Contents

Introduction

To provide a comprehensive background for the following chapters that focus on the interaction of human mesenchymal stromal cells (hMSCs) with multiple myeloma (MM) cells, this

Aims

This project defines these aims:

- Characterize the interaction between myeloma cells and mesenchymal stromal cells
- Develop methods
- Face the challenge of time-dependent cell adhesion through
- Provide tools to analyze multidimensional cell adhesion data

Summarising Discussion

Time-Lapse Microscopy Added Intuition to Exploratory Cell Biology

- When starting this project, dissemination has not been the main topic. - Surprisingly, Time-lapse identified detaching cells - Hence, Time-lapse proved pivotal for this project, shifting the focus onto in vitro dissemination.

Microscopy holds vast amounts of information. Cell movements themselves add a lot more info. Time-lapse video has proven invaluable for exploratory cell biology

the most important key insight on the mechanism of dissemination identified by timelapse was Cell Division - further insights were multiple time measurements

measuring the minimum time for detachments to begin, or the time required for daughter cells to re-attach to the hMSC monolayer. Such mechanistic insights

Other methods like RNAseq and survival analysis did provide molecular and clinical connections, time-lapse microscopy documented cell interactions as-is, but allowed for a deep and intuitive understanding of cryptic molecular data, placing the conclusions into a context that answer key questions about potential and limits of this study, such as the aggregation behavior of INA-6 cells.

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.

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'*).

Outlook: High-Value Research Topics for Myeloma Research

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

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.

Time as a Key Parameter: The area Thermodynamics of started with scientists measuring how long it takes for gases to cool down. The author claims, by measuring the time it takes for cancer cells to detach could lead to breakthroughs in research of myeloma dissemination.

- Cell adhesion is highly time-dependent. - Cell detachment is required for metastasis and dissemination -

key mechanistic insights

measuring the minimum time for detachments to begin, or the time required for daughter cells to re-attach to the hMSC monolayer. Such mechanistic insights

The author recommends high time resolutions, e.g. 1 frame every 15 min, which is a high res-

olution for common live cell imaging when compared to Purschke et al. (2010). Time-resolution was mostly limited by available disk space. Investing into more hard drives is worth it, since

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

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`.

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. 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 addi-

tion 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 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. Semi-automation using python significantly enhanced this agility, allowing rapid statistical testing and visualization of data, which would have taken considerably longer if done manually. This capability enabled real-time adjustments to the experimental technique during live microscopy sessions, integrating raw data tables directly into Python scripts for immediate analysis. 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 significant 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 be 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-analysis and re-

plotting are often overlooked as bottlenecks in the reproducibility of scientific research. This challenge is exemplified in the field of quantitative PCR (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 the complete redoing of figures, which could hamper efforts to re-analyse and apply the latest techniques to existing datasets. 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.

Conclusion 1: 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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Appendices

A Supplementary Data & Methods

A.1 Figures

A.2 Tables

A.3 Materials & Methods

B Documentation of plotastic