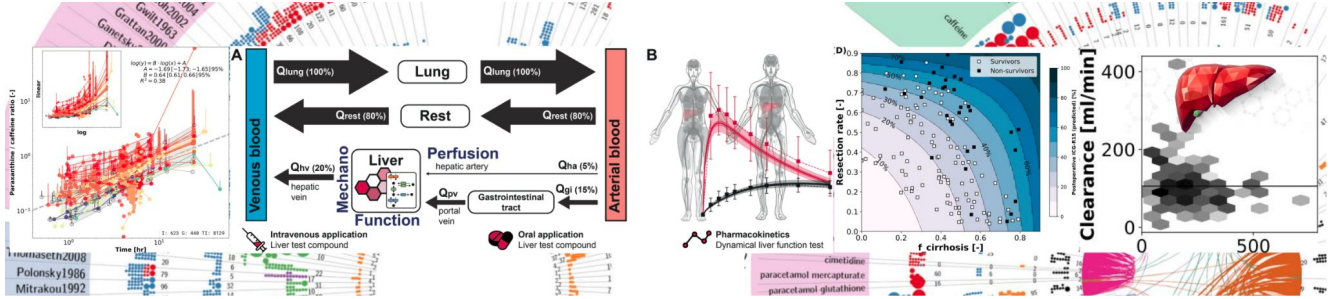


# Pharmacokinetics Modeling Course

## Structural Models

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# 🎯 Teaching Goals

By the end of this section, you should be able to:

1. **Explain the relationship** between Dose, Volume of Distribution (V), and Clearance (CL) using a simple algebraic model.
2. **Recognize variability** in pharmacokinetic parameters (such as CL and V) between different drugs and how this impacts drug exposure.
3. Develop a **basic understanding of physicochemical properties** (e.g., lipophilicity, molecular weight, solubility) and how they relate to pharmacokinetic behavior.
4. Understand the concept and utility of a **parameter scan** in pharmacokinetic modeling.
5. **Explore the effects** of changing V, Dose, or CL on drug concentration.

# Structural models as algebraic equations

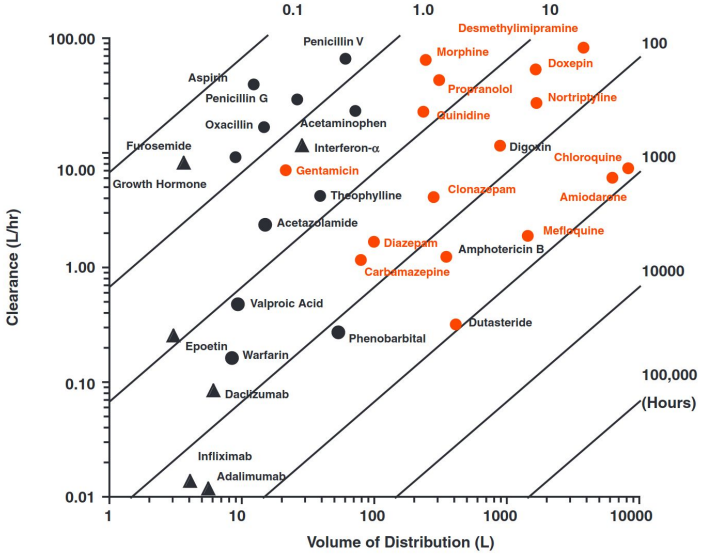
- simplest representation is an **algebraic equation** representing a **one-compartment model**
- drug being administered as single intravenous dose
- relationship between
  - independent variable time (t)
  - dependent variable concentration (C)
  - C depends on Dose, clearance (CL), and distribution volume (V)

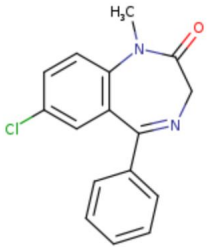
$$C_{(t)} = \frac{\text{Dose}}{V} e^{-\frac{CL}{V}.t}$$

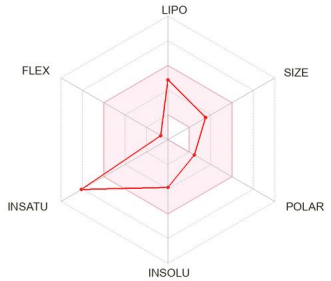
Mould DR, Upton RN. **Basic concepts in population modeling, simulation, and model-based drug development.** CPT Pharmacometrics Syst Pharmacol. 2012 Sep 26;1(9):e6. doi: 10.1038/psp.2012.4. PMID: 23835886; PMCID: PMC3606044.

# 🏃 Physicochemical properties 🏃

- Drugbank lookup (properties & SMILES) https://go.drugbank.com/
- Prediction tool http://www.swissadme.ch




**PROPERTIES**

| | |
|---|---|
| **State** | Solid |

**Experimental Properties**

| PROPERTY | VALUE |
|---|---|
| melting point (°C) | 138-140 |
| boiling point (°C) | 140 °C |
| water solubility | 10 mg/mL |
| logP | 1.18 |
| pKa | 3.5 |

# Structural models as algebraic equations

- Parametrization with clearance (CL) and volume of distribution (Vd)
- Simulation of concentration time course after given Dose

$$C_{(t)} = \frac{\text{Dose}}{V} e^{-\frac{CL}{V}.t} \qquad (1)$$

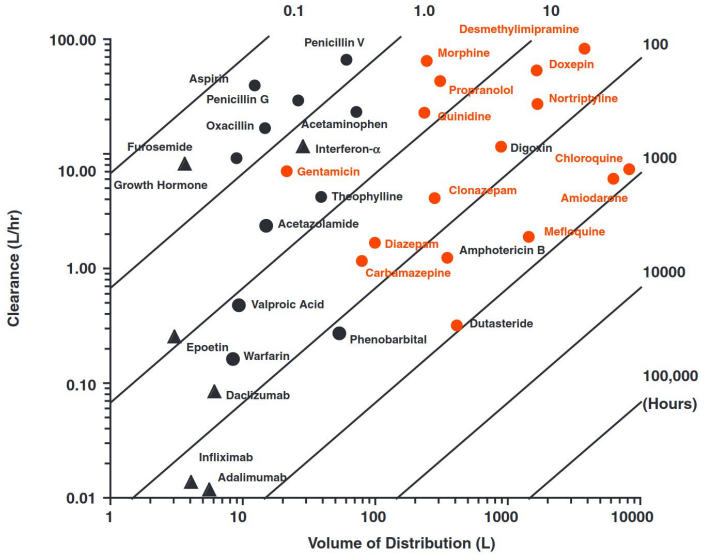



**FIGURE 5-8** Clearance (*ordinate*) and volume of distribution (*abscissa*) of selected acidic (*black circle*) and basic (*colored names*), as well as protein (*black triangle*), drugs vary widely. Diagonal lines on the fully logarithmic plot show the combinations of clearance and volume values with the same half-lives (hours). Note that drugs with very low clearance and very large volumes (*lower right-hand quadrant*) are uncommon; their half-lives are often too long for these drugs to be used practically in drug therapy. Note also that large protein drugs have volumes of distribution close to plasma volume (3 L) and that basic compounds tend to have larger volumes of distribution than acids. Digoxin and dutasteride are neutral compounds, while amphotericin B is both a weak acid and a weak base.


Mould DR, Upton RN. **Basic concepts in population modeling, simulation, and model-based drug development.** CPT Pharmacometrics Syst Pharmacol. 2012 Sep 26;1(9):e6. doi: 10.1038/psp.2012.4. PMID: 23835886; PMCID: PMC3606044.

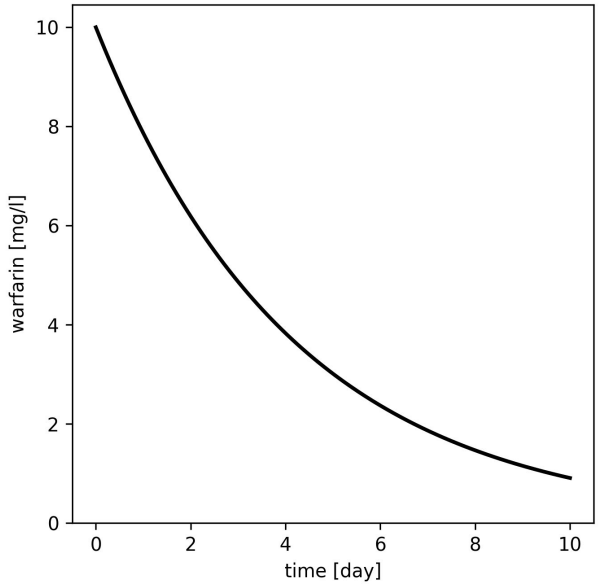
# Implementation Example

```python
from matplotlib import pyplot as plt
import numpy as np

# Warfarin
V = 10  # [l]
CL = 0.1  # [L/hr]
Dose = 100  # [mg]
t = np.linspace(start=0, stop=10*24, num=200)  # [hr]
C = Dose/V * np.exp(-CL/V * t)  # [mg/l]

# plot
f, ax = plt.subplots(nrows=1, ncols=1, figsize=(5, 5), dpi=300)
ax.plot(t/24.0, C, label="warfarin", color="black", linewidth=2.0)
ax.set_xlabel("time [day]")
ax.set_ylabel("warfarin [mg/l]")
ax.set_ylim(bottom=0)
plt.show()
```

$$C_{(t)} = \frac{\text{Dose}}{V} e^{-\frac{CL}{V}.t} \qquad (1)$$

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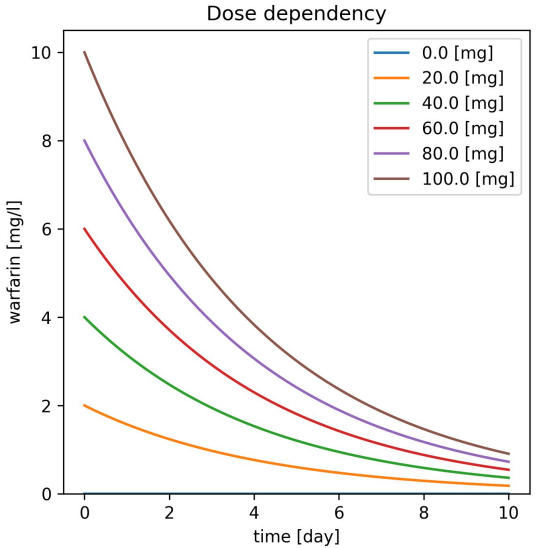
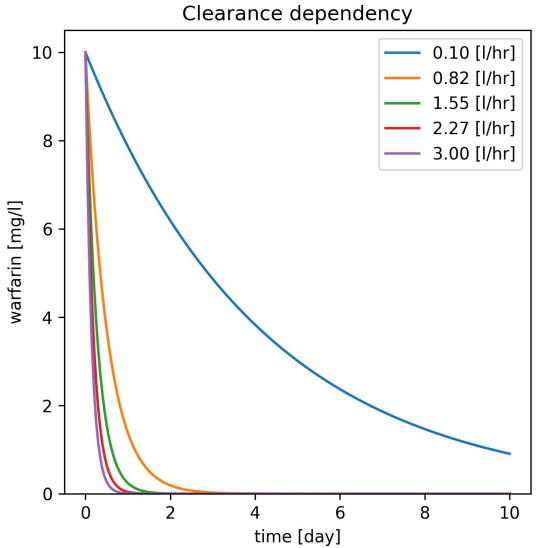
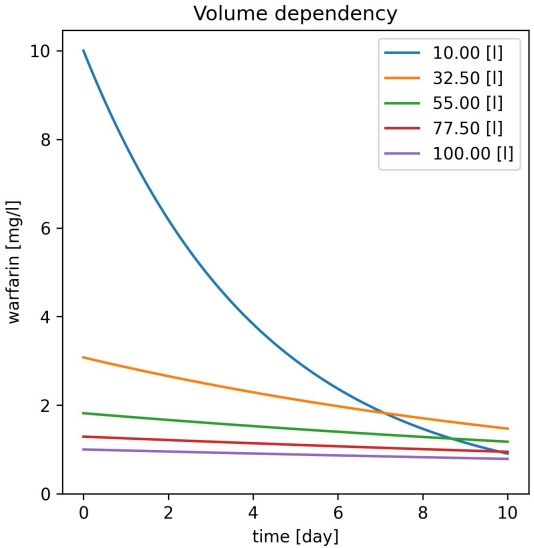
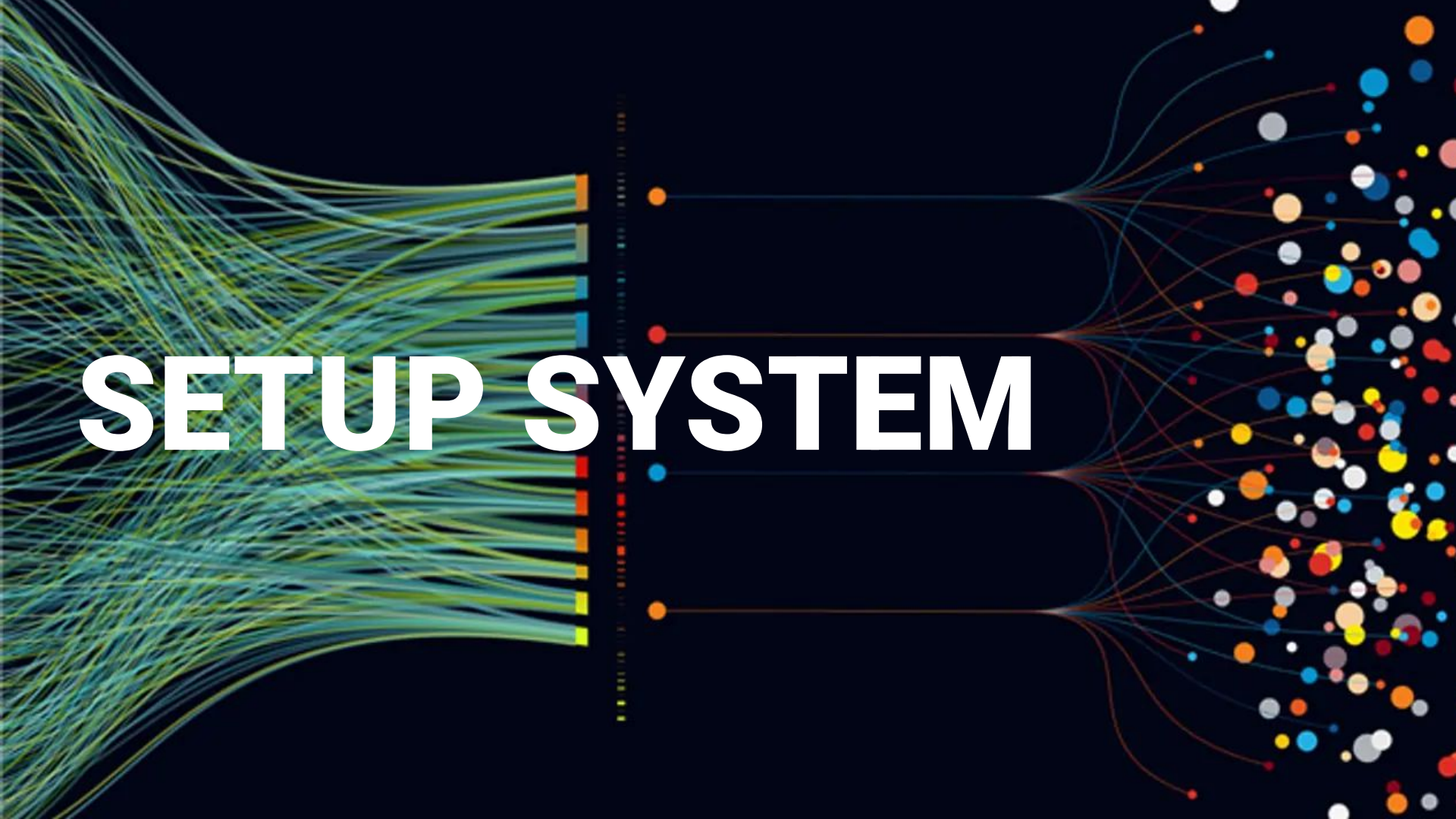
# Parameter scans

$$C_{(t)} = \frac{\text{Dose}}{V} e^{-\frac{CL}{V}.t} \qquad (1)$$



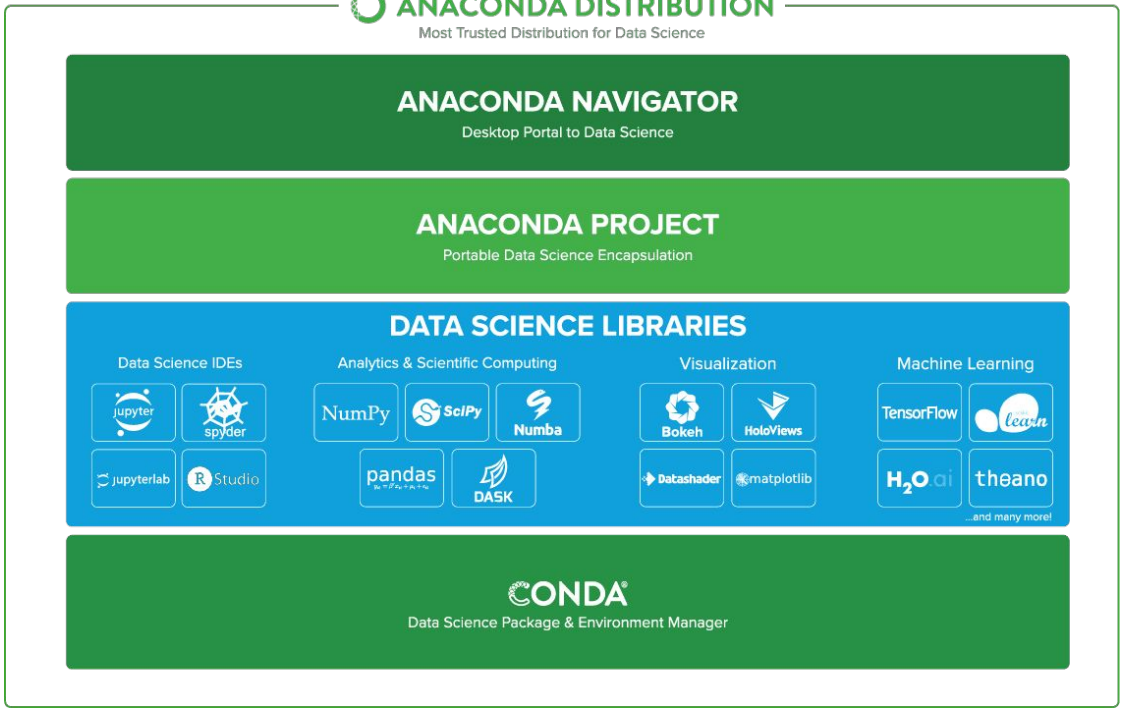

SETUP SYSTEM

# Install Anaconda

Install Anaconda Distribution
https://docs.anaconda.com/free/anaconda/#installation

**Anaconda® Distribution is a free Python/R data science distribution that contains:**

- conda - a package and environment manager for your command line interface
- Anaconda Navigator - a desktop application built on conda, with options to launch other development applications from your managed environments
- 250 automatically-installed packages that work well together out of the box
- access to the Anaconda Public Repository, with 8000 open-source data science and machine learning packages



# Setup conda environment

- create conda environment `mb19`
  - open terminal
  - create environment
    `conda create -n mb19`
  - install packages
    `pip install numpy scipy matplotlib pandas`

## Activating/Deactivating environments

- To see a list of environments: **conda env list**

```
vperezg@login1:/home/vperezg>conda env list
# conda environments:
#
base                  *  /prod/apps/conda/3
bio-computation          /prod/apps/conda/3/envs/bio-computation
machine-learning         /prod/apps/conda/3/envs/machine-learning
machine-learning-gpu     /prod/apps/conda/3/envs/machine-learning-gpu
prosado                  /prod/apps/conda/3/envs/prosado
qiime2-2019.7            /prod/apps/conda/3/envs/qiime2-2019.7
quantum-chem             /prod/apps/conda/3/envs/quantum-chem
```

- To load an env: **conda activate <env_name>**

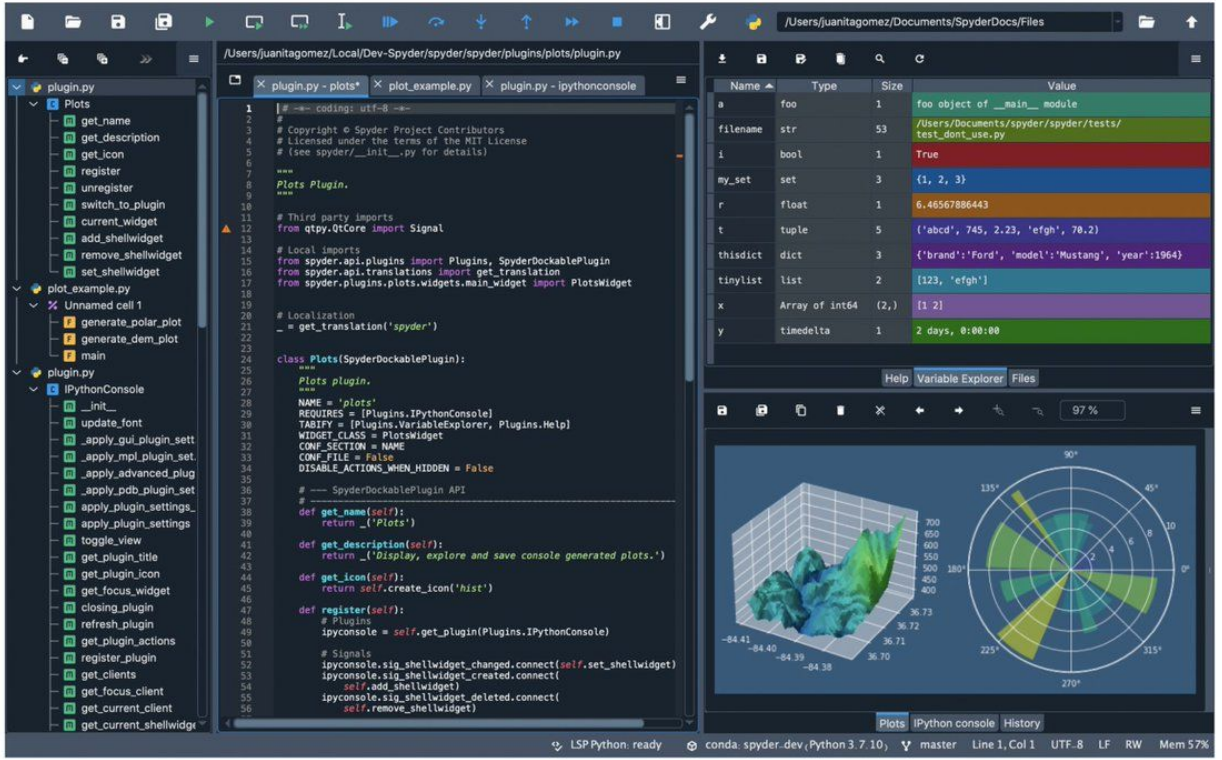
```
vperezg@login1:/home/vperezg>conda activate bio-computation
(bio-computation) vperezg@login1:/home/vperezg>
```

- To unload: **conda deactivate**

```
(bio-computation) vperezg@login1:/home/vperezg>conda deactivate
vperezg@login1:/home/vperezg>
```

# Install Spyder

- available via the **anaconda navigator**
- alternative use **Jupyterlab**
- alternative use **Jupyter notebooks**



# Jupyterlab instance

https://itbportal.biologie.hu-berlin.de/koenigcourse/hub/login