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Introduction

Multidimensional Data in Biomedical Research

As modern biosciences advance, researchers increasingly encounter datasets that are influenced by a variety of independent variables, such as time, dosage, and environmental conditions. These variables introduce multidimensional complexity into datasets, challenging traditional analysis methods. For instance, cell adhesion studies, which are crucial for understanding cellular interactions and cancer metastasis, often require analyses across multiple time points and varying adhesion molecule concentrations, demonstrating a time-dependent variability that significantly impacts biological interpretations (Rebl et al., 2010; McKay et al., 1997; Bolado-Carrancio et al., 2020).

Multidimensional data encompass datasets where multiple *independent variables* (here reffered to as *factors*) can influence one *dependent variables* (*outcomes*) (Krzywinski & Savig, 2013). In biomedicine, dependent variables are often continuous (intervals or ratios), whereas independent variables are often categorical (ordinal or nominal), respectively. Categorical variables comprise discrete values called categories or *levels*, which are assigned to experimental conditions or measurement modalities, for example the factor *'time'* could comprise three levels: *'0 h'*, *'24 h'*, and *'48 h'*. Such setups are attractive, because they are compatible with common hypothesis tests, such as ANOVA etc. (Motulsky, 2018): If the levels of one factor are associated with a different outcome, that factor is considered to have an influence on the dependent variable. Multiple factors address multiple hypotheses, including the influence from each individual factor, but also potential interactions between factors. This makes it crucial to design analysis strategies that can reveal the true structure and value of the data (Krzywinski & Savig, 2013).

A primary example of multidimensional data is multiplex RT-qPCR, where the expression levels of various genes are measured across different samples under varying conditions (Bustin, 2014). Here, the dependent variable is typically the fold change expression values derived from $\Delta\Delta$Ct calculations (Brankatschk et al., 2012). The independent variables include the genes being measured and the experimental conditions under which the samples are processed.

Microscopy data further illustrate the complexity of multidimensional datasets (Rueden et al., 2017). In this context, the dependent variable might be a quantifiable feature, such as cell count or morphological metrics extracted from image analyses. The independent variables can expand immensely to include factors such as well-plate coordinates in a 96-well plate, Z-positions in confocal microscopy, and time points in time-lapse studies.

Lastly, big-data aggregation tools like `Metascape` provide a rich source of multidimensional data by integrating various dependent variables, such as gene expression fold changes and associated p-values, with independent variables spanning gene identifiers, gene ontology terms, and

ontology classes derived from multiple databases (Y. Zhou et al., 2019). Despite the provision of summarized graphical outputs, the raw data often remain in complex, nested formats within Excel sheets, posing significant challenges for hypothesis-driven research.

This extensive integration of multiple dimensions requires sophisticated visualization and analysis techniques. While basic statistical visualizations suffice for one- or two-dimensional data, more complex data sets necessitate advanced techniques, which allow researchers to visualize and interact with data in ways that elucidate the underlying patterns and relationships (Dunn et al., 2017). However, the gap between available visualization tools and the needs of clinicians or biologists without extensive bioinformatics training remains wide, emphasizing the need for intuitive, user-friendly tools that bridge this knowledge gap and enhance the accessibility of complex data analyses (Dunn et al., 2017).

Nontransparencies in Biomedical Data Analyses

The advent of advanced technologies in biosciences has ushered in an era of *big data*, characterized by unprecedented volumes and complexities of data (Bubendorf, 2001; A. Yang et al., 2017; Ekmekci et al., 2016). This rise has been paralleled by significant challenges in data analysis, particularly impacting the reproducibility of scientific research. Studies such as the Baker (2016) survey revealed that more than 70 % of researchers have tried and failed to reproduce another scientist's experiments, highlighting a reproducibility crisis that questions the reliability of scientific findings (Begley & Ioannidis, 2015; Ioannidis, 2005).

Reproducibility is considered foundational to scientific research, ensuring that findings are reliable and verifiable. Still, its meaning requires precise definition (Goodman et al., 2016). The common understanding of scientific reproduction implies not only that detailed information is provided to enable independent repetition (*transparency*), but also that time and effort is invested into repeating the experiments (*corroboration*). However, since modern biomedical journals are demanding novelty research, and since experiments have become highly specialized and time-intensive, repeating someone else's work is considered neither interesting[3] nor possible for most publications (Flier, 2022; Peng, 2011). Hence, the meaning of reproducibility is confined to *transparency*, a concept that has been applied to many fields, including clinical trials (Goodman et al., 2016; Committee on Strategies for Responsible Sharing of Clinical Trial Data et al., 2015).

Nevertheless, there is a surprising amount of evidence for nontransparencies in biomedical data analyses: For Microarray-based miRNA profiling, raw data was not reported in more than

[3]Flier (2022): *"There are no scientists with the interest, resources, or incentives to "repeat" or confirm this vast sea of published work, so whether the findings they report are reproducible will simply never be assessed."*

40 % of 127 articles, making independent verification impossible (Witwer, 2013). The same study also found that re-analysis of data often times did not support the original conclusions. Furthermore, 44 % of 233 preclinical articles describe statistical tests insufficiently, while few don't describe them at all (Gosselin, 2021). Another study reviewed 147 papers in the field of optometrics and found that 91 % did not discuss their rationale of correcting p-values for multiple comparisons (e.g. Bonferroni correction) (Armstrong, 2014). However, given that the exact use of multiple comparisons corrections has been under debate for decades, it is reasonable to assume that researchers lack the confidence to report their technique in detail (Perneger, 1998; Moran, 2003; Sullivan & Feinn, 2021). In general, p-values are target of extreme scrutiny and also the cause of many arguments, which themselves are of questionable statistical reasoning[4] (Leek & Peng, 2015). Additionally, statistical illiteracy is a well-known problem among clinicians (Lakhlifi et al., 2023). Among biomedical researchers, 77 % state that they have not received formal training in data literacy, including visualization and public deposition of data, although they understand its high relevance (Federer et al., 2016). Correspondingly, it has been communicated that there is a lack of intuitive tools to embed computational work into publications, but also a lack of bioinformaticians to translate computation into clinics (Mesirov, 2010; Smith et al., 2018; Gómez-López et al., 2019). Therefore, nontransparencies in biomedical analyses are not only caused by a habit[5] of insufficient reporting, but could be exacerbated by the confusions caused by currently available methodologies and the lack of proper training.

Semi-Big Data: Big Enough to Cause Problems

Recent advances in big data analysis have significantly improved the standardization of both raw data availability and processing pipelines (Gomez-Cabrero et al., 2014). Particularly in RNAseq analysis, automation and the use of sophisticated software have established standards that enhance reproducibility across studies. For example, tools such as `STAR` and `HISAT` for sequence alignment, and `Cufflinks` and `DESeq` for differential expression analysis, rely on scripts that standardize processing steps to produce repeatable and verifiable results (Dobin et al., 2013; Kim et al., 2015; Trapnell et al., 2012; Love et al., 2014). These frameworks not only automate data handling but also ensure that data analysis protocols are followed consistently, reducing human error and variability between different users or laboratories.

However, this level of standardization and automation has not been mirrored in the analysis of *semi-big data*. Semi-big data, as introduced in this thesis, describes datasets that are on the cusp of manageability: substantial enough to overwhelm manual analysis methods yet not

[4] Leek & Peng (2015): *"Arguing about the P value is like focusing on a single misspelling, rather than on the faulty logic of a sentence"*

[5] Peng (2011): *"[...] old habits die hard, and many will be unwilling to discard the hours spent learning existing systems."*

sufficiently large or uniform to justify the heavy computational frameworks developed for big data. Such data are frequently generated in experiments like automated microscopy or multiplex qPCR, where the scale and complexity of the data can vary significantly depending on the experimental design and objectives (Krzywinski & Savig, 2013).

Researchers often revert to basic tools such as *Microsoft Excel* for analyzing these semi-big datasets (Incerti et al., 2019). While Excel provides familiarity and immediate accessibility, it lacks the sophisticated data handling capabilities necessary for efficient and error-free processing of complex (multidimensional) datasets. This reliance on manual methods not only makes the analysis laborious and prone to mistakes but also significantly impedes the reproducibility of research findings. The time and effort required to replicate analyses done manually mean that validating findings from semi-big data can be prohibitively challenging for peer reviewers and other researchers in the field.

Given these challenges, there is a critical need for developing new tools and frameworks specifically tailored for semi-big data. These tools should bridge the gap between the simplicity of user-friendly software like Excel and the robust, script-based automation seen in big data frameworks. By providing standardized, repeatable, and easy-to-use methods for handling complex datasets, such tools could significantly enhance the reliability and efficiency of research involving semi-big data, ultimately supporting broader scientific inquiry and verification.

The Shortcomings of Common Biomedical Analysis Tools

Interactive software systems commonly used for exploratory data analysis in biomedical research often lack mechanisms to track and reproduce the researcher's actions systematically. Even when analysis is performed using scripting languages, the integration of results from multiple packages without a coherent record of the commands and code used undermines reproducibility. This practice can obscure analysis, making it difficult, if not impossible, for other researchers to replicate the results (Leek & Peng, 2015; Peng, 2011; Mesirov, 2010; Localio et al., 2018).

A particularly illustrative example is *GraphPad Prism*, a tool ubiquitously employed across biomedical disciplines for statistical analysis. Despite its widespread use, it does contribute to data analysis nontransparencies due to *Prism*'s closed-source nature and the common journal practice of not requiring detailed methodological transparency in its usage, a practice that is common in biostatistics literature (Gosselin, 2021; Localio et al., 2018). Furthermore, *GraphPad Prism* still requires manual data entry and lacks the robustness and automation necessary for handling multidimensional or semi-big data. Although, *GraphPad Prism* is compatible *"multiple variable tables"* —similar to long-form tables known from Wickham (2014)—, but does not automatically graph these kinds of tables, but only user specified subsets (*GraphPad Prism 10*

User Guide, 2024).

Moreover, *Microsoft Excel*, another staple in data processing in biomedicine, is notoriously inadequate for handling multidimensional data and complex statistical analyses. Its limitations include poor error tracking, absence of change documentation (audit trails), and a propensity for introducing errors that often go unnoticed, such as converting gene names to dates (Ziemann et al., 2016). To compensate for these shortcomings, *Microsoft* has recently integrated a Python interpreter into *Excel*, allowing researchers to automate tasks and analyze data efficiently and correctly (Excel, 2023).

Indeed, many common tools in biomedicine allow for scripting or automation to handle semi-big data more effectively. For example, `Fiji/ImageJ`, a popular image processing platform, supports extensive macro and scripting capabilities (Rueden et al., 2017). These features enable researchers to automate batch processing of image data, streamlining tasks that would otherwise require laborious manual input. Similarly, `PyMOL`, a leading tool in protein structural biology, utilizes Python scripting to automate complex tasks, allowing for detailed molecular modeling and visualization that are reproducible and scalable across datasets (*PyMOL*, 2024; Rigsby & Parker, 2016).

Although automation scripts used in tools like `Fiji/ImageJ` and `PyMOL` improve transparency for publishing singular data analysis pipelines, they still face challenges that can impede their reproducibility (Peng, 2011; Sandve et al., 2013): These scripts sometimes require specialized software environments, where setting up dependencies and configurations can be complex enough to discourage replication efforts. Additionally, these scripts do not always provide comprehensive outputs of intermediate steps, which is crucial for verifying and understanding the progression of data analysis (Sandve et al., 2013).

On the other hand, when scripts are designed to be more generalized and distributed — for instance, as a `Fiji/ImageJ` plugin or a standalone application — they can make substantial contributions to scientific research by enabling other researchers to apply these tools to their own data sets (Narzt et al., 1998; Wilkinson et al., 2016). However, this approach also comes with its own set of challenges (Sandve et al., 2013). These generalized tools often lack comprehensive user-manuals (*documentation*) and are not thoroughly tested across different platforms or data sets, which can lead to unexpected errors that can not be fixed by the user. Moreover, even when these tools are available, they frequently suffer from low adoption rates, meaning that few people are familiar with the details of such tools, further decreasing the confidence and reproducibility in the final results.

Given these complexities, there is a pressing need for new analytical tools specifically designed for semi-big data. These tools must strike a balance between the ease of use found in basic software and the robust, analytical capabilities of more sophisticated systems. By providing

standardized workflows, comprehensive documentation, and ensuring cross-platform compatibility, these tools can significantly enhance reproducibility. They not only allow researchers to perform analyses more efficiently but also ensure that these analyses are robust, transparent, and easily verifiable by the broader scientific community.

This thesis presents a software environment developed in Python, designed to bridge this gap. It demonstrates that even minimal coding skills can be leveraged to create powerful tools that standardize and accelerate the analysis of semi-big data, ultimately fostering more reproducible and trustworthy scientific research.

Modern Standards of Software Development

A main reason to write software is to define reusable instructions for task automation (Narzt et al., 1998). The complexity of software code makes it prone to errors, which can prevent its usage by persons other than the author himself. This is a problem for the general scientific community, as the software is often essential for reproduction (Sandve et al., 2013). Hence, modern journals aim to enforce standards to software development, including software written and used by biological researchers (Smith et al., 2018). Here, we provide a brief overview of the standards utilized by `plotastic` that ensure its reliability and reproducibility by the scientific community (Peng, 2011).

Modern software development is a long-term commitment of maintaining and improving code after initial release (Boswell & Foucher, 2011). Hence, it is good practice to write the software such that it is *scalable*, *maintainable* and *usable*. *Scalability* or, to be precise, *structural scalability* means that the software can easily be expanded with new features without major modifications to its architecture (Bondi, 2000). This is achieved by writing the software in a modular fashion, where each module is responsible for a single function. *Maintainability* means that the software can easily be fixed from bugs and adapted to new requirements (Kazman et al., 2020). This is achieved by writing the code in a clear and readable manner, and by writing tests that ensure that the code works as expected (Boswell & Foucher, 2011). *Usability* is hard to define (Brooke, 1996), yet one can consider a software as usable if the commands have intuitive names and if the software's manual, termed *documentation*, is up-to-date and easy to understand for new users with minimal coding experience. A software package that has not received an update for a long time (approx. one year) could be considered abandoned. Abandoned software is unlikely to be fully functional, since it relies on other software (dependencies) that has changed in functionality or introduce bugs that were not expected by the developers of all dependencies. Together, software that's scalable, maintainable and usable requires continuous changes to its codebase. There are best practices that standardize the continuous change of the codebase, including version control, continuous integration (often referred to as CI), and software testing.

Version control is a system that records changes to the codebase line by line, documenting of the detailed history of the codebase, including the person and timepoint of every change. This is required to isolate new and experimental features into newer versions and away from the stable version that's known to work. The most popular version control system is `Git`, which is considered the industry standard for software development (Chacon & Straub, 2024). `Git` can use GitHub.com as a platform to store and host codebases in the form of software repositories. GitHub's most famous feature is called "pull request". A pull request is a request from anyone registered on GitHub to include changes to the codebase (as in *"please pull this into your main code"*). One could see pull requests as the identifying feature of the open source community, since it exposes the codebase to potentially thousands of independent developers, reaching a workforce that is impossible to achieve with closed source models used by paid software companies.

Continuous integration (CI) is a software development practice in which developers integrate code changes into a shared repository several times a day (Duvall et al., 2007). Each integration triggers the test suite, aiming to detect errors as soon as possible. The test suite includes building the software, setting up an environment for the software to run, and then executing the programmed tests, ensuring that the software runs as a whole. Continuous integration is often used together with software branches. Branches are independent copies of the codebase that are meant to be merged back into the original code once the changes are finished. Since branches accumulate multiple changes over time, this can lead to minor incompatibilities between the branches of all developers (integration conflicts), which is something that CI helps to prevent.

Continuous integration especially relies on a thorough software testing suite. Software testing is the practice of writing code that checks if the codebase works as expected (Myers et al., 2011). The main type of software testing is unit testing, which tests the smallest units of the codebase (functions and classes) in isolation (Listing 1). Software testing is automated by specialized frameworks that execute the tests and report the results, a popular example being `pytest`, which is utilized by `plotastic` (Krekel et al., 2004).

Listing 1: Example of an arbitrary Python function and its respective unit test function. The first function simply returns the number 5. The second function tests if the first function indeed returns the number 5. The test function is named with the prefix "`test_`" and is placed in a file that ends with the suffix "`_test.py`". Testing frameworks such as `pytest` scan the repository for files that end with "`_test.py`" and execute the functions that start with "`test_`". Note that code after "`#`" is considered a comment and won't be executed.

```python
# Define a function called "give_me_five" that returns the number 5
def give_me_five():
    return 5
# Define a test function asserting that "give_me_five" returns 5
def test_give_me_five():
    assert give_me_five() == 5
```

The quality of the software testing suite is measured by the code coverage, the precision of the tests, and the number of test-cases that are checked. The code coverage is the percentage of the codebase that is called by the testing functions, which should be as close to 100% as possible, although it does not measure how well the code is tested. The precision of the test is not a measurable quantity, but it represents if the tests truly checks if the code works as expected. The number of test-cases is the number of different scenarios that are checked by the testing functions, for example testing every possible option or combinations of options for functions that offer multiple options.

Together, the standards of software development, including version control, continuous integration, and software testing, ensure that the software is scalable, maintainable, and usable. This is especially important for software that is used by the scientific community, as it ensures that the software is working as expected at defined versions years after publishing scientific results.

What makes Python an "Easy" Programming Language?

Here, we provide a general overview of the Python programming language, explaining terms like *"type"*, *"method"*, etc., in order to prepare readers without prior programming experience for the following chapters. We also describe the design principles of Python to lay out the key concepts that differentiate Python compared to other programming languages. A more detailed tutorial on Python that's specialized for bioscientists is found in Ekmekci et al. 2016

Languages such as Python are considered *"high-level"*, which means that it is designed to be easy to read and write, but also independent of hardware by hiding (*"abstracting"*) underlying details (*The Python Language Reference*, 2024). A key principle of Python is the emphasis on implementing a syntax that is concise and close to human language (Listing 2, Listing 3).

Listing 2: Example of readable Python code. This one-line code returns the words (string) `"Hello, World!"` when executed. The command is straightforward and easy to understand.

```python
print("Hello, World!")
# Expected output: Hello, World!
```

Listing 3: Example of less readable code written in the low-level programming language C. This code is doing exactly the same as the Python code in Listing 2, but is harder to understand because more steps are needed, including the import of a library `stdio.h` and the definition of a function called `main`. Note that C uses `//` to begin comment sections.

```c
#include <stdio.h>          // Import functions for standard input & output
int main() {                // Define a function called 'main'
    printf("Hello, World!");
    return 0;
}
// Expected output: Hello, World!
```

Furthermore, Python is an *interpreted* language, which means that the code is executed line by line. This makes coding easier because the programmer can see the results of the code immediately after writing it, and error messages point to the exact line where the error occurred (Listing 4). This is in contrast to *compiled* languages, where the code has to be compiled into machine code before it can be executed. The advantage of compiled languages is that the code runs faster, because the machine code is optimized for the hardware.

Listing 4: Example of an error message. Since Python is case-sensitive, the error is caused by misspelling the variable name `hi` as `Hi`. The error message begins with the type of error (`NameError`), followed by a traceback that shows the sequence of function calls that led to the error. The traceback located the source of the error in the file `errormessage.py` and points to the line that caused the error. Finally, the error message explains the error, stating that `'Hi'` is undefined.

```
hi = "Hello World"  # Define a variable 'hi' with the value "Hello World"
print(Hi)           # Print the value of the undefined variable 'Hi'

# Expected Output:
# ---------------------------------------------------------------------------
# NameError                                 Traceback (most recent call last)
# File /Users/martinkuric/Documents/errormessage.py:2
#       1 hi = "Hello World"
# ----> 2 print(Hi)

# NameError: name 'Hi' is not defined
```

Python automates tasks that would otherwise require an advanced understanding of computer hardware, like the need for manual allocation of memory space. This is achieved by using a technique called *"garbage collection"*, which automatically frees memory space that is no longer needed by the program. This is a feature that is not present in low-level programming languages like C or C++, that were designed to maximize control over hardware.

Another hallmark of Python is its *dynamic typing system*. In Python the type is inferred automatically during code execution (Listing 5). This is in contrast to *statically* typed languages like C, where the type of a variable has to be declared explicitly and cannot be changed during code execution (Listing 6) (*The Python Language Reference*, 2024).

Listing 5: Example of dynamic typing in Python. The variable "`a`" is assigned the value 5, which is of type integer. The variable "`a`" is then overwritten with the value "`Hello, World!`", which is of type string. Python allows dynamic re-assignment of variables with different types. Note that code after "`#`" is considered a comment and won't be executed.

```
a = 5  # Type integer
a = 5.0  # Type float
a = 'Hello, World!'  # Type string
a = True  # Type boolean
a = False  # Type boolean
a = [1, 2, 3]  # Type list of integers
a = {'name': 'Regina'}  # Type dictionary
```

Dynamic typing makes Python a very beginner-friendly language, since one does not have to keep track of the type of each variable. However, this also makes Python a slower language,

Listing 6: Example of static typing in C. The variable "a" is declared as an integer (`int`), and can only store integers. The variable "a" is then assigned the value 5, which is an integer. The variable "a" is then assigned the value `'Hello, World!'`, which is a string. This results in a compilation error, because the variable "a" can only store integers. Note that code after "//" is considered a comment and won't be executed.

```
int a;  // Declare type as integer
a = 5;
a = 'Hello, World!';  // Compilation error!
```

because the interpreter has to check the type of each variable during code execution. Also, developing code with dynamic typing systems is prone to introducing bugs (`TypeError`), because it allows unexperienced developers to convert variables from one type to another without noticing, leading to unexpected behavior. Hence, larger Python projects require disciplined adherence to programming conventions. One such convention is *type hinting*, which is a way to explicitly note the type of a variable. Type hinting does not have an effect on the code, but it makes the code more readable and understandable for other developers, and allows for development environments to detect type errors before execution (Listing 7) (van Rossum et al., 2014).

Listing 7: Example of type hints used in Python. Explicitly stating the type of the variable is optional and does not change the behavior of the code, but behaves exactly as shown in Listing 5.

```
a: int = 5
a: str = 'Hello, World!'
```

To make Python as easy as possible, python packages aim to reduce the amount of code that has to be written by the user. For example, the package `matplotlib` is a plotting library where every command is written such that the user immediately understands its purpose, like plotting a line or labeling an axis (Listing 8). Hence `matplotlib` code is a sequence of simple function calls, where the state of the plot is modified and saved in the background line by line.

Listing 8: Example of using pre-written functions of a Python package. The functions of the package `matplotlib.pyplot` become accessable by importing the package as `plt`, where plt serves as an alias (or rather shortcut) to access the functions of the package. Then, two arbitrary lists are defined, `x` and `y`. These datapoints are plotted (scatterplot) using the function `plot` The plots x- and y-axes are then labeled and saved as an image. The code is written in a sequence of function calls, where the state of the plot is saved in the background. The plot is then displayed using the function `show`.

```
import matplotlib.pyplot as plt  # Make functions accessible via plt
x = [1, 2, 3, 4, 5]              # Define arbitrary x values
y = [1, 4, 9, 16, 25]            # Define arbitrary y values
plt.plot(x, y)                   # Plot x against y
plt.xlabel('Timepoint')          # Add a label to the x axis
plt.ylabel('Foldchange')         # Add a label to the y axis
plt.title('Gene Expression')     # Add a title above the plot
plt.savefig('plot.png')          # Save plot as image onto harddrive
plt.show()                       # Show the plot preview
```

However, when no pre-written functions or packages are available, Python offers the tools of

a general purpose programming language to write and deploy custom code easily. Programming styles can be classified into two main paradigms: *functional* and *object-oriented* programming, which can be understood as different ways to structure code. Python supports both paradigms. In *functional* programming, the code is written in a way that the program is a sequence of function calls, where each function call returns a value that is used in the next function call (Listing 9). This approach is useful when multiple actions have to be performed on the same data and the structure of the data is relatively simple, for example a string of a DNA sequence.

Listing 9: Example of functional programming in Python. The code defines a function called "`find_restriction_site`" that finds the position of a restriction site in a DNA sequence. The function "`cut`" uses the function "`find_restriction_site`" to cut the sequence at the restriction site. To execute both functions, we first define an arbitrary DNA sequence and then call the function `cut` passing the sequence as an argument.

```
def find_restriction_site(sequence: str):  # Define a function
    return sequence.find('GCGC')           # Find the position of 'GCGC'

def cut(sequence: str):                        # Define another function
    position = find_restriction_site(sequence) # Use the function above
    return sequence[position:]                 # Cut sequence at the position

seq1 = 'TGAGCTGAGCTGATGCGCTATATTTAGGCG'  # Define an arbitrary sequence
seq1_cut = cut(seq1)                     # Cut the sequence
print(seq1_cut)                          # Show the result
# Expected output: GCGCTATATTTAGGCG
```

When the data itself gains in complexity, for example when storing not just the gene sequence, but also the promoter sequence, an *object-oriented* approach is more suitable (Listing 10). Object-oriented programming is a programming paradigm that uses objects and classes. An object is a collection of both data and functions, and a class is a blueprint for creating objects. The data of an object is stored as *attributes*. Functions that are associated with an object are called *methods*. A major benefit of using an object oriented versus a functional approach is that the data itself programmable, enabling the programmer to define the behavior of the data through methods. This is achieved by using '`self`' to reference the objects themselves inside the class. `self` can be understood as *"this object"*, and is a placeholder for objects that are to be created from the blueprint. `self` is required to access attributes and methods before specific objects are created in order to program how the objects are to be changed when calling methods.

When designing software, both functional and object oriented programming can be used together, where object oriented programming is often used to design the program's overall architecture, and functional programming is used to implement the algorithms of the program's features. This allows for scalability of the software, as every single class is extended through the addition of new methods.

Listing 10: Example of object oriented programming in Python. The class is called "Gene" and acts as a blueprint to create Gene objects. Gene has four methods, "__init__", "find_promoter", "find_restriction_site" and "cut". The method "__init__" is called when creating ("initializing") an object, which fills the object with user-defined data. The parameter "self" is a placeholder for the objects that are to be created. "find_promoter" is a method that finds the position of the promoter in the gene and is called during object initialization.

```python
class Gene:                                 # Define a Gene class
    def __init__(self, sequence: str):      # Define how a Gene object is created
        self.sequence: str = sequence       # Save sequence as attribute
        self.promoter: str = self.find_promoter()  # Automatically find promoter
        # Add further Gene attributes here
    def find_promoter(self):                # Define how to find the promoter
        return self.sequence.find('TATA')
    def find_restriction_site(self):        # Define how to find restriction site
        return self.sequence.find('GCGC') # Find the position of 'GCGC'
    def cut(self):                          # Define how to cut the DNA sequence
        position = self.find_restriction_site()   # Call the method above
        return self.sequence[position:]   # Cut the gene at the position

gene1 = Gene(sequence='TGAGCTGAGCTGATGCGCTATATTTAGGCG')   # Create Gene object
print(gene1.cut())                          # Cut gene and show result
# Expected output: GCGCTATATTTAGGCG
```

Furthermore, classes can be expanded in their functionalities through *inheritance* (Listing 11). Inheritance is a feature of object-oriented programming that allows a class to access every attribute and method of a parent class. For example, one could extend the class "Gene" with a class "mRNA", by writing a class "mRNA" that inherits from the class "Gene".

Listing 11: Example of inheritance in Python. The class "mRNA" inherits from the class "Gene", and has two methods, "__init__" and "find_stopcodon". "find_stopcodon" loops through a list of stop codons (`for x in list`): For each stop codon, the position is found. If a codon wasn't found, the `.find()` method returns -1, which leads to a different print message. Note that `f""` formats strings to include variables.

```python
class mRNA(Gene):          # Define the mRNA class, inheriting from Gene class
    def __init__(self, sequence: str):   # Define how an mRNA object is created
        super().__init__(sequence)       # Get attributes from parent class
        self.sequence = self.sequence.replace('T', 'U')  # Replace T with Uracil
    def find_stopcodons(self):           # Define how to find stop codons
        for stopcodon in ['UGA','UAA','UAG']:   # Loop over stop codons
            position: int = self.sequence.find(stopcodon)   # Find the position
            if position == -1:           # If position is -1, codon wasn't found
                print(f"{stopcodon} not found") # Message if not found
            else:                        # If position isn't -1, codon was found
                print(f"{stopcodon} found at {position}")

mrna1 = mRNA(sequence='TGAGCTGAGCTGATGCGCTATATTTAGGCG')  # Create an mRNA object
mrna1.find_stopcodons()                  # Show the position of stop codons
# Expected outputs:
# UGA found at 0
# UAA not found
# UAG found at 24
```

Together, Python is not just beginner-friendly, but also well respected for its ease in de-

velopment, which is why it is widely used in professional settings for web development, data analysis, machine learning, biosciences and more (Ekmekci et al., 2016; Rayhan & Gross, 2023).

The Potential of Python Data Science Packages for Biomedicine

Python includes a vast number of built-in packages used for basic data-types, software development, simple math operations, etc., (*The Python Language Reference*, 2024). Still, Python relies on packages developed by its users to provide specialized tools for data analysis. A Python package consists of multiple Python *modules*, where each module is a text-file with a `.py` ending containing Python code. Famous examples of such packages are `pytorch` and `tensorflow`, that are used to build models of artificial intelligence, including *ChatGPT* (Paszke et al., 2019; Abadi et al., 2016; Radford et al., 2019). Here, we outlay the most important packages used for `plotastic` in Chapter 2 and present examples how these packages are utilized in modern biomedical research.

`Interactive Python`: The standard Python interface is insufficient for data science, because it lacks the tools to quickly and conveniently visualize and explore data. `IPython` can be understood as an enhanced version of the standard Python interpreter, designed to improve the interactivity of Python code execution (Perez & Granger, 2007). `IPython` introduces features like rich media support to display graphics, but also helps users to use correct python data types through dynamic type introspection, detecting errors in the code. This functionality is akin to what *MATLAB* and *RStudio* provide through their advanced graphical user interfaces and extensive debugging tools. `IPython` is most often utilized in the form of *Jupyter Notebooks*.

`Jupyter`: `Jupyter` is an evolution of `IPython`, introducing the *Jupyter notebook* format, which has the file-ending `.ipynb` (Kluyver et al., 2016). Jupyter Notebooks are documents that combine both code and text structured as *code cells* and *markdown cells*, respectively. Markdown cells allow the author to provide additional information with text formatting, for example structuring the document with headings and subheadings, adding hyperlinks, images and mathematical formulas. Code cells can be executed individually, displaying the output directly below the cell. This allows for an interactive exploration of data, but also makes Jupyter Notebooks a very human-readable format that outlays data analysis in a clear manner with precise and reproducible documentation of all data processing steps. Another major benefit of Jupyter Notebooks are interchangable *Kernels*, allowing the execution of code in different programming languages, such as R, Julia, and C++ (Giorgi et al., 2022). Today, Jupyter Notebooks have become a standard format compatible with collaborative platforms like *Google Colab* and *JupyterLab*, but also professional software development tools like *VS Code*, and *PyCharm*. For biomedical research, Jupyter Notebooks are a powerful solution for improving reproducibility: They elegantly combine both documentation and code execution into a concise

presentation of the data analysis process, hence being an intuitive tool to both capture and embed computational work directly into papers, a requirement postulated by Mesirov (2010). Jupyter notebooks are increasingly found in the supplemental of modern publications of both bioinformatics and wet-lab research (Taskiran et al., 2024; Bosch-Queralt et al., 2022; Howe & Chain, 2015).

`NumPy`: Central processing units (CPU) usually execute one instruction on one data point at a time. For manipulating tabular data, this is inefficient as the same instruction must be repeatedly loaded for every data point. `NumPy` accelerates the mathematical capabilities of Python by enabling large-scale operations on multi-dimensional arrays and matrices with high efficiency (Harris et al., 2020). One key feature of `NumPy` is the implementation of "vectorization" or SIMD (Single Instruction, Multiple Data) instructions. SIMD allows multiple data points to be processed simultaneously, significantly speeding up operations that are inherently parallelizable, such as matrix addition or multiplication. `NumPy`'s syntax and functional approach to array manipulation have set a standard for matrix computation, influencing the design of advanced AI frameworks such as `PyTorch` and `mlx`, which mirrors several of `NumPy's` functionalities to facilitate ease of use for those familiar with `NumPy` (Paszke et al., 2019; Hannun et al., 2023). This standardization has made `NumPy` an attractive tool not only in genomics (Ding et al., 2023), but also for modern clinical applications like imaging technologies and augmented-reality in surgery (Thompson et al., 2020).

`Pandas`: Tables are the most common way to store experimental results. `Pandas` extends Python with a tabular datatype, called `DataFrame`, which allows for easy data manipulation with integrated indexing (Mckinney, 2011). The intuitive interface of Pandas can be likened to *Microsoft Excel*; however, it is vastly more powerful due to its speed, functionality, and ability to handle larger datasets, e.g. by running efficient `numpy` vectorization in the background. Unlike *Excel*, Pandas enables automation by summarizing processing commands into scripts, documenting each step, and ensuring reproducibility. `Pandas` is used in biomedicine for data wrangling, data cleaning, and data analysis, as it allows for the integration of multiple data sources into a single table (Santos et al., 2020).

`matplotlib`: `matplotlib` is a plotting library that provides a wide range of static, animated, and interactive plots and graphs Listing 8 (Hunter, 2007). It serves as the foundation for many visualization tools and is particularly valued for its flexibility and customization options. For example, `Pandas` uses `matplotlib` to plot column datapoints directly from a `DataFrame` object, creating histograms or scatter plots, which is useful for preliminary data analysis and checking data distributions. However, `matplotlib` uses a low-level syntax, hence plots generated by `matplotlib` can be cumbersome to format and customize.

`seaborn`: While the low-level syntax of `matplotlib` is valued for its flexibility, formatting

publication grade plots can be laborious, and its inconsistent syntax can make it difficult to remember the correct commands for different plot types. `seaborn` is a high-level interface on top of `matplotlib` that offers a more intuitive and highly standardized syntax across a wide array of plot types (Waskom, 2021). `seaborn` also integrates closely with `Pandas` data structures: It automatically groups datapoints, calculates measures of both central tendency (e.g. mean, median) and variance (e.g. standard deviation), and displays them into the plot (e.g. error bars). This completely replaces manual calculation of descriptive statistics. `seaborn` also offers intuitive grouping (*facetting*) of data points, which simplifies the creation of complex visualizations involving multidimensional data, making it easier to reveal patterns and relationships via color encoding, faceting, and automated statistical fits. This is particularly useful in biomedical research for visualizing and understanding complex datasets, such as large quantities of protein data (Krzywinski & Savig, 2013; Weiss, 2022). `seaborn` could indirectly contribute to improving reproducibility in biomedical research by making visualizations of complex data very accessible through an easy and standardized syntax.

`Pingouin`: Integrating both data visualization and statistical analysis is beneficial for researchers who wish to conduct advanced statistical analysis without switching between different software environments. `Pingouin` is designed to be a user-friendly statistical tool that offers a straightforward syntax for performing statistical tests, which are commonly implemented in R (Vallat, 2018). Unlike R, `Pingouin` integrates seamlessly within the Python ecosystem, which allows combining data manipulation, analysis, and visualization all in one platform. This improves reproducibility by reducing the number of software tools required to analyze data. Despite its potential to streamline the data analysis process, `Pingouin` has not been widely adopted by biomedical research, yet. One example of a study that utilized `Pingouin` is the work of Kelly et al. (2023) in the field of Patient Public Involvement (PPI), producing an ethical matrix that allows for the inclusion of stakeholder opinion in medical research design. This lack of `Pingouin`'s adoption in biomedicine could be due to recent development and the dominance of R in the field. However, since Python offers multiple benefits over R in syntax, software development, runtime performance and integration with other tools (like including performant C++ code), `Pingouin` is an attractive standard for future statistical analyses in biomedicine (Gorelick & Ozsvald, 2020).

Together, these python packages form the backbone of modern data analysis in Python, often times combining software from different languages to accelerate certain features, while retaining the ease of use and readability that Python is known for. This is particularly advantageous in the field of biomedicine, where the requirements of modern data analysis are often complex and require a high degree of flexibility and customization.

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Two new interleukin-6 dependent plasma cell lines carrying a chromosomal abnormality involving the IL-6 gene locus.Abstract Two plasma cell lines, INA-6 and JK-6, have been initiated and continuously cultured from two patients with malignant plasma cell diseases. Both cell lines are EBNA negative and show morphological and immunophenotypical features of plasma cells. INA-6 expresses the CD39 and CDw75 antigens, JK-6 is strongty positive with CD38 and CD39 antibodies. By flow cytometry they were non-reactive with Ia antibodies and B ceil reagents CD19, CD20, CD21, CD22, and CD24. While INA-6 cells are releasing kappa light chains only, JK-6 cells produce IgG kappa. Both cell lines could only be initiated with IL-6 supplemented medium and remained IL-6 responsive throughout continuous culture. INA-6 is strictly dependent on IL-6. No spontaneously secreted IL-6 was found nor could it be induced by IL-1beta /TNFalpha stimulation. Molecular analysis with RT-PCR revealed mRNA for the IL-6 receptor in both lines. No IL-6 mRNA was detectable in INA-6 cells, while in JK-6 minute amounts were observed. Cytogenetic analysis of both lines revealed, among other abnormalities, a deletion (7)(p13). lnterestingly, the 7p deletion affects the location ot the IL-6 gene. ln both cell lines, IL-6 dependent proliferation could be inhibited by IFNalpha. IFNalpha had growth regulatory effects only on JK-6: While high concentrations were inhibitory, low IFNalpha amounts were clearly stimulatory. A wide variety of other cytokines including GM-CSF and IL-11 did not have the capacity to influence proliferation. These plasma cell lines do not only allow to turther characterize regulatory events in plasma cell neoplasias but also provide tools to study therapeutic interventions. (n.d.). Retrieved 2023-03-22, from https://www.cellosaurus.org/cellopub/CLPUB00060

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Appendices

A Supplementary Data & Methods

A.1 Figures

A.2 Tables

A.3 Materials & Methods

B Documentation of plotastic