

How to set up your 3DM package.

This guide is for registered 3DM users that have a 3DM account. If you don't have an account yet please first request a 3DM account here:

<https://accounts.bio-product.nl/>

The main steps to install your 3DM package are:

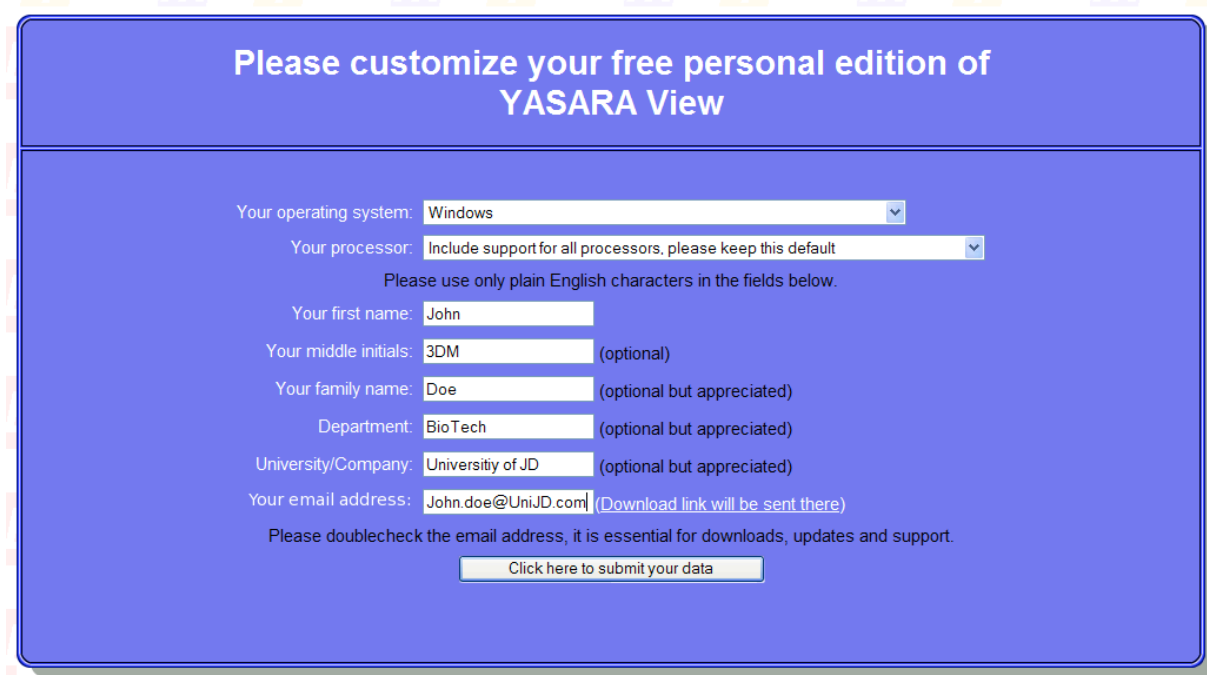
1. Request Yasara if you don't already have Yasara. Otherwise update Yasara to the newest version.
2. Connect yasara with 3DM
3. Install Utopia

1a. Yasara installation instructions for new users:

If you are new to Yasara, go to www.yasara.org, select "Downloads" -> "Yasara for new users" and have a look which Yasara version you would like. The free "Yasara view" works only on the "Nuclear Receptors – ligand binding domain (Demo 2008)" 3DM system. All other versions work on all your 3DM databases. If you like to tryout Yasara with the 3DM module you can first request the free Yasara View and use it with the Nuclear Receptor database.

To get 3DM integrated with Yasara you have to **type "3DM" in the "your middle initials" field** (see figure 1). This is really important, do NOT forget this!!!!

Note: If you already downloaded YASARA once, don't do it again, but [request an update instead](#).



Please customize your free personal edition of
YASARA View

Your operating system:

Your processor:

Please use only plain English characters in the fields below.

Your first name:

Your middle initials: (optional)

Your family name: (optional but appreciated)

Department: (optional but appreciated)

University/Company: (optional but appreciated)

Your email address: ([Download link will be sent there](#))

Please doublecheck the email address, it is essential for downloads, updates and support.

[Click here to submit your data](#)

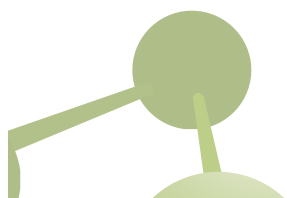


Figure 1. Example of a Yasara request by John Doe. Note the use of “3DM” at the middle initials field that is needed to include the 3DM plugin in the Yasara package.

After requesting Yasara you will get an email with download and installation instructions.

1b. Yasara installation instructions for existing yasara users:

If you already are a Yasara user, please request an update via www.yasara.org to get the latest version. Make sure to type “3DM” in the “Update from yasara version” field to have 3DM included in the Yasara package (see fig 2.). Correct examples are:

1.1.1 3DM

3DM 13.1.15

3DM

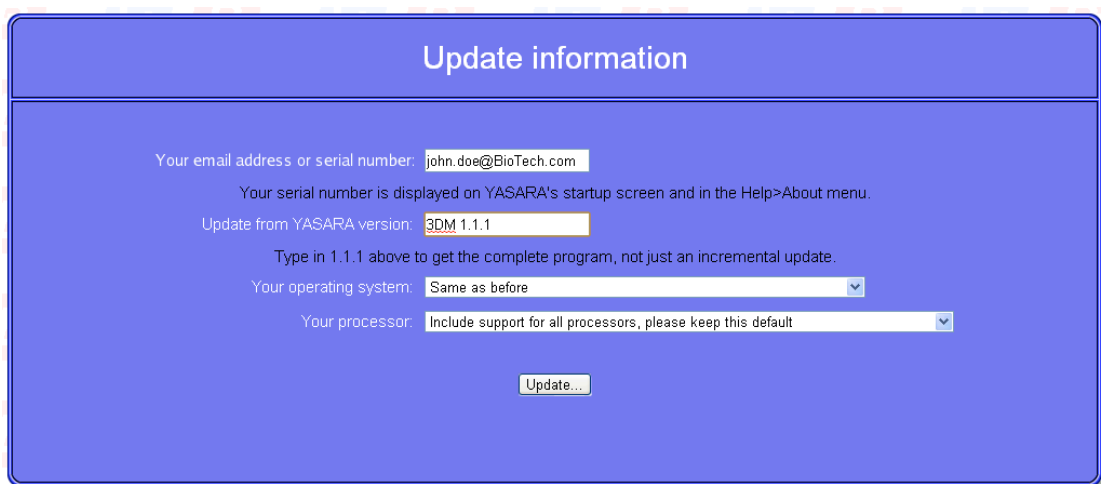
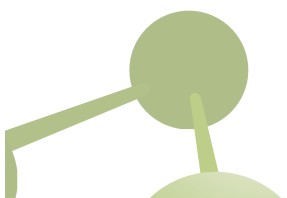
A screenshot of the "Update information" dialog box in Yasara. The dialog has a blue header with the title "Update information". Below the header, there are several input fields and a button. The first field is "Your email address or serial number:" with the value "john.doe@BioTech.com". Below it is a note: "Your serial number is displayed on YASARA's startup screen and in the Help>About menu." The next field is "Update from YASARA version:" with the value "3DM 1.1.1". Below it is a note: "Type in 1.1.1 above to get the complete program, not just an incremental update." The next field is "Your operating system:" with a dropdown menu showing "Same as before". The next field is "Your processor:" with a dropdown menu showing "Include support for all processors, please keep this default". At the bottom center is a button labeled "Update...".

Figure 1. Example of a Yasara update request by John Doe. Note the use of “3DM” at the “Update from Yasara version” field that is needed to include the 3DM plugin in the Yasara package.

2. The Yasara 3DM connection:

After installing Yasara, you should have a 3DM option between the “Analyze” and “View” options (Figure 3). If not you probably have not installed the correct python version. You can update/get python directly from the help menu in Yasara (see figure 2). Use this to install python and restart Yasara. If you still don’t have the 3DM option, please let us know (support@bio-product.nl).



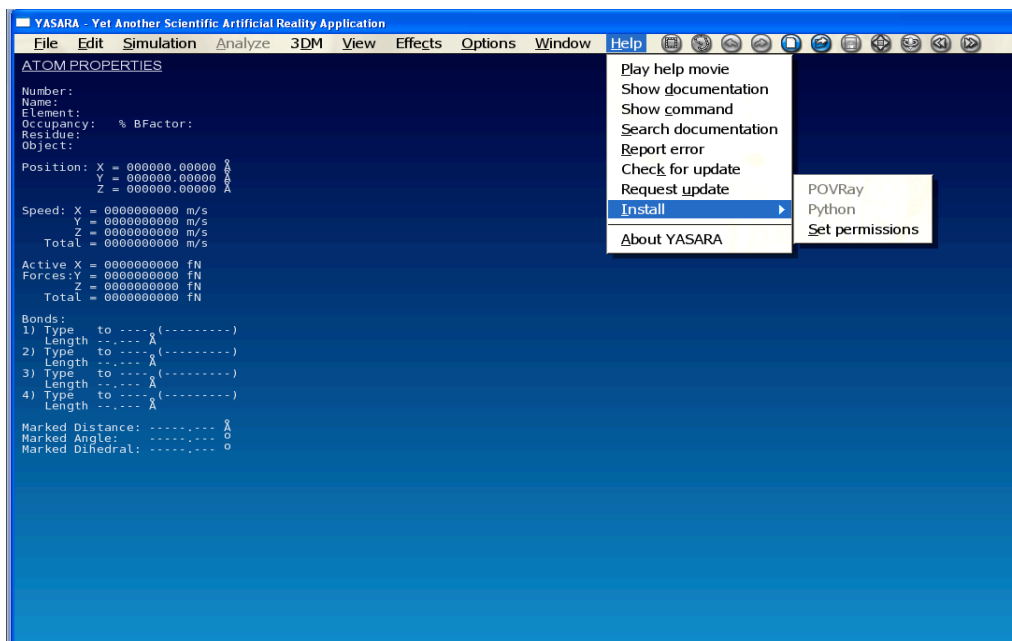

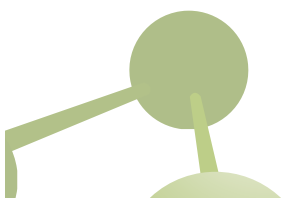


Figure 3. Yasara interface after installation of the 3DM plugin. Here the Help option was selected where Yasara offers the option the install python.

If you have requested the free Yasara View the 3DM-Yasara connection only works for the nuclear receptor ligand binding domain structures. You can try out how it works using nuclear receptor structures. For convenience we have prepared an example scene file containing two nuclear receptor structures which can be downloaded here: <https://3dm.bio-product.nl/guest-user/demo.sce> and opened with Yasara (File -> Load -> Yasara Scene). Just try out the different 3DM options and see what happens. If asked for a password, use your 3DM credentials. You can also find 3DM data by right clicking on amino acids. Note that the data in the Heads Up Display is clickable to retrieve the underlying data (figure 4).

By selection structures from the 3DM system yasara will understand the 3D alignment numbering used in the 3DM alignment. This ensures the coupling of the structures to other data in the 3DM database. There are two ways to select structures from 3DM:

1. Use the 3DM option in Yasara -> “select data from 3DM” and give a PDB name (e.g. 1A28).
2. You can also select structures directly from the 3DM websites (first login via 3DM.bio-product.nl and select the nuclear receptors – ligand binding domain demo 2008 system or to your own 3DM if you have one). Once logged in you can export structures to Yasara by generating a Yasara scene file via the “visualize data in structure” () option in the green banner once you have logged into the demo nuclear receptor 3DM system. This is how the example scene file was generated.



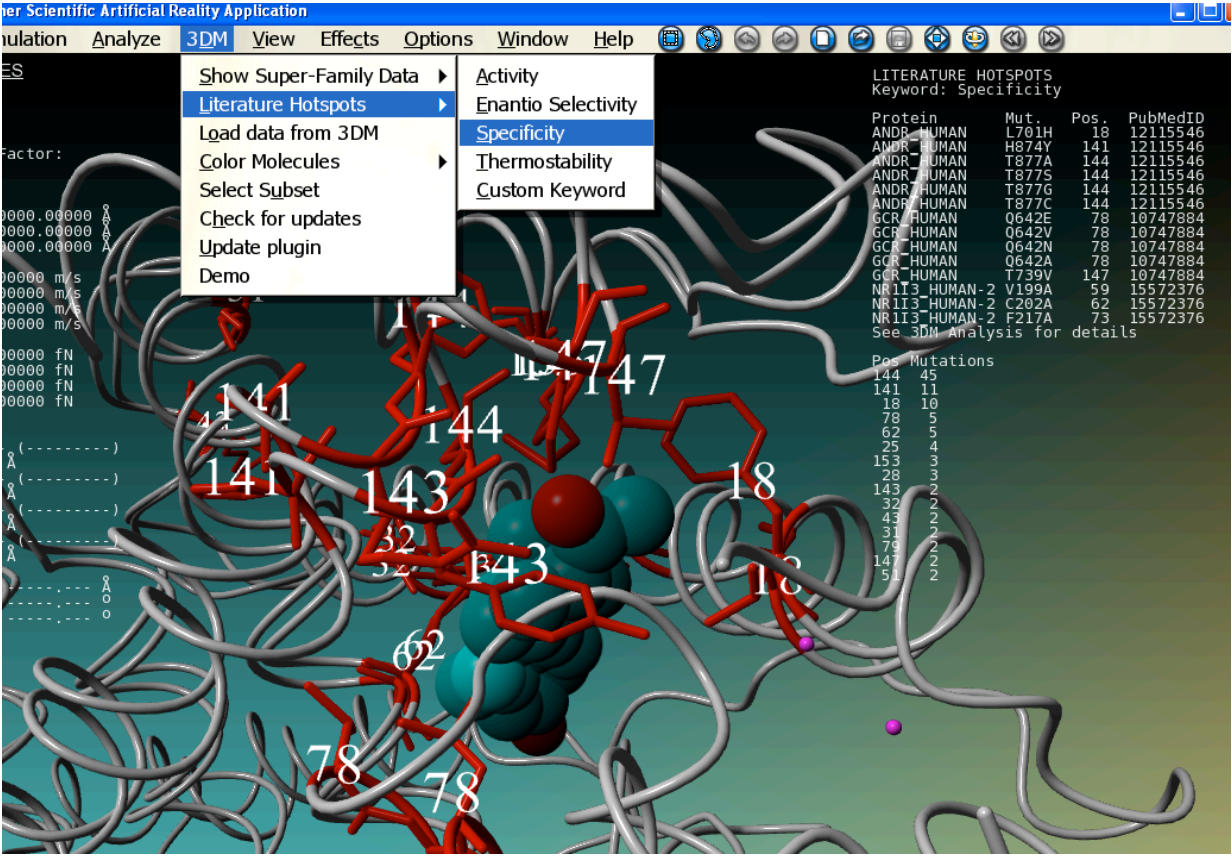
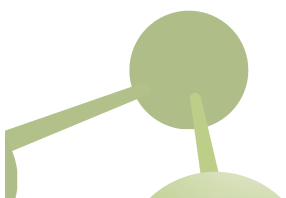


Figure 3. Yasara screenshot. Here mutations that are reported in literature to effect specificity are shown in red. Note that the heads up display on the top right contains links to the corresponding articles.



3. Installing Utopia Documents:

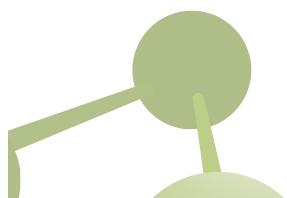
- Download Utopia from getutopia.com (Mac or Windows releases available: for Linux there is a beta-version which will probably work as well)
- Install the software

First, make sure Utopia has the right credentials:

- Run Utopia Documents
- Go to Edit - Preferences and click on the Plugins tab
- Put your 3DM username and password in the required fields
- Hit apply and close the preferences window
- Restart Utopia

Now open a paper.

- Download the demo paper from <https://3dm.bio-product.nl/guest-user/demo-paper.pdf> and open it with Utopia.
- After a couple of seconds, a number of 'boxes' should appear on the right. Additional data about the paper is displayed here.
- Click on the 'Bio-Product 3DM' box, and select the "Nuclear receptor – Ligand binding domain (Demo 2008)" 3DM system to annotate this paper with (if you don't see the Bio-Product box at this point you probably gave the wrong password)
- During the annotation you will see a white spinner in the blue bar on the left. When it is done the annotation process is complete. The first time you annotate a paper it can take up to 10 seconds, but after that it becomes quicker. If not, let us know.
- Scroll through the paper and hit the spacebar once in a while.
- The elements that are colored red are clickable. You can click on proteins, mutations and residues. You will see information retrieved from the 3DM database appears in the right banner. These things are again clickable. Just try them out and see how it works (see figure 3).



Structural Basis for Accommodation of Nonsteroidal Ligands in the **Androgen Receptor***

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The mechanism by which the **androgen receptor (AR)** distinguishes between agonist and antagonist ligands is poorly understood. **AR** antagonists are currently used to treat prostate cancer. However, mutations commonly develop in patients that convert these compounds to agonists. Recently, our laboratory discovered selective **androgen receptor** modulators, which structurally resemble the nonsteroidal **AR** antagonists bicalutamide and hydroxyflutamide but act as agonists for the **androgen receptor** in a tissue-selective manner. To investigate why subtle structural changes to both the ligand and the receptor (*i.e.* mutations) result in drastic changes in activity, we studied structure-activity relationships for nonsteroidal **AR** ligands through crystallography and site-directed mutagenesis, comparing bound conformations of R-bicalutamide, hydroxyflutamide, and two previously reported nonsteroidal androgens, S-1 and R-3. These studies provide the first crystallographic evidence of the mechanism by which nonsteroidal ligands interact with the wild type **AR**. We have shown that changes

in the compounds to agonists exist and represent a significant problem with currently prescribed prostate cancer drugs that target the **AR** (2–4). Different **AR** mutations cause agonism for hydroxyflutamide (HF, active form of flutamide) as compared with bicalutamide, suggesting that these ligands do not antagonize the **AR** by the same mechanism. Our recent report of the **W741L** R-bicalutamide crystal structure (5) demonstrated that R-bicalutamide induces the same overall fold of the **AR** ligand binding domain (LBD) observed in steroidal androgen-bound **AR** LBD crystal structures when bound to a mutant **AR** associated with resistance. Additionally, mutations to **Thr377** (4, 6) have been shown to result in agonist activity for HF as well as steroidal **AR** antagonists (7). Subtle differences in the AR–ligand interaction therefore are responsible for the activity of **androgen** antagonists. The recent discovery of nonsteroidal **AR** agonists by structural modification of bicalutamide and HF further reinforces this finding (8–10).

To date, multiple docking solutions have been reported to explain how the extra bulk on bicalutamide as compared with steroidal andro-

Back

 Mutation: "T377A"
 3D Mutation record

Thr 377 Ala
 3D number: 144
 in
 ANDR_HUMAN

 Protein
 UniProt | Bio-Product details

 Residue
 YASARA score | Bio-Product details

Other data

Conservation

Residue type occurrences at this position in the superfamily.



Mutations (at this position)

Mutations (at equivalent positions)

Downloaded from www.jbc.org

Figure 3. Screen shot of Utopia when correctly connected to 3DM.

5. Prepare yourself!

After installing everything, please watch the demo movie and consult our publications at www.bio-product.nl.

Please note that we regularly organize 3DM courses. 3DM is a complex program that has many powerful options. To get maximum value out of 3DM we advise to follow the 3DM/Yasara/Utopia course. These courses contain a large practical component in which participants solve real life problems from different fields (protein engineering, homology modeling, and drug design) with 3DM themselves. Information about the course can be found here: <http://www.bio-product.nl/#course>

Please connect to our linkedin Bio-Product & 3DM group to get news and updates: http://www.linkedin.com/groups/BioProduct-3DM-4633861?home=&gid=4633861&trk=anet_ug_hm

Enjoy 3DM!

The Bio-Product team!

