

T.C.
YILDIZ TEKNİK ÜNİVERSİTESİ
KİMYA-METALURJİ FAKÜLTESİ



PROTEİN YAPISINA DAYALI SANAL TARAMA
YAKLAŞIMINA ALTERNATİF KİMYASAL YAPI VEKTÖRÜ
BAZLI DERİN ÖĞRENME MODELİ

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BİTİRME TEZİ
BİYOMÜHENDİSLİK BÖLÜMÜ

Danışman
Dr.Öğr.Üyesi Alper Yılmaz

İstanbul, 2021

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MODELİ

Birinci İsim SOYİSİM ve İkinci İsim SOYİSİM tarafından hazırlanan tez çalışması 15/06/2021 tarihinde aşağıdaki jüri tarafından Biyomühendislik bölümünde kabul edilmiştir.

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Danışmanım Dr.Öğr.Üyesi Alper Yılmaz sorumluluğunda tarafımca hazırlanan Protein Yapısına Dayalı Sanal Tarama Yaklaşımına Alternatif Kimyasal Yapı Vektörü Bazlı Derin Öğrenme Modeli başlıklı çalışmada veri toplama ve veri kullanımında gerekli yasal izinleri aldığımı, diğer kaynaklardan aldığım bilgileri ana metin ve referanslarda eksiksiz gösterdiğimi, araştırma verilerine ve sonuçlarına ilişkin çarpıtma ve/veya sahtecilik yapmadığımı, çalışmam süresince bilimsel araştırma ve etik ilkelerine uygun davrandığımı beyan ederim. Beyanımın aksinin ispatı halinde her türlü yasal sonucu kabul ederim.

15/06/2021

Birinci İsim SOYİSİM İkinci İsim SOYİSİM

TEŞEKKÜR

Foremost, we are grateful to have completed our thesis under the supervision of Asst. Prof. Alper Yılmaz who has supported us and educated us on the topic of our project and has inspired us to work at our best.

Besides our professor, we would like to thank our friends and families for their moral support and understanding. They have done their best to help us on matters that they can and we are grateful.

June, 2021

Birinci İsim SOYİSİM

İkinci İsim SOYİSİM

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KISALTMA LİSTESİ

CBOW	Continuous Bag Of Words
CNN	Convolutional Neural Networks
DTI	Drug-Target Interactions
LBVS	Ligand-Based Virtual Screening
LSTM	Long Short Term Memory
PDB	Protein Data Bank
ReLU	Rectified Linear Unit
RNN	Recurrent Neural Networks
RCSB	Research Collaboratory for Structural Bioinformatics
SBVS	Structure-Based Virtual Screening
SMILES	Simplified Molecular-Input Line-Entry System
SVM	Support Vector Machine
3D	Three Dimensional
3DGCN	3D Graph Convolutional Network

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Protein Yapısına Dayalı Sanal Tarama Yaklaşımına Alternatif Kimyasal Yapı Vektörü Bazlı Derin Öğrenme Modeli

Sanal tarama, in-silico ilaç tasarımı ve keşfinin bir dalıdır ve lider bileşikler elde etmek için kimyasal kütüphanelerde hesaplama yoluyla araştırmaya dahil edilir. Bu alanı ilerletmek için birçok yöntem vardır ve bu yöntemlerden biri olan derin öğrenme uygulamaları günümüzde popülerlik kazanmaya başlamıştır. Derin öğrenme, oldukça büyük verilerden çok hızlı bir şekilde öğrenme yeteneği ile birçok bilim alanında tercih edilen, makine öğreniminin bir alt alanıdır.

Yapı bazlı sanal tarama metodları genellikle moleküllerin teker teker kenetlenmesini gerçekleştirerek en iyi bağlanan bileşikler ortaya çıkarır, ancak bu işlem zaman harcayan, pratik olmayan, maliyetli bir işlemdir. Bu tezin amacı, derin öğrenme yaklaşımını kullanarak bu gibi sorunların üstesinden gelmektir.

Öncelikle, PDBbind veritabanından, kenetlenmiş konformasyonda proteinler ve ligantlar içeren bir veri seti indirildi. Daha sonra, ligantlar denetimsiz bir model olan Mol2vec aracılığıyla vektör haline getirildi ve IChem yazılımı kullanarak proteinler üzerindeki kaviteles tespit edildi. Hem kaviteles hem de ligantlar üzerindeki veriler elde edildikten sonra, derin sinir ağı sonuçta verilen kaviteye bağlanacak bir ligant bulmak için yapılandırıldı.

Sonuç olarak, oluşturulmuş model başarılı bir şekilde moleküler yapıyı tahmin ettiği ve tahmin edilen ligant moleköl yapıları, halihazırda bağlanan ligant molekülleriyle yakın benzerlik taşıdığı görüldü. Oluşturulan modelin doğruluğu %95 olarak tespit edildi.

Anahtar Kelimeler: Sanal tarama, derin öğrenme, makine öğrenmesi, protein ve ligant etkileşimleri, yapay sinir ağıları, biyoenformatik

YILDIZ TEKNİK ÜNİVERSİTESİ
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ABSTRACT

A Deep Learning Model Using Chemical Structure Embedding as an Alternative to Structure-Based Virtual Screening

Birinci İsim SOYİSİM

Department of Biongeneering
Master of Science Thesis

Advisor: Asst.Prof.Dr. Alper YILMAZ
Co-advisor: Assoc. Prof. Dr.

Virtual screening is a branch of in-silico drug design and discovery and it is involved with searching through chemical libraries computationally, to obtain lead compounds. Recently, various methods have been emerging to advance this field and more specifically deep learning applications have started to gain popularity. Deep learning is a subfield of machine learning that has the ability to learn from enormous data very rapidly, making it a desirable application for many fields of science.

Structure-based virtual screening methods mainly perform molecular docking of molecules one by one to a target molecule making this process rather time-consuming and impractical and thus can become costly. The purpose of this thesis is to employ deep learning to overcome such issues.

Initially, we have downloaded a data set from PDBbind that contains proteins and ligands in docked conformation. Then, we have generated the cavities on the proteins by using the IChem toolkit while embedding the ligands using an unsupervised model that is called Mol2vec. Once both the data on cavities and ligands are generated, the deep neural network was constructed to ultimately find a ligand that would bind to the given cavity.

In conclusion, our model has successfully predicted molecular structures that were very similar to already known molecules that reside in the specified cavity with 95%

accuracy.

Keywords: Virtual screening, deep learning, machine learning, protein and ligand interactions, artificial neural networks, docking, bioinformatics.

1.1 Literature Review

Istanbul is a beautiful city of stunning architecture, history and culture. You'll find ancient and modern colleges, fascinating museums and galleries, and plenty of parks, gardens and green spaces in which to relax. Although the city is spread over a large area, you will have easy reach to anywhere you would like to go thanks to a variety of modern and developed transportation systems diversing from interchangeable rail systems to long-way metrobus lines.

İkinci paragrafa başlamak için iki defa enter'a basıyoruz.

Theorem 1.1. *Let f be a function whose derivative exists in every point, then f is a continuous function.*

Theorem 1.2 (Pythagorean theorem). *This is a theorem about right triangles and can be summarised in the next equation*

$$x^2 + y^2 = z^2 \quad (1.1)$$

And a consequence of theorem 1.2 is the statement in the next corollary.

Sonuç 1.1. *There's no right rectangle whose sides measure 3cm, 4cm, and 6cm.*

Unnumbered theorem-like environments are also possible.

Yorum 1.1. This statement is true, I guess.

And the next is a somewhat informal definition

Tanım 1.1. Fibration A fibration is a mapping between two topological spaces that has the homotopy lifting property for every space X .

Lemma 1.1. *Given two line segments whose lengths are a and b respectively there is a real number r such that $b = ra$.*

İspat. To prove it by contradiction try and assume that the statemenet is false, proceed from there and at some point you will arrive to a contradiction. ■

You can reference theorems such as 1.2 when a label is assigned.

Lemma 1.2. *Given two line segments whose lengths are a and b respectively there is a real number r such that $b = ra$.*

1.2 Objective of the Thesis

There are two airports in Istanbul. Atatürk Airport is on the European Side of the city, and Sabiha Gökçen Airport is on the Asian Side. As both of the airports are located outside the city centre you may find the taxi fees fairly expensive. The taxi from Atatürk Airport to Yıldız Central Campus will cost around Euro 35-40. In case you arrive at the Sabiha Gökçen Airport, you will need to pay double this amount to get here and you will also have to add the bridge fee to it. Communication with the taxi driver will be much easier if you write down the address and hand it to him.

1.3 Hypothesis

You may only use this method of transport from the Atatürk Airport. You can easily reach the station by following the “Metro” signs. If you have difficulties, you can easily ask airline staff for directions. In order to get on the metro, you need to buy a token from the counter. You need to use this token to go through the turnstiles in order to get to the train. You can enjoy the journey without getting stressed as you will go from the first station the last station. You can easily come out at the Aksaray Station, the last station, by following the signs. We suggest you get a taxi from here. Your location is not too close to Yıldız Central Campus but it is also not too far. The taxi from here will cost approx. Euro15.

2

DENKLEM, RESİM, ALGORİTMA ÖRNEKLERİ

Istanbul is a beautiful city of stunning architecture, history and culture. You'll find ancient and modern colleges, fascinating museums and galleries, and plenty of parks, gardens and green spaces in which to relax. Although the city is spread over a large area, you will have easy reach to anywhere you would like to go thanks to a variety of modern and developed transportation systems as well as interchangeable rail systems to long-way metrobus lines.



Şekil 2.1 Landscape design of Yıldız Technical University

In Figure 2.1, landscape design of Yıldız Technical University is illustrated.

2.1 History

The stages our university has passed through in its distinguished past are outlined below. Kondüktör Mekteb-i Âlisi/ The Conductors (Technicians) School of Higher

Education (1911-1922). The Kondüktör Mekteb-i Âlisi/Conductors (Technicians) School of Higher Education was founded in 1911 in order to meet the “science officer” (known previously as conductors, and today as technicians) requirement of the Municipality Public Works Section. The school was modeled on the syllabus of the “Ecole de Conducteur” and was affiliated with the Ministry of Public Works. Enrolment began on 22 August 1911. Harita 2.1 de İTÜ haritasıdır.



Harita 2.1 The Istanbul Technical School

Nafia Fen Mektebi/ The School of Public Works (1922-1937): The school’s name was changed to Nafia Fen Mektebi/ School of Public Works in 1922 and the duration of education was increased to 2.5 years in 1926 and 3 years in 1931.

2.2 Historical Advancements in the University

The school was established as an autonomous higher education and research institution with Law no. 1184 of State Engineering and Architectural Academies published on 3 June 1969.

Law no. 1472 ruled for the closing of special vocational schools in 1971, and engineering schools were affiliated with the Istanbul State Engineering and Architectural Academy.

2.2.1 The Yıldız University Period

The Istanbul State Engineering and Architectural Academy and affiliated schools of engineering and the related faculties and departments of the Kocaeli State Engineering and Architecture Academy and the Kocaeli Vocational School were merged to form Yıldız University with decree law no.41 dated 20 June 1982 and Law no. 2809 dated 30 March 1982 which accepted the decree law with changes.

The new university incorporated the departments of Science-Literature and Engineering, the Vocational School in Kocaeli, a Science Institute, a Social Sciences Institute and the Foreign Languages, Atatürk Principles and the History of Revolution, Turkish Language, Physical Education and Fine Arts departments affiliated with the Rectorate.

2.2.2 The Yıldız Technical University Period

Law no. 3837 dated 3 July 1992 renamed our university Yıldız Technical University. The Engineering Faculty was divided into four faculties and restructured as the Electrical-Electronics, Construction, Mechanical and Chemical-Metallurgy Faculties and also included the Faculty of Economics and Administrative Sciences within its organization. The Kocaeli Faculty of Engineering and the Kocaeli Vocational School were released from our university to be restructured as Kocaeli University. Today our university has 9 Faculties¹, 2 Institutes, the Vocational School of Higher Education, the Vocational School for National Palaces and Historical Buildings, the Vocational School for Foreign Languages and more than 20,000 students .

2.2.2.1 Mission

Our mission is to create a university which pioneers education, scientific research, technological development and artistic work aimed at the progress of society and the increase of the quality of life within an understanding of national and international solidarity; and educates creative, enterprising, questioning and ethical students equipped with universal values, who constantly renew themselves, aim for lifelong learning and are capable of analysis and synthesis.

$$\Delta l = h\Delta\theta \quad (2.1)$$

¹2 of these faculties are located at Yıldız Campus, and the other ones are located at Davutpaşa Campus



Şekil 2.2 Side view of Graduate School of Natural and Applied Sciences, Yıldız Technical University, Çukursaray, İstanbul [10]

$$\frac{\Delta l}{\Delta t} = h \frac{\Delta \theta}{\Delta t} \quad (2.2)$$

$$\lim_{\Delta t \rightarrow 0} \frac{\Delta l}{\Delta t} = \lim_{\Delta t \rightarrow 0} h \frac{\Delta \theta}{\Delta t} \quad (2.3)$$

$$\lim_{\Delta t \rightarrow 0} \frac{\Delta l}{\Delta t} = \frac{dl}{dt} \quad (2.4)$$

Here's more complex formula example.

2.2.3 Skip-gram

Skip-gram metodunda bir kelime girilir ve daha sonra belirli pencere etrafındaki kelimeler tahmin ettirilir. Tek bir girdi değerinden etrafındaki kelimeleri çıktı olarak alabiliyoruz. Skip-gram modeli, verilen corpus'a göre her kelimenin kelime vektörlerini eğitir. Cümle içinde bir kelime ($W(t)$) verildiğinde, mevcut kelimenin $W(t)$ olasılığıyla. skip-gram, yakındaki $w_i(t - k \leq i \leq t + k)$ kelimelerinin $P(W(t+i) | W(t))$ olasılıklarını tahmin edebilir. Her sözcük vektörü yakındaki kelimelerin konumlarını

yansıtır. Skip-gram modelinin amacı aşağıdaki değeri en üst düzeye çıkarmaktır:

$$E = \frac{1}{n} \sum_{t=1}^n \left(\sum_{-k \leq i \leq k, i \neq 0} \log_2 P(W(t+i)|W(t)) \right) \quad (2.5)$$

2.3 Algoritma gösterimi

Algoritma örnekleri tablo olarak alınır. Tablo 2.1’de görüldüğü üzere programlama diline göre format gösterimi, satır numarası gösterimi mümkündür.

Table 2.1 Construction of the Model

```

1 from keras.datasets import imdb
2 from keras import models
3 from keras.callbacks import ModelCheckpoint
4 from keras import layers
5 from keras import optimizers
6 from keras import losses
7 from keras.callbacks import EarlyStopping, ModelCheckpoint
8 from keras.models import load_model
9 import csv
10 import matplotlib.pyplot as plt
11 import pandas as pd
12 import numpy as np
13 import sys
14 import argparse

```

2.4 Tablo örnek

Tablo 2.2’de tablo başlığı boyalı halde gösterilmiştir.

Tablo 2.2 Cavity Point Features and Pharmacophore Matching Rules

Property	Name	Residue	Closest Protein Atom
Hydrophobic(HYD)	CA	Gly	Hydrophobic
Aromatic(AR)	CZ	Phe	Aromatic
Acceptor(HBA)	O	Ala	Donor
Donor(HBD)	N	Ala	Acceptor
Acceptor/Donor(HBAD)	OG	Ser	Acceptor/Donor
Positive Ionizable(D+)	NZ	Lys	Negative Ionizable
Negative Ionizable(A-)	OD1	Asp	Positive Ionizable
Null(DU)	DU	Cub	None

3

ATIF ÖRNEKLERİ

Bu tezde IEEE ya da APA stili, kaynakça gösteriminde kullanılmalıdır. "main.tex" isimli dosyada bunu belirtebilirsiniz. Varsayılan ayar IEEE şeklindedir. Eğer APA stilini kullanmak isterseniz:

usepackage[eng,phd]ytuthesis

satırına 3. parametre olarak authoryear eklemeniz gerekmektedir.

usepackage[eng,phd,authoryear]ytuthesis gibi

Kaynak atıfları, noktadan önceki en son öge olmalıdır. Şekil, tablo vs. ye yapılan atıflar, kaynak atıfından önce olmalıdır.

Kaynakları bibtex formatında Google Scholar'dan edinmenizi öneririz. Edindiğiniz bu bilgileri, tezdeki "references.bib" dosyasına yapıştırın.

"Kanser ölümcül bir hastalıktır. [1]'ye göre çoğunlukla göğüs, kolon ve kan kanseri tür olarak yaygındır. [2]'de yazmış olduğu kitabında histopatolojik görüntülerin, kanserin erken teşhisinde kullanılan bir veri türü olup Yunanca "Doku hastalıkları bilimi" anlamına geldiğini belirtmiştir.Bu alanda oluşturulan verileri [3, 4] akademik çalışmalarında incelemiştir."

Kaynakça sayfası ve kaynak numaralandırılması, eklediğiniz bilgiler ve yerleri çerçevesinde otomatik olarak oluşturulacaktır.

3.1 National Agency

Currently 2199 higher education institutions in 31 countries are participating in Erasmus. Since the creation of Erasmus in 1987, 1.2 million students have benefited from an Erasmus study period abroad. The Erasmus budget for the year 2004 is more than € 187.5 million.

Generally, National Agencies are founded in the participatory countries so as to utilize EU Education and Youth programs by organizing and coordinating activities in cooperation with the relevant parties. National Agency, a part of State Planning Agency, is responsible for the coordination of the European Union Education Programs in Turkey.

3.2 About YTU

Yıldız Technical University is one of the seven government universities situated in İstanbul besides being the 3rd oldest university of Turkey with its history dating back to 1911. It is regarded as one of the best universities in the country as well. Our university has 10 Faculties, 2 Institutes, the Vocational School of Higher Education, the Vocational School for National Palaces and Historical Buildings, the Vocational School for Foreign Languages and more than 25,000 students. As YTU our mission is to create a university which pioneers education, scientific research, technological development and artistic work aimed at the progress of society and the increase of the quality of life within an understanding of national and international solidarity

3.3 Application Procedure

You are expected to attach the following documents to the online application module.

- Application form
- Learning agreement
- Dormitory request form
- Signed documents
- ID Card

3.4 Money Exchange

The most convenient way to get money in Turkey is by using your home bank ATM/ cash card or a credit card in a Turkish ATM/ bancomat/ cash machine.

But if you want to exchange cash, plenty of places will do it for you. Currency Exchange Offices are found in tourist and market areas. They offer better exchange rates than most banks, and may or may not charge a commission. Offices in market

areas tend to offer better exchange rates than those in tourist areas. Shop around for the best rate and the lowest (or no) commission.

3.5 After a Car Accident

The following is a step-by-step guide on what to do if you are involved in a traffic accident in Turkey. From 1 April 2008 it is no longer necessary to call the police to the scene of an accident in the following circumstances:

- When - the accident involves two or more vehicles
- Where there is only material damage to vehicles
- When no one is injured or killed

Where all concerned parties agree to the cause and who is liable for the accident and providing each driver completes the correct form and all parties involved sign each form, including witnesses if any.

You should then submit the form to your insurance company who will use the form in conjunction with the other insurance companies concerned to settle liability. (For more details about how to access the form and instructions how to complete the form, please look at the end of this document.)

If agreement cannot be reached, you should immediately call 155 for Traffic Police assistance and follow the guide below: Do Not Move Your Vehicle from the point of impact unless invited to do so by the traffic police or gendarme.

It is not advisable to accept an offer of financial settlement from the other parties involved. Wait for the police to arrive. Once the police arrive, you will be breathalysed and asked to produce your driving license and logbook. A preliminary report of the accident will be compiled by the police at the scene of the accident. Only when this report has been made, should you move your vehicle. It can take half an hour for the police to arrive at the scene of an accident. Do not move your vehicle.

It is essential to obtain the result of the breathalyzer test and the official police report in order to make a successful insurance claim. You will be asked to collect this within three days from the District Police Station.

This leaflet has been prepared by the British Embassy in Ankara for the convenience of enquirers. Although all care has not been taken in its production, neither Her

Majesty's Government nor any Consular Official in the British Embassy in Ankara takes any responsibility for its precise accuracy or for the consequences of any action taken in accordance with its contents.

Tablo 3.1 Erasmus country codes for different national agencies according to the type of the countries

No.	National Agencies	Erasmus Code	ISO Code	NA Identifier	Type of Country
1	Austria	A	AT	AT	EU
2	Belgium (Flemish speaking)	B	BE	BEFL	EU
3	Belgium (French speaking)	B	BE	BEFR	EU
4	Bulgaria	BG	BG	BG	Candidate
5	Czech Republic	CZ	CZ	CZ	EU
6	Cyprus	CY	CY	CY	EU
7	Denmark	DK	DK	DK	EU
8	Estonia	EE	EE	EE	EU
9	Germany	D	DE	DE	EU
10	Spain	E	ES	ES	EU
11	Finland	SF	FI	FI	EU
12	France	F	FR	FR	EU
13	Greece	G	GR	GR	EU
14	Hungary	HU	HU	HU	EU
15	Iceland	IS	IS	IS	EEA
16	Ireland	IRL	IE	IE	EU
17	Italy	I	IT	IT	EU
18	Latvia	LV	LV	LV	EU
19	Liechtenstein	FL	LI	LI	EEA
20	Lithuania	LT	LT	LT	EU
21	Luxembourg	LUX	LU	LU	EU
22	Malta	MT	MT	MT	EU
23	Netherlands	NL	NL	NL	EU
24	Norway	N	NO	NO	EEA
25	Poland	PL	PL	PL	EU
26	Portugal	P	PT	PT	EU
27	Romania	RO	RO	RO	Candidate
28	Slovak Republic	SK	SK	SK	EU
29	Slovenia	SI	SI	SI	EU
30	Sweden	S	SE	SE	EU

Tablo 3.2 Area codes for different subjects

Area Code	Subject
1	Agricultural sciences
2	Culture
3	Economics
4	Technology
5	Horticulture
6	Fisheries
7	Forestry
8	Animal
9	Tropical Agriculture
10	Others

4 RESULTS AND DISCUSSION

Once you have opened this page you will either have to log in if you are already registered, or register if this is your first visit to this page. When you first register, an e-mail will be automatically sent to you confirming your registration and giving you your password. Once you have logged in you will be able to access the registration form, and you should enter all their details.

Please note that when you have entered your university code and the name of your department, only information which is relevant to your university and department, and which is covered by the relevant bilateral agreement will be displayed.

When you have completed the form, you will find at the bottom of the page a button called 'Attach Files'. This provides a link to where you can attach your completed university application form and Learning Agreement. If you have any special conditions or modifications to the Learning Agreement, you have to contact with your relevant departmental coordinator.

When you are finished, click 'Save' and then 'Send', in order the forms to be sent to this office. Once we have your completed forms we can pass them on to your coordinator here in Yıldız Technical University. Please note that The EU Office cannot make any changes to their form once it has been submitted. Once an understanding has been reached by the coordinators about their application, a Letter of Invitation will be prepared and sent to you.

- [1] *American cancer society*. [Online]. Available: <https://www.cancer.org/treatment/understanding-your-diagnosis/tests/testing-biopsy-and-cytology-specimens-for-cancer.html> (visited on 10/31/2019).
- [2] H. Mohan, *Textbook of pathology*. Jaypee Brothers, Medical Publishers Pvt. Limited, 2018.
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Yıldız Technical University is a major public comprehensive teaching and research university with high aspirations. It has devoted itself to a leading role in contributing through partnerships to socio-cultural and socioeconomic developments at the international level. It has had three years of experiences of participating in the ERASMUS program and its delivery of student and staff mobility has generally been above the national average for Turkey. We are also interested in the programs of LLP such as Comenius, Grundtvig, Leonardo da Vinci. We are going to consider organizing or participating in IP, CD or Thematic Network in the near future. Within the context of the Erasmus Program 2007 – 2013, it is aimed to provide students, faculty and staff with more effective research, teaching, and service. With the Erasmus activities, we try to assess where we stood in the past, where we stand today and where we are going to stand in the future, comparing our current position with our peers. With respect to the objectives of the institutionalization of Erasmus student and staff mobility, we try to make our students and our academic staff benefit educationally, linguistically and culturally from the experience of learning in other European countries. We aim to mobilize 2.5 % of our students and 1.5% of teaching staff, by the year 2011. We will focus on the technical areas and near and new EU countries because of the exchanging our experiences.

A.1 After a Car Accident

The following is a step-by-step guide on what to do if you are involved in a traffic accident in Turkey. From 1 April 2008 it is no longer necessary to call the police to the scene of an accident in the following