the first ~2 years, the new supercomputer has been idle for a major fraction of its up time

Now we get 20 times more capacity, compared to a factor of 5 in previous acquisitions

Does this imply that during the first years of the operational time, the new supercomputers would be idle 80% (doing nothing)?

What we need now is a change of mindset

Please figure out new research questions that require >10 times more HPC capacity – problems that you did not even dare to approach before