Case Study Template 2

Please complete 3 short case studies (max. 2 pages each). These case studies can be updates of the ones that have already been submitted (if so please note this in the case study title) or new case studies that have been developed in the current reporting period.

1. Title of Case Study:

Engineering bacteriophages for treating antimicrobial resistance using all-atom models of entire viruses

2. Grant Reference Number: EP/L000253/1

3. One sentence summary: Development of an atomistic model of the entire PCV2 virus using a molecular dynamics simulation that has allowed us to model the structure and dynamics of the PCV2 virus test system over a microseconds timescale.

4. One paragraph summary: The goal of this project was to study an atomistic model of the entire PCV2 virus using molecular dynamics simulation. The developed model has been used to understand how alterations to the structure of the virus enhance its potential AMR (antimicrobial resistance) properties as phage therapy agents.

5. Key outputs in bullet points:

- Formulation of recommendations for applying the approach to larger viruses for effective phage therapy method developments.

- Collaboration with Odessa University (Ukraine), Centro Nacional de Biotecnologia (Spain).

- Training of PhD students.

6. Main body text

State-of-the-art computers can model very large biomolecular systems (e.g. organelles, cellular membranes, entire viruses) at atomistic resolution using highly efficient supercomputers and complementary numerical methods ('Molecular Dynamics' (MD)) that can simulate molecular systems of millions of atoms in size; and knowledge of the average 3d structural coordinates for almost all atoms in the system derived from high resolution experimental techniques, e.g. X-ray crystallography and cryo-electron microscopy. All-atom MD computer models can provide information about, and unique insights into, complex biomolecular systems which it is impossible to obtain by any other means; e.g., the reconstruction of the parts of the molecular system that cannot be revealed experimentally (typically flexible or variable parts of the structure), and an understanding of dynamics at physiological temperature. Simulation of viruses is most realistic because, in contrast to other large biomolecular systems, viruses are self-contained biological units, which exist in isolation from the rest of the organism (although they cannot reproduce in isolation). Computer models of cellular organelles, for example, necessarily consider only part of the system that interacts with the rest of the cell via complicated, poorly understood mechanisms

making comparison with the experimental results difficult. For viruses, interaction with aqueous solution is the only external force that defines the structure and dynamics and modelling of water is well developed in MD. The main difficulty in computer modelling of entire viruses is the number of atoms in the model, which is very large (at the edge of feasibility of such simulations). This is because the surrounding water should be included in the system explicitly as water molecules, (not as a continuum), and the number of water molecules can reach 95% of the number of atoms in the whole system. It has been recognised that the water surrounding biomolecules plays the major role in controlling the dynamics, emphasising certain motions whilst restricting others.

Antimicrobial resistance (AMR) is a growing problem for many bacterial infections, including those produced by E. coli. For E. coli, a well-studied phage is the (+)ssRNA phage MS2. Its genome of 3569 bp and a small icosahedral capsid (~27nm in diameter) makes it a suitable candidate for all-atom MD simulations. MS2 has been used as a carrier for drug molecules and as such could be used in non-conventional phage therapy to tackle AMR. MS2 is not the best candidate for phage therapy, but it has all relevant properties, is well studied and relatively small. We will use it as a proof-of-concept system to develop methodologies which can be applied to other phages.

The goal of this project was to develop an atomistic model of the entire MS2 virus. The developed model can be used to understand how alterations to the genome enhance their potential AMR properties as phage therapy agents. Packaging the genome inside the capsid problem will also need to be considered. The genome structure is more difficult to measure experimentally, in contrast to the capsid. Even though significant work has been done, e.g., unconventional approaches will be needed.

ARCHER resources have been used for classical MD simulations of a very large biological system where all atoms of the system were included. We have completed the simulations of a different virus, PCV2, which is smaller than the target virus MS2. Our current work concentrates on MS2.

7. Names of key academics and any collaborators:

- **Prof. Makoto Taiji group (K-computer, MDGRAPE), Laboratory for Computational Molecular Design, Computational Biology Research Core, RIKEN Quantitative Biology Center (QBiC), Kobe, Japan.**
- **Prof. Reza Khayat group, City College of New York, United States.**
- **Dr Michael Stich, Aston Univeristy.**

8. Sources of significant sponsorship (if applicable):

(Amount, sponsoring organisation, date)

9. Who should we contact for more information?

Email: D.Nerukh@aston.ac.uk Phone number: +44 (0)121 204 3533

10. Please indicate if you would like this case study to be included on the Consortium's ARCHER web-page.

Yes