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Abstract	Parkinson's disease (PD) is neurodegenerative disease (ND) related to the lost of dopaminergic neurons that elevates first by motor and later also by non-motor (dementia, depression) disabilities. Actually, there is no cure for ND as we are not able to revive death cells. Our purpose was to find, with help of data mining and machine learning (ML), rules that describe and predict disease progression in two groups of PD patients: 23 BMT patients that are taking only medication; 24 DBS patients that are on medication and on DBS (deep brain stimulation) therapies. In the longitudinal course of PD there were three visits approximately every 6 months with the first visit for DBS patients before electrode implantation. We have estimated disease progression as UPDRS (unified Parkinson's disease rating scale) changes on the basis of patient's disease duration, saccadic eye movement parameters, and neuropsychological tests: PDQ39, and Epworth tests. By means of ML and rough set theory we found rules on the basis of the first visit of BMT patients and used them to predict UPDRS changes in next two visits (global accuracy was 70% for both visits). The same rules were used to predict UPDRS in the first visit of DBS patients (global accuracy 71%) and the second (78%) and third (74%) visit of DBS patients during stimulation-ON. These rules could not predict UPDRS in DBS patients during stimulation-OFF visits. In summary, relationships between condition and decision attributes were changed as result of the surgery but restored by electric brain stimulation.

Keywords (separated by '-')	Neurodegenerative disease - Rough set - Decision rules - Granularity

Multimodal Learning Determines Rules of Disease Development in Longitudinal Course with Parkinson's Patients

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Abstract Parkinson's disease (PD) is neurodegenerative disease (ND) related to the lost of dopaminergic neurons that elevates first by motor and later also by non-motor (dementia, depression) disabilities. Actually, there is no cure for ND as we are not able to revive death cells. Our purpose was to find, with help of data mining and machine learning (ML), rules that describe and predict disease progression in two groups of PD patients: 23 BMT patients that are taking only medication; 24 DBS patients that are on medication and on DBS (deep brain stimulation) therapies. In the longitudinal course of PD there were three visits approximately every 6 months with the first visit for DBS patients before electrode implantation. We have estimated disease progression as UPDRS (unified Parkinson's disease rating scale) changes on the basis of patient's disease duration, saccadic eye movement parameters, and neuropsychological tests: PDQ39, and Epworth tests. By means of ML and rough set theory we found rules on the basis of the first visit of BMT patients and used them to predict UPDRS changes in next two visits (global accuracy was 70% for both visits). The same rules were used to predict UPDRS in the first visit of DBS patients (global accuracy 71%) and the second (78%) and third (74%) visit of DBS patients during stimulation-ON. These rules could not predict UPDRS in DBS patients during stimulation-OFF visits. In

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summary, relationships between condition and decision attributes were changed as result of the surgery but restored by electric brain stimulation.

Keywords Neurodegenerative disease · Rough set · Decision rules · Granularity

1 Introduction

We have very limited knowledge about brain's plastic properties and compensatory mechanisms related to continuous death of neuron in the Central Nervous System. Till now, we did not achieve to construct an artificial NN with a similar to the brain compensatory mechanisms. Late diagnoses of the neurodegenerative diseases (ND) such as Alzheimer (AD) or Parkinson's (PD) is side effect of the brain plasticity as patients for a decade or two do not notice that cells in their brains are dying several time faster than in other people. As a consequence, the first symptoms are diagnosed when large parts of their brain are dead and we do not know how to recover dead cells. We can only make precise diagnoses of symptoms and in the PD case use medication to supplement lack of the neurotransmitter—dopamine.

Specialized in PD neurologists after many tests and by using their experience can implement individually adjusted therapy. However, in many cases therapy should be corrected and adjust with the disease development, but doctors have very limited time for each patient. Also their tests and approaches to patients may differ and changing doctor may lead to confusions and changes in the therapy. We propose to improve doctors' diagnoses by additional more automatic eye movement measurements. In addition, data mining and machine learning (ML) procedures based on rough set theory may improve prediction of disease development and optimize medications.

We have developed intelligent methods of symptom classification [1] that are similar to that found in the visual system for the complex objects recognition [2]. A fast and precise object classification in the visual system is possible as certain patterns are in-born and others are changing by continuous learning processes (brain plastic changes) [2]. Our algorithms follow visual system intelligent approach [2].

It is important to estimate the disease stage because it determines different sets of therapies. The neurological standards are based on Hoehn and Yahr and the UPDRS (Unified Parkinson's Disease Rating) scales. The last one is more precise and it will be used in this study. We would like to estimate disease progression in different groups of patients that were tested during three visits every half-year. Our method may lead to introduce more precise follow up and introduction of the possible internet-treatment.

2 Methods

Our data are from 47 Parkinson Disease (PD) patients divided into two groups: (1) 23 BMT (best medical treatment) patients that were only on medications; (2) 24 DBS patients on medication and DBS therapies. These went for the Deep Brain

Stimulation (DBS) implantation to the Institute of Neurology and Psychiatry WUM. The main indication for DBS are "wearing off' medication. All patients were tested in the following sessions: MedON/MedOFF sessions (sessions with or without medication). In addition DBS patients were also tested in StimON/StimOFF session were DBS stimulation was switched ON or OFF. All combinations gave four sessions: (1) MedOFFStimOFF; (2) MedOFFStimON; (3) MedONStimOFF; (4) MedONStimON. Details of these procedures were described earlier [2]. Tests of different motor and non-motor tasks (UPDRS = $\Sigma_I{}^{IV}$ UPDRS$_i$) and neuropsychological tests were performed by neurologists from Warsaw Medical University. Fast eye movements (EM)—reflexive saccades (RS) were recorded as described in details before [1, 3]. Each patient sat watching a computer screen and has to follow randomly in delay and direction, horizontally moving to the right or the left dot after fixating on the starting point in the middle of the screen [3]. These EM tests were repeated ten times in each described above session. The following parameters of RS were measured: the delay (latency) related to time difference between the beginning of the light spot movements and the beginning of the eye movement; saccade's amplitude in comparison to the light spot amplitude; max velocity of the eye movement; duration of saccade defined as the time from the beginning to the end of the saccade.

Detailed procedures and orders of sessions were also described before [1].

Institutional Ethic Committee at the Warsaw Medical University approved all procedures.

2.1 Theoretical Basis

Our data mining analysis follows rough set theory after Zdzislaw Pawlak [4]). Our data are represented as a decision table where rows represented different measurements (may be obtained from the same or different patients) and columns were related to different attributes. An information system [4] is as a pair $S = (U, A)$, where U, A are finite sets: U is the universe of objects; and A is the set of attributes. The value $a(u)$ is a unique element of V (where V is a value set) for $a \in A$ *and* $u \in U$.

We define as in [4] the *indiscernibility relation* of any subset B of A or $IND(B)$ as: $(x, y) \in IND(B)$ or $xI(B)y$ iff $a(x) = a(y)$ for every $a \in B$ where the value of $a(x) \in V$. It is an equivalence relation $[u]_B$ that we understand as a *B-elementary granule*. The family of $[u]_B$ gives the partition U/B containing u will be denoted by $B(u)$. The set $B \subset A$ of information system S is a reduct $IND(B) = IND(A)$ and no proper subset of B has this property [5]. In most cases, we are only interested in such reducts that are leading to expected rules (classifications). On the basis of the reduct we have generated rules using four different ML methods (RSES 2.2): exhaustive algorithm, genetic algorithm [6], covering algorithm, or LEM2 algorithm [7].

A **lower approximation** of set $X \subseteq U$ in relation to an attribute B is defined as $\underline{B}X = \{u \in U : [u]_B \subseteq X\}$. The **upper approximation** of X *is* defined as $\overline{B}X = \{u \in U : [u]_B \cap X \neq \phi\}$. The difference of $\overline{B}X$ *and* $\underline{B}X$ is the boundary region of

X that we denote as $BN_B(X)$. If $BN_B(X)$ is empty then set than X is *exact* with respect to B; otherwise if $BN_B(X)$ is not empty and X is not *rough* with respect to B.

A decision table (training sample in ML) for S is the triplet: $S = (U, C, D)$ where: C, D are condition and decision attributes [8]. Each row of the information table gives a particular rule that connects condition and decision attributes for a single measurements of a particular patient. As there are many rows related to different patients and sessions, they gave many particular rules. Rough set approach allows generalizing these rules into universal hypotheses that may determine optimal treatment options for an individual PD patient. The decision attribute D is giving a particular object (patient's state) classification by an expert (neurologist). Therefore a decision table classifies data by *supervised learning (ML)* where teaching is related to decisions made by neurologist(s). Each raw is an example of the teacher's decision.

It is well known that neurodegenerative processes start to accelerate a decade or two before the first PD symptoms and these processes are not exactly same in different patients. As a consequence, different patients need different treatments. The most neurologists use their intuition based on general medical rules and experiences to adapt an individual treatment plan. We would like to find rules more precisely dependent on an individual patient symptoms but also enough universal to describe symptoms of many different patients. Different rules' granularities (abstraction) are similar to complex objects recognition [2] and may simulate association processes of an ideal neurologist.

In our previous works [1, 3] we have divided experimental tests into several subsets, learned rules, tested each subset in several terms and averaged precisions of our predictions in order to get global precision (classical n-fold approach). In present study, we have used data from different treatments and group of patients for training and testing. The purpose was to find what are limits of rules that may predict symptoms development of patients with different treatments in different disease stages.

We have used the RSES 2.2 (Rough System Exploration Program) [9] with implementation of RS rules to process our data.

3 Results

All 47 PD patients have mean age of 56 ± 11.7 (SD) years with mean disease duration of 8.3 ± 3.7 years and BMT patients (only medication) and DBS patients (medication and with implanted electrodes in the basal ganglia, in our case in the subthalamic nucleus [3]).

In the BMT group of 23 patients with mean age of 57.8 ± 13 (SD) years; disease duration was 7.1 ± 3.5 years. The second DBS group of 24 patients with mean age of 53.7 ± 9.3 (SD) years; disease duration was 9.5 ± 3.5 years (statically significant longer disease duration than BMT-group: $p < 0.025$). These statistical data are related to the data obtained during the first visit for each group: so-called BMT W1 (visit one) and DBS W1 (visit one).

3.1 Rules for Longitudinal Study in Same Population of BMT Patients

Only on medication—BMT patients were tested in two sessions (session 1: without, and session 3: with medication) three times every half-year. In Table 2 are data from three patients for the first visit.

The full table has 23 (subjects) × 2 (sessions) = 46 objects (measurements). In the Table 1 are values of nine attributes for three subjects where: P# is the patient number; t_dur is the duration of the disease; UPDRS—unified PD rating scale, which is the best indicator of the disease stage; PDQ39—PD quality of life test; Epworth—sleep disturbances test; there are four parameters describing saccades: SccDur is the mean duration of 10 saccades; SccLat is the mean latency of saccades, SccAmp is the mean amplitude of 10 saccades, SccVel is the mean velocity of saccades; and S#—session number (Table 2).

In the next step, using RSES, we have completed reduction and discretization of all attributes except of the patient number (see reduct in [1, 3] and Method section). In the table below (Table 4) for the same data as Table 3 we have performed discretization as range of attributes' values and reductions marked by '*'. Notice that only latency of saccades was significant as other parameters of saccades: duration, amplitude and velocity were reduced.

In the first column patient's number (P#) is symbolic attribute as well as S# (session number in the third column) and they are not discretized; in the second column is patient's disease duration divided in two groups longer and shorter than 9.7 year; in the fourth column is PDQ39—39 questions related to PD quality life divided into two groups; the next Epworth sleeping test—two groups; and in the next four columns are parameters of saccades, but only the latency was important and divided into three ranges; in the last column is UPDRS (decision attribute) divided into four ranges. Each row gives a particular rule, e.g. the first one:

$$('P\#' = 4)\,\&\,('t\_dur' = ''(-Inf, 9.7)'')\,\&\,('S\#' = 1)\,\&\,('PDQ39' = ''(-Inf, 55.0)'')$$
$$\&\,('Epworth' = ''(-Inf, 3.0)''))\,\&\,('SccLat' = ''(-Inf, 181.5)'') \Rightarrow ('UPDRS' = ''(36.0, 45.0)'') \quad (1)$$

We can read Eq. 1 that for patient #4 *and* with disease duration below 9.7 years *and* in session #1 *and* with PDQ39 below 55 *and* with Epworth below *and* with saccade latency shorten than 181.5 ms *then* patient's UPDRS is between 36.0 and 45.0. We found with the RSRS help 70 rules with UPDRS decision values in 4 ranges e.g.:

$$(S\# = 3)\,\&\,(PDQ39 = ''(-Inf, 50.5)'') \Rightarrow (UPDRS = ''(-Inf, 33.5)''\,[12]) \quad (2)$$

$$(t\_dur = ''(-Inf, 5.65)'')\,\&\,(S\# = 3)\,\&\,(Epworth = ''(-Inf, 14.0)'') => (UPDRS = ''(-Inf,\ 33.5)''\ [7]) \quad (3)$$

Both rules (Eq. 2—12 cases, Eq. 3—7 cases) have one condition attribute session number (S#) and the same decision attribute limits. A simplified interpretation is that if a patient is on appropriate dose of medication (S# = 3) and fulfills some additional conditions then his/her UPDRS will be below 33.5.

Table 1 Part of the information table for BMT patients

P#	t_dur	UPDRST	PDQ39	Epworth	SccLat	SccDur	SccAmp	SccVel	S#
4	5.2	44	7	2	152.3	53.7	10	340.4	1
4	5.2	14	7	2	162.1	57.3	9.1	319.8	3
5	10.2	40	46	6	253	51.1	12.1	454.3	1
5	10.2	31	46	6	221.7	50.4	10.6	467.5	3
7	6.4	44	70	3	233	62.4	10	302.4	1
7	6.4	22	70	3	247	56	9.7	371	3

Table 2 Discretized-table extract for BMT patients

P#	t_dur	S#	PDQ39	Epworth	SccLat	SccDur	SccAmp	SccVel	UPDRS
4	"(−Inf,9.7)"	1	"(−Inf,55.0)"	"(−Inf,3.0)"	"(−Inf,181.5)"	*	*	*	"(36.0,45.0)"
4	"(−Inf,9.7)"	3	"(−Inf,55.0)"	"(−Inf,3.0)"	"(−Inf,181.5)"	*	*	*	"(−Inf,24.0)"
5	"(9.7,Inf)"	1	"(−Inf,55.0)"	"(3.0,Inf)"	"(181.5,395.0)"	*	*	*	"(36.0,45.0)"
5	"(9.7,Inf)"	3	"(−Inf,55.0)"	"(3.0,Inf)"	"(181.5,395.0)"	*	*	*	"(24.0,36.0)"
7	"(−Inf,9.7)"	1	"(55.0,Inf)"	"(3.0,Inf)"	"(181.5,395.0)"	*	*	*	"(36.0,45.0)"
7	"(−Inf,9.7)"	3	"(55.0,Inf)"	"(3.0,Inf)"	"(181.5,395.0)"	*	*	*	"(−Inf,24.0)"

Table 3 Confusion matrix for UPDRS of **BMT W2** by rules obtained from **BMT W1**

		Predicted				
		"(36.0, 45.0)"	"(−Inf, 24.0)"	"(24.0, 36.0)"	"(45.0, Inf)"	ACC
Actual	"(36.0, 45.0)"	0.0	1.0	1.0	4.0	0.0
	"(−Inf, 24.0)"	0.0	11.0	0.0	0.0	0.65
	"(24.0, 36.0)"	0.0	5.0	3.0	1.0	0.5
	"(45.0, Inf)"	0.0	0.0	2.0	18.0	0.78
	TPR	0.0	1.0	0.33	0.9	

Table 4 Confusion matrix for UPDRS of **BMT W3** by rules obtained from **BMT W1**

		Predicted				
		"(36.0, 45.0)"	"(−Inf, 24.0)"	"(24.0, 36.0)"	"(45.0, Inf)"	ACC
Actual	"(36.0, 45.0)"	0.0	2.0	3.0	3.0	0.0
	"(−Inf, 24.0)"	0.0	11.0	0.0	0.0	1.0
	"(24.0, 36.0)"	0.0	5.0	1.0	0.0	0.17
	"(45.0, Inf)"	0.0	0.0	1.0	20.0	0.95
	TPR	0.0	0.61	0.2	0.87	

We have used machine learning and rough set theory [6] in order to predict (confusion matrix) precision of rules obtained from the first visit W1 to data from the second (half-year later W2—Table 3) and the third (one year later W3—Table 4) visits.

TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: the global coverage was 1.0 and the **global accuracy was 0.7**.

Cross validation (sixfold) of the first visit BMT W1 data gave the global accuracy 0.896 and global coverage 0.35. TPR for above digitalization were 0, 0.38. 0.56, 0.44, accuracy: 0, 0.312, 0.625, and 0.5. In this *train-and-test* procedure we have used ML classifier based on the decomposition tree.

TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: the global coverage was 1.0 and the **global accuracy was 0.7**.

In BMT (medication only) patients UPDRS increases with time, as medications cannot cure the disease. Our predictions are consistent, even with continues disease development rules (mechanisms) are the same.

Table 5 Confusion matrix for UPDRS of **DBS W1** by rules obtained from **BMT W1**

		Predicted				
		"(43.0, 63.0)"	"(−Inf, 33.5)"	"(33.5, 43.0)"	"(63.0, Inf)"	ACC
Actual	"(43.0, 63.0)"	6.0	1.0	4.0	4.0	0.429
	"(−Inf, 33.5)"	0.0	16.0	1.0	0.0	0.941
	"(33.5, 43.0)"	2.0	1.0	2.0	0.0	0.4
	"(63.0, Inf)"	2.0	0.0	0.0	10.0	0.833
	TPR	0.6	0.94	0.29	0.71	

3.2 *Rules for Longitudinal Study Between Different Patients Populations*

As mentioned above, the second group of PD patients (DBS patients) was under medication and brain stimulation treatments. In the most cases DBS procedure is performed in the later stage of PD development, which means that patients have larger UPDRS. Therefore, we have obtained rules from the same data as above but with higher UPDRS values. The first visit test results from DBS patients (DBSW1) were before the electrodes implantation surgery—patients were tested with or without medications (Table 5).

TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: the global coverage was 1 and the **global accuracy was 0.708**, coverage for decision classes: 1, 1, 1, 1. Classification was based on rules generated from the reduct calculated with genetic algorithm method.

Notice that there are problems with predicting UPDRS values higher than 63 as from tables above (Tables 3 and 4) these values do not appear in the BMT patients.

TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: the global coverage was 0.2 and the **global accuracy was 0.78**, coverage for decision classes: 0.8, 0.11, 0.125, 0.0.

As in Table 5 BMT group results could not predict UPDRS values above 63 as such values are spare in the BMT group.

TPR: True positive rates for decision classes; ACC: Accuracy for decision classes: the global coverage was 0.562 and the **global accuracy was 0.741**, coverage for decision classes: 0.75, 0.528, 0.625, 0.0.

For DBS W3 group predictions for both UPDSR ranges: high above 63 and also (33.5, 43.0) are bad (0). As predictions for the second range were very good (1) in DBS W1 and W2 groups, it looks that longer period of stimulation might change relationships between different attributes.

Table 6 Confusion matrix for UPDRS of **DBS W2** by rules obtained from **BMT W1**

		Predicted				
		"(43.0, 63.0)"	"(−Inf, 33.5)"	"(33.5, 43.0)"	"(63.0, Inf)"	ACC
Actual	"(43.0, 63.0)"	4.0	0.0	0.0	0.0	1.0
	"(−Inf, 33.5)"	2.0	2.0	0.0	0.0	0.5
	"(33.5, 43.0)"	0.0	0.0	1.0	0.0	1.0
	"(63.0, Inf)"	3.0	0.0	0.0	0.0	0.0
	TPR	0.67	1.0	1.0	0.0	

Table 7 Confusion matrix for UPDRS of **DBS W3** by rules obtained from **BMT W1**

		Predicted				
		"(43.0, 63.0)"	"(−Inf, 33.5)"	"(33.5, 43.0)"	"(63.0, Inf)"	ACC
Actual	"(43.0, 63.0)"	2.0	1.0	0.0	0.0	0.667
	"(−Inf, 33.5)"	1.0	18.0	0.0	0.0	0.947
	"(33.5, 43.0)"	3.0	2.0	0.0	0.0	0.0
	"(63.0, Inf)"	0.0	0.0	0.0	0.0	0.0
	TPR	0.33	1.0	0.0	0.0	

In Tables 6 and 7 we have compared predictions based on only medication patients (BMT) with DBS patient population when their brain stimulation was ON. We were unable to predict UPDRS development when these patients were without stimulation. As many rules have patient numbers, global coverage in Table 6 was 20% and in Table 7 only 21%, but obtained accuracies were sufficient. It is not the case for the data from visits 2 and 3 obtained without electric brain stimulation.

4 Discussion

There are standard neurological procedures that are changing every several years (as e.g. UPDRS procedures) based on statistical approach for many PD cases and effectiveness of their treatments. However, different clinical centers may have different rules that are also not in the same way interpreted by different neurologists. New

procedures, new technologies and data constantly improve PD patients' treatments, but one may still doubt (as some patients do) if the actual procedures are optimal for this individual case (for me). We propose to use the data mining and machine learning in order to compare different neurological protocols and their effectiveness. But still there are several problems related to their precision and objectivities. Probably, the best future approach will be to perform all tests automatically, process them with intelligent algorithms and to submit results to the doctor for his/her decision. Another, more advanced approach that we were testing in this work, would be to create a new 'Golden Standard' for each new case on the basis of already successfully treated patients. As each individual has different set of symptoms, it is probably more optimal to gather data from many different patients with some similarities in symptoms to that actually treated subject. Alternative problem is how symptoms are developing in time that is another additional challenge. We have demonstrated, in the present work, that we can estimate symptoms and their time development (longitudinal course) in one population treated in a similar way (e.g. the most popular in PD is only medication treatment). This result may give the basic (locally optimal) follow-ups. If patient is doing significantly worse then others (rules), his/her treatment is not optimal, and should be changed. In the next step, we may use rules obtained from different clinics to make them even more universal and optimal. It was the first part of our approach. In the second part, we have tested different patient population with different treatments. Can we in this case find optimal way of different treatments? The second group of patients were in more advanced stage of disease so it was not possible to get 100% coverage like in the first case. The second group with longitudinal study had a new treatment (brain stimulation) that started from the second visit. We have tested if the same treatment in different populations gives similar results. We have covered 50% cases and got 64% accuracy (Table 6). In next two visits, patients got two treatments: medication (medication ON and OFF) and electric brain stimulation (ON and OFF). We have analyzed these treatments as two different sets: (1) StimOFF: medication ON and OFF; (2) StimON: medication ON and OFF. As a result, it was not possible to get sufficient accuracy in set 1, but we got good accuracy for the set 2—with the brain stimulation. Coverage was about 20% (different patients) but accuracy for the second visit DBSW2 was 78 and 60% for the second visit. In the future, we may look for additional condition attributes in order to improve global accuracy. The reason that our rules did not apply to symptoms of patients without brain stimulation was probably related to the surgery. Inserting electrodes in basal ganglia (into or near STN) may destroy connections between different structures. Functions of these connections are expressed by our rules, disturbing them destroyed functionality of our rules. It is interesting that electric stimulation can revoke our rules again.

5 Conclusions

Presented work is a continuation of our previous findings [1, 3], comparing classical approach used by most neurologists and based on their partly subjective experience

and intuitions with the intelligent data processing (machine learning, data mining) classifications. We have analyzed two longitudinal studies that have patients in different disease stages and with different treatments in order to predict UPDRS changes in time. BMT patients have only medication treatment and more advanced DBS group has medication and brain stimulation treatments. We began by finding rules for the first visit of BMT group of patients and we have applied successfully these rules to match symptoms and treatments of all other visits of BMT patients. We have also applied these rules to individual patients belonging to the DBS group. We were only successful with prediction of symptoms for patients before surgery, or after surgery only when stimulation was ON. Without stimulations, after surgery, rules were changed that was probably related to the side effects of the procedure. We have demonstrated that the parameters of eye movements and neuropsychological data are sufficient to predict longitudinal symptom developments (UPDRS) in different groups of PD patients.

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Chapter 17

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