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Subject: Evolutionary algorithm

Posted by [pc419714@ohio.edu](mailto:pc419714@ohio.edu) on Tue, 12 Feb 2019 16:20:15 GMT

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When I use the evolutionary algorithm and select a scaffold it says the selected structures are left untouched. However the scaffolds are mutated. Is there any way to just mutate the R groups only and leave the skeletons unchanged? We are doing this to conform with certain criteria.

Thanks for this amazing software!

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Subject: Re: Evolutionary algorithm

Posted by [thomas](#) on Tue, 12 Feb 2019 17:40:50 GMT

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When you define the first generation of molecules, then you may double click any of them to open the structure in the structure editor. Use the lasso tool and select the scaffold, which should not be touched. When selected, all scaffold atoms and bonds should be drawn in red. Then close the editor. In the list of first generation molecules, the unmutable scaffolds should still be drawn in red. When starting the evolution, these atoms and bonds won't be changed in any way. I just checked that this is still working. See example image...

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### File Attachments

1) [elib.png](#), downloaded 596 times

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Subject: Re: Evolutionary algorithm

Posted by [pc419714@ohio.edu](mailto:pc419714@ohio.edu) on Wed, 13 Feb 2019 22:05:52 GMT

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Thank you so much!

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Subject: Re: Evolutionary algorithm

Posted by [pc419714@ohio.edu](mailto:pc419714@ohio.edu) on Thu, 14 Feb 2019 03:28:56 GMT

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Also, I am wondering about clustering using flexophores. This measure is supposed to give you a measure of biological activity..... Does this mean that it predicts binding to specific proteins? Will it tell you what a given molecule will bind if I generated the flexophores and then clustered? It supposedly takes a lot of time and memory so I wanted to make sure before I did it. I just wanted to know which kinases my molecules bind, so I selected find similar compounds in file for a large data set of known kinase inhibitors and found which ones were similar. I did not use the flexophores though. Would the flexophores give me more information on the function of my molecules than skelspheres would? Thanks again!

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Subject: Re: Evolutionary algorithm  
Posted by [thomas](#) on Thu, 07 Mar 2019 15:25:14 GMT  
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When you have a few active molecules on a given target and intend to search a large compound collection for similar compounds in order to find more potential active ones, then the fastest approach is to use chemical(=graph) similarity of some kind, e.g. the SkeletonSpheres descriptor. Very similar compounds often have similar activities. The drawback of this approach is that this won't do scaffold hopping, which mean that you won't find structures with a substantially different structure core or substitution pattern. The idea of the flexophore (<https://pubs.acs.org/doi/abs/10.1021/ci700359j> addresses this issue. It was designed to compare the representative conformer sets of two molecules concerning their protein-binding potential. It classifies atoms that may contribute to binding using PDB statistics. The flexophore considers molecules similar, if they contains atoms that have similar binding behaviour to protein atoms if these atoms' relative 3D orientations are also similar. Depending on the conformational flexibility of individual molecules and the target you may achieve a significantly higher hit rate compared to random or diverse selection, if you preselect screening candidates by flexophore similarity.

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Subject: Re: Evolutionary algorithm  
Posted by [pc419714@ohio.edu](#) on Thu, 14 Mar 2019 21:08:19 GMT  
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thanks

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Subject: Re: Evolutionary algorithm  
Posted by [sansun](#) on Sun, 10 May 2020 04:24:31 GMT  
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For flexophore, is it possible to somehow use known binding conformation for one of the molecules and then do the calculation for others relative to it.

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Subject: Re: Evolutionary algorithm  
Posted by [thomas](#) on Sun, 10 May 2020 13:32:37 GMT  
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not yet, but we are currently updating the flexophore algorithm. Providing one-conformer flexophore similarity is a natural next step. You may look into PheSA similarity as fitness criterion for the evolutionary library. PheSA (pharmacophore enhanced shape alignment) is not documented yet and still evolving, but the newest unofficial DataWarrior update ([openmolecules.org/datawarrior/dw521win.zip](https://openmolecules.org/datawarrior/dw521win.zip) & [dw521x.zip](https://openmolecules.org/datawarrior/dw521x.zip) for Windows and Linux/Max, respectively) seems to work quite well. For PheSA-fitness you supply a ligand in its binding conformation and the fitness function give a high score if at least one candidate conformer may superpose nicely with the binding ligand conformer considering both: shape and pharmacophore

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features. The zip file contains just the DataWarrior.exe (datawarrior.jar for Linux/Mac) to replace the official 521 version. If you update this way, note that the flexophore is also updated, but not final yet. Thus, for using the flexophore, I recommend using the official 521 version.

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Subject: Re: Evolutionary algorithm

Posted by [sansun](#) on Wed, 13 May 2020 13:08:03 GMT

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Great, looking forward to the official release.

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