



## Hebrew University Looks to Commercialize Optimization Algorithm for Drug Discovery Applications

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By Bernadette Toner

**Yissum**, the technology-transfer arm of the Hebrew University of Jerusalem, is exploring commercialization plans for a stochastic optimization algorithm that can be used to winnow down large compound libraries to a handful of molecules with the highest probability of possessing specific drug-like characteristics.

The technology, called Dralgo, is based on a method called Iterative Stochastic Elimination, or ISE, developed more than a decade ago by Amiram Goldblum, a professor in Hebrew University's School of Pharmacy. According to the university, the approach improves upon other selection approaches, which tend to identify either global or local minima, because it is able to find both simultaneously.

ISE is a general optimization approach, but Goldblum's team has been focused on applying it to a number of drug discovery applications, including the production of focused compound libraries with optimized drug-like properties, and the creation of bioactivity indexes that can rank the likelihood that molecules will interact with specific targets. The researchers are also using the approach to identify single molecules that would target multiple proteins for use in cancer and other multi-factorial diseases.

While many computational drug-discovery methods are based on chemical structures, "we are not focusing on structures, but on properties," Goldblum told BioInform.

The method relies on molecular descriptors, such as molecular weight or the number of rotatable bonds, which are used to classify a training set of molecules as either active or inactive based on their ability to pass through a range of values for each descriptor. The complete set of property ranges that identifies the active molecules comprises a filter.

"We optimize the filters in order to get the best distinction between the actives and the inactives," Goldblum said, "and then we get a whole set of filters as a result, and those filters all together constitute a model." The model is then used to grade any given molecule's probability of being active or inactive along a scale called the Drug-Like Index.

The team can build models to select molecules with particular characteristics, such as oral bioavailability, solubility, blood-brain barrier passage, and the like.

In addition, the fact that the approach is not tied to molecular structure increases the likelihood of identifying novel molecules, Goldblum said. "Instead of relying on what's called scaffold hopping ... we get molecules that were never examined before. We never get a me-too candidate because we do not compare structures at all."

The process is relatively quick. It takes around two days to create a new model and then about one day to run the calculation on a single CPU. The most time-consuming step, Goldblum said, is calculating the properties for the molecules in the initial data set, which usually takes three or four days, depending on the size of the database.

Goldblum's team has validated the approach in several collaborations. In one study with colleagues at Hebrew University, the team applied ISE to the ZINC database of more than 2 million molecules in an effort to identify acetylcholinesterase inhibitors for Alzheimer's disease. The researchers first developed an ISE model to distinguish active inhibitors and non-inhibitors and then applied it to ZINC to identify 10 molecules that were predicted to have the desired biological activity. Of these, three were experimentally validated, and none of them had ever been patented or mentioned in the literature, Goldblum said.

In another study, conducted with researchers at Goethe University, Goldblum and colleagues used Dralgo to design a protein drug against chronic myeloid leukemia using a database of 10 80 protein sequences. The method pinpointed 10 peptides for in vitro studies, and six of those were found to inhibit CML cell proliferation.

Goldblum said that he hasn't compared the method directly to structure-based approaches, so he can't rule out the fact that they might have identified the same molecules. "What I can say is that our method finds new molecules that were not known before and their structures are completely different from the original ones that we studied," he said.

In a paper published in February in the Journal of Chemical Information and Modeling, Goldblum and colleagues compared ISE's ability to predict oral bioavailability with several other algorithms — including neural networks, support vector machines, decision trees, and the nearest-neighbor method — and found that the accuracy of the ISE models offered a 13 percent improvement over that of any other classification method.

Alexander Tropsha, chair of the division of medicinal chemistry and natural products at the University of North Carolina's Eshelman School of Pharmacy, whose work focuses on computational drug design, said that he is familiar with ISE, which he called "quite novel," though he hasn't used it.

"Models developed with the [ISE] method have been shown to have very high accuracy for predicting whether a compound is likely to be a drug," he said, adding that the findings in the recent paper show a "substantial improvement" over other methods.

Yissum is currently working on commercializing the technology, but Goldblum said that he and his colleagues have not decided yet on the exact business model they'd like to pursue. "I think we have an excellent technology that still requires some thinking about the best business model," he said.

"We would be glad to provide a service for companies who are looking for new molecules and they could use our method," he said. "Whether they use it on our computer or as a program on their computer we have not decided yet."

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