Family System Dynamics and Type I Diabetic Glycemic Variability: A Vector-Auto-Regressive Model

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1. Introduction

1.1. Introduction

"If you're not confused, you're not paying attention"
~ Tom Peters, *07.11.1942

Freud and some of his colleagues have been widely criticized for lack of quantitative research evidence for their elaborate models. They presented detailed case reports instead – and modern researchers in various academic fields might provide more support for qualitative approaches than expected (e.g. Silverman, 2000; Miles and Huberman, 1994). Concurrently, psychosomatic researchers such as Uexküll (Uexküll, Adler, Herzog, Joraschky, Köhle, Langewitz, Söllner & Wesiack, 2010) or Meissner (2006) have called for a more integrated perspective on the mind-body relationship honoring the complexity of dynamic dependencies and intertemporal reciprocal cause and effect relationships among different psychic as well as somatic variables. Arguably this latter quest stands in contradiction to multiple regression analysis, a cornerstone of quantitative research, in which a clear distinction between cause and effect, independent and dependent variables, is essential. Relatively recent research in econometric theory has, however, challenged this old paradigm by introducing vector autoregressive analysis, where all variables in a system are dependent on past values (lags) of themselves and the other variables in the system (e.g. Lütkepohl & Krätzig, 2004).

The old dilemma between qualitative and quantitative research (if it can be reduced to that) is also a central theme in all past research on the psychosomatic aspects of diabetes in insulin dependent children and adolescents (e.g. Minuchin, Rosman & Baker, 1978; Coyne & Anderson, 1989). One reason may lie in both, complex somatic mechanisms surrounding glycemic metabolic stability as well as the added psycho-social complexity provided by the fact that individuals (i.e. parents) other than the patient have significant influence on (and legal responsibility for) the daily treatment of the disease. Yet, diabetes is just one of the many challenges any average child/ adolescent may encounter while growing up. As a result, the researcher may find one of the most prototypical webs of interconnected psycho-somatic dynamic interdependencies, as described by Meissner (2006) above.

With one out of 600 US or European school-age children suffering from insulin dependent diabetes mellitus (Ahmed & Ahmed, 1985; Seiffge-Krenke, 1998a) and just

about 33 per cent of diabetics between 13 and 19 years of age managing to maintain tolerable glycemic control and a HbA_{1c} below 8, and furthermore 6.3 per cent suffering from at least one episode of major hypoglycemia within the last three months (Swift, Seidman & Stein, 1967; Thomsett, Shield, Batch & Cotterill, 1999), the subject matter seems to warrant further investigation. Especially in light of the devastating immediate and long-term effects of poor diabetic control such as kidney failure, blindness, polyneuropathy, and even death, to name but a few.

1.2. Research Objectives

In this work I explain and demonstrate a new quantitative approach to the study of families with insulin dependent diabetic children and their glycemic management. The methodology has been adopted from econometric theory (e.g. Lütkepohl and Krätzig, 2004) and is based on vector autoregression. A case vignette will also be presented.

My mission is twofold: First, I intend to provide an alternative to a purely qualitative or traditionally quantitative (multiply regressive) methodology – which both have their merits as much as their specific shortcomings. Secondly, I present a case report on a family with an insulin dependent diabetic adolescent, quantitatively portraying the effects of the emotions of various family members on the glycemic variability of the diabetic.

1.3. Contribution of Research

The primary objective of this research is to demonstrate an entirely new quantitative approach to the traditionally qualitative case study concept, thus marring the merits of both. In addition, clinical findings from this work may spur new ideas for all sorts of future research on psychosomatic underpinnings of families with children and adolescents suffering from chronic illness, but, of course, can not be generalized for clinical practice. Focus is not only put on a mere coping process within the family, but also on how each emotional being of the family impacts on both somatic and psychic variables of the patient and vice versa.

1.4. Structure of Thesis

First, I will review extant research on psychosomatic aspects of insulin dependent type I diabetic children and their families. Additionally, I will provide a brief introduction to econometric theory on vector autoregression. A section on methodology will then apply vector autoregression to a case study of a family with a type I diabetic minor, not before a case vignette is presented to provide real-life insight into the case. Possible amendments to contemporary vector autoregression will be discussed. Research findings of this particular case study will be presented and interpreted in words and graphical representations, not just for that sake, but also to demonstrate innovative avenues for comprehensive presentation of highly quantitative results from VAR modeling in general. Limitations of this work and possible trajectories for future research will be discussed. The findings of this study will be compared and contrasted with popular findings from quantitative and qualitative research on psychosomatic aspects of type I diabetes in the family setting.

2. Literature Review

2.1. Introduction

For the sake of clarity, not all the literature with some relevance to this thesis will be reviewed. A focus lies on topics with high relevance or recent publication. First, some preliminary remarks to the concept of diabetes in general will be presented. Chronically instable diabetes in minors will be reviewed more extensively with subsections on the chronic nature of diabetes and the concomitant family dynamics, as well as on the concept of what some authors have termed "brittle diabetes" (e.g. Gale & Tattersall, 1979; Kent, Gill & Williams, 1994, Brosig, Leweke, Milch, Eckhard & Reimer, 2001). Finally, vector autoregression and multivariate time series analysis, rooted in econometric theory, will be briefly reviewed to provide some foundation for the concepts discussed in the following sections.

2.2. Diabetes Mellitus

Although this may seem gratuitous to readers with a medical background, others may find this thesis to be incomplete without some brief introduction to the concept of diabetes. The following brief review of those aspects of the disease with some relevance to the comprehension of this research, is mainly based on current guidelines on diabetes for physicians in Germany ("Deutsche Diabetes Gesellschaft", "AWMF – Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften"), which are published online and frequently updated by expert conventions according to current research developments (Kerner & Brückel, 2011; Böhm, Dreyer, Fritsche, Fürchtenbusch, Gölz & Mertin, 2011). My presentation of the disease is by no means exhaustive.

According to aforementioned sources, there are various subcategories of diabetes, the most well-known of which may be diabetes type I and II. Common to all is the lack of or dysfunctional regulation of blood glucose levels via insulin, a hormone physiologically secreted in the pancreatic gland to reduce blood glucose levels. Both, excessive levels of blood glucose (hyperglycemia) and particularly low levels of blood glucose (hypoglycemia) cause severe immediate (coma, death) and long-term effects (organ failures, blindness, polyneuropathy, to name but a few). While diabetes type II may be caused by either or both, insulin resistance in bodily cells or lack of insulin production and secretion in the pancreatic gland, diabetes type I occurs due to a destruction of the ß-cells, physiologically producing insulin in the pancreatic gland.

Reasons for this destruction may be of autoimmune (diabetes type Ia) or idiopathic (diabetes type Ib) nature. Type I diabetes usually manifests in children and is the focus of this research. For the autoimmune diabetes type Ia various antibodies can be screened for in blood examinations (ICA, IAA, GAD65A, IA-2, ZnT8). However, for the diagnosis of both types of diabetes certain benchmark markers related to blood glucose levels have been established: HbA_{1c}[1] above or equal to 6.5% (48 mmol/mol), plasma glucose levels at any time or two hours after administration of the oral glucose tolerance test above or equal to 200 mg/dl (11.1 mmol/l), or plasma fasting glucose levels above or equal to 126 mg/dl (7.0 mmol/l). Whenever one of these markers is above its normal range, the diagnosis of diabetes is established. Before such testing, usually, various clinical symptoms, such as increased thirst, polydipsia, polyuria, weight loss, skin manifestations, and general signs of decreases in performance initiate medical attention.

The cornerstone of treatment for type I diabetics is the subcutaneous injection of different types of insulin (rapid acting, long acting, and "normal" acting insulin) in aiming to keep blood glucose levels at a constant level with ideally a HbA_{1c} below 7.5 per cent (individual goals may be above this benchmark) and no hypoglycemic derailments. The application of insulin has to both satisfy a base level need for the hormone, as well as modulate spikes in blood glucose due to the intake of calories. As a result, for the patient (or its primary care giver), either the amount of calories consumed can be matched with the insulin administered or vice versa. The first method is usually referred to as conventional insulin treatment and requires a strict mealtime regimen. The second is called intensified insulin treatment and usually requires more frequent injections and blood glucose control measurements. Generally speaking, patients have to check their blood glucose levels at least three times a day (morning, lunch, evening) and whenever they observe signs of blood glucose derailments (for the recognition of which they should be trained). For blood glucose measurements, patients are trained to pinch themselves with a lancet to obtain a drop of blood (usually from the tip of a finger), which can be analyzed with an automated hand held device. In case blood sugar is too low, glucose must be consumed; in case of hyperglycemia insulin must be administered. In addition, carbohydrate intake through food and drink must be

[1] HbA_{1c} refers to glycated haemoglobin (a protein in red blood cells carrying oxygen), the percentage of which provides a measure for the blood glucose levels of a person for the past eight weeks (in the absence of distorting factors such as anemia, blood transfusions, pregnancy, etc.).

determined at all times and matched with insulin administration in a strict temporal relation (depending on the type of insulin).

As if such complex (and painful) self-treatment is not enough, various complications can also affect blood glucose: Physical activity (sports) will usually reduce the demand for insulin. Somatic stress, such as infectious diseases or surgery, and various hormones (such as adrenalin, cortisol, or growth hormones) will also influence the need for insulin/ blood glucose in various ways – especially during adolescence. Some of these phenomenons have been described with specific terms such as the "dawn phenomenon"[2] or "somogyi phenomenon"[3]. Since both of these will result in hyperglycemia in the morning (before breakfast), but require completely opposite therapeutic actions, nightly measurements of blood glucose are necessary to determine the adequate response. This is not to mention the effect of other medication or (not uncommon in adolescents) the consumption of alcohol (causing hypoglycemia), which will also impact on glycemic management – often with some delay in time, making it even more difficult to retrace cause and effect.

All in all, crucial to the appreciation of this work, diabetic management requires the patient or its primary care giver (as in the case of small children) to constantly pay close attention to complex physiological processes, plan all actions (including the time and amount of food intake) in advance, and engage in frequent (and often painful) monitoring and interventional actions, with little room for spontaneity or behavior considered normal in healthy children and adolescents. Disregard of such strict regimen will have dire consequences immediately (hypo- hyperglycemic coma, death) and in the longer term (organ failures, dialysis, blindness, polyneuropathy, arteriosclerosis, diabetic foot syndrome, general susceptibility to skin infections, etc.). For patients and care givers, excessive fears of diabetic derailments can be just as detrimental to quality of life and psychosomatic health as can be the neglect of monitoring and treating the disease.

[2] Due to increased secretion of growth hormones over night, blood glucose will be too high in the morning (past six am) despite proper insulin administration the previous evening (Herold, 2012).
[3] Due to too much insulin in the evening the patient suffers from hypoglycemia during the night (often around 3 to 4 am) which triggers the secretion of opposing hormones and a hyperglycemia in the morning (Herold, 2012).

2.3. Chronically Instable Diabetes in Minors

2.3.1. Chronic Diseases, Diabetes and Family Matters – An Introduction to its Psychosomatic Aspects

All chronic diseases are associated with increased prevalence of mood disorders and depression (Harris, 2003). This can be evidenced for adults as much as for children (e.g. Kogon, Vander, Weiss, Smith, Flynn, & McCauley, 2013). One source, examining a total of 91.642 families, claims parents of chronically sick children to be 30 times more likely to report developmental, emotional and behavioral problems (including attention deficit/ hyperactivity disorder, depression, learning problems, and challenging behaviors) in their children, than parents of healthy children – an effect prevailing even after adjustment for social and demographic factors (Blackman & Conaway, 2013). Other sources add on to that by drawing attention to the high prevalence of alexithymia – the sub-clinical inability to identify and describe emotions in the self (Sifneos, 1973) – in chronically ill children (Brosig & Zimmer, 2014). Most sources agree with Blackman and Conaway (2013), that "attention to these common co-morbidities will not only result in enhanced quality of life but will also promote better adherence to medical recommendations and, thereby, optimal disease control."

Diabetes type 1 is a typical chronic disease affecting children as much as adults. The prevalence of depression in diabetics in general may be up to 25 per cent (Anderson, Freedland, Clouse, Lustman, 2001), or even 30 per cent (Dziemidok, Makara-Studzińska, & Jarosz, 2011), or three times higher than in non-diabetic populations (Harris, 2003).

The inner workings of these correlations, including possible cause and effect chains, remain the subject of present research. On the one hand, the negative effect of such psychological factors, including depression, on disease management in type 1 diabetics (blood glucose levels) has been widely researched (e.g. Robertson, Stanley, Cully, & Naik, 2012). On the other hand, less prominent, there is also some research on how blood glucose impacts on the mood of the patients – in which depressive symptoms are often taking a more severe course than in non-diabetic populations (Dziemidok, Makara-Studzińska, & Jarosz, 2011). Among the most specific of such research, high blood glucose levels were associated with negative moods in type 1 diabetics (Hermanns, Scheff, Kulzer, Weyers, Pauli, Kubiak, & Haak, 2007; Van Tilburg, McCaskill, Lane, Edwards, Bethel, Feinglos, & Surwit, 2001). Most other research

remains less specific, more general in its propositions, thus encouraging research such as this – with more focus on details (even if it is for the price of small study populations).

In an attempt to tie together some of the results of extant work on the subject, elaborate models, intending to map the various interdependencies of type 1 diabetes with a diverse set of environmental factors surrounding the patient, have been developed. One well-established model by Whittemore, Jasper, Guo, and Grey (2010) has recently been modified and re-published to (among other things) better represent the effect of family members on the patient. This thesis intends to focus on these relationships. Understandably, aforementioned frameworks lack the amount of detail on model component definitions and component interactions, I aim to examine in this case study. The family, as what I believe to be a germinal component of managing diabetes in minors, has to be moved into the spotlight of much more specific research. Not only the question how it affects the diabetes of the child or adolescent is of interest, but similarly, how the diabetes affects the family as a whole and individuals within it.

For young children (ages 2 – 7), parental fear of hypoglycemia, parental depressive symptoms, and child mealtime behaviours were identified as three major factors predicting parental stress (Patton, Dolan, Smith, Thomas, & Powers, 2011). 58 and 68 per cent of the variances of stress frequency and stress difficulty, respectively, were associated with parental depressive symptoms and fear. Parental discomfort may not only be problematic for its own merits, but also because parental perceived burden of diabetes management is one major factor in prohibiting optimal glycemic control (Butler, Zuehlke, Tovar, Volkening, Anderson and Laffel, 2008). This relationship may not only be due to direct cause and effect chains in children who are too young to manage diabetic control themselves, which makes them particularly dependent on their parents, but, as this study will suggest, may be rooted in subconscious effects of affect states of parents on affect and blood sugar states of their (otherwise self-competent) adolescent child. Streisand, Swift, Wickmark, Chen and Holmes (2005) summarize the state of cumulative findings on the topic and provide encouragement for research such as this: "*Though [this] research clearly indicates that parent psychological and behavioral functioning are important, little is known about the specific nature of these parents' pediatric parenting stress*."

2.3.2. Brittle Diabetes

One out of 600 United States or European school-age children suffers from insulin dependent diabetes mellitus (Ahmed & Ahmed, 1985; Seiffge-Krenke, 1998a). Four pillars underlying overall treatment of a chronic disease such as type 1 diabetes in minors are described as being composed of a) the evidence-based individually adjusted medical treatment, b) adequate and normalized schooling of the minors, close relatives, and other care-givers, c) close monitoring of treatment success through specific parameters which allow to evaluate adherence to the treatment protocol, and d) positive feedback for patients and their parents during regular and recurring medical appointments (e.g. Brosig & Zimmer, 2014). Despite such efforts, widely applied in modern medicine, just about 33 per cent of diabetics between 13 and 19 years of age manage to maintain tolerable glycemic control and a HbA_{1c} below 8; 6.3 per cent suffered at least one episode of major hypoglycemia within the last three months (Swift, Seidman & Stein, 1967; Thomsett, Shield, Batch & Cotterill, 1999).

Fonagy, Moran, Lindsay, Kurtz, and Brown (1987) provided evidence of 44 per cent of the variance in blood glucose control to be statistically explained by psychological variables in these patients and their parents. Additionally, in a randomized controlled study, Moran, Fonagy, Kurtz, Bolton, and Brook (1991) demonstrated how an intensive inpatient treatment program including psychoanalytic psychotherapy could effectively improve diabetic control in children. In light of such findings, it is not surprising that for at least four decades researchers have strived to identify the psychosomatic aspects responsible for the devastating statistics evidencing poor glycemic control in minors – especially during puberty.

Based on elaborate qualitative case analyses of what they then termed "psychosomatic diabetes" Minuchin, Rosman, and Baker (1978) described young diabetics with frequent derailments as having difficulty in handling stress, showing a tendency to internalize anger and being somewhat immature in their ability to cope with challenging situations. Recurring familial structures were analyzed as featuring enmeshment, rigidity, overprotectiveness and lack of conflict resolution and referred to as the "psychosomatic family." They explain how extreme proximity and intensity in family interactions, blurred boundaries between subgroups, poor interpersonal differentiation, too much concern for each others' welfare, conflict avoidance, and a strong commitment to maintaining the status quo, all add up to spark and reinforce psychosomatic symptoms. Minuchin et al. (1978) went even further by linking blood

glucose derailments in type 1 diabetic children with a previous rise in the concentration of free fatty acids (FFAs) in the blood. (This is similar to our study in that biological markers were linked to psychic ones.) Subsequently, they conducted experimental studies provoking a rise in FFAs by triggering conflict within the family, thus causing strong emotions in all family members. Unlike this study, they did not focus on specific affects which could have been linked to a rise in FFAs, but chose to describe overall observer impressions of family situations leading up to the change in FFAs. Interestingly, they also evidenced the rise in FFAs to last significantly longer and exhibit higher amplitudes in diabetic children, than in healthy children in a similar family conflict situation. I believe this research to be a first step toward further clarifying and detailing some of the links between biological markers and much more specific psychic parameters (than those formulated in extant research) in a family system with an insulin dependent diabetic child.

However, even ten years after the initial Harvard-publication of Minuchin et al.'s (1978) United States grant-supported findings, critics concluded: "…as we conducted research and therapy with the families of diabetic children, we were impressed with both the limit of the formulation of the family's role in diabetes offered in 'Psychosomatic Families' and the uncritical acceptance that the book continued to enjoy." (Coyne & Anderson, 1989). In their rather pointed article entitled "The 'Psychosomatic Family' reconsidered II: Recalling a defective model and looking ahead" Coyne and Anderson (1989) criticize Minuchin et al. (1978) primarily for their bold, yet statistically (allegedly) poorly supported statements on the "typical psychosomatic family" and their overgeneralizations of these overall "weak" findings on familial situations in one psychosomatic illness to various psychosomatic illnesses. More specifically, small sample sizes and poor documentation of methodology (or lack thereof) are being highlighted.

Later (more quantitative) research has focused on different aspects of interactions between glycemic control in adolescent diabetics and their family environment, often with inconsistent findings (Leonard, Jang, Savik, & Plumbo, 2005; Seiffge-Krenke, 1998b): Luyckx and Seiffge-Krenke (2009) confirmed previous research findings underscoring good glycemic control to be linked to high scores of positive self-concept and a family climate perceived as organized and controlled (Seiffge-Krenke, 1998b; Weist, Finney, Barnard, Davis, & Ollendick, 1993). By contrast, Davis et al. (Davis, Delamater, Shaw, La Greca, Eidson, Perez-Rodriguez &

Nemery, 2001) found parental restrictiveness to be associated with poor, a warm family climate with good glycemic control. Butler, Skinner, Gelfand, Berg and Wiebe (2007) found intensive maternal control to be related to depressed moods, which is noteworthy since associations between poor glycemic control and depressive symptoms have been well established (e.g. McGrady & Hood, 2010; McGrady, Laffel, Drotar, Repaske, & Hood, 2009). Burroughs, Harris, Pontious, and Santiago (1997) reviewing 32 studies in their meta-analysis found diabetics with supportive and cohesive families embracing open and emphatic communication to be most likely to have good metabolic control, as opposed to families with frequent conflicts. Seiffge-Krenke (1998b) reports that adolescents with diabetes generally perceived their family climates to be significantly less cohesive and stimulating than healthy adolescents and suggests discrepancies in the empirical research may be due to lack of control for confounding variables. All in all, there is little doubt, more research on specific variable interactions surrounding the family context of diabetic minors is needed, which I intend to at least partially provide through this thesis.

In an attempt to tie various results into one picture, some authors have adopted the term "brittle diabetes" to describe chronic glycemic instability with no apparent explanation (e.g. Gale & Tattersall, 1979; Kent, Gill & Williams, 1994). Brosig et al. (2001) have reviewed literature to identify three possible lines of reasoning behind brittle diabetes:

- Conscious and unconscious manipulations of the patient cause instable blood glucose values (Schade, Drumm, Duckworth & Eaton, 1985; Schade, Drumm, Eaton & Sterling, 1985);
- Strong affect states cause the release of hormones destabilizing glycemic metabolism (Dutour, Boiteau, Dadoun, Feissel, Atlan & Oliver, 1996; Tattersall, 1988);
- A dysfunctional doctor-patient-relationship, based on the physician struggling with counter transference and the patient being impaired by lack of object consistency due to bonding pathology, add up and result in ineffective diabetic management (Brosig, Kupfer & Brähler, 1997; Minuchin, Baker Rosman, Liebman & Milman, 1975; Moran & Fonagy, 1987; Moran, Fonagy, Kurtz, Bolton & Brook, 1991).

Brosig et al. (2001) propose, the dissolution of the parent-child relationship during adolescence challenges the diabetic minor with the repression of unconscious desires for protection and provisioning, which in the case of brittle diabetes leads to the loss of rational control over diabetic management (Brosig et al. 2001). Consecutive derailments of blood glucose levels are the result of unconscious acting out, mistakes in nutritional intake, and improvident physical activity – all in conjunction with strong detached affect states, which remain unconscious to the diabetic and hence undigested psychologically. While such complex psychodynamic reasoning may not be proved or disproved quantitatively, studies such as this can provide empirical evidence for specific variable interaction surrounding brittle diabetes, which may serve as a base for such theories.

In conclusion, it seems that extant research reviewed above is either highly quantitative and sound methodologically, but clinically unpractical because findings are out of context, with unclear relevance and significance, contradictory even, or is beautifully coherent and memorable, but lacks trustworthiness due to the entirely qualitative nature of its methodology. This work intends to suggest one possible remedy to this dilemma by applying highly quantitative methodology (discussed next) to a simultaneously qualitatively reviewed and analyzed case study. This discussion will be continued in the discussion chapter, where it can be integrated with the empirical findings from this case analysis.

2.4. Vector-Autoregression and Multivariate Time Series Analysis

The question as to what existed first – chicken or egg, is not just an issue in psychosomatic medicine. Yet, here particularly, Meissner (2006) among others has called for a more realistic perspective on the mind-body relationship (and vice versa) without any a priori ascriptions of cause and effect, of dependent and independent variable status, but more focus on time and thus the dynamic of relationships between parameters. He suggests a more detailed view on the complexity of dynamic dependencies and intertemporal reciprocal cause and effect relationships among different psychic as well as somatic variables.

With less abstraction, applied to the subject matter of brittle diabetes in minors, we are looking for the following: A research methodology which does **not** start out by setting up an equation where for example glycemic stability is the dependent variable

and the emotional states of the child and her parents are independent variables, but rather allows for the model to determine whether certain emotional states will cause specific glycemic outcomes or (unexpectedly) the relationship works in the opposite direction (i.e. glycemic states cause emotional states) or even both (certain glycemic states at a specific point in time cause particular emotional states in specific individuals today which then bring about other glycemic states in the diabetic tomorrow). It becomes quite obvious that traditional multiply regressive methods can not provide such features, but will always come with some pre-determination.

Even univariate time series analysis, mapping the course of a clearly defined dependent variable through past observations of that variable itself (termed autocorrelation) and (possibly) a set of further independent variables, does not provide the methodological flexibility we desire. However, such (and similar) time series analyses have been applied to the psychosomatic and psychiatric realms in various studies (Crane, Martin, Johnston, & Goodwin, 2003; Dancey, Taghavi, & Fox, 1998; Dohnert, Wilz, Adler, Gunzelmann & Brähler, 2001; Fuller, Stanton, Fisher, Spitzmuller, Russell & Smith, 2003; Kupfer, Brosig, & Brähler, 2005; Lévesque, Savard, Simard, Gauthier, & Ivers, 2004; Posener, DeBattista, Veldhuis, Province, Gordon & Schatzberg, 2004; Reid, Towell, & Golding, 2000; van Vliet, Onghena, Knapen, Fox, & Probst, 2003; Weinberger & Gomes, 1995). What we are looking for is multivariate time series analysis in the form of a vector-autoregressive (VAR) model, a methodology so far somewhat foreign to psychosomatic medicine, but increasingly popular in econometrics and business.

In econometric theory VAR modeling was perceived as follows: In order to provide a more realistic time series modeling approach, in 1980, Sims introduced vector autoregression (VAR) analysis, a multivariate extension of the classical univariate autoregressive time series models. It allows treating a set of variable as jointly driven by the lagged values of all variables in the system. Thereby, no a priori assignment of dependent and independent variables is required and reciprocal causality is admitted.

The expert reader of this thesis may wish for some in-depth information on the specific requirements to be met before VAR-modeling can be applied to a set of data: A central requirement for the correct application of the standard versions of both univiariate and multivariate time series models is the stationary nature of all considered

time series[4]. Otherwise, as already pointed out by Granger (1974) drawing on Yule (1926), so called spurious correlations might result. These exhibit high t-statistic and R^2 values much more frequently than commonly expected despite the lack of any real relationship between the variables analyzed. Consequently, false but seemingly statistically significant relationships between a dependent variable and its regressors might be the outcome of working with non-stationary data. Various statistical methods have been developed for testing for non-stationary data, e.g., the augmented versions of the Dickey-Fuller-Test (Dickey & Fuller, 1979, 1981).

If a series is non-stationary (which is not the case with the data analyzed in this thesis), often taking first differences (i.e. the value of its second most recent observation is subtracted from the most recent one) might result in a stationary series suitable for further analysis. Alternatively, one might test for cointegration between non-stationary variables, i.e. whether there exist relationships between the variables resulting in stationary error terms of the model (e.g., Granger & Weiss, 1983; Engle & Granger, 1987; Granger, 1983 for univariate models, and Johansen, 1991 for applications in the context of VAR-models, which are labeled Vector Error Correction models or VEC-models in this case). On a less theoretical level, a cointegration equation describes the equilibrium relationship which the considered variables will adhere to amongst each other in the long run. Therefore, a VEC-model additionally models the short run dynamics and the speed of adjustment towards the long-run relationships for each variable. This is the rationale behind the label of error correction, which is not necessary in VAR-models with stationary data, because there is no difference between short run and long run dynamics.

Given that the variables used in the present study turn out to be stationary time series, only the standard VAR model will be considered and further econometric reasoning may be sacrificed in light of the medical nature of this thesis. The latter is also the reason why I will, for reasons of comprehensiveness, address the issues of VAR model selection (just as one multiply regressive equation is selected from a pool of less useful ones) and interpretation for the selected VAR-model by means of Cholesky impulse response analysis in the next section. Similarly, the additional adjustments to

[4] Assuming a normal distribution of stochastic components, a variable or lagged values thereof are defined to be stationary if its mean and variance remain constant over time (Pierse, 2010). More general theoretical definitions are provided by Lütkepohl and Krätzig (2004).

the selected VAR-model, based on an optimized multivariate lag selection process developed by Winker (1995; 2000) and Savin and Winker (2013) will for practical reasons be presented in the methods section. Readers looking for more general information on vector autoregressive time series modeling, VAR model selection, Cholesky impulse response analysis or the optimized multivariate lag selection process are referred to original literature by Lütkepohl and Krätzig (2004), Winker (1995; 2000) and Savin and Winker (2013).

2.5. Conclusion

Important concepts for the context of this thesis have been discussed according to its twofold objective of applying innovative econometric methodology to psychosomatic research, while also providing a case study of brittle diabetes – serving for its own merit as much as for the sake of an example to which econometric methodology can be applied to.

3. Methods

3.1. Introduction

As discussed in the previous chapter, the use of vector autoregressive (VAR) models for the analysis of time series data in psychosomatic medicine allows treating a set of variables as jointly driven by the lagged values of all variables in the system with no a priori assignment of dependent and independent status being necessary. In this chapter I intend to describe how the quantitative time-series data was collected from a family of three over a period of 120 days. I also present a qualitative account of the somatic and psychological background of the case I analyze in the VAR model. More specific details of the application of the VAR model to the case data collected will be discussed.

3.2. The Patient – A Case Vignette

3.2.1. Somatic History

At age four Debby presented for the first time with a short history of polyuria, polydipsia, loss of appetite, and fungal infection of the genital area. Initial blood tests revealed a haemoglobin A_{1c} (HbA_{1c}) value of 9.1 % (normal range 4%-6.3%) without metabolic acidosis, and positive antibodies against islet cells and GAD65, thus confirming the diagnosis of type I diabetes.

Debby had a history of poorly controlled bronchial asthma and allergic diseases. The family anamnesis was negative for diabetes mellitus. Subcutaneous insulin treatment with regular and NPH insulin twice a day was initiated. The patient was readmitted at age 6 due to nocturnal hypoglycaemia with impaired consciousness. During this hospital stay Debby suffered from a tonic-clonic seizure related to profound hypoglycaemia on the basis of a change to the insulin type administered during her stay. In her parents, this further promoted fear of hypoglycaemia[5] and mistrust against hospital personnel.

Despite frequent visits to an outpatient clinic, recurrent stationary hospitalizations, intensive counselling, and various insulin therapies, the girl's metabolic control remained unstable over the following years. The objective of an HbA_{1c} value < 7 % could never be achieved.

[5] Parental fear of hypoglycaemia is a common complication to diabetes treatment in minors (Barnard, Thomas, Royle, Noyes and Waugh, 2010).

3.2.2. Psychological Background

Debby and her parents sought for intensified family treatment, because the patient`s diabetic condition could not, as previously described, be stabilized by means of the "treatment as usual-approach" with individual and family-based counseling, detailed and repetitive information about glycemic control mechanisms (including the influence of nutrition), sport, and other aspects of blood sugar regulation. Debby and her mother seemed to be caught in a constant power struggle over glycemic control. Both were terrified somewhat irrationally, but based on the patient's somatic history, about the danger of hypoglycemia. They were taking the risk of higher blood sugar levels in order to evade "sharp and life-threatening declines". Her father seemed more distant to the matter, but started crying, when Debby's somatic history with hypoglycemic crises and seizures came up. At this point, he did not fail to underscore his deeply rooted mistrust in the hospital's capacity to control this case of diabetes and his profound fears of hypoglycemia.

In six family sessions every two weeks during the time of this study, the family recalled Debby's shock of being diagnosed with diabetes type 1 and the family's long-standing distrust concerning the interdisciplinary diabetes team, which seemed to them too superficial, not adapted to the individual needs of the patient, and finally, too harsh in terms of communication-habits. The therapist confronted them with their specific type of collusion concerning (in-)dependence, in which both parents, in their manifest statements, advocated for more self-confidence and extended duties on the side of their daughter, but on a latent level, gave hints to their "beloved little girl" of not yet being in charge of the blood sugar monitoring. The mostly hidden conflict resulted in unclear paths of communication concerning diabetic control, unclear distributions of duties within the family members, and, as a result of the arrangement, deep dissatisfaction with the failure to meet sugar-benchmarks.

3.3. Quantitative Data Collection and Analysis

3.3.1. Collecting the Raw Data

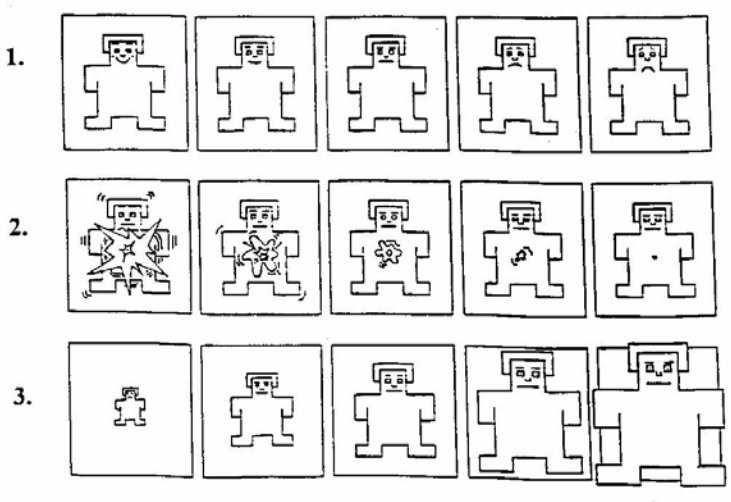
The participating family, composed of two biological parents and their type 1 diabetic adolescent, completed a structured diary over a period of 120 days. Extant research in the psychosomatic realm has provided examples for such diary-based data collection (e.g. Appelt & Strauß, 1985; Wilz, Adler, Gunzelmann, & Brähler, 1997). This form of diary based data collection is also referred to as ecological momentary

assessment with many benefits in terms of accuracy and validity of measurements (see Ebner-Priemer & Trull, 2009 for details).

In the diary (on a daily basis), each family member completed a self assessment manikin (SAM, see figure I below) as developed by Lang (Bradley & Lang, 1994; Hamm & Vaitl, 1993; Lang, 1980) on their affective valence (negative – positive), activation (calm - excited), and control (a sense of being absent - present), while also recording unusual events which may have influenced their emotions. The adolescent additionally recorded at least three measurements of blood glucose levels (morning, lunch, evening), and up to as many as were taken on a particular day. For an excerpt from the adolescent's diary please refer to exhibit 1 in the appendix.

Based on the daily blood glucose measurements, standard deviations were calculated for each day as a measure for glycemic variability. Recent research has identified glycemic variability as the most precise predictor of diabetic control – followed by the HbA_{1c}-value in second place (Hirsch & Brownlee, 2005; Hirsch, 2005; Zaccardi, Pitocco, & Ghirlanda, 2009; Penckofer, Quinn, Byrn, Ferrans, Miller & Strange, 2012), due to glycemic variability being the best known predictor for diabetic complications (Hirsch, 2005; Zaccardi, Pitocco, & Ghirlanda, 2009; Penckofer et al., 2012) and micro-vascular derailments in particular (Risso, Mercuri, Quagliaro, Damante, & Ceriello, 2001). The descriptive statistics (means, standard deviations) of all ten time series variables, as well as two additional time series composed of the daily means of blood glucose recordings and the number of recordings per day, are presented in exhibit 2 of the appendix.

Figure I: The Self Assessment Manikin (original presentation)



Legend: first line – valence/ pleasure, second line – activation/ arousal, third line - dominance

Source: Bradley, M. M. & Lang, P. J. (1994). Measuring emotion: The Self-Assessment Manikin and the Semantic Differential. *Journal of behavior therapy and experimental psychiatry*, *25*(1), 49–59.

Although, the SAM (figure I above) is historically much more established as a measure for emotion, than glycemic variability is for diabetic control, some comment on its origins shall be in order. As Lang (1969) put it, emotional response can be measured in at least three different ways – affective (verbal or other) reports, physiological reactions, and overt behavioral acts. The SAM is an inexpensive, easy non-verbal pictorial assessment technique for quickly assessing an individual's report of affective response to various stimuli in the three basic emotional dimensions of pleasure, arousal and dominance (Lang 1980). These three basic dimensions were initially suggested by Wundt (1896), who labeled them "lust" (pleasure), "spannung" (tension) and "beruhigung" (inhibition). Bradley and Lang (1994) were able to demonstrate that various measures of emotional response, such as the Semantic Differential scale devised by Mehrabian and Russell (1974), did not deliver results which could not be reduced to the same information the SAM provided. They also cited

studies in which the SAM had been used to measure emotional responses to all sorts of stimuli and been drawn on in different language settings, with children and with various study populations suffering from psychiatric diseases (Bradley & Lang, 1994).

3.3.2. Constructing a VAR Model

Resulting from this data collection and primary analysis are ten time series: Three time series for each of the three family members from the SAM – affective valence, arousal and dominance, as well as one time series recording glycemic variability. With these ten time series a VAR model was estimated using EViews 7.1 (QMS, Quantitative Micro Software, Irvine CA). Augmented Dickey Fuller Tests (Dickey & Fuller, 1979, 1981) rejected the null hypothesis of non-stationary data for all ten time series (see previous chapter), thus endorsing the construction of a VAR model instead of a vector error correction model (VECM). Since econometric theory has not focused much on the scale of VAR-variables, we have also ignored the fact that the nine emotional variables are of ordinal scale, which is uncommon for the economic data VAR models are usually applied to.

Any VAR model requires the user to select a maximum number of lags, which, in more practical terms, refers to how far back in time the user wants to search for past recordings of all variables to predict the present value of one variable. The farther back in time the user decides to extend a search, the more explanatory variables (lags) need to be included in the model (Lütkepohl, 2005; Lütkepohl & Krätzig, 2004). (Means to evade this rule, as developed by Winker (1995, 2000) and Savin and Winker (2013), will be discussed later.)

Unfortunately including more explanatory variables (incorporating more past recordings) is a double edged sword, since this will provide a VAR model more representative of reality (goodness of fit), but also one with less explanatory power (lower adjusted R^2). The latter is due to the tremendous penalty inflicted by the large number of explanatory variables (lags) in the model resulting in high estimation variance (Lütkepohl, 2005; Lütkepohl & Krätzig, 2004). So, for instance, for this study, the number of past days included for lag length determination, would have to be multiplied by the number of time series (ten) plus control variables (controlling for effects due to it being a holiday or weekend etc.) to represent the total number of variables in the final model. Logically large numbers of variables will frequently be achieved in VAR models, resulting in large penalties to the coefficient of determination

(R^2), thus yielding very low adjusted R^2 values for these models. Readers not versed to VAR methodology may therefore believe the results of a VAR study with such low adjusted R^2 values to be almost irrelevant in clinical terms, which must not be the case.

The number of lags included in a VAR model is also referred to as the order of the VAR model. Lag order selection for a VAR model extensively influences the estimation precision of impulse response analyses, to be applied to the final model in the next step, which is why various information criteria can be calculated to aid in determining the most appropriate number of lags to be included (Lütkepohl, 2005). In table 1, I considered various information criteria proposed by econometric methodology. According to Lütkepohl (2005) the Akaike Information Criterion (AIC) and Final Prediction Error (FPE) may have better properties than the Hannan-Quinn Information Criterion (HQ) or Schwarz Information Criterion (SC) in determining the appropriate VAR model for small samples (at least 16 observations). While AIC and FPE tend to asymptotically overestimate, the asymptotically consistent HQ and SC more frequently underestimate the order of a VAR. Lütkepohl (2005) concludes (p.151) that for small samples, models based on AIC or FPE tend to deliver superior forecasts even if their order should be incorrect.

Table 1: Criteria Considered For Appropriate Lag Number Selection

Selection Criterion	**Number of lags suggested**
LR: Sequential Modified Likelihood Ratio Test Statistic (each test at 5% level)	1
FPE: Final Prediction Error	1
AIC: Akaike Information Criterion	7
SC: Schwarz Information Criterion	0
HQ: Hannan-Quinn Information Criterion	0
Endogenous variables: glycemic variability, affective valence, activation and control for all three family members *Exogenous variables:* control variable	

In estimating the various information criteria (utilizing EViews), the user has to manually enter the maximum lag length to be tested for. Both, Lütkepohl and Krätzig

(p.110, 2004), as well as Lütkepohl (p. 146, 2005), emphasize the importance of the purpose and underlying subject matter of a study in determining the appropriate order of the VAR model. Hence, I chose 7 days as the maximum lag length to be tested by information criteria, since one week is an internationally and historically consistent entity of time, in many ways organizing human interaction. As can be derived from Table 1, information criteria suggested the construction of a VAR model with either 1 or 7 lags, or did not provide useful information at all.

Lütkepohl (p. 157, 2005) further concludes that "…it may be a good strategy to compare the order estimates obtained with different criteria and possibly perform analyses with different VAR orders". Consequently, I further analyzed both, a VAR model with just one lag (as proposed by the LR-test and FPE), and one with seven lags (as proposed by AIC). Since Lütkepohl (2005) describes the FPE and AIC to deliver superior information for small samples (even if the exact lag length suggested should be incorrect), this further supports the construction of two VAR models.

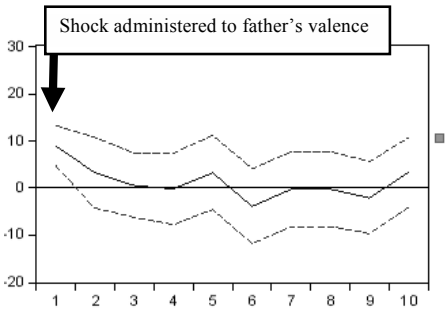
Once the VAR models are computed with EViews, the coefficients provided in the VAR estimation output for each variable have the limitation of including simultaneous dependencies and indirect links among the VAR variables. For increased significance of results, literature (e.g. Lütkepohl, 2005; Lütkepohl & Krätzig, 2004) recommends Cholesky Impulse Response Analysis for the identification of dynamic effects. Cholesky Impulse Response Analysis was conducted at a 95 per cent confidence level for both models. In more practical terms, Cholesky Impulse Response Analysis provides information as to what effect a random shock (change in value) to one of the time series in the system will have on another over a certain period of time.
Focus was put on two questions: First, shocks to which variables will result in a change in glycemic variability? Secondly, which variables will be affected if a shock is induced to glycemic variability?

In order to conduct Cholesky Impulse Response Analysis, the user needs to predetermine which variables are likely to be the most rapidly adapting to an external shock to the system. For the Cholesky ordering of the variables, I determined glycemic variability to be the most rapidly adapting variable for the purpose of contemporaneous effects of shocks in Impulse Response Analysis. It was followed by affective valence, activation and control of the adolescent, of its mother and finally its father. This Cholesky ordering seemed prudent, since extant literature in the psychosomatic realm

has primarily focused on the diabetic patient herself and, in a second step, on her mother (see first chapter). There is little to no research linking glycemic variability and emotions of a diabetic adolescent to her father, most likely because the male parent is traditionally seen as more distant to the raising of children than the female?

The workings of Impulse response analysis can be illustrated by the following example: Figure II below reproduces one of the impulse response graphs. It shows the effect a shock to the father's valence (making him sad) will have on his daughter's glycemic variability over the next couple of days. The extent of the effect to glycemic variability is displayed on the y-axis, while time (days) is tracked on the x-axis. We can see how glycemic variability will increase significantly (ca. 10 standard deviations) on the first day, because the top and bottom graphs showing the 95 per cent confidence interval (two standard deviations of the mean) and the mean (graph in the middle) of glycemic variability are well above the base line (which is mapping the expected course of glycemic variability if no shock to the system had occurred). During the second day after the shock, glycemic variability begins to stabilize and fluctuates around the blood sugar level as before the shock was administered (base line).

Figure II: Impulse Response of Glycemic Variability to a Shock Administered to the Father's Valence (making him sad)



y-axis: glycemic variability; **x-axis:** time in days; **base line:** blood glucose level before shock. The top and bottom lines represent 2 SD from the middle line (mean).

Overall, all significant effects observable in response to either a change in some emotional time series (first research question) or change in blood sugar (second research

question) persisted over less than four full days. After four days the mean fluctuated somewhere around the- base line, with the base line included within the 95 per cent confidence interval.

Without the intention to foreclose the results chapter, it shall be disclosed here that the coefficients of determination R^2 indicate the incorporated variables to capture 11.11 and 64.56 per cent of the variance for the VAR models with lag one and seven, respectively. Not surprisingly, the very large number of explanatory variables in the models (for lag one: 110, for lag seven: 710) resulted in significant penalties in the calculation of adjusted R^2 with values of 0.028 and 0.041, respectively. This is not uncommon for VAR estimation and is one of the reasons why other criteria, such as the tests for lag length identification criteria discussed above, are much more relevant and commonplace in VAR model evaluation. However, going one step further, a relatively new methodology entitled the Optimized Multivariate Lag Selection Process has also been adjusted and applied to the ten time series, thus constructing a third VAR model with completely different advantages (higher adjusted R^2) and limitations (no Cholesky Impulse Response Analysis, more a priori determinations similar to classic multiply regressive systems). The Optimized Multivariate Lag Selection Process and hence the construction of a third VAR model will be discussed next.

3.3.3. Introducing the Optimized Multivariate Lag Selection Process to VAR Modeling

Any VAR model requires the user to select a maximum number of lags, as discussed in the previous section. The farther back in time the user decides to go to predict a current value of a variable, the more explanatory variables (lags) need to be included in the model resulting in far below average adjusted R^2 values. The latter is due to the tremendous penalty inflicted by the large number of explanatory variables (lags) in the model resulting in high estimation variance (Lütkepohl, 2005; Lütkepohl & Krätzig, 2004). This substantial drawback weakened the substance of empirical findings derived from VAR models, because researchers would either present results through models with teeth clatteringly low R^2 values, or adopt models only incorporating the effects of events preceding the predicted value of a variable by one day/ one unit of time in the VAR (see for example Wild, Eichler, Friedrich, Hartmann, Zipfel & Herzog, 2010).

The versed VAR methodologist may long have wondered for the possibility to include only such lags which, in lay terms, provide more benefit to the coefficient of determination (R^2) than inflicting damage to its adjusted value. So for illustrative purposes, if one decided (for whatever reason or because one of the lag length determination criteria suggests so) to include the last 7 days/ units of time in a VAR model to predict a current value of a variable, but realizes that for instance just days -7, -4, and -2 serve as predicators of the current value, why not just include these three days in the equation predicting the value of the variable, instead of all days? Until recently methodological literature did not provide for this possibility (Lütkepohl, 2005; Lütkepohl & Krätzig, 2004).

In order to alleviate this shortcoming in this study, a computer code implementing a statistical procedure recently published in parts in Savin and Winker (2013) and Winker (2000; 1995), referred to as the optimized multivariate lag selection process, was developed. It allows (contrary to previous practice) to exclude such explanatory variables (lags) from the VAR model which add little to its goodness of fit (estimated representativeness of reality) while nonetheless reducing its explanatory power (adjusted R^2). The "price" for this advantage is that so far no Cholesky Impulse Response Analysis tool has been developed to be applied to the output. More a priori predeterminations somewhat similar to traditional multiply regressive systems have to be made. However, this "admittance of holes" to the lag structure (equations organizing the explanatory variables) allows to present an additional VAR-based model exhibiting more detailed dynamics with a smaller number of parameters – for the data in this case resulting in an about tenfold increase of the adjusted R^2 value for the prediction of some variables (such as glycemic variability).

The process of applying the Optimized Multivariate Lag Selection Process will be detailed next. First, the standard vector autoregressive (VAR) model was constructed, using EViews 7.1 (QMS, Quantitative Micro Software, Irvine CA), based on the ten time series I mentioned above. The novel contribution now is to maximize the informational content of the model by minimizing an information criterion (Savin & Winker, 2013; Winker, 2000; Winker, 1995). Equations (seemingly unrelated multiple regressions) predicting the variables of interest are created without including all the lags as in common VAR models.

In more concrete terms, drawing on Winker (2000, 1995) and Savin and Winker (2013), given the huge discrete search space of all possible lag structures to predict any one variable with a maximum lag length of seven, but without the lags with no added value to the predicting equation, heuristic optimization algorithms are used to this end. For this process, a computer code was developed using Matlab R2011b with an interface to EViews 7.1, which implements an Genetic Algorithm for the search of an optimized lag structure making use of information criteria (the Bayesian Information Criterion, BIC) as in the standard selection procedure [see Savin and Winker, 2013 for more details]. By providing an approximation to the minimum of the information criterion, the resulting model exhibits an optimized tradeoff between a good fit to the multivariate dynamics of the data and model parsimony.

As a result, I obtained a model with only 70 parameters, but still cover effect delays up to one week. Since the maintained lags are selected based on their joint informational content (as measured by the information criteria), the procedure results in a model with much higher explanatory power (for predicting glycemic variability adjusted R^2 value of 0.20 as opposed to 0.02 for the standard model with only one lag) and a richer temporal dynamic.

Given the rich temporal dynamics between all variables of the model, besides considering single equations, the calculation of impulse response functions would be of interest. However, the zero constraints of the VAR model with holes preclude the application of standard methods for the calculation of confidence bands.

3.4. Conclusion

In conclusion, the three models constructed for this study all have individual advantages and disadvantages. For the purposes of inducing discussion on the application of econometric methodology to time series analysis in psychosomatic research, as much as outlining the prospects and boundaries of time series analysis itself, the actual results of this study have little relevance at first sight. Yet, I also want to showcase ways to graphically present the results derived from the rather abstract mathematical procedures described in this chapter for more clinically oriented applications. This will be one of my objectives for the next chapter. In a concluding chapter, I intend to return to the opening discussion of this thesis, thus critically reflecting on the overall value, potentials and contingencies of applying such highly

quantitative research approaches as vector autoregressive time series analysis and its extensions to psychosomatic explorations.

4. Research Findings

4.1. Introduction

This chapter is divided into two main sections. In the first, the results from the VAR models with one and seven lags adhering to conventional VAR methodology adopted from econometrics (see Lütkepohl and Krätzig, 2004) will be presented. In the second section, the results from the extension to contemporary VAR modeling provided by Winker (1995, 2000) and Savin and Winker (2013), termed the Optimized Multivariate Lag Selection Process, will be demonstrated. Focus is put on avenues for creative graphical presentations of the mathematically dry subject matter in order to showcase how clinical implications can be derived from such highly quantitative time series modeling.

4.2. The First and Second (Conventional) VAR Model

Two vector autoregression (VAR) models with dynamics acting on 1 and 7 days were computed. The coefficients of determination R^2 indicate that the incorporated variables capture 11.11 and 64.56 per cent of the variance for the VAR models with lag one and seven, respectively. Not surprisingly, the very large number of explanatory variables in the models (for lag one: 110, for lag seven: 710) results in significant penalties in the calculation of the adjusted R^2 with values of 0.028 and 0.041, respectively. This is not uncommon for VAR estimation and is one of the reasons why other criteria, such as the tests for lag length identification criteria discussed above, are much more relevant and commonplace in VAR model selection and evaluation.

Unlike in contemporary multiply regressive models, the coefficients provided in the VAR estimation output for each variable do not provide a complete picture due to simultaneous dependencies and indirect links of the VAR variables. For this reason, literature (e.g. Lütkepohl, 2005; Lütkepohl & Krätzig, 2004) recommends Cholesky Impulse Response Analysis for the identification of dynamic effects, which I conducted at a 95 per cent confidence level for both models. It provides information as to what effect a random shock (change in value) to one of the variables in the system will have on the others. Focus was put on two questions:

First, shocks to which variables will result in a change in glycemic variability. In lay terms I ask, what will happen to the patient's blood sugar if one of the family members encounters a situation making him or her happy, sad, excited, calm, more or less dominant.

Secondly, which variables will be affected if a shock is given to glycemic variability? This refers to asking what effect a change in blood sugar in the patient (for whatever reason) will have on the emotions of both, the adolescent herself and her parents. Both questions were answered twice, based on both VAR models. Thereby, the effect with a specific lag was considered as significant, if the corresponding point-wise confidence band at the 95 percent level did not include the zero line at some horizon (see methods chapter for details and an example).

In answering the first question, both models provided evidence that glycemic variability would increase with shocks inducing sadness in the adolescent patient or her father. In addition, the VAR model with lag seven showed that glycemic variability would also increase whenever the adolescent's mother felt in control and would decrease whenever the adolescent herself felt calm and dominant (present to the current environment and situation). In order to provide a complete presentation, it be stated, that opposite changes in affect would also result in opposite movements of glycemic variability.

Next, I will examine the results to the second research question: Which variables will be affected by a shock to glycemic variability for whatever reason? In the VAR model with one lag, a shock increasing glycemic variability would result in the adolescent's father feeling in control. In the model with seven lags, a shock increasing glycemic variability would result in the patient feeling sad and her father feeling calm. Of course, shocks decreasing glycemic variability would be linked to the opposite familial emotions.

Globally speaking, all significant impulse responses discussed above persisted over less than four full days after a shock, to then fluctuate somewhere around the base line. For that reason, a display of all impulse response graphs would have provided little added value. At the same time, a graphical representation providing a simplified and transparent overview of results was desirable. Figures III and IV are schematic displays of the impulse response analysis results for the one and seven lagged VAR models, respectively.

Figure III: Impulse Response Results for VAR with Lag 1

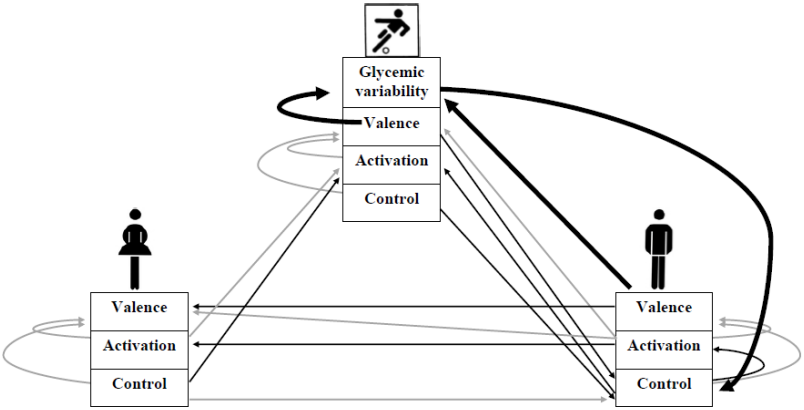
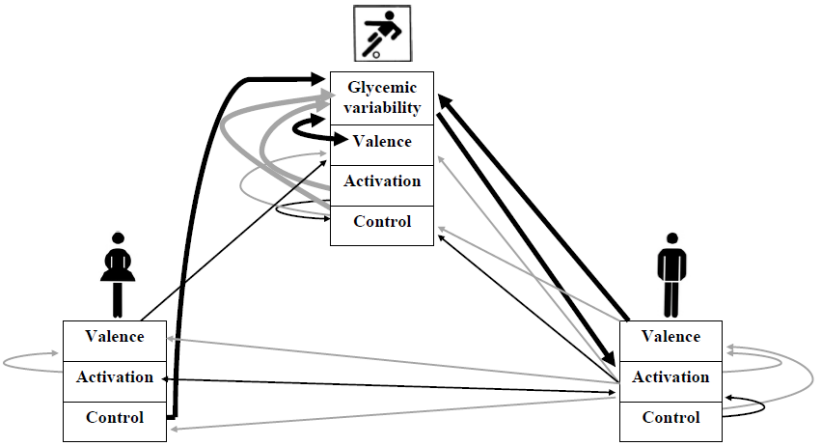


Figure IV: Impulse Response Results for VAR with Lag 7



Legend to Figures III and IV

Arrows display the effect a shock to one variable will have on other variables over the next 1 - 3 days

VAR Impulse Response with negative Correlation

VAR Impulse Response with positive Correlation

(correlations involving glycemic variability are boldface)

shocks increasing glycemic variability –> high SD of blood sugar

shocks increasing valence –> sadness

shocks increasing activation –> inner calmness

shocks increasing control –> dominance

shocks decreasing glycemic variability, valence, activation or control –> low blood sugar SD, happiness, excitement, feeling out of control (respectively)

The most clinically relevant results displayed in the graphical representations can be summarized as follows:

Generally speaking, the seven lagged VAR (partially supported by the model with one lag) showed: The adolescent feeling happy, calm and in control will reduce her glycemic variability and hence diabetic derailment. A non-dominating mother and a happy father will also reduce the adolescent's glycemic variability. Shocks from inside or outside the family, deliberate or not, increasing glycemic variability in the adolescent affect only the adolescent and her father: In the model with one lag, the male parent will feel in charge. In the model with seven lags, the adolescent will be sad and her father will calm down.

In addition to the linkages between glycemic variability and emotions discussed above, figures 2 and 3 also display various further linkages between family emotions also evidenced by impulse response analysis. So for example, in the model with seven lags activation (excitement) in one parent, also leads to activation in the other parent. While this linkage seems to be rather commonplace, other linkages may or may not be representations of pathological interaction between family members. The analysis of such hints would be of interest to a therapist trying to identify and modify dysfunctional family structures and interactions. Yet, such observations are not the focus of this research. Their mentioning is just for the sake of completeness and to provide a possibly interesting trajectory for future research. For such purposes it also be noted that both graphical representations were conceived using Microsoft Word – no technically advanced or costly software tools are required.

4.3. A Third Model: Results from the Optimized Multivariate Lag Selection Process

The optimized multivariate lag structure selection process provides one equation of seemingly unrelated multiple regression for each of the ten time series. Three of them directly involve glycemic variability in addition to the one for glycemic variability itself, which shall be presented last (lags in parentheses).

affective valence of the adolescent = $\alpha_1$glycemic variability (-6) + $\alpha_2$valence adolescent (-1) ($R^2 = 0.25$, adj. $R^2 = 0.24$)

Thus, the pleasure/ displeasure of the adolescent is predicted by her glycemic variability six days earlier and her pleasure/ displeasure one day earlier. Since this should suffice as an example for reading the equation properly, the remaining equations are presented without individual explanatory comments.

affective valence of the mother = $\alpha_3$dominance adolescent (-7) + $\alpha_4$valence mother (-5) + $\alpha_5$arousal mother (-6) + $\alpha_6$arousal father (-4) + $\alpha_7$arousal father (-6)
($R^2 = 0.21$, adj. $R^2 = 0.18$)

affective valence of the father = $\alpha_8$valence adolescent (-3) + $\alpha_9$valence adolescent (-5) + α_{10}arousal mother (-5) + α_{11}dominance father (-3) ($R^2 = 0.21$, adj. $R^2 = 0.18$)

arousal of the adolescent = α_{12}arousal adolescent (-1) + α_{13}arousal adolescent (-3) + α_{14}arousal adolescent (-7) + α_{15}valence mother (-4) + α_{16}arousal mother (-3) + α_{17}valence father (-2) + α_{18}valence father (-6) ($R^2 = 0.30$, adj. $R^2 = 0.25$)

arousal of the mother = α_{19}glycemic variability (-3) + α_{20}arousal adolescent (-7) + α_{21}dominance adolescent (-5) + α_{22}arousal mother (-5) + α_{23}arousal mother (-7) + α_{24}dominance mother (-1) + α_{25}dominance father (-6) ($R^2 = 0.29$, adj. $R^2 = 0.24$) [i]

arousal of the father = α_{26}valence mother (-4) + α_{27}dominance mother (-6) + α_{28}arousal father (-1) + α_{29}arousal father (-2) + α_{30}arousal father (-6) + α_{31}dominance father (-1)
($R^2 = 0.19$, adj. $R^2 = 0.15$)

dominance of the adolescent = α_{32}valence adolescent (-1) + α_{33}arousal adolescent (-5) + α_{34}arousal father (-1) + α_{35}dominance father (-1) ($R^2 = 0.25$, adj. $R^2 = 0.22$)

dominance of the mother = α_{36}valence mother (-7) + α_{37}dominance mother (-1) + α_{38}dominance mother (-3) + α_{39}dominance father (-5) ($R^2 = 0.65$, adj. $R^2 = 0.64$)

dominance of the father = α_{40}glycemic variability (-1) + α_{41}dominance child (-6) + α_{42}valence mother (-5) + α_{43}valence mother (-7) + α_{44}dominance mother (-4) + α_{45}dominance mother (-6) + α_{46}valence father (-1) + α_{47}valence father (-3) + α_{48}arousal father (-3) + α_{49}dominance father (-2) ($R^2 = 0.34$, adj. $R^2 = 0.27$)

glycemic variability (of the adolescent) = $ß_1$glycemic variability (-4) + $ß_2$arousal mother (-3) + $ß_3$arousal mother (-7) + $ß_4$dominance mother (-4) + $ß_5$dominance mother (-7) + $ß_6$valence father (-5) + $ß_7$valence father (-6) + $ß_8$arousal father (-3) + $ß_9$arousal father (-7) + $ß_{10}$dominance father (-2) + $ß_{11}$dominance father (-5) ($R^2 = 0.28$, **adj. $R^2 = 0.20$**)

Tables displaying the coefficients, their standard error, t-statistic, and probability for all ten equations presented above will be portrayed here:

Table 2: Coefficients and Their Statistical Properties

	Coefficient	Std. Error	t-Statistic	Prob.
α_1	0.008371	0.002505	3.341682	0.0009
α_2	0.439050	0.071648	6.127902	0.0000
α_3	0.196661	0.072361	2.717768	0.0067
α_4	0.193472	0.070105	2.759765	0.0059
α_5	0.166062	0.072169	2.301002	0.0216
α_6	-0.093081	0.038780	-2.400229	0.0166
α_7	0.083885	0.023675	3.543200	0.0004
α_8	-0.133217	0.045307	-2.940347	0.0033

α_9	0.135556	0.044104	3.073571	0.0022
α_{10}	-0.096673	0.029864	-3.237170	0.0012
α_{11}	-0.220601	0.061646	-3.578496	0.0004
α_{12}	-0.083390	0.031821	-2.620595	0.0089
α_{13}	0.167024	0.043985	3.797288	0.0002
α_{14}	0.499978	0.148744	3.361336	0.0008
α_{15}	0.235265	0.063599	3.699206	0.0002
α_{16}	-0.118392	0.039810	-2.973946	0.0030
α_{17}	-0.177384	0.058985	-3.007251	0.0027
α_{18}	0.327619	0.062900	5.208601	0.0000
α_{19}	-0.006755	0.002888	-2.339111	0.0195
α_{20}	-0.516945	0.178245	-2.900191	0.0038
α_{21}	-0.973039	0.242951	-4.005083	0.0001
α_{22}	0.190612	0.063265	3.012915	0.0026
α_{23}	-0.212629	0.060467	-3.516477	0.0005
α_{24}	-0.560562	0.136662	-4.101828	0.0000
α_{25}	-0.464339	0.146477	-3.170045	0.0016
α_{26}	-0.090665	0.041861	-2.165871	0.0305
α_{27}	0.447149	0.069911	6.395994	0.0000
α_{28}	0.234203	0.065907	3.553560	0.0004
α_{29}	-0.225144	0.058588	-3.842809	0.0001
α_{30}	0.129774	0.038175	3.399442	0.0007
α_{31}	0.182089	0.037975	4.795004	0.0000
α_{32}	-0.077998	0.029281	-2.663826	0.0078
α_{33}	-0.325788	0.065003	-5.011909	0.0000

α_{34}	0.215753	0.065266	3.305758	0.0010
α_{35}	-0.259613	0.081614	-3.181004	0.0015
α_{36}	0.200644	0.061428	3.266334	0.0011
α_{37}	0.292372	0.060802	4.808558	0.0000
α_{38}	-0.186054	0.064022	-2.906069	0.0037
α_{39}	-0.233369	0.086570	-2.695740	0.0071
α_{40}	0.004900	0.001217	4.024947	0.0001
α_{41}	0.367140	0.102177	3.593182	0.0003
α_{42}	-0.128680	0.045575	-2.823477	0.0048
α_{43}	-0.111369	0.043503	-2.560006	0.0106
α_{44}	-0.186954	0.067466	-2.771067	0.0057
α_{45}	-0.187772	0.065392	-2.871465	0.0042
α_{46}	-0.192931	0.048915	-3.944164	0.0001
α_{47}	-0.201673	0.062378	-3.233079	0.0013
α_{48}	-0.092639	0.048991	-1.890956	0.0589
α_{49}	0.154373	0.062922	2.453387	0.0143
Determinant residual covariance	9.14E-05			

	Coefficient	Std. Error	t-Statistic	Prob.
β_1	-0.197322	0.076111	-2.592545	0.0097
β_2	3.639513	1.583793	2.297973	0.0218
β_3	-4.889116	1.647518	-2.967565	0.0031
β_4	22.52994	3.969363	5.675959	0.0000
β_5	-6.340918	3.554736	-1.783794	0.0747

$ß_6$	9.565170	3.704850	2.581797	0.0100
$ß_7$	9.249940	2.865721	3.227788	0.0013
$ß_8$	7.562806	2.651011	2.852801	0.0044
$ß_9$	10.96846	2.600148	4.218400	0.0000
$ß_{10}$	13.04606	3.522259	3.703891	0.0002
$ß_{11}$	11.03846	4.583850	2.408120	0.0162
Determinant residual covariance	9.14E-05			

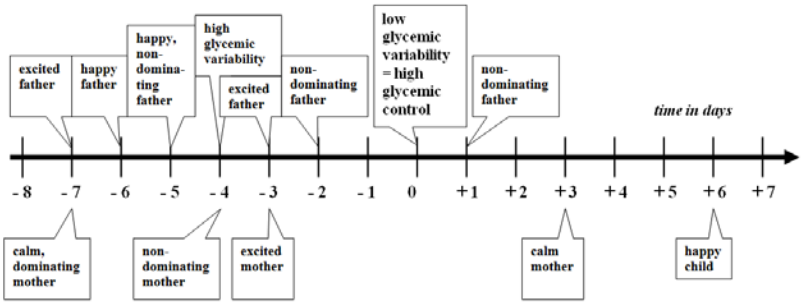
The application of a novel statistical methodology allowed me to disentangle the data and generate statistically reliable results in the form of ten equations. The dynamic of the results pertaining to glycemic variability,[6] taking into account the direction of coefficients, can be summarized as follows:

Low glycemic variability and therefore *good* diabetic control will correlate with the following: high glycemic variability four days earlier, an excited mother three days earlier, a calm mother seven days earlier, a non-dominating mother four days earlier, a dominating mother seven days earlier (although statistically insignificant), a happy father both five and six days earlier, an excited father both three and seven days earlier, and a non-dominating father both two and five days earlier. Low glycemic variability will also correlate with a happy child six days later, a calm mother three days later, and a non-dominating father one day later.

For more clarity, a graphical representation of these results shall be presented next (figures V – IX). Not just in order to express the more regressive, less dynamic nature of the results, the images presenting results from the Optimized Multivariate Lag Selection Process are constructed entirely different from those provided earlier for the VAR models analyzed with Cholesky Impulse Response Analysis. Again, relying on Microsoft Word, timelines were created stressing the augmented focus on specific temporal relations between the variables instead of the dynamic focus earlier with the classic VAR analysis.

[6] As already noted in the methods chapter, it has to be taken into account that additional dynamic interactions arise due to spillover between equations, which are not considered here – one of the disadvantages in comparison to conventional VAR modeling.

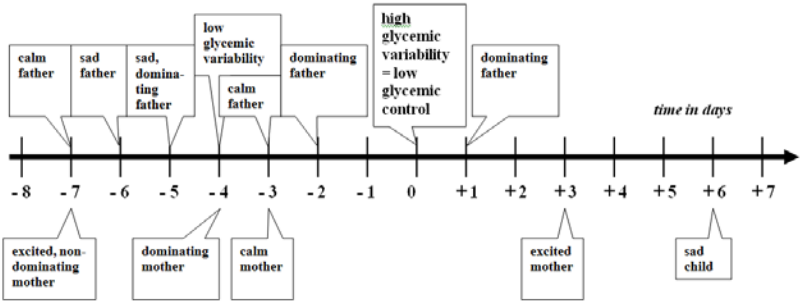
Figure V: Timeline displaying effects correlating with high glycemic control



Legend: The graph depicts a psycho-somatic cycle in which various emotional states of all involved family members influence glycemic variability of the adolescent patient and vice versa.

Similarly, poor glycemic control (high glycemic variability) will correlate with low glycemic variability four days earlier, a calm mother three days earlier, an excited mother seven days earlier, a dominating mother four days earlier, a non-dominating mother seven days earlier (although statistically insignificant), a sad father both five and six days earlier, a calm father both three and seven days earlier, and a dominating father both two and five days earlier. High glycemic variability will also correlate with a sad child six days later, an excited mother three days later, and a dominating father one day later.

Figure VI: Timeline displaying effects correlating with poor glycemic control

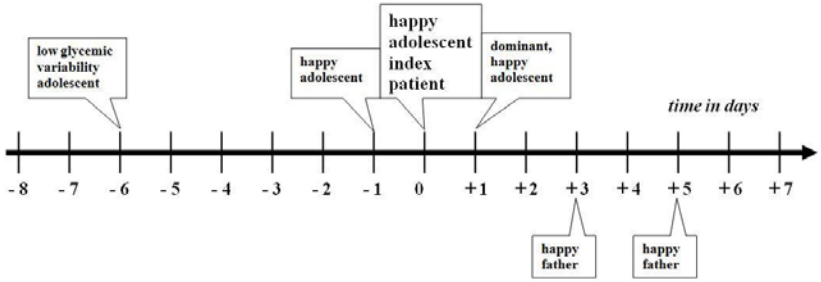


Legend: The graph depicts a psycho-somatic cycle in which various emotional states of all involved family members influence glycemic variability of the adolescent patient and vice versa.

In clinical terms, this means, good diabetic control was preceded by attentive and alert ("high arousal", excited) parents with a positive attitude ("happy father"), at the same time refraining from too much overwhelming presence ("low dominance"). Similarly, phases of good diabetic management were followed by a continuously distant father ("low dominance"), unfortunately a less alert mother ("low arousal"), and a content ("happy") adolescent index patient.

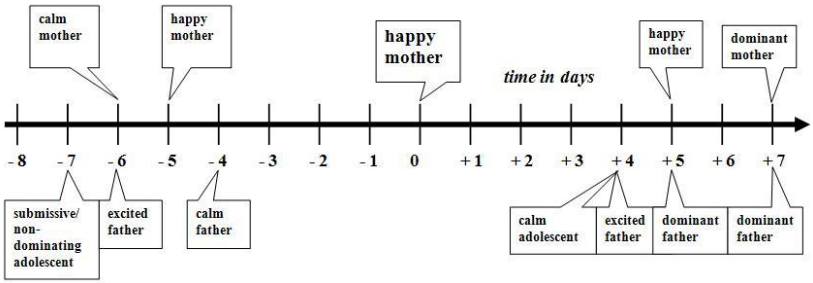
Similar to the above, now mostly self-explanatory graphical representations were constructed for the effects surrounding the affective valence of all three family members. I picked these three timelines for more detailed examination because the appropriate measurement of depressive symptoms (which at least at a distance somewhat relates to affective valence) in diabetics in general remains to be a topic of current debate in the literature (i.e. Hofmann, Köhler, Leichsenring, & Kruse, 2014).

Figure VII: Timeline displaying effects correlating with affective valence in the adolescent index patient



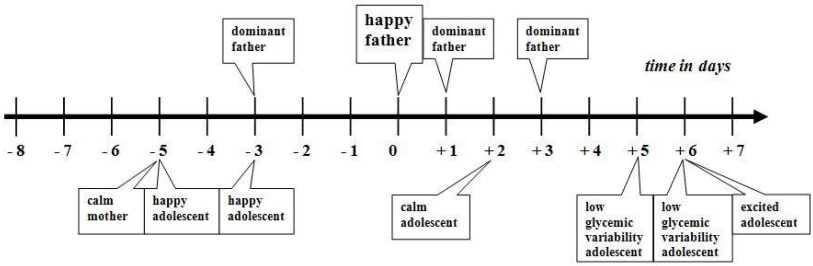
Legend: The graph depicts a psycho-somatic cycle in which various emotional states of all involved family members influence affective valence (pleasure) of the adolescent patient and vice versa.

Figure VIII: Timeline displaying effects correlating with affective valence in the mother of the adolescent index patient



Legend: The graph depicts a psycho-somatic cycle in which various emotional states of all involved family members influence affective valence (pleasure) of the mother to the adolescent patient and vice versa.

Figure IX: Timeline displaying effects correlating with affective valence in the father of the adolescent index patient



Legend: The graph depicts a psycho-somatic cycle in which various emotional states of all involved family members influence affective valence (pleasure) of the father to the adolescent patient and vice versa.

Similar or different image representations could be conceived for activation and dominance in all family members based on the seemingly unrelated multiply regressive equations presented in this section. The tradeoff between accuracy of graphical presentation and facility of inspection is the primary challenge in their design.

4.4. Conclusion

In conclusion, the results demonstrate the distinctive scopes, potentials and contingencies of different time series analysis models. As for the key research question, which affect states in individual family members will affect diabetic control (glycemic variability), all three models provide somewhat similar results: For instance, maternal dominance, which some might interpret as excessive overprotectiveness, will result in poor diabetic stability (high glycemic variability). This increases the credibility of the results and statistical methodology of this thesis – especially, since this finding is in line with extant research discussed in the literature on instable diabetes in children and adolescents (i.e. Minuchin et al., 1978; Davies et al., 2001; Butler et al., 2007). Nevertheless, it should be stressed here, once again, that the clinical results derived from this case study can not be generalized to inform clinical practice on a broader scale.

5. Discussion

5.1. Introduction

First, I intend to integrate and review the various results of this case study and the process of different time series analysis methodologies through which they were derived and discuss how they fit in with extant literature. Limitations and avenues for future research will be addressed. Beyond that, a more general discussion on psychosomatic research on brittle diabetes will be entered to build a bridge to the introductory remarks on extant qualitative and quantitative approaches to the subject matter and the vigorous discussion which has subsequently endured in the literature.

5.2. The Scope, Prospects and Limitations of this Study and its Method(s)

The scope of this empirical time series case study on glycemic variability is twofold: A creative exploration of new psychosomatic aspects of familial affect interplay surrounding an adolescent suffering from what has recently been termed brittle diabetes, and providing perspectives on innovative statistical methodology (adopted from econometric theory) to do so in a highly quantitative fashion. Three competing models were presented with no contradictions between them as far as the principal results on glycemic variability are concerned. As already mentioned in the methods chapter, the VAR models involving Cholesky Impulse Response Analysis are better able to portray the dynamic effects between the family members' individual affect states and glycemic variability. The aspect of specific temporal relations and traditional measures of methodological quality, such as the adjusted coefficient of determination, take a back seat to the aforementioned distinctive features. By contrast, the Optimized Multivariate Lag Selection Process offers three advantages:

- Increases in the adjusted coefficient of determination R^2 for the model prediction of glycemic variability by factor ten (adjusted R^2 value of 0.20 as opposed to 0.02) while also incorporating significant effects of explanatory variables (lags) stemming from a longer period of time preceding the predicted event than is the case in most conventional VAR models (with just 1 or 2 lags).
- A more precise timeline of effects of various variables on each other – including glycemic variability and vice versa (for example "a non-dominating mother four days prior to a set day will increase glycemic control" instead of "a non-dominating mother somewhere up to four days prior to a set day will increase glycemic control").

- Additional relationships between variables which did not reach statistical significance earlier or took more time to take effect than the time frame of the earlier (conventional VAR) models allowed for.

Yet, it seems premature to declare the Optimized Multivariate Lag Selection Process superior on all counts, given the dynamic aspects – so potently outlined in the contemporary VAR models – are at least partially lost due to the absence of Cholesky Impulse Response Analysis. In essence, the advantages over traditional VAR modeling are bought with a methodological step back toward more multiply regressive properties. In conclusion, no one model is superior to the others, but each has specific features to offer, which complement one another in providing a vivid picture of both interpersonal and intertemporal emotional dynamics in interplay with diabetic management.

One of the results confirmed by both the conventional seven lagged VAR model and the Optimized Multivariate Lag Selection Process pertains to the detrimental effect of maternal dominance on diabetic control. According to the Optimized Multivariate Lag Selection Process, this can be extended to paternal dominance. The latter model also suggests specific temporal relationships: Glycemic variability in the child could be linked to maternal dominance four days earlier and paternal dominance both two and five days earlier. Similar results, linking parental (particularly maternal) overprotectiveness with poor diabetic management have been reported in both qualitative and quantitative literature (Minuchin et al., 1978; Davis et al., 2001; Butler et al., 2007). This increases the trustworthiness of such findings. The methodology of this research may be a first step toward further clarifying and empirically detailing some of the links between particular biological markers (blood sugar) and much more specific psychic parameters of the family members surrounding the diabetic child, than the statistical approaches chosen in extant literature were able to.

However, it is also important to keep in mind the most significant limitation inherent to the otherwise advantageous in-depth exploration the case study design of this thesis allowed. As Kruse, Schmitz, and Thefeld (2003) point out, results may be different for different social or demographic confounding factors, sample characteristics, and definitions of variables. Thus, no generalizations of any sort should be informed by the results of this work. Arguing to similar effect, Luyckx and Seiffge-Krenke (2009) suggest there to be at least three separate developmental classes of glycemic control based on the age of adolescents with type 1 diabetes. They describe

each developmental stage as having its own characteristics in family structure and self-concept. Laron, Galatzer, Amir, Gil, & Karp (1989) found at least three periods of adjustment to diabetes type I diagnoses, each with specific psychological changes within the patient and her family. Again, both studies point to the fact that the results presented in this case study are highly unlikely to hold for all children and adolescents suffering from brittle diabetes. Both, the age of the patient and the time having passed since being first diagnosed, may have effects on family system dynamics. Yet, it seemed important to develop a methodology to empirically research much more detailed understandings of the factors surrounding familial affect interplay and its relationship to diabetic control (Streisand et al., 2005). Such interaction may be difficult to explore over longer time-spans or with more participants given various environmental mediators (Seiffge-Krenke, 1998b). Future research involving more participants should be able to draw on this work in order to define variables and key interrelations on which to focus in developing a trustworthy empirical methodology.

With respect to the time series variables adopted in this study, I have already reasoned for their overall superior validity in the methods chapter. Yet, in the context of limitations to this study, there are two suggestions for further scrutiny in future research in order to maximize the validity of the time series variables presented here:

For one, critics may raise the topic of increased prevalence of alexithymia in type I diabetics (e.g. Friedman, Vila, Even, Timsit, Boitard, Dardennes, Guelfi, & Mouren-Simeoni, 2003; Manfrini, Bruni, Terminio, Poterzio, Ricci, Sforza, Pantano, Costanza, Valente, Ganz, & Pozzilli, 2005; Naundorf, Brosig, Bayer-Pörsch, & Stingl, 2014) and the possible impact of that condition on participants' SAM responses. The concept of alexithymia first popularized by Nemiah and Sifneos (1973; Nemiah, Freyberger, & Sifneos, 1976) describes individuals with a limited ability to recognize affect states and/ or express them verbally, limited imaginative capabilities, and a functional way of reasoning with a strong external fact-based orientation. As reasons for the syndrome, neuropsychological defects, deficits in verbal development, and counter-transferrence phenomena in a therapeutic relationship are discussed (Naundorf et al., 2014). Regardless of its cause, alexithymia could possibly impact the ability of participants of this study (or future studies) in their daily completion of the self-assessment manikin, despite its non-verbal nature in the assessment of affect. For the purposes of this research, the patient has been negatively screened for alexithymia with

the German version of the widely accepted Toronto-Alexithymia-Scale (TAS-26). Similar measures should be taken in future research and the topic of alexithymia should be further explored, especially since findings so far are inconsistent: While some researchers (Eriksson, Gustavsson, Hilding, Granath, Ekbom, & Ostenson, 2012) found no correlation between alexithymia and glycemic regulation, several studies found linkages between the phenomenon and the conscientious recording of blood sugar self-measurements (Housiaux, Luminet, Van Broeck, & Dorchy, 2010; Luminet, de Timary, Buysschaert, & Luts, 2006) – essential to proper diabetic management and meaningful study participation.

Another suggestion for future research involves the optimization of the measurement for diabetic control. This idea was developed in a research cooperation of the author of this thesis with Prof. Dr. P. Winker of the Department of Economics (Justus-Liebig-University, Giessen) and Prof. Dr. A. Colubi, Prof. Dr. A. Blanco-Fernandez, and Ms. M. García-Bárzana of the Department of Statistics and Operational Research of the University of Oviedo, Spain: The literature review chapter provides extensive reasoning for the adoption of glycemic variability as a measure for the quality of diabetic treatment success – superior even to the HbA_{1c} (Hirsch & Brownlee, 2005; Hirsch, 2005; Zaccardi, Pitocco, & Ghirlanda, 2009; Penckofer et al., 2012; Risso, Mercuri, Quagliaro, Damante, & Ceriello, 2001). Regardless, the construction of an interval variable for glycemic variability based on the centre and the radius of a set of measurements (from a single day), instead of the more comprehensive standard deviation of those recordings, may entail additional accuracy for the variable.

Specifically, such a proposed interval-valued blood sugar variable construct, would be composed of two real-valued variables, namely a centre and a radius emerging from the blood sugar recordings of a given day. Such approach might entail higher determination coefficients and smaller mean square errors, in comparison to current models partially for the following rationale: While the consideration of mean and standard deviation measurements merely implies the summarization of the daily range, the interval obtained from the mid-point and the radius represents the real daily range of actual blood sugar recordings through the patient. In a practical example: Given three measurements of blood sugar in a certain day, say 235, 254 and 272 mg/dl, the interval obtained from (mean; sd) is [235.1644,272.1689], which does not include the measurement 235 mg/dl, whereas with the (mid; spr) concept of a variable it is indeed contained in the daily range [235,272]. Unfortunately, no VAR analysis, much less the

Optimized Multivariate Lag Selection Process has so far been conducted with interval variables – entailing a myriad of challenges to advanced mathematics. For this reason the aforementioned research cooperation has, as a first step, returned to the construction of a multiply regressive model for the raw data examined in this thesis. The results of this completely separate statistical analysis of this data, representing a fourth model solution, has also provided evidence for detrimental effects of maternal overprotectiveness on glycemic stability in the diabetic adolescent (adj. R^2 12.31%), but lacked the vivid portrayal of specific variable interrelations the three models presented in this thesis are able to offer. Mathematical details of this fourth model have, for reasons of clarity – and to avoid the loss of focus (on VAR analysis) in this thesis – been secluded to the appendix (see exhibit 3: "A fourth model: Multiple regression with an interval variable for glycemic variability").

Future research may also look at correlations between glycemic control in the patient and emotions of individuals outside of the core family, who have frequent contact and/ or influence on the patient, as already suggested by Minuchin et al. (1978). If, and to what extent, individuals beyond the primary care givers (usually the parents) have influence on minor diabetics may vary significantly from case to case depending on social structures surrounding the patient. Borus and Laffel (2010), in their review of challenges faced by adolescents when managing type I diabetes, described mixed findings on the role of peer influence. They caution that perception of social situations from the point of view of the adolescent patient and reality (in terms of what his social surroundings really think and feel) may differ substantially. For example, a diabetic adolescent may perceive his social status to be compromised by admitting the disease although that may not be the case. If influences from beyond the core family are present, which has been doubted (e.g. Helgeson, Reynolds, Escobar, Siminerio, & Becker, 2007; La Greca, Auslander, Greco, Spetter, Fisher & Santiago, 1995), they may be difficult to explore, due to the difficulties of identifying, reaching, and recruiting all relevant individuals for participation in a study.

Just as the effect of attachment figures (beyond the parents) on the diabetic minor would be of interest, the same holds true for the opposite direction of impacts. For instance, another German research fellowship explored quality of life for siblings to minors suffering from type I diabetes (Grundlach et al., 2006), but remained empty handed in their search for indication of differences to siblings of "healthy" families.

Research on such effects will face the same challenges as explorations of the opposite interrelations.

In addition to the relevance of this work for future inquiries into brittle diabetes, as outlined above, the same or different linkages between family member's emotions and biological parameters identified in this study may also be useful in suggesting specific toeholds for interventional advice in family therapy. In the case history of the family on study, the therapist was able to confront the parents with their collusion hindering a higher degree of independence of their daughter and thus her acceptable blood sugar management. Critics will certainly argue the experienced therapist will not need such elaborate technological support in arriving at meaningful therapeutic interventions. Yet, in a time where evidence based medicine is rapidly evolving in importance, particularly in the psychosomatic and psychiatric realm, such technological aid may be a powerful tool in providing reproducible and well documentable rationale for psychotherapeutic interventions. As further critique on this study, it did not look at the type of relationships and communication styles within the familial system, a German study group has already addressed partially by drawing on attachment theory, thus identifying three parental relationship types with differences in coping strategies and quality of relationship (Slesazeck, Würz, Kapellen, Kiess, & Brähler E., 2003). So in conclusion, therapeutic experience and merit is required, no matter how clear and conclusive links between family system dynamics and blood sugar management may appear in the statistical analysis of a family. Also, therapists should always keep in mind Seiffge-Krenke's (amongst others') caution: Medical and developmental needs of any adolescent must not coincide at all times (Seiffge-Krenke, 1998b). Hence, the results of this research should not mislead the reader to equate good glycemic control with adequate functional psychological development of the adolescent or satisfying quality of life within the family; interrelations between such parameters need to be explored separately.

5.3. Critical Reflections on Quantitative versus Qualitative Research on Brittle Diabetes

A more substantial contribution of this thesis is the demonstration and practical application of the Optimized Multivariate Lag Selection Process to VAR analysis, resolving an essential shortcoming in VAR analysis of (relatively) small samples.

Hence, this contribution to literature will have relevance beyond the case study approach, but also to VAR-based studies of larger cohorts of patients as for example presented in Wild et al. (2010) – significantly increasing either the number of effects (lags) analyzed (as would be the case in Wild et al., 2010) or the statistical reliability (i.e. the adjusted R^2) with which results are presented. All in all, mathematically refined quantitative methodological approaches relying on modern computational technology can generate more specific, reproducible and thus trustworthy results than purely qualitative (narrative) accounts – while still honoring the benefits of the case study approach aiming to explore previously unforeseen avenues fit for further vested inquiry (often costly to perform).

Yet, I dare to inquire critically, if the added mathematical complexity honors the overall value of the results a case study approach can provide. Revisiting the opening comments of this work in the context of brittle diabetes, it seems interesting to note that particularly the most highly acclaimed and clinically widely trusted research on brittle diabetes has also been the most severely and broadly criticized. So for instance, more than ten years after the initial publication of the pioneering work of Minuchin et al. in 1978 (on what they called "psychosomatic diabetes") entitled "Psychosomatic Families", critics commented as follows: "…as we conducted research and therapy with the families of diabetic children, we were impressed with both the limit of the formulation of the family's role in diabetes offered in 'Psychosomatic Families' and the uncritical acceptance that the book continued to enjoy." (Coyne & Anderson, 1989). In their rather pointed article entitled "The 'Psychosomatic Family' reconsidered II: Recalling a defective model and looking ahead" Coyne and Anderson (1989) criticize Minuchin et al. (1978) primarily for their bold, yet statistically (allegedly) poorly supported statements on the "typical psychosomatic family"[7] and their overgeneralizations of these overall "weak" findings on familial situations in one psychosomatic illness to various psychosomatic illnesses. More specifically, small sample sizes and poor documentation of methodology (or lack thereof) is being highlighted.

[7] Minuchin et al. (1978) describe the "psychosomatic family" as featuring enmeshment, rigidity, overprotectiveness and lack of conflict resolution and the children affected by brittle diabetes as having difficulty in handling stress, showing a tendency to internalize anger and being somewhat immature in their ability to cope with challenging situations.

Reflecting on such valid criticism in light of my own impressions on both the subject of brittle diabetes in adolescents as well as on the various shortcomings of contemporary statistical approaches to time series data in psychosomatic medicine, I believe in there being a case for both sides: On the one hand, I must vigorously support critics (i.e. Coyne and Anderson 1989) in their call for much more detailed and sophisticated reports on and publication of statistical methodology in such complex and intricate research situations as are present in multivariate time series analysis. The reason lies in there being vast room for pitfalls and error with this type of research. On the other hand, however, with the change of statistical approach, the results drawn from a given set of data may change somewhat, despite both methodologies being perfectly valid and academically accepted. The most striking example for such phenomenon in this work involves the fact that the Optimized Multivariate Lag Selection Process did not (and the conventional one lagged VAR model only partially) evidenced any effect of the adolescent's own emotions on its glycemic variability, although the seven lagged conventional VAR model showed such linkage (along with extant literature on diabetes). Similarly, further linkages (of lesser magnitude to the focus of this study) drawn in the VAR model with seven lags are absent in that with one lag and vice versa. Of course, various reasons for all this inconsistency, involving the lack of Cholesky Impulse Response Analysis for the third model, the deliberate elimination of certain lags from the VAR system in the third model, the reduced time frame from which lags were recognized in the one lagged VAR model (also resulting in different dynamics within the variables that were recognized), and many more, can all be called upon as rationale for why certain effects may have appeared in one model but not the other.

Still one wonders, how this (agreeably small) imprecision of highly quantitative research is any different from the (possibly – but not necessarily – larger) inaccuracy of qualitative research due to subjectivity? Not to mention the potential for human error, also present in any quantitative method (despite cross checking of results among different qualified individuals)? Noteworthy – and in taking up the cudgels for Minuchin et al. (1978, 1975) – the one finding clinically observable before conducting any statistical testing at all, namely that of a dominating mother having a negative effect

on glycemic control of her child, was also a finding both methodologies of this research were able to support at a high level of significance. [8]

Additionally, I ponder critics of Minuchin et al. (1978) may not have realized the vastness of data inherent even in a small sample in time series analysis – an apprehension possibly supported by the fait accompli of most of them failing to provide any statistically evidenced findings on the subject of brittle diabetes themselves. Not to mention the individual specificity of psychosomatic reactions (Brosig, Kupfer, & Brähler, 1993; Brosig et al. 2001) in patients, which may make it near impossible to generate comprehensive and detailed models on brittle diabetes applicable to each and every patient. In that sense, well documented, empirical case analysis drawing on both qualitative and quantitative (time series analysis) findings may be of higher clinical relevance than expected. They may involve the careful observation of the clinically experienced therapist as much as a sound (and progressive) statistical approach.

5.4. Conclusion

The preceding chapter has highlighted the fact, that the actual clinical results from this case study come second (at best) to much broader reflections and explorations on the application of innovative research methodologies to psychosomatic studies involving time series analysis – a form of research becoming more and more popular in this field (see for instance Wild et al., 2010, Crane et al., 2003; Dancey, Taghavi, & Fox, 1998; Dohnert et al., 2001; Fuller et al., 2003; Kupfer, Brosig, & Brähler, 2005; Lévesque et al., 2004; Posener et al., 2004; Reid, Towell, & Golding, 2000; van Vliet et al., 2003; Weinberger & Gomes, 1995 – and many more). If nothing else, I hope to have broadened researchers' horizons to look beyond the psychological realm, the medical field even, in their quest to find the best fitting methodology for a given research question. Cooperation between different academic disciplines may be essential to fulfill the high expectations of modern evidence based medicine and its vigorous quality measures for academic research.

[8] Amusingly, one might find what Minuchin et al. (1978) described as overprotectiveness in families with brittle diabetes, is very similar, if not the same, to what this research was able to pinpoint in terms of exaggerated control of a mother over her glycemically out of control child.

6. Conclusion

6.1. Introduction

The objective of this chapter is to recite the key findings in the time series analysis of this case study on a family of three with an adolescent suffering from brittle diabetes. Rationale and research objectives of this thesis are briefly revisited. Key implications for future research are discussed.

6.2. Key Findings

Three statistical models (and a fourth model in the appendix), as well as a qualitative case vignette were presented based on the set of raw data stemming from a classical family of three, consisting of biological parents and their adolescent daughter suffering from brittle diabetes.

Generally speaking, the lag 7 VAR model, taking into account events of the past seven days, (partially supported by the model with one lag, only considering events of the past day) showed: The adolescent feeling happy, calm and in control will reduce her glycemic variability and hence diabetic derailment. A non-dominating mother and a happy father will also reduce the adolescent's glycemic variability. Shocks from inside or outside the family, deliberate or not, increasing glycemic variability in the adolescent affect only the adolescent and her father: In the model with one lag, the male parent will feel in charge. In the model with seven lags, the adolescent will be sad and her father will calm down.

Through the introduction and first ever application of the Optimized Multivariate Lag Selection Process to psychosomatic research, more specific temporal relations between affect states and the biological marker of glycemic variability were isolated at statistical significance: *Low* glycemic variability and therefore *good* diabetic control correlated with high glycemic variability four days earlier, an excited mother three days earlier, a calm mother seven days earlier, a non-dominating mother four days earlier, a happy father both five and six days earlier, an excited father both three and seven days earlier, and a non-dominating father both two and five days earlier. Low glycemic variability also correlated with a happy child six days later, a calm mother three days later, and a non-dominating father one day later. In clinical terms, this means for this third model, good diabetic control was preceded by attentive and alert ("high arousal", excited) parents with a positive attitude ("happy father"), at the same time refraining from too much overwhelming presence ("low dominance"). Similarly, phases

of good diabetic management were followed by a continuously distant father ("low dominance"), unfortunately a less alert mother ("low arousal"), and a content ("happy") adolescent index patient.

6.3. Future Research

First of all, the application of methodology presented here for the study of a larger number of families would be desirable to generate results fit for more generally applicable implications. Electronic soft- and hardware facilitating raw data collection and analysis would be desirable for this end. For instance, tablet devices with a connection to the World Wide Web and a central data recording and control station in a research center could not only ensure and enforce conscientious and timely data recording by participants, but also serve as a motivator for patients and their families to join such research studies.

Numerous medical content related limitations have already been discussed in the discussion chapter. These provide for various avenues for future research. Furthermore, while brittle diabetes continues to be an important research area in psychosomatic medicine for all age groups, there are a number of other chronic diseases, which could be studied in a similar fashion: Colitis Ulcerosa, Morbus Crohn, various rheumatoid diseases, celiac disease/ non-tropical sprue, to name but a few. Similarly, for brittle diabetes or any other chronic disease, additional psychic and social parameters beyond affect states as much as a plethora of biological parameters could be researched. Various classification systems for the comprehensive assessment of somatic and psychic parameters have been published for most chronic diseases (e.g. the Best-/ Crohn's-Disease-Activity-Index for Morbus Crohn) and readily offer themselves for such research.

In addition, various unresolved statistical challenges should be scrutinized: The ordinal scale of the nine time series representing affect states should be addressed by either reviewing and possibly modifying the self assessment manikin (Lang 1980; Bradley and Lang, 1994) to change the scale of affect recordings, or econometric theory for the construction of VAR models should be researched to provide more theoretical and practical background to VAR model construction with ordinary scale variables. More importantly, it would be of interest to develop a Cholesky Impulse Response Analysis application to the Optimized Multivariate Lag Selection Process, as this would eliminate possible simultaneous dependencies and indirect links among the VAR

variables, which might presently distort results. Research on such shortcomings, as well as other statistical weaknesses should be left to econometrics or similar mathematical disciplines, despite the vested interest various medical scientists would have in the further tailoring of VAR methodology to medical applications.

6.4. Conclusion

Key findings from this case study and major avenues for future research have been summarized in this chapter. Much more research is needed not only as far as medical aspects are concerned, but also in the further development and tailoring of the statistical procedures applied in this thesis. Cooperation between academic disciplines and an open mind for novel approaches to old problems will be essential components for scientific progress.

7. Executive Summary/ (Zusammenfassung)

Statistical approaches rooted in econometric methodology, so far foreign to psychosomatic medicine, have provided dynamic psycho-somatic models on brittle diabetes[9] in yielding to Meissner's (2006) and others' call for a more integrated view on mind-body relationships with no a priori cause and effect assignments to interacting variables. The conception and portrayal of such models is the focus of this work, in addition to the clinical findings they provide on the case study otherwise primarily serving as an example for their application.

Over 120 days, this structured diary time series case study explored the mutual interactions of individual affect states in a classic three person family with its type 1 diabetic adolescent's daily blood glucose variability and vice versa. Glycemic variability was measured through daily standard deviations of blood glucose recordings (at least three per day). For the same period of time, affect states were captured individually utilizing the self-assessment manikin (Lang, 1980; Bradley & Lang, 1994) on affective valence (positive – negative), arousal (high – low), and dominance (sense of being absent – sense of being present). Auto- and cross-correlating the stationary absolute (level) values of the mutually interacting parallel time series data sets through standard vector autoregression (VAR, Lütkepohl, 2005; Lütkepohl & Krätzig, 2004) and a newly conceived Optimized Multivariate Lag Order Selection Process (Winker, 1995, 2000; Savin & Winker, 2013) allowed for the formulation of three predominantly consistent models.

In the two standard VAR models Cholesky Impulse Response Analysis was applied at a 95 per cent confidence level, cumulatively evidencing for an adolescent being happy, calm, and experiencing high dominance to exhibit less glycemic variability and hence diabetic derailment. A non-dominating mother and a happy father also seemed to reduce glycemic variability. Random external shocks to the two VAR models increasing glycemic variability affected only the adolescent and her father: In one model, the male parent exhibited high dominance; in the other, he calmed down while his daughter turned sad. All effects lasted for less than four full days. In the third model based on the Optimized Multivariate Lag Selection Process, more specific temporal relations between affect states and the biological marker of glycemic

[9] Brittle diabetes is a term adopted to describe difficult to control insulin dependent diabetes mellitus with frequent hypo- and hyperglycemic derailments (e.g. Gale & Tattersall, 1979; Kent, Gill & Williams, 1994, Brosig et al., 2001).

variability were isolated at statistical significance: *Low* glycemic variability and therefore *good* diabetic control correlated with high glycemic variability four days earlier, an excited mother three days earlier, a calm mother seven days earlier, a non-dominating mother four days earlier, a happy father both five and six days earlier, an excited father both three and seven days earlier, and a non-dominating father both two and five days earlier. Low glycemic variability also correlated with a happy child six days later, a calm mother three days later, and a non-dominating father one day later.

Graphical representations were proposed for all three models – the intention being a demonstration of avenues for clinically oriented presentations of arguably rather abstract quantitative findings. Additionally, a multiply regressive approach to the data with interval-valued variables and a qualitative case vignette were presented, to complement these highly quantitative models.

Extant literature on brittle diabetes in children and adolescents and the family dynamics complementing it was reviewed in light of all findings. The recurring correlation between maternal dominance and poor glycemic control was recognized. In addition, the prospects and contingencies arising from applying econometric theory to psychosomatic questions were discussed throughout this thesis. The value and limitations of qualitative and quantitative research on brittle diabetes in general, as well as pertaining to this study, received particular attention.

Zusammenfassung

Der Psychosomatischen Medizin bisher fremde statistische Anwendungen der Ökonometrie konnten, unter Berücksichtigung der Forderung Meissners (2006) und anderen nach einer ganzheitlicheren Betrachtungsweise der Körper-Seele-Beziehung, ohne a priori Festlegung von Ursache-Wirkungs-Beziehungen zwischen interagierenden Variablen, dynamische psycho-somatische Modelle zum Brittle Diabetes[10] liefern. Die Konzeption und Darstellung solcher Modelle am Fallbeispiel ist Fokus dieser Arbeit – zusätzlich zu den klinischen Ergebnisse der Fallstudie an sich.

Im Rahmen einer Einzelfall-Zeitreihenanalyse, basierend auf strukturierten Tagebuchaufzeichnungen über 120 Tage, wurden die wechselseitigen Interaktionen zwischen Affekten der Mitglieder einer klassischen dreiköpfigen Familie und der

[10] Brittle Diabetes beschreibt den schwer einstellbaren, durch häufige hypo- und hyperglykäme Krisen gekennzeichneten, insulinabhängigen Diabetes mellitus (z.B. Gale & Tattersall, 1979; Kent, Gill & Williams, 1994, Brosig et al., 2001).

Blutzuckervariabilität des Typ-I diabetischen Jugendlichen exploriert. Die Blutzuckervariabilität wurde mittels der täglichen Standardabweichung der Blutzuckermessungen (mindestens drei pro Tag) verfolgt. Für den gleichen Zeitraum wurden die Affektzustände für jedes Familienmitglied mittels self-assessment manikin (Lang, 1980; Bradley & Lang, 1994) im Sinne von Valenz (positiv – negativ), Erregung (hoch – niedrig) und Dominanz (Gefühl der Abwesenheit – Gefühl der Präsenz) erhoben. Korrelationen und Autokorrelationen zwischen den stationären Werten der wechselseitig interagierenden parallel erhobenen Zeitreihen konnten mittels Vektorautoregression (VAR, Lütkepohl, 2005; Lütkepohl & Krätzig, 2004) und dem Optimized Multivariate Lag Order Selection Process (Winker, 1995, 2000; Savin & Winker, 2013) in Form von drei weitgehend übereinstimmenden Modellen dargestellt werden.

Durch die zwei Standard-VAR-Modelle konnte mittels Cholesky Impulsantwortfolgen mit einem 95 Prozent Konfidenzintervall insgesamt gezeigt werden, dass Gefühle von Glück, innerer Ruhe und hoher Dominanz bei der Jugendlichen mit weniger Blutzuckervariabilität und daher weniger diabetischen Entgleisungen verbunden waren. Eine nicht-dominante Mutter und ein glücklicher Vater schienen ebenfalls die Blutzuckervariabilität zu reduzieren. Zufällige extern verursachte Anhebungen der Blutzuckervariabilität zeigten in beiden VAR-Modellen nur auf die Jugendliche und ihren Vater Einfluss: In einem Modell zeigte der Vater erhöhte Dominanz, in dem anderen innere Ruhe und seine Tochter Traurigkeit. Alle Effekte konnten für weniger als vier Tage nachgewiesen werden. In dem dritten, auf den Optimized Multivariate Lag Selection Process basierenden Modell, konnten spezifischere zeitliche Relationen zwischen den Affektzuständen und dem biologischen Marker der Blutzuckervariabilität mit statistischer Signifikanz nachgewiesen werden: *Niedrige* Blutzuckervariabilität und daher eine *gute* diabetische Stoffwechselkontrolle korrelierte mit hoher Blutzuckervariabilität vier Tage vorher, einer erregten Mutter drei Tage vorher, einer ruhigen Mutter sieben Tage vorher, einer nicht-dominanten Mutter vier Tage zuvor, einem glücklichen Vater sowohl fünf als auch sechs Tage zuvor, einem erregten Vater drei und sieben Tage zuvor und einem nicht-dominanten Vater zwei und fünf Tage vorher. Niedrige Blutzuckervariabilität korrelierte auch mit einer glücklichen Jugendlichen sechs Tage später, einer ruhigen Mutter drei Tage danach und einem nicht-dominanten Vater am nächsten Tag.

Für alle drei Modelle wurden graphische Darstellungen vorgeschlagen – mit dem Ziel Wege für eine klinisch orientierte Präsentation der eher abstrakten quantitativen Ergebnisse zu finden. Außerdem wurde eine statistische Bearbeitung mittels Multipler Regression mit Intervallvariablen, sowie eine qualitative Fallvignette vorgestellt, um die höchst quantitativen Modelle zu ergänzen.

Literatur zum Brittle Diabetes in Kindern und Jugendlichen und den damit einhergehenden Familiendynamiken wurden unter dem Gesichtspunkt der Ergebnisse besprochen. Die wiederkehrende Korrelation zwischen mütterlicher Dominanz und schlechter Blutzuckereinstellung wurde erwähnt. Weiterhin wurden die Chancen und Risiken der Anwendung ökonometrischer Theorie auf psychosomatische Fragestellungen innerhalb der gesamten Arbeit diskutiert. Dabei wurde besonderes Augenmerk auf den Wert und die Grenzen qualitativer und quantitativer Darstellungen beim Brittle Diabetes allgemein als auch in Bezug auf diese Studie gelegt.

8. Abbreviations

AIC → Akaike Information Criterion

BIC → Bayesian Information Criterion

FFA → Free Fatty Acid

FPE → Final Prediction Error

HQ → Hannan-Quinn Information Criterion

LR → Sequential Modified Likelihood Ratio Test Statistic

OLS → Ordinary Least Squares

R^2 → Coefficient of Determination

SAM → Self Assessment Manikin

SC → Schwarz Information Criterion

VAR → Vector Autoregression, Vector Autoregressive

VEC → Vector Error Correction

VECM → Vector Error Correction Model

9. List of Tables and Figures

10. Reference List

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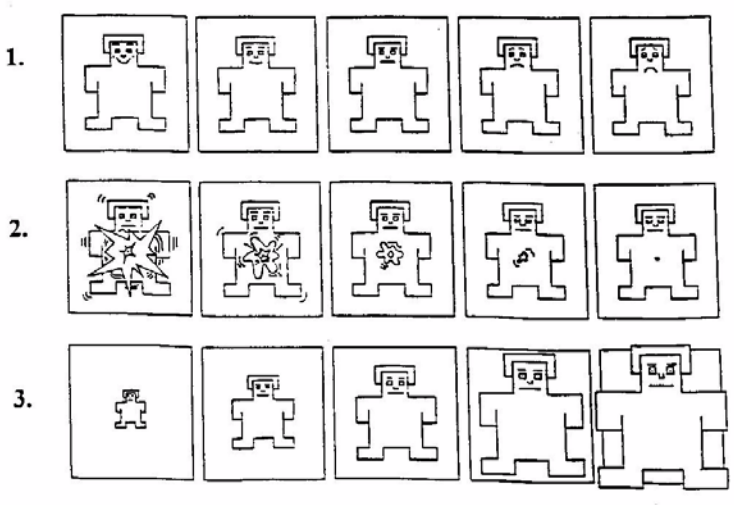
11. Appendices

Exhibit 1: An Excerpt from the Adolescent's diary (blank)

Tagebuch (Self assessment manikin SAM) **Datum:_____**

Im Folgenden siehst Du drei Reihen von unterschiedlichen Männchen. Schau sie Dir an und versuche täglich gegen 20:00 Uhr Abends die Spannbreite deiner heutigen Gefühlszustände den Männchen zuzuordnen. Du hast dabei die Möglichkeit, in **jeder Reihe** eine Linie (mit Anfangs- und Endpunkt) zwischen zwei Figuren einzuzeichnen. Bitte nicht vergessen oben rechts das Datum des heutigen Tages einzutragen.



Falls irgendein **Ereignis** Deine **Stimmung** mit beeinflusst haben sollte, bitte ich dies auf der Rückseite einzutragen. Herzlichen Dank für Deine Mitarbeit.

Blutzucker Morgens:

Blutzucker Mittags:

Blutzucker Abends:

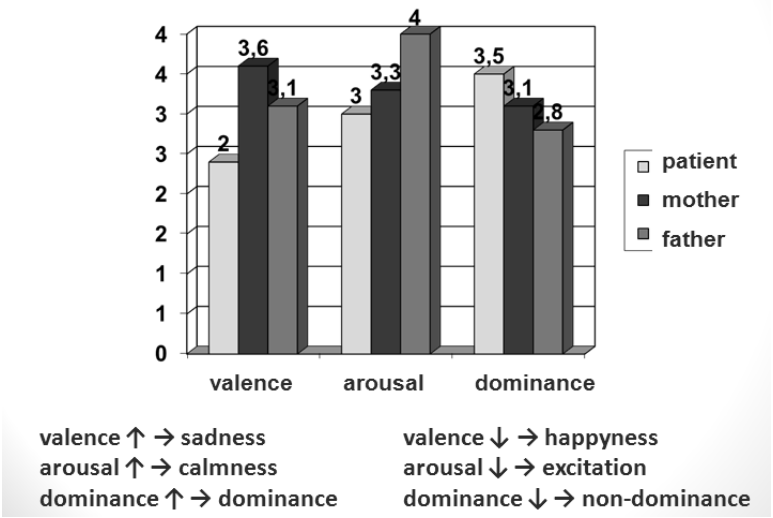
Weitere Blutzucker-Messungen:

Exhibit 2: Descriptive Statistics on the Ten Time Series

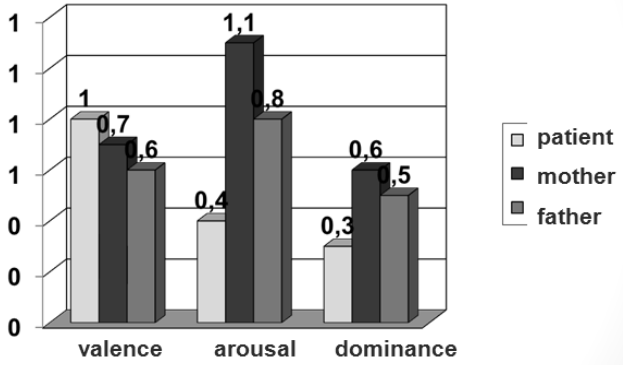
a) Statistics on Blood Sugar Measurements

	# of meas.	BZMW	BZSD
mean	4.26	216.99	55.36
median	4.00	216.75	52.35
max	9.00	315.00	147.79
min	2.00	118.88	17.32
standard deviation	0.70	34.41	23.74
N	119	119	119

b) Means of Affect Variables



c) Standard Deviations of Affect Variables



valence ↑ → sadness
arousal ↑ → calmness
dominance ↑ → dominance

valence ↓ → happyness
arousal ↓ → excitation
dominance ↓ → non-dominance

Exhibit 3: A Fourth Model: Multiple Regression with an Interval Variable for Glycemic Variability

The proposed multiple regression model involves the dependent interval-valued variable "blood sugar in the current day", y_{BS}, and the independent interval-valued variable "blood sugar in the previous day", x_{BS}, and, for each family member, the real-valued affect variables "valence" (denoted by Valc – sadness of the child, Valm – sadness of the mother and Valf – sadness of the father respectively), "arousal" (Errc, Errm and Errf) and "dominance" (Domc, Domm and Domf). High values of the valence variable are interpreted as sadness and low values as feelings of pleasure in the family member. By contrast, high values for arousal and dominance are interpreted as such (excitement for arousal and a sense of presence for dominance).

Given the nine real-valued independent variables Valence, Dominance and Arousal stored in the vector X_R and the interval-valued variable representing the blood sugar yesterday x_{BS}, the model can be expressed as follows:

$$\mathbf{y_{BS} = x_{BS}^{M}\, bm1 + x_{BS}^{S}\, b_{s1} + x_{BS}^{C}\, b_{s2} + x_{BS}^{R}\, b_{m2} + X_R b_1^{*} + \varepsilon}$$

where x_{BS}^{M} = mid x_{BS} [1 ±0], x_{BS}^{S} = spr x_{BS} [0 ± 1], x_{BS}^{C} = mid x_{BS} [0 ± 1] and x_{BS}^{R} = spr x_{BS} [1 ± 0], working with the real-valued variables containing the mid-points of the blood sugar in the previous day (midxBS) and the radius (spr x_{BS}); X_R can contain any combination of real-valued variables (for instance X_R = (Domc, Errc) or X_R = (Valm, Domf, Errc), or any other combination). $\varepsilon = (\varepsilon_1, \ldots, \varepsilon_n)t$ is such that $E(\varepsilon \mid x_{BS}^{M}, x_{BS}^{S}, x_{BS}^{C}, x_{BS}^{R}, X_R) = 1^n\Delta$. The notation of the variables comes from M=mid, S=spread, C=center, R=radius, and bmi (for all i in {1, 2}) is used to represent the coefficients related to the mids, bsi those ones related to the spreads (and is used to remark that b1 is not a real number, as bmi and bsi, but a vector of intervals whose size depends on the dimension of X_R).

A backwards stepwise regression is implemented, when in each step one emotional variable is removed from the model. The estimation process is solved by least-squares, where the problem becomes a constrained quadratic problem to assure the existence of the residuals in accordance with the interval arithmetic (Blanco-Fernández, Corral, & Gonzalez-Rodriguez, 2011). The objective function in the problem is split in two parts, one related to the mids and another to the spreads. This simplifies its

resolution, as those coefficients related to the mids are not affected by constraints and are obtained straightforward by ordinary least squares (OLS) and only the estimation of the coefficients related to the spreads is addressed with the constrained problem. For further details see Blanco-Fernández, García Bárzana, Colubi, & Kontoghiorghes (2014). For reasons of comprehensiveness, among the different models obtained with the backwards stepwise regression, only that one providing the best results (in terms of adjusted determination coefficients) is considered. The results are summarized in Table 1.

Exhibit 3, Table 1:

Variables	$\widehat{\Delta}$	$\widehat{b_{m_1}}$	$\widehat{b_{m_2}}$	$\widehat{b_{s_1}}$	$\widehat{b_{s_2}}$	$\widehat{b_1^*}$
y_{BS}, x_{BS}	[93.623, 201.949]	0.168	-0.0264	0.070	0	[10.067, 10.067]
Val_m						[8.383, 8.383]
Err_m						[-10.407,-8.314]
Dom_m						

Legend: Chosen model providing the best adj. R^2. The first column contains the variables, the second column the estimated residuals and columns 3, 4 and 5 the estimated regression coefficients. The adjusted R^2 is 0.1224.

A preliminary study of the variables is to be conducted. Some normality tests based on the Shapiro-Wilks test are carried out, the null hypothesis H0 being: the variable is normal. The p-values are summarized in the following table:

Exhibit 3, Table 2:

Variables	**midX_{BS}**	**sprX_{BS}**	**Dom_c**	**Dom_m**	**Dom_f**	**Err_c**
p-values	0.240	0.006165	2.2e-16	9.451e-11	7.881e-06	2.2e-16
Variables	**Err_m**	**Err_f**	**Val_c**	**Val_m**	**Val_f**	
p-values	7.182e-07	2.213e-07	2.177e-08	1.105e-07	4.579e-06	

Considering a 0.05 significance level, only $midx_{BS}$ is normal, so the classical methodology to make inferences is not applicable. This is the reason why bootstrap techniques need to be applied (Efron, 1993).

As the considered case-based study is applied to a time series dataset, it is important to justify the validity of applying a regression model instead of an autoregressive model. Therefore, some Durbin Watson (DW) correlation tests are developed, where the null hypothesis is H0: the residuals from the linear regression are uncorrelated against H1: the errors follow a stationary first order autoregression. The DW tests are performed separately for the mids and the spreads. The results for the model highlighted in Table 1 are summarized in Table 3.

Exhibit 3, Table 3:

Model	**p-value mid**	**p-value spr**	**p-value**
Model	0.9792	0.2580	0.9921

Legend: "p-value mid" denotes the p-values obtained when the variables involved to compute the residuals are those ones related to the mids, i.e., X_{BS}^{M} and X_{BS}^{R}. Analogous to this, "p-value spr", being in this case involved X_{BS}^{S} and X_{BS}^{C}. Finally, in the last column is the "p-value" of the residuals computed using the d_T distance as $(1 - r)\,(midY - mid\hat{Y}) + r(spry - spr\hat{Y})$

In order to justify the significance of the variables, a bootstrap test is carried out to test the null hypothesis, H0: The coefficient is equal to zero.

The results indicate the mother's affective variables (arousal, dominance and valence), followed by the child's blood sugar variable in the previous day (X_{BS}) to be the major predictors of its blood sugar variable the current day (Y_{BS}, with adj. R^2 12.31%). %). Working with the standardized coefficients of the proposed model, maternal dominance the day before is evidenced to have a negative effect on the adolescent's glycemic variability (i.e. high maternal dominance results in high glycemic variability). By contrast, positive maternal valence, followed by high arousal in terms of effect size, both have positive impacts on diabetic control (low glycemic variability). Low glycemic variability one day before correlates with low glycemic variability the next day. As was to be expected with multiply regressive methodologies, these results lack the scope and clarity of the results delivered in the other three models presented in this thesis, but partially support their findings.

12. List of Publications

Günther, M.P., Winker, P., Böttcher, C., & Brosig B. (2013). Family system dynamics and type 1 diabetic glycemic variability: A vector-auto-regressive model, *Families, Systems, and Health*, 31 (2), 194-204. (doi: 10.1037/a0032314)

13. Academic Integrity Statement (German)

Erklärung zur Dissertation

„Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nichtveröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten sowie ethische, datenschutzrechtliche und tierschutzrechtliche Grundsätze befolgt. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, oder habe diese nachstehend spezifiziert. Die vorgelegte Arbeit wurde weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt und indirekt an der Entstehung der vorliegenden Arbeit beteiligt waren. Mit der Überprüfung meiner Arbeit durch eine Plagiatserkennungssoftware bzw. ein internetbasiertes Softwareprogramm erkläre ich mich einverstanden.“

_____

Ort, Datum Unterschrift

14. Acknowledgements

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