ChemLetter

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Paul Hopkins, Chair

In this issue

Dear Friend of Chemistry,

Universities are not known for being nimble. In part, this is by design. Our discovery mission does demand that we stay at the cutting edge of knowledge and its application, which might suggest the need for rapid change. But our at least equally important missions of education and as the storehouse of human knowledge do not afford the luxury of abandoning the past. By design we want our faculty members to stay with us for many years, we build our buildings to last, and we change our curriculum at a deliberate pace. It is thus easy to think of the University as unchanging. For our many graduates whose degrees were awarded in the last year or two or even five, it is indeed probably hard for them to detect significant change.

But things do change, significantly, with time. My twenty-year service as chair of Chemistry has provided me with a perspective that is rare, at least among those who serve in administrative roles that afford a broad view of events. Most faculty members who serve for a time in administration have had quite enough after perhaps five years. My two decades does not exactly qualify as geologic in scale, but it is a long time, and a lot has happened in Chemistry in those years.

At the end of the current academic year, I expect to turn the keys to the Office of the Chair over to a new occupant. As such, this is probably my last "Letter from the Chair" to you. The time seems right to share a brief summary of some things that have changed across the last two decades. I will focus mostly on changes in the Department of Chemistry, but I will also share a few broader observations.

Most of the changes I will describe are for the positive. But I must start with a negative that is having broad impact. One of the biggest changes in public higher education during the past twenty years has been the shift in who pays for a student's education. Though some continue to argue that the rising price of public higher education is due to a bloating of administrative costs, the reality is much less sinister. The inflation-adjusted cost of education per student at the University of Washington has changed little in twenty years. What has changed is that the proportion of this cost paid by the state went down and the proportion paid as tuition by the student correspondingly rose. It is that simple. As I write, our legislature is debating whether to "buy back" some of this tuition increase by allocating an above-inflationary increase in the state-provided higher education budget. It appears that doing so would either require cuts in the state-provided budget for other services that many would call essential, or an increase in taxes. We should know the outcome this summer. Many of us believe that public education is predominantly a public good, and should be substantially subsidized.

Another change across the past two decades at our institution and many of our on and off campus science peers is the rising number of students earning undergraduate degrees in the sciences. The undergraduate major programs at the UW in biochemistry, biology, chemistry, mathematics, and physics all grew significantly in this era. In the case of the Department of Chemistry, our majors programs (we offer the B.A. and B.S. in both biochemistry and chemistry) grew from graduating about 100 per year in 1995 to about 400 per year in 2015. You probably know from previous messages that by the latter measure we believe we are running the largest program in the U.S. At the UW, enrollments in the

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The Degree of Rate Control:

How much does the energy of each transition state and intermediate affect the rate of a multistep reaction?

—Charles T. Campbell, *Professor and B. Seymour Rabinovitch Endowed Chair in Chemistry*

By many chemists, reaction rates have not been much considered, but in industrial use of chemical reactions, their rates are often of central importance. This is universally true for reactions that make or use fuels, that make bulk chemicals, and that clean up pollution from such processes, since these reactions are run in such high volume annually. In addition, rates are crucial for atmospheric and oceanographic modelling. Thus, rates are of central importance to mankind's energy and environmental future. I describe here some recent fundamental advances in our lab that make it much easier to understand reaction rates and even tune them to our advantage.

The reactions described above generally occur via complex mechanisms that combine many elementary reactions to produce the product, or perhaps more commonly, multiple products. For a century, the concept of a "rate-determining step" has been of central importance in understanding the overall rate of such multistep reaction mechanisms, and indeed is a dominant theme in undergraduate study of reaction rates (i.e., chemical kinetics). Yet a rigorous method for identifying the rate-determining step in a reaction mechanism was lacking for most of that period, and the literature is replete with debates about which step in a reaction is the rate-determining step (RDS). Still, in undergraduate kinetics, we were shown how rate laws (i.e., expressions for how the rate depends on the concentrations of reactants and products) can be derived if we assume one step or another in the RDS. The most common example is the Michaelis-Menten rate law for enzyme catalysis. When these rate laws fit the measured kinetics (rates versus concentrations), we usually know the rate-determining step. But this approach only works when there is a single rate-determining step. In the vast majority of reactions of most importance to our energy and environmental future, there is not a single RDS. Instead, a few steps are simultaneously rate controlling. Dealing with this complexity has proven to be a grand challenge in science, and of special importance in industrial processing of fuel, chemicals, and pollutants.

To deal in a quantitative way with this complexity, I introduced a concept called the "degree of rate control" (DRC) of elementary steps. It is defined using a partial derivative (a mathematical operation dreaded by most undergraduate students), so I will avoid its strict definition here. In short, the DRC for any given elementary step in the mechanism equals the fractional change in the net rate to the product of interest per tiny fractional increase in the rate constant for that step, holding all else constant. When there is only one RDS, its DRC equals 1 and the DRC equals 0 for all other steps. To my knowledge, no other method had been developed which unambiguously defines the rate-determining step as this does. This concept of the DRC has been used by chemical engineers to great advantage in identifying the bottlenecks in catalytic reactions and, through that, finding better catalytic materials or conditions. In fact, it is taught at the undergraduate level to chemical engineering students in some of the best departments in the country. It is generally utilized in computer-based models for rates, wherein all the step's rate constants and inlet concentrations are the input and the net rate to each product and selectivity (and now DRCs for each step) are the output. I am proud that this concept was spread to the chemical engineering community by my colleague Professor James Dumesic of the University of Wisconsin (a member of the National Academy of Engineering and a pioneer of many industrially important process improvements, most recently for biomass utilization).

By extending that idea, we later found an even more powerful idea than identifying the DRC for each step: to identify the DRC for every transition state and intermediate, i.e., focussing on the species involved rather than the steps. This was initiated by two researchers in Danish industry (Carsten Stegelmann and Anders Andreasen), the first of

whom I had hosted in my lab as an exchange student from Denmark. They had a great idea, but were unable to make a consistent definition of the DRC *for species*, so they asked for my help. I realized that concepts from transition state theory held the key. We finally settled on a powerful definition of the DRC *for species* that again used the dreaded partial derivative. In short, the DRC for any given species in the mechanism is defined as the fractional change in the net rate to the product of interest per tiny fractional decrease in the energy of that species, keeping the energies of all other species constant. (More strictly, one must replace 'energy' here with 'standard-state free energy', or G^0, and divide it by our old friend 'RT' from the ideal gas law: PV=nRT.) Because of the exponential relationship between rate constants and G^0/RT, it turns out that, when defined in this way, the DRC for any transition state exactly equals my earlier DRC for its elementary step. This definition, however, now enabled us to determine DRCs for all the reaction intermediates as well. In a reaction energy diagram (see example in Figure 1), the maxima are the transition states and the minima are these inter-mediates. We thus now had a way to quantify the extent to which the energy of each maximum and minimum in the reaction energy diagram affects the net rate.

It turned out that only a few such species have non-zero DRCs even in the most complex mechanisms to which this has been applied (up to 70 elementary steps). For most species, the rate is not affected by their energies and their DRCs are zero! The few species with large DRCs are, however, crucial to know. They are the few species whose energies one could adjust to achieve a faster or slower net reaction rates to the desired product. Their relative energies could be adjusted by a variety of practical chemical approaches, such as adding or modifying a catalyst, modifying the solvent, or simply modifying a reactant's molecular structure to affect electronic or steric control on the relative energies of the key species.

Since the species with the largest DRCs are the key ones whose relative energies most strongly influence the net reaction rate, they also identify the species whose energetics must be most accurately measured or calculated to achieve an accurate kinetic model for any reaction mechanism. Thus, identifying these rate-controlling transition states and intermediates has proven to be very important for both applied and basic research.

So far, everything I have described is quite general, and applies to all classes of reactions, whether in a single phase (as in gas phase or liquid solutions) or heterogeneous (as in catalytic or electrochemical reactions happening on solid surfaces at interfaces between a solid phase and gas or liquid). Thus, it applies to everything from solution-phase reactions so common in organic and inorganic synthesis to atmospheric modelling, biochemical pathways, fuel cells, batteries, synthesis of nanomaterials, and industrial catalytic reactor beds. It has already been applied to achieve basic understanding in a few of these areas. (It fails, however, for processes which create species with populations of quantum states that are not in thermal equilibrium, as in photochemistry.)

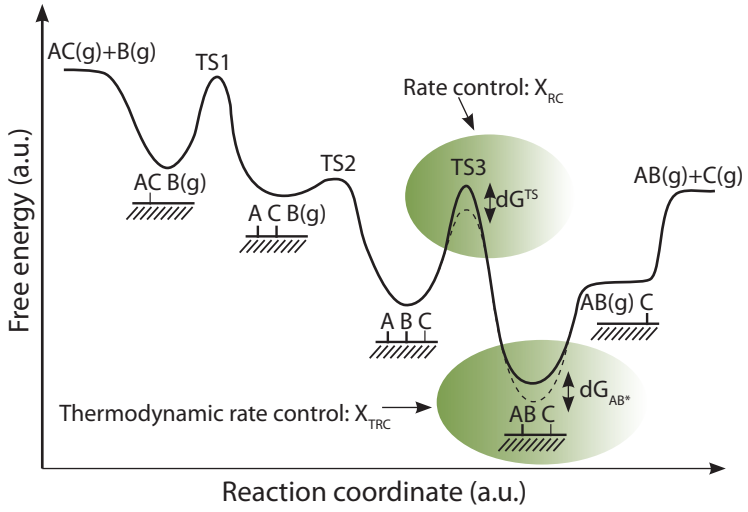

Figure 1. Example energy diagram for a surface-catalysed gas reaction. The net reaction is: AC(g) + B(g) → AB(g) + C(g). Here, the intermediates and transition states are bonded to a solid catalyst's surface. The dashed curves show incremental decreases in the free energy of one transition state, TS3, and one intermediate (adsorbed AB plus adsorbed C), as used in the definition of their degrees of rate control (DRC, written here as X_{RC} and X_{TRC}, respectively).

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The Degree of Rate Control

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For the rest of this tutorial, I will focus only on the last of these application areas: industrial reactors where the reactants flow as liquids or gases through a tube packed with a solid catalyst and products flow out the exit. The vast majority of products (in cost) from the chemical and fuels industry, and the resulting pollutant cleanup, result from such reactions. Similarly, future scenarios for cleaner energy and greener chemical processing depend very heavily on developing new reactions of this type. Thus, there is great motivation for finding solid materials that make better catalysts for such applications. We have recently shown how the degree of rate control can be used to find better catalyst materials, which I describe next.

The reaction rate for a catalytic reaction can be calculated easily with a computer if we know the energy (or, more precisely, G^0) of every adsorbed intermediate and transition state in the reaction mechanism. Computational methods based on quantum mechanics allow reasonably accurate estimates of the energies of adsorbed intermediates and transition states on different materials. Thus, one can, in principle, estimate the rates on different materials based on calculations alone, with no experiments. By comparing computed rates on many different materials, one might then discover materials that, according to these theoretical estimates, have better activity or selectivity, or are cheaper to produce, than the best known catalysts. These can then be experimentally tested to verify that they are better, much like testing candidates in drug discovery. This can accelerate the discovery process. Computational discovery of new catalysts is a new and exciting field that has grown tremendously in the past five years. Nearly every good chemical engineering department in the country has a young faculty member doing this.

However, because the quantum mechanical calculations required are so costly, some approximations are required in order to estimate rates on the large number of materials that must be screened to find a better catalyst. This field of computational catalyst discovery only really took off when the appropriate approximations were discovered by Jens Nørskov, a professor of physics at the Technical University of Denmark (and now in the Department of Chemical Engineering at Stanford University). He found that on the surfaces of metal catalysts, the energies of all the adsorbed intermediates and transition states varied from material to material approximately as a linear combination of only two energies that are very fast to calculate on different materials: the energy of a carbon atom and the energy of an oxygen atom on that surface. He thus could calculate how the net rate of the catalytic reaction varies as a simple function of these two energies, which he called the "descriptors", since they alone characterize each new material and define its rate. An example result of this now widely used approach is shown in Figure 2. Note that the Ni_3Fe alloy was predicted here to have better activity than the industrially-preferred nickel catalyst, as subsequently verified experimentally. (Ruthenium and cobalt are similarly active but too expensive.)

Having attended the kickoff workshop for President Obama's "Materials Genome Initiative" (for scientific funding) at the White House, I am confident that successes like these in catalyst discovery by Nørskov and his students (many of whom moved into faculty positions), coupled with similar successes in computational discovery of better materials in other application areas, are what inspired that initiative. Another sign of Nørskov's success are the 50,000 citations to his papers, more than 6,000 in 2014 alone. Clearly, his is widely considered as highly important work!

There are two problems with Nørskov's approach, however, both related to its limited accuracy in rate predictions. Rate errors result from errors in the energies, which arise from two unrelated effects: (1) The state of the art in quantum mechanical computations of the energies of adsorbed intermediates and transition states is density functional theory (DFT), and it has errors compared to experiments as outlined below. (2) Even if DFT can be improved to have much better accuracy (which I fully expect to happen in the next decade, discussed further below), the estimation of energies of adsorbed intermediates and transition states as linear combinations of the energies of carbon and oxygen atoms on the surface has substantial errors. We recently developed a new method for computational screening of catalysts that circumvents the need for these linear scaling relations and is actually faster than Nørskov's approach for typical reactions, unless

one is screening more than 1,000 different materials. It uses the DRC values on the best known catalyst to predict the rates for new materials by essentially integrating the defining equation for each DRC. In collaboration with Dr. Felix Studt (one of Nørskov's former students who works in Nørskov's Stanford Catalysis Center, SUNCAT), we recently tested our new method and found it to be indeed more accurate than Nørskov's method for materials that are similar to the best know catalysts (i.e., located close to it in "descriptor space," i.e., the xy grid of a volcano plot like Figure 2). Experience teaches that this is usually the case (for example, Ni_3Fe is similar to, or close to, Ni here).

Why is our method faster but more accurate than Nørskov's? By calculating the DRCs for all the species on the best known catalyst, we quickly discover the identities of the few species whose energies determine the rate and selectivity. After that, we only need to use quantum mechanics to calculate the energies of these few species on each new material. This completely eliminates the need for the inaccurate linear scaling relations of Nørskov, which are also computationally very slow to develop for each new reaction studied. Thus, we win on both accuracy and computer time costs! However, it is only more accurate for materials that are similar to the reference material used to estimate the DRC values. The weakness of our method is that it uses another approximation not needed in Nørskov's approach: It assumes that the DRCs are the same for all materials as on the reference material. This is a good approximation for similar materials (within 0.5 eV or 50 kJ/mol of the reference material on a plot like Figure 2), but fails miserably as one moves further away. I am sure that this problem can be solved by recalculating the DRCs for new reference materials as one moves further away from the original reference. This will slow down the calculation, but I estimate that it still will remain faster than Nørskov's method for studies of fewer than 100 new materials.

Much of the federal funding for my group over the past decade has been for accurate measurements of the energies of adsorbed intermediates and transition states for catalytic reactions. Intermediates include species like -CH, $-CH_2$, $-CH_3$, –OH, $-OCH_3$, -OOCH and $-C(CH_3)_3$ on surfaces like platinum. These are the simplest examples of the most common classes of adsorbed intermediates in catalysis, yet until our measurements, no one had ever measured their energies on any surface. This was enabled by our invention of a new heat detector for the calorimeter invented by Sir David King at Cambridge University, which improved its sensitivity by orders of magnitude.

It turns out that these adsorption energies will be crucial in solving the other accuracy problem mentioned above: the errors in state of the art quantum mechanical computations of the energies of adsorbed intermediates and transition states. This problem severely limits both

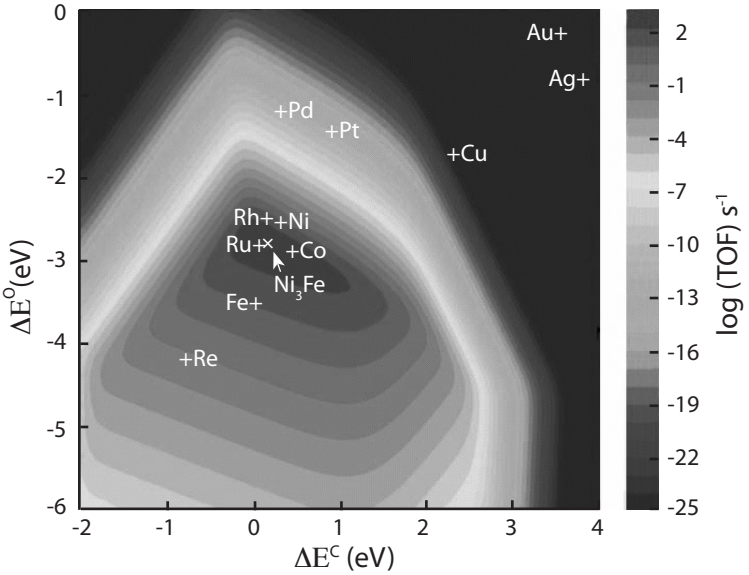

Figure 2. An example of computational catalyst discovery using the method pioneered by Jens Nørskov. Theoretical volcano of the rate of the production of methane from syngas, CO and H_2, calculated by Nørskov and his group (*Proceedings of the National Academy of Sciences of the USA,* **2011,** *108,* 937.). The turnover frequency (TOF, or rate per surface metal atom) is plotted as a function of the energies of carbon and oxygen atoms on the surface. These energies correspond to selected transition metals and alloys, as depicted. Reaction conditions are: 573 K, 40 bar H_2, 40 bar CO.

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FOCUS ON RESEARCH: The Degree of Rate Control

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Nørskov's method and our new method for computational catalyst discovery. The large magnitude of these errors was not anticipated until our recent measurements. We just wrote a collaborative paper with Nørskov where we compared 39 accurately measured adsorption energies on late transition metals to theoretical results from the most widely used versions of DFT. For 25 strong chemisorption reactions whose energies averaged −127 kJ/mol, the average (RMS) errors in DFT varied from 20 to 35 kJ/mol depending on the DFT method. Even worse, for the 14 reactions with large van der Waals contributions to the surface bonding, whose average energy is only −66 kJ/mol, the RMS errors in DFT ranged from 37 to 66 kJ/mol. Most importantly, this benchmark database of 39 accurate experimental adsorption energies will be used to validate the energy accuracy of new versions of DFT and other quantum mechanical methods, which are currently being developed very actively around the world by theoreticians. These better methods in turn will enable improvements in the predictive ability of our new method for fast computational catalyst discovery.

In summary, the degree of rate control offers a very powerful approach to both applied and basic research, since it gives ideas for practical changes to improve net reaction rates (by modifying the reactants, solvent or catalysts to control the relative energies of these key species) and to improve microkinetic models for complex mechanisms (by improving the accuracy of the kinetic parameters associated with these key species). It is similar to the concept of a rate-determining step, but more direct to apply and much more general and widely applicable in research.

Acknowledgments

I gratefully acknowledge Paul Hopkins for his continuous support throughout his twenty years as chair of our department, for his selfless dedication to providing the institutional infrastructure necessary to achieve our research and educational goals, and for his friendship. I also acknowledge the Department of Energy, Office of Basic Energy Sciences, Chemical Sciences Division for its support of this work. ■

WELCOME!

Ashleigh Theberge

Dr. Ashleigh Theberge completed her undergraduate studies in chemistry at Williams College, performing research with Professors Thomas Smith, Dieter Bingemann, Lois Banta, and Heather Stoll. She received her Ph.D. in chemistry with Professor Wilhelm Huck at the University of Cambridge in the field of droplet-based microfluidics. While pursuing her Ph.D., she was a visiting researcher at the Université de Strasbourg with Professor Andrew Griffiths, where she developed microfluidic methods for drug synthesis and screening. She completed her NIH postdoctoral fellowship with Professors David Beebe, William Ricke, and Wade Bushman at the University of Wisconsin–Madison, studying molecular mechanisms of prostate cancer using microscale culture and analysis platforms. She is presently an NIH K Award Scholar at the University of Wisconsin–Madison.

Dr. Theberge will launch her research program at the University of Washington in January 2016. Her research centers on the development and use of microfluidic technologies to understand the chemical signaling processes underlying disease, with a particular interest in steroid hormones in prostate disease and testis development and oxylipins involved in the immune response. She will develop new methods for microscale cell culture, small molecule isolation, and metabolomics. ■

FACULTY INTRODUCTIONS

We are delighted to welcome three new assistant professors to our department for the 2015–2016 academic year. Below are brief descriptions of their education and work history and their areas of research. Look for more detailed profiles in future issues of the *ChemLetter*.

Dan Fu

Dr. Dan Fu completed his undergraduate studies in chemistry at Peking University. He earned his Ph.D. in chemistry with Professor Warren Warren at Princeton University, where he developed novel nonlinear absorption microscopy for visualizing non-fluorescent biomolecules and applied it to early melanoma diagnosis. Dr. Fu briefly conducted postdoctoral work on quantitative phase microscopy with the late Professor Michael Feld at the Massachusetts Institute of Technology before moving to his current postdoctoral position at Harvard University with Professor X. Sunney Xie. While at Harvard, Dr. Fu has focused on the development of multiplex and hyperspectral stimulated Raman scattering microscopy, which he has applied to the study of biological problems such as lipid metabolism, drug transport, and cell growth.

Dr. Fu will launch his research program at the University of Washington in the summer of 2015. He will focus on the development of novel quantitative optical spectroscopy and imaging techniques to study the spatial-temporal dynamics of biomolecules in living biological cells and organisms, with an overarching goal of using analytical and physical chemistry approaches to explore the cellular mechanisms of complex diseases, develop early disease diagnosis tools, and establish effective drug screening processes. ■

Alshakim Nelson

Dr. Alshakim Nelson completed his undergraduate studies in chemistry at Pomona College in 1999. He received his Ph.D. in organic chemistry from the University of California, Los Angeles in 2004, where he studied carbohydrate-containing polymers and macrocycles with Professor J. Fraser Stoddart. He was then an NIH postdoctoral fellow at the California Institute of Technology working for Professor Robert Grubbs on olefin metathesis catalysts for the formation of supramolecular ensembles. Dr. Nelson joined IBM Almaden Research Center as a research staff member in 2005, where he focused on synthesizing building blocks that enable large area nanomanufacturing via self-assembly. His research interests also include silicon-based polymers for lithographic applications, magnetic nanoparticles, directed self-assembly of nanoparticles, and hydrogen bonding block copolymers. Dr. Nelson has more than 40 publications and 11 issued patents, and in 2011, he was designated as an IBM Master Inventor. In 2012, he became manager of the Nanomaterials Group, which includes the Synthetic Development Lab.

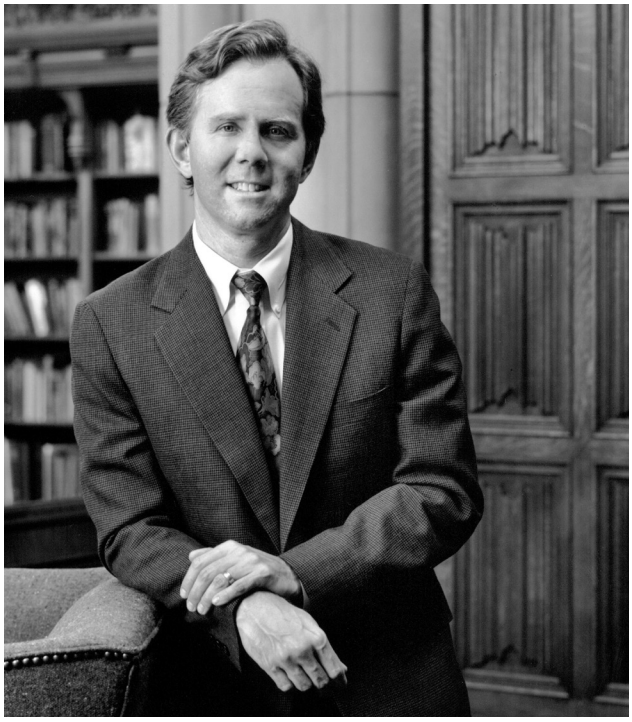
Dr. Nelson will begin his research program at the University of Washington in September 2015. His research will focus on the synthesis, characterization, and patterning of polymeric and supramolecular materials for the bio-interface. ■

humanities and social sciences were in most cases stagnant or even in decline over this same period. Students in the current generation are career oriented, and believe that a focus in science or engineering will advantage them.

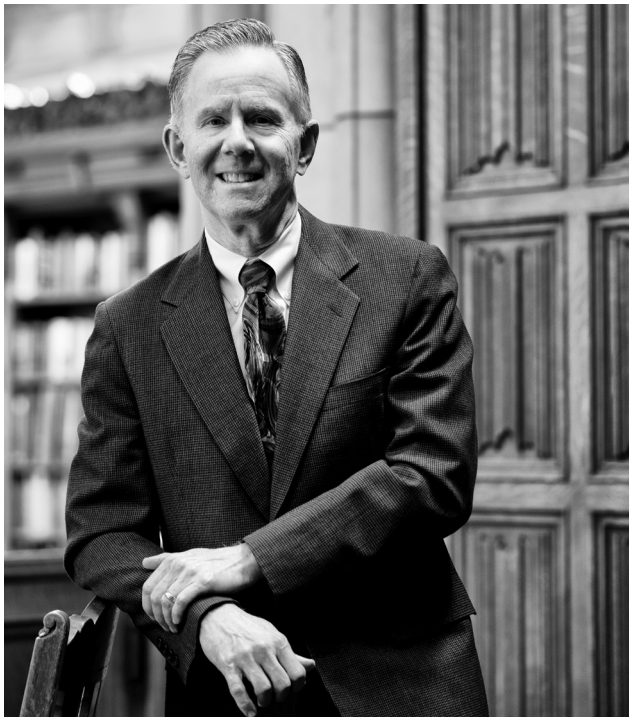
Because freshman (general) and sophomore (organic) chemistry courses are a foundational requirement for many degrees in science and engineering, enrollments in these classes have also risen relentlessly. Enrollments in these first- and second-year courses have doubled across the two decades. To give you a sense of scale, at the UW more than 2,000 students now enroll in the introductory general chemistry (CHEM 142) during Autumn Quarter alone. Today in Chemistry we have a team of five highly capable lecturers without whom we could not possibly accommodate all of these enrollments. The number of tenure-track faculty is basically unchanged in the past twenty years.

Some aspects of how we instruct undergraduates have changed and some have not. Computers and associated technologies played a small role in instruction two decades ago, but are central today. Students communicate with their instructors electronically, from one-on-one emails to virtual office hours where a professor drawing on an electronic tablet works out problems that students at home can see on their computer screen. Students are quizzed over course material using computer-delivered and graded problems. Some faculty members have "flipped" their classrooms, providing students with videos to watch before class so that face-to-face class time can then be used to integrate course materials in more sophisticated ways. Some faculty members believe that these tools do improve student learning.

The size of our graduate program also grew during the past two decades, from about 170 students in residence to about 220, or an increase of about 30%. The number of post-doctoral associates working with our faculty approximately doubled, from thirty to sixty. This growth has led to an increase in research activities, and this creates a more vibrant intellectual environment for all of our students, including the undergraduates. The funding for this expansion came from competitively won federal grants, the dollar amount of which rose by four-fold during the two decades. We



Mary Levin, University Photography



Xiaosong Li

Changing of the Chair. On July 1, 2015, Professor D. Michael Heinekey will succeed Professor Paul Hopkins, pictured above soon after starting as chair in 1995 and today.

compete favorably with the very best institutions nationally as we recruit our graduate students and postdocs. By many of these measures we today resemble a top ten department of chemistry nationally.

The research program in which our undergraduate and graduate students and postdoctoral associates participate has continued to evolve in the past two decades. The interface of chemistry with biology is particularly active today. Research with biological implications is present or even dominant in all of the traditional areas: analytical, inorganic, organic, and physical. Likewise, materials-related chemistry has continued to expand. Advances of critical societal importance, such as in the areas of human health and energy, will require the insights of chemists in these biological and materials areas. Another change is the increased importance of theoretical calculations. Theory and experiment are nearly equal partners today. A related longstanding trend is the growth of research programs whose scope and breadth require collaboration among individuals with complementary skills. Synthetic chemist, spectroscopist, and theorist today team up to take on challenges no one of them could surmount alone. An engineer may well also be a member of the team, participating in translating from fundamental discovery to functioning device, and even to the marketplace. Increasingly, the assembly of such teams is becoming a requirement to maintain research funding. A rising fraction of our research grant portfolio supports large teams of scientists and engineers pursuing some shared goal.

I noted above that the size of the tenure-track faculty of chemistry has not changed much in two decades. But the identity of our tenure-track members surely did. If tenure-track faculty members were radioisotopes, they would have a half-life of about ten years. Of the roughly forty tenure-track faculty members who were with us in 1995, only about a quarter remain twenty years later. Most of the thirty who left during this period retired, but some moved to other academic institutions. The vast majority of our new hires were at the assistant professor level, new colleagues who have joined us after completing postdoctoral research, usually elsewhere. This coming Autumn Quarter we expect to have fourteen faculty members at the assistant professor level! The perception of the academy as a place full of folks with gray hair does not reflect UW Chemistry today (though a few of us do fit the description).

Another behind-the-scenes activity has become more frequent during the past two decades. It has long been the case that higher education institutions attempt to poach one another's faculty members. The optimist might characterize this as a healthy element of the academy, the movement of talented individuals around the nation assuring the exchange of knowledge and points of view. But the quality of our program suffers when we lose an outstanding faculty member, and it is expensive to launch a replacement. We thus do our best to fend off such poaching. The price of the rising quality of our department is an increased frequency of outside offers. The majority of these offers are declined. It speaks highly of UW Chemistry that our faculty members have in the past two decades turned down offers of tenured faculty positions at outstanding schools such as Caltech, Cornell, Illinois, Michigan, Texas at Austin, and Yale.

Because chemistry remains a laboratory-based science, a great chemistry department needs great laboratory space. In 1994, the "new" Chemistry Building to the south of Bagley opened. With about 55,000 assignable square feet, and including research as well as undergraduate instructional laboratory space (for sophomore organic lab), this expansion supplemented spaces, most of them outdated, in then nearly sixty-year old Bagley Hall. During the past two decades we have been methodically renovating spaces in Bagley Hall, now nearly eighty years old, and in the Chemistry Library Building. In two decades, we have renovated a total of nearly 50,000 assignable square feet, most of it in Bagley. A number of these renovations yielded state-of-the art research spaces, including temperature controlled, low vibration spaces for spectroscopists and highly ventilated wet labs for synthetic chemists. I am personally proudest, though, of our having at long last renovated all four of the large rooms in which freshman general chemistry laboratory instruction is provided. The dark and dingy freshman labs in Bagley that had seen limited or even no renovations since opening in 1937 are today colorful, brightly lighted and inviting. Our junior and senior undergraduate majors are also today all taught in renovated laboratory spaces. Some of these renovations afforded opportunity for energy conservation, as we moved to modern low-flow fume hoods that protect scientists, but reduce heating and cooling costs. There is much of Bagley Hall still left to renovate.

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LETTER FROM THE CHAIR, CONTINUED FROM PAGE 9

Most of my "Letters from the Chair" have included a shout-out to all of our donors who provide gifts large and small. During the past two decades the number of dollars Chemistry spends annually that have their origin in gifts has increased nearly ten-fold. And the Department's endowment has also grown ten-fold. Though expenditures from gifts remain a small percentage of the total cost of our operation, these gift-derived funds are especially valuable because they come with fewer restrictions on their use than federal or state funds. Just one example is the competition to retain our faculty when private schools try to lure them away: gift funds play a critical role in our defenses. And gift funds are playing a rising role in helping students afford higher education. Thank you donors!

I have recounted mainly successes that can be quantified (we are scientists, after all). It is important to acknowledge another success, one that cannot be quantified: UW Chemistry in 2015 is a welcoming and supportive environment for students, staff, and faculty members. This did not happen by chance. It is the faculty and staff of our department who set the tone. When we hire faculty or staff members, we seek excellence, but we also seek individuals who will contribute positively to our environment. In so doing, everyone wins. Our students sense that our goal is their success, and it helps to make our subject less intimidating, and thus to improve their learning. The faculty and staff we depend upon for our excellence enjoy this environment, and it contributes to our ability to recruit and retain them.

The progress made in Chemistry at the UW over the past decades owes much to those who came before us, and thus set the stage, and many colleagues on our faculty and staff who moved us forward. I close my last "Letter from the Chair" with thanks to three people whose contributions were particularly critical.

Paul Cross was the chair of UW Chemistry from 1949 to 1961. Cross is said to have brought the department into the modern era, recruiting outstanding faculty members, urging them to participate in research, and to apply for newly-available federal funding. He transitioned UW Chemistry from a regional to a national focus.

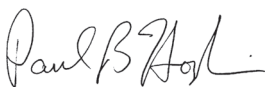
Alvin Kwiram, who was the chair of UW Chemistry from 1977 to 1987, picked up where Cross left off, urging the department to greater heights in all things. The only mistake he ever made was hiring me. Kwiram is a home-run hitter. Every at bat did not yield a home run, but many did. Kwiram hired many of the faculty members whose contributions have advanced us in the succeeding decades. Kwiram advocated for and won the Chemistry Building that has been central to our success. Today, nearly thirty years after he left the chair's office, his fingerprints remain everywhere! I feel fortunate to call Kwiram both a mentor and a friend.

Finally, I must thank another friend and colleague with whom I have worked closely every workday for fifteen of the past twenty years. (He worked elsewhere during a five year hiatus in his service to Chemistry, but we recruited him back.) Gary Pedersen leads the staff of more than sixty persons who support our instructional and research programs. He also works closely with the faculty on various issues. Pedersen's analytical, organizational, and people skills, along with his fundamental sense of fairness, mean that jobs get done right and people are satisfied with the outcome (even when the outcome is not in their favor). He has been a joy to work with. We are extremely fortunate to have him.

In selecting these three for thanks, I do not mean to slight others. Countless faculty and staff members have contributed; they all have my thanks.

What of the future? That will be decided by others. But I am confident that there are many, many successes yet to come. The foundation of our program is strong. There will surely be challenges ahead, but we are as prepared as anyone in higher education to meet them head on.

Thank you for your support through all these years! With very best wishes,



Paul B. Hopkins
Professor and Chair

P.S. Perhaps the next "Letter from the Chair" can relate more timely news, such as the addition of at least three new tenure-track faculty members this coming fall, the recruitment of the largest graduate class in our history, and that seven of our current graduate students won NSF pre-doctoral fellowships in the most recent competition!

Advancements in the High-Throughput Isolation of Rare Cells and Single-Cell Analysis

—Robbyn Perdue, Ph.D.

The advent of rare cell and single-cell technologies is impacting our fundamental understanding of disease and its response to clinical interventions. Among the most provocative findings is that a minority of cells often dominates the progression of disease,[1] as is the case in acquired resistance of bacterial colonies to antibiotics or the metastasis of cancer to sites distant from a primary tumor. It has become clear that the advancement of medical treatment of the most intractable illnesses hinges on the identification and analysis of rare cells.

Human tissues are comprised of ensembles of cells having widely varied characteristics. These cells are usually classified into clearly delineated cell types (e.g., erythrocytes versus leukocytes in blood). Within a given cell type, additional differences in cell composition and behavior (collectively described as the cell phenotype) can be related to distinct functional roles (e.g., individual neurons in a signaling network) or in some cases, dysfunction.

A cell phenotype is considered rare when it has an abundance of less than one cell per microliter.[2] Analysis of these rare cells can aid in diagnosis, prognosis, and treatment of disease.[3] For example, fetal nucleated red blood cells (nRBCs) isolated from the maternal bloodstream provide a minimally invasive means to obtain genetic information about the developing fetus. Pathogen-infected cells, such as those impacted by viruses, if found, can aid in diagnosis of infectious disease. In the treatment of cancer, rare cells can also serve as prognostic indicators or even drug targets, as is the case with cancer stem cells (thought to be especially prolific and capable of seeding new tumors) and circulating tumor cells (CTCs).

There are numerous rare cell isolation techniques that have been developed over the last decade. The vast majority of rare cell platforms employ microfluidics as the device framework.[3,4,5] Microfluidic devices are comprised of channels, on the order of a few to hundreds of microns in diameter, and the devices frequently incorporate active components, such as valves, mixers, filters, or sensors with features at the nanometer to micron scale. This microarchitecture has several distinct advantages including facile handling of nano- to microliter sample volumes, low reagent consumption, and the ability to integrate several functions into a single device–thus forming a "lab on a chip." A feature that is particularly beneficial for rare cell applications is a reduction in sample losses due to the elimination of manual transferring and processing steps.

Strategies to detect and isolate rare cells depend upon their unique phenotypic characteristics, which may include size, deformability, dielectric properties, and biomarkers such as sugars and proteins (antigens) at the cell surface.[5,6] The features targeted for isolation must yield the desired capture efficiency (percentage of rare cells recovered), purity (absence of non-target cells in the recovered fraction), and cell viability. The cell detection and isolation mechanisms can also drastically impact the device throughput (the volume of sample processed per unit time). Finally, techniques that require minimal sample preparation are advantageous because of their economy in terms of time, effort, reagents, and sample loss.

A suite of microfluidic technologies for rare cell isolation and single-cell analysis has been developed by the research group of Daniel Chiu, A. Bruce Montgomery Professor of Chemistry, at the University of Washington. Recently, the Chiu group has focused its efforts on the isolation of circulating tumor cells.[7–10] CTCs are cells that have escaped from a solid tumor and entered the peripheral blood. They are exceedingly rare, present at just a few cells per milliliter, or about one in a billion cells in whole blood.[3,5]

How do these CTCs escape from tumor tissue? Tumors can be highly vascularized due to the recruitment of blood vessels to the tumor via a process called angiogenesis. Tumor cells are separated from blood circulation by a thin basement membrane (a protein fiber matrix) and blood capillary walls, which are often comprised of a single layer of endothelial cells. In a process called intravasation, tumor cells can acquire phenotypic characteristics that allow them to crawl across these barriers and enter the bloodstream. These CTCs have diagnostic value in that they can serve as a "liquid biopsy" that provides information about the tumor from whence they originated. Furthermore, a high number of CTCs in circulation has been correlated with poor prognosis.

Rare Cells and Single-Cell Analysis

—continued from page 11

It has been estimated that a gram of tumor tissue can release up to one million cancer cells into the bloodstream per day.[11] While the vast majority of these cells die in circulation,[5,6] CTCs have the potential to exit the bloodstream and enter another tissue (extravasation) where they can either lie dormant or seed the growth of new tumors. In this way, CTCs play a central role in cancer metastasis and therefore, the analysis of CTCs can yield valuable information about the metastatic process and lead to treatment strategies aimed at the prevention of cancer spread.

CTCs can be isolated from other cells in circulation based on several distinguishing features.[5] They are larger in diameter than red blood cells (RBCs), platelets, and most white blood cells (WBCs), which permits separation of CTCs by size-based filtration. CTCs are also more electrically polarizable, allowing them to be separated from other blood components by dielectrophoretic force. Additionally, the proteins present on the cell membrane of CTCs can aid in their identification. Cancer cells originating from epithelial tissues will express epithelial markers (surface antigens) and have higher coverage of adhesion proteins. These features have allowed capture of CTCs on solid supports by both immunoaffinity (antibody capture) and non-specific interactions (e.g., on a roughened glass surface), respectively.

Professor Chiu and his research group have developed a technology that can isolate cancer cells from blood with capture efficiencies exceeding 93% and at a throughput of 50 μL/min.[7] To achieve this result, first, the CTCs are labeled using fluorescently-tagged antibodies that bind to CTC-specific surface antigens. Then the blood sample is divided into virtual aliquots, which are ranked based on the presence or absence of a CTC. Aliquots containing a CTC are fluidically sorted to a filter, which removes RBCs and retains the CTCs and some WBCs. Once on the filter, cells undergo secondary labeling with fluorescent antibodies to confirm CTC identity and to characterize other biomarkers of interest (e.g., stem cell markers) (Figures 1a and 1b). This technology, called ensemble decision aliquot ranking (eDAR) was featured on the May 2012 cover of the journal *Angewandte Chemie* (Figure 2).[7]

eDAR has several distinct advantages over competing technologies. First, as mentioned above, eDAR has very high throughput, allowing 1 mL of blood to be processed in twenty minutes. Second, the blood sample is subjected to minimal processing–only a labeling step before CTC

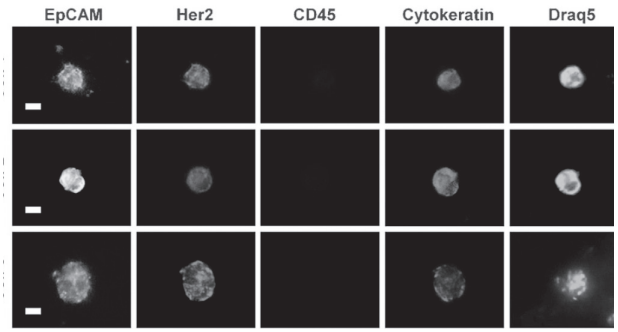
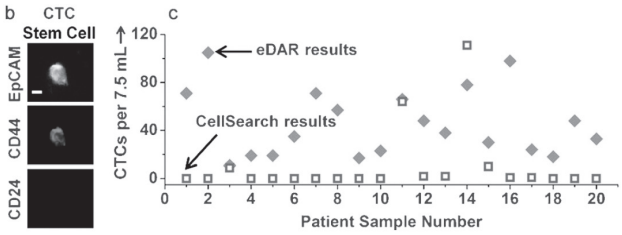


Figure 1a



Figures 1b and 1c

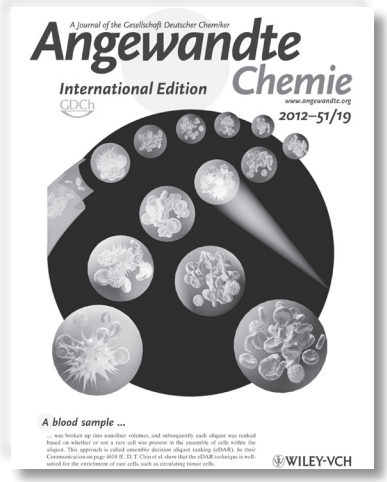


Figure 2

detection by eDAR. In contrast, many other techniques require lysis of RBCs or centrifugal isolation of the nucleated cell fraction (which contains WBCs and CTCs) from the blood, thus increasing the risk of loss or damage of CTCs. Third, the cells isolated cells by eDAR have been demonstrated by subsequent growth in culture to retain a high degree of viability. This feature is key to enabling certain downstream analysis approaches that require more than single cells as starting material. A gentle CTC isolation technique can also minimize perturbation of phenotypic characteristics (e.g., gene expression patterns) of interest. Finally, all of these advantages are achieved while maintaining a high capture efficiency.

In a side-by-side comparison between eDAR and what is currently the only FDA-approved CTC detection technology, CellSearch (Veridex), eDAR isolated on average 4.5-fold more CTCs from twenty patient samples from breast cancer patients (Figure 1c).[7] Furthermore, eDAR found CTCs in twelve samples for which CellSearch found none. Significantly, eDAR identified cancer stem cells among the CTCs detected (Figure 1b).[7]

The Chiu group has continued to advance eDAR technology. They have recently simplified device architecture with an in-plane slit filter.[10] Further chip designs have enabled sorting of separate CTC populations and increased purity of CTCs via sequential sorting steps. Most recently, Chiu and co-workers have developed an on-filter sequential fluorescent labeling and bleaching protocol for isolated CTCs.[9] This protocol enables analysis of ten biomarkers with only four-color fluorescence imaging (Figure 3). They demonstrated imaging of tumor cell markers linked to the invasiveness (growth, adhesion, and migration) of the cells. Finally, eDAR is being benchmarked with clinical samples for early detection and stratification of breast cancer.

Moving forward, eDAR will be coupled to downstream modalities, developed by the Chiu group, to aid in the analysis of rare cells. For example, the group has designed a self-digitization (SD) chip, which spontaneously divides an aqueous sample into isolated nanoliter-scale droplets in microchambers.[12,13] This SD chip was recently used to quantify gene expression (mRNA copy number) in individual cells via digital quantitative reverse transcription polymerase chain reaction (qRT-PCR).[13] The SD technology also holds promise for parallel single-cell PCR.

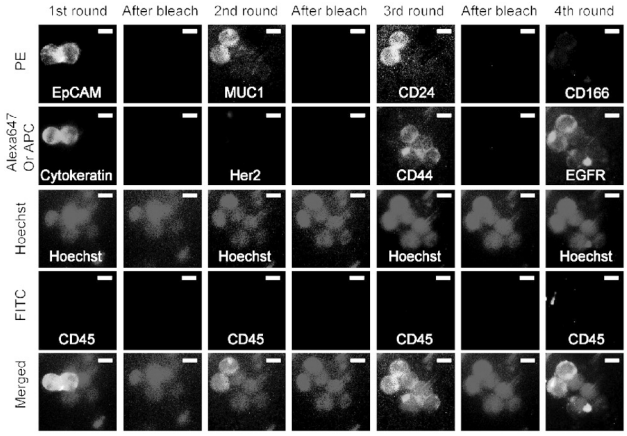


Figure 3

With the development of these rare cell and single-cell technologies, the Chiu group is poised to answer questions in cancer biology, and metastasis in particular, that have heretofore been inaccessible to available research tools.

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GRADUATE STUDENT PROFILE

Mycah Uehling

by Zoha Syed

Gojko Lalic

Mycah Uehling

Endless hours are spent by young Lego users building cities, civilizations, and creations stemming from the depths of their imaginations. Mycah Uehling, a graduate student in the Department of Chemistry, was no exception.

"As a child I enjoyed playing with toys that I was able to tinker with, for example Lincoln Logs, K'NEX, Legos, etc. As I got older this led to my general fondness of using my hands to make things...I became fond of organic chemistry because once again I was able to make stuff," Uehling said.

As an undergraduate student at Pacific Lutheran University (PLU), Uehling enjoyed various subjects, from math to Chinese. Initially a premed student, he became interested in organic chemistry after his sophomore year. His first experience with research, and a stepping stone to finding his future adviser, came one summer.

"Professor Neal Yakelis at PLU encouraged me to do summer research and focus on organic chemistry," Uehling said. "After a few months of research I was hooked."

Following graduation, Uehling started graduate school at the University of Washington. After hearing from Yakelis about UW Professor Gojko Lalic, a former colleague of Yakelis' at the University of California, Berkeley, Uehling knew whose lab he wanted to join. But the transition from undergraduate studies to graduate studies wasn't all fun and games.

"For me, primary school through undergrad, school was structured. There were clear expectations about what to do, the homework assignments, what is on the exam, etc.," Uehling said. "Once you are in graduate school, there really is no limit to what you can do or what you can achieve; with that kind of freedom it can be challenging to be successful because you are left to determine what is important or not."

As a young graduate student, Uehling worked on perfecting the art of making decisions that would ultimately lead to greater efficiency and greater productivity. It was hard to find a balance when it came to deciding whether to do exactly as told or deviate from what is expected. However, with time, practice, and some trial and error, he was able to find a happy medium. His work in the laboratory was the first tangible result.

During his graduate career, Uehling has studied transition metal catalysis, focusing on the functionalization of unsaturated carbon-carbon bonds. His recent projects include hydrobromination of alkynes and hydroalkylation of terminal alkynes, both published in the *Journal of the American Chemical Society*. His strategy was one of sustained momentum and never losing sight of the chemistry that was occurring in the reaction flask.

"Don't relax once you figure something out. It's human nature, but it is really important to keep up momentum. (It took me four years to learn not to do this)," Uehling said. "Read all of the literature around your project early to understand what is important to other people (or at least what strategies work to solve problems) who have worked on similar things."

The hardest part about chemistry for Uehling, even now, lies outside of the lab. "I feel the most uncomfortable when writing something that isn't good enough yet, like a first draft of an introduction. For me this comes from not having a deep enough understanding of the background literature," Uehling said. "If I am looking up references while I am writing, it isn't pretty, but it is usually the way I do it. I can say that [in] comparing my writing now to what I did for my second year exam, it has gotten a lot better."

After more than five years here, Uehling will soon be graduating to the next stage in his chemistry career: a postdoctoral position at the Massachusetts Institute of Technology, working for Professor Stephen Buchwald. Looking back, Uehling recognizes the biggest obstacle he and other graduate students often face: themselves.

"The chemicals are on the shelf [and] the NMR is open for reservation. I think the students that do the best, do experiments first and ask for permission later."

Moving forward, organic chemistry will always be the science that allowed Uehling to tinker—in the process, learning things he never knew before and putting together the pieces of the story that is a new reaction.

According to Uehling: "Organic chemistry is like building things with Legos. Each piece is like an organic fragment, [and] they fit together a certain way." ■

Xing Yee Gan

by Zoha Syed

On a typical Seattle morning, Xing Yee Gan walked into her honors general chemistry class. Professor Jim Mayer was out that day, so in his place was a substitute: Professor Daniel Gamelin. Little did Gan know the class would be the start of her undergraduate research career.

Gan was born in Kota Bharu, Malaysia and didn't move to the United States until she was 18. She finished her senior year at Fossil Ridge High School in Fort Collins, Colorado, before starting at the University of Washington. It was in high school that Gan was drawn to chemistry.

"Chemistry complements both physical and natural sciences," Gan said. "It helps us understand biological and natural systems through physical principles. That means chemistry provides a gateway to use those fundamentals to mimic natural systems."

It was in the honors general chemistry series that Gan began thinking more about the material being presented in class, and how it could be applied. It was after listening to Gamelin's lecture when she took the plunge.

"Professor Gamelin enthusiastically talked about ruby lasers and their role in the history of inorganic chemistry," Gan said. "His research was too complex for me to fully comprehend but he was the first person I had ever met that was so passionate about his work."

She soon joined the Gamelin group and began studying the effects of doping zinc oxide nanocrystals with magnesium. She was interested in seeing how the impurity affects the electronic structure of the conduction band of the nanocrystals by monitoring the infrared spectra. In the process, she learned a variety of skills and techniques.

"I have worked on different projects including the syntheses and characterizations of different undoped and doped colloidal nanocrystals," Gan explained. "I learned to synthesize nanocrystals in both aerobic and anaerobic conditions. I was also trained to handle the nanocrystals in a nitrogen atmosphere glove box. I learned to add electrons to the nanocrystals using photodoping and quantifying them via chemical titrations."

Aside from chemistry, Gan says one of the most important skills she learned in the Gamelin group was how to work individually as well as with others.

"I am also close friends with many of [my] colleagues, which makes me realize the importance of a healthy work environment," Gan said.

After her undergraduate studies, Gan plans to attend the University of Pittsburgh where she will continue her chemistry career in the study of nanomaterials. Looking back on her undergraduate career, Gan learned a lot when it came to balance.

"You just have to know how to prioritize your life. Be sure to know that priorities change with time on a temporary basis. School, research, and fun are equally important," Gan said.

As for finding a research group, she suggests attending group meetings to find a good fit as well as plenty of seminars to learn as much as possible.

"Don't give up if you think research is hard. It is supposed to be a long haul, but it is immensely rewarding," Gan said, an important piece of advice she received from Gamelin.

If all else fails, finding a professor who you truly admire, as in Gan's case, paves a wonderful path, ruby lasers optional. ■

Kevin McHugh

Xing Yee Gan (front, middle) with members of Professor Daniel Gamelin's research group: (front, left to right) Arianna Marchioro and Kathryn Knowles and (back, left to right) Charlie Barrows, Emily Tsui, and Jose Araujo.

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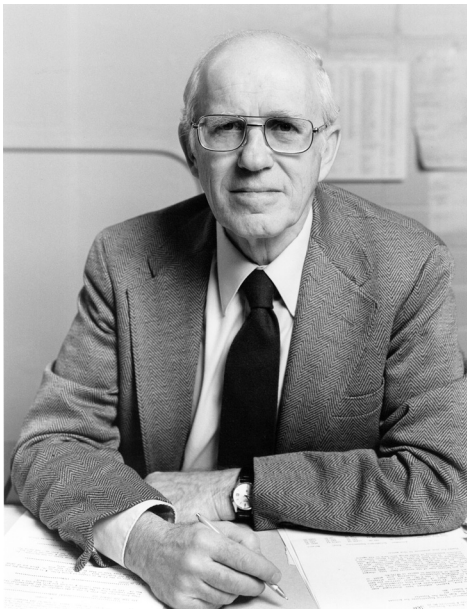
Chemical Dynamics and the Rabinovitch Legacy: A Symposium in Memory of B. S. Rabinovitch

When: Saturday, May 30, 2015
9:00 a.m.–6:00 p.m.

Where: 131 Bagley Hall
University of Washington
Seattle, Washington



Courtesy of Department of Chemistry

Invited Speakers

Emily A. Carter, *Princeton University*
F. Fleming Crim, *National Science Foundation and University of Wisconsin–Madison*
Sharon Hammes-Schiffer, *University of Illinois at Urbana-Champaign*
Stephen R. Leone, *University of California, Berkeley*
David J. Nesbitt, *University of Colorado, Boulder, JILA, and NIST*
John C. Tully, *Yale University*
Ahmed H. Zewail, *California Institute of Technology*

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