

University of Groningen

The non-existent average individual

Blaauw, Frank Johan

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Blaauw, F. J. (2018). *The non-existent average individual: Automated personalization in psychopathology research by leveraging the capabilities of data science*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Based on:

Blaauw, F. J., van der Krieke, L., Bos, E. H., Emerencia, A. C., Jeronimus, B. F., Schenk, M., ... de Jonge, P. (2014). HowNutsAreTheDutch: Personalized feedback on a national scale. In *AAAI Fall Symposium on Expanding the Boundaries of Health Informatics Using AI (HIAI'14): Making Personalized and Participatory Medicine A Reality* (pp. 6–10).

Van der Krieke, L., Jeronimus, B. F., Blaauw, F. J., Wanders, R. B. K., Emerencia, A. C., Schenk, H. M., ... de Jonge, P. (2016). HowNutsAreTheDutch (HoeGekIsNL): A crowdsourcing study of mental symptoms and strengths. *International Journal of Methods in Psychiatric Research*, 25(2), 123–144.

Chapter 1

Introduction

Imagine a world that takes place on a single sheet of paper. A world with no height, no depth. A world that only exists in *two dimensions*. In this world the most complex shapes are squares — not cubes, circles — not spheres, and so forth. To some this world is known as *Flatland* (Abbot, 1884). Flatland is a world that only exists on the x, y -plane. Like our world, Flatland is a world inhabited by numerous living creatures; *Flatlanders*. Flatlanders themselves are shapes consisting of a number of corners or angles (e.g., rectangles, pentagons, hexagons, heptagons, up to a possibly infinite number of angles, viz., circles). Buildings and other structures in Flatland are materialized using a variety of different shapes and orientations. An abstract world like Flatland might be a hard to visualize for people living in *Spaceland* (a world with three dimensions, our world), but one can think of Flatland as what one sees when leveling eyes with a table top.

In Abbot's *Flatland: A Romance of Many Dimensions*, Abbot describes a male persona in his day-to-day life in Flatland, *Mr. A. Square*. A. Square explains to us what the world looks like from his perspective. For him, Flatland is *the world*, like earth is our world. One day, A. Square runs into the 'Monarch of the world'. Another world that is, as this monarch is the king of *Lineland*. Lineland, as one might have guessed, is a world that consists only of a single dimension and exists in parallel to Flatland. The creatures that live in this world consist only of a single line¹ and movement in this world is either forward or backward, like a caterpillar trapped in a tube. In the book, A. Square speaks with this (rather arrogant) king, who describes him the way things work in Lineland. He explains that *Linelanders* have been fully adapted to be

¹Lines in this case are considered to be unidimensional, with a length and a 'height' of $\lim_{h \rightarrow 0} h$.

able to live in this unidimensional world². A. Square is astonished to learn about this unidimensional world, and is eager to tell the king about his world, Flatland. He rapidly begins explaining this, in his opinion, far more beautiful world of not one, but two dimensions. Unfortunately, the conversation is not very fruitful:

“Behold me — I am a Line, the longest in Lineland, over six inches of Space — ” the king said

“Of Length”, the Flatlander ventured to suggest.

“Fool,” said the king, “Space is Length. Interrupt me again, and I have done.”

— From Edwin A. Abbot, *Flatland: A Romance of Many Dimensions*

A. Square is left baffled and does not understand how the king is not amazed by Flatland. The story progresses and a short while later another peculiar event occurs. While A. Square is just roaming around in his pentagonal house, a strange creature seems to have appeared out of nowhere; a shape with the ability to grow and shrink (which is generally considered impossible in both Flatland and Lineland). Furthermore, A. Square is not able to detect any angles on this mysterious intruder³, and it seems that he has encountered a *perfect circle*, an entity of extreme rarity in Flatland and one with the highest of ranks. A. Square speaks to this extraordinary entity, which replies that it is a *Solid*; a Sphere, and not a plane Figure. He explains that he in fact consists of an infinite number of stacked Circles, of sizes varying from a point to a circle with a diameter of several centimeters.

After some attempts of the Sphere to explain his world, Spaceland, A. Square cannot comprehend the event that just unfolded before his eyes:

“Monster,” I shrieked, “be thou juggler, enchanter, dream, or devil, no more will I endure thy mockeries. Either thou or I must perish.” And saying these words I precipitated myself upon him.

— From Edwin A. Abbot, *Flatland: A Romance of Many Dimensions*

Although their relation seems to improve in the remainder of Abbot’s work, the inherent difficulty of understanding and trusting systems or worlds of different dimensions is evident. The story of Flatland illustrates nicely the complexity involved in thinking outside of the dimensionality one is familiar with. Though the worlds of A. Square, the monarch, and the sphere share similarities, they are not compatible and the creatures use different notions of space-time. If one is used to a high dimensional system, it can be hard to acknowledge the existence of lower dimensional systems. The contrary is even more compelling; for people used to a low number

²For example, they possess exceptional auditory senses.

³Although there are only two dimensions in Flatland, Flatlanders have devised certain techniques to distinguish the number of edges a shape has, as this is of vital importance for their culture and hierarchy.

of dimensions, it can be challenging (if not impossible) to think about and visualize a higher dimensional world. This dilemma coincides, in my opinion, with the current practice in many fields of research, in particular in the field of *psychopathology research*.

Psychopathology research is the field of science that focuses on the psychological and behavioral dysfunctions that occur in mental illnesses. Traditionally, research in this field is rooted in the perspective of studying groups of individuals, and by generalizing found concepts to each person (Lamiell, 1998). Although such perspective is practical and useful in certain cases, this generalization has frequently been called into question (Lamiell, 1981). The main shortcoming of this approach is the neglect of the *individual* dimensions: the dimensions that capture the heterogeneity *within* an individual, as opposed to the heterogeneity *between* individuals. These methods in research stand perpendicular on clinical practice. While in clinical practice the day-to-day functioning of the individual is paramount, research usually focuses on ever larger population samples over long time intervals, disregarding the importance of the individual.

This dissertation aims to bridge the gap between the diverged ‘group’-dimensions and ‘individual’-dimensions in psychopathology research. We combine computer science, statistics, and psychopathology research to give the individual person a central role in modern psychopathology research. The notion of dimensionality is a leitmotif throughout this work, and is applied in different contexts. On the one hand, we refer to dimensionality from a computer science and statistical viewpoint, in which we use the notion of dimensionality to denote the number of variables modeled in a system. As such, each variable describes a certain feature of a group of individuals, or an individual in particular. On the other hand, dimensionality is referred to from the philosophy of psychological diagnosis. We hypothesize that mental illnesses are not necessarily binary, and that actually the combination of various dimensions could in fact describe various gradations of psychopathology. In other words, merely classifying someone as ‘ill’ versus ‘healthy’ might not be sufficient.

1.1 A Classification System

General medicine revolves around the concepts of diagnoses and treatment. A large part of diagnosis focuses on systematic analysis of the symptoms patients might show. The goal of diagnosis is then to find the ‘latent’ illness, or common cause of these symptoms. In other words, the goal is to go from a higher dimensional set of symptoms, to a lower (or uni)dimensional set of illnesses. In general medicine this

method works well, which underlies its dissemination to the field of psychopathology research and practice.

The traditional conceptualization of psychological illnesses and diagnosis thereof is similar to this approach. When a patient shows particular symptoms, they are diagnosed with the associated illness. For instance, a person is considered to suffer from a major depressive disorder (MDD) whenever adhering to the following criteria, as laid out by the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM)⁴:

Major depressive disorder

1. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (i) depressed mood or (ii) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

- (a) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (*Note:* In children and adolescents, can be irritable mood.)
 - (b) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
 - (c) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 % of body weight in a month), or decrease or increase in appetite nearly every day. (*Note:* In children, consider failure to make expected weight gain.)
 - (d) Insomnia or hypersomnia nearly every day.
 - (e) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
 - (f) Fatigue or loss of energy nearly every day.
 - (g) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
 - (h) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
 - (i) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
2. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
 3. The episode is not attributable to the physiological effects of a substance or another medical condition.

⁴The DSM is a manual that presents a classification of mental disorders and the related criteria, with the goal to diagnose these mental disorders in a reliable and unified manner (American Psychiatric Association, 2013).

Note: Criteria 1 to 3 represent a major depressive episode.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion 1, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

4. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
5. There has never been a manic episode or a hypomanic episode.

Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

— Copied fragment from DSM-V, American Psychiatric Association (2013)

However, there is ample debate whether this approach is the optimal way to define and classify mental health problems; a debate which has intensified over the past decades (Kapur, Phillips, & Insel, 2012; Kendler & First, 2010; Kendler, Zachar, & Craver, 2011; Wakefield, 1992). The DSM brought standardization in diagnoses and treatment in a field that used to be heavily fragmented, and served as a means to offer a shared clinical language. Nonetheless, DSM categories have been criticized for their lack of empirical support and the absence of an underlying theoretical framework (Kapur et al., 2012; Kendler et al., 2011; Wardenaar & de Jonge, 2013; Whooley, 2014). As columnist Brooks (2013, May 23) sharply addresses in the *New York Times*: “*Mental diseases are not really understood the way, say, liver diseases are understood, as a pathology of the body and its tissues and cells*” (p. A19). Furthermore, Allan Frances — the chair of the team creating the DSM-IV — describes constructs such as ‘schizophrenia’ to be useful, but also points out that these constructs are mere descriptions of psychiatric problems, instead of diseases (Frances, 2014). Although the DSM system is essential in psychiatric practice, scientists raised concerns about its use, and argued that the current classification system hampers our understanding of psychiatric disorders and can lead to scientific stagnation (Dehue, 2014; T. Insel, 2013; Kapur et al., 2012; Whooley, 2014).

Besides fundamental methodological concerns revolving around the design of the DSM, the traditional dichotomous approach (‘ill’ as opposed to ‘healthy’ indi-

viduals; mentally ‘normal’ as opposed to mentally ‘abnormal’; Frances, 2014) has also given rise to concerns.

Firstly, the expression of a symptom can be highly heterogeneous between (and within) individuals. While some DSM criteria already specify variability between and within individuals, such as having symptoms ‘most of the day, nearly every day’ versus ‘most days’, these specifications lack a solid empirical foundation, and do not allow for the identification of course fluctuations (Horwitz & Wakefield, 2007; Hyman, 2007; Kapur et al., 2012; Kupfer, First, & Regier, 2002; Wardenaar & de Jonge, 2013; Widiger & Samuel, 2005), or for sequential expressions, such as a shift from sadness to anxiety over time (Doré, Ort, Braverman, & Ochsner, 2015; Kessler et al., 2005; Stossel, 2014). While DSM categories are presented as homogeneous disease entities, combinations of different illnesses prevail (so-called comorbidity), implying that the boundaries between diagnostic categories are necessarily fuzzy (Clark, Watson, & Reynolds, 1995; Kendler, 2012; Krueger & Markon, 2006; Ormel et al., 2013; van Loo, Romeijn, de Jonge, & Schoevers, 2013; Widiger & Samuel, 2005). For example, it is not uncommon for a person to experience both symptoms of anxiety disorder and symptoms of depressive disorder (e.g., Kessler, Merikangas, & Wang, 2007; Lamers et al., 2011), and that people are even diagnosed with both disorders, while according to DSM-V these disorders are mutually exclusive. Additionally, treatment effects tend to be rather non-specific, for example, antidepressants do not only decrease depression (Olfson & Marcus, 2009; Roest et al., 2015), and even genetic predispositions defy DSM disorder boundaries in twin (Kendler, 1996), family (K. Dean et al., 2010), and genome-wide association studies (O’Dushlaine et al., 2015).

Secondly, the descriptive consensus-based DSM categories imply a dichotomy of disordered versus healthy people: subjects either fulfill a sufficient number of polythetic diagnostic disorder classification criteria (see the earlier provided fragment of the DSM-V entry for MDD) or they do not (Kendler & Parnas, 2014; Krueger & Markon, 2006). Research suggests, however, that mental strengths and symptoms are generally continuously distributed in the population, without any evident ‘zone of rarity’, and that existing cutoffs are arbitrary and inconsistent (e.g., Gutiérrez et al., 2008; Kendell & Jablensky, 2003; Kendler, 2012; Ormel et al., 2013; Widiger & Sankis, 2000). Mental health problems that might require care can be located at the extreme ends of continuously distributed mental state dimensions (Clark & Watson, 1991; Durbin & Hicks, 2014; Krueger, 1999; Mineka, Watson, & Clark, 1998).

Although a dimensional approach to psychopathology regains influence in psychiatry (Dumont, 2010; Kendler, 2012; Kendler & Parnas, 2014), research into an empirical foundation remains imperative. An alternate world in which these concepts coincide and become the rule rather than the exception is one in which both the

dimensionality of the illness, in which an illness could comprise various combinations and degrees of symptoms, and the dimensionality of the symptoms, in which a symptom could be expressed with different levels and could vary over time, are taken into account. In such a world view, the needs of the individual suffering from psychopathology can be better fulfilled. The individual does not need to exceed a threshold of prerequisites for a mental illness category, but is rather evaluated and treated based on the combination of the symptoms experienced.

New approaches to psychopathology research have since emerged, relaxing the notion of illness and focusing on symptoms instead (Fried, 2015). One of these approaches is through the lenses of graph and network analysis. A graph or network is defined as a set of nodes and a set of edges connecting these nodes, and forming a graph (Newman, 2010). Applied to psychopathology, the nodes can represent symptoms and the edges can denote the interactions or correlations between these symptoms. An illness is then not represented by a diagnosis, but rather by the emerging structure of its symptoms and their interactions. One of the first approaches to apply this 'network perspective' was performed by Cramer, Waldorp, van der Maas, and Borsboom (2010), who investigated the notion of comorbidity by inspecting networks of symptoms existing in multiple psychological disorders. This network perspective allows for a more flexible approach than the relatively rigid DSM categories. For example, when a person suffers from both symptoms of anxiety and depression, according to the DSM these symptoms are considered to originate from only one illness; either depression or anxiety disorder. In the network approach however, an illness is manifested by the various combinations of symptoms and their interactions (possibly in a unique way). By relaxing the notion of disorder and shifting towards a network of symptoms and interactions, we can attain new perspectives on psychopathology research.

Apart from using this network perspective to retrieve information on the *macro*-level, namely on the level of symptoms (e.g., Borsboom, Cramer, Schmittmann, Epskamp, & Waldorp, 2011; Cramer et al., 2010; van Borkulo et al., 2015), the network perspective has also been used to map out *micro*-level relations, that is, the moment-to-moment variability of experiences, mood, and other factors (e.g., Bos et al., 2017; Bringmann et al., 2013; Wichers, 2014; Wichers, Wigman, & Myin-Germeys, 2015). This micro-level perspective is of special interest, as it can serve as a means to alleviate the group-level dependence in psychopathology research, and enable for a more individualistic and personalized approach.

1.2 Group and Individual Data to Improve Well-being

Attempts at sustaining and enhancing well-being, and improving mental health are predominantly based on *nomothetic* research (van der Krieke, 2014). In nomothetic (or cross-sectional) research, samples of the population are investigated to find generic laws of patients' well-being (Allport, 1937). Nomothetic research builds upon the assumption of homogeneity. Most studies in the field of psychopathology research focus on large groups for performing their research (Lamiell, 1998; Molenaar, 2004). A data sample is once (or a small number of times) collected from a population, generally as large as possible, and this sample is generalized to all individual members of the population that the sample is supposed to be drawn from. As a consequence, the majority of evidence-based treatment guidelines in health care apply to a *non-existent average individual* and they do not sufficiently account for the fact that each person is different and should be treated as such (Allport, 1937; Barlow & Nock, 2009; Lamiell, 1998). Although these large group based studies have proved useful for giving insight in underlying population mechanisms, they are often only marginally useful for providing reliable knowledge on the level of the individual (Hamaker, 2012; Molenaar & Campbell, 2009). The heterogeneity among and within people is large and although a part of the underlying biological underpinnings might be shared between all individuals, a large part is possibly unique, and is hard to generalize. This nomothetic approach has been criticized for leading to knowledge that is 'true on average' (Lamiell, 1998). Disregarding the fact that these results hold for the group and not necessarily for the individual, can lead to inaccuracies, a phenomenon researchers have coined the *ecological fallacy* (Piantadosi, Byar, & Green, 1988). The same holds for the effectiveness of medicine, which might be effective on average, but can show variance in their effectiveness on the individual level (Rothwell, 1995).

Recently, researchers have called for a more personal approach in mental health care (Hamaker, 2012; Molenaar & Campbell, 2009), which can be realized by means of (quantitative) *idiographic* research (Allport, 1937). Where nomothetic research focuses on *between* person variation, idiographic research focuses on the variation *within* people⁵. That is, research in which an individual compares themselves over time. In a typical quantitative idiographic study a person completes multiple, repetitive assessments within a specified time period, resulting in a time series data set. Promising techniques that are widely used to support such research in psychopa-

⁵Note that the notion of 'nomothetic' and 'idiographic' research have, since reintroduced by Allport in 1937 (after Munsterberg in 1899), diverged from the terms as originally introduced by Windelband in 1980 (Hurlburt & Knapp, 2006; Lamiell, 1998). In the present work, we adhere to the notion of these terms as used by Allport (1937).

thology are *diary studies*, or experience sampling method (ESM; Csikszentmihalyi & Larson, 1987) and ecological momentary assessment (EMA; Shiffman, S., & Stone, 1998)⁶ methods. In EMA and ESM participants repeatedly assess themselves for a certain period of time (usually days to weeks), by filling-out a single or a set of questionnaires on a relatively high frequency (e.g., daily or multiple times per day). These techniques rely on the ambulatory collection of longitudinal self-report data. Due to the inherent chronological ordering applied in these techniques, the collected data is a time series. Such data provides insight into the *intraindividual* variability of psychological factors over time (viz., the moment-to-moment fluctuations). Moreover, when the time series data is analyzed with specialized statistical techniques, cause-effect relationships can be revealed between features measured in the repeated assessments (Emerencia et al., 2016; van der Laan & Rose, 2017). Such relationships are of particular interest because they allow for prediction, which might pave the way for influencing the cause when the effect is not desirable. As a result, idiographic research and time series assessments can form the basis for highly personalized treatment advice.

Health researchers face significant challenges regarding data collection, data analysis, and the generation of feedback, when conducting idiographic research and attempting to make the idiographic results available for practice. This has hampered implementation of idiographic research on a large scale. We hypothesize that the challenges in idiographic research could be tackled by automating part of the data collection, data analysis, and feedback generation processes in order to realize a highly *personalized medicine*. Self-evidently, automated analysis of large amounts of data on an ever larger scale has a strong connection to the field of computer science. Measuring people on large scales nowadays, where computers and information and communication technology (ICT) play a large role in our day to day lives, could be considered impractical and perhaps infeasible without the use of such technology. Moreover, the usefulness of computer science becomes apparent when the aim is to provide users with personalized feedback and advice based on the specific individual. Applying manual analysis for generating such advice is not scalable, and automated techniques need to be devised to enable practical implementations. One way to go forward with such automated techniques is by means of model based simulations (Blaauw, van der Krieke, Emerencia, Aiello, & de Jonge, 2017a; Borsboom et al., 2016; Jebb, Tay, Wang, & Huang, 2015). Such model based simulations could measure hypothetical outcomes in so called ‘counterfactual’ experiments, and use these outcomes as proxies for actual (and practically impossible) full controlled ex-

⁶Although the terms EMA and ESM originate from different research processes (Trull & Ebner-Priemer, 2009), they are often used interchangeably. In the present work we do not make a distinction between the two and use the terms ESM, EMA, and diary study interchangeably.

periments (Rubin, 1974). This search for automated analysis techniques is the topic of Part II, where we further explore the use of automated analysis for personalized feedback methods.

As always, there are drawbacks to the realization of a highly personalized medicine. While traditional, nomothetic approaches aim to generate knowledge that proves effective for a large group of people, a personalized approach aims at subgroups of people, and does not propose general approaches that suit all people. This subgrouping can introduce new issues, such as the *curse of dimensionality*.

1.3 Back to Dimensionality, and its Curse

The notion of curse of dimensionality highlights the various problems encountered when working with high-dimensional data (viz., a high number of variables or covariates; Bellman, 1961). When explaining this notion in terms of combinatorics, the so-called *curse* becomes apparent. Suppose we define dimensionality as the number of features included in a simple model. Let us hypothesize a relation between two variables: age and gender, on some measure of mental health. If we would stratify people based on these two dimensions only, and for simplicity we would consider age as $a = \{x \in \mathbb{N}_0, 0 \leq x \leq 122\}$ (Whitney, 1997, August 5) and we consider gender to be a binary variable $s = \{\sigma, \varphi\} = \{0, 1\}$, we would end up with a matrix of possibilities $\mathbf{G} = a \otimes s$, where $\mathbf{G} \in \mathbb{N}_0^{123 \times 2}$. In other words, with just two dimensions, any person in the world belongs to exactly one of 246 *strata* (or cells in the matrix). If we were to add a third dimension, say education, and for simplicity assume everyone could be measured on a level $e = \{0 \dots 10\}$, this would increase the number of strata to $\mathbb{N}_0^{123 \times 2 \times 11}$. Adding this single dimension thus increases the number of strata to 2 706. In fact, the number of strata increases exponentially with the number of dimensions. As such, even after adding a reasonably low number of features (viz., dimensions), we could end up with a single person per stratum, and only a few features are needed to describe any individual uniquely (see, e.g., El Emam & Dankar, 2008; Koot, 2012, for examples of this phenomenon with respect to privacy and anonymity).

This curse is what both fuels and hinders the implementation of a *true* personalized medicine (a medicine personalized for every individual). On the one hand, such large heterogeneity among people makes it very difficult to solely rely on un-specific group data, and apply a *one-size-fits-all* approach. On the other hand, the fact that every person can be considered unique makes it practically impossible to create treatments and medicine for a specific individual (Louca, 2012).

An often used misinterpretation of the term ‘personalized medicine’ is that it

has the goal to offer specific treatments for *each* individual in isolation, while in fact the vision is to tailor treatments not necessarily to individuals in separation, but to smaller strata as opposed to the infamous one-size-fits-all approach (Lesko, 2007; Louca, 2012; National Research Council, 2011). More recently, a different term was coined partly to prevent this misinterpretation: *precision medicine*. The goal of precision medicine is neither to use general treatments for each individual, nor to create a specific treatments for each individual in separation. Its goal is to find a *Goldilocks zone* of the level of personalization involved. Precision medicine focuses on small groups of stratified individuals (Jameson & Longo, 2015; Louca, 2012). The use of more information defining the individual could enable a more personalized (or precise) medicine, as defined in Section 1.2.

In this dissertation we *do* investigate applications which focus on providing a true personalized medicine, that is, applications that have a large component solely based on data retrieved from the individual. We therefore deliberately distinguish precision medicine from *true* personalized medicine, especially in terms of personalized advice. We use the term personalized advice for advice focused and based on the individual, and precision advice for personalization based on (smaller) groups of individuals.

1.4 Scope and Contribution of this Dissertation

This dissertation presents our research on methods that could serve as a catalyst for personalization in the field of mental health. We performed several studies to investigate and mitigate the challenges related to personalization described in the current chapter, namely the challenges regarding data collection, data analysis, and the generation of feedback. We provide an overview of these studies, and give conclusions and directions for future research. The present work provides ideas useful for general practice; both in terms of research and in terms of clinical practice.

Our work mainly revolves around two large scale Dutch research projects: HoeGekIsNL (or in English: HowNutsAreTheDutch), and Leefplezier. These projects have *inter alia* been started to provide an insight in the moment-to-moment fluctuations in individual well-being. The novel individual and longitudinal way in which HowNutsAreTheDutch (HND) and Leefplezier collect data poses several challenges which one would not experience when performing 'regular', cross-sectional studies. Challenges like: "how to analyze such personal data sets?", "how can these data sets be analyzed on a large scale?", "should we just neglect the fact that there is a group which could help make our results more robust?", "how can we reduce the burden of intensive studies for the individual?", and "how can we do this on a large scale?" These challenges are

addressed in this dissertation.

The challenges related to data collection are investigated using the aforementioned research projects. We set up two Dutch national studies to measure psychopathology in general and elderly populations, and we devised a generic architecture for building such e-mental health platforms. These platforms are created to collect both cross-sectional and individual data. We acknowledge the fact that the use of the intensive longitudinal self-report methods for collecting individual data (viz., EMA) has various drawbacks, for instance the burden for participants to fill out the questionnaires and the inherent subjectiveness of the data. Filling out questionnaires a number of times a day is cumbersome, and arguably not the way to go forward, especially when asking questions that can be replaced by automated methods, such as sensors. Moreover, EMA self-reported sleep duration or physical activity have been shown to be unreliable (Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008), and from this perspective, sensor data can be expected to be more reliable and objective than corresponding EMA questions. To resolve these drawbacks, we developed a way to collect such individual data in a ubiquitous manner. As such, we propose a platform to collect data in a less intrusive manner, whilst still being applicable in large scale research in a platform named *Physiqua*.

We approach the challenge of analyzing data from these studies from three viewpoints. Firstly we take the individualistic route, in which we focus on creating models purely based on data retrieved from the individual, that is, *true* personalized research. Secondly, we approach the challenges from the opposite side by showing how we can use longitudinal group data to make highly adaptive, stratified predictions, and aim for a precision medicine. Finally, we combine the power of the individualistic and group perspective, and approach our problem from a combination of both viewpoints — a group-powered individualistic approach. In this third approach, we propose and implement a framework that allows for the combination of the large data sets collected from a group-based study with the relatively small data sets collected for the individual, with the goal of finding statistical parameters for the individual and the group.

1.5 Outline

The overall structure of this dissertation takes the form of eleven chapters subdivided into two parts. Before this division, we present a brief overview of the recent history and state of the art of idiographic psychopathology research, the means to collect such data, and methods to analyze these data in the next chapter.

After introducing this background, we explore our psychopathology research

platforms in Part I. In this part, we provide an overview of the different platforms created for the present work, namely HowNutsAreTheDutch and Leefplezier. First in Chapter 3, we provide an overview of the platforms, and show the decisions and thought process behind both platforms. We describe the different types of data collected using these platforms and the rationale behind these different forms of data collection. After this initial introduction, we provide a generalized service-oriented architecture (SOA) by analyzing the architectures of HND and Leefplezier in Chapter 4. In this chapter we dive into the architectural details of both platforms and make a comparison in order to come to a general architecture for similar e-mental health platforms. Finally, in Chapter 5 we provide several descriptive statistics and general results obtained from these studies.

In the second part of this dissertation, we explore the analysis of data, such as the data collected in Part I. In Chapter 6, we approach this data set from the individualistic point of view, or the so-called *true* personalized perspective. We provide an algorithm to perform analysis on a time-series only containing information about a single individual. We propose Automated Impulse Response Analysis (AIRA), an algorithm / approach to create personalized feedback showing how the individual could improve his or her well-being.

In Chapter 7, we approach the analysis problem from a different perspective, that is, the perspective of the group, by applying a machine learning methodology. Machine learning is “*the capacity of a computer to learn from experience, i.e., to modify its processing on the basis of newly acquired information.*”⁷ We describe the machine learning pipeline we created to answer questions about stratified individuals, using data retrieved at the group level. Our aim in this chapter is to predict the chronicity of above clinical threshold levels of depression. The pipeline applies a method that allows the created estimators to be of high dimension, and therefore might be useful for prediction.

In Chapter 8, we combine the approaches used in Chapter 6 and Chapter 7, and use the power of the group whilst we tailor our parameters of interest to the individual. In this chapter we describe and apply two novel machine learning techniques known as Online SuperLearner (OSL) combined with the online one-step estimator (OOS). In this two step approach we first use OSL to train a series of machine learning estimators in a similar fashion as we did in Chapter 7, but now using time series data like in Chapter 6. Then we use the OOS to *target* our estimator towards a specific parameter of interest.

Chapter 9, shows our perspectives on the challenge of reducing the impact of an EMA on its participants. We describe Physiqal, our platform to aid researchers

⁷‘Machine learning.’ (n.d.) In *Oxford Living Dictionaries*. Retrieved from https://en.oxforddictionaries.com/definition/machine_learning.

in combining sensor measurements with EMA. We describe the architecture and philosophy of the Physiqua platform, and demonstrate its practical usefulness by performing a two-case case study and analyzing the results.

In Chapter 10, we provide an elaborate discussion of our research and the proposed solutions, and in Chapter 11 we conclude the work and provide directions for future research.