► quick way to identify interactions that should be investigated further.

Predicting how untested compounds will interact with proteins in the body, as Drugable attempts to do, is more challenging. In setting up the website, Cardozo's group selected about 600,000 molecules from PubChem and the European Bioinformatics Institute's ChEMBL, which together catalogue millions of publicly available compounds. The group evaluated how strongly these molecules would bind to 7,000 structural 'pockets' on human proteins also described in the databases. Computing giant Google awarded the researchers the equivalent of more than 100 million hours of processor time on its supercomputers for the mammoth effort.

The team came up with ranked docking scores describing some 4 billion potential drug-protein interactions. Then the group cross-referenced the target proteins with those in the NLM's Gene Expression Omnibus database, which shows where in the body different genes that code for proteins are expressed. This allowed them to predict where the drug might act, says Cardozo: if Drugable finds an interaction for a protein that is highly expressed in a certain tissue, chances are good that the effect would manifest itself in that tissue.

Pharmaceutical companies have been doing similar computational predictions for years, says Jeremy Jenkins, a researcher at the Novartis Institutes. But he says that Novartis, which has a library of 1.5 million public and proprietary compounds, has never attempted to analyse as many proteins and drugs at once as Drugable has done.

Cardozo hopes that Drugable will be particularly helpful in evaluating psychiatric drugs, which often act in ways that are difficult to measure. As a demonstration, Cardozo's group applied Drugable's algorithm to clozapine and chlorpromazine, two drugs often prescribed to treat schizophrenia.

As expected, Drugable showed that the two drugs bind most strongly to receptors for the neurotransmitters serotonin and dopamine, which are expressed in the parts of the brain involved in higher information processing. But it found that clozapine, which also stabilizes mood disorders such as depression, binds strongly to a particular dopamine receptor called DRD4, which is expressed in the brain's pineal gland — a known mood regulator.

The group also found that clozapine binds to a receptor in the part of the brain that regulates saliva production; excessive salivation is a known side effect of clozapine. Although the biochemical explanations for mood regulation and salivation have been proposed before, Cardozo says that Drugable can be used to reveal the most plausible mechanisms. ■

RUNZHI ZHANG

The red turpentine beetle has wiped out more than 10 million pine trees in China in the past 15 years.

ECOLOGY

China battles army of invaders

Raft of control measures slows the march of alien species.

BY JANE QIU IN QINGDAO

When China kicked open the doors to international trade in the late 1970s, not everything that came in was welcome. Along with Western goods and new technologies, alien organisms infiltrated the country. A comprehensive survey now reveals that almost 550 non-native species, from viruses to fish and mammals, have become invasive in the country (see 'Space invaders'). They are costing an estimated US\$15 billion in losses each year, with damage to crops and forests a particular problem.

"As the volume of international trade has grown exponentially, so has the number of alien species," said Li Bo, director of the Office for Management of Alien Species in the Ministry of Agriculture, Beijing, at the second International Congress on Biological Invasions in Qingdao last month.

Since 2000, China has tightened its regulations on importing plant materials and has enforced strict quarantine requirements. It has also spent more than \$1 billion establishing databases of invasive species, monitoring their spread, researching invasive mechanisms and ecological impact, and developing control technologies. This has led to an "explosion of research", says Wan Fanghao, an ecologist at

the Chinese Academy of Agricultural Sciences' Institute of Plant Protection in Beijing.

Wan is currently finalizing a \$10-million, decade-long project funded by the Ministry of Science and Technology to study invasive species in agriculture and forestry. At the Qingdao meeting, where some of the results were presented, scientists showed how a better understanding of what makes an alien species invasive could aid in the development of effective controls.

A case in point is the whitefly *Bemisia tabaci*, an insect that feeds on plant vascular tissue called phloem. It causes damage both directly through feeding and indirectly through the transmission of plant viruses, and has wreaked havoc on vegetable and cotton production in all of China's provinces except Tibet. In a major outbreak in 2009, "a quarter of vegetable farms nationwide, about 200,000 hectares, were plagued, which reduced the yields by 50% to 80%", says Liu Shusheng, an entomologist at Zhejiang University in Hangzhou.

Researchers have now managed to halt the whitefly's march. Strategies such as planting crop varieties that are resistant to the pest, separating individual seedlings to minimize pest spread, applying low levels of pesticides and implementing biological control with natural enemies means that "there haven't been major

outbreaks since 2009”, says Wan.

Another invader that has been brought under control is the red turpentine beetle (*Dendroctonus valens*). In North America, the beetle mainly attacks dead or ailing trees. But the beetles, which were introduced to China in the 1980s, have wiped out more than 10 million pine trees in northern provinces since 1999.

A study led by Sun Jianghua, an entomologist at the Chinese Academy of Sciences' Institute of Zoology in Beijing, found that the interaction between the beetles and their symbiotic fungus *Leptographium procerum* is key to their 'personality change' in China (J. Sun *et al. Annu. Rev. Entomol.* **58**, 293–311; 2013). Since its arrival, “the fungus has mutated into novel genotypes”, says Sun. One of these induces trees to release large amounts of the compound 3-carene — a strong attractant to the beetles — that is not released in response to the North American fungal variant.

The finding has led to a series of successful projects to trap beetles using 3-carene. The approach, says Sun, is part of an integrated pest-management programme, launched in 2007, that also includes the use of other chemical attractants and pesticides, and efforts to replace single-species forests with a mix of plants.

As a result, the spread of the red turpentine

SPACE INVADERS

China currently has 544 invasive species, a fourfold increase on the number in 1900.

beetle is mostly under control, says Sun. Fewer than 1 in 1,000 trees are now infected, compared with the staggering 3 in 10 that were affected in Shanxi province in 2001, during one of the worst outbreaks.

Sun's findings raise the possibility of a potential 'reinvansion' of the United States by the red turpentine beetle and its Chinese fungal variant, says Daniel Simberloff, an ecologist at the University of Tennessee in Knoxville. “The policy implications are huge,” he adds.

What is happening in China matters to the rest of the world, says Helen Roy, an ecological entomologist at the Centre for Ecology

and Hydrology in Wallingford, UK. Biological invasions are “two-way traffic”, she says. Most of the forest pest species in North America originally came from China and some of its exports have wreaked havoc in Europe.

When dealing with invasive species, international collaboration is extremely important, says Roy. She has been studying the invasion of the harlequin ladybird (*Harmonia axyridis*) in Europe and, by working with Chinese researchers, is now trying to understand the insect's behaviour and natural enemies in the hope of developing effective control measures.

But administrative issues in China sometimes hamper scientists' efforts, says Wan. For instance, many alien species enter China by piggybacking on imports of rubbish from developed countries (waste disposal is big business in China). But it is unclear which ministry is in charge of inspection and monitoring of the cargo. Moreover, tackling invasive species often involves multiple ministries. “There needs to be better coordination and more data sharing between them,” says Sun.

In any case, the problem of invasive species will not go away, says Wan. “With climate warming, increasing international trade and rapid urbanization, the problem of biological invasions will only get worse,” he says. “We need to keep a close eye on potential troublemakers.” ■