

progenitor cells become progressively more differentiated and are eventually destined to stop proliferating. Predictably, self-renewal is an essential property of some cancer cells, and at least some genes that regulate normal stem-cell self-renewal also do so in cancer cells<sup>7–9</sup>. This suggests that cancers arise either from normal stem cells or from progenitor cells in which self-renewal pathways have become activated (Fig. 1b).

Using serial transplantation, Singh *et al.*<sup>1</sup> demonstrated that at least some of the CD133<sup>+</sup> brain-cancer cells can renew themselves. By contrast, the ability of CD133<sup>-</sup> cancer cells to proliferate was limited. Soon after injection of the CD133<sup>-</sup> cells into the brain, they stopped growing, leaving behind a small cluster of quiescent tumour cells.

This outcome is reminiscent of the observation that many women with small clusters of metastatic breast-cancer cells in their bone marrow, who did not receive any treatment, survived for years without progression of their cancer<sup>10</sup>. One explanation for this tumour dormancy is that the microscopic clusters of cancer cells did not contain cancer stem cells and so, like the CD133<sup>-</sup> brain-cancer cells, were unable to grow further. Taken together with the observation that circulating cancer cells in the blood are an indicator of prognosis in breast-cancer patients<sup>11</sup>, this suggests that the use of markers to reveal cancer stem cells could help in making decisions about treatments.

The identification of cancer stem cells is a significant step in the fight against these

dreaded diseases: because self-renewal is essential if tumours are to grow, agents that target such cells may be effective treatments. A possible complication is that the mechanisms known to regulate cancer-stem-cell self-renewal also regulate the process in normal stem cells. Unlike normal stem cells<sup>12</sup>, however, the expansion of cancer stem cells is not tightly regulated, implying that there are significant differences between the normal and the cancerous self-renewal pathways. This gives hope that the isolation of cancer stem cells, coupled with our knowledge of the mutations causing cancer, will result in ways to eliminate cancer cells while sparing normal tissues. ■

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the activation barriers and transition-state vibrational frequencies for all the relevant elementary surface reactions; second, to couple these through statistical mechanical methods involving transition-state theory and kinetic Monte Carlo simulations of the reaction process. Vibrational frequencies for all the intermediates and transition states, also calculated quantum mechanically, are used to incorporate entropy considerations into the calculated rate constants. Monte Carlo simulations, which are in widespread use in science, allow a highly complicated system to be sampled efficiently in a number of random configurations, the upshot being a description of the system as a whole. Kinetic Monte Carlo takes this a step further, allowing efficient sampling of the tremendous range of different timescales necessary to describe all the different elementary steps, and thus simulate the kinetics of the whole system.

In this way, Reuter *et al.* were able to calculate net catalytic reaction rates on solid surfaces under conditions similar to those used in industrial processes. Other workers have used a related approach to investigate different types of phenomena<sup>2</sup>, but this application to catalytic reaction rates is a particularly demanding test. Reuter *et al.* have achieved impressive accuracy in calculating the steady-state rates of the catalytic oxidation of carbon monoxide (a reaction performed by the catalytic converters of automobiles) over a model ruthenium oxide (RuO<sub>2</sub>) catalyst. Their rates agree almost perfectly with excellent experimental rate measurements, performed by a different group at the same institute<sup>3</sup>, over a wide range of reaction conditions. The beauty of Reuter and colleagues' method is that it allows one to identify which elementary steps control the reaction rates and how their rates are affected by reaction conditions and, in principle, by surface structure. This is just what is needed to guide the development of better catalysts.

There is, unfortunately, one major limitation associated with the accuracy of quantum-mechanical calculations when applied to chemisorbed species on surfaces. The quantum method used by Reuter *et al.* is a version of density functional theory (DFT) that achieves nearly state-of-the-art accuracy in predicting the energies of such systems. Nevertheless, the authors admit that this can still be off by as much as 30 kJ per mol in estimating activation barriers. Given this drawback, it is surprising that they were able to achieve such impressive accuracy in their calculated carbon monoxide oxidation rates over RuO<sub>2</sub>. They attribute this agreement with experimental rates to an effect they imply is generic to catalytic reactions — the combined action of many elementary steps that simultaneously affect the rate.

Although I agree that surface-catalysed reactions generally have many elementary

Chemistry

# Towards tomorrow's catalysts

Charles T. Campbell

The ability to predict and modify the rate-determining steps in chemical reactions would be a boon in designing better catalysts. Technical innovations in computer simulations bring that goal closer.

Chemical conversions driven by catalysts are essential to modern society. But we must do better: sustaining industrial and economic growth, while protecting the environment, will necessitate developing more efficient processes. In particular, there is a pressing need for new solid catalysts for mixed-phase, or heterogeneous, reactions. Such reactions tend to involve large volumes, and they are the basis of, for example, more efficient ways of reducing plant and automotive emissions, and of producing cleaner fuels such as hydrogen or methanol.

A way forward lies in predicting how the details of a catalyst's surface structure control key kinetic parameters in the reaction mechanism. One such parameter is the activation barrier, which, if known for the

rate-controlling elementary steps, allows the relevant rates to be calculated. These in turn enable accurate predictions of both the rate of production of the desired products and the branching ratios to undesired products, knowledge of both of which is essential to ensure a successful outcome in terms of energy efficiency and environmental impact. Writing in *Physical Review Letters*, Reuter *et al.*<sup>1</sup> herald a powerful new approach that should ultimately help make prediction possible.

Reuter and his colleagues show just how close science has come to using *ab initio* theoretical methods to calculate net catalytic reaction rates on complex solid surfaces. They have applied an elegant method that they call “*ab initio* statistical mechanics”, which involves two stages — first, using first-principles quantum mechanics to calculate

steps, I doubt that this explanation for the accuracy of Reuter and colleagues' method can be extended to other catalytic reactions. It is well known that there are usually fewer than three rate-controlling steps in such reactions, in spite of their mechanistic complexity. Indeed, under many conditions there is a single rate-determining step<sup>4-6</sup>. The degree of rate control is usually greater than 0.5 for the most important step in such reactions, and it is unity when there is just one rate-determining step. A degree of rate control of 0.5 means that any (differential) error in the rate constant of that step would lead to an error in the net catalytic reaction's rate by that same factor, scaled by 0.5 (ref. 6). An error of 30 kJ per mol in the activation energy for such a step could thus cause the net mechanism's rate at 500 K to be in error by more than a factor of 500!

It would be interesting to apply the degree of rate control<sup>6</sup> to the authors' kinetic model so as to estimate which step in this reaction's mechanism has the largest degree of rate control. If its degree of rate control is greater than 0.3, it must mean that the authors were rather lucky in getting the activation barrier for this key step as accurately as they did with DFT, or in having its error cancel with other errors.

Another complication in tackling such complex systems is the difficulty of guessing which of the elementary steps are relevant, so that they can be included in the kinetic Monte Carlo simulation. Sometimes, processes on surfaces occur by rather unexpected elementary steps. Fortunately, this problem has been solved by Henkelman and Jonsson<sup>7,8</sup>. Unlike the situation in traditional kinetic Monte Carlo, in their method the atoms are not assumed to sit on lattice sites, and a list of all possible transitions need not be specified beforehand. Rather, their method elegantly finds the relevant transitions on the fly during the simulation.

Reuter and colleagues' paper<sup>1</sup> is important: it indicates that the day is not so far distant when computational methods can achieve the necessary chemical accuracy to guide catalyst development. Already, new *ab initio* approaches<sup>9-11</sup> are on the horizon that promise improvements in energy accuracy relative to current DFT methods, with acceptable costs in increased computer time.

Meanwhile, experiments will remain essential: in the foreseeable future, the best microkinetic models for solid-catalysed reactions will continue to be those that also incorporate experimentally measured activation energies for elementary steps. But the theoretical approach of Reuter *et al.* will be an essential complement to overall strategies intended to reveal structure-function relationships in heterogeneous catalysis. ■

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### Evolutionary biology

## Butterfly mimics of ants

Jeremy A. Thomas and Josef Settele

Large blue butterflies are notable for their rarity and ability to dupe ants, and they are endangered. A genetic reconstruction of how social parasitism evolved among them will overturn conservation priorities.

Ants are such formidable predators that perhaps 100,000 other species of insect have evolved mechanisms to coexist with them<sup>1</sup>. Adaptations include armour to resist attack, mimicry to avoid detection, and secretions such as honeydew to feed or appease them<sup>2</sup>. In general, both partners benefit: in return for honeydew, the ants protect aphids from enemies. But natural selection can also favour cheats. It is a short evolutionary step from possessing the attributes to live safely among ants to deploying them against a colony.

Thus, among insects as diverse as butterflies, crickets, beetles and flies are specialist 'social parasites', perhaps 10,000 species in all, equipped to penetrate the highly protected chambers inside ant nests and feed, isolated

from enemies, on the rich resources concentrated there. Writing on page 386 of this issue, Als and co-workers<sup>3</sup> provide the first molecular-genetic reconstruction of one such evolutionary pathway, that of large blue butterflies (genus *Maculinea*), including the pathway's divergence into two remarkable strategies for exploiting ants.

The large blues form a small genus that has become an icon for conservation across Europe and Asia. The adults fly in summer, laying eggs on specific plants. After two to three weeks of eating flowers, the caterpillar settles beneath its food plant to await discovery by red ants (*Myrmica*). By secreting hydrocarbons that mimic those made by *Myrmica*<sup>4</sup>, the caterpillar tricks a foraging worker into taking it into the nest, where it is



Figure 1 A cuckoo butterfly. This species (Rebel's large blue, *Maculinea rebeli*) survives in a few European alpine meadows. Its white eggs are laid on a particular plant, cross-leaved gentian, and the young caterpillar initially feeds on the flowers. The caterpillar then tricks a species of red ant, *Myrmica schencki*, into taking it into the ant nest. There it lives like a cuckoo (inset), being fed by nurse ants that are fooled by the insect's chemical and behavioural mimicry of the ant's own grubs, before completing its life cycle with the pupa and adult stages.

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