Contents

Abbreviations

aMM asymptomatic Multiple Myeloma . . . 2

BM Bone Marrow . . . 2

BMME Bone Marrow Microenvironment . . . 68

BMPC Bone Marrow Plasma Cell . . . 5

BMSC Bone Marrow Stromal Cell . . . 4

CM hMSC-conditioned medium . . . 30

CM-INA6 MSC-Conditioned-Medium-treated INA-6 . . . 44

CAM Cell Adhesion Molecule . . . 4

CLI Command Line Interface . . . 64

ECM Extracellular Matrix . . . 4

EMT Epithelial-Mesenchymal Transition . . . 3

GUI Graphical User Interface . . . 64

hMSC human Mesenchymal Stromal Cell . . . 66

LLM Large Language Model . . . 67

MA MSC-adhering . . . 39

MSC Mesenchymal Stromal Cell . . . 6

MGUS Monoclonal Gammopathy of Undetermined Significance . . . 2

MM Multiple Myeloma . . . 68

MMR Multiple Myeloma Relapse . . . 3

MBD Multiple Myleoma related Bone Disease . . . 9

nMA non-MSC-adhering . . . 39

OS Overall Survival . . . 47

PCL Plasma Cell Leukemia . . . 2

PFS Progression-Free Survival . . . 47

SP Solitary Plasmacytoma . . . 2

SASP Senescence-Associated Secretory Phenotype . . . 9

Introduction

Aims

This PhD thesis is designed to bridge significant gaps in the understanding and analysis of myeloma cell behavior and the handling of complex biomedical datasets. The specific aims are as follows:

- Develop an *in vitro* model to elucidate the mechanisms of myeloma cell dissemination in interaction with mesenchymal stromal cells (hMSCs), focusing particularly on:
  - Observing and quantifying cell proliferation, attachment, and detachment dynamics using time-lapse microscopy.
  - Isolating and characterizing distinct myeloma subpopulations interacting with hMSCs to understand differential gene expression related to cell adhesion and patient survival.
- Design and implement a Python-based software tool, `plotastic`, to facilitate the analysis of multidimensional datasets generated in biomedical research. This tool will aim to:
  - Streamline the data analysis process, making it more efficient and reproducible.
  - Integrate visualization and statistical analysis capabilities to ensure that data analysis protocols are aligned with the ways in which data is visualized.
  - Provide a case study demonstrating the application of `plotastic` in the analysis of *in vitro* dissemination experiments, emphasizing the tool's ability to handle semi-big data and enhance reproducibility.
- Synthesize the findings from the experimental and software development components to advance the understanding of myeloma dissemination and improve research practices in biomedical data analysis.

These aims are crafted to address both the biological and technical challenges in current cancer research methodologies and data science applications in biomedicine, fostering advancements that could lead to novel therapeutic strategies and more robust scientific inquiries.

Summarising Discussion

Potential and Challenges of Time-Lapse Microscopy for Exploratory Cell Biology

Exploratory cell biology, as a field, emphasizes the discovery and characterization of novel cellular phenomena, often utilizing emerging technologies to visualize and analyze the underlying mechanisms of cell behavior. This approach is powerful because it allows scientists to observe and hypothesize about cellular processes in real-time, which can lead to unexpected insights and breakthroughs.

Direct Observation of Complexity and Novelty: In this project, time-lapse microscopy was transformative, shifting the initial research focus towards *in vitro* myeloma cell dissemination when making the unexpected — or argueably insignificant — observation of cancer cells detaching from aggregates. For the author, time-lapse microscopy provides an observation method that's unmatched in intuition and directness. Unlike RNA sequencing, which can obscure biological processes behind complex and cryptic data, time-lapse microscopy offers a clear view into the dynamic cellular events as they unfold. This method was particularly effective in revealing the detachment of cells following division, a phenomenon that might be overlooked in static analyses. Multiple parameters can be read out in parallel, such as both time and aggregate size for detachments to begin. Also, complex cellular behavior can be deduced from movement, as the lack of movement was interpreted as re-attachment of INA-6 daughter cells to the human Mesenchymal Stromal Cell (hMSC) monolayer, which allowed for measuring the duration of nMA-INA6 existing until re-attaching and turning into MA-INA6. This information was helpful when designing experiments to prove that cell division is a key mechanism for dissemination initiation, requiring precise timing to capture the detachment of daughter cells after cell division. Together, live cell imaging enabled key mechanistic insights in understanding the dynamics involved in multicellular interactions by integrating the study of multiple phenomena at once.

Technical Requirements for Robust Statistics: The utility of time-lapse microscopy in our study required high-resolution temporal and spatial imaging to capture rare cellular events with sufficient frequency to distinguish between singular occurrences and reproducible phenomena. We utilized 1 frame every 15 min, which is a time resolution to capture cell migration (Huth et al., 2010), but for analyzing more intricate movements or intracellular processes, higher temporal resolution is required. Predicting the observed total surface area can be difficult prior to the experiment. We acquired a large surface area of up to 13 mm^2, of which we manually assessed approximately a quarter to gather enough events for statistical analysis for each time bin. Such extensive automated video acquisition poses high demands on microscopy equipment, including an incubation setup and

motorized stage top. The total size of video files can also complicate storage, transfer and analysis. The raw video data from chapter 1 comprises 80 GB (BioStudies, n.d.); however, far more data was acquired due to protocol optimizations and treatments that were not shown in the thesis. File size could have been reduced by acquiring in an 8-bit image format, although a larger bit-depth could be necessary for precise and/or sensitive fluorescence microscopy. Minimizing the acquired surface area could have reduced file size as well, however the meniskus of the medium led to significant shading effects that complicated the choice of the surface area for phase contrasting.

***The cells are doing ...that thing again!*:** The exploratory assessment of video data begins with the search of scientific novelties. In order to correctly identify cellular phenomena that are relevant to the research question, a deep understanding of cell biology is required, e.g. in field of cell dynamics to read migratory behavior (Nalbant & Dehmelt, 2018). This is a challenge for both students and experienced researchers, since finding the academically correct terms to describe observations is especially difficult for novel phenomena or a sequence of events that can overlap. *After all, cell biology is taught using textbooks, not videos.* For this project in particular, the used terminology was revised frequently, e.g. shifting from *mobile interaction* to *non MSC adhering cells*, from *homotypic interaction* to *aggregation*, from *in vitro metastasis* to *detachment event*. These frequent shifts were caused by a constant struggle of finding the middle-ground between describing observations precisely and integrating results from other experiments, but also by the need to find terms that stay comprehensive in presentations and publication. This gap between observations and their description could be bridged by currently available multimodal Large Language Models (LLMs) like `ChatGPT-4o`: By matching recorded phenomena with descriptions and images that were amassed in the literature over decades, researchers not only use established terminology instead of inventing new terms, but also minimize the risk of missing potential discoveries.

Making Articles from Video Data: A significant challenge remains in how to effectively present these dynamic observations in a publishable format, as traditional scientific publications are not equipped to display video data. This project used both manual assessment and automated approaches for this problem. For characterizing the attachment/detachment dynamics and cell division, manual analysis was a viable option, but it was very time-consuming and required a thoughtful categorization strategy and a disciplined, bias-free execution. For fluorescent cell cycle profiling however, an automated approach was necessary to reach throughput, precision and cell number. For this, *Intellesis* was used, which is a machine learning-based pixel segmentation software. *Intellesis*, makes image analysis accessible to biologists without expertise in image processing, enabling the conversion of image and video data into analyzable quantitative outputs. This approach allowed the automated extraction of fluorescence brightness for every single nucleus among tens of thousands of DNA-stained nuclei, followed by plotting the distribution of DNA-amounts. Using *Intellesis*, this project effectively entered the field of *image cytometry* (Gupta et al., 2019), achieving high levels of automation along with a single-cell precision that's comparable to flow cytometry (Appendix A.1: Fig. 3). Although

this work has not applied *Intellesis* to time-lapse microscopy, this exemplifies the vast quantitative potential of microscopy — or rather image cytometry — in general.

Make Intellesis Training Easier and more Robust: This project has invested a lot of time in training the machine learning software *Intellesis* to segment images.

Some image types remain challenging for machine learning-based software like *Intellesis*, such as

phase contrast images, which have low contrast between cell edges and the background, making cell separation difficult during pixel segmentation.

phase contrast images are more challenging for machine learning based software like *Intellesis*, since cell edges have low contrast to the background and single cells are hard to distinguish. This can require extensive annotation of training images, which can be time-consuming and frustrating. This could be alleviated by introducing pre-processing steps that emphasize the features of interest and/or reduce image features that are irrelevant for the analysis. For example when discerning cell morphology, cell edges can be enhanced using edge enhancing filters, while noise and irrelevant small details can be removed by applying a median filter that preserves edges. Both filters are available in Zen. This approach simplifies the task for machine learning algorithms and reduces the amount of training data required by avoiding the classifier to learn irrelevant image features.

In summary, the implementation of time-lapse microscopy in this project not only enhanced our understanding of myeloma cell behavior but also emphasized the need for innovative solutions to integrate dynamic cellular data into the rigid frameworks of scientific communication. The evolution of microscopy and image analysis into image cytometry continues to push the boundaries of what can be observed and understood about cell dynamics in disease and health.

Novel Methods of Isolating Adhering Subpopulations

In this work, innovative *in vitro* methodologies (Well Plate Sandwich Centrifugation and V-Well adhesion Assay) were developed. this was required to fill in gaps of isolating cells with minimized variability introduced by user-bias to clearly separate subpopulations and precisely quantify them.

It is evident that direct or indirect contact with MM can have different effects on both hMSCs and Myeloma cells and methods to differentiate between those are crucial for understanding the change of the Bone Marrow Microenvironment (BMME) during Multiple Myeloma (MM) progression (Fairfield et al., 2020; Dziadowicz et al., 2022)

cite all those methods for cell isolation! - Turning around wellplates: Doesn't allow isolation, just quantification - The author did not show all his washing experiments - Washing is very bad (data not shown): Highly dependent on user: position of cell on well bottom (border cells receive less force),

position of pipette tip in well (depth, angle and position on bottom) - This motivated us to explore more reproducible methods

It's a challenge: either quantify cell population, or isolate them! - It's better to specialize in one method, than to do both poorly - Well Plate Sandwich Centrifugation is badly suited for quantification, but possible - we switched to developing V-well adhesion assay for quantification - We realized, V-well isolation allows both ultra precise quantification and isolation of small amounts of cells! - unmatched precision through centrifugation, no washing - But V-well pellets comprise only few cells requiring a lot of technical replicates and an untiring pipetting hand

The Well Plate Sandwich Centrifugation (WPSC) used two different techniques to dissociate MA-INA6 cells from the hMSC monolayer. This had no impact on the ratio of isolated MA-INA6 to nMA-INA6, since nMA-INA6 isolation was performed prior to dissociation using the same protocol consistently. We tried this to test if MACS was really necessary, after all it is costly, time-consuming, introduces an antibody bias and requires cell cold-treatment during antibody: Strong pipetting (*'Wash'*) and repeated Accutase treatment followed by magnetic activated cell sorting (*'MACS'*).

Dynamic Regulation of Adhesion Factors During Dissemination

One main question arises:

INA-6 was initially isolated from plasma cell leukemia as an extramedullary plasmacytoma located in the pleura from a donor of age. There is not much more information available on the background of that patient (*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.; Burger, Guenther, et al., 2001). But assuming that This is a highly advanced stage of myeloma. However, Chapter 2 shows that adhesion factors are lost during MM progression. INA-6 are highly adhesive to hMSCs.

This is a contradiction that needs to be resolved.

For example, circulating MM cells show lower levels of integrin $\alpha 4\beta 1$ compared to those residing in the BM. Furthermore, treatment with a syndecan-1 blocking antibody has been shown to rapidly induce the mobilization of MM cells from the BM to peripheral blood in mouse models, suggesting that alterations in adhesion molecule expression facilitate MM cell release (Zeissig et al., 2020).

However, INA-6 do not express adhesion factors. They do that only in hMSC presence Hence MAINA-6 could be a smaller fraction of MM cells, specialized on preparing a new niche for the rest of the MM cells. This could be a reason why they are so adhesive.

This assumption dictates that aggressive myeloma cells gain the ability to dynamically express adhesion factors. It could be that INA-6 has gained the capability to express adhesion factors fast in order to colonize new niches, such as pleura from which they were isolated.

This shows that not just the stage of the disease, but also the location of the myeloma cells plays a role when considering adhesion factors. According to this, this thesis predicts a low expression of adhesion factors in circulating myeloma cells, but a high expression in adhesive cells, e.g. non-circulating, or rather those

indeed CD138 paper isolated cells from circulating MM cells (Akhmetzyanova et al., 2020)

indeed, temporal subclones have been identified (Keats et al., 2012).

Subsets of Adhesion Factors Contribute To Different Steps of Adhesion

- adhesion molecules during vascular involvement have these adhesion molecules: JAM-C and CD138. - NONE of Them were shown in Chapter 2 of this study, (except for JAM-B)

- One has to consider that intravasation and/or extravasation would require a different set of adhesion factors than adhesion to BM or extramedullary environments.

This has great implications for targeting adhesion factors for therapy, as it suggests that different adhesion factors should either be antagonized or agonized depending on the function of the adhesion factor. According to this assumption, adhesion factors involved in intra- and extravasation adhesion

should be antagonized, while adhesion factors involved in BM adhesion — as identified in Chapter 2 — should be agonized. Indeed, Adhesion factors for endothelium were shown to decrease tumour burden in mouse models (Asosingh et al., 2001; Mrozik et al., 2015)

Bou Zerdan et al. (2022): "Classically, the BMM has been divided into endosteal and vascular niches"

Together, a detailed mapping of the niches available in the bone marrow is required to understand the adhesion factors required for each niche. This is a highly complex task, as the bone marrow is a highly complex organ.

What Triggers Release: One Master Switch, Many Small Switches, or is it just Random?

Papers like Akhmetzyanova et al. (2020) make it seem as if there is one molecule that decides if a myeloma cell is circulating or not.

It's less about one clear (molecular) mechanism that decides that a myeloma cell decides to become a disseminating cell, but rather a indirect consequence of a combination of many processes. These processes are: - Loss of adhesion factors or dynamic expression of adhesion factors - Loss of dependency from bone marrow microenvironment - asdf

Our thesis postulates that there is no big switch that decides if a myeloma cell detaches from the bone marrow, *it simply happens* once these processes are present.

Outlook: High-Value Research Topics for Myeloma Research Arising from this Work

As an Outlook, the Author lists research topics arising from this work that have great potential for breakthroughs in myeloma research.

Anti tumor effects of MSCs: This thesis has discussed the pro-tumor effects of MSCs. However, MSCs have also been shown to have anti-tumor effects (Galderisi et al., 2015). This work has also shown that primary hMSCs can induce apoptosis in INA-6 6 cells initially — probably through the action of death domain receptors —, but inhibit apoptosis during prolonged culturing.

This shows that hMSCs could be leveraged as a therapeutic target that could prevent myloma progression.

Cell Division as a Mechanism for Dissemination Initiation: The author describes how

the detachment of daughter cells from the mother cell after a cycle of hMSC-(re)attachment and proliferation could be a key mechanism in myeloma dissemination. This mechanism was shown in other studies of extravasation. The author sees great potential in this mechanism as a target for future research. It is probably under-researched due to requirement of sophisticated time-lapse equipment, yet the simplicity of detachment through cell division is intriguing through its simplicity. It implies asymmetric cell division. Cancer cells are known to divide asymmetrically, e.g. moving miRNAs to one daughter cell.

Lists of Adhesion Gene Associated With Prolonged Patient Survival: The author lists adhesion genes that are associated with prolonged patient survival. These genes are highly expressed in myeloma samples from patients with longer overall

At this time we could be on the verge of a new era of myeloma therapy, including bi-specific antibodies and cell based approaches (Morè et al., 2023; Engelhardt et al., 2024). Currently, available CAR-T Cell therapies (ide-cel, cilta-cel) are extremely expensive, but show complete remission rates of up to 80 % and a 18-month progression free survival rate of 66 % (Bobin & Leleu, 2022). An affordable "off-the-shelf" CAR-T Cell product could become reality since the problem of deadly graft-versus-host disease during allogeneic transplantation seems to be solvable (Qasim et al., 2017), hence, research groups and biotech companies are racing towards developing a safe allogeneic CAR-T Cell technology (Depil et al., 2020).

Conclusion 1: Cancer & Myeloma & Dissemination is bad

lorem ipsum yes yes very bad

Semi-Automation was Critical for Establishing *in vitro* Methods

In vitro research is valued for their speed at creating precise data (Moleiro et al., 2017). In this work, the development and publication of innovative *in vitro* methodologies necessitated the adoption of semi-automated data analysis tools. These novel methods introduced complexities that span multiple experimental parameters, making the results multidimensional. This demanded precise, efficient and standardized data handling capabilities which were facilitated by Python tools like `seaborn` and `plotastic` (Waskom, 2021; Kuric & Ebert, 2024).

Inherent Multidimensionality of Adhesion Studies: Cell adhesion studies often involve multiple independent parameters, posing significant analytical challenges. Two critical dimensions are particularly notable: *'Subpopulation'* and *'Time'*. Analyzing cell adhesion often involves isolation of adherent and non-adherent subpopulations, effectively introducing *'Subpopulation'* as a vital

dimension in the dataset (Dziadowicz et al., 2022). This study specifically categorized cells into three levels of MSC-interaction: CM-INA6, nMA-INA6, and MA-INA6, representing INA-6 cells incubating in MSC-conditioned medium, INA-6 cells not adhering to MSCs, and INA-6 cells adhering to MSCs, respectively. Furthermore, the dynamic nature of cell adhesion processes is profoundly influenced by the factor *'Time'*, making it a crucial experimental parameter for investigation (Rebl et al., 2010; McKay et al., 1997; Bolado-Carrancio et al., 2020). This work includes extensive time-lapse microscopy experiments utilizing a high time resolution (1 frame every 15 min), similar to those time resolutions used by Purschke et al. (2010). This precision was required for key mechanistic insights on hMSC-INA-6 interaction dynamics. These included identifying rolling movements of nMA-INA6 daughter cells around MA-INA6 mother cells, measuring the minimum time for INA-6 detachments to begin, and measuring the time required for daughter cells to re-attach to the hMSC monolayer, etc. Next to mechanistic insights, adhesion time played a crucial methodological role in this study as well: During the V-Well adhesion experiments, we did not know initially how long INA-6 cells required to form strong adhesion with hMSCs before pelleting nMA-INA6, but required a timepoint with hour precision to capture detachments after cell division that was accelerated through prior cell cycle synchronization at M-Phase.

The extensive facetting features of `seaborn` and `plotastic` were essential for visualizing these multidimensional datasets, allowing for quick exploration of the data (Waskom, 2021).

Further Contributions and Remedies to Multidimensional Complexity: In addition to *'Subpopulation'* and *'Time'*, this study faced additional layers of complexity that were managed through semi-automated analysis.

Experiments typically involved at least three biological replicates and corresponding technical replicates. Although replicates were not treated as independent variables — instead serving for displaying variance — they can add substantially to the data management workload. In this work, semi-automation nullified the manual burdens of handling technical replicates: `pandas` was used to automate aggregation of technical replicates into means after removing technical outliers thorugh z-score thresholding, while the jupyter notebook format allowed for reviewing filtered data for specific data losses. The removal of technical noise was especially relevant for qPCR data, where low gene expression can lead to sudden increase in Ct value (non-detects). In fact, the decision to remove or impute non-detects is under active discussion, however, available algorithms are hard to understand for non bioinformaticians, but also do not separate biological from technical variance, which is considered bad practice by Motulsky (2018) (McCall et al., 2014; Sherina, 2020). Semi-automation also nullified the burden of handling biological replicates: The automatic aggregation of datapoints during plotting is a key feature of `seaborn`, on which `plotastic` was built. Without such automation, calculating means and standard deviations for simple barplots would have required extensive manual computation in *Microsoft Excel*, or tedious plot configurations in *GraphPad Prism* due to limited

facetting functionality of multiple variable tables (*GraphPad Prism 10 User Guide*, 2024).

Replicates can expand datasets as this factor comprises a lot of levels. Similarly, the factor *'Gene'* multiplied the dataset by a total of 30 genes when validating RNAseq data with RT-qPCR. With three subpopulations, one timepoint, eleven biological replicates, and three technical replicates, the qPCR dataset used in this study grew to 2970 datapoints to be statistically analyzed and visualized. This is a manageable size for manual analysis, but the effort involved illustrates the definition of semi-big data.

Methodological variability also introduced additional dimensions: The Well Plate Sandwich Centrifugation (WPSC) used two different techniques to dissociate MA-INA6 cells from the hMSC monolayer: Strong pipetting (*'Wash'*) and repeated Accutase treatment followed by magnetic activated cell sorting (*'MACS'*). These variations, recorded as the factor *'method'*, further complicated the dataset. Although this distinction is not discussed in this work — rather pooled into one group —, this showcases how protocol changes can add dimensions to the dataset that are not necessarily relevant for the biological question but essential for method optimizations and validation.

Agility During Establishment of V-Well Assay: The concept of agility in laboratory research, inspired by the Agile Manifesto's principle of *"Responding to change over following a plan"* (*Manifesto for Agile Software Development*, 2001), is increasingly relevant in biomedical research (West, 2018; Quanbeck et al., 2022). This adaptive approach was particularly crucial during the development of the V-Well adhesion assay in this study. This experiment was planned such that the author performed fluorescent readout using microscopy and preliminry analysis, while a technical assistant prepared the samples for the next timepoint. Semi-automation accelerated the preliminary data analysis and visualization to a point that results were reviewable before the next sample timepoint was prepared and ready for fluorescent readout. This enabled immediate adjustments to the experimental protocol inbetween sample measurements, allowing for quick troubleshooting of small and avoidable problems that are often unforeseeable when establishing new methodologies. Without such agility, these problems would have been identified after the experiment, requiring a complete re-run of a very work-intensive experiment that included cell cycle synchronization. Such an agile and adaptive work environment, facilitated by python tools and `seaborn`, proved invaluable for refining the *in vitro* methods being developed.

Additionally, the simplicity offered by `seaborn` for complex data plotting, such as the cell cycle profiling shown in Appendix A.1: Fig. 3, which required minimal code to produce a detailed series of 24 histograms, underscores the utility of semi-automation in enhancing laboratory efficiency. While this work does not quantify the full benefits of semi-automation, the author's experiences suggest potential impacts on the speed and adaptability of method development in biomedical research.

`plotastic` Exceled in Re-Doing Statistical Analyses and Plots

Establishing new methods of *in vitro* dissemination required not just innovative experimental protocols, but also adaptive ways to visually present complex data. This need for adaptability is crucial during the publication process, where researchers must often experiment with different ways to visually represent their findings to best convey their significance. This process typically involves frequent adjustments to how data is displayed in plots. Such adjustments become especially cumbersome when subsequent adjustments are involved. Traditional tools (*Microsoft Excel* or *Graphpad Prism*) fail at handling semi-big data, while Python packages like *seaborn* reach their limits in terms of adaptability, making the development of `plotastic` a critical step in this work.

`plotastic` addresses these challenges by not only automating statistics, but also by enhancing the adaptability of data visualization as well, making it easier to modify how data is presented without repetitive manual adjustments. The author saw four key steps that required streamlining through `plotastic`:

1. Re-arranging facets
2. Plotting multiple layers of different plot types
3. Statistical Re-Analysis and Re-Annotation
4. Fine-Tuning for publication grade quality

These adjustment steps made re-plotting tedious, since a change in prior steps required a complete re-work of following steps, something which `plotastic` prevented. Its key design feature is the centralized storage of facetting parameters (`x`, `hue`, `col`, `row`). These parameters define which data points are shown on the x-axis, what categories are highlighted by color (`hue`), and how data is grouped into separate plots (by columns and/or rows) into separate plots. This centralization means that once these parameters are set, they not only automate statistical analysis, but also can be automatically applied across all subsequent adjustments made to the plot. This contrasts with `seaborn`, where changing these parameters required adjusting multiple lines of subsequent code.

Re-arranging Facets: `plotastic`'s `.switch()` method allowed for easily shifting the arrangement of plots — for example, switching the data represented on the x-axis with that represented by color — to explore different perspectives of the data quickly. This proved particularly useful when trying to find the most effective way to illustrate complex interactions or trends that might not be immediately apparent. In `seaborn`, changing facets is easy and proved useful during intermediate data analysis, but unfeasable when plots involved multiple layers, sophisticated style edits or statistical annotations, as this can require re-writing subsequent adjustments.

Plotting Multiple Layers of Different Plot Types: Modern journal standards increasingly demand the representation of individual datapoints alongside aggregated data, for example plotting datapoints above a bar- or boxplots. `seaborn` does not automate this, but can require calling two

plotting functions in sequence, e.g. `sns.boxplot()` followed by `sns.swarmplot()`. This can get repetitive, as adjusting the style of these plots to match each other, e.g. defining the point size or transparency of individual data points to fit into a barplot. `plotastic` was designed for multi-layered plotting, offering single-line functions for plot combinations with pre-configured style-parameters.

Statistical Re-Analysis and Re-Annotation To the author's knowledge, `plotastic`'s capability of streamlining statistical re-analysis is unique and unmatched. `seaborn` alone can not perform this without multiple lines of `statannotations` (Charlier et al., 2022). `plotastic` automates the inclusion of statistical annotations directly into plots. This is a significant enhancement because it ensures that any statistical significance noted in the data is immediately visible and correctly updated whenever the data presentation is changed. This feature proved particularly useful during the peer review process of Kuric et al. (2024), where a reviewer asked for a complete statistical analysis of Chapter 1 5 D, which at that time included only paired t-tests between selected groups.

Fine-Tuning for Publication Grade Quality: `plotastic` simplified the creation of publication-quality figures by automating style adjustments that are typically manually coded with `matplotlib` when using `seaborn`. These include adjustments like angled x-axis labels or consistent visual styles across multiple figures, which are important for maintaining the professional appearance of published data.

Outlook: Could `plotastic` Address a Re-Analysis Bottleneck? Re-doing analyses and plots is often overlooked bottlenecks in the reproducibility of scientific research, although it does overlap with two principles of the FAIR-guidelines for scientific data management and stewardship: Interoperability[9] and Re-Usability (Wilkinson et al., 2016). This challenge was exemplified during this work's experiments using RT-qPCR. The field of qPCR, where reproducibility issues have been notoriously prevalent. As Bustin (2014) noted, many publications using PCR-based methods have been seriously flawed, underscoring the need for updated approaches (Bustin et al., 2013; Ruiz-Villalba et al., 2021). Furthermore, the evolution of the $\Delta\Delta$Ct formula over recent years highlights the dynamic nature of data analysis standards in biomedicine (Pfaffl, 2001; Ramakers et al., 2003; Ruijter et al., 2021). Despite these challenges, current data analysis infrastructures seldom facilitate a smooth revision or complete redoing of figures, which could hamper efforts to re-analyse and apply the latest techniques to existing datasets, which could be requested e.g. during peer-review (Wilkinson et al., 2016). In response, `plotastic` was specifically designed to streamline the reconfiguration and reanalysis of data visualizations. This work serves as a case study showing that — according to the author's experiences — the manual effort involved was effectively reduced, making the task of re-analysis seem a lot more inviting, especially for handling semi-big data.

[9] Wilkinson et al. (2016): *"Interoperability — the ability of data or tools from non-cooperating resources to integrate or work together with minimal effort."*

Conclusion 2: Demonstrating the Advantages of Semi-Automation in Biomedical Research Methodologies

This thesis illustrates the challenges and solutions associated with managing the inherent complexity of adhesion studies and related methodologies, such as Cell Cycle profiling. These methodologies necessitate sophisticated data handling tools to address two primary challenges: (1) the multidimensionality of semi-big data and (2) the rapid iterative loop of results evaluation and protocol adjustments, a process for which *in vitro* methods are valued.

`seaborn` and `plotastic` have been instrumental in addressing these challenges. `seaborn` facilitated the rapid processing of intermediate results during method development, while `plotastic` was crucial for crafting publication-grade analyses and figures, filling in the capabilities that `seaborn` lacks. This includes facilitating the easy (re-)design of visualizations and statistical analyses, which are critical for late-stage data processing.

Though this work does not provide empirical evidence quantifying the benefits of semi-automation, it serves as a practical case study demonstrating the transformative potential of such technologies in biomedical research. The integration of semi-automation tools streamlined complex *in vitro* methodologies, significantly enhancing operational agility. This case study bridges biomedical research with bioinformatics, highlighting how semi-automation can reduce data analysis workloads and enable researchers to focus more on exploratory research within the laboratory setting.

To the author's experience, the gained efficiencies not only saved valuable time but also enhanced the clarity and communicative power of the research findings. This is particularly crucial in fields like myeloma dissemination, where precise and transparent data presentation is essential for advancing understanding and treatment strategies. This conclusion suggests a need for further empirical research to validate these benefits more broadly and encourage wider adoption of semi-automation tools in biomedical research.

However, adopting `plotastic` poses its own set of challenges, particularly in the realm of biomedicine where researchers may prefer graphical user interfaces (GUIs) over command-line interfaces (CLIs). While `plotastic` offers a powerful CLI that is efficient and capable of handling complex data manipulation and visualization tasks, the transition from GUIs to CLIs can be intimidating for those accustomed to more visual interaction with software. This barrier can be mitigated by the integration of tools like ChatGPT, which can facilitate the use of CLIs by offering context understanding, code assistance, and error identification.

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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

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A.2 Tables

A.3 Materials & Methods

B Documentation of plotastic