5-2　理論・計算分子科学研究領域の評価

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Report on first visit to IMS, 1–4 October 2024

1. Scientific discussions with members of the IMS faculty

Prof. Hiroshi Yamamoto

I had a very interesting discussion with Prof. Yamamoto about his work on chirality and the CISS (chirality induced spin selectivity) effect, in which he showed me the results of his experiment revealing giant spin polarisation in a chiral superconductor. Prof. Yamamoto was one of the first to become interested in the CISS effect as a result of a visit to IMS by Ron Naaman, and the experiments he has since done on it are quite remarkable. He has found a spin polarisation of around 80% in the chiral superconducting device he has fabricated, which is comparable to the spin polarisation found in earlier work on photoelectron currents through DNA. Both effects are too large to be explained by any simple theory so a great deal of theoretical work is now being done to try to understand them. These experiments performed at IMS have therefore made a truly significant contribution to an exciting new field.

Prof. Shinji Saito

I first met Prof. Saito when he visited Oxford around five years ago, and I am of course well aware of his work as an Editor for the Journal of Chemical Physics (JCP), where he has published a number of very fine papers. It was therefore a pleasure to meet him again and to hear about his recent work on dynamic phenomena in condensed phase systems. He described how he has constructed an accurate Frenkel exciton model for the photosynthetic light harvesting complex LHCII and then presented a wonderfully detailed analysis of hydrogen bond dynamics in supercooled water. Both studies struck me as absolutely first rate. This is the best work that has been done on either of these problems to date.

Prof. Masahiro Ehara

Prof. Ehara is an expert in accurate (correlated) electronic structure theory and its application to interesting chemical problems. His more recent work has focussed on the development of new methodology and on the application of time-dependent density functional theory (TD-DFT) to the excited states of systems that are beyond the reach of correlated wavefunction techniques. He began by describing a new inverse design method he has developed to target specific properties of molecule-nanoparticle systems. He then described his recent applications of TD-DFT to problems ranging from the photoluminescence and conductivity of carbon and BN materials to the suitability of nanoclusters for heterogeneous catalysis. These are topical studies and they seemed to me to have been executed extremely well, at least in part because of Prof. Ehara's expertise with more accurate techniques (TD-DFT is only safe in the hands of those who understand its limitations!).

Associate Prof. Kei-ichi Okazaki

Prof. Okazaki gave me a truly beautiful presentation about his work on biomolecular machines. He began by explaining how his group's molecular dynamics simulations of the F_1 catalytic motor in ATP synthase had provided mechanistic insight into the ATP synthesis/proton pump reversal experiments performed by Dr. Kobayashi. The simulations were published along with the experimental data in *Nature Communications* in 2023 and they have since resulted in Dr. Kobayashi winning an early career award from the

Biophysical Society of Japan. Prof. Okazaki then went on to describe how his simulations of the "inward open" → "outward open" transition in a transmembrane transporter protein have led to an interesting prediction that is currently being tested by his experimental collaborators: When the wild type protein is put into alpha-fold the resulting folded structure is purely "outward open," whereas when a D280 mutant is put into alpha-fold it is purely "inward open." He also described how the use of "shallow multiple sequence alignment (MSA)" rather than the default optimisation setting in alpha-fold results in structures along the reaction path between "outward open" and "inward open," as can be verified by running molecular dynamics from these intermediate structures. This is an intriguing result that seems to open up the possibility of gaining mechanistic insight from alpha-fold optimisations. Prof. Okazaki ended his presentation by describing his coarse-grained simulations of membrane deformations induced by the protein Pacsin 1. These too were interesting: The standard cartoon is that the protein squeezes the membrane until it breaks but his simulations suggest that quite the opposite happens: The protein instead stretches the membrane locally resulting in narrower sections nearby, which are where the breaks then presumably occur. Indeed some recent high speed atomic force microscopy experiments seem to corroborate this. Needless to say I found Prof. Okazaki's presentation extremely impressive from beginning to end.

Associate Prof. Hisashi Okumura

Prof. Okumura's presentation was focussed on using molecular dynamics simulations to shed light on the important problem of amyloid-β (Aβ) peptide aggregation. He began by describing his atomistic molecular dynamics simulations of β-hairpin formation in Aβ40 and Aβ42 (a variant with two extra residues that is known to aggregate faster than Aβ40). These simulations found the Arg5 residue to form a hydrogen bond to one of the two additional residues in Aβ42, a prediction has since been supported by Arg5 mutation experiments performed by Prof. Kato. Hence Arg5 appears to be the key residue that explains the greater tendency of Aβ42 to form β-hairpins, which presumably also explains why it aggregates faster. To investigate this further, Prof. Okumura is now performing some very large-scale (32 peptide) molecular dynamics simulations of the aggregation kinetics of Aβ40 and Aβ42 in aqueous solution. While the preliminary results of these simulations look interesting, their statistical errors are still too large to draw any firm conclusions from, despite the fact that the calculations have already been running for 5 years. This is clearly because Prof. Okumura has chosen to do fully atomistic simulations, which require a great deal of computer time for such large systems. I would strongly encourage him to develop a cheaper coarse-grained model and use that instead. Coarse-grained models are not always as reliable as atomistic simulations, but with the atomistic simulations he has already done he has more than enough data to fit a coarse-grained model that should be good enough to capture the processes he is interested in at the thermodynamic state point he is studying, for example with the help of modern machine-learning techniques. I hope this suggestion helps and that by next year he will be in a position to show me some well-converged Aβ aggregation kinetics results.

Prof. Akihito Ishizaki

I have followed Prof. Ishizaki's research for a number of years and enjoyed meeting him and listening to his talks at conferences, so it was a real pleasure for me to end my meetings by hearing about his latest research interests. Prof. Ishizaki is a deep thinker who works on difficult problems. He outlined his preliminary attempts to go beyond the usual assumption of a Gaussian environment by considering a quantum system in the presence of Poisson noise, his work on entangled photons that suggests the possibility of a simpler alternative to four-wave mixing experiments, and his work on the use of network modelling to find the excitation energy transfer bottlenecks in the photosystem II super-complex. All of this work is profound and at the very forefront of modern condensed

phase quantum dynamics. Prof. Ishizaki's move to Tokyo will be a serious blow to the IMS and I sincerely hope that the institute will be able to find someone of equal stature to fill his shoes.

2. Visits to IMS Facilities

Prof. Ehara kindly showed me the computer cluster at the Research Centre for Computational Science, and Prof. Matsui kindly gave me a guided tour of the UVSOR Synchrotron Facility. Both were thoroughly enjoyable. I found the UVSOR Facility especially interesting as I have never visited a synchrotron before. Prof. Matsui explained its operation to me extremely clearly and knowledgeably. His enthusiasm for the facility was delightful!

3. Discussion with the Director General

Prof. Yoshihito Watanabe

I began my visit with a meeting with the Director General, Prof. Watanabe. Much of our discussion focussed on retention and other difficulties associated with running the IMS in the current financial climate (the Yen has decreased in value by 35% against the dollar in the last three years so overheads are now exceptionally high), and on some of the initiatives he has put in place to overcome them. These include increased support for PIs in receipt of large research grants, the option for those with sufficient grant income to support their research to extend their retirement age from 65 to 70, and the idea of encouraging Associate Professors whose research activity has not enabled them to secure promotions at top tier universities to apply for promotions at provincial universities instead. All of these initiatives strike me as sensible and in line with what other institutions (including my own) are doing to remain competitive. For example, Prof. Omori has recently secured a very significant grant for quantum computing, the overheads of which contribute 4% to the total budget of IMS. New "designated professorships" have been created with competitive salaries and a tenure of up to 10 years to enable him to recruit suitably qualified project leaders for this grant. Another example concerns the theoretical and computational molecular science group. In the last few years, this group has been very strong indeed under Prof. Ishizaki (an expert in condensed phase quantum dynamics), Prof. Ehara (an expert in electronic structure theory), and Prof. Saito (an expert in statistical mechanics and simulation). However, Prof. Ishizaki has recently accepted an offer from Toyko University, and Profs. Ehara and Saito are both approaching retirement age. The search for a replacement for Prof. Ishizaki is already underway, and I hope the planned increase in retirement age for those with active research grants will help the IMS to retain Profs. Ehara and Saito for a while longer before they too are eventually replaced.

4. Final thoughts and a recommendation

The "no promotion" policy of the IMS is a contentious one that has been highlighted in several previous reports on the institute. Historically, the policy seems to have succeeded in its goal. The vast majority (more than 80%) of previous IMS Associate Professors have in fact been promoted to positions elsewhere, and more than 90% of these have moved to Full Professorships at universities in Japan. Since the brightest researchers are often the best teachers, and there is no undergraduate teaching at IMS, this has clearly been beneficial for the education of Japanese scientists. However, the policy is problematic for the few who do not manage to secure outside promotions, and potentially also for the institute itself, since these people are then stuck in IMS with no foreseeable career development until retirement. Encouraging these people to apply for promotions at provincial universities and/or alternative roles within IMS (such as university research administrators) is clearly sensible. But more importantly, my impression from some of the

conversations I have had during this visit is that the recruitment and retention of Full Professors at IMS is becoming more difficult than it once used to be. Given this, and the fact that the institute nurtures some of the very best Associate Professors in Japan, it does seem strange to me that they are not allowed to apply for Full Professorships at IMS when they become available, in competition with external candidates. This would not significantly impact the flow of scientific talent from IMS to the universities, since the competition with external candidates would ensure that internal promotions remained rare. But it would give the IMS more scope to hire the best possible candidates to its Full Professorships and thereby help to safeguard its future international standing.