INTERNATIONAL RESEARCH AND REVIEWS IN SCIENCE AND MATHEMATICS

EDITORS

PROF. DR. AYŞEGÜL İYIDOĞAN

PROF. DR. GÜNAY ÖZTÜRK

DECEMBER 2023

SERÜVEN YAYINEVİ

Genel Yayın Yönetmeni / Editor in Chief • C. Cansın Selin Temana

Kapak & İç Tasarım / Cover & Interior Design • Serüven Yayınevi

Birinci Basım / First Edition • © Aralık 2023

ISBN • 978-625-6760-44-8

Serüven Yayınevi / Serüven Publishing
Türkiye Adres / Turkey Address: Kızılay Mah. Fevzi Çakmak 1. Sokak
Ümit Apt No: 22/A Çankaya/ANKARA
Telefon / Phone: 05437675765
web: www.seruvenyayinevi.com
e-mail: seruvenyayinevi@gmail.com

Baskı & Cilt / Printing & Volume
Sertifika / Certificate No: 47083

International Research and Reviews in

SCIENCE AND MATHEMATICS

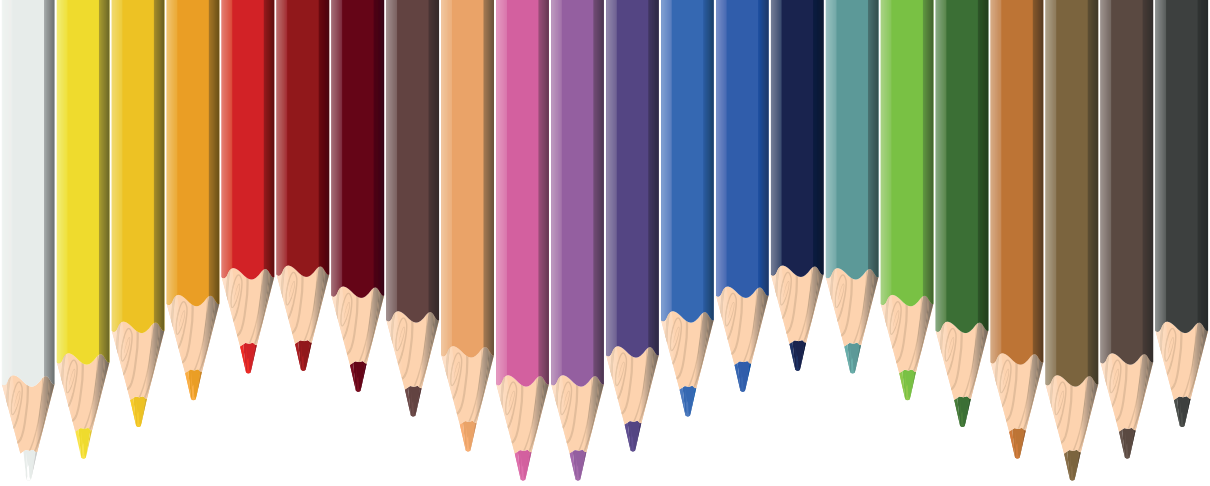
December 2023

Editors

PROF. DR. AYŞEGÜL İYİDOĞAN
PROF. DR. GÜNAY ÖZTÜRK

SERÜVEN YAYINEVİ

CONTENTS



Chapter 1

STURM-LIOUVILLE PROBLEMS INCLUDING BOUNDARY CONDITIONS POLYNOMIALLY DEPENDENT ON THE EIGENPARAMETER WITH DIFFERENTIABLE POTENTIAL

Ayşe KABATAŞ[1]

1 Asst. Prof. Dr.; Karadeniz Technical University, Science Faculty, Department of Mathematics. akabatas@ktu.edu.tr ORCID No: 0000-0003-3273-3666

INTRODUCTION

Consider the Sturm-Liouville problem $L := L(s, D_0, D_1)$ of the form

$$-y'' + s(x)y = \mu y, \quad x \in (0, \pi) \tag{1}$$

$$D_\xi(y) := P_{\xi 1}(\mu)y'(\pi\xi) + P_{\xi 0}(\mu)y(\pi\xi) = 0, \quad \xi = 0,1$$

where μ is the real spectral parameter, $s(x)$ is a real-valued, its derivative exists and is an integrable function on $(0, \pi)$. Also,

$$P_{\xi k}(\mu) = \sum_{j=0}^{r_{\xi k}} P_{\xi k j}\, \mu^{r_{\xi k}-j}, \quad r_{\xi k} \geq 0, \quad \xi, k = 0,1 \tag{2}$$

are arbitrary polynomials of degree $r_{\xi k}$ with real coefficients such that $P_{\xi 1}(\mu)$ and $P_{\xi 0}(\mu)$ have no common zeros for $\xi = 0,1$.

Sturm-Liouville problems have long been of interest to physicists, mathematicians and engineers for its application in physics (Başkaya, 2020; Başkaya, 2021b; Coşkun et al., 2019; Kabataş, 2022a; Kabataş, 2022b; Levitan, 1987; Marchenko, 1977; Pöschel and Trubowitz, 1987; Zhang et al., 2022). In recent years, more and more researchers are interested in these second-order linear ordinary differential equations especially with seperated boundary conditions (Başkaya, 2018a; Başkaya, 2018b; Başkaya, 2021a; Coşkun and Başkaya, 2010; Coşkun and Başkaya, 2018; Coşkun and Kabataş, 2013; Coşkun and Kabataş, 2016; Coşkun et al., 2017; Freiling and Yurko, 2010; Kabataş, 2023a; Kabataş, 2023b).

In this chapter, our aim is to obtain asymptotic formulae for the solutions of the Sturm-Liouville problem *L*. Besides, approximations on the derivatives of the solutions are given. These results are essential for obtaining the eigenfunctions of L, and hence for determining Green's functions which are useful to give some expansion theorems and sampling representations for transforms associated with the related problem.

We suppose without loss of generality that *s* has a mean value zero, i.e., $\int_0^\pi s(t)dt = 0$.

THE METHOD

To calculate the asymptotic solutions of the problem L we use the following method.

As similar to (Harris, 1997), we reduce (1) to the Riccati equation

$$v' = -\mu + s - v^2. \tag{3}$$

We set

$$S(x,\mu) := Re\{v(x,\mu)\}, \quad W(x,\mu) := Im\{v(x,\mu)\}$$

where $v(x,\mu)$ is a complex-valued solution of (3). It was shown in (Harris, 1997) that any nontrivial real-valued solution, z, of (1) can be expressed as

$$z(x,\mu) = c_1 \exp\left(\int_0^x S(t,\mu)dt\right)\cos\{c_2 + \int_0^x W(t,\mu)dt\} \tag{4}$$

with

$$z'(x,\mu) = c_1 S(x,\mu)\exp\left(\int_0^x S(t,\mu)dt\right)\cos\{c_2 + \int_0^x W(t,\mu)dt\}$$

$$-c_1 W(x,\mu)\exp\left(\int_0^x S(t,\mu)dt\right)\sin\{c_2 + \int_0^x W(t,\mu)dt\}. \tag{5}$$

We suppose that there exist functions $A(x)$ and $\eta(\mu)$ so that

$$\left|\int_x^\pi e^{2i\mu^{1/2}t}\, s'(t)dt\right| \le A(x)\eta(\mu)$$

where

(i) $A(x) := \int_x^\pi |s'(t)|\, dt$ is a decreasing function of x,

(ii) $A(x) \in L[0,\pi]$,

(iii) $\mu^{-1/2}\eta(\mu) \to 0$ as $\mu \to \infty$.

For $s' \in L[0,\pi]$, the existence of A and η functions may be established for μ positive as follows. We note that, avoiding the trivial case $\int_x^\pi |s'(t)|\,dt = 0$, so $\left|\int_x^\pi e^{2i\mu^{1/2}t}\, s'(t)dt\right| \le \int_x^\pi |s'(t)|\,dt < \infty$. If we define

$$F(x,\mu) := \begin{cases} \dfrac{\left|\int_x^\pi e^{2i\mu^{1/2}t} s\prime(t)dt\right|}{\int_x^\pi |s\prime(t)|dt}, \text{if} \int_x^\pi |s'(t)|\,dt \neq 0, \\ 0, \qquad \text{if} \quad \int_x^\pi |s'(t)|\,dt = 0 \end{cases} \tag{6}$$

then $0 \le F(x,\mu) \le \pi$ and we set $\eta(\mu) := sup_{0\le x\le\pi} F(x,\mu)$. $\eta(\mu)$ is well-defined by (6) and $\mu^{-1/2}\eta(\mu) \to 0$ as $\mu \to \infty$ (Başkaya, 2018c).

We now approximate to a solution of (3) on $[0,\pi]$. For this reason, we set

$$v(x,\mu) := i\mu^{1/2} + \sum_{n=1}^{\infty} v_n(x,\mu)$$

and choose v_n so that

$$\begin{aligned} v'_1 + 2i\mu^{1/2}v_1 &= s, \\ v'_2 + 2i\mu^{1/2}v_2 &= -v_1^2, \\ v'_n + 2i\mu^{1/2}v_n &= -\left(v_{n-1}^2 + 2v_{n-1}\sum_{m=1}^{n-2} v_m\right), \quad n \ge 3. \end{aligned}$$

Solution of above equation for $n = 1,2,3,\ldots$

$$\begin{aligned} v_1(x,\mu) &= -e^{-2i\mu^{1/2}x}\int_x^\pi e^{2i\mu^{1/2}t}\, s(t)dt, \\ v_2(x,\mu) &= e^{-2i\mu^{1/2}x}\int_x^\pi e^{2i\mu^{1/2}t}\, v_1^2(t,\mu)dt, \\ v_n(x,\mu) &= e^{-2i\mu^{1/2}x}\int_x^\pi e^{2i\mu^{1/2}t}\left[v_{n-1}^2 + 2v_{n-1}\sum_{m=1}^{n-2} v_m\right]dt, \quad n \ge 3. \end{aligned}$$

As a result of these, the asymptotic form of $S(x,\mu)$ and $T(x,\mu)$ are obtained in (Başkaya, 2018c) as follows

$$S(x,\mu) = -\frac{1}{2}\mu^{-\frac{1}{2}}s(\pi)\sin 2\mu^{1/2}(\pi - x) + \frac{1}{2}\mu^{-1/2}\cos\left(2\mu^{1/2}x + \xi_x\right)$$

$$+O\left(\mu^{-1}\eta^2(\mu)\right), \tag{7}$$

$$W(x,\mu) = \mu^{1/2} + \frac{1}{2}\mu^{-1/2}s(\pi)\cos 2\mu^{1/2}(\pi - x) - \frac{1}{2}\mu^{-1/2}s(x)$$

$$-\frac{1}{2}\mu^{-1/2}\sin(2\mu^{1/2}x + \xi_x) + O\left(\mu^{-1}\eta^2(\mu)\right), \tag{8}$$

where

$$\sin\xi_x := \int_x^\pi s'(t)\cos 2\mu^{1/2}tdt, \quad \cos\xi_x = \int_x^\pi s'(t)\sin 2\mu^{1/2}tdt.$$

THE RESULTS

We define $r_{\xi 0} = r_{\xi 1} \geq 0$, $\xi = 0,1$. The other cases can be treated similarly. Without loss of generality we put $P_{\xi 10} = 1$.

Let $\varphi(x,\mu)$ and $\psi(x,\mu)$ be solutions of equation (1) with initial conditions

$$\varphi(0,\lambda) = P_{01}(\mu), \quad \varphi'(0,\lambda) = -P_{00}(\mu), \tag{9}$$

$$\psi(\pi,\lambda) = P_{11}(\mu), \quad \psi'(\pi,\lambda) = -P_{10}(\mu). \tag{10}$$

Theorem 1. The solutions, $\varphi(x,\mu)$ and $\psi(x,\mu)$ satisfy the following equalities, respectively.

(i)

$$\varphi(x,\mu) = \frac{P_{01}(\mu)}{cos[tan^{-1}\gamma(\mu)]}exp\left(\int_0^x S(t,\mu)dt\right)$$

$$\times cos\left[tan^{-1}\gamma(\mu) + \int_0^x W(t,\mu)dt\right] \tag{11}$$

where

$$\gamma(\mu) = \frac{S(0,\mu)}{W(0,\mu)} + \frac{P_{00}(\mu)}{P_{01}(\mu)W(0,\mu)},$$

(ii)

$$\psi(x,\mu) = \frac{P_{11}(\mu)}{cos[tan^{-1}\beta(\mu)]} exp\left(-\int_x^\pi S(t,\mu)dt\right)$$
$$\times cos\left[tan^{-1}\beta(\mu) - \int_x^\pi W(t,\mu)dt\right]$$

where

$$\beta(\mu) = \frac{S(\pi,\mu)}{W(\pi,\mu)} + \frac{P_{10}(\mu)}{P_{11}(\mu)W(\pi,\mu)}.$$

Proof. *(i)* Using (4), (5) and (9) we find

$$\begin{aligned} \varphi(0,\mu) &= c_1 \cos c_2 = P_{01}(\mu), \\ \varphi'(0,\mu) &= c_1 S(0,\mu)\cos c_2 - c_1 W(0,\mu)\sin c_2 = -P_{00}(\mu). \end{aligned}$$

So,

$$c_1 = \frac{P_{01}(\mu)}{\cos c_2} \tag{12}$$

and

$$c_2 = \tan^{-1}\gamma(\mu). \tag{13}$$

The proof is completed by substituting the values (12) and (13) into (4).

(ii) From (4), (5) and (10) it can be written

$$\psi(\pi,\mu) = c_1 \exp\left(\int_0^{\pi} S(t,\mu)dt\right)\cos\left[c_2 + \int_0^{\pi} W(t,\mu)dt\right] = P_{11}(\mu),$$

$$\psi'(\pi,\mu) = c_1 \exp\left(\int_0^{\pi} S(t,\mu)dt\right)\{S(\pi,\mu)\cos\left[c_2 + \int_0^{\pi} W(t,\mu)dt\right] - W(\pi,\mu)\sin\left[c_2 + \int_0^{\pi} W(t,\mu)dt\right]\} = -P_{10}(\mu).$$

Thus, we obtain

$$c_1 = \frac{P_{11}(\mu)}{\exp\left(\int_0^{\pi} S(t,\mu)dt\right)\cos\left[c_2 + \int_0^{\pi} W(t,\mu)dt\right]}$$

and

$$c_2 = \tan^{-1}\beta(\mu) - \int_0^{\pi} W(t,\mu)dt.$$

For the proof, these values of c_1 and c_2 are used in (4).

Now, asymptotic approximations will be given for the solutions, $\varphi(x,\mu)$ and $\psi(x,\mu)$.

Theorem 2. As $\mu \to \infty$, we have

(i)

$$\varphi(x,\mu) = \mu^{r_{01}}\cos\left(\mu^{\frac{1}{2}}x\right) - \mu^{r_{01}-\frac{1}{2}}\{P_{000} - \frac{1}{2}\left[xs(x) - \int_0^x t\, s'(t)dt\right]\} \times \sin\left(\mu^{\frac{1}{2}}x\right) + O(\mu^{r_{01}-1}),$$

(ii)

$$\psi(x,\mu) = \mu^{r_{11}}\cos\left[\mu^{\frac{1}{2}}(\pi - x)\right] + \mu^{r_{11}-\frac{1}{2}}\{P_{100} - \frac{1}{2}[xs(x) - \pi s(\pi) + \int_x^{\pi} t\, q'(t)dt]\}\sin\left[\mu^{\frac{1}{2}}(\pi - x)\right] + O(\mu^{r_{11}-1}).$$

Proof. *(i)* We evaluate the terms in (11) as $\mu \to \infty$. Together with (2), (7) and (8) we obtain

$$\gamma(\mu) = \frac{S(0,\mu)}{W(0,\mu)} + \frac{P_{00}(\mu)}{P_{01}(\mu)W(0,\mu)}$$

$$= \left\{-\frac{1}{2}\mu^{-1}s(\pi)\sin\left(2\mu^{\frac{1}{2}}\pi\right) + \frac{1}{2}\mu^{-1}\cos\xi_0 + O\left(\mu^{-\frac{3}{2}}\eta^2(\mu)\right)\right\}$$

$$\times\left\{1 - \frac{1}{2}\mu^{-1}\left[s(\pi)\cos\left(2\mu^{\frac{1}{2}}\pi\right) - s(0) - \sin\xi_0\right] + O\left(\mu^{-\frac{3}{2}}\eta^2(\mu)\right)\right\}$$

$$+\frac{P_{000}\mu^{r_{00}} + O(\mu^{r_{00}-1})}{\mu^{r_{01}+\frac{1}{2}} + \frac{1}{2}\mu^{r_{01}-\frac{1}{2}}\left[s(\pi)\cos\left(2\mu^{\frac{1}{2}}\pi\right) - s(0) - \sin\xi_0\right] + O\left(\mu^{r_{01}-\frac{1}{2}}\right)}$$

$$= -\frac{1}{2}\mu^{-1}s(\pi)\sin\left(2\mu^{\frac{1}{2}}\pi\right) + O\left(\mu^{-1}\eta(\mu)\right) + O\left(\mu^{-\frac{3}{2}}\eta^2(\mu)\right)$$

$$+\left\{P_{000}\mu^{-\frac{1}{2}} + O\left(\mu^{-\frac{3}{2}}\right)\right\}\left\{1 + O(\mu^{-1}) + O\left(\mu^{-\frac{3}{2}}\eta^2(\mu)\right)\right\}$$

$$= P_{000}\mu^{-\frac{1}{2}} - \frac{1}{2}\mu^{-1}s(\pi)\sin\left(2\mu^{\frac{1}{2}}\pi\right) + O\left(\mu^{-1}\eta(\mu)\right) \qquad (14)$$

It is clear from (14) that

$$tan^{-1}\gamma(\mu) = P_{000}\mu^{-\frac{1}{2}} - \frac{1}{2}\mu^{-1}s(\pi)\sin\left(2\mu^{\frac{1}{2}}\pi\right) + O\left(\mu^{-1}\eta(\mu)\right).$$

So,

$$\cos[tan^{-1}\gamma(\mu)] = 1 - \frac{1}{2}(P_{000})^2\mu^{-1} + \frac{1}{2}P_{000}\mu^{-3/2}s(\pi)\sin\left(2\mu^{\frac{1}{2}}\pi\right) + O\left(\mu^{-\frac{3}{2}}\eta(\mu)\right), \quad (15)$$

$$\sin[tan^{-1}\gamma(\mu)] = P_{000}\mu^{-\frac{1}{2}} - \frac{1}{2}\mu^{-1}s(\pi)\sin\left(2\mu^{\frac{1}{2}}\pi\right) + O\left(\mu^{-1}\eta(\mu)\right) \quad (16)$$

From (15)

$$\frac{P_{01}(\mu)}{\cos[tan^{-1}\gamma(\mu)]} =$$

$$= \frac{\mu^{r_{01}} + O(\mu^{r_{01}-1})}{1 - \frac{1}{2}(P_{000})^2\mu^{-1} + \frac{1}{2}P_{000}\mu^{-3/2}s(\pi)\sin\left(2\mu^{\frac{1}{2}}\pi\right) + O\left(\mu^{-\frac{3}{2}}\right)}$$

$$= \mu^{r_{01}} + O(\mu^{r_{01}-1}). \quad (17)$$

Now, we must calculate asymptotic formulae for $\int_0^x S(t,\mu)dt$ and $\int_0^x W(t,\mu)dt$ by using (7) and (8). Applying a change of order of integration and integration by parts satisfies following equalities

$$\int_0^x S(t,\mu)dt = \int_0^\pi S(t,\mu)dt - \int_x^\pi S(t,\mu)dt$$

$$= -\frac{1}{4}\mu^{-1}\{s(\pi)\left[1 - \cos\left(2\mu^{\frac{1}{2}}\pi\right)\right] - \int_0^\pi s'(t)dt + \sin\xi_0\}$$

$$+\frac{1}{4}\mu^{-1}\{s(\pi)\left[1-\cos\left[2\mu^{\frac{1}{2}}(\pi-x)\right]\right]-\int_x^{\pi}s'(t)dt$$

$$+\sin\left(2\mu^{\frac{1}{2}}x+\xi_x\right)\}+O\left(\mu^{-\frac{3}{2}}\eta^2(\mu)\right)$$

$$=\frac{1}{4}\mu^{-1}\{s(\pi)\left[\cos\left(2\mu^{\frac{1}{2}}\pi\right)-\cos\left[2\mu^{\frac{1}{2}}(\pi-x)\right]\right]+s(x)-s(0)$$

$$+\sin\left(2\mu^{\frac{1}{2}}x+\xi_x\right)-\sin\xi_0\}+O\left(\mu^{-\frac{3}{2}}\eta^2(\mu)\right) \qquad (18)$$

and

$$\int_0^x W(t,\mu)dt=\int_0^{\pi}W(t,\mu)dt-\int_x^{\pi}W(t,\mu)dt$$

$$=\mu^{\frac{1}{2}}\pi-\frac{1}{2}\mu^{-\frac{1}{2}}\left[\pi s(\pi)-\int_0^{\pi}t\,s'(t)dt\right]+\frac{1}{4}\mu^{-1}$$

$$\times\left[s(\pi)\sin\left(2\mu^{\frac{1}{2}}\pi\right)-\cos\xi_0\right]-\mu^{\frac{1}{2}}(\pi-x)$$

$$-\frac{1}{2}\mu^{-\frac{1}{2}}\left[xs(x)-\pi s(\pi)+\int_x^{\pi}t\,s'(t)dt\right]$$

$$-\tfrac{1}{4}\mu^{-1}\left[s(\pi)\sin\left[2\mu^{\frac{1}{2}}(\pi-x)\right]-\cos\left(2\mu^{\frac{1}{2}}x+\xi_x\right)\right]$$

$$+O\left(\mu^{-\frac{3}{2}}\eta^2(\mu)\right)$$

$$= \mu^{\frac{1}{2}}x - \frac{1}{2}\mu^{-\frac{1}{2}}\left[xs(x) - \int_0^x t\,s'(t)dt\right] + \frac{1}{4}\mu^{-1}$$

$$\times [\sin\left(2\mu^{\frac{1}{2}}\pi\right) - \sin\left[2\mu^{\frac{1}{2}}(\pi - x)\right] + \cos\left(2\mu^{\frac{1}{2}}x + \xi_x\right)$$

$$-\cos\xi_0] + O\left(\mu^{-\frac{3}{2}}\eta^2(\mu)\right). \quad (19)$$

From (18) we find

$$\exp\left(\int_0^x S\,(t,\mu)dt\right) = 1 + \frac{1}{4}\mu^{-1}\{s(\pi)[\cos\left(2\mu^{\frac{1}{2}}\pi\right)$$

$$-\cos\left[2\mu^{\frac{1}{2}}(\pi - x)\right]] + s(x) - s(0) + \sin\left(2\mu^{\frac{1}{2}}x + \xi_x\right) - \sin\xi_0\}$$

$$+O\left(\mu^{-\frac{3}{2}}\eta^2(\mu)\right). \quad (20)$$

and with (15), (16) and (19) it is obtained that

$$\cos\left[tan^{-1}\gamma(\mu)+\int_0^x W(t,\mu)dt\right]=\cos\left(\mu^{\frac{1}{2}}x\right)-\mu^{-\frac{1}{2}}$$

$$\times\left[P_{000}-\tfrac{1}{2}\textstyle\int_0^x s(t)dt\right]\sin\left(\mu^{\frac{1}{2}}x\right)+O\left(\mu^{-\frac{1}{2}}\eta(\mu)\right). \quad (21)$$

Finally; (17), (20) and (21) are replaced in (11) and the proof is done.

(ii) The proof is similar to part *(i)*.

In the following theorem, we seek the derivatives of $\varphi(x,\lambda)$ and $\psi(x,\lambda)$.

Theorem 3. As μ → ∞, we have

(i)

$$\varphi'(x,\mu)=-\mu^{r_{01}+\frac{1}{2}}\sin\left(\mu^{\frac{1}{2}}x\right)+\mu^{r_{01}}\{\tfrac{1}{2}\left[xs(x)-\textstyle\int_0^x t\,s'(t)dt\right]$$

$$-P_{000}\}\cos\left(\mu^{\frac{1}{2}}x\right)+O\left(\mu^{r_{01}-\frac{1}{2}}\right), \quad (22)$$

(ii)

$$\psi'(x,\mu)=\mu^{r_{11}+\frac{1}{2}}\sin\left[\mu^{\frac{1}{2}}(\pi-x)\right]+\mu^{r_{11}}\{\frac{1}{2}[xs(x)-\pi s(\pi)$$

$$+\int_x^\pi t\,s'(t)dt]-P_{100}\}\cos\left[\mu^{\frac{1}{2}}(\pi-x)\right]+O\left(\mu^{r_{11}-\frac{1}{2}}\right).$$

Proof. *(i)* The equality (5) is used for the proof. With the initial conditions (9) we have obtained the values of c_1 and c_2 as in (12) and (13). If these values are replaced in (5), it is simply derived that

$$\varphi'(x,\mu) = \frac{P_{01}(\mu)}{\cos[tan^{-1}\gamma(\mu)]}\exp\left(\int_0^x S\,(t,\mu)dt\right)\{S(x,\mu)$$

$$\times\cos\left[tan^{-1}\gamma(\mu) + \int_0^x W\,(t,\mu)dt\right]$$

$$-W(x,\mu)\sin\left[tan^{-1}\gamma(\mu) + \int_0^x W\,(t,\mu)dt\right]\}. \qquad (23)$$

We get the asymptotic approximation of (23) by using the results (15)-(19). This gives the equality (22).

The proof of *(ii)* is similar.

REFERENCES

Başkaya, E. (2018a). Asymptotics of eigenvalues for Sturm-Liouville problem including eigenparameter-dependent boundary conditions with integrable potential. New Trends in Mathematical Sciences, 6(3), 39-47.

Başkaya, E. (2018b). Asymptotics of eigenvalues for Sturm-Liouville problem including quadratic eigenvalue in the boundary condition. New Trends in Mathematical Sciences, 6(3), 76-82.

Başkaya, E. (2018c). Asymptotics of eigenvalues for Sturm-Liouville problem with eigenparameter dependent-boundary conditions. New Trends in Mathematical Sciences, 6(2), 247-257.

Baskaya, E. (2020). Periodic and semi-periodic eigenvalues of Hill's equation with symmetric double well potential. TWMS Journal of Applied and Engineering Mathematics, 10(2), 346-352.

Başkaya, E. (2021a). Asymptotic eigenvalues of regular Sturm-Liouville problems with spectral parameter-dependent boundary conditions and symmetric single well potential. Turkish Journal of Mathematics and Computer Science, 13(1), 44-50.

Başkaya, E. (2021b). On the gaps of Neumann eigenvalues for Hill's equation with symmetric double well potential. Tbilisi Mathematical Journal, 8, 139-145.

Coşkun, H., and Başkaya, E. (2010). Asymptotics of eigenvalues of regular Sturm-Liouville problems with eigenvalue parameter in the boundary condition for integrable potential. Mathematica Scandinavica, 107(2), 209-223.

Coşkun, H., and Başkaya, E. (2018). Asymptotics of eigenvalues for Sturm-Liouville problem with eigenvalue in the boundary condition for differentiable potential. Annals of Pure and Applied Mathematics, 16(1), 7-19.

Coşkun, H., Başkaya E., and Kabataş, A. (2019). Instability intervals for Hill's equation with symmetric single well potential. Ukrainian Mathematical Journal, 71(6), 977-983.

Coşkun, H., and Kabataş, A. (2013). Asymptotic approximations of eigenfunctions for regular Sturm-Liouville problems with eigenvalue parameter in the boundary condition for integrable potential, Mathematica Scandinavica, 113(1), 143-160.

Coşkun, H., and Kabataş, A. (2016). Green's function of regular Sturm-Liouville problem having eigenparameter in one boundary condition. Turkish Journal of Mathematics and Computer Sciences, 4, 1-9.

Coşkun, H., Kabataş, A., and Başkaya. E. (2017). On Green's function for boundary value problem with eigenvalue dependent quadratic boundary condition. Boundary Value Problems. Article number:71.

Freiling, G., and Yurko, V. (2010). Inverse problems for Sturm-Liouville equations with boundary conditions polynomially dependent on the spectral parameter. Inverse Problems, 26.

Harris, B. (1997). The form of the spectral functions associated with Sturm-Liouville problems with continuous spectrum. Mathematika, 44(1), 149-161.

Kabataş, A. (2022a). Eigenfunction and Green's function asymptotics for Hill's equation with symmetric single well potential. Ukrainian Mathematical Journal, 74(2), 218-231.

Kabataş, A. (2022b). On eigenfunctions of Hill's equation with symmetric double well potential. Communications Faculty of Sciences University of Ankara Series A1 Mathematics and Statistics, 71(3), 634-649.

Kabataş, A. (2023a). One boundary value problem including a spectral parameter in all boundary conditions. Opuscula Mathematica, 43(5), 651-661.

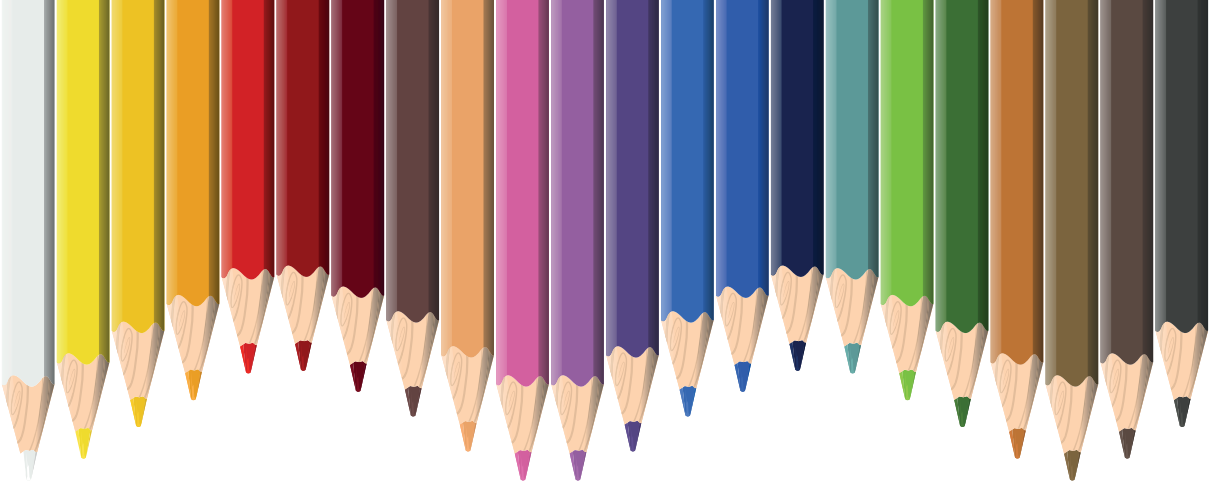
Kabataş, A. (2023b). Sturm-Liouville problems with polynomially eigenparameter dependent boundary conditions. Sakarya University Journal of Science, 27 (6), 1212-1219.

Levitan, B. M. (1987). Inverse Sturm-Liouville Problems. Utrecht : VNU Science Press.

Marchenko, V. A. (1977). Sturm-Liouville Operators and Their Applications. Kiev: Naukova Dumka.

Pöschel, J., and Trubowitz, E. (1987). Inverse Spectral Theory. New York: Academic Press.

Zhang, H. Y., Ao, J. J., and Li, M. L. (2022). Dependence of Eigenvalues of Sturm-Liouville Problems with Eigenparameter-Dependent Boundary Conditions and Interface Conditions. Mediterranean Journal of Mathematics, 19.



Chapter 2

METHODS FOR THE DETERMINATION OF SUCCINYLACETONENYLACETONE*

S. Meral KARACAN[1]
Behice Yavuz ERDOĞAN[2]
A.NUR ONAR[3]

1 Public Health Laboratory, Samsun,Türkiye, ORCID ID: 0000-0001-6060-3231
2 Ondokuz Mayıs University,Technical Vocational School Of Higher Education, Department of Food Technology Programmes, Samsun, Türkiye, ORCID ID: 0000-0003-4375-4323
3 Ondokuz Mayıs University, Faculty of Science, Department of Chemistry, Samsun, Türkiye, ORCID ID: 0000-0001-8984-7758.
* A large part of this study is based on the PhD thesis titled "Development of a capillary electrophoretic quantification method for succinyl acetone and investigation of its electrochemical behavior" supported by OMU Project No. F-445.(Samsun - 2010)
Phd: Dr. S. Meral KARACAN Süpervisor: Prof.Dr. A. Nur ONAR

Introduction

Approximately 4% of babies are born with a genetic disorder. This rate reaches 8-15% with the problems that occur in later ages. Today, approximately 30% of patients who apply to pediatric centers are examined due to a genetic disease. Most genetic diseases are diseases for which there is no cure yet. Every person is at risk of a certain genetic disease. However, in some families this risk is higher. With the help of genetic counselors, the risks of genetic diseases that will occur in individuals and their children to be born can be determined. Along with genetic counseling, genetic diagnostic methods developed play an important role in the diagnosis of these diseases (http://www.genetikbilimi.com/prenantal.htm). Today, it is known that early diagnosis of genetic diseases is extremely important. Early diagnosis can prevent the occurrence of defects and prolong and improve the quality of life in incurable diseas.

Thyrosinemia type I is characterized by progressive hepatic, renal and neurological disease. If left untreated, there is a high mortality rate in childhood due to porphyria-like syndrome with liver failure, recurrent bleeding, hepatocellular carcinoma and respiratory failure (Shinka et al., 2005).

Thyrosinemia type I is characterized by progressive hepatic, renal and neurological disease (Lindblad B 1977, Chris Stinton 2017). Untreated, there is a high mortality rate in childhood due to porphyria-like syndrome with liver failure leading to liver transplantation, recurrent bleeding, hepatocellular carcinoma and respiratory failure (Van Spronsen FJ, 1994, shinka et al., 2005). Tyrosinemia type I is caused by the absence of the enzyme fumarylacetoacetase hydrolase (FAH), which is essential for the metabolism of the amino acid tyrosine(Lindblad B et all., 1977). FAH deficiency leads to the accumulation of the metabolites fumarylacetoacetate and maleylacetate. Together these two substances form succinylacetone. Succinylacetone (SA,4,6 dioxoheptanoic acid) is not found in normal body fluids, but the presence of succinylacetone in blood and urine is a sign of thyrosinemia (Cansever et al., 2005).

Genetic or various metabolic disorders can be detected by monitoring amino acids or other organic acids in biological fluids such as plasma, urine or amniotic fluid. Amniotic fluid helps protect the fetus and plays an important role in the development of fetal organs, including the liver, kidneys, stomach and intestine. If there is an abnormality in fetal development or if the age of the pregnant woman is over thirty-five years, the amniotic fluid is biochemically investigated (Tuma et al., 2006). The prevalence of trisonamine type 1 is approximately 1 in 100,000 people worldwide, but is higher in countries such as Turkey, Canada and India (Couce et all,2019).

Most of the methods developed for the determination of tyrosinemia type I are chromatographic methods. In chromatographic methods, mass spectrometry has been most commonly used as a detector. The most important drawback of both chromatographic and mass spectrophotometric methods is their high cost. In addition, in mass spectrophotometric methods, the internal standard that must be used for analysis must be an isotope suitable for the substance being analyzed. In addition, in chromatographic methods, the excessive amount of pre-treatments to be applied to the sample before analysis, the volatility problem especially in gas chromatography, the large volumes of chemicals used and the longtime of analysis are the features that negatively affect the preference of these methods.

This study focuses on the diagnostic methods developed to identify succinylacetone (SA,4,6 dioxoheptanoic acid), the causative agent of thyrosinemia type 1, a genetic metabolic disorder.

2.General Information

2.1. Amniotic Fluid Analysis

Amniotic fluids can be analyzed directly by dilution or after extraction. Nelson et al. (1999) developed a capillary electrophoretic method for the determination of oxalate in amniotic fluid. Indirect absorbance determination of oxalate was achieved with a ground electrolyte based on chromate modified with ethylenediaminotetetraacetic acid (EDTA). Since the high level of inorganic chloride (about 4mg/mL) interfered with the determination, they passed the sample through a cation resin (Ag+). Interference of amniotic fluid proteins in separation was avoided by using a simple water-based dilution system. This method improved the analytical retrievability of oxalate added to amniotic fluid by 96% (Nelson et al, 1999). Examples of studies on the extraction of amniotic fluid are available in the literature. For example, Cyr et al. (2006) used a liquid-liquid extraction method to extract succinylacetone from amniotic fluid.

In this method, they added 13C5-succinylacetone as an internal standard into 1mL of amniotic fluid and added H_2SO_4 and o-(2,3,4,5,6 pentafluorabenzyl)hydroxylamine hydrochloride (PFBHA) into the amniotic fluid to form oxime at room temperature. They adjusted the pH to 1 with hydrochloric acid and saturated the amniotic fluid with sodium chloride. In the last step, they rapidly shook and extracted the acidified sample with ethyl acetate and diethyl ether (Cyr et al., 2006).

Nemutlu et al. (2009) used solid phase extraction method to extract seven cephalosporins in amniotic fluid. They chose Strata X, a polymeric resin, for the extraction process. They recovered sephalosporins from Strata X in acidic

environment with methyl alcohol (Nemutlu et al., 2009).

2.2. Tyrosinemia

Tyrosine is an amino acid found in many plant and animal proteins and is mainly broken down in the liver. Tyrosinemia is a group of autosomal recessive disorders of tyrosine metabolism.

Within this group

*transient tyrosinemia

*tyrosinemia type I

* tyrosinemia type II

* includes tyrosinemia type III.

Transient tyrosinemia occurs in neonates when the enzyme 4-hydroxyphenylpyruvate dioxygenase does not mature physiologically. Tyrosinemia type I occurs in the absence of fumarylacetoacetase hydrolase, Tyrosinemia type II in the absence of tyrosine aminotransferase and Tyrosinemia type III in the absence of 4-hydroxyphenylpyruvate dioxygenase. These can be identified by monitoring newborns, as tyrosine levels are increased in each of them.

Tyrosinemia type II, also known as Richner-Hanhart Syndrome, is an autosomal recessive disorder of tyrosine metabolism in the blood. The occurrence rate is less than 1 in 250,000. It was first described in a family in which eight members had palmoplantar keratosis and recurrent keratitis.

Thyrosinemia type III is characterized by acute intermittent loss of muscle coordination, seizures, stupor and mild impairment of mental activity, with normal liver function.

Thyrosinemia type I can occur in an acute or chronic form, depending on the amount of the FAH enzyme. The acute form, which is more severe, can cause symptoms such as failure to thrive, vomiting, diarrhea, fever, jaundice, edema, enlarged liver, and the acute form can cause progressive liver disease that can lead to death in the first year of life. The chronic form is similar, but chronic disease and Fanconi syndrome have milder features. Other distinguishing features are hypertrophic obstructive cardiomyopathy, abdominal crisis, hypertension, palineuropathy and hepatoma (Macsai et al, 2001).

When a baby is diagnosed with tyrosinemia type I, the first thing to do is to limit the amount of tyrosine and phenylalanine amino acids given. For

this, there are special infant prescriptions to meet the needs of babies. The use of 2-(2-nitro - 4 - trifluoromethylbenzoyl) - 1, 3 cyclohexadione (NTCB), a substance that reduces the toxic effect of tyrosine in the body, in combination with the diet has been shown to reduce the symptoms of tyrosinemia type I, resulting in healthy and normal growth of children. NTCB greatly reduces the levels of succinylacetone, maleylacetoacetate and fumarylacetoacetate in biological fluids. In the past, a child with tyrosinemia type I would definitely need a liver transplant. Today, liver transplantation greatly reduces the levels of succinylacetone, maleylacetoacetate and fumarylacetoacetate in NTBC biological fluids. In the past, a child with tyrosinemia type I would definitely need a liver transplant.Today, liver transplantation is only performed in cases of cancer or severe liver damage thanks to NTBC (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=276700). Figure 1 shows the tyrosine degradation pathway and the effect of the healing agent NTBC.

In tyrosinemia type I, increased levels of succinylacetone (Figure 2) and nonspecific amino acids in urine are observed. Confirmation of the diagnosis of tyrosinemia type I requires measurement of FAH activity in tissue. Fibroblasts, erythrocytes, lymphocytes or liver tissue are used as tissue. Thyrosinemia type II is characterized only by an increased amount of tyrosine in the urine and blood. If tyrosinemia type III is present, urinary organic acids, 4-hydroxyphenyllactate, 4-hydroxyphenylacetate and 4-hydroxyphenylpyruvate are increased. Low activity of 4-hydroxyphenylpyruvate deoxygenase can be demonstrated in liver and kidney biopsy specimens (Mascai et al., 2001).

2.3.Diagnostic Methods for Thyrosinemia Type I

As a result of the literature searches, it has been observed that the diagnosis of Thyrosinemia TypeI in newborns can be made by measuring the enzyme activity or by determining the amount of Succinylacetone. These studies are summarized below.

2.3.1.Methods for Measuring Enzyme Activity

The diagnosis of tyrosinemia TypeI can be made by measuring the activity of the enzyme fumarylacetoacetase in various tissues. It has been shown that fumarylacetoacetase can be measured in several tissues, and by measuring enzyme activity in lymphocytes and fibroblasts, homozygotes can be distinguished from heterozygotes and non-carriers.

Successful prenatal diagnosis has been shown to be made by analysis of cured amniotic fluid cells from amniocentesis at sixteenth and twentieth week of pregnancy (Kvittingen et al., 1985).

Holme et al. (1985) determined fumarylacetoacetase activity in umbilical cord and erythrocytes. Their findings are clinically important. This assay can be performed without cell culture and the results should be obtained within a day or two after taking the biopsy because of the possibility of premature termination of the diseased pregnancy. Holme et al. (1985) observed that the fumarylacetoacetase activity present in normal erythrocytes facilitates the rapid diagnosis of genetic tyrosinemia and the identification of heterozygotes. This allows for enzyme replacement therapy by blood transfusion. Replacement of 10-20% of erythrocytes with normal erythrocytes probably provides the patient with enough enzyme to break down all of the fumarylacetoacetate formed from tyrosine (Holme et al., 1985).

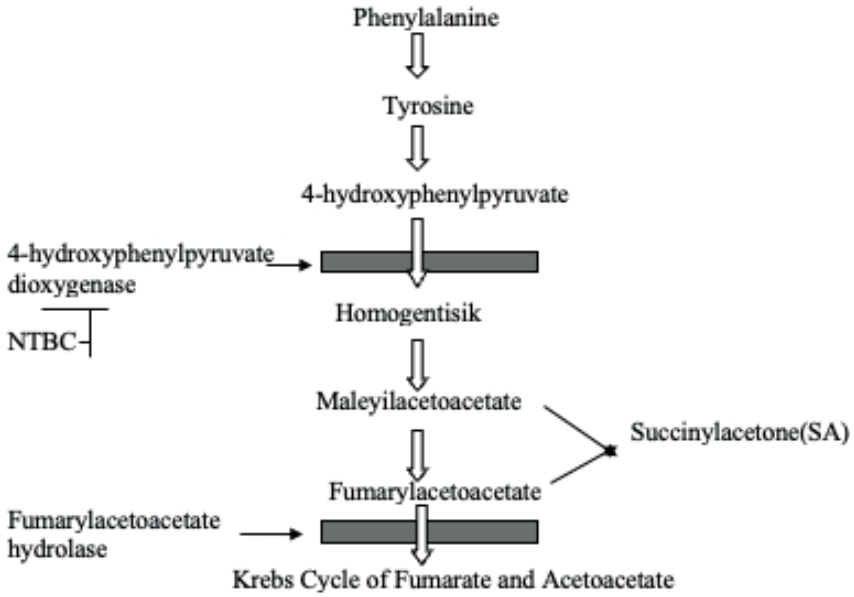


Figure 1. *Tyrosine degradation pathway and the effect of the healing agent 2-(2-nitro-4itrifluoromethylbenzoyl)-1,3-cyclohexadiene (NTBC) (Cry et al., 2006).*

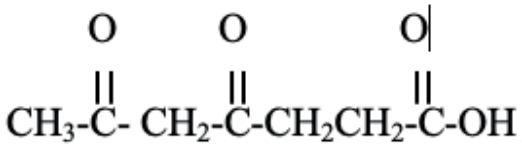


Figure 2. *Chemical Structure of succinylacetone.*

2.3.2. Determination of Succinylacetate Amount

The quantification of succinylacetone for the diagnosis of tyrosinemia type I was performed using spectroscopic (Lian-shu et all), chromatographic and capillary electrophoretic techniques (Cry et al., 2006).

Chromatographic methods are routinely available for the determination of living components and components that may be present in the living body. Several chromatographic methods have been developed for tyrosinemia type I. These are Gas chromatography (GC) and Liquid chromatography (LC) techniques. Many clinical laboratories use gas chromatography/ mass spectrometry (GC/MS) to determine succinylacetone in urine and serum. Gas chromatography is a very efficient technique for the analysis of various compounds. The mixture of compounds in a biological fluid is first separated chromatographically and then identified in a mass spectrometer. The drawback of this technique is that it requires a long time for sample pre-treatment, derivatization and analysis.

2.3.2.1. Diagnostic Methods by Tandem Mass Spectrometry

In a total of 190 patients with suspected tyrosinemia, tandem mass spectrometry was used to measure succinylacetone levels in the blood. Eleven patients, nine males and two females, aged between 2 months and 6 years, were diagnosed with tyrosinemia type 1. Succinylacetone levels in the blood of the patients were significantly increased (7.26-31.09 μmol/L), with a mean of (14.2 ± 7.8) μmol/L (Lian-shu Han et all,2012).

A method based on the quantification of succinylacetone in dried blood spots by ultra-performance liquid chromatography tandem mass spectrometry was developed and studied. Succinylacetone extracted from a single 3/16-inch sample collection paper disk containing dried bloodstain was derivatized, separated on an Acquity UPLC BEH C(18) column (2.1 x 50 mm, 1.7 microm) and detected by electrospray ionization tandem mass spectrometry. The succinylacetone derivative eluted in 0.6 min and the full run time was 1 min. The calibration plot was linear up to 100 micromol/L and the limit of detection (S/N = 3) was 0.2 micromol/L. Intra-day (n = 13) and inter-day (n = 10) variations were better than 10%. With the present method, the succinylacetone cut-off level in dried blood spots from healthy infants was 0.63 micromol/L (n = 151). The succinylacetone concentration in dried blood spots from patients with tyrosinemia type 1 (n = 11) was 6.4-30.8 micromol/L(Osama Y Al-Dirbashi et all,).

Flow injection electrospray ionization tandem mass spectrometric method for succinylacetone (SA) was studied in 250 microL of urine using d5-SA as internal standard and in 3 mm dried blood spots using 13C4-SA as

internal standard. The selectivity and sensitivity of the analysis was ensured by a mono-Girard T derivative. The normal range of measured SA in infant urine (n=20) is 0.013-0.27 micromol/mmol creatinine. The normal range of measured SA neonatal blood spot (n=152) is 0-0.30 micromol/L. Blood spots from children with hepatorenal tyrosinemia type 1 and kept at room temperature for up to 7 years yielded SA concentrations of 0.9-5.7 micromol/L. (Johnson et all,2007)

2.3.2.2. Diagnostic Methods by Gas Chromatography/Mass Spectrometry (GC/MS)

In a GC/MS study, Cry et al. (2006) developed a reliable method for the determination of succinylacetone in nanomolar quantities in amniotic fluid and plasma. 13C5-Succinylacetone was used as internal standard and the study consisted of a three-step sample treatment process consisting of oximation, solvent extraction and trimethylchlorosilane (TMCS) derivatization. In addition to metabolite stability, the ion intensity (m/z) for succinylacetone was recorded at 620 and the ion intensity (m/z) for the internal standard at 625. The precision of the measurements, the linearity of the method, the lower limit of detection (LOD), the lower limit of quantification (LOQ) for succinylacetone and the recorded ion intensities (m/z) of the internal standard made this analysis valid. The method NTNC yield was used to quantify succinylacetone in the patient's plasma and in the amniotic fluid sample of the affected fetus. The results showed that the GC/MS method can be a valuable tool for metabolic evaluation and clinical uses (Cry et al., 2006).

In another study, Shinka et al. (2005) showed that 5-aminolevulinate (5ALA) accumulated due to the inhibition of porphyrin synthesis by succinylacetone can also be used for the identification of metabolites. Succinylacetone is a potent activity inhibitor of 5-aminolevulinate dehydratase. The accumulation of succinylacetone causes an increase in 5-aminolevulinate (5-ALA) in the body, which is why 5-ALA is found in large amounts in the urine of a patient with tyrosinemia type I. Neotanal monitoring of birth defects of metabolism is performed using blood or urine dried filter paper. The use of dried urine paper is difficult for the diagnosis of tyrosinemia type I because succinylacetone can degrade on filter paper during storage and transit. In this study, the stability of 5-ALA, another diagnostic marker of tyrosinemia type I, on filter papers was studied. They observed that while 10% of the original level of succinylacetone was recovered after two weeks at room temperature, more than 80% of 5-ALA was recovered. Therefore, despite the insufficient recoverability of succinylacetone from dried urine filter papers for the diagnosis of Thyrosinemia type I, 5-ALA was readily detected, allowing diagnosis (Shinka et al., 2005).

Cerda et al. (2008) were granted a patent by the United States for their work to determine succinylacetone. The patent work concerns the measurement and/or determination of succinylacetone and one or more added biological analytes. The method involves derivatizing succinylacetone by interacting the sample with an extraction solution containing a 1-3 carbon alcohol (methyl alcohol, ethyl alcohol) and a strong base (hydrazine, aryl hydrazine). The derivatized succinylacetone in the sample is then analyzed by GC-MS. The derivatized form of succinylacetone is 3-(5-methyl-1H-pyrazal-3-yl)pyropionic acid. Cerda et al. (2008) also measured and/or determined succinylacetone using an esterification reagent. Accordingly, they derivatized succinylacetone solution and evaporated it to dryness, then esterification reagent was added to the sample to form the ester of succinylacetone at different times and temperatures. As esterification reagent; 3N hydrochloric acid and butyl alcohol as well as 1N hydrochloric acid and methyl alcohol (Cerda et al., 2008).

2.3.2.3. Liquid Chromatography/Mass Spectrometry (LC/MS-MS) Diagnostic Method

Magera et al. (2006) determined the amount of succinylacetone in dried blood drops by tandem mass spectrometry/liquid chromatography. In this method, the dried blood drop is an aqueous solution containing succinylacetone labeled with deuterium as an internal standard. Succinylacetone and the internal standard, after oxidation and solubilization, were combined and analyzed by LC/MS-MS. The ion intensities (m/z) for succinylacetone were (m/z) 212-156 and for the internal standard were (m/z) 214-140. The analysis time is five minutes. They found a significant reduction in the number of positive error results in the monitoring of newborns with this method and showed that this method can also be used in laboratories monitoring patients intervened for tyrosinemia type I (Magera et al., 2006).

2.3.2.4. Diagnosis Method by Capillary Electrophoresis

Capillary electrophoretic techniques have become the preferred techniques due to their many advantages and recent developments in this field.

Cansever et al. (2005) developed a capillary electrophoretic method for the rapid determination of succinylacetone in urine samples. Separation was achieved by inverted polarity using a capillary coated with a positively charged polyelectrolyte as well as by adding a cationic surfactant to the buffer. Under these conditions, urine samples were injected directly into the capillary without any pretreatment. They demonstrated the applicability of the method by determining succinylacetone in the urine of patients with genetic tyrosinemia type I. Diagnostic peaks at expected migration times were determined for all patients (Cansever et al., 2005).

Conclusion

Succinylacetone is a genetic disease marker and its early diagnosis is extremely important. In this article, the methods developed for the determination of Succinylacetone and the studies carried out are presented and the importance of early diagnosis and treatment of hereditary diseases is emphasized once again and it is aimed to contribute to the studies to be carried out in this way.

REFERENCESS

Al-Dirbashi, O.Y., Rashed, M.S., Jacob, M., Al-Ahaideb, L.Y., Al-Amoudi, M., Rahbeeni, Z., Al- Sayed, M.M., Al-Hassnan, Z., Al-Owain, M., Al-Zeidan, H. (2008). Improved method method to determine succinylacetone in dried blood spots for diagnosos of trosinemia type 1 using UPLC-MS/MS. Biomed Chromatogr. Nov;22(11):1181-1185.

Cansever, M.Ş., Erim, F.B. (2005): Determination of urinary succinyacetone by capillary elecropho-resis for the diagnosis of tyrosinemia type I. Journal of Chromatography B 818: 309-311.

Cerda, B., Cherkasskiy, A., Li, Y. (2008): United states Patent Application Publication, Pub. No. US2008/0274563 A1.

Chris, S., Julia, G., Karoline, F., Aileen, C., Samantha, J., Hannah, F., Paul, S., and Sian Taylor-P.

(2017).Newborn screening for Tyrosinemia type 1 using succinylacetone – a systematic re-view of test accuracy.Orphanet J Rare Dis. 12: 48.

Couce, M. L., Sánchez-Pintos, P. , Aldámiz-Echevarría, L. , Vitoria, I. , Navas, V. , Martín-Hernández, E., García-Volpe, C. , Pintos G. , Peña-Quintana, L., Hernández, T., , Gil, D., Sánchez-Valverde, F., Bueno, M., Roca, I. , López-Ruzafa, E. and Díaz-Fernández, C. (2019). Evolution of tyrosinemia type 1 disease in patients treated with nitisinone in Spain. Medicine Baltimore 98(39).

Cry D., Giguére R., Vilain G., Lemieux B., Drouin R. (2006): A GC/MS validated method for the nanomolar range determination of succinyacetone in amniotic fluid and plasma: An analytical tool for tyrosinemia type I. Journal of Chromatography B 832: 24-29.

De Laet, C., Dionisi-Vici, C., Leonard, J.V., McKiernan, P., Mitchell, G., Monti, L., De Baulny, H.O., Pintos-Morell, G., Spiekerkoetter,U.(2013). Recommendations for the management of tyrosinaemia type 1. Orphanet Journal of Rare Diseases. Biomedcentral.com.article 1750-1172. 8.

http://www.genetikbilimi.com/genbilim/prenantal.htm(2010).

http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=276700(2010).

Holme, E., Lindblad, B., Lindstedt, S.(1985). Possibilities for treatment and for early prenatal diag-nosis of hereditary tyrosinemia. Lancet 1 (8427):527.

Hinka, T., Ohse, M., Inoue, Y., Kuhara, T. (2005). Stability of 5-aminoevulinic acid on dried urine filter paper for a dignostic marker of tyrosinemia type I. Journal of Chromatography B 823:44–46.

Johnson, D. W., Gerace, R., Ranieri E., Trinh, M. , Fingerhut, R.(2007). Analysis of succinylaceto-ne, as a Girard T derivative, in urine and dried bloodspots by flow injection electrospray ioni-zation tandem mass spectrometry. Rapid Commun Mass Spectrom 21(1):59-63.

Kvittingen, E.A., Steinmann, B., Gitzelmann, R., Leonard ,J.V., Andria, G., Børresen, A.L., Moss-man, J., Micara, G., Lindblad, B. (1985). Prenatal diagnosis of hereditary tyrosinemia by de-termination of fumarylacetoacetase in cultured amniotic fluid cells. Pediatr Res. Apr;19(4):334-337.

Lian-shu, H., Jun, Y., Wen-juan, Q, Hui-wen, Z., Yu, W., Wen-jun, J, Xiao-lan, G., Xiao-yan, L., Jing, J., Xue-fan, G.(2012). Application of succinylacetone levels measurement in the blood and urine in the diagnosis of tyrosinemia type 1. Zhonghua Er Ke Za Zhi 2012 Feb;50(2):126-30.

Macsaı, M. S., Schwartz, T.L., Hınkle, D., Hummel, M. B., Mulhern, M. G., ve Rootman, D. (2001). Tyrosinemia Type II: Nine Cases of Ocular Signs and Symptoms 132: 522-527.

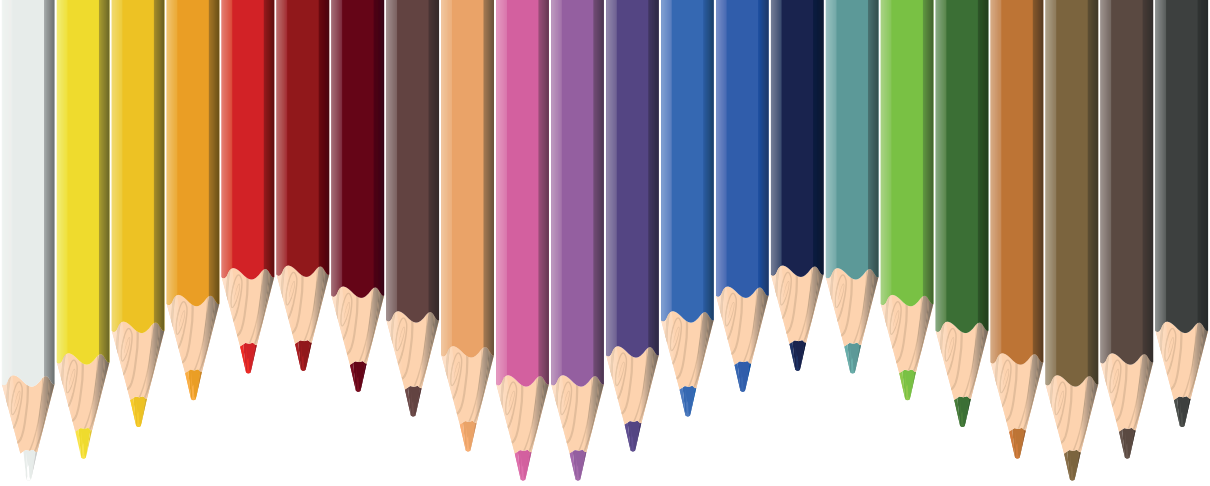
Magera, M.J., Gunawardena, N. D., Hahn, S. H., Tortorelli S., Mitchell, G.A., Goodman, S. I., Ri-naldo, P., Matern, D. (2006). Molecular Genetics and Metabolism 88: 16-21.

Nelson, B. C. , Rockwell, G.F., Campfield, T., O'Grady, P., Hernandez, R. M., Wise, S. A. (2000). Capillary electrophoretic determination of oxalate in amniotic fluid. Analytica Chimica Acta 410: 1-10.

Nemutlu, E., Kır, S., Katlan, D., Bekşaç, M.S. (2009). Simultaneous Multiresponse optimization of an HPLC Method to separate seven Cephalosporins in plasma and amniotic fluid: Aplication to validation and quantification of cefepime, cefixim and cefoperazone. Talanta 80(1):117-26.

Tuma, P., Samcova, E., Andelova, K. (2006). Determination of free amino acids and related compo-unds in amniotic fluid by capillary electrophoresis with contactless conductivity detection. Jo-urnal of Chromatography B 839:12-18.

Van Spronsen, F.J., Thomasse, Y., Smit,G.P.A., Leonard, J.V., Clayton, P.T., Fidler,V., Berger,R., Heymans, H.S.A.(1994). Hereditary tyrosinemia type 1: a new clinical classification with dif-ference in prognosis on dietary treatment. Hepatology; 20(5):1187–1191.



Chapter 3

NOVEL CHEMICAL SYNTHESIS APPROACHES FOR OPIOID RECEPTOR MODULATION

Ebrar Nur ÖZKAN[1]

1 Atatürk University, Department of Chemistry, Faculty of Natural Sciences, Architecture and Engineering, Erzurum, Turkey

1. Introduction

Opioids are receptors that play a vital role in various medical applications critical to human health. These receptors are central in the management of pain, anesthesia during surgical procedures, and relief for cancer patients, among other treatment options. However, the use of opioids has also been associated with significant issues such as severe side effects, addiction, and the risk of misuse. Consequently, the development of new drugs targeting opioid receptors and the improvement of existing treatments have become top priorities for the medical community.

This article focuses on examining opioid receptor modulation and discusses novel chemical synthesis approaches in this context. The effectiveness and safety of drugs targeting opioid receptors have been the subject of research for many years. The addictive potential and side effects of current opioid drugs have defined the limits of their usage.

In this context, recent advancements in chemical synthesis have made it possible to explore new approaches to opioid receptor modulation. These approaches encompass a variety of methods, ranging from molecular-level structural modifications to a better understanding of receptor structures and high-throughput screening techniques. This article will delve into the details of these new approaches and evaluate their potential contributions to the development of drugs targeting opioid receptors.

Opioid receptor modulation holds the potential to offer improved treatment options for medical issues such as pain management, addiction management, and neuropathic pain. Therefore, the significance of novel chemical synthesis approaches and drug development strategies in this field is steadily increasing. This article aims to shed light on this crucial subject and contribute to the future development of drugs targeting opioid receptors.

The opioid crisis, marked by a surge in opioid-related deaths and addiction rates, has underscored the urgency of finding safer and more effective alternatives to current opioid medications.

The adverse effects and potential for misuse associated with traditional opioids have prompted researchers and pharmaceutical companies to explore innovative solutions to address these challenges.

One promising avenue in this pursuit is the development of novel chemical synthesis approaches aimed at fine-tuning the interaction between opioid receptors and pharmacological agents. These approaches not only seek to enhance the analgesic properties of opioids but also aim to mitigate their addictive potential and side effects. Achieving this delicate balance between

pain relief and safety has become a paramount objective in opioid research.

Moreover, the advent of cutting-edge technologies, including computational modeling and structural biology, has provided researchers with unprecedented insights into the three-dimensional structures of opioid receptors.

This newfound knowledge allows for more precise drug design, increasing the likelihood of creating compounds that selectively target specific receptor subtypes while minimizing off-target effects.

In this article, we will delve into the recent breakthroughs and innovative strategies in chemical synthesis that have paved the way for the development of next-generation opioid medications. We will explore the mechanisms behind these novel approaches, the structural insights driving them, and their potential applications in clinical settings. By doing so, we hope to highlight the transformative potential of these advancements in opioid receptor modulation, offering a glimmer of hope in the ongoing battle against pain and addiction while promoting patient well-being and safety.

2. Opioid Peptides

The discovery narrative of opioid peptides commenced with the initial belief in the presence of morphine-like substances in the brain [3]. The first discovered opioid peptide, dynorphin, was identified by Goldstein and colleagues [4]. Enkephalins, the first described endogenous opioid peptides, were characterized in 1975 by Hughes and Kosterlitz [5]. Due to their locations within the central nervous system, endogenous opioids can function as neurotransmitters. Furthermore, they also play roles in hormone secretion and thermoregulation [1].

1.1. Endogenous Opioid-Cell Membrane Interaction

Endogenous opioids, such as enkephalins and dynorphins, engage in intricate interactions with cell membranes, particularly within the central nervous system. These interactions play a pivotal role in modulating neurotransmission and regulating various physiological processes [6].

Endogenous opioids, being peptide molecules, possess specific binding sites on the surface of neuronal cell membranes. These binding sites are integral components of opioid receptors, namely mu (μ), delta (δ), and kappa (κ) receptors, which are abundantly distributed throughout the nervous system. When endogenous opioid peptides bind to their corresponding receptors on the cell membrane, a cascade of events is initiated [7].

This interaction results in the inhibition of adenylate cyclase, which in

turn reduces the production of cyclic AMP (cAMP), a critical secondary messenger in many intracellular signaling pathways. Consequently, neuronal excitability decreases, leading to the suppression of pain signals and the modulation of mood and emotion [8].

Furthermore, endogenous opioids also influence the release of neurotransmitters, including gamma-aminobutyric acid (GABA) and glutamate, which are vital for the regulation of neuronal activity and synaptic transmission. This modulation of neurotransmitter release contributes to the overall effects of endogenous opioids on pain perception and emotional responses [9].

2.2. Opioid Receptors

There are three primary families of opioid receptors, namely mu (μ), kappa (κ), and delta (δ) receptors, with their highest concentrations found in the central nervous system. Additionally, these receptors are distributed in peripheral organs such as the gastrointestinal system, reproductive system, heart, lungs, and liver [7]. In healthy individuals, these receptors are activated by endogenous peptides produced in response to various stimuli. Notable endogenous peptides include endorphins, enkephalins, and dynorphins. Opioid receptors are typically denoted by Greek letters [10,11].

2.2.1. Mu (μ) Receptor

The mu (μ) opioid receptor is a pivotal component of the opioid receptor family and plays a substantial role in mediating the effects of opioids. These receptors are predominantly found within the central nervous system, especially in regions associated with pain perception and reward, such as the brainstem, thalamus, and limbic system. However, they are not limited to the central nervous system and are also distributed in peripheral tissues, including the gastrointestinal tract and immune cells [12].

Activation of mu receptors by endogenous peptides like endorphins and exogenous opioid drugs leads to a cascade of intracellular events. Upon activation, mu receptors inhibit adenylate cyclase, reducing the production of cyclic AMP (cAMP), a key secondary messenger in signal transduction pathways. This reduction in cAMP levels ultimately diminishes neuronal excitability, resulting in the suppression of pain signals and alterations in mood and emotional responses [13].

The mu receptor's significance extends to its role in pain management. Activation of mu receptors lead to potent analgesia, making it a primary target for opioids used in clinical pain relief. However, this activation also carries the risk of side effects such as respiratory depression, constipation,

and the potential for addiction.

Understanding the mu receptor's intricate mechanisms is crucial in the development of novel chemical synthesis approaches aimed at modulating its function. Such approaches aim to harness the receptor's analgesic properties while minimizing its adverse effects, offering the potential for more effective and safer pain management strategies [14].

2.2.2. Kappa (κ) Receptor

The kappa (κ) opioid receptor is another essential member of the opioid receptor family, distinct from the mu (μ) receptor, and it plays a significant role in the modulation of pain perception and various physiological processes. Kappa receptors are widely distributed throughout the central nervous system, with notable concentrations in regions associated with pain processing, mood regulation, and stress responses.

Activation of kappa receptors occurs in response to endogenous peptides like dynorphins and certain exogenous opioid drugs. When these receptors are engaged, they initiate a series of intracellular events, including the inhibition of adenylate cyclase and subsequent reductions in cyclic AMP (cAMP) levels. This leads to decreased neuronal excitability and contributes to the modulation of pain signals, as well as mood regulation.

One distinguishing feature of kappa receptors is their involvement in the regulation of the stress response. Activation of these receptors have been linked to dysphoria and sedation, which are in contrast to the euphoria often associated with mu receptor activation. This aspect of kappa receptor function has generated interest in developing novel therapeutic agents for mood disorders and stress-related conditions [15].

Additionally, kappa receptors are associated with the potential for less addictive and analgesic tolerance-forming effects compared to mu receptors, making them a promising target for the development of opioid medications with reduced abuse potential. Understanding the intricate workings of the kappa (κ) opioid receptor is vital for developing innovative chemical synthesis approaches aimed at modulating its function. Such approaches have the potential to offer new strategies for pain management and mood disorder treatment, potentially reducing the adverse effects and addictive potential associated with traditional opioid medications [16].

2.2.3. Delta (δ) Receptor

The delta (δ) opioid receptor is a fundamental member of the opioid receptor family, distinct from both the mu (μ) and kappa (κ) receptors, and it contributes significantly to the complex landscape of opioid signaling. Delta

receptors are widely distributed throughout the central nervous system, with notable concentrations in areas associated with pain perception, emotional responses, and cognitive processes [17].

Activation of delta receptors primarily occurs in response to endogenous opioid peptides, including enkephalins. When these receptors are engaged, they initiate a series of intracellular events, which include the inhibition of adenylate cyclase and subsequent reductions in cyclic AMP (cAMP) levels. This reduction in cAMP levels leads to a decrease in neuronal excitability, contributing to the modulation of pain signals and the regulation of mood and emotions [18].

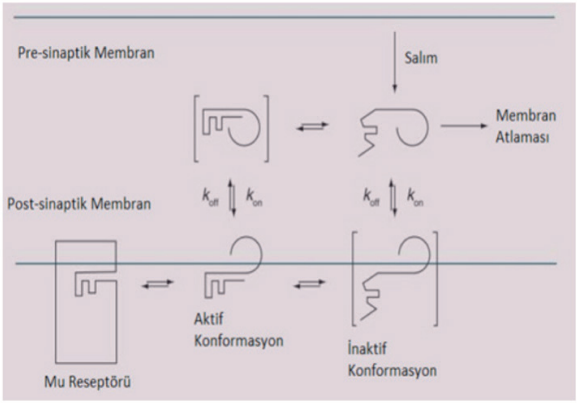


Fig1.*Schwyzer's Membrane Compartment model is used with permission from [6].*

One remarkable aspect of delta receptors is their role in both analgesia and mood regulation. Delta receptor activation has been linked to the modulation of emotional responses and the potential alleviation of depressive symptoms. This dual function makes delta receptors an intriguing target for research into novel chemical synthesis approaches for pain management and mood disorders. Furthermore, delta receptors are associated with a lower risk of addiction and tolerance development compared to mu receptors. This characteristic raises the possibility of developing opioid medications with reduced abuse potential by selectively targeting delta receptors. Understanding the intricate mechanisms of delta (δ) opioid receptors is crucial for the development of innovative chemical synthesis approaches aimed at modulating their function. These approaches hold the potential to provide alternative strategies for pain relief and mood disorder treatment, potentially minimizing the side effects and addictive potential associated with traditional opioid medications [19].

In summary, the delta (δ) opioid receptor is a vital member of the opioid receptor family, with widespread distribution in the central nervous system. Its functions encompass pain modulation, mood regulation, and cognitive

processes, making it a compelling target for research into novel chemical synthesis approaches for pain management and mood disorder treatment [20].

2.2.4. Sigma (σ) Receptor

The sigma (σ) receptor is a distinct class of receptors in the opioid receptor family, although it differs from the classic mu (μ), kappa (κ), and delta (δ) opioid receptors. While historically considered part of the opioid receptor family, recent research has revealed significant differences in their pharmacological and functional properties [37].

Sigma receptors are primarily divided into two subtypes: sigma-1 (σ1) and sigma-2 (σ2) receptors. These receptors are distributed throughout various tissues in the body, including the central nervous system, where they are involved in modulating neural signaling [20,21].

Unlike traditional opioid receptors, sigma receptors are not activated by endogenous opioid peptides or conventional opioid drugs like morphine or oxycodone. Instead, they interact with a diverse array of ligands, including various drugs, neurosteroids, and other compounds. This wide ligand-binding profile has led to investigations into the sigma receptors' role in various physiological processes, including mood regulation, cognitive function, and neuroprotection [22].

Sigma-1 receptors have gained attention for their involvement in cellular stress responses, calcium signaling, and the modulation of various neurotransmitter systems. They are located within the endoplasmic reticulum, influencing cellular processes beyond opioid-related functions [23].

Sigma receptors are also notable for their potential in drug development, particularly in the context of neuropsychiatric disorders and neurodegenerative diseases. Targeting sigma receptors with selective ligands holds promise for developing innovative therapies. In summary, sigma (σ) receptors represent a unique class within the opioid receptor family, distinct from the classic mu, kappa, and delta receptors. Their wide-ranging pharmacological profile and involvement in various physiological processes make them an intriguing area of research in the fields of neuropsychiatry and neuropharmacology [24,25].

1.3. **Medical Signifance of Opioids**

Opioids hold immense medical significance due to their remarkable ability to alleviate pain, making them indispensable in various clinical settings. These potent analgesic compounds primarily target opioid receptors in the central nervous system, modulating pain perception and providing effective pain relief. The medical uses of opioids extend beyond pain management and encompass diverse applications [26].

Pain Management: Opioids are widely employed to treat acute and chronic pain, ranging from post-surgical recovery and cancer-related pain to pain associated with traumatic injuries or various medical conditions. Their effectiveness in alleviating pain is attributed to their action on mu (μ) receptors, which suppress pain signals and enhance pain tolerance [27].

Table1.*Opioid peptides and the receptors they act on [26]*

	Mu	Delta	Kappa
Endojen Peptidler			
Enkefalinler	Agonist	Agonist	
β-endorfinler	Agonist	Agonist	
Dinorfin A	Agonist		Agonist
Agonistler			
Morfin	Agonist		Zayıf agonist
Kodein	Zayıf agonist	Zayıf agonist	
Fentanil	Agonist		
Meperidin	Agonist	Agonist	
Metadon	Agonist		
Antagonistler			
Nalokson	Antagonist	Zayıf antagonist	Antagonist
Naltrekson	Antagonist	Zayıf antagonist	Antagonist

Anesthesia: Opioids are integral components of anesthesia protocols, contributing to pain control and sedation during surgical procedures. Their use in anesthesia ensures patient comfort and aids in the management of intraoperative and postoperative pain. Cough Suppression: Certain opioids, such as codeine and hydrocodone, are employed as antitussives to suppress coughing. They act on cough reflex centers in the brain, providing relief for individuals with persistent or severe coughs. Diarrhea Management: Opioid medications, including loperamide, can effectively alleviate diarrhea by slowing down intestinal motility and reducing excessive bowel movements. This application is particularly valuable in managing diarrhea associated with conditions like irritable bowel syndrome. Addiction Treatment: In a paradoxical role, opioids like methadone and buprenorphine are used to manage opioid addiction. These medications, administered in controlled settings, help individuals overcome addiction by reducing cravings and withdrawal symptoms, allowing for a more gradual and manageable recovery [28].

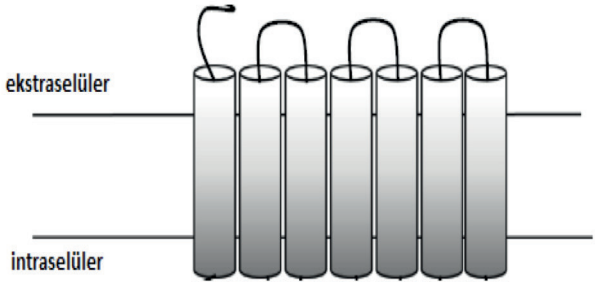


Fig2.*It is allowed to be used from the opioid receptor structure [11].*

Palliative Care: Opioids play a crucial role in palliative care, improving the quality of life for patients with advanced, life-limiting illnesses. They provide relief from severe pain and distressing symptoms, enabling patients to experience comfort and dignity in their final stages of life [33].

Despite their undeniable medical utility, opioids also pose significant challenges, including the potential for addiction, overdose, and adverse side effects. As a result, ongoing research aims to develop safer and more effective opioid medications and alternative pain management strategies, including novel chemical synthesis approaches, to maximize their benefits while minimizing risks [29].

Table2.*Precursors and receptors of endogenous opioid peptides [12]*

Reseptör	Prekürsör	Peptid
DOP	Pro-enkefalin	[Met]-enkefalin [Leu]-enkefalin
KOP	Pro-dinorfin	Dinorfin-A Dinorfin-B
MOP	POMC, Bilinmiyor	β-Endorfin Endomorfin-1 Endomorfin-2

Opioids are essential tools in the field of medicine, offering relief from pain and distress in various clinical scenarios. Understanding their medical significance and continually refining their use is essential to ensure safe and effective patient care. Cancer Pain Management: Opioids play a crucial role in managing pain associated with cancer, especially in cases of advanced or metastatic disease. They provide relief from severe cancer-related pain, improving the quality of life for cancer patients undergoing treatment or palliative care.

Trauma and Emergency Medicine: Opioids are indispensable in emergency medicine and trauma settings. They offer rapid pain relief to

patients experiencing severe injuries, burns, or acute pain episodes, allowing for more effective assessment and treatment.

Chronic Pain Conditions: Chronic pain conditions, such as neuropathic pain and fibromyalgia, often require long-term pain management strategies. Opioid medications, when used judiciously and under medical supervision, can offer relief for patients living with chronic pain [41].

Sedation and Anxiety Reduction: Opioids are occasionally used to induce sedation and reduce anxiety in medical procedures, such as endoscopy or minor surgeries. Their calming effect can enhance patient comfort and cooperation during these procedures.

While opioids provide invaluable therapeutic benefits, their potential for misuse and addiction necessitates careful prescribing, monitoring, and patient education. The opioid crisis, characterized by increasing rates of opioid misuse and overdose deaths, underscores the importance of striking a balance between ensuring access to effective pain relief and minimizing the risks associated with opioid use [35,36].

Researchers and healthcare professionals continue to explore innovative approaches to opioid therapy, including the development of abuse-deterrent formulations, non-opioid pain management strategies, and alternative treatments. These efforts aim to maximize the medical benefits of opioids while addressing the critical need for safer and more responsible opioid use in healthcare [31].

1.4. **The Opioid Crisis and New Solutions**

The opioid crisis represents one of the most pressing public health challenges of our time. It is characterized by the widespread misuse, addiction, and overdose deaths associated with both prescription and illicit opioids. This crisis has far-reaching societal and healthcare consequences, necessitating urgent action and the exploration of new solutions [30].

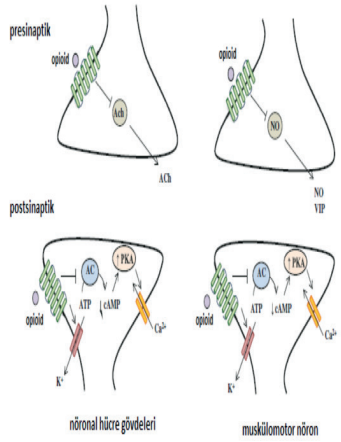


Fig3.*Opioid-neuron interaction used with permission from [14].*

The crisis's origins can be traced, in part, to the overprescription of opioid pain medications in the late 20th and early 21st centuries. This contributed to a surge in opioid availability and misuse, with many individuals becoming addicted to prescription opioids and transitioning to more potent and dangerous drugs, such as heroin and synthetic opioids like fentanyl [32,33].

In response to the crisis, various stakeholders, including healthcare providers, policymakers, and researchers, have been actively seeking new solutions to mitigate its devastating effects:[34]

Enhanced Prescribing Practices: Healthcare providers are implementing stricter guidelines for opioid prescribing, focusing on the careful evaluation of pain conditions, non-opioid pain management options, and education for patients about the risks of opioid use.

Abuse-Deterrent Formulations: Pharmaceutical companies are developing opioid medications with abuse-deterrent properties. These formulations make it more challenging to crush, snort, or inject the drugs, reducing their potential for misuse.

Opioid Overdose Reversal Agents: The widespread distribution of naloxone, an opioid overdose reversal agent, to first responders and community members has saved countless lives. This approach aims to rapidly counteract opioid overdoses and prevent fatalities [35].

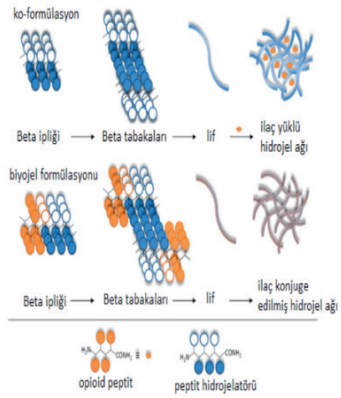


Fig4.*Illustration of biogel formulation and coformulation used with permission from [59].*

Alternative Pain Management: Healthcare professionals are exploring alternative pain management strategies, such as physical therapy, cognitive-behavioral therapy, and non-opioid medications, to reduce reliance on opioids for chronic pain treatment [36].

Innovative Medications: Researchers are investigating novel medications that target opioid receptors with reduced addiction potential and side effects. These efforts aim to develop safer and more effective pain management options [37].

Public Awareness and Education: Public health campaigns and educational initiatives are raising awareness about the risks of opioid misuse, addiction, and overdose. These efforts empower individuals to make informed decisions about their healthcare.

Treatment and Recovery Support: Expanding access to addiction treatment programs, including medication-assisted treatment (MAT), counseling, and support networks, is essential for individuals struggling with opioid use disorder to achieve recovery [42].

While these solutions represent important steps in addressing the opioid crisis, ongoing research and collaboration across healthcare, government, and community sectors are crucial. Combating the opioid crisis requires a comprehensive and multifaceted approach that balances pain management needs with addiction prevention and treatment efforts [39].

The opioid crisis has prompted the development and implementation of new solutions aimed at reducing opioid misuse and its devastating consequences. These efforts focus on responsible prescribing, harm reduction, alternative treatments, and public education to address the multifaceted challenges posed by opioid use in modern society [45,51].

1.5. **Novel Chemical Synthesis Approaches**

In the pursuit of safer and more effective opioid medications, novel chemical synthesis approaches have emerged as a promising avenue of research. These approaches focus on the design and development of opioid compounds with enhanced therapeutic profiles while minimizing the risk of addiction and adverse effects.

Molecular-Level Modifications: Researchers are exploring precise molecular modifications to opioid structures to optimize their binding affinity and selectivity for specific receptor subtypes. By fine-tuning the chemical properties of opioids, it becomes possible to create compounds that deliver potent analgesia with reduced side effects and addictive potential [40].

Bileşik	Kod	Sekans
1	OP1	H-Dmt-DArg-Phe-Phe-NH_2
2	OP2	H-Dmt-DLys-Phe-Phe-NH_2
3	OP3	H-Dmt-DArg-Aba-βAla-NH_2
4	OP4	H-Dmt-Pro-Phe-Phe-NH_2
5	OP5	H-Dmt-Pro-Trp-Phe-NH_2
6	OP1-GEL2	H-Dmt-DArg-Phe-Phe-Gln-Phe-Gln-Phe-Lys-NH_2
7	OP1-GEL4	H-Dmt-DArg-Phe-Phe-Gln-β^3hPhe-Phe-Gln-Phe-Lys-NH_2
8	OP2-GEL1	H-Dmt-DLys-Phe-Phe-Glu-Phe-Gln-Phe-Lys-NH_2
9	OP2-GEL2	H-Dmt-DLys-Phe-Phe-Gln-Phe-Gln-Phe-Lys-NH_2
10	OP3-GEL2	H-Dmt-DArg-Aba-βAla-Phe-Gln-Phe-Gln-Phe-Lys-NH_2
11	OP4-GEL1	H-Dmt-Pro-Phe-Phe-Glu-Phe-Gln-Phe-Lys-NH_2
12	OP4-GEL2	H-Dmt-Pro-Phe-Phe-Gln-Phe-Gln-Phe-Lys-NH_2
13	OP5-GEL2	H-Dmt-Pro-Trp-Phe-Gln-Phe-Gln-Phe-Lys-NH_2
14	GEL1	H-Phe-Glu-Phe-Gln-Phe-Lys-NH_2
15	GEL2	H-Phe-Gln-Phe-Gln-Phe-Lys-NH_2
16	GEL4	H-Phe-Glu-β^3hPhe-Phe-Gln-Phe-Lys-NH_2

Fig5.*Opioid pharmacophores (OP), biogel and hydrogelator (GEL) sequences [59]*

Structure-Based Drug Design: Advances in structural biology, including the determination of opioid receptor crystal structures, have provided invaluable insights. This knowledge allows for the rational design of opioid ligands that interact with receptors in a highly specific manner. Such targeted drug design enhances efficacy while minimizing off-target effects [38].

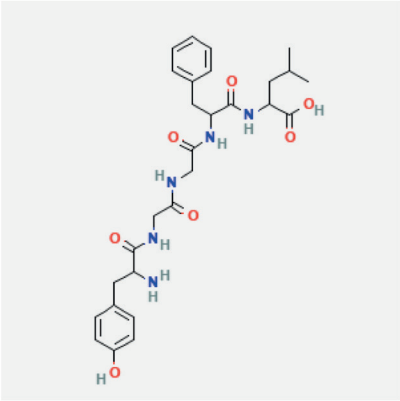


Fig6. *[Leu]-enkephalin structure used with permission from [61].*

High-Throughput Screening: High-throughput screening techniques enable the rapid evaluation of vast libraries of chemical compounds for their potential as opioid receptor modulators. This approach accelerates the discovery of novel opioid ligands, facilitating drug development [41].

Multi-Target Approaches: Some researchers are exploring multi-target approaches, aiming to develop compounds that simultaneously interact with multiple opioid receptor subtypes. This strategy seeks to harness the synergistic effects of receptor modulation while reducing the risk of tolerance and addiction. Abuse-Deterrent Formulations: In addition to novel compounds, there is a focus on developing abuse-deterrent formulations of existing opioids [42].

These formulations make it more challenging for individuals to misuse the drugs through crushing, snorting, or injecting, thereby reducing the potential for addiction [53].

Pharmacokinetic Enhancements: Optimizing the pharmacokinetic properties of opioid medications is another key aspect. This includes the development of extended-release formulations that provide prolonged pain relief while minimizing the frequency of dosing, enhancing patient compliance, and reducing the risk of misuse [43].

Combinatorial Chemistry: Combinatorial chemistry approaches involve creating libraries of diverse opioid compounds with a wide range of structural variations. This methodology enables the identification of novel ligands with improved pharmacological profiles. Novel chemical synthesis approaches represent a critical frontier in the quest for safer and more effective opioid medications. They offer the potential to transform pain management and addiction treatment by providing healthcare professionals with a broader arsenal of therapeutic options. Moreover, these approaches align with the

imperative to address the opioid crisis by minimizing the risk of addiction and overdose associated with traditional opioids.

Novel chemical synthesis approaches are at the forefront of opioid research, offering innovative strategies to optimize opioid medications for pain relief while mitigating the risks of addiction and adverse effects. These approaches hold great promise in improving patient outcomes and reshaping the landscape of opioid pharmacotherapy [55].

1.6. **Opioid Receptor Modulation and Clinical Applications**

The modulation of opioid receptors represents a pivotal aspect of opioid research with far-reaching clinical implications. Understanding how to finely tune the activity of these receptors opens the door to more effective and safer clinical applications in pain management, addiction treatment, and beyond [44].

Pain Management: Opioid receptor modulation is at the core of pain management strategies. By developing compounds that selectively target specific receptor subtypes, researchers aim to achieve potent analgesia while minimizing the side effects associated with traditional opioids. This approach holds promise for enhancing the quality of life for individuals suffering from chronic pain conditions [45].

Addiction Treatment: The modulation of opioid receptors is also central to addiction treatment. Medications like methadone and buprenorphine, which interact with these receptors, help individuals overcome opioid addiction by reducing cravings and withdrawal symptoms. This approach is a critical component of medication-assisted treatment (MAT) programs [52].

Mood and Mental Health: Opioid receptor modulation has implications for mood regulation and mental health. Research into how opioids affect mood and emotions has opened new avenues for the treatment of mood disorders, such as depression and anxiety. Targeting specific receptor subtypes may lead to innovative therapies with fewer side effects [54].

Neurological Disorders: Opioid receptor modulation extends to neurological disorders. Researchers are exploring the potential of opioids in the treatment of conditions like Parkinson's disease, where these compounds may have neuroprotective effects and alleviate motor symptoms [46].

Cancer-Related Symptoms: Opioid receptor modulation plays a role in managing symptoms associated with cancer, such as pain and nausea. Developing opioids with improved receptor selectivity may lead to more

effective palliative care for cancer patients.

Neuroinflammation and Immune Response: Opioid receptors are also present in the immune system, influencing immune responses and inflammation. Modulating these receptors holds potential for treating conditions characterized by abnormal immune activity and inflammation [47].

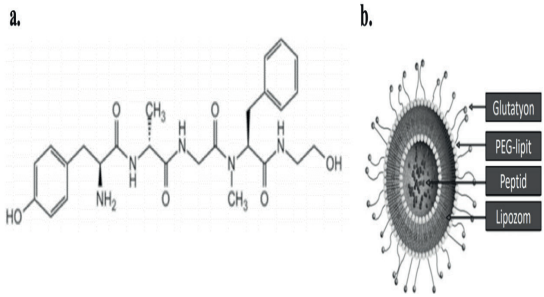


Fig7.*The opioid peptide DAMGO and b) The structure of the developed liposomes was used with permission from [65].*

Personalized Medicine: The ability to modulate opioid receptors in a targeted manner paves the way for personalized medicine approaches. Tailoring opioid therapies to an individual's genetic and physiological profile may maximize therapeutic benefits while minimizing adverse effects [35,48].

Combination Therapies: Combining opioids with other medications, such as non-opioid analgesics or adjuvant therapies, is an area of active research. Synergistic effects may allow for lower opioid doses and reduced risks.

In clinical applications, the goal of opioid receptor modulation is to optimize treatment outcomes while minimizing the potential for addiction, tolerance, and side effects. This research is closely intertwined with the broader efforts to address the opioid crisis and improve the safety and efficacy of opioid-based medications.

Opioid receptor modulation plays a central role in various clinical applications, spanning pain management, addiction treatment, mood disorders, and neurological conditions. Research in this field continues to drive innovation, offering the potential for more effective and personalized medical interventions while addressing the challenges posed by opioid use in healthcare [50].

1.7. **Drug Development Processes**

Drug development is a complex and multifaceted process that transforms scientific discoveries into safe and effective medications for clinical use. This journey typically consists of several phases:

1. Discovery and Research: Drug development starts with the discovery phase, where researchers identify potential drug candidates. This involves extensive laboratory work, target identification, and screening of compounds for their biological activity [51].

2. Preclinical Testing: Promising drug candidates move to preclinical testing, where they undergo rigorous testing in vitro (in the lab) and in vivo (in animals). Researchers assess safety, efficacy, and dosage levels, as well as potential side effects.

3. Investigational New Drug (IND) Application: If preclinical testing is successful, the drug's sponsor submits an IND application to regulatory authorities (e.g., the FDA in the United States). This application outlines the drug's proposed clinical trials, including study protocols, safety data, and manufacturing information [52].

4. Clinical Trials: Clinical trials consist of three phases:

- Phase I trials involve a small group of healthy volunteers to assess safety, dosage, and side effects.
- Phase II trials expand the study to a larger group of patients to evaluate efficacy and side effects further.
- Phase III trials involve a more extensive patient population to confirm efficacy, monitor side effects, and compare the drug to existing treatments.

5. New Drug Application (NDA): If clinical trials demonstrate safety and efficacy, the sponsor submits an NDA to regulatory authorities. This application contains comprehensive data from all phases of testing [53].

6. Regulatory Review: Regulatory agencies like the FDA or the European Medicines Agency (EMA) review the NDA, assessing the drug's risks and benefits. Approval is granted if the drug is deemed safe and effective for its intended use.

7. Post-Marketing Surveillance: After approval and market release, the drug continues to be monitored for safety and effectiveness. This phase, known as post-marketing surveillance or Phase IV, helps identify rare or long-term side effects.

8. Manufacturing and Distribution: Drugs are manufactured on a large scale and distributed to healthcare providers and pharmacies. Quality control ensures consistent production.

9. Marketing and Access: The drug's manufacturer promotes the product to healthcare professionals and the public, informing them of its benefits and risks. Access to the medication is facilitated through pharmacies and healthcare systems [54].

10. Lifecycle Management: As a drug ages, manufacturers may seek additional uses (indications), explore new formulations (e.g., extended-release versions), or address emerging safety concerns.

The drug development process is lengthy, often taking over a decade and involving substantial financial investments. Many drug candidates do not make it past preclinical testing or clinical trials due to safety concerns or lack of efficacy. However, successful drug development leads to new treatments that improve patient health and quality of life. Additionally, regulatory agencies continually update safety standards and monitor medications in circulation to ensure ongoing patient safety [55].

The drug development process is a complex and multifaceted procedure that transforms scientific discovery into a medical treatment. Each stage of this process requires a highly meticulous and systematic approach, and the development of new drugs typically takes a decade or more. The drug development process begins with the discovery and research phase. In this phase, potential drug candidates are identified, and they are tested through laboratory work [56].

This involves target identification and the screening of compounds for their biological activity. It marks the initiation of drug discovery, encompassing the determination of potential molecular targets and the assessment of compound biological activities [27].

Following the discovery phase, promising drug candidates undergo preclinical testing. These tests rigorously evaluate the safety, efficacy, dosage levels, and potential side effects of the compounds, both in vitro (in the lab) and in vivo (in animals). Such testing ensures that the drug is safe and effective for human use before proceeding to clinical trials [34].

Upon successful completion of preclinical testing, the drug development process advances to clinical trials, typically consisting of three phases: Phase I, Phase II, and Phase III. Phase I trials involve a small group of healthy volunteers to assess safety, dosage, and side effects. Phase II trials expand the study to a larger group of patients to evaluate efficacy and side effects further. Phase

III trials involve a more extensive patient population, confirming efficacy, monitoring side effects, and comparing the drug to existing treatments.

If clinical trials demonstrate safety and efficacy, the drug's sponsor submits a New Drug Application (NDA) to regulatory authorities. This application contains comprehensive data from all phases of testing. Regulatory agencies, such as the FDA or the European Medicines Agency (EMA), review the NDA, assessing the drug's risks and benefits. Approval is granted if the drug is deemed safe and effective for its intended use [57].

After approval and market release, the drug continues to be monitored for safety and effectiveness in the post-marketing surveillance phase, also known as Phase IV. This phase helps identify rare or long-term side effects.

Manufacturing and distribution of the drug follow, with quality control measures ensuring consistent production. The drug is marketed to healthcare professionals and the public to inform them of its benefits and risks, with access facilitated through pharmacies and healthcare systems [58].

The drug development process, although lengthy and involving substantial financial investments, is a critical component of medical progress. Many drug candidates do not advance beyond preclinical or clinical testing due to safety concerns or lack of efficacy. However, successful drug development leads to new treatments that improve patient health and quality of life. Regulatory agencies continually update safety standards and monitor medications in circulation to ensure ongoing patient safety [29].

3. Conclusion

Among the key topics discussed in this article, the impact of molecular modifications on the efficacy and side effects of opioid drugs is emphasized. Novel chemical synthesis approaches offer substantial potential for optimizing the binding affinities and selectivity of opioid drugs to receptors, potentially leading to the development of drugs with fewer side effects and lower addiction risk [59].

Furthermore, addressing significant societal challenges, such as the opioid crisis, is a focal point of this article. New chemical synthesis approaches and safer opioid medications may play a crucial role in mitigating this crisis and reducing addiction. Enhancing the effectiveness of addiction treatment medications can also contribute to improved overall health for individuals struggling with addiction.

These novel approaches in opioid receptor modulation hold great promise for future medical applications. However, realizing these promises will require further research and collaboration. The advancements in the

safety and efficacy of opioid drugs discussed in this article have the potential to enhance the quality of life for patients and improve public health. Moreover, the findings and discussions presented in this article shed light on the critical need for innovation in the field of pain management. Chronic pain is a pervasive issue affecting millions of individuals worldwide, and conventional opioid medications often come with a host of side effects and risks. The exploration of novel chemical synthesis methods offers hope for the development of more precise and targeted pain relief solutions, ultimately improving the lives of those who suffer from chronic pain conditions [60,61].

The opioid crisis, which has reached alarming proportions in many regions, demands urgent attention and multifaceted solutions. While the development of safer opioid medications is a significant step, addressing addiction as a complex medical and societal issue requires a comprehensive approach. The insights provided in this article underscore the role of science and research in combatting addiction and highlight the potential of pharmaceutical interventions as part of a broader strategy [62].

Looking ahead, the research and innovations discussed in this article have the potential to reshape the landscape of opioid-based medications. They offer the possibility of a future where patients can receive effective pain relief and addiction treatment with reduced risks and improved outcomes. However, it is essential to approach these developments with caution, recognizing the importance of rigorous testing, regulatory oversight, and ongoing surveillance to ensure the safety and efficacy of these emerging therapies.

In closing, serves as a testament to the ever-evolving nature of medical research and the pursuit of solutions to some of the most pressing healthcare challenges of our time. The collaborative efforts of scientists, healthcare professionals, policymakers, and the pharmaceutical industry will play a crucial role in translating these advancements into tangible benefits for patients and society [63].

References

Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008;11(2 Suppl):S133-53.

Pathan H, Williams J. Basic opioid pharmacology: an update. Br J Pain. 2012;6(1):11-6. DOI: 10.1177/2049463712438493.

Schwarzer C. 30 years of dynorphins--new insights on the- ir functions in neuropsychiatric diseases. Pharmacol Ther. 2009;123(3):353-70. DOI: 10.1016/j.pharmthera.2009.05.006.

Goldstein A, Tachibana S, Lowney LI, Hunkapiller M, Hood L. Dynorphin-(1-13), an extraordinarily potent opioid pep- tide. Proc Natl Acad Sci U S A. 1979;76(12):6666-70. DOI: 10.1073/pnas.76.12.6666.

Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. Identification of two related pentapeptidesfrom the brain with potent opiate agonist activity. Nature. 1975;258(5536):577-80. DOI: 10.1038/258577a0.

Li Y, Lefever MR, Muthu D, Bidlack JM, Bilsky EJ, Polt R. Opioid glycopeptide analgesics derived from endogenous en- kephalins and endorphins. Future Med Chem. 2012;4(2):205- 26. DOI: 10.4155/fmc.11.195.

Feng Y, He X, Yang Y, Chao D, Lazarus LH, Xia Y. Current research on opioid receptor function. Curr Drug Targets. 2012;13(2):230-46. DOI: 10.2174/138945012799201612.

Mansour A, Khachaturian H, Lewis ME, Akil H, Watson SJ. Autoradiographic differentiation of mu, delta, and kappa opi- oid receptors in the rat forebrain and midbrain. J Neurosci. 1987;7(8):2445-64.

Dhawan BN, Cesselin F, Raghubir R, Reisine T, Bradley PB, Portoghese PS, et al. International Union of Pharmaco- logy. XII. Classification of opioid receptors. Pharmacol Rev. 1996;48(4):567-92.

ReinscheidRK,NothackerHP,BoursonA,ArdatiA,Henning- sen RA, Bunzow JR, et al. Orphanin FQ: a neuropeptide that activates an opioidlike G protein-coupled receptor. Science. 1995;270(5237):792-4. DOI: 10.1126/science.270.5237.792.

Lemos Duarte M, Devi LA. Post-translational Modifications of Opioid Receptors. Trends Neurosci. 2020;43(6):417-32. DOI: 10.1016/j.tins.2020.03.011.

Pan Z, Hirakawa N, Fields HL. A cellular mechanism for the bidirectional pain-modulating actions of orphanin FQ/no- ciceptin. Neuron. 2000;26(2):515-22. DOI: 10.1016/s0896- 6273(00)81183-6.

McDonald J, Lambert D. Opioid receptors. Continuing Educa- tion in Anaesthesia Critical Care & Pain. 2005;5(1):22-5. DOI: 10.1093/bjaceaccp/mki004.

SobczakM,SałagaM,StorrMA,FichnaJ.Physiology,signa- ling, and pharmacology of opioid receptors and their ligands in the gastrointestinal tract: current concepts and future pers- pectives. J Gastroenterol. 2014;49(1):24-45. DOI: 10.1007/ s00535-013-0753-x.

Salgado S, Kaplitt MG. The Nucleus Accumbens: A Compre- hensive Review. Stereotact Funct Neurosurg. 2015;93(2):75- 93. DOI: 10.1159/000368279.

Li CH, Chung D. Isolation and structure of an untriakonta- peptide with opiate activity from camel pituitary glands. Proc Natl Acad Sci U S A. 1976;73(4):1145-8. DOI: 10.1073/ pnas.73.4.1145.

Danielson PB, Dores RM. Molecular evolution of the opioid/orphanin gene family. Gen Comp Endocrinol. 1999;113(2):169-86. DOI: 10.1006/gcen.1998.7206.

Hökfelt T, Ljungdahl A, Terenius L, Elde R, Nilsson G. Im- munohistochemical analysis of peptide pathways possiblyrelated to pain and analgesia: enkephalin and substance P. Proc Natl Acad Sci U S A. 1977;74(7):3081-5. DOI: 10.1073/ pnas.74.7.3081.

McLaughlin P. Proenkephalin-Derived Peptides. In: Kastin A, editor. Handbook of Biologically Active Peptides. 2 ed: Aca- demic Press; 2013.

Snyder SH. Opiate receptors and beyond: 30 years of neu- ral signaling research. Neuropharmacology. 2004;47 Suppl1:274-85. DOI: 10.1016/j. neuropharm.2004.06.006.

Zagon IS, Verderame MF, McLaughlin PJ. The biology of the opioid growth factor receptor (OGFr). Brain Res Brain Res Rev. 2002;38(3):351-76. DOI: 10.1016/ s0165-0173(01)00160-6.

McLaughlin PJ. Regulation of DNA synthesis of myocardial and epicardial cells in developing rat heart by [Met5]enkep- halin. Am J Physiol. 1996;271(1 Pt 2):R122-9. DOI: 10.1152/ ajpregu.1996.271.1.R122.

North RA, Tonini M. The mechanism of action of nar- cotic analgesics in the guinea-pig ileum. Br J Pharmacol. 1977;61(4):541-9. DOI: 10.1111/j.1476-5381.1977. tb07546.x.

Akil H, Watson SJ, Young E, Lewis ME, Khachaturian H, Walker JM. Endogenous opioids: biology and function. Annu Rev Neurosci. 1984;7:223-55. DOI: 10.1146/annurev. ne.07.030184.001255.

Zagon IS, McLaughlin PJ. Endogenous opioid systems re- gulate growth of neural tumor cells in culture. Brain Res. 1989;490(1):14-25. DOI: 10.1016/0006-8993(89)90425-3.

Henry MS, Gendron L, Tremblay M-E, Drolet G. Enkepha- lins: Endogenous Analgesics with an Emerging Role in Stress Resilience. Neural Plasticity. 2017;2017:1546125. DOI: 10.1155/2017/1546125.

Mains RE, Eipper BA, Ling N. Common precursor to cor- ticotropins and endorphins. Proc Natl Acad Sci U S A. 1977;74(7):3014-8. DOI: 10.1073/pnas.74.7.3014.

Loh HH, Tseng LF, Wei E, Li CH. beta-endorphin is a potent analgesic agent. Proc Natl Acad Sci U S A. 1976;73(8):2895-8. DOI: 10.1073/pnas.73.8.2895.

Lee MW, S.L. Beta-Endorphin. In: Fink G, editor. Encyclope- dia of Stress. 2 ed: Academic Press; 2007.

Comb M, Seeburg PH, Adelman J, Eiden L, Herbert E. Pri- mary structure of the human Met- and Leu-enkephalin pre- cursor and its mRNA. Nature. 1982;295(5851):663-6. DOI: 10.1038/295663a0.

Teschemacher H, Opheim KE, Cox BM, Goldstein A. Iso- lation. Life Sciences. 1975;16(12):1771-5. DOI: https://doi. org/10.1016/0024-3205(75)90271-4.

Goldstein A, Fischli W, Lowney LI, Hunkapiller M, Hood L. Porcine pituitary dynorphin: complete amino acid sequence ofthe biologically active heptadecapeptide. Proc Natl Acad Sci U S A. 1981;78(11):7219-23. DOI: 10.1073/pnas.78.11.7219.

James IF, Fischli W, Goldstein A. Opioid receptor selec- tivity of dynorphin gene products. J Pharmacol Exp Ther. 1984;228(1):88-93.

Sharma SK, Klee WA, Nirenberg M. Opiate-dependent mo- dulation of adenylate cyclase. Proc Natl Acad Sci U S A. 1977;74(8):3365-9. DOI: 10.1073/pnas.74.8.3365.

North RA, Williams JT, Surprenant A, Christie MJ. Mu and delta receptors belong to a family of receptors that are coupled to potassium channels. Proc Natl Acad Sci U S A. 1987;84(15):5487-91. DOI: 10.1073/pnas.84.15.5487.

Jin W, Lee NM, Loh HH, Thayer SA. Dual excitatory and inhibitory effects of opioids on intracellular calcium in neu- roblastoma x glioma hybrid NG108-15 cells. Mol Pharmacol. 1992;42(6):1083-9.

Barg J, Belcheva MM, Rowiński J, Coscia CJ. kappa-Opio- id agonist modulation of [3H]thymidine incorporation into DNA: evidence for the involvement of pertussis toxin-sensi- tive G protein-coupled phosphoinositide turnover. J Neuroc- hem. 1993;60(4):1505-11. DOI: 10.1111/j.1471-4159.1993. tb03314.x.

Nikolarakis KE, Almeida OFX, Yassouridis A, Herz A. Presy- naptic auto- and allelo-receptor regulation of hypothalamic opioid peptide release. Neuroscience. 1989;31(1):269-73. DOI: https://doi.org/10.1016/0306-4522(89)90049-3.

Woods AS, Kaminski R, Oz M, Wang Y, Hauser K, Goody R, et al. Decoy peptides that bind dynorphin noncovalently prevent NMDA receptor-mediated neurotoxicity. J Proteome Res. 2006;5(4):1017-23. DOI: 10.1021/pr060016+.

Kanemitsu Y, Hosoi M, Zhu PJ, Weight FF, Peoples RW, McLaughlin JS, et al. Dynorphin A inhibits NMDA recep- tors through a pH-dependent mechanism. Mol Cell Neurosci. 2003;24(3):525-37. DOI: 10.1016/s1044-7431(03)00214-8.

Shippenberg TS, Zapata A, Chefer VI. Dynorphin and the pathophysiology of drug addiction. Pharmacol Ther. 2007;116(2):306-21. DOI: 10.1016/j.pharmthera.2007.06.011.

Chavkin C. Dynorphin--still an extraordinarily potent opioid peptide. Mol Pharmacol. 2013;83(4):729-36. DOI: 10.1124/ mol.112.083337.

Zadina JE, Hackler L, Ge LJ, Kastin AJ. A potent and selec- tive endogenous agonist for the mu-opiate receptor. Nature. 1997;386(6624):499-502. DOI: 10.1038/386499a0.

Gu Z-H, Wang B, Kou Z-Z, Bai Y, Chen T, Dong Y-L, et al. Endomorphins: Promising Endogenous Opioid Peptides for the Development of Novel Analgesics. Neurosignals. 2017;25(1):98-116. DOI: 10.1159/000484909.

Zadina JE, Gerall AA, Kastin AJH, L., Ge LJZ, X. Endomorp- hins: novel endogenous mu-opiate receptor agonists in regi- ons of high mu-opiate receptor density. . Ann N Y Acad Sci.

1999;897:136-44.

Zadina JE, Nilges MR, Morgenweck J, Zhang X, Hackler L, Fasold MB. Endomorphin analog analgesics with reduced abuse liability, respiratory depression, motor impairment, to- lerance, and glial activation relative to morphine. Neuropharmacology. 2016;105:215-27.

ZupančičO,RohrerJ,ThanhLamH,GrießingerJA,Bernkop- Schnürch A. Development and in vitro characterization of self- emulsifying drug delivery system (SEDDS) for oral opioid peptidedelivery.DrugDevIndPharm.2017;43(10):1694-702. DOI: 10.1080/03639045.2017.1338722.

Lalatsa A, Lee V, Malkinson JP, Zloh M, Schätzlein AG, Uc- hegbu IF. A prodrug nanoparticle approach for the oral delivery of a hydrophilic peptide, leucine(5)-enkephalin, to the brain. Mol Pharm. 2012;9(6):1665-80. DOI: 10.1021/mp300009u.

Karls MS, Rush BD, Wilkinson KF, Vidmar TJ, Burton PS, Ruwart MJ. Desolvation Energy: A Major Determi- nant of Absorption, But Not Clearance, of Peptides in Rats. Pharmaceutical Research. 1991;8(12):1477-81. DOI: 10.1023/A:1015882030289.

Egleton RD, Mitchell SA, Huber JD, Palian MM, Polt R, Da- vis TP. Improved blood-brain barrier penetration and enhan- ced analgesia of an opioid peptide by glycosylation. J Pharma- col Exp Ther. 2001;299(3):967-72.

Brownson EA, Abbruscato TJ, Gillespie TJ, Hruby VJ, Davis TP. Effect of peptidases at the blood brain barrier on the perme- ability of enkephalin. J Pharmacol Exp Ther. 1994;270(2):675- 80.

Shen WC. Oral peptide and protein delivery: unfulfilled pro- mises? Drug Discov Today. 2003;8(14):607-8. DOI: 10.1016/ s1359-6446(03)02692-8.

Sadekar S, Thiagarajan G, Bartlett K, Hubbard D, Ray A, McGill LD, et al. Poly(amido amine) dendrimers as absorp- tion enhancers for oral delivery of camptothecin. Int J Pharm. 2013;456(1):175-85. DOI: 10.1016/j.ijpharm.2013.07.071.

WengH,HuL,HuL,ZhouY,WangA,WangN,et al. The complexation of insulin with sodium N-[8-(2- hydroxybenzoyl)amino]-caprylate for enhanced oral delivery: Effects of concentration, ratio, and pH. Chinese Chemical Letters. 2022;33(4):1889-94. DOI: https://doi.org/10.1016/j. cclet.2021.10.023.

Dan N, Samanta K, Almoazen H. An Update on Pharmaceu- tical Strategies for Oral Delivery of Therapeutic Peptides and Proteins in Adults and Pediatrics. Children (Basel). 2020;7(12). DOI: 10.3390/children7120307.

ArodaVR,BlondeL,PratleyRE.AneweraforoRalpeptides: SNAC and the development of oral semaglutide for the treat- ment of type 2 diabetes. Reviews in Endocrine and Metabolic Disorders. 2022;23(5):979-94. DOI: 10.1007/s11154-022- 09735-8.

Fan W, Xia D, Zhu Q, Li X, He S, Zhu C, et al. Functional na- noparticles exploit the bile acid pathway to overcome multiple barriers of the intestinal epithelium for oral insulin delivery. Biomaterials. 2018;151:13-23. DOI: 10.1016/j.biomaterials.2017.10.022.

Chen G, Kang W, Li W, Chen S, Gao Y. Oral delivery of pro- tein and peptide drugs: from non-specific formulation app- roaches to intestinal cell targeting strategies. Theranostics. 2022;12(3):1419-39. DOI: 10.7150/thno.61747.

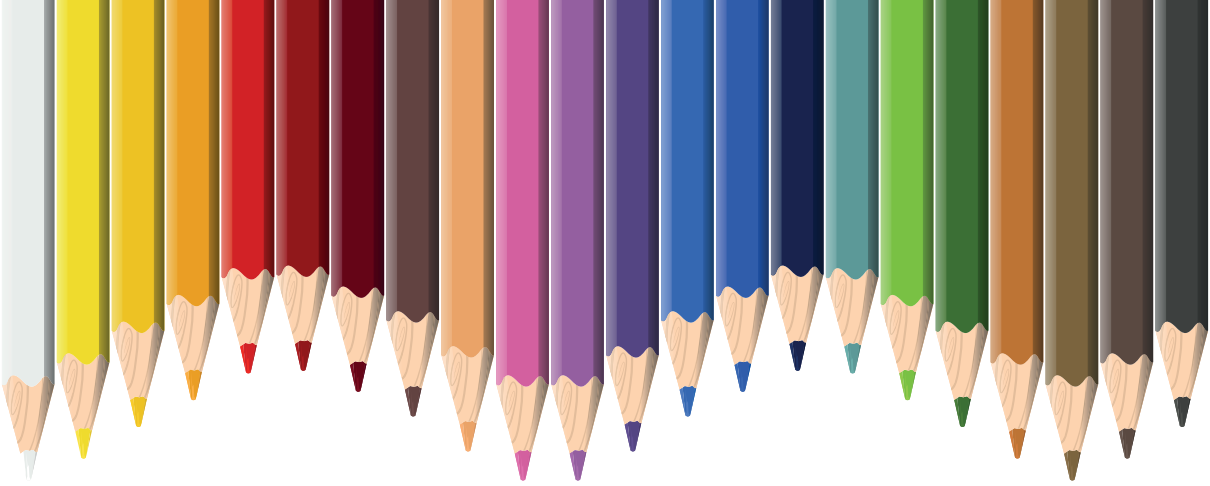
Martin C, Dumitrascuta M, Mannes M, Lantero A, Bucher D, Walker K, et al. Biodegradable Amphipathic Peptide Hydro- gels as Extended-Release System for Opioid Peptides. Journal of Medicinal Chemistry. 2018;61(21):9784-9. DOI: 10.1021/ acs.jmedchem.8b01282.

Dasgupta A, Mondal JH, Das D. Peptide hydrogels. RSC Ad- vances. 2013;3(24):9117. DOI: 10.1039/c3ra40234g.

[Leu]Enkephalin 2021 [Available from: https://pubchem.ncbi. nlm.nih.gov/compound/Leu_enkephalin.

Siew A, Le H, Thiovolet M, Gellert P, Schatzlein A, Uchegbu I. Enhanced Oral Absorption of Hydrophobic and Hydrophilic Drugs Using Quaternary Ammonium Palmitoyl Glycol Chito- san Nanoparticles. Molecular Pharmaceutics. 2012;9(1):14-28. DOI: 10.1021/mp200469a.

ChengWP,GrayAI,TetleyL,HangTleB,SchätzleinAG,Uc- hegbu IF. Polyelectrolyte nanoparticles with high drug loading enhance the oral uptake of hydrophobic compounds. Biomac- romolecules. 2006;7(5):1509-20. DOI: 10.1021/bm060130l.



Chapter 4

BIENERGIES FOR SYMPLECTIC REGULAR CURVE ACCORDING TO EQUIFORM FRAME IN 4-DIMENSIONAL SYMPLECTIC SPACE

Esra Çiçek ÇETİN[1]

1 Dr. Esra Çiçek Çetin e-mail: esracicek23@gmail.com

INTRODUCTION

The word symplectic was first used by Weyl in the sense of complex to describe symplectic groups. Some scientist accept symplectic geometry as the language of classical mechanics. In fact, the basis of Hamilton and Kaehler manifolds, which play an important role in mathematics and theoretical physics, is based on symplectic geometry. Symplectic geometry is at the core of geometric optics. On the other hand, symplectic geometry has important connections with dynamical systems, integrable systems, algebraic geometry and global analysis.

(Gil Medrano, 2001:15) introduced energy on the unit vector fields and then expressed relationship between volume and energy of vector fields. (Chacon and, Naveira,2004:105) authors discussed energy of distrubutions, with practice the Quaternionic Hopf fibrations. Also,(Altın, 2011:63) computed on the energy and pseudo angle of frenet vector fields in R_v^n. (Körpınar and Ünlütürk,2022:26) characterizated a new wersion of bienergies and biangles for curve framed by extended darboux frame. According to these studies in (Körpınar and Demirkol,2021:72) authors computed curvature and torsion dependent energy of elastica and nonelastica for a light-like curve in the Minkowski Space. In (Körpınar,2014:53) author obtained new characterization for minimizing energy of biharmonic particles in Heisenberg spacetime, and introduced new version of energy for involute of slant helix with bending energy in the Lie groups. Afterwards, In (Güven,Valencia,2014:47) authors investigate environmental cast and elastic curves on surfaces. There are many papers according to the subject.

According to our opinion, bienergies should be researched equiform frame in symplectic space. Because we know that symplectic curves play an important role in modern geometry. Also symlectic space are studied by some geometers in (Çetin and Bektaş,2019:2) Finally, in (Kamran,Olver,Tenenblat,2009:11) authors introduced the form of symplectic arc length for curves. And they constructed an adapted symplectic Frenet frame and expressed 2n - 1 local differential invariants that they called symplectic curvatures of the curve. In this study, we firstly obtain the energies and the angle of Frenet vector fields with symplectic equiform frame in symplectic 4-space. Then we compute the bienergies of Frenet vector fields in symplectic space by using the values energies and angles. Then, we express an example for symplectic regular curve.

MATERIALS AND METHODS

Let us introduced some definition for symplectic space.

For, any vectors $,u = (x^1, x^2, \dots, x^n, y^1, \dots, y^n),\ v = (\xi^1, \dots, \xi^n, \eta^1, \dots, \eta^n) \in R^{2n}$

Symplectic inner product is given by

$$< u, v >= \Omega(u, v) = \sum_{i=1}^{n} (x_i \eta_i \wedge y_i \xi_i)$$

4-dimensional symplectic space $Sim = (R^4, \Omega)$ is the vector space R^4 equipped with the standard symplectic form, written as

$$\Omega = \sum dx_i \wedge dy_i$$

(Kamran,Olver,Tenenblat,2009:11)

Let V be a vector space on the field of real numbers R. If , for each u, v

$$\Omega(u, v) = -\Omega(v, u\ )$$

It is called antisymmetric blinear transformation.

Symplectic space with symplectic inner product can be written as

$$< u, v > = \Omega(u, v) = \sum_{i=1}^{2} (x_i \eta_i - y_i \xi_i)$$

$$= x_1 \eta_1 + x_2 \eta_2 - y_1 \xi_1 - y_2 \xi_2$$

here $u = \{x_1, x_2, y_1, y_2\}$ and $v = \{\xi_1, \xi_2, \eta_1, \eta_2\}$

Additionally, The tangent vectors $\{a_1, a_2, a_3, a_4\}$ satisfying the equations

$$\langle a_i, a_j \rangle = \langle a_{2+i}, a_{2+j} \rangle = 0 \qquad 1 \le i, j \le 2,$$

$$\langle a_i, a_{2+j} \rangle = 0 \qquad 1 \le i \ne j \le 2,$$

$$\langle a_i, a_{2+i} \rangle = 1 \qquad 1 \le i \le 2$$

For symplectic frame, Structure equations are defined by

$1 \le i, j \le n$

$$da_i = \sum_{k=1}^{n} w_{ik} a_k + \sum_{k=1}^{n} \varphi_{ik}\, a_{k+n}$$

$$da_{i+n} = \sum_{k=1}^{n} \theta_{ik} a_k + \sum_{k=1}^{n} w_{ik}\, a_{k+n}$$

Here, $\varphi_{ij} = \varphi_{ji}, \qquad \theta_{ij} = \theta_{ji}$
(Kamran,Olver,Tenenblat,2009:11)

Definition 1. Let $z(t)$ be a symplectic regular curve in $Sim = (R^4, \Omega)$. Then the following non-degeneracy condition is satisfied

$$\langle \dot{z}, \ddot{z} \rangle \neq 0$$

for all $t \in R$.

Definiton 2. Let $z(t)$ be a symplectic regular curve ,$t_0 \in R$, then the symplectic arc length s of a symplectic regular curve is given

$$s(t) = \int_{t_0}^{t} \langle \dot{z}, \ddot{z} \rangle^{1/3}\, dt$$

for all $t \geq t_0$.

If

$$\int_{t_1}^{t_2} \langle \dot{z}, \ddot{z} \rangle^{1/3}\, dt = t_2 - t_1 \qquad (t_1, t_2 \in I) \quad t_1 \le t_2$$

symplectic regular curve is said to parametrized by symplectic arc length. The symplectic arc length parameter corresponds to the equaffine arc length for plane curves.

Taking the extrerior differential of above equation, the symplectic arc length element is obtained by

$$ds = \langle \dot{z}, \ddot{z} \rangle^{1/3} dt$$

And the arc length derivative operator is

$$D = \frac{d}{ds} = \langle \dot{z}, \ddot{z} \rangle^{-1/3} \frac{d}{dt}$$

In our notion, the symplectic arc length derivative operator is defined by

$$z' = \frac{dz}{ds}$$

Definiton 3. A symplectic regular curve is parametrized by symplectic arc length if it satisfies

$$\langle \dot{z}, \ddot{z} \rangle = 1$$

for all $t \in R$.

Example 1. Let $z: I \to R^4$

$$z(s) = (-sins, sins, coss, sins)$$

Here,

$$z'(s) = (-coss, coss, -sins, coss)$$

And

$$z''(s) = (sins, -sins, -coss, -sins)$$

It is obvious that z is symplectic regular curve ,since

$$\langle \dot{z}(s), \ddot{z}(s) \rangle = 1$$

Let $z(s)$ be a symplectic regular curve parametrized by arc length with $\{a_1, a_2, a_3, a_4\}$ a symplectic frame. Then, Frenet equations can be written by

$$a_1{}'(s) = a_3(s)$$

$$a_2'(s) = H_2(s) a_4(s)$$

$$a_3'(s) = k_1(s)a_1(s)$$

$$a_4'(s) = a_1(s) + k_2(s)a_2(s)$$

where $H_2(s) = cost(\neq 0)$.

1. Equiform Differential Geometry On Symplectic Space

In this section, we define the equiform parameter and define frame which is according to equiform frame in symplectic space. Let α be a curve parameterized by the arc length s in symplectic space. The equiform parameter of the curve α(s) is defined

$$\rho = \frac{1}{k_1}$$

$$\sigma = \int \frac{ds}{\rho} = \int k_1\, ds$$

$$\frac{ds}{d\sigma} = \rho$$

We investigate Frenet vectors in Equiform Differential geometry on symplectic space.

$$V_1 = \frac{dz}{d\sigma} = \frac{dz}{ds}\frac{ds}{d\sigma} = a_1\rho$$

Similarly, differentiating Frenet vectors, we obtain

$$V_2 = a_2\rho$$

$$V_3 = a_3\rho$$

$$V_4 = a_4\rho$$

Here , differentiating above equations and using Frenet frame (1) ,

$$\nabla_\alpha V_1 = \left(\frac{da_1}{ds}\rho + a_1\frac{d\rho}{ds}\right)\rho$$

$$\nabla_\alpha V_1 = a_3\rho + a_1\dot{\rho}\rho$$

That is , we find

$$\nabla_\alpha V_1 = V_3 + V_1\dot{\rho}$$

By differentiatin again, we obtain

$$\nabla_\alpha V_2 = \frac{d(a_2\rho)}{ds}\rho$$

$$\nabla_\alpha V_2 = \left(\frac{da_2}{ds}\rho + a_2\frac{d\rho}{ds}\right)\rho$$

$$\nabla_\alpha V_2 = \rho H_2 a_4 \rho + \dot{\rho} a_2 \rho$$

That is , we get,

$$\nabla_\alpha V_2 = \rho H_2 V_4 + \dot{\rho} V_2$$

And similarly,

$$\nabla_\alpha V_3 = \frac{dV_3}{d\sigma} = \frac{d(a_3\rho)}{ds}\frac{ds}{d\sigma}$$

$$\nabla_\alpha V_3 = \left(\frac{da_3}{ds}\rho + a_3\frac{d\rho}{ds}\right)\rho$$

that is,

$$\nabla_\alpha V_3 = K_1 a_1 \rho\rho + a_2\rho^2 + \rho\dot{a_3}\rho$$

Thus, we obtain,

$$\nabla_\alpha V_3 = V_1 + \rho V_2 + \dot{\rho} V_3$$

And

$$\nabla_\alpha V_4 = \frac{dV_4}{d\sigma} = \frac{d(a_4\rho)}{ds}\frac{ds}{d\sigma}$$

$$\nabla_\alpha V_4 = \left(\frac{da_4}{ds}\rho + a_4\frac{d\rho}{ds}\right)\rho$$

Similarly,

$$\nabla_\alpha V_4 = \left((a_1 + K_2 a_2)\rho + a_4\dot{\rho}\right)\rho$$

$$\nabla_\alpha V_4 = (a_1\rho + K_2\rho a_2 + a_4\dot{\rho})\rho$$

Hence, we get,

$$\nabla_\alpha V_4 = a_1\rho + K_2\rho\rho a_2 + \dot{\rho}a_4\rho$$

Thus the equiform Frenet formulas can be given as

$$\begin{aligned}
\nabla_\alpha V_1 &= K_1 V_1 + \rho V_3 \\
\nabla_\alpha V_2 &= K_1 V_2 + K_2 V_4 \\
\nabla_\alpha V_3 &= K_1 V_3 + V_1 + \rho V_2 \\
\nabla_\alpha V_4 &= \rho V_1 + K_3 V_2 + K_1 V_4
\end{aligned}$$

(2.1)

And Frenet equations are shown with matrix form as follows,

$$\frac{d}{ds}\begin{pmatrix} V_1(s) \\ V_2(s) \\ V_3(s) \\ V_4(s) \end{pmatrix} = \begin{pmatrix} K_1(s) & 0 & \rho & 0 \\ 0 & K_1(s) & 0 & K_2(s) \\ 1 & \rho & K_1(s) & 0 \\ \rho & K_3(s) & 0 & K_1(s) \end{pmatrix}\begin{pmatrix} V_1(s) \\ V_2(s) \\ V_3(s) \\ V_4(s) \end{pmatrix}$$

With symplectic curvature functions,

$$K_1 = \dot{\rho} \quad , \; K_2 = \rho H_2, \qquad K_3 = \frac{K_2}{K_1}$$

3. Energy and angle of frame fields of a Symlectic Curve

Definition 3.1. Let (M_1, g_1) and (M_2, g_2) be two Riemannian manifolds. Then the energy of differentiable map

$$f: (M_1, g_1) \to (M_2, g_2)$$

can be written as

$$energy\ (f) = \frac{1}{2}\int \sum_{i=1}^{n} g_2(df(e_\alpha), df(e_\alpha))_v$$

where $\{e_\alpha\}$ is a local basis of the tangent space and v is the canonical volume in M_1.

Definition 3.2. Let z is a symplectic curve according to symplectic equiform frame in R_1^4 and $\{V_1(s), V_2(s), V_3(s), V_4(s)\}$ is the Frenet frame of z. Angle between arbitrary Frenet vectors is defined by formula

$$A(V_i) = \int_0^s \left\| D_{V_i} V_i(s) \right\| du$$

Definition 3.3. Let X be a vector field in R_1^4, then the bienergy of the X is given as the formula

$$energy_2\ (X) = \int_0^s \Omega \left\| D^2{}_{V_i} V_i(s), D^2{}_{V_i} V_i(s) \right\| ds \tag{3.1}$$

Definition 3.4. Biangle between arbitrary Frenet vectors given by

$$A_2(V_i) = \int_0^s \left\| D^2{}_{V_i} V_i(s) \right\| ds \tag{3.2}$$

Lemma 3.1. Let $\{V_1(s), V_2(s), V_3(s), V_4(s)\}$ be symplectic equiform frame fields of a symplectic regular curve in R_1^4. Then second differentials of frenet frame are written as

$$D^2{}_{V_1} V_1(s) = \left(K_1(s) + {K_1}^2(s) + \rho\right) V_1(s) + \rho^2 V_2(s) + [2K_1(s)\rho + K_1(s)] V_3(s)$$

$$D^2{}_{V_1} V_2(s) = (\, K_2(s)\rho) V_1(s) + \left[K_1'(s) + {K_1}^2(s) + K_2(s)K_3(s)\right] V_2(s) + [2K_1(s)K_2(s) + K_2'(s)] V_4(s)$$

$$D^2{}_{V_1} V_3(s) = 2K_1(s) V_1(s) + [2K_1(s)\rho + K_1(s)] V_2(s) + \left[\, K_1(s) + {K_1}^2(s) + \rho\right] V_3(s) + \rho K_2(s) V_4(s) \tag{3.3}$$

$$D^2{}_{V_1} V_4(s) = [K_1(s) + 2K_1(s)\rho] V_1(s) + [K_3'(s) + 2K_1(s)K_3(s)] V_2(s) + \rho^2 V_3(s) + [K_2(s)K_3(s) + K_1'(s) + {K_1}^2(s)] V_4(s)$$

Proof . It is easily seen by differentianting the (3.3) equation of (1).

Theorem 3.1. Let z be a symplectic regular curve which is parametrized by symplectic arc lenght with symplectic equiform frame of $\{V_1(s), V_2(s), V_3(s), V_4(s)\}$. Then bienergies of symplectic equiform frame vector fields with symplectic metric are given by

$$energy_2\left(V_1(s)\right) = energy_2\left(V_2(s)\right) = energy_2\left(V_3(s)\right) = energy_2\left(V_4(s)\right) = 0 \qquad (3.4)$$

Proof. It is obtained by using the values of (3.3) in (3.1).

Theorem 3.2. Let z be a symplectic regular curve which is parametrized by symplectic arc lenght according to symplectic equiform frame of $\{V_1(s), V_2(s), V_3(s), V_4(s)\}$. Then bienergy of vector field X is obtained as

$$energy_2\left(X\right) = 0 \qquad (3.5)$$

Proof. The vector fields X can be written according to symplectic equiform frame as follows

$$X = x_1(s)V_1(s) + x_2(s)V_2(s) + x_3(s)V_3(s) + x_4(s)V_4(s)$$

where $x_i(s)$, $(i = 1,2,3,4)$ are scalar functions. Based on the symplectic frenet frame, the second derivativeof the vector field X is obtained as

$$\begin{aligned} D^2{}_X X = \Big[&\left(x_1'(s) + x_1(s)K_1(s) + x_3(s) + \rho x_4(s)\right)' + x_1'(s) \\ &+ x_1(s)K_1(s) + x_3(s) + \rho x_4(s) + x_1'(s)K_1(s) \\ &+ x_1(s){K_1}^2(s) + x_3(s)K_1(s) + K_1(s) + {x_1}^2(s)\rho + x_3'(s) \\ &+ x_3(s)K_1(s) + x_2(s)K_2(s)\rho + \rho x_4'(s) \\ &+ \rho x_4(s)K_1(s)\Big] V_1(s) \end{aligned}$$

$$\begin{aligned} &+ \Big[\left(x_2'(s) + \rho x_3(s) + x_2(s)K_1(s) + x_4(s)K_3(s)\right)' + \\ &\left(x_2'(s)K_1(s) + x_2(s){K_1}^2(s) + \rho x_3(s)K_1(s) + 2x_4(s)K_1(s)K_3(s) + \right. \\ &{x_1}^2(s)\rho^2 + x_3'(s)\rho + x_3(s)K_1(s) + x_2(s)K_2(s)K_3(s) + \\ &\left. x_4'(s)K_3(s) + \right)\Big] V_2(s) \end{aligned}$$

$$\begin{aligned} &+ \Big[\left({x_1}^2(s)\rho + x_3'(s) + x_3(s)K_1(s)\right)' + \left(x_1'(s)\rho + \right. \\ &x_1(s)K_1(s)\rho + x_3(s)\rho + x_4(s)\rho^2 + {x_1}^2(s)\rho K_1(s) + x_3'(s)K_1(s) + \\ &\left. x_3(s){K_1}^2(s)\right)\Big] V_3(s) \end{aligned}$$

$$+\left[\left(x_4'(s)+x_2(s)K_2(s)+x_4(s)K_1(s)\right)'+\right.$$
$$\left(x_2(s)K_2(s)+2x_2(s)K_1(s)K_2(s)+x_4'(s)K_1(s)+x_3(s)\rho K_2(s)+\right.$$
$$\left.\left.x_4(s)K_2(s)K_3(s)+x_4(s){K_1}^2(s)\right)V_V(s)\right] \quad (3.6)$$

Using the (3.6) in the equation (3.1) the bienergy of the vector field X is obtained as in (3.5).

Example 3.1.

$$z(s)=\frac{1}{\sqrt{5}}\left(\sin hs,\frac{1}{2}s^2+2s,\cos hs\,,\frac{1}{2}s^2-2s\right)$$

Figure 1. Then,

$$a_1(s)=z'(s)=\frac{1}{\sqrt{5}}(chs,s+2,shs,s-2)$$

and

$$a_3(s)=z''(s)=\frac{1}{\sqrt{5}}(shs,1,chs,1).$$

Thus $z(s)$ is a symplectic regular curve. In addition

$$a_2(s)=\frac{1}{\sqrt{5}}(\frac{4}{5}chs,-\frac{1}{5}(s+2),\frac{4}{5}shs,-\frac{1}{5}(s-2),$$

$$a_4(s)=\tfrac{5}{4\sqrt{5}}(4shs,-1,4chs,-1).$$

Since $\rho=1$, we obtain Frenet vectors respect to equiform frame ,

$$a_1(s)=V_1(s)=\frac{1}{\sqrt{5}}(chs,s+2,shs,s-2)$$

$$a_2(s)=V_2(s)=\frac{1}{\sqrt{5}}(\frac{4}{5}chs,-\frac{1}{5}(s+2),\frac{4}{5}shs,-\frac{1}{5}(s-2)$$

$$a_3(s)=V_3(s)=\frac{1}{\sqrt{5}}(shs,1,chs,1)$$

$$a_4(s) = V_3(s) = \frac{5}{4\sqrt{5}}(4shs, -1{,}4chs, -1)$$

We obtain

If z is a elastic curve , then

$$energy_2\left(V_1(s)\right) = 0$$

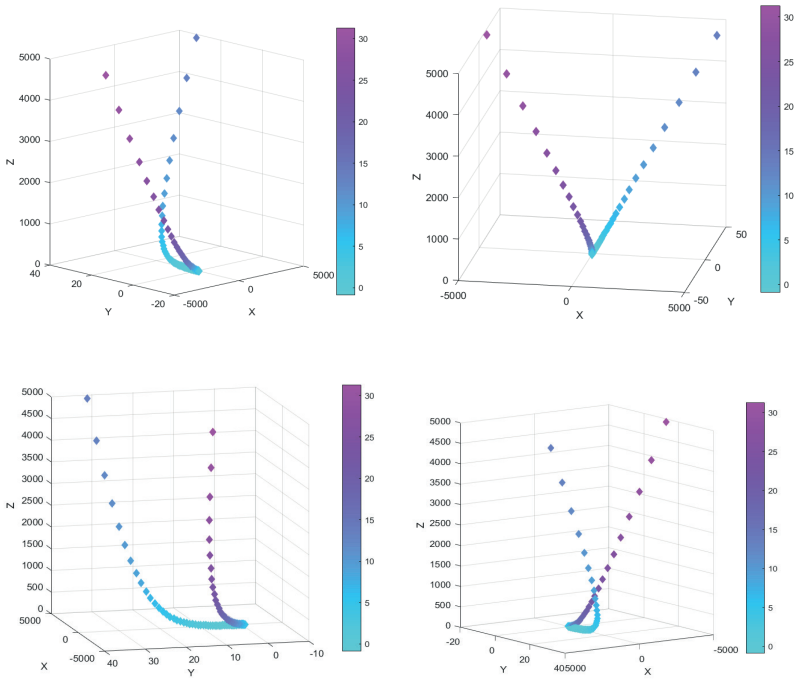


Figure 1. Symplectic regular curve $z(s)$

This curve in R^4 is plotted with a code that represents the fourth dimension with a color scale.

REFERENCES

1. Körpınar T., Ünlütürk Y., (2022), A new wersion of bienergies and biangles for curve framed by extended darboux frame, Soft Computing, 26, 45-54.

2. Körpınar T., and Demirkol R.C. ,(2021), Curvature and Torsion Dependent energy of Elastica and Nonelastica for a light-like curve in the Minkowski Space, Ukr. Math.J.,72(8), 1267-1279.

3. Altın A,, (2011), On the energy and pseudo angle of frenet vector fields in R_v^n, 63(6): 969-975.

4. Carmo MP, (1976), Differential Geometry of curves and surfaces, Prentice – Hall, New Jersey

5. Chacon PM, Naveira AM, (2004),"Corrected energy of distrubution on Riemann manifolds", Osaka J Math,, 41:97-105.

6. Chacon PM, Naveira AM, Weston JM, On the energy of distrubutions, with application to the Quaternionic Hopf fibrations". Monatsh Math,133, 281-294.

7. Gil MedranoO (2001), Relationship between volume and energy of vector fields", Differ.Geom. Appl., 15,137-152.

8. Guven J, Valencia DM, Vazquez-Montejo J,(2014), Environmental bias and elastic curves on surfaces. Phys A Math Theory 47, 355201.

9. Körpınar T., (2014), New characterization for minimizing energy of biharmonic particles in Heisenberg spacetime. Int. J.Phys ,53,3208-3218.

10. Körpınar T (2019b), A new version of energy for involute of slant helix with bending energy in the Lie groups, Acta Sci Technol 41(e36569): 1-8.

11. Çetin E.Ç., Bektaş M., (2019),The characterizations of affine symplectic curves in R^4", Mathematics mdpı, 7(1), 110.

12. Çetin E.Ç., Bektaş M., (2019) Some new characterizations of symplectic curve in 4-dimensional symplectic space, Communications in advanced mathematical Sciences, 2(4), 331-334.

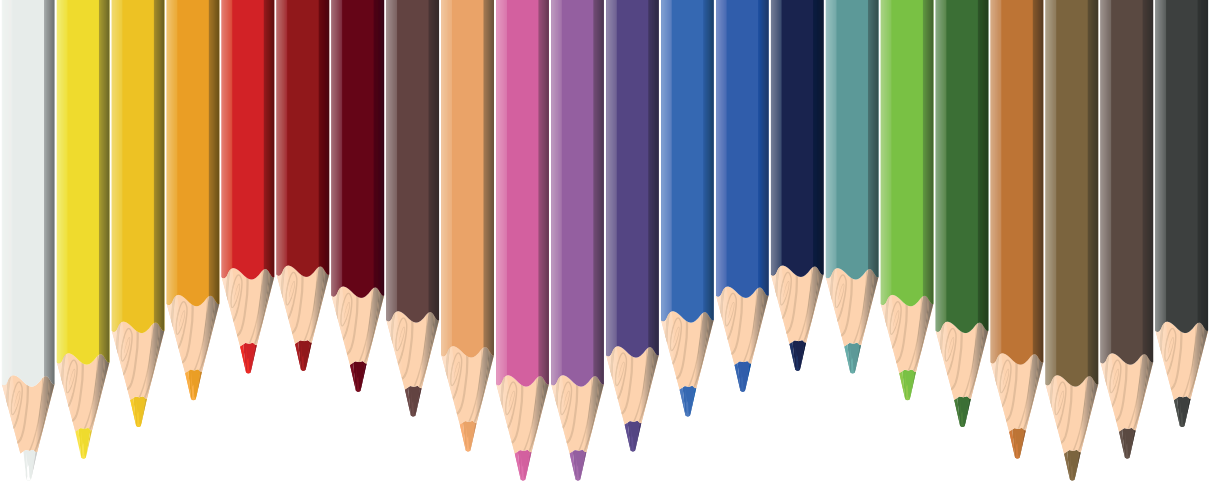
13. Çetin E.Ç., Bektaş M.,(2020),k-type slant helices for symplectic curve in 4-dimensional symplectic space, Facta Universitatis, Series: Mathematics and Informatics,35,641-646.

14. Kamran N., Olver P., Tenenblat K., (2009), Local symplectic invariants for curves, Commun. Contemp. Math.,11,165-183.

15. Chern S. S., and Wang H.C., (1947), Differential geometry in symplectic space, Science

Report Nat. Tsing Hua Univ. 4, 453-477; reprinted in S.S. Chern, Selected

Papers, Vol. II,pp. 165-191,.



Chapter 5

OSCULATING CURVES ACCORDING TO EQUIFORM FRAME IN 4-DIMENSIONAL SYMPLECTIC SPACE

Esra Çiçek ÇETİN[1]

1 Dr. Esra Çiçek Çetin e-mail: esracicek23@gmail.com

1.Introduction

In differential geometry, the theory of curves is wide and important area of study for many authors. For instance, helices, slant helices, rectifying curves, osculating curves have been characterized by using their curvature elements.Also among these special defined curves an interesting one is osculating curves defined by its osculating planes contain a fixed point. Along a space curve , there exist three planes called, the normal plane (spanned by a_2,a_3), osculating plane (spanned by a_1,a_2)and rectifying plane (spanned by a_1,a_3) by the help of normal curves, osculating curves and rectifying curves respectively. Rectifying curves and Darboux vectors play some important roles in mechanic and kinematics. According to our opinion, position vector of a curve should be researched in symplectic space. Because we know that symplectic curves play an important role in modern geometry. Also symlectic space are studied by some geometers in (Çetin and Bektaş,2019:7,2019:2)and(Kapovic, Milson,1996:44) .There are many papers according to the subject.

In (Deshmukh ,Chen and Alshammari,2018:42) defined rectifying curves in E^3. Then (İlarslan andNeŝović,2008:41, 2009:62,2012:61) introduced some characterizations of osculating curves on different space. According to these studies in (Shaikh and Ghosh,2020:51),(Franklin,1926:28) authors defined rectifying and osculating curves on a smooth surface. The geometers introduce associated directional curves in various spaces. Also in the authors focused on the associated curves in E_1^3.

Due to the popularity of the properties of such special curves there are many works related to this subject in different aspects (Kamran , Olver and Tenenblat K., 2009:11),(Valiquette,2012:30) ,(Bozkurt , Gök , Okuyucu and Ekmekçi 2013:10)

The word symplectic was first used by Weyl in the sense of complex to describe symplectic groups. Some scientist accept symplectic geometry as the language of classical mechanics. In fact, the basis of Hamilton and Kahler manifolds, which play an important role in mathematics and theoretical physics, is based on symplectic geometry. The origin of Hamilton mechanics is symplectic geometry, and the base-spaces of classical systems play an important role in the structure of symplectic manifold. Symplectic geometry is at basis of optics. On the other hand, symplectic geometry also has important connections with dynamic systems, integrable systems, algebraic geometry and global analysis.

Inspired by the above work , we focused on the osculating curves curves according to of 4-dimensional symplectic space.

2. Preliminaries

Let us introduced some definition for symplectic space.

For, any vectors $,u = (x^1, x^2, \dots, x^n, y^1, \dots, y^n),\ v = (\xi^1, \dots, \xi^n, \eta^1, \dots, \eta^n) \in R^{2n}$

Symplectic inner product is given by

$$< u, v >= \Omega(u, v) = \sum_{i=1}^{n} (x_i \eta_i \wedge y_i \xi_i)$$

4-dimensional symplectic space $Sim = (R^4, \Omega)$ is the vector space R^4 equipped with the standard symplectic form, written as

$$\Omega = \sum dx_i \wedge dy_i$$

(Kamran , Olver and Tenenblat K., 2009:11)

Let V be a vector space on the field of real numbers R. If , for each u, v

$$\Omega(u, v) = -\Omega(v, u)$$

It is called antisymmetric blinear transformation.

Symplectic space with symplectic inner product can be written as

$$< u, v > = \Omega(u, v) = \sum_{i=1}^{2} (x_i \eta_i - y_i \xi_i)$$

$$= x_1 \eta_1 + x_2 \eta_2 - y_1 \xi_1 - y_2 \xi_2$$

here $u = \{x_1, x_2, y_1, y_2\}$ and $v = \{\xi_1, \xi_2, \eta_1, \eta_2\}$

Additionally, The tangent vectors $\{a_1, a_2, a_3, a_4\}$ satisfying the equations

$$\langle a_i, a_j \rangle = \langle a_{2+i}, a_{2+j} \rangle = 0 \qquad 1 \le i, j \le 2,$$

$$\langle a_i, a_{2+j} \rangle = 0 \qquad 1 \le i \ne j \le 2,$$

$$\langle a_i, a_{2+i} \rangle = 1 \qquad 1 \le i \le 2$$

For symplectic frame, Structure equations are defined by

$1 \le i, j \le n$

$$da_i = \sum_{k=1}^{n} w_{ik} a_k + \sum_{k=1}^{n} \varphi_{ik}\, a_{k+n}$$

$$da_{i+n} = \sum_{k=1}^{n} \theta_{ik} a_k + \sum_{k=1}^{n} w_{ik}\, a_{k+n}$$

Here, $\varphi_{ij} = \varphi_{ji}, \qquad \theta_{ij} = \theta_{ji}$
(Kamran , Olver and Tenenblat K., 2009:11)

Let $z(t) : R \to R^4$ be a local parametrized symplectic regular curve. Throughout this paper, we use z to be defined on an open interval of R. And we use the notation z to indicate differentiation with respect to the parameter t:

$$\dot{z} = \frac{dz}{dt}$$

Definition 1. Let $z(t)$ be a symplectic regular curve in $Sim = (R^4, \Omega)$. Then the following non-degeneracy condition is satisfied

$$\langle \dot{z}, \ddot{z} \rangle \neq 0$$

for all $t \in R$.

Definiton 2. Let $z(t)$ be a symplectic regular curve ,$t_0 \in R$, then the symplectic arc length s of a symplectic regular curve is given

$$s(t) = \int_{t_0}^{t} \langle \dot{z}, \ddot{z} \rangle^{1/3}\, dt$$

for all $t \geq t_0$.

If

$$\int_{t_1}^{t_2} \langle \dot{z}, \ddot{z} \rangle^{1/3}\, dt = t_2 - t_1 \qquad\qquad (t_1, t_2 \in I) \quad t_1 \leq t_2$$

symplectic regular curve is said to parametrized by symplectic arc length. The symplectic arc length parameter corresponds to the equaffine arc length for plane curves.

Taking the extrerior differential of above equation, the symplectic arc length element is obtained by

$$ds = \langle \dot{z}, \ddot{z} \rangle^{1/3} dt$$

And the arc length derivative operator is

$$D = \frac{d}{ds} = \langle \dot{z}, \ddot{z} \rangle^{-1/3} \frac{d}{dt}$$

In our notion, the symplectic arc length derivative operator is defined by

$$z' = \frac{dz}{ds}$$

Definiton 3. A symplectic regular curve is parametrized by symplectic arc length if it satisfies

$$\langle \dot{z}, \ddot{z} \rangle = 1$$

for all $t \in R$.

Example 1. Let $z: I \to R^4$

$$z(s) = (-sins, sins, coss, sins)$$

Here,

$$z'(s) = (-coss, coss, -sins, coss)$$

And

$$z''(s) = (sins, -sins, -coss, -sins)$$

It is obvious that z is symplectic regular curve ,since

$$\langle \dot{z}(s), \ddot{z}(s) \rangle = 1$$

Let $z(s)$ be a symplectic regular curve parametrized by arc length with $\{a_1, a_2, a_3, a_4\}$ a symplectic frame. Then, Frenet equations can be written by

$$a_1{}'(s) = a_3(s)$$
$$a_2'(s) = H_2(s)a_4(s)$$
$$a_3'(s) = k_1(s)a_1(s)$$
$$a_4'(s) = a_1(s) + k_2(s)a_2(s)$$

where $H_2(s) = cost(\neq 0)$.

1. Equiform Differential Geometry On Symplectic Space

In this section, we introduce the equiform parameter and define frame which is according to equiform frame in symplectic space. Let α be a curve parameterized by the arc length s in symplectic space. The equiform parameter of the curve α(s) is defined

$$\rho = \frac{1}{k_1}$$

$$\sigma = \int \frac{ds}{\rho} = \int k_1 \, ds$$

$$\frac{ds}{d\sigma} = \rho$$

We investigate Frenet vectors in Equiform Differential geometry on symplectic space.

$$V_1 = \frac{dz}{d\sigma} = \frac{dz}{ds}\frac{ds}{d\sigma} = a_1\rho$$

Similarly, differentiating Frenet vectors, we obtain

$$V_2 = a_2\rho$$

$$V_3 = a_3\rho$$

$$V_4 = a_4\rho$$

Here , differentiating above equations and using Frenet frame (1) ,

$$\nabla_\alpha V_1 = \left(\frac{da_1}{ds}\rho + a_1\frac{d\rho}{ds}\right)\rho$$

$$\nabla_\alpha V_1 = a_3\rho + a_1\dot{\rho}\rho$$

That is , we find

$$\nabla_\alpha V_1 = V_3 + V_1\dot{\rho}$$

By differentiatin again, we obtain

$$\nabla_\alpha V_2 = \frac{d(a_2\rho)}{ds}\rho$$

$$\nabla_\alpha V_2 = \left(\frac{da_2}{ds}\rho + a_2\frac{d\rho}{ds}\right)\rho$$

$$\nabla_\alpha V_2 = \rho H_2 a_4\rho + \dot{\rho}a_2\rho$$

That is , we get,

$$\nabla_\alpha V_2 = \rho H_2 V_4 + \dot{\rho}V_2$$

And similarly,

$$\nabla_\alpha V_3 = \frac{dV_3}{d\sigma} = \frac{d(a_3\rho)}{ds}\frac{ds}{d\sigma}$$

$$\nabla_\alpha V_3 = \left(\frac{da_3}{ds}\rho + a_3\frac{d\rho}{ds}\right)\rho$$

that is,

$$\nabla_\alpha V_3 = K_1 a_1 \rho\rho + a_2\rho^2 + \rho\dot{a_3}\rho$$

Thus, we obtain,

$$\nabla_\alpha V_3 = V_1 + \rho V_2 + \dot{\rho}V_3$$

And

$$\nabla_\alpha V_4 = \frac{dV_4}{d\sigma} = \frac{d(a_4\rho)}{ds}\frac{ds}{d\sigma}$$

$$\nabla_\alpha V_4 = \left(\frac{da_4}{ds}\rho + a_4\frac{d\rho}{ds}\right)\rho$$

Similarly,

$$\nabla_\alpha V_4 = \left((a_1 + K_2 a_2)\rho + a_4\dot{\rho}\right)\rho$$

$$\nabla_\alpha V_4 = (a_1\rho + K_2\rho a_2 + a_4\dot{\rho})\rho$$

Hence, we get,

$$\nabla_\alpha V_4 = a_1\rho + K_2\rho\rho a_2 + \dot{\rho}a_4\rho$$

Thus the equiform Frenet formulas can be given as

$$\nabla_\alpha V_1 = K_1 V_1 + \rho V_3$$

$$\nabla_\alpha V_2 = K_1 V_2 + K_2 V_4$$

$$\nabla_\alpha V_3 = K_1 V_3 + V_1 + \rho V_2$$

$$\nabla_\alpha V_4 = \rho V_1 + K_3 V_2 + K_1 V_4$$

(2.1

And Frenet equations are shown with matrix form as follows,

$$\frac{d}{ds}\begin{pmatrix} V_1(s) \\ V_2(s) \\ V_3(s) \\ V_4(s) \end{pmatrix} = \begin{pmatrix} K_1(s) & 0 & \rho & 0 \\ 0 & K_1(s) & 0 & K_2(s) \\ 1 & \rho & K_1(s) & 0 \\ \rho & K_3(s) & 0 & K_1(s) \end{pmatrix}\begin{pmatrix} V_1(s) \\ V_2(s) \\ V_3(s) \\ V_4(s) \end{pmatrix}$$

With symplectic curvature functions,

$$K_1 = \dot{\rho} \quad , \; K_2 = \rho H_2, \qquad K_3 = \frac{K_2}{K_1}$$

It is known that arbitrary curve z in E_1^4 is called osculating curve of the first or second kind if its position vector always lies in the orthogonal complement ${a_3}^{\perp}$ or ${a_4}^{\perp}$ respectively [6].

So, the position vector of the symplectic osculating curve of the first and the second kind osculating curve satisfies equation

$$z(s) = \lambda(s)V_1(s) + \mu(s)V_2(s) + \upsilon(s)V_3(s) \tag{2.2}$$

$$z(s) = \lambda(s)V_1(s) + \mu(s)V_2(s) + \upsilon(s)V_4(s) \tag{2.3}$$

3. Osculating curves According to Equiform Frame in Symplectic space

Theorem 3.1. Let z be symplectic curve in symplectic space with vector fields V_2 and V_3. Then z is congruent to the first kind osculating curve, $K_2 = 0$ for eachs.

Proof. Firstly, suppose that z is the first kind osculating curve on equiform frame in symplectic space. Then its position vector satisfies relation (2.2) with respect to s and using Frenet equations (2.1), we can easily see that

$$z' = \boldsymbol{\lambda}' V_1 + \boldsymbol{\lambda} V_1' + \mu' V_2 + \mu V_2' + \upsilon' V_3 + \upsilon V_3'$$

And using (2.1) we obtain

$$z' = \boldsymbol{\lambda}' V_1 + \boldsymbol{\lambda}(K_1 V_1 + \rho V_3) + \mu' V_2 + \mu(K_1 V_2 + K_2 V_4) + \upsilon' V_3 + \upsilon(K_1 V_3 V_1\, \rho V_2)$$

or

$$z' = (\boldsymbol{\lambda}' + \boldsymbol{\lambda} K_1 + \upsilon)V_1 + (\mu' + \mu K_1 + \upsilon\rho)V_2 + (\boldsymbol{\lambda}\rho + \upsilon' + \upsilon K_1)V_3 + (\mu K_2)V_4$$

Thus,

$$\boldsymbol{\lambda}' + \boldsymbol{\lambda} K_1 + \upsilon = \frac{1}{\rho}$$

$$\mu' + \mu K_1 + \upsilon\rho = 0$$

$$\boldsymbol{\lambda}\rho + \upsilon' + \upsilon K_1 = 0$$

$$\mu K_2 = 0$$

and from last equation, we obtain

i) If $\mu = 0, \upsilon = 0, \boldsymbol{\lambda} = \mathbf{0}$

ii) If $\mu \neq 0, K_2 = 0$.

Theorem 3.2. Ever symplectic curve with vector fields V_2 and V_3 lying fully in symplectic space is the second kind osculating curve.

Differentiating equation (2.3), with respect to s and using Frenet equations (2.1), we obtain

$$z' = \boldsymbol{\lambda}' V_1 + \boldsymbol{\lambda} V_1' + \mu' V_2 + \mu V_2' + \upsilon' V_4 + \upsilon V_4'$$

And using (2.1) we obtain

$$z' = \boldsymbol{\lambda}' V_1 + \boldsymbol{\lambda}(K_1 V_1 + \rho V_3) + \mu' V_2 + \mu(K_1 V_2 + K_2 V_4) + \upsilon' V_4 + \upsilon(\rho V_1 + K_3 V_2 + K_1 V_4)$$

or

$$z' = (\boldsymbol{\lambda}' + \boldsymbol{\lambda} K_1 + \upsilon\rho) V_1 + (\mu' + \mu K_1 + \upsilon K_3) a_2 + (\boldsymbol{\lambda}\rho) V_3 + (\mu K_2 + \upsilon' + \upsilon K_1) V_4$$

Thus we get,

$$\begin{aligned} \boldsymbol{\lambda}' + \boldsymbol{\lambda} K_1 + \upsilon\rho &= \frac{1}{\rho}, \\ \mu' + \mu K_1 + \upsilon K_3 &= 0 \\ \boldsymbol{\lambda}\rho &= 0 \\ \mu K_2 + \upsilon' + \upsilon K_1 &= 0 \end{aligned} \tag{2.4}$$

From (2.4) equations, we get

$$\upsilon = \frac{1}{\rho},$$

and

$$\boldsymbol{\lambda} = 0$$

$$\mu K_2 + (\frac{1}{\rho})' + \frac{1}{\rho} K_1 = 0$$

$$\mu = \frac{2\rho\rho' - \rho^2 K_1}{\rho^4 K_2}$$

Theorem 3.3. Let $z(s)$ be a unit speed symplectic curve in symplectic space with vector fields V_2 and V_3 lying fully in symplectic space. If z is the second kind osculating curve, then the following statements hold:

i) The tangential and the principal normal component of the position vector z are respectively written by

$$\langle z, V_1\rangle = 0, \qquad \langle z, V_2\rangle = -\frac{1}{\rho}$$

ii) The second binormal component of the position vector z is

$$\langle z, a_4\rangle = \frac{2\rho\rho' - \rho^2 K_1}{\rho^4 K_2}$$

Proof. First assume that z is congruent to the second kind osculating curve in R^4. By using relation (2.3) and (2.4), the position vector of z can be given as

$$z(s) = \frac{2\rho\rho' - \rho^2 K_1}{\rho^4 K_2} V_2 + a_4 = (-k_2 s + c)a_2 + \frac{1}{\rho} V_4 \qquad (2.5)$$

i) $\langle z, V_1\rangle = 0$, $\langle z, V_2\rangle = -\frac{1}{\rho}$

ii) $\langle z, V_4\rangle = \frac{2\rho\rho' - \rho^2 K_1}{\rho^4 K_2}$

Relation (2.4) easily see that relations i) ii) are satisfied, which proves statements i), ii).

Conversely, suppose that statement (i) holds. By taking the derivative of the equation

$$\langle z, V_2\rangle = -\frac{1}{\rho}$$

and

$$\langle z', V_2\rangle + \langle z, V_2{}'\rangle = -(\frac{1}{\rho})'$$

Thus, we get,

$$\langle \lambda' V_1 + \lambda V_1' + \mu' V_2 + \mu V_2' + \upsilon' V_4 + \upsilon V_4', V_2\rangle + \langle \lambda V_1 + \mu V_2 + \upsilon V_4, (K_1 V_2 + K_2 V_4)\rangle = 0$$

And we obtain ,

$$\langle z, V_3 \rangle = 0$$

which means that z is congruent to the second kind osculating curve. If statement (ii) holds, similarly, we obtain that z is congruent to the second osculating curve.

Example 3.1.

Let's take the following curve

$$z(s) = \frac{1}{\sqrt{5}}\left(shs, \frac{1}{2}s^2 + 2s, chs, \frac{1}{2}s^2 - 2s\right).$$

Figure 1. Then,

$$a_1(s) = z'(s) = \frac{1}{\sqrt{5}}(chs, s+2, shs, s-2$$

$$a_3(s) = z''(s) = \frac{1}{\sqrt{5}}(shs, 1, chs, 1).$$

$$a_2(s) = \frac{1}{\sqrt{5}}(\frac{4}{5}chs, -\frac{1}{5}(s+2), \frac{4}{5}shs, -\frac{1}{5}(s-2),$$

$$a_4(s) = \frac{5}{4\sqrt{5}}(4shs, -1, 4chs, -1).$$

Since $\rho = 1$, we obtain Frenet vectors respect to equiform frame ,

$$a_1(s) = V_1(s) = \frac{1}{\sqrt{5}}(chs, s+2, shs, s-2)$$

$$a_2(s) = V_2(s) = \frac{1}{\sqrt{5}}(\frac{4}{5}chs, -\frac{1}{5}(s+2), \frac{4}{5}shs, -\frac{1}{5}(s-2)$$

$$a_3(s) = V_3(s) = \frac{1}{\sqrt{5}}(shs, 1, chs, 1)$$

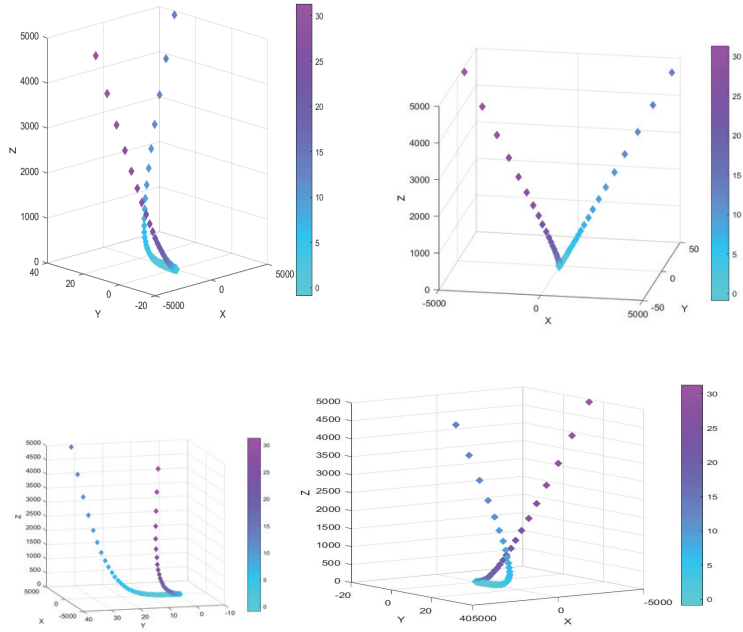


Figure 1. Symplectic regular curve $z(s)$

This curve in R^4 is plotted with a code that represents the fourth dimension with a color scale.

We obtain

$$\langle z, V_3 \rangle = 0$$

$$k_1 = \langle a_3', a_3 \rangle = \frac{1}{5} \quad , \quad \rho = \frac{1}{k_1} = 5$$

α is congruent to the second kind osculating curve.

$$k_2 = \langle a_4', a_4 \rangle = \frac{4}{25}$$

$$H_2 = -\langle a_2', a_2 \rangle = 5$$

REFERENCES

[1] Deshmukh S., Chen B. Y., Alshammari S H., (2018),On Rectifying curves in Euclidean 3-space, Turkish Journal of Mathematics , 42(2), 609-620, 2018

2] Kamran N., Olver P., Tenenblat K., (2009)., Local symplectic invariants for curves. Commun. Contemp. Math., 11(2): 165-183.

[3] İlarslan K., Neŝović E., (2008),Some characterizations of osculating curves in the Euclidean space, Demonstratio Mathematica, 41(4), 931-940,.

[4] Shaikh A. A., Ghosh P.R,(2020), Rectifying and osculating curves on a smooth surface, Indian Journal of Pure and Applied Mathematics, 51(1), 67-75,.

[5] Valiquette F., (2012), Geometric affine symplectic curve flows in R^4.Diff. Geo. Appl. 30(6) : 631-641.

[6] İlarslan K., Neŝović E., (2009)The first and the second kind osculating curves in Minkowski space-time, Comp. Rend. Acad bulg. Sci . , 62(6), 677-686.

[7] Franklin P., (1926), Osculating curves and surfaces, Transactions of American Mathematical Society, **28**(3), 400-416,.

[8] Bozkurt Z., Gök I., Okuyucu O Z., Ekmekçi F N., (2013),Characterizations of rectifying, normal and osculating curves in three dimensional compact Lie groups.Life Science Journal, 10(3), 819-823,.

[9] İlarslan K., Neŝović E., (2012) ,Some characterizations of null osculating curves in the Minkowski space-time, Proceedings of the Estonian Academy of Sciences, 61(1), 1,.

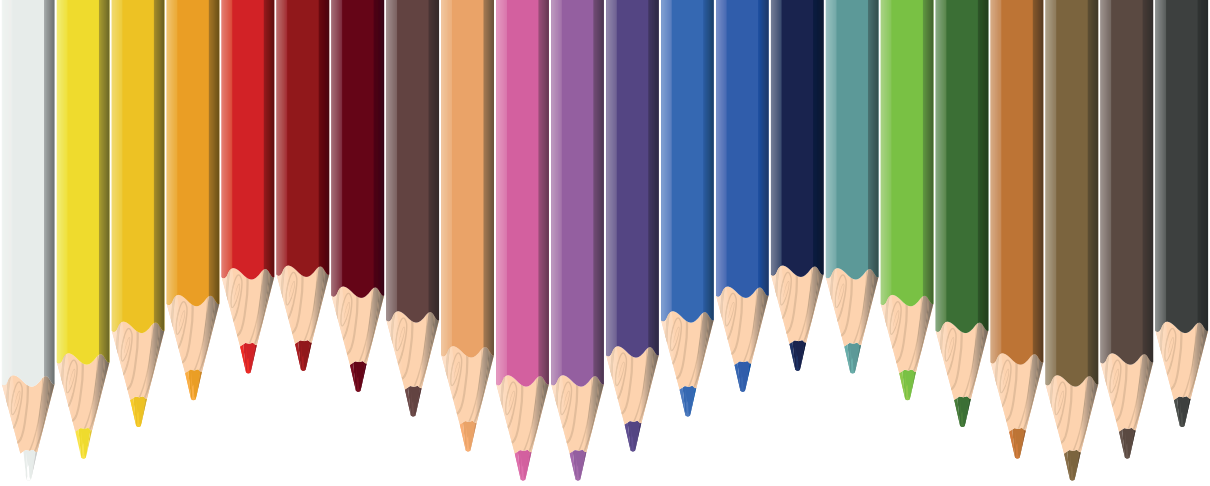
[10] İlarslan K ., Kılıç N, Erdem H A , (2017), Osculating curves in 4 –dimensional semi- Euclidean space with index 2, Open Mathematics , 15(1), 562-567,.

[11]Çetin E.Ç, Bektaş M., (2019), The characterizations of affine symplectic curves in R^4, Mathematics , **7**(1), 110.

[12] Çetin E.Ç, Bektaş M., (2019) ,Some new characterizations of symplectic curve in 4-dimensional symplectic space, Communications in advanced mathematical Sciences , **2**(4), 331-334.

[13] Çetin E.Ç, Bektaş M., (2020),k-type slant helices for symplectic curve in 4-dimensional symplectic space, Facta Universitatis, Series: Mathematics and Informatics, **35**,641-646.

[14] Kapovic M., Milson J J., (1996),The symplectic geometry of polygons in Euclidean space, Journal of Differential Geometry, 44(3), 479-513,.



Chapter 6

USED IN CALCULATING THE THICKNESS OF THIN FILMS METHODS AND DEVICES

Gizem AYAS[1]
İbrahim BOZ[2]

1 (Öğr.Gör). (Gizem AYAS) Kurumu: (Mardin Artuklu üniversitesi, Makine Bölümü,)
2 .(Öğr.Gör). (İbrahim BOZ) Kurumu: (Mardin Artuklu üniversitesi, Elektrik Bölümü,)

1. INTRODUCTION

Thin products are used in many technological products with high economic value. Semiconductor technology is among the widest application areas of films today. Nanometer-level thin films are used in microelectronic devices such as diodes, transistors, sensors and photovoltaic systems. The material of thin films produced at the micrometer level is used for the purpose of mechanical properties and surface standards (Temel, 2015).

Thin films are used as high-tech materials in the optical, electronic, magnetic, chemical and mechanical industries because when bulk materials are coated, they are given many properties that they cannot provide on their own. Material proportions and their proportions include not only composition but also appropriate production methods and structure and/or control values of micro coins (EROL,M 2001). The importance of semiconductors in technological applications is quite great. Advances in electronics and computer technology have been made possible by better payments of semiconductors and thus technological developments have accelerated. In addition, when produced in large quantities, they can be used as electronic circuit elements because they behave in a completely different way and with new features.

The characteristic properties of these semiconductor thin films and related applications are influenced by several factors such as grain size, crystallization, forbidden energy gap and resistivity (SZE, SIMONM, 1981). The particle capacity of the semiconductor affects electricity, especially the forbidden energy range. In recent years, the gaps between the structure and physical properties of semiconductor thin films, solids obtained in various ways, have been investigated (CALIXTO and Ark 2005). Optical, electrical and flexible examination of semiconductor thin films used in electronic circuit elements, especially in solar energy systems, is of great technological importance (POORTMANS, J. et al, 2006.).

2.THİN FİLM

Thin film; They are surfaces created by coating a substrate with a thickness ranging from 10 nm to 1 μm. This limitation given for thickness is not absolute. Films up to 2 Angistroms are in the thick film category. In measuring the basic properties of the material on a solid material as a substrate, a solid material is formed in the form of a thin film both by a direct physical process and by chemical or electrochemical reactions. What needs to be emphasized here is that measuring small film thickness, which is an important feature of the film and the parameter that limits the properties of the film, is not simple. Thin films form a good physical structure as a direct result of their small thickness, large surface to volume ratio and growth techniques. As thin films form, deviations begin between the properties of the substance in powder form

and its properties after the thin film is formed. In different environmental conditions; Structural, electrical and optical properties of thin films have begun to be emphasized. Although thin films have a large surface area, their volume ratio causes them to have small thickness and microstructures, so these films can be exposed to gas absorption and diffusion events (KİTTEL, C., 1996). The basis of today's technology is semiconductor thin films. There are many methods that can be used for the production of thin films. Production stages are determined according to the production method of thin films.

3. THIN FILM THICKNESS MEASURING SYSTEM USAGE AREAS

Thin Film Thickness Measurement System is used in many different industries and application areas and is useful for a variety of purposes in these areas. Here are some of the common uses of thin film thickness measurement systems:

Semiconductor Manufacturing: The semiconductor industry frequently uses thin-film coatings in the production of microchips and other electronic components. Thin film thickness measurement is used to check the quality and suitability of these coatings.

Solar Cells and Photovoltaic Applications: Solar cells and photovoltaic panels use thin-film coatings. Thickness measurement is used to increase panel efficiency and optimize production processes.

Optoelectronic and Photonic Products: Optoelectronic components are found in thin-film coatings in products such as lasers, optical fibers, and optical networks. Thickness measurement is important to evaluate the performance of these components.

Glass Coatings and Optical Products: The glass industry uses thin-film coatings on eyeglass lenses, lenses and other optical products. Thickness measurement is used to check optical quality and surface finish.

Medicine and Biomedical Devices: Thin film coatings on the surfaces of biomedical devices are used to provide corrosive resistance and biocompatibility. Thickness measurement is used to determine the quality and suitability of coatings.

Microelectronics Packaging: Thin film packaging is widely used for microelectronic devices. Thickness measurement is important to control the quality and integrity of these packages.

Protective Coatings and Surface Modification: Protective coatings of metal, glass, and plastic surfaces use thin-film coatings. Thickness measurement is used to evaluate the durability and performance of coatings.

Food and Beverage Industry: Barrier coatings in food and beverage packaging are used to extend the shelf life of products.

Energy Storage and Fuel Cells: Energy storage devices and fuel cells are areas where thin film coatings are used. Thickness measurement is used to monitor and optimize the performance of these coatings.

4.METHODS OF METHODS OF THİN FİLMS

Thin Film Thickness Measurement System is generally based on optical measurement principles and sends a light or radiation source onto the surface to precisely determine the thickness of the thin film. The operating principle of these systems may vary across different technologies, but the most commonly used principles and devices include:

a)Irradiance (Ellipsometry): Ellipsometry uses changes in optical polarization to measure thin film thickness and surface properties. The system uses a pearl light beam from a special light source. When light hits the thin film, it is reflected on the surface and the polarization state changes. The changing polarization state is used to calculate the thickness and optical properties of the thin film.

b) Spectrophotometry: Spectrophotometry works through the reflection or transmission of light sent to the surface of the thin film. The light source uses a spectrometer that produces light of different wavelengths. As the light hits the surface of the thin film, some of it is reflected or transmitted. A spectrometer measures the spectrum of reflected or transmitted light. These spectra are analyzed to determine the thickness and optical properties of the thin film.

c)Interferometry: Interferometry uses the reflection of light from the surface and the interference patterns created at different wavelengths to measure the thickness of the thin film. Interferometric systems measure phase changes of reflected light waves, and these changes are used to calculate thin film thickness.

d)Ultrasonic Measurement: Ultrasonic thin film thickness measurement works by sending and reflecting or passing sound waves to the thin film. The speed of sound waves is used to determine the thickness of the thin film.

Each of these principles is used to measure the thickness of thin film to different precisions and can vary depending on the sampling system, the properties of the material for which you want to measure the film thickness, and your requirements. As a result, thin film thickness measurement systems are an important tool for controlling and characterizing the quality and properties of surfaces and coatings. Some of the devices used are listed below.

1- Spectroscopic Ellipsometer device.

2- X-Ray Diffraction device

3-Scanning Electron Microscope (SEM)

4.1 SPECTROSCOPİC ELLİPSOMETER DEVİCE.

Ellipsometer is used to determine the refractive indices of semiconductors. Ellipsometer enables the acquisition of information about the polarization parts of the vector of a wave and the optical system that modifies it. By means of parts of a polarized light cycle, the light is affected by the optical system being examined. This interaction is valid when monochromatic and polarized light is sent under the desired angle of incidence, polarization changes by changing the boundaries of the media with different optical properties, and the light can be kept at the boundary at a certain angle. By determining the polarization of the reflected or transmitted beam, the production optical data used can be determined. From here, the amount of the path is determined.

The relationship between absorption and related relations can be found from Lambert Beer's law.

Şekil 4.1. *J.A. WoollamCo.,Inc. SPECTROSCOPİC ELLİPSOMETER DEVİCE*

4.2.X-Ray Diffraction device (XRD)

A simple formula and a geometrical condition were proposed as a result of the diffraction of Bragg waves by a set of parallel planes. There is a difference between the diffraction of light through a slit and the diffraction of x-rays in a crystal. In diffraction of light, the angle of incidence and the angle resulting from diffraction are not equal to each other, and there is a relationship between these two angles, wavelength and width of the slit. The Bragg diffraction condition states that the angle of incidence and angle of reflection are equal. However, reflection can only be observed when the angle of incidence is appropriate to the wavelength and the distance between two consecutive planes is appropriate.

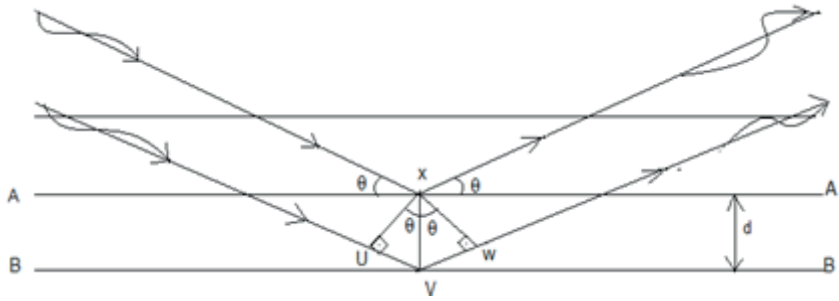


Figure 4.2. *Illustration of Bragg reflection and thickness (d)*

Let's assume that the X-rays are directed parallel towards the single crystal. These x-rays interact with all the atoms in the crystal where they can travel. Here we consider that x-rays interact with a series of parallel planes of atoms making an angle θ. As a result of the interaction with the first of these planes, a reflection component with a reflection angle of θ will be formed, and this component is quite weak if the x-rays travel deep into the crystal. Since this first plane has a periodic pattern, this plane acts as a two-dimensional diffraction grating for x-rays and the weak components will be reflected to different diffraction degrees at different angles θm.

$$2d\sin\theta = n\lambda \tag{4.1}$$

In the second and all subsequent planes, the components of the reflected energy will similarly occur at specific angles of reflection. Since x-rays can travel deep into the crystal in thousands of successive planes to reveal different weak components, it is obvious that destructive interference at most angles of incidence between the x-ray beam and sets of planes will prevent the visibility of well-defined planes. It can be seen in figure 2.1 that the x-ray beam exposed to reflection from the second plane will travel 2dsinθ more than the ray reflected from the first plane. Each reflected component will combine constructively if the interplane distance is an exact multiple of the

wavelength. As a result, the efficient condition for reflection, namely Bragg's Law;

It happens like this. Here n is an integer. Where d in the equation is the thickness of the thin film and λ is the wavelength of the light sent by the device. In general, it is clear that single wavelength x-rays will not cause constructive interference when they come towards the crystal at a random angle. Both wavelength and angle must be changed until Bragg's law is realized. Although Bragg's law is necessary to obtain efficient reflection, it is not sufficient due to factors affecting reflection. The efficient reflection to be obtained from a special plane such as (hkl) is related to whether parameters such as structure factor and atomic scattering factor allow this reflection (Blakemore 1989).

In addition, X-ray diffraction is a method used to determine the structure of crystals.

Figure 4.3. *Rikagu Ultima III x-ray diffractometer*

4.3. SCANNİNG ELECTRON MİCROSCOPE (SEM)

The human eye's ability to see very fine details is limited. For this reason, optical devices have been developed that allow smaller details to be seen by replacing the light paths that transmit images with lenses. By using electronic and optical systems together, devices have been developed to obtain images that can be processed and analyzed at high magnifications.

The scanning electron microscope, designed within the framework of electroscopic principles, is one of the devices that serve this purpose. In the

Scanning Electron Microscope (SEM), the image is obtained by focusing electrons accelerated with high voltage on the sample and scanning this electron beam on the sample surface.

It is achieved by collecting the effects that occur as a result of various interferences between electrons and sample atoms during the process, in appropriate sensors, and transferring them to the screen of a cathode ray tube after passing through signal amplifiers.

In modern systems, the signals from these sensors are converted into digital signals and given to the computer monitor. Both the discrimination power, depth of focus and image and analysis combining feature expand the usage area of the scanning electron microscope.

Scanning Electron Microscope consists of three basic parts: Optical Column, Sample Cell and Imaging System. In short; Scanning Electron Microscope (SEM) creates images by scanning samples with a high-energy electron beam. The thickness of the thin film can be calculated on the resulting image and marked with images.

Figure 4.4. *ZeissEvo 50 scanning electron microscope (SEM)*

5. CONCLUSION AND RECOMMENDATIONS

The thickness of thin films produced with appropriate technologies can be measured with the methods and devices mentioned above. In this way, you can choose the thin film you measure according to the area you want to use, and even produce films of desired thickness.

5. REFERENCES

Blakemore, J.S. (1985). Solid State Physics, Cambridge University Press, Cambridge, United Kingdom.

CAFEROV,T., 1998. Yarıiletken Fiziği-1. Yıldı zTeknik Üniversitesi Basım-Yayın

Merkezi,İstanbul.200s.

CALİXTO-RODRİGUEZM.,TİBURCİO-SİLVER A.,ORTİZA.andSANCHEZ-JUAREZ

A.,2005. Optoelectronicalproperties of indium süflide thinfilmspreparedbyspraypyrolysisforphotovoltaicapplications. Thin Solid Films 480–481, 133–137.

EROL,M.,2001,KatıHalFiziği Ders Notları,DokuzEylülÜniversitesiBuca Eğitim Fakültesi Fizik Eğitimi Bölümü, (yayımlanmamış).

FOX,M., Optical Properties of Solid, Oxford Master SeriesinCondenselMatterPhysics, Oxford University Pres Inc., New York, 2001.

KAVCAR,N., 2001, Uygulamalı Fizik II Ders Notları, Dokuz Eylül Üniversitesi BucaEğitim Fakültesi Fizik Eğitimi Bölümü, 130., (yayımlanmamış).

KİTTEL,C.,1996, Katıhal Fiziğine Giriş, (Çeviren:BekirKaraoğlu), Güven Kitap Yayın Dağıtım Ltd. Şti, 434s.

LUQUEA.,HEGEDUS,S.,2003,HandbookofPhotovoltaicScienceandEngineering,U-SA, 1179 s.

MARKVART,T.,2003,PracticalHandbookofPhotovoltaics,USA,1015 s.

MOSST.S.,1954TheBreakdownoftheband-gap-common-cationrule: originofthes-mallbandgapofInNProc.Phys. Soc. London, Sect. B **67**, 775.

ORAL,M.,1979,Güneş Pilleri,İzmirİlkerMatbaası,59s.

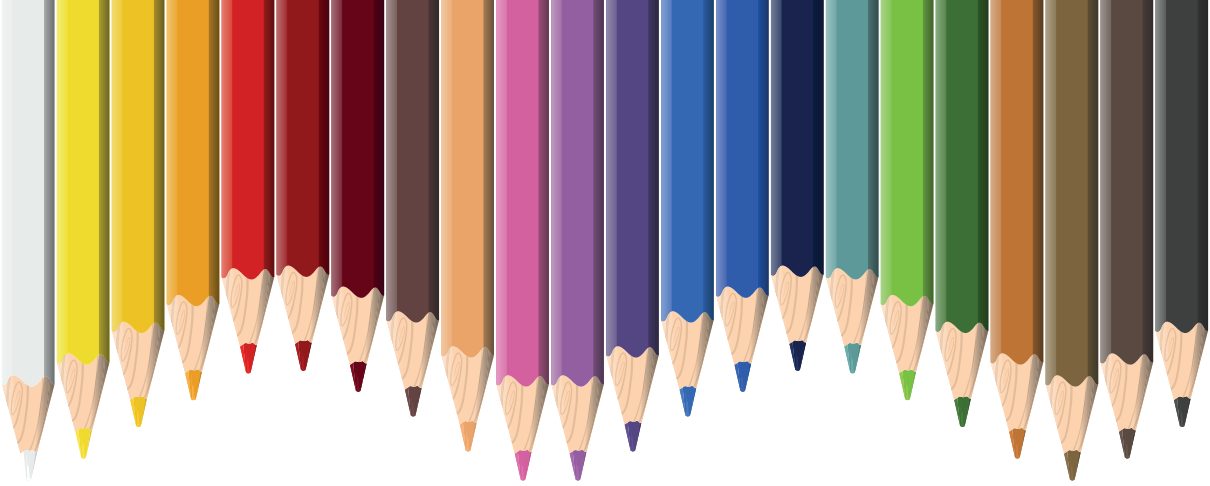
POORTMANS,J.,ARKHIPOV, V.,2006,Thin FilmSolarCells, Enland,471 s.

SZE,SİMONM.,Physicsof SemiconductorDevices(Wiley-Interscience,NewYork,NY) 1981.

SEYAM M.A.M., 2001.Optical andelectricalpropertiesof indiummonosulfide (InS) thinfilms. Vacuum 63, 441–447.

TEMEL, S. (2015). MgO)x(ZnO)1-x İnce Filmlerinin Üretimi ve Karakterizasyonu. (Doktora Tezi).

EskiŞehir Osmangazi Üniversitesi, Fen Bilimleri Enstitüsü, Fizik Ana Bilim Dalı, EskiŞehir



Chapter 7

ANALYSIS OF THE SEMI-LINEAR PSEUDO-PARABOLIC INVERSE COEFFICIENT PROBLEM

İrem BAĞLAN[1]

1 Kocaeli University, Faculty of Arts and Sciences, Department of Mathematics, Kocaeli, Türkiye (ORCID: 0000-0002-1877-9791) isakinc@kocaeli.edu.tr

INTRODUCTION

Differential equations are utilized in the field of applied mathematics to model physical events mathematically. Studies on geometric surfaces and problems in mechanical fields have given rise to the need for partial differential equations. Partial differential equations are employed to solve problems in various physical, chemical, and biological domains, leading mathematicians to focus on these equations [1].

The term "heat" refers to the energy transfer resulting from temperature differences. Heat transfer is a physical phenomenon commonly used in nature and our daily lives through various tools. Although knowledge about heat transfer has generally been demonstrated experimentally, the theory of heat transfer is rapidly advancing today through analytical and numerical solutions. Heat transfer finds extensive applications in engineering, such as in gas turbines, nuclear reactors, renewable energy, and more.

Pseudo-parabolic differential equations are used in diffusion, thermoelectricity, chemical water flow, and population dynamics. There has been a notable surge in endeavors aimed at devising approximate analytical or fully numerical solutions, reflecting a broader shift toward leveraging advanced computational techniques to address complex problems in diverse scientific and engineering domains for non-local boundary value problems. Finite difference schemes have been applied to obtain numerical solutions for one-dimensional non-local boundary value problems [2,3,4,5,6,7,8]. Many instances of periodic boundary conditions manifest in the realms of heat transfer and life sciences, contributing to their significance.. These problems are solved using boundary conditions.

Boundary conditions can be local or non-local, with non-local conditions being the most challenging. Periodic boundary conditions also fall into this category [10,11,12,13]. Periodic boundary conditions are used in problems involving wave theories, including those related to the moon. The significant efforts have been made to study approximate analytical or completely numerical solutions.

Inverse problems are addressed in the fields of physics and engineering when dealing with problems that cannot be directly computed. These problems are used in finding unknown properties in the environment, studying acoustic wave scattering, defining flying objects, designing submarines, and remote sensing [13,14,15].

In this study, the inverse pseudo-parabolic quasi-linear problem with periodic boundary conditions has been solved. The singularity, existence, convergence, and stability of the solution have been examined. Fourier and Picard methods will be employed for the analytical solution to find the inverse coefficient and solution.

1.Basic Concept

$c\nu_t = k\Delta\nu + \Delta(x,t)$ parabolic(heat) equation

$\nu(x,t)$	At time t, at point x
$\Delta(x,t)$	Heat source
k	Thermal conductivity coefficient
c	heat of warming

Tanım: Pseudo parabolic(heat) equation,

$$c\nu_t = k\Delta\nu + c\varepsilon\frac{\partial}{\partial t}\Delta\nu + \Delta(x,t)$$

$\nu(x,t)$	At time t, the temperature at point x
$\Delta(x,t)$	Heat source
k	Thermal conductivity coefficient
c	heat of warming

Pseudo parabolic(heat) equation with nonlinear heat source,

$$c\nu_t = k\Delta\nu + c\varepsilon\frac{\partial}{\partial t}\Delta\nu + \Delta(x,t,\nu)$$

Tanım. Let $h(x)$, 2π a periodic function.

$$h(x) = \frac{a_0}{2} + \sum_{k=1}^{\infty} a_k Coskx + b_k Sinkx$$

is called a Fourier series. a_0, a_k, b_k are named Fourier coefficients.

Tanım. x_n converges to x, it is said to be convergent. If this space is complete, it is named a Banach space.

Tanım. Let the points (x,t_1) and (x,t_2) be defined in a region D.

$$\|f(x,t_1) - f(x,t_2)\| \le M\|t_1 - t_2\|$$

satisfies the Lipschitz condition, it is said to have Lipschitz continuity. M is the Lipschitz constant.

2. SEMİ-LİNEAR PSEUDO-PARABOLİC PROBLEM

The Fourier method and the iteration method will be employed to explore the solution's existence and uniqueness in addressing the given problem. This investigation will focus on examining the following problem in the course of this study.

$$T_t - T_{xx} - \varepsilon T_{xxt} - j(t)T = f(x,t,T) \quad (1)$$

$$T(0,t) = T(\pi,t),\ t \in [0,T] \quad (2)$$

$$T_x(0,t) = T_x(\pi,t),\ t \in [0,T] \quad (3)$$

$$T(x,0) = \varphi(x),\ x \in [0,\pi] \quad (4)$$

$$s(t) = \int_0^{\pi} xT(x,t)dx, t \in [0,T] \quad (5)$$

Let's consider the periodic boundary condition semi-linear parabolic equation defined in the region $\Omega:=\{0<x<\pi,0<t<T\}$ as the problem (1)-(4). Here, the non-linear term is denoted as f=f(x,t,T). The conditions (2)-(3) represent periodic boundary conditions, (4) is the initial condition, and s(t) is an additional integral condition [9].

2.1. Solution of the Semi-Linear Pseudo-Parabolic Problem

If we solve the problem (1)-(5) using the Fourier method:

$$\begin{aligned} T(x,t) &= \frac{1}{2}\left(\varphi_0 e^{\int_0^t j(\tau)d\tau} + \frac{2}{\pi}\int_0^t\int_0^\pi f(x,t,T)dxdt \right) \\ &+\sum_{k=1}^{\infty}\left[\varphi_{ck} e^{\frac{-(2k)^2 t}{1+\varepsilon(2k)^2}-\int_0^t j(\tau)d\tau} + \frac{2}{\pi(1+\varepsilon(2k)^2}\int_0^t\int_0^\pi e^{\frac{-(2k)^2(t-\tau)}{1+\varepsilon(2k)^2}-\int_0^t j(\tau)d\tau}\cos 2kxf(x,t,T)dxdt \right]\cos 2kx \\ &+\sum_{k=1}^{\infty}\left[\varphi_{sk} e^{\frac{-(2k)^2 t}{1+\varepsilon(2k)^2}-\int_0^t j(\tau)d\tau} + \frac{2}{\pi(1+\varepsilon(2k)^2}\int_0^t\int_0^\pi e^{\frac{-(2k)^2(t-\tau)}{1+\varepsilon(2k)^2}-\int_0^t j(\tau)d\tau}\sin 2kxf(x,t,T)dxdt \right]\sin 2kx \end{aligned} \tag{5}$$

where

$$\varphi_0 = \frac{2}{\pi}\int_0^\pi \varphi(x)dx,\ \varphi_{ck} = \frac{2}{\pi}\int_0^\pi \varphi(x)\cos 2kxdx,\ \varphi_{sk} = \frac{2}{\pi}\int_0^\pi \varphi(x)\sin 2kxdx. \tag{6}$$

$$s'(t) = \int_0^\pi xu_t dx, 0 \le t \le T \tag{7}$$

From (1) and (7)

$$\begin{aligned} j(t) &= \frac{1}{s(t)}\left[-s'(t) + \frac{\pi^2}{2}f_0 \right] \\ &+\frac{\pi}{2s(t)}\sum_{k=1}^{\infty}\frac{-(2k)^2 t}{1+\varepsilon(2k)^2}\left(\varphi_{sk} e^{\frac{-(2k)^2 t}{1+\varepsilon(2k)^2}-\int_0^t j(\tau)d\tau} + \frac{1}{1+\varepsilon(2k)^2}\int_0^t f_{sk} e^{\frac{-(2k)^2 t}{1+\varepsilon(2k)^2}-\int_0^t j(\tau)d\tau}d\tau \right) \\ &-\frac{1}{s(t)}\sum_{k=1}^{\infty} f_{sk} \end{aligned} \tag{8}$$

Defination. The pair {j(t), T(x, t)} is recognized as the solution in the context of the inverse coefficient problem (1)-(4).

Defination. For $\{T(t)\}=\{T_0(t),\ T_{ck}(t),T_{sk}(t),k=1,...\}$,

$\|T(t)\|=\max_{0\le t\le T}\left|\frac{T_0(t)}{2}\right|+\sum_{k=1}^{\infty}(\max_{0\le t\le T}|T_{ck}(t)|+\max_{0\le t\le T}|T_{sk}(t)|)$ the norm for the set is called the Banach norm.

Lemma: Let the following conditions be satisfied:

(a) $s(t)\in C^1[0,T]$

(b) $\varphi(x)\in C^{\{3,3\}}([0,\pi])$.

(c)

1) $f(x,t,T)\in C^{\{2,2,0\}}(D)$,

2) $\left|\frac{\partial f(x,t,T)}{\partial x}-\frac{\partial f(x,t,\bar{T})}{\partial x}\right|\le l(x,t)\left|T-\bar{T}\right|$,

$l(x,t)\in L_2(D)$

Theorem: If the conditions of the lemma are satisfied, a solution to the problem (1)-(4) does indeed exist.

Proof: If we iterate on the Fourier coefficients in equation (5), we obtain the following equalities:

$$T_0^{(N+1)}(t)=T_0^{(0)}(t)+\frac{2}{\pi}\int_0^t\int_0^\pi f(x,t,T^{(N)})dxdt$$

$$T_{ck}^{(N+1)}(t)=T_{ck}^{(0)}(t)+\frac{2}{\pi(1+\varepsilon(2k)^2}\int_0^t\int_0^\pi e^{\frac{-(2k)^2(t-\tau)}{1+\varepsilon(2k)^2}\int_0^t j(\tau)d\tau}\cos 2kx f(x,t,T^{(N)})dxdt \qquad (9)$$

$$T_{sk}^{(N+1)}(t)=T_{sk}^{(0)}(t)+\frac{2}{\pi(1+\varepsilon(2k)^2}\int_0^t\int_0^\pi \frac{-(2k)^2(t-\tau)}{1+\varepsilon(2k)^2}-\int_0^t j(\tau)d\tau \sin 2kxf(x,t,T^{(N)})dxdt$$

Lemmaya göre $T^{(0)}(t)\in B,\ t\in[0,T]$ dır.

Applying Cauchy, Lipschitzs, Hölder, Bessel inequality,

$$\begin{aligned}
&\left\|T^{(1)}(t)\right\|\leq\max_{0\leq t\leq T}\left\|\frac{T_0^{(1)}(t)}{2}\right\|+\sum_{k=1}^{\infty}\left(\max_{0\leq t\leq T}\left\|T_{ck}^{(1)}(t)\right\|+\max_{0\leq t\leq T}\left\|T_{sk}^{(1)}(t)\right\|\right)\\
&\leq\frac{\left\|\varphi_0\right\|}{2}+\sum_{k=1}^{\infty}\left(\left\|\varphi_{ck}\right\|+\left\|\varphi_{sk}\right\|\right)\\
&+\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)\left\|l(x,t)\right\|\left\|T^{(0)}(t)\right\|\\
&+\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)M
\end{aligned}\qquad(10)$$

From the theorem $T^{(1)}(t)\in B,\ t\in[0,T].$ For N,

$$\begin{aligned}
&\left\|T^{(N+1)}(t)\right\|\leq\max_{0\leq t\leq T}\left\|\frac{T_0^{(N)}(t)}{2}\right\|+\sum_{k=1}^{\infty}\left(\max_{0\leq t\leq T}\left\|T_{ck}^{(N)}(t)\right\|+\max_{0\leq t\leq T}\left\|T_{sk}^{(N)}(t)\right\|\right)\\
&\leq\frac{\left\|\varphi_0\right\|}{2}+\sum_{k=1}^{\infty}\left(\left\|\varphi_{ck}\right\|+\left\|\varphi_{sk}\right\|\right)\\
&+\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)\left\|l(x,t)\right\|\left\|T^{(N)}(t)\right\|\\
&+\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)M
\end{aligned}\qquad(11)$$

$T^{(N)}(t)\in B,\ t\in[0,T],\ T^{(N+1)}(t)\in B,\ t\in[0,T].$

$\{T(t)\}=\{T_0(t),\ T_{ck}(t),T_{sk},k=1...\}\in B.$

If we iterate in equation (8), we obtain

$$j^{(N)}(t)=\frac{1}{s(t)}\left[-s'(t)+\frac{\pi^2}{2}f_0\right] \\ +\frac{\pi}{2s(t)}\sum_{k=1}^{\infty}\frac{-(2k)^2t}{1+\varepsilon(2k)^2}\left(\varphi_{sk}e^{\frac{-(2k)^2t}{1+\varepsilon(2k)^2}-\int_0^t j^{(N)}(t)d\tau}+\frac{1}{1+\varepsilon(2k)^2}\int_0^t f_{sk}e^{\frac{-(2k)^2t}{1+\varepsilon(2k)^2}-\int_0^t j^{(N)}(t)d\tau}d\tau\right) \\ -\frac{1}{s(t)}\sum_{k=1}^{\infty}f_{sk} \tag{12}$$

For N

$$\left\|j^{(N+1)}(t)\right\|\le\left\|\frac{s'}{s}\right\|+\frac{\pi^2}{4\sqrt{6}s}\sum_{k=1}^{\infty}\left\|\varphi''_{ck}\right\|+\frac{\pi}{\|s\|}\left(1+\frac{\sqrt{6}}{12}+\frac{\sqrt{3}}{12}\right)\|l\|\left\|T^{(N)}\right\| \\ +\frac{\pi}{\|s\|}\left(1+\frac{\sqrt{6}}{12}+\frac{\sqrt{3}}{12}\right)M$$

$$T^{(N)}(t)\in B,\ j^{(N)}(t)\in C^1[0,T],\quad j^{(N+1)}(t)\in C^1[0,T].$$

Theorem: If the conditions of the lemma are satisfied, a solution to the problem (1)-(4) does indeed unique.

Proof: T(t),K(t) and j(t),I(t) are two solutions.

Using Cauchy, Lipschitzs, Hölder, Bessel inequality,

$$\|T(t)-K(t)\|\le\left(1+\frac{\sqrt{6}}{12}+\frac{\sqrt{3}}{12}\right)\|l(x,t)\|\ \|I(t)-j(t)\| \\ +\left(1+\frac{\sqrt{6}}{12}+\frac{\sqrt{3}}{12}\right)\|l(x,t)\|\ \|T(t)-K(t)\|.$$

From Gronwall inequality

$$\|T(t)-K(t)\|\le\left(1+\frac{\sqrt{6}}{12}+\frac{\sqrt{3}}{12}\right)\|l(x,t)\|\ \|T(t)-K(t)\| \tag{13}$$

then

$$T(t) = K(t), I(t) = j(t).$$

2.2 Convergence of the Semi-Linear Pseudo-Parabolic Problem

$T^{(N+1)}(t) \to T^{(N)}(t),\ t \in [0,T], N \to \infty$ ve
$j^{(N+1)}(t) \to j^{(N)}(t),\ t \in [0,T], N \to \infty.$

Applyinng Cauchy, Lipschitzs, Hölder, Bessel inequality,

$$\left\|T^{(1)}(t) - T^{(0)}(t)\right\| \leq \left(\sqrt{\frac{T}{\pi}} + \frac{\sqrt{\pi}}{2\sqrt{3}}\right)\|I(x,t)\|\left\|T^{(0)}(t)\right\| + \left(\sqrt{\frac{T}{\pi}} + \frac{\sqrt{\pi}}{2\sqrt{3}}\right)M \tag{14}$$

Let we get $A = \left(\sqrt{\frac{T}{\pi}} + \frac{\sqrt{\pi}}{2\sqrt{3}}\right)\|I(x,t)\|\left\|T^{(0)}(t)\right\| + \left(\sqrt{\frac{T}{\pi}} + \frac{\sqrt{\pi}}{2\sqrt{3}}\right)M.$

$$\left\|j^{(1)}(t) - j^{(0)}(t)\right\| \leq \frac{\pi}{\|s\|}\left(1 + \frac{\sqrt{6}}{12} + \frac{\sqrt{3}}{12}\right)\|1\|\left\|T^{(1)} - T^{(0)}\right\| + \frac{\pi}{\|s\|}\left(1 + \frac{\sqrt{6}}{12} + \frac{\sqrt{3}}{12}\right)\left\|j^{(1)}(t) - j^{(0)}(t)\right\|$$

$$\left\|j^{(1)}(t) - j^{(0)}(t)\right\| \leq \frac{B}{1-C}\|1\|\left\|T^{(1)} - T^{(0)}\right\|$$

$$\left\|T^{(2)}(t)-T^{(1)}(t)\right\| \leq$$
$$\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)\left(1+\frac{BT}{1-C}\right)\|l(x,t)\|\,A$$

For N

$$\left\|j^{(N+1)}(t)-j^{(N)}(t)\right\| \leq \frac{B}{1-C}\|l\|\left\|T^{(N+1)}-T^{(N)}\right\|$$

$$\left\|T^{(N+1)}(t)-T^{(N)}(t)\right\| \leq$$
$$\left\{\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)\left(1+\frac{BT}{1-C}\right)\right\}^{N}\|l(x,t)\|^{N}\,\frac{A}{\sqrt{N!}}$$

$T^{(N+1)}(t)\to T^{(N)}(t),\ t\in[0,T],N\to\infty$ ve $j^{(N+1)}(t)\to j^{(N)}(t),\ t\in[0,T],N\to\infty$

Let show $T^{(N+1)}(t)\to T(t),\ t\in[0,T],N\to\infty$ ve $j^{(N+1)}(t)\to j(t),\ t\in[0,T],N\to\infty.$

Using Cauchy, Lipschitzs, Hölder, Bessel inequality

$$\left\|T(t)-T^{(N+1)}(t)\right\| \leq$$
$$\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)\|l(x,t)\|\left\|T(t)-T^{(N+1)}(t)\right\|$$
$$+\left\{\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)\left(1+\frac{BT}{1-C}\right)\right\}^{N}\|l(x,t)\|\frac{A}{\sqrt{N!}}$$
$$+\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)M\left\|j(t)-j^{(N+1)}(t)\right\|$$

$$\left\|j(t)-j^{(N+1)}(t)\right\| \leq \frac{B}{1-C}\|l\|\left\|T-T^{(N+1)}\right\|$$

From Gronwall inequality

$$\left\|T(t)-T^{(N+1)}(t)\right\|^2 \le$$
$$2\left[\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)\left(1+\frac{BT}{1-C}\right)\frac{A}{\sqrt{N!}}\left\|l(x,t)\right\|\right]^2$$
$$+\exp 2\left\{\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)\left(1+\frac{BT}{1-C}\right)\right\}^2\left\|l(x,t)\right\|^2$$

$$T^{(N+1)}(t)\to T(t),\ t\in[0,T],N\to\infty \text{ ve } j^{(N+1)}(t)\to j(t),\ t\in[0,T],N\to\infty$$

2.3. Stability of the Semi-Linear Pseudo-Parabolic Problem

Theorem: If the conditions of the lemma are verified, the problem (1)-(4) is stable.

Proof: Let $\Delta=\{\varphi,j,f\}$ ve $\overline{\Delta}=\{\overline{\varphi},\overline{j},\overline{f}\}$.

M_i ,i=1,…

$$\left\|j(t)\right\|\le M_1,\ \left\|\overline{j}(t)\right\|\le M_1,\ \left\|\varphi(t)\right\|\le M_2,\ \left\|\overline{\varphi}(t)\right\|\le M_2,$$

$$\left\|\Delta\right\|\le\left\|j\right\|+\left\|\varphi\right\|+\left\|f\right\|.$$

Applying Cauchy, Lipschitzs, Hölder, Bessel inequality,

$$\left\|T(t)-\overline{T}(t)\right\|\le$$
$$M_3\left\|\Delta-\overline{\Delta}\right\|$$
$$+M_4\left(\int_0^t\int_0^\pi l^2(x,\tau)\left\|T-\overline{T}\right\|^2dxd\tau\right)^{\frac{1}{2}}$$

$$M_3=\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)\left\|l(x,t)\right\|$$

$$M_3=\left(\sqrt{\frac{T}{\pi}}+\frac{\sqrt{\pi}}{2\sqrt{3}}\right)\left(1+\frac{BT}{1-C}\right)$$

From Gronwall ,

$$\left\|T(t)-\overline{T}(t)\right\|^2 \leq$$
$$2M^2{}_3\left\|\Delta-\overline{\Delta}\right\|^2$$
$$+\exp 2M^2{}_4\left(\int_0^t\int_0^\pi l^2(x,\tau)\left\|T-\overline{T}\right\|^2 dxd\tau\right)$$

$\Delta \to \overline{\Delta}$ then $j(t) \to \overline{j}(t)$.

3. REFERENCES

[1] Rundell W., The solution of initial-boundary value problems for pseudoparabolic partial differential equations, Proc. Roy. Soc. Edin. Sect. A., 1975, Vol.74, 311-326.

[2] Lavrenyuk S.P. and Ptashnyk, M.B., On certain nonlinear pseudoparabolic variational inequalities without initial conditions, Ukr. Math. Jour., 1999, Vol. 51, 3.

[3] Halilov H., On mixed problem for quasilinear pseudoparabolic equation,Applicable Analysis, 2000, Vol.75, 1-2.

[4] Halilov H, Çiftçi, I., On Fourier method for a quasilinear pseudo-parabolic equation with periodic boundary condition, Int. J. Pure Appl. Math., 2009, Vol. 52, 717-727.

[5] Baglan I., Kanca F., The continuous dependence and numerical approximation of the solution of the quasilinear pseudo-parabolic problem with periodic boundary condition, Journal of Advances in Mathematics, 2014, Vol. 5 (3).

[6] Baglan I., Determination of a coefficient in a quasilinear parabolic equation with periodic boundary condition, Inverse Problems in Science and Engineering, 2014, Vol. 23 (5), 884-900.

[7] Cao Y., Yin J.X., Wang C.P., Cauchy problems of semilinear pseudo-parabolic equations, Journal of Differential Equations, 2009, Vol. 246, 4568-4590.

[8] Nakhushev A.M., Equations of mathematical biology, Moscow, (in Russian), 1995.

[9] Ionkin N.I., Solution of a boundary-value problem in heat conduction with a non-classical boundary condition, Differential Equations, 1977, Vol. 13, 204-211.

[10] Baglan I, Canel T., Fourier method for higher order quasi-linear parabolic equation subject with periodic boundary conditions, Turkish Journal of Science, 2021, Vol. 6 (3), 148-155.

[11] Brown J.W., Churchill R.V., Fourier series and boundary value problems, McGraw-Hill, 5 th Edition, Inc., Singapur, 1993.

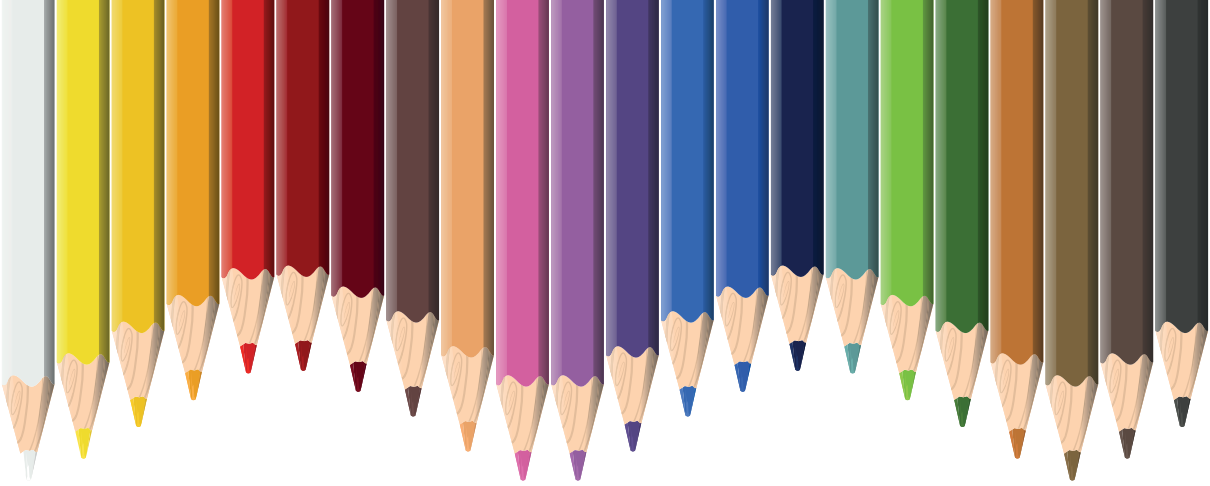
[12] Baglan I., Canel T., Analysis of inverse Euler-Bernoulli equation with periodic boundary conditions, Turkish Journal of Science, 2022, Vol. 7(3), 146-156.

[13] Ciftci I., Halilov H., Fourier method for a quasilinear parabolic equation with periodic boundary condition, Hacettepe Journal of Mathematics and Statistics, 2008, Vol. 37(2), 69-79.

[14] Mehraliyev Y., Allahverdiyeva S., and Ramazanova A., On one coefficient inverse boundary value problem for a linear pseudoparabolic equation of the fourth order, AIMS Mathematics, 2023, Vol. 8(2), 2622-2633.

[15] Rashedi, K., and Yousef, S. A., Ritz-Galerkin method for solving a class of inverse problems in the parabolic equation, International Journal of Nonlinear Science, 2011, Vol. 12 (1), 498-502.

[16] Nakamura S. I., On an Inverse Problem for Quasilinear Parabolic Equations, Tokyo Journal of Mathematics, 1998, Vol. 21(2), 463-469.



Chapter 8

LOG INVERSE MUTH DISTRIBUTION : INFERENCE

Kutluhan ŞAHİN[1]
Cenker BİÇER [2]

1 Kutluhan Şahin, ORCID :0000-0002-5807-6791, kutluhaansahin@gmail.com.
2 Assoc.Prof.Dr., Cenker BİÇER, Kırıkkale Univ., Dep. of Statistics. ORCID: 0000-0003-2222-3208, cbicer@kku.edu.tr.

INTRODUCTION

It is a universally accepted fact among researchers that for data analysis to yield accurate results, the data must be modeled based on an appropriate or closest-to-correct model. There are many probability distributions that can be used to model data, and the selection of the optimal distribution depends on a number of factors, such as the central tendency of the data, the spread of the data, and the symmetry of the data. Although many model probability distributions exist in the vast statistical literature, there is still a need for probability distributions that will optimal model different types of data. In recent years, researchers have paid great attention to presenting more flexible probability distribution models, taking into account this fact. They have put forward valuable models by using base distribution transformations or adding additional parameters to an existing model by their studies.

Newly derived distribution models provide more flexibility and improve modeling performance compared to base distributions. It can be said that the support sets of most of these new distributions are limited to the real-line or the positive semi-real line. However, in recent years, a number of new probability distributions have been proposed that offer different approaches to how data can be modeled on the (0, 1) interval. It has also been exemplified in studies that these models offer more flexible and efficient modeling performance than famous distributions such as beta, and Kumaraswamy in modeling certain data types such as percentiles, ratios, and fractions. The following are some of the most notable studies on unit distributions: In the study by Mazucheli et al (2018), a two-parameter distribution named the unit-Weibull distribution is introduced. This new distribution offers an alternative to the Beta and Kumaraswamy distributions. Furthermore, Monte Carlo simulations demonstrate that the maximum likelihood estimations are nearly unbiased and consistent (Mazucheli et al, 2018). The unit-half-normal distribution, presented by (Bakouch et al, 2021), provides a new option for modeling percentage, proportion, and fraction data. Proposed by (Karakaya et al, 2022), the unit-Lindley distribution is a single-parameter distribution obtained by transforming the Lindley distribution to the unit interval. In the study introduced by (Pourdarvish et al, 2015), the exponentiated Topp-Leone distribution, a generalization of the Topp-Leone distribution, is proposed. Researchers have investigated the mathematical properties, hazard rate functions, and parameter estimation methods of this new distribution. (Gómez-Déniz et al, 2014) introduce the log-Lindley distribution, which has specific applications, particularly in insurance and inventory management. The log-xgamma distribution, presented by (Altun and Hamedani, 2018), represents a unit probability distribution on the interval [0, 1]. Researchers have discussed the modeling performance of the log-xgamma distribution in various applications in detail. The unit-inverse Gaussian distribution, proposed by (Ghitany et al, 2019), is a two-parameter alternative distribution for modeling data in the [0, 1] interval. The other two most notable studies on unit distribution are the unit Ishita (Demirci Biçer and Biçer, 2022) and the exponentiated unit Teissier (Biçer and Demirci Biçer 2022).

These studies highlight the importance of developing new unit distributions and provide valuable insights into their properties and applications. The proposed distributions offer flexible modeling options for data on the unit interval and have been shown to provide better fits than existing distributions. The availability of these distributions expands the range of statistical tools available for analyzing unit data and opens up new possibilities for research and applications in various fields.

In this study, we aim to contribute to the existing literature on unit distributions by deriving the log inverse Muth distribution. By building on the insights and methodologies presented in the referenced studies, we will develop a new single-parameter distribution that is specifically tailored for modeling unit data. We think that deriving the log inverse Muth distribution (LIMD) will offer a valuable addition

to the existing suite of unit distributions and provide researchers with a powerful tool for analyzing unit data.

We structure the remaining parts of this paper as outlined below. The section titled "Inverse Muth and log inverse Muth Distributions" is dedicated to the derivation of LIMD. In the section labeled "Statistical Characteristics of the LIMD" we explore fundamental properties of LIMD, including survival, hazard, reserved hazard, and the distribution of its order statistics. The "Inference" section delves into several estimation methods for estimating the parameters of LIMD. A thorough numerical investigation is carried out in the "Simulation Study" section to assess the performance of the estimator proposed in this paper. Finally, the findings and conclusions are summarized in the "Conclusions" section.

INVERSE MUTH AND LOG INVERSE MUTH DISTRIBUTIONS

The inverse Muth distribution is a single-parameter probability distribution defined on the positive real line. The distribution was first introduced by (Saroj et al, 2022). The cumulative distribution function (cdf) of the distribution is

$$F(y;\alpha) = e^{\frac{y-e^{\frac{\alpha}{y}}y+\alpha^2}{y\alpha}}, y > 0 \tag{1}$$

and the corresponding probability density function (pdf) is

$$f(y,\alpha) = \frac{e^{-\frac{-1+e^{\frac{\alpha}{y}}}{\alpha}+\frac{\alpha}{y}}(e^{\frac{\alpha}{y}}-\alpha)}{y^2}, y > 0 \tag{2}$$

where $\alpha, (0 < \alpha \leq 1)$ is the shape parameter of the inverse Muth distribution. The distribution has many characteristics that are useful in modeling positive data. Some of these characteristics are as follows:

- Expectation $E(X) = I_1 + I_2$, where

$$I_1 = \int_0^a y^{k-2}\left(e^{\frac{\alpha}{y}}-\alpha\right) exp\left\{\frac{\alpha}{y}-\frac{1}{\alpha}\left(e^{\frac{\alpha}{y}}-1\right)\right\} dy$$

$$I_2 = \int_a^\infty y^{k-2}\left(e^{\frac{\alpha}{y}}-\alpha\right) exp\left\{\frac{\alpha}{y}-\frac{1}{\alpha}\left(e^{\frac{\alpha}{y}}-1\right)\right\} dy.$$

- Survival Function $S(y) = 1 - e^{\frac{y-e^{\frac{\alpha}{y}}y+\alpha^2}{y\alpha}}$

- Hazard Function $H(y) = \frac{e^{\frac{1}{\alpha}+\frac{\alpha}{y}}(-e^{\frac{\alpha}{y}}+\alpha)}{\left(-e^{\frac{e^{\frac{\alpha}{y}}}{\alpha}}+e^{\frac{1}{\alpha}+\frac{\alpha}{y}}\right)y^2}$

and

- Reserved Hazard function $\xi(y) = \frac{e^{-\frac{-1+e^{\frac{\alpha}{y}}}{\alpha}+\frac{\alpha}{y}\left(\frac{\alpha}{e^{\frac{\alpha}{y}}-\alpha}\right)}}{y^2}}{e^{\frac{y-e^{\frac{\alpha}{y}}y+\alpha^2}{y\alpha}}}$.

- Quantile function $\phi(u) = \frac{\alpha^2}{(\alpha log(u)-\alpha W_{(-1)}(-(e^{(-1/\alpha)}u)/\alpha)-1)}$

Now we derive the LIMD. The cdf of LIMD can be obtained through exponential transformation $X = e^{-y}$ by considering the inverse Muth distribution. We organize definition of LIMD according to following description.

Definition 1. Suppose X is a random variable from the LIMD with parameter α $(0 < \alpha \leq 1)$. The cdf and the pdf of the LIMD are as follows:

$$F(x,\alpha) = 1 - e^{\frac{1-e^{-\frac{\alpha}{ln(x)}}}{\alpha}-\frac{\alpha}{ln(x)}}, \qquad 0 < x < 1 \tag{3}$$

and

$$f(x,\alpha) = \frac{e^{\frac{1-e^{\frac{\alpha}{ln\left(\frac{1}{x}\right)}}}{\alpha}+\frac{\alpha}{ln\left(\frac{1}{x}\right)}}\left(e^{\frac{\alpha}{ln\left(\frac{1}{x}\right)}}-\alpha\right)}{x\left[ln\left(\frac{1}{x}\right)\right]^2}, 0 < x < 1 \tag{4}$$

respectively. Figures 1 and 2, respectively, show graphical behavior of LIMD's pdf and cdf for different parameter values. In particular, by examining Figure 1, it is easy to understand how the central tendency and shape of the distribution are affected by α's values. Additionally, they can help researchers to understand what types of data the distribution can model in practical applications, and they provide important insights to researchers by playing a significant role in the model selection process.

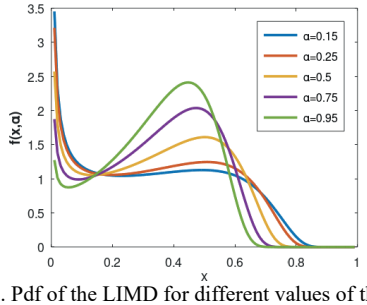


Figure 1. Pdf of the LIMD for different values of the parameter α.

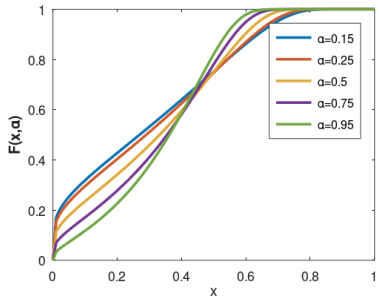


Figure 2. Cdf of the LIMD for different values of the parameter α.

STATISTICAL CHARACTERISTICS OF LIMD

In this subsection, we will investigate the basic properties of the LIMD. These properties include the hazard rate function, survival function, and pdf of its order statistics. The significance of these properties lies in their ability to elucidate the statistical characteristics of the distribution and their utility in practical applications.

For a random variable X following the LIMD with parameter α, considering the cdf (3) and pdf function (4), we can easily derive its survival function,$S(x;\alpha)$ as

$$\begin{aligned} S(x;\alpha) &= 1 - F(x;\alpha) \\ &= 1 - \left(e^{\frac{1-e^{-\frac{\alpha}{\ln(x)}}}{\alpha}} \frac{\alpha}{\ln(x)} \right). \end{aligned} \tag{5}$$

Then, we have the hazard rate function (hrf) and the reserved hrf

$$H(x;\alpha) = \frac{e^{-\frac{\alpha}{ln[x]}} - \alpha}{x ln[x]^2} \tag{6}$$

and

$$\xi(x,\alpha) = \frac{e^{1/\alpha}\left(e^{-\frac{\alpha}{\log(x)}} - \alpha\right)}{x \log^2(x)\left(e^{\frac{\alpha}{\log(x)} + \frac{e^{-\frac{\alpha}{\log(x)}}}{\alpha}} - e^{1/\alpha}\right)} \tag{7}$$

respectively. Figure 3 lucidly portrays characteristic tendency of hrf associated with the LIMD.

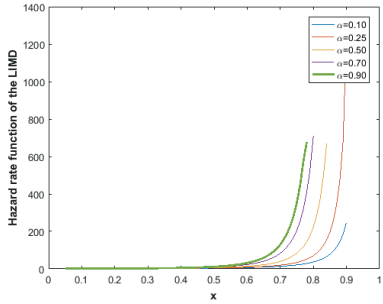


Figure 3. Hazard rate function of the LIMD for various values of α.

Consider a sample $X_1, X_2, \ldots, X_n$ drawn from the LIMD. Let $X_{(1)} \cdots X_{(n)}$ represent the corresponding order statistics, arranged in ascending order $(X_{(_1)} <\cdots< X_{(n)})$. The pdf of the i-th order statistic, $X_{(i)}$, is given by

$$f_{X_{(i)}}(x) = \frac{n!}{(i-1)!\,(n-i)!} F(x)^{i-1} f(x)(1-F(x))^{n-i}$$

$$= \frac{n!}{(i-1)!\,(n-i)!} \left(1 - e^{\frac{1-e^{-\frac{\alpha}{\ln(x)}}}{\alpha} - \frac{\alpha}{\ln(x)}}\right)^{i-1} \left(e^{\frac{1-e^{-\frac{\alpha}{\ln(x)}}}{\alpha} - \frac{\alpha}{\ln(x)}}\right)^{n-i}$$

$$\times \left(\frac{e^{\frac{1-e^{\frac{\alpha}{ln\left(\frac{1}{x}\right)}}}{\alpha} + \frac{\alpha}{ln\left(\frac{1}{x}\right)}} \left(e^{\frac{\alpha}{ln\left(\frac{1}{x}\right)}} - \alpha\right)}{x\left[ln\left(\frac{1}{x}\right)\right]^2} \right) \tag{8}$$

Hence we obtain the pdfs of 1^{th} and n^{th} order statistics are

$$f_{X_1}(x) = f(x) n \left(e^{\frac{1-e^{-\frac{\alpha}{\ln(x)}}}{\alpha} - \frac{\alpha}{\ln(x)}}\right)^{n-1}$$

and

$$f_{X_{(n)}}(x) = f(x) n \left(1 - e^{\frac{1-e^{-\frac{\alpha}{\ln(x)}}}{\alpha} - \frac{\alpha}{\ln(x)}}\right)^{n-1}.$$

ESTIMATION

Let us assume that a set of random variables $X_1, X_2, \ldots, X_n$, iid LIMD with α and this sample's observations are represented by $x_1, x_2, \ldots, x_n$. We, now, write the likelihood function of the LIMD based on these measurements as

$$L = \prod_{i=1}^{n} \frac{e^{\frac{1-e^{-\frac{\alpha}{\log(x_i)}}}{\alpha} - \frac{2\alpha}{\log(x_i)}} \left(1 - \alpha e^{\frac{\alpha}{\log(x_i)}}\right)}{x_i \log^2(x_i)}$$

and the log-likelihood function is

$$\ln(L) = \sum_{i=1}^{n} \log\left(1 - \alpha e^{\frac{\alpha}{\log(x_i)}}\right) - 2\alpha \sum_{i=1}^{n} \frac{1}{\log(x_i)} - \frac{\sum_{i=1}^{n} e^{-\frac{\alpha}{\log(x_i)}}}{\alpha} - 2\sum_{i=1}^{n} \log(\log(x_i)) - \sum_{i=1}^{n} \log(x_i) + \frac{n}{\alpha} \quad (9)$$

To find the maximum likelihood estimator of the parameter α, we need to solve the score function given by equation (10) by setting it to zero.

The score function for α is:

$$\frac{\delta \ln(L)}{\delta \theta} = \frac{\sum_{i=1}^{n} e^{-\frac{\alpha}{\log(x_i)}}}{\alpha^2} + \sum_{i=1}^{n} \frac{-\frac{\alpha e^{\frac{\alpha}{\log(x_i)}}}{\log(x_i)} - e^{\frac{\alpha}{\log(x_i)}}}{1 - \alpha e^{\frac{\alpha}{\log(x_i)}}} - \frac{\sum_{i=1}^{n} -\frac{e^{-\frac{\alpha}{\log(x_i)}}}{\log(x_i)}}{\alpha} - 2\sum_{i=1}^{n} \frac{1}{\log(x_i)} \quad (10)$$

$$-\frac{n}{\alpha^2} = 0$$

Solving this equation analytically can not be straightforward due to its complexity. Therefore, any suitable numerical methods, or software tools like Octave's "fmincon" function or R's "mle" function can be employed to find the maximum likelihood estimate of the parameter α.

We'll now explore the least-squares estimator for determining α. To achieve this, we'll assume the availability of an ordered random sample, denoted as $X_{(1)}, X_{(2)}, \ldots, X_{(n)}$, drawn from the LIMD with parameter α, and $x_{(1)}, x_{(2)}, \ldots, x_{(n)}$ implies its a realization. The least-squares estimator of α is obtained by minimizing the Q_{LSE}:

$$Q_{LSE} = \sum_{i=1}^{n} \left(\left(1 - e^{\frac{1-e^{-\frac{\alpha}{ln(x_{(i)})}}}{\alpha} - \frac{\alpha}{ln(x_{(i)})}} \right) - P_i \right)^2 .$$

Here, $P_i = \frac{i}{n+1}$ represents for the i_th observation. Since this objective function involves nonlinear terms, an explicit form of the least-squares estimators are not obtainable. However, to solve this, the same numerical methods mentioned in the maximum likelihood estimation part can be applied here.

Furthermore, It is possible to minimize the objective function Q_{WLSE} to obtain weighted least-squares estimators of α :

$$Q_{WLSE} = \sum_{j=1}^{n} \frac{(n+1)^2(n+2)}{j(n-j+1)} \left(\left(1 - e^{\frac{1-e^{-\frac{\alpha}{ln(x_{(i)})}}}{\alpha} - \frac{\alpha}{ln(x_{(i)})}} \right) - P_j \right)^2 .$$

with respect to α. See (Swain and Wilson, 1985) for more information on least squares estimation methodology).

SIMULATION STUDY

In this section of the study, a comprehensive simulation study is designed to show the performance of the maximum likelihood estimator (mle), least squares estimator (lse), and weighted least squares estimator (wlse), which were obtained in the previous section, in estimating the unknown α parameter of the LIMD. In the simulation study, four different sample sizes (30, 50, 100, and 200) and different parameter values (0.1, 0.25, 0.5, 0.75, and 0.90) are considered. In each combination, parameter estimates are obtained using mentioned estimators. The bias and Mean Square error values are then calculated using the obtained estimates. The obtained simulated results are presented in tables Table 1-5. The criteria used to evaluate the performance of the estimators are mean square error (MSE) and bias, which are defined as follows:

$$MSE = \frac{1}{m} \sum_{i=1}^{n} \left(\theta - \hat{\theta}_i \right)^2$$

and

$$Bias = \frac{1}{m} \sum_{i=1}^{n} \hat{\theta}_i - \theta,$$

respectively, where m is the number of simulation repetitions and $\hat{\theta}$ implies estimation of the parameter θ.

Table 1: Simulated results for the values of parameter $\alpha = 0.10$

			Mean of Estimation	Bias	MSE
α	n	method			
0.1	30	mle	0.153476214	0.053476	0.028571
		lse	0.141615964	0.041616	0.035129
		wlse	0.143708844	0.043709	0.035129

	50	mle	0.131364918	0.031365	0.014351
		lse	0.130573159	0.030573	0.022313
		wlse	0.131926413	0.031926	0.022313
	100	mle	0.120288039	0.020288	0.007211
		lse	0.105813627	0.005814	0.013426
		wlse	0.116600142	0.0166	0.013426
	200	mle	0.114580849	0.014581	0.00463
		lse	0.110122656	0.010123	0.008413
		wlse	0.13310729	0.033107	0.008413

Table 2: Simulated results for the values of parameter $\alpha = 0.25$

			Mean of Estimation	Bias	MSE
α	n	method			
0.25	30	mle	0.275182673	0.025183	0.027836
		lse	0.208288307	0.041712	0.048071
		wlse	0.208889291	0.041111	0.048071
	50	mle	0.271188158	0.021188	0.009576
		lse	0.238224459	0.011776	0.033313
		wlse	0.24386204	0.006138	0.033313
	100	mle	0.259166219	0.009166	0.008811
		lse	0.231871969	0.018128	0.021999
		wlse	0.247444927	0.002555	0.021999
	200	mle	0.265637064	0.015637	0.003454
		lse	0.247189456	0.002811	0.013301
		wlse	0.274373152	0.024373	0.013301

Table 3: Simulated results for the values of parameter $\alpha = 0.50$

			Mean of Estimation	Bias	MSE
α	n	method			
0.50	30	mle	0.520728827	0.020729	0.017645
		lse	0.436030001	0.06397	0.05309
		wlse	0.466227066	0.033773	0.05309
	50	mle	0.512465086	0.012465	0.011578
		lse	0.437455143	0.062545	0.034313
		wlse	0.471359287	0.028641	0.034313
	100	mle	0.499151596	0.000848	0.009802
		lse	0.465443358	0.034557	0.019065
		wlse	0.484615148	0.015385	0.019065
	200	mle	0.505376979	0.005377	0.00411
		lse	0.490176305	0.009824	0.010557
		wlse	0.510033285	0.010033	0.010557

Table 4: Simulated results for the values of parameter $\alpha = 0.75$

			Mean of Estimation	Bias	MSE
α	n	method			
0.50	30	mle	0.8069779	0.056978	0.018932
		lse	0.675202258	0.074798	0.066464
		wlse	0.720704678	0.029295	0.066464
	50	mle	0.74238362	0.007616	0.009129
		lse	0.661559791	0.08844	0.032912
		wlse	0.702456805	0.047543	0.032912
	100	mle	0.754680371	0.00468	0.005239
		lse	0.714371244	0.035629	0.012465
		wlse	0.735084613	0.014915	0.012465
	200	mle	0.761740761	0.011741	0.003006
		lse	0.730913847	0.019086	0.008687
		wlse	0.751508812	0.001509	0.008687

Table 5: Simulated results for the values of parameter $\alpha = 0.90$

			Mean of Estimation	Bias	MSE
α	n	method			
0.50	30	mle	0.884853591	0.015146	0.010422
		lse	0.766270038	0.13373	0.058547
		wlse	0.808772488	0.091228	0.058547
	50	mle	0.902853398	0.002853	0.0077
		lse	0.825790226	0.07421	0.024392
		wlse	0.865442477	0.034558	0.024392
	100	mle	0.910524757	0.010525	0.004144
		lse	0.878932998	0.021067	0.007511
		wlse	0.900266009	0.000266	0.007511
	200	mle	0.90428627	0.004286	0.002022
		lse	0.880769062	0.019231	0.003612
		wlse	0.892754829	0.007245	0.003612

The results, provided by Tables 1–5, show that the ML estimator of the parameter α generally has lower bias and MSE values than the others. Therefore, it can be concluded that the ML estimator outperforms the other estimators. Additionally, it is observed that bias and MSE values generally decrease for all estimators as the sample size (n) increases. Thus, we can conclude that the estimators are asymptotically consistent and unbiased. Finally, from Tables 1–5, it is seen that bias and MSE values generally increase for all estimators as the value of parameter α increases.

CONCLUSION

LIMD has been derived in this study, and various examinations have been conducted to explore its properties and numerical applications. The study obtained the several characteristics of the distribution.

Additionally, the formal behaviors of the distribution's probability density, cumulative distribution, and hazard rate functions were analyzed using various graphical representations. Furthermore, parameter estimation was a significant focus of this research. Various estimation techniques, including maximum likelihood, least squares, and weighted least squares methods, were applied to estimate the unknown parameters of the distribution. The effectiveness of the obtained estimators in parameter estimation was evaluated, considering bias and mean square error criteria, through an extensive simulation study. In conclusion, this research not only introduced the LIMD but also provided several insights into its properties and its inference problem. We think that the findings of this study will open avenues for further research in the field of probability distributions and their modeling capabilities.

REFERENCES

1. Mazucheli, J., Menezes, A. F. B., & Ghitany, M. E. (2018). The unit-Weibull distribution and associated inference. *J. Appl. Probab. Stat*, *13*(2), 1-22.

2. Bakouch, H. S., Nik, A. S., Asgharzadeh, A., & Salinas, H. S. (2021). A flexible probability model for proportion data: Unit-half-normal distribution. *Communications in Statistics: Case Studies, Data Analysis and Applications*, *7*(2), 271-288.

3. Karakaya, K., Korkmaz, M. C., Chesneau, C., & Hamedani, G. G. (2022). A new alternative unit-Lindley distribution with increasing failure rate. *Scientia Iranica*.

4. Pourdarvish, A., Mirmostafaee, S. M. T. K., & Naderi, K. (2015). The exponentiated Topp-Leone distribution: Properties and application. *Journal of Applied Environmental and Biological Sciences*, *5*(7), 251-256.

5. Gómez-Déniz, E., Sordo, M. A., & Calderín-Ojeda, E. (2014). The Log–Lindley distribution as an alternative to the beta regression model with applications in insurance. *Insurance: Mathematics and Economics*, *54*, 49-57.

6. Altun, E., & Hamedani, G. G. (2018). The log-xgamma distribution with inference and application. *Journal de la Société Française de Statistique*, *159*(3), 40-55.

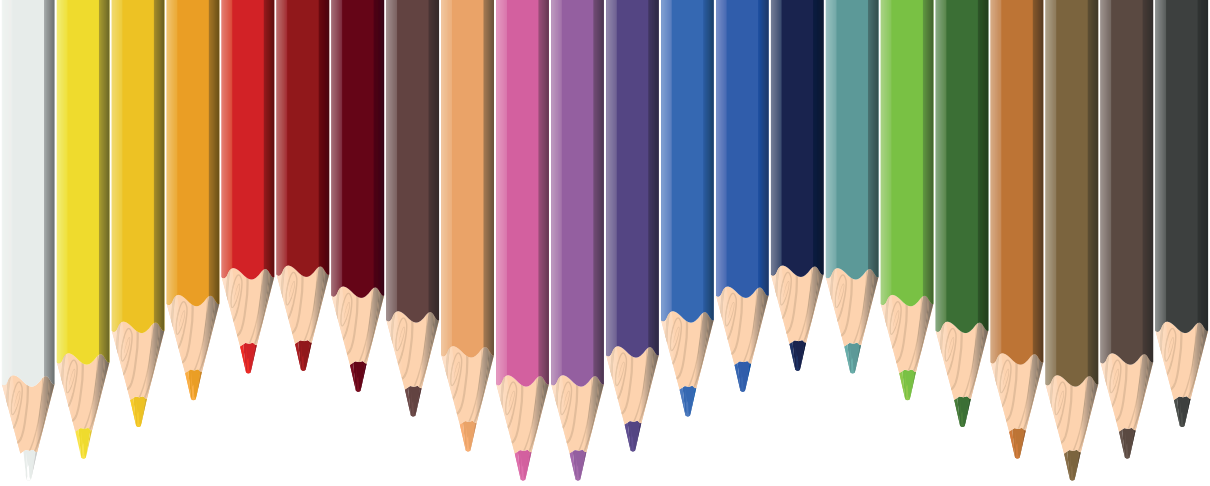
7. Ghitany, M. E., Mazucheli, J., Menezes, A. F. B., & Alqallaf, F. (2019). The unit-inverse Gaussian distribution: A new alternative to two-parameter distributions on the unit interval. *Communications in Statistics-Theory and methods*, *48*(14), 3423-3438.

8. Demirci Biçer, H., & Biçer C. (2022). Unit Ishita Distribution With Inference. *Research & Reviews in Science and Mathematics, October 2022*.

9. Biçer, C., & Demirci Biçer, H. (2022). Exponentiated Unit Teissier Distribution. *Research & Reviews in Science and Mathematics*, December 2022, 61.

10. Saroj, A., Sonker, P. K., & Kumar, M. (2022). Statistical properties and application of a transformed lifetime distribution: inverse muth distribution. *Reliability: Theory & Applications*, *17*(1 (67)), 178-193.

11. Swain, J. J., & Wilson, J. R. (1985, December). Fitting Johnson distributions using least squares: simulation applications. In *Proceedings of the 17th conference on Winter simulation* (pp. 150-157).



Chapter 9

NEW APPROACH TO SLANT HELICES IN SYMPLECTIC SPACE

Mehmet BEKTAŞ[1]

1 Doç. Dr., Bartın Üniversitesi, Ortak Dersler Bölümü. muratyumluhistory@gmail.com, myumlu@bartin.edu.tr.

In recent years, by the coming theory of the curves, researches extend some special curves. Some of them are helices, slant helices, Bertrand curves, associated curves, adjoint curve etc. There are many studies on these special curves. Especially a general helices and slant helices are used for many applications. A general helices is defined that its tangent vector fields makes a constant angle with a fixed direction called the axis of general helices. The notion of slant helices defined by (Izumiya and Takeuchi,2004:28) based on the property that the principal normal lines of the curve make a constant angle with a fixed direction. Moreover, (Kula and Yaylı,2005:167) obtained slant helices and their spherical indicatries. Later, slant helices subject are also presented in 3,4, and n-dimensional space, respectively in different dimensions (Yılmaz M. Y., Bektaş M., 2018:10,) (Yılmaz M. Y., Bektaş M.,2020:5) (Ali A.Lopez R. and Turgut M.,2012:17) and (Çetin E.Ç., Bektaş M.,2020:35). Afterwards, another properties of helices are discussed in (Ferrandez A., Gimeněz A. and Lucas P., 2002:35). Furthermore, there are many studies about symplectic curves in 4-dimensional symplectic space (Çetin , E., Bektaş M.,Yıldırım Yılmaz M.,2022:43,2023:3), (Çetin,E.,Bektaş M.,2023:3),(Çetin, E., Bektaş M., 2019:7) , (Çetin,E., Bektaş M., 2019:2) and),(Çetin, E., Bektaş M., 2022:13)

Recently, further characterizations of helices to Minkowski space are given (Önder M., Kazaz M., Kocayiğit H. and Kılıç O., 2008:3,), (Ferrandez A., Gimeněz A. and Lucas P., 2002:35), and other spaces (F. Valiquette,2012:30)

The word symplectic was first used by Weyl in the sense of complex to describe symplectic groups. Some scientist accept symplectic geometry as the language of classical mechanics. In fact, the basis of Hamilton and Kahler manifolds, which play an important role in mathematics and theoretical physics, is based on symplectic geometry. The origin of Hamilton mechanics is symplectic geometry, and the base-spaces of classical systems play an important role in the structure of symplectic manifold. Symplectic geometry is at basis of optics. On the other hand, symplectic geometry also has important connections with dynamic systems, integrable systems, algebraic geometry and global analysis. Symplectic geometry is studied by geometers (Kamran N., Olver P., and Tenenblat K.. 2009:11),Symplectic spaces were first studied by Chern and Wang as local symplectic invariants of Euclidean subspaces (S.S. Chern and H.C.Wang., 1947:4). Symplectic space differs from Euclidean space in terms of metric and arc length. Kamran obtained the Frenet frame of curves using local symplectic invariants Authors, introduced the concept of symplectic arc length for curves. And they constructed an adapted

symplectic Frenet frame and expressed 2n - 1 local differential invariants that they called symplectic curvatures of the curve

In this paper, we focus on some characterizations of (k,m)- type slant helix in symplectic regular curves.

2. Preliminaries

Let us introduced some definition for symplectic space.

For, any vectors $u = (x^1, x^2, \dots, x^n, y^1, \dots, y^n)$, $v = (\xi^1, \dots, \xi^n, \eta^1, \dots, \eta^n) \in R^{2n}$

Symplectic inner product is given by

$$< u, v >= \varphi(u, v) = \sum_{i=1}^{n} (x_i \eta_i \wedge y_i \xi_i)$$

4-dimensional symplectic space $Sim = (R^4, \varphi)$ is the vector space R^4 equipped with the standard symplectic form, written as

$$\varphi = \sum dx_i \wedge dy_i$$

(Kamran N., Olver P., and Tenenblat K.. 2009:11),

Let V be a vector space on the field of real numbers R. If , for each u, v

$$\varphi(u, v) = -\varphi(v, u)$$

It is called anti symmetric bilinear transformation.

Symplectic space with symplectic inner product can be written as

$$< u, v >= \varphi(u, v) = \sum_{i=1}^{2} (x_i \eta_i - y_i \xi_i)$$
$$= x_1 \eta_1 + x_2 \eta_2 - y_1 \xi_1 - y_2 \xi_2$$

here $u = \{x_1, x_2, y_1, y_2\}$ and $v = \{\xi_1, \xi_2, \eta_1, \eta_2\}$

Additionally, the tangent vectors $\{a_1, a_2, a_3, a_4\}$ satisfying the equations

$$\langle a_k, a_l \rangle = \langle a_{2+k}, a_{2+l} \rangle = 0 \qquad 1 \le k, l \le 2,$$
$$\langle a_k, a_{2+l} \rangle = 0 \qquad 1 \le k \ne l \le 2,$$
$$\langle a_k, a_{2+l} \rangle = 1 \qquad 1 \le k \le 2$$

for symplectic frame, structure equations are defined by

$1 \le i, j \le n$

$$da_i = \sum_{k=1}^{n} w_{ik} a_k + \sum_{k=1}^{n} \varphi_{ik}\, a_{k+n}$$

$$da_{i+n} = \sum_{k=1}^{n} \theta_{ik} a_k + \sum_{k=1}^{n} w_{ik}\, a_{k+n}$$

Here, $\varphi_{ij} = \varphi_{ji}, \qquad \theta_{ij} = \theta_{ji}$

(Kamran N., Olver P., and Tenenblat K.. 2009:11),

Let $z(t) : R \to R^4$ be a symplectic regular curve parametrized by symplectic arc length with symplectic frame. Throughout this paper, we make some notations and calculations for later

use.We show that z to indicate differentiation with respect to the parameter t:

$$\dot{z} = \frac{dz}{dt}$$

Definition 2.1. Let $z(t)$ be a symplectic regular curve in $Sim = (R^4, \varphi)$. Then the following non-degeneracy condition is satisfied

$$\langle \dot{z}, \ddot{z} \rangle \neq 0$$

for all $t \in R$.

Definiton 2.2. Let $z(t)$ be a symplectic regular curve, with symplectic arc length s. Then z(s) can be written as

$$s(t) = \int_{t_0}^{t} \langle \dot{z}, \ddot{z} \rangle^{1/3}\, dt$$

for all $t \geq t_0$.

If

$$\int_{t_1}^{t_2} \langle \dot{z}, \ddot{z} \rangle^{1/3}\, dt = t_2 - t_1 \qquad (t_1, t_2 \in I) \quad t_1 \leq t_2$$

symplectic regular curve is said to parametrized by symplectic arc length. The symplectic arc length parameter corresponds to the equaffine arc length for plane curves.

Taking the extrerior differential of above equation, the symplectic arc length element is obtained by

$$ds = \langle \dot{z}, \ddot{z} \rangle^{1/3} dt$$

And the arc length derivative operator is

$$D = \frac{d}{ds} = \langle \dot{z}, \ddot{z} \rangle^{-1/3} \frac{d}{dt}$$

In our notion, the symplectic arc length derivative operator is defined by

$$z' = \frac{dz}{ds}$$

Definiton 2.3. A symplectic regular curve is parametrized by symplectic arc length if it satisfies

$$\langle \dot{z}, \ddot{z} \rangle = 1$$

for all $t \in R$.

Example 2.3. Let $z: I \to R^4$

$$z(s) = (-sins, sins, coss, sins)$$

Here,

$$z'(s) = (-coss, coss, -sins, coss)$$

and

$$z''(s) = (sins, -sins, -coss, -sins)$$

It is obvious that z is symplectic regular curve ,since

$$\langle \dot{z}(s), \ddot{z}(s) \rangle = 1$$

Let $z(s)$ be a symplectic regular curve parametrized by arc length with $\{a_1, a_2, a_3, a_4\}$ a symplectic frame. Then, Frenet equations can be written by

$$\begin{aligned} a_1{}'(s) &= a_3(s) \\ a_2'(s) &= H_2(s)a_4(s) \\ a_3'(s) &= k_1(s)a_1(s) \\ a_4'(s) &= a_1(s) + k_2(s)a_2(s) \end{aligned} \qquad (2.1)$$

where $H_2(s) = const(\neq 0)$ (Kamran N., Olver P., and Tenenblat K.. 2009:11),

3. (k, m) −type slant helices

Theorem 3.1. Let z be a symplectic regular curve in $Sim = (R^4, \Omega)$. Then, z is (1,2)-type slant helix iff

$$\frac{k_1(s)}{k_2(s)} = const. \qquad (3.1).$$

Proof . Suppose that z is a $(1,2)$ −type slant helix. Then for any constant vector field U, we have

$$\langle a_1(s), U\rangle = c_1 \qquad (3.2) \quad \text{and}$$

$$\langle a_2(s), U\rangle = c_2 \qquad (3.3)$$

where c_1, c_2 are constant.

Differentiating (3.2) and using Frenet equations (2.1), we obtain

$$< a_3(s), U >= 0$$

and differentiating again, we get

$$k_1(s) < a_1(s), U > + < a_2(s), U >= 0$$

and

$$k_1(s)c_1 + c_2 = 0$$

We find that

$$k_1(s) = -\frac{c_2}{c_1}$$

Similarly, differentiating (3.3) and using Frenet equations (2.1), we find

$$H_2(s) < a_4(s), U >= 0$$

Taking the derivative of equation , we have

$$< a_1(s), U > + k_2(s) < a_2(s), U >= 0$$

and

$$c_1 + k_1(s)c_2 = 0$$

finally, we obtain

$$k_2(s) = -\frac{c_1}{c_2}$$

So, we can easily obtain (3.1).

Theorem 3.2 . There are no (1,3)- type slant helix in Sim=($\mathbb{R}^4$,Ω).

Proof. Suppose that z is a (1,3)- type slant helix in Sim=($\mathbb{R}^4$,Ω). Then, we can write

$$\langle a_1(s), U\rangle = c_1. \qquad (3.4)$$

and

$$< a_3(s), U >= c_3 \qquad (3.5)$$

Differentiating (3.4) and using Frenet equations (2.1), we obtain

$$< a_3(s), U >= 0$$

So, this is contradiction. There are no (1,3) - type slant helix in $Sim = (\mathbb{R}^4, \Omega)$.

Theorem 3.3. Let z be a symplectic curve in $Sim = (\mathbb{R}^4, \Omega)$. Then z is (1,4)-type slant helix iff

$$k_1(s) = -\frac{1}{k_2(s)} \tag{3.6}$$

Proof. Suppose that z is a (1,4)- type slant helix., Thus, for any vectors U, we have

$$\langle a_1(s), U\rangle = c_1 \tag{3.7}$$

and

$$\langle a_4(s), U\rangle = c_4 \tag{3.8}$$

$c_1, c_4$are constant. Differentiating (3.7) equation and using Frenet equations (2.1), we obtain

$$< a_3(s), U >= 0$$

and differentiating again, we get

$$k_1(s) < a_1(s), U > + < a_2(s), U >= 0$$

and

$$< a_2(s), U >= -c_1 k_1(s)$$

Differentiating (3.8) equation and using Frenet equations (2.1), we obtain

$$< a_1(s), U > + k_2(s) < a_2(s), U >= 0$$

So, we can write

$$c_1 - k_2(s) c_1 k_1(s) = 0$$

Hence, we get

$$k_1(s) = -\frac{1}{k_2(s)}$$

Theorem 3.4. Let z be a symplectic curve in $Sim = (\mathbb{R}^4, \Omega)$. Then z is (2,3) -type slant helix iff

$$k_1(s) = \frac{1}{k_2(s)} \tag{3.9}$$

Proof. Suppose that z is a (2,3)- type slant helix. So, for any constant vector field U, we have

$$\langle a_2(s), U\rangle = c_2$$

(3.10)

and

$$< a_3(s), U >= c_3 \tag{3.11}$$

where c_2, $c_3$are constant. Differentiating (3.10) equation and using Frenet equations (2.1), we obtain

$$H_2(s) < a_4(s), U >= 0$$

and

$$< a_1(s), U > + k_2(s) < a_2(s), U >= 0$$

and

$$\langle a_1(s), U \rangle = -c_2 k_2(s)$$

Similarly , Differentiating (3.11) equation and using Frenet equations (2.1), we obtain

$$k_1(s) < a_1(s), U > + < a_2(s), U >= 0$$

$$< a_1(s), U >= -\frac{c_2}{k_1(s)}$$

So, we can easily see that

$$k_1(s) = \frac{1}{k_2(s)}$$

Theorem 3.5. There are no (2,4)- type slant helix in Sim=($\mathbb{R}^4$,Ω).

Proof. Suppose that z is a (2,4)- type slant helix. Then for any constant vector field U, we have

$$\langle a_2(s), U \rangle = c_2 \tag{3.12}$$

and

$$\langle a_4(s), U \rangle = c_4 \tag{3.13}$$

where c_2, c_4 are constant. Differentiating (3.12) equation and using Frenet equations (2.1), we obtain

$$H_2(s) < a_4(s), U >= 0$$

and

$$H_2(s) c_4 = 0$$

Thus, we can easily seen that

$$c_4 = 0$$

So, this is contradiction. There are no (2,4)- type slant helix in $Sim = (\mathbb{R}^4, \Omega)$.

Theorem 3.5. Let z be a symplectic curve in $Sim = (\mathbb{R}^4, \Omega)$. Then z is (3,4)-type slant helix iff

$$\langle a_2(s), U\rangle = -\frac{k_2(s)H_2(s)c_4 + c_3}{k_2{}'(s)}$$

Proof. Suppose that z is a (3,4)- type slant helix. Then for a constant vector field U, we have

$$< a_3(s), U >= c_3 \tag{3.14}$$

and

$$\langle a_4(s), U\rangle = c_4$$

(3.15) where c_3, c_4 are constant.

Differentiating (3.14) equation and using Frenet equations (2.1), we obtain

$$k_1(s) < a_1(s), U > + < a_2(s), U >= 0$$

and

$$k_1'(s) < a_1(s), U > + k_1(s) < a_3(s), U > + H_2(s) < a_4(s), U >= 0$$

we obtain

$$k_1'(s) < a_1(s), U > + k_1(s)c_3 + H_2(s)c_4 = 0$$

Similarly , Differentiating (3.15) equation and using Frenet equations (2.1), we obtain

$$< a_1(s), U > + k_2(s) < a_2(s), U >= 0$$

and

$$< a_3(s), U > + k_2'(s) < a_2(s), U > + k_2(s)H_2(s)c_4 = 0$$

and

$$c_3 + k_2'(s) < a_2(s), U > + k_2(s)H_2(s)c_4 = 0$$

so, we can easily see that

$$\langle a_2(s), U\rangle = -\frac{k_2(s)H_2(s)c_4 + c_3}{k_2{}'(s)}$$

Example 3.1. Let's take the following curve

$$z(s) = \frac{1}{\sqrt{5}}\left(shs, \frac{1}{2}s^2 + 2s, chs, \frac{1}{2}s^2 - 2s\right).$$

Figure 1. Then,

$$a_1(s) = z'(s) = \frac{1}{\sqrt{5}}(chs, s + 2, shs, s - 2)$$

and

$$a_3(s) = z''(s) = \frac{1}{\sqrt{5}}(shs, 1, chs, 1).$$

Thus $z(s)$ is a symplectic regular curve. In addition

$$a_2(s) = \frac{1}{\sqrt{5}}(\frac{4}{5}chs, -\frac{1}{5}(s + 2), \frac{4}{5}shs, -\frac{1}{5}(s - 2),$$

$$a_4(s) = \frac{5}{4\sqrt{5}}(4shs, -1, 4chs, -1).$$

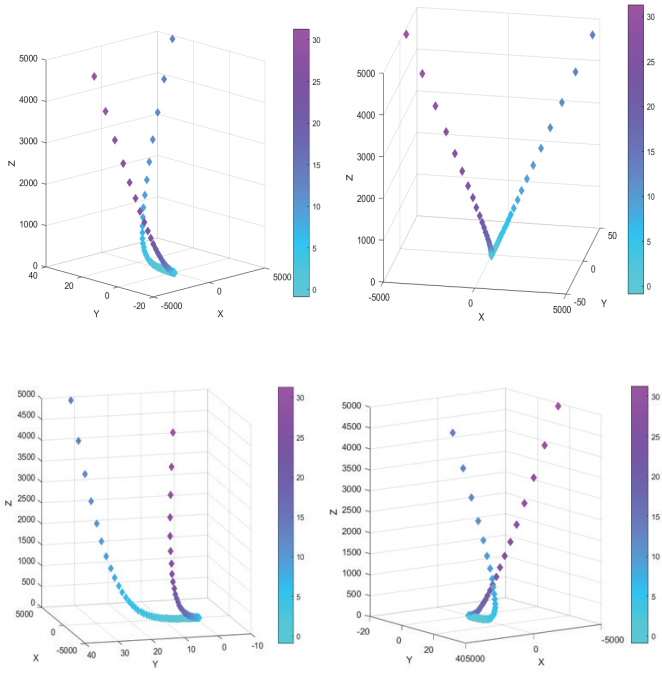


Figure 1. Symplectic regular curve $z(s)$

This curve in R^4 is plotted with a code that represents the fourth dimension with a color scale.

References

[1] Önder M., Kazaz M., Kocayiğit H. and Kılıç O., (2008), B_2-slant helix in Euclidean 4-space E^4,Int J. Cont. Mat. Sci, 31443-1440

[2] Çetin E., Bektaş M.,Yıldırım Yılmaz M., (2022) Osculating curves in 4-dimensional symplectic space, Prespacetime Journal 13(3),.

[3] Izumiya S. and Takeuchi N., (2004), New special curves and developable surfaces, Turk. J. Math. 28 ,153-163.

[4] Çetin , E**.,** Bektaş M.,Yıldırım Yılmaz M., (2023) Some Characterizations of Rectifying Curves in 4-symplectic space, Prespacetime Journal 14(3),.

[5] Ali A. and Lopez R. and Turgut M., (2012), k-type partially null and pseudo null slant helices in Minkowski 4-space, Math. Commun. 17 93-103. MR2946135.

[6] Ferrandez A., Gimeněz A. and Lucas P., (2002), Null generalized helices in Lorentz-Minkowski space , J. Phys. A: Math. Gen. 35 8243-8251. Mr1946488.

[7] Çetin , E., Bektaş M., (2023),On the Associated curves of a null and pseudo null curve in R_1^4. Prespacetime Journal 14(3),.

[8] Valiquette F., (2012), Geometric affine symplectic curve flows in R^4.Diff. Geo. Appl. 30(6) :, 631-641.

[9] Kamran N., Olver P., and Tenenblat K.. (2009),Local symplectic invariants for curves. Commun. Contemp. Math., 11(2): 165-183.

[10] Çetin , E., Bektaş M.,Yıldırım Yılmaz M.,(2022), On the Associated curves of Frenet Curve in R_1^4, Cumhuriyet Science Journal , 43(2),273-276.

[11] Kula, L. Yaylı Y., (2005),On slant helix and its spherical indicatrix, App. Math. and Comput., 169, , pp. 600-607.

[12] Yılmaz M. Y., Bektaş M.,(2018) Slant helices of (k,m) -type in E^4,Acta Univ. Sapientiae Math, 10(2), 395-401.

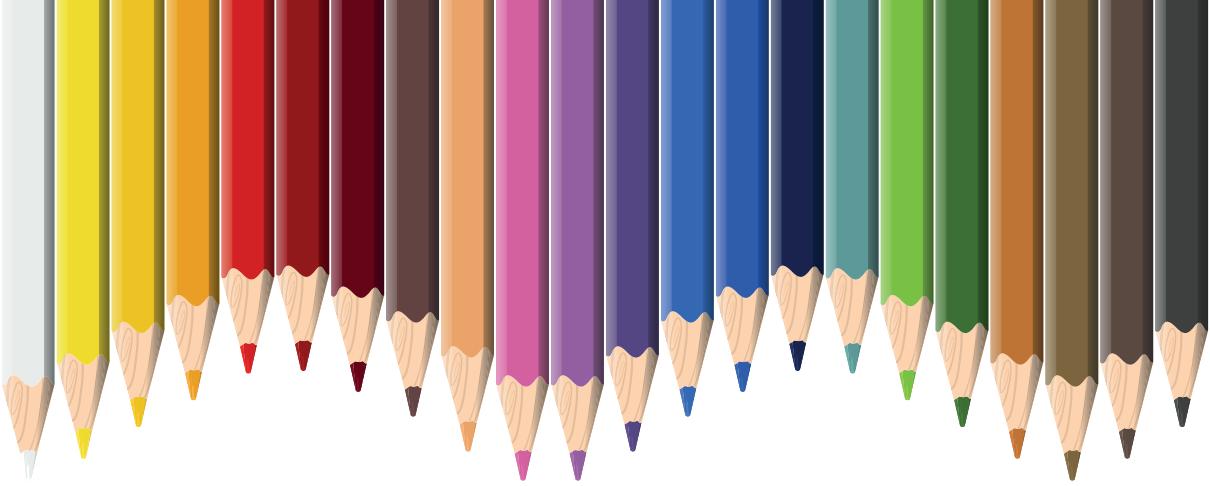
[13] Yılmaz M. Y., Bektaş M., (2020), (k,m) -type slant helices for partially null and pseudo null curves in Minkowski space $E_1{}^4$, Applied Mathematics and Nonlinear Sciences, 5(1),515-520.

[14] Çetin E.Ç., Bektaş M., (2019)The characterizations of Affine symplectic curves in R^4,Mathematics mdpı, 7(1), 110.

[15] Çetin E.Ç., Bektaş M.,(2019) Some new characterizations of symplectic curve in 4-dimensional symplectic space, Communications in advanced mathematical Sciences , 2(4),331-334.

[16] Çetin E.Ç., Bektaş M., (2020)k-type slant helices for symplectic curve in 4-dimensional symplectic space, Facta Universitatis, Series: Mathematics and Informatics, ,641-646.

[17] Chern S.S. and Wang H.C., (1947),Differential geometry in Symplectic spaces. Science Report Nat.Tsing Hua Univ.4, 453-477, reprinted in S.S. Chern, Selected Papers, Vol. II,pp. 165-191,(1947).



Chapter 10

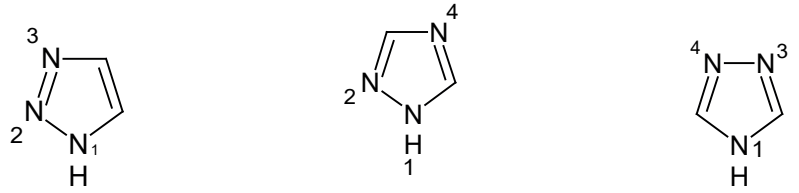
SYNTHESIS OF TRIAZOLE DERIVATIVE COMPOUNDS AND THEIR IMPORTANCE IN PHARMACOLOGY

Tayyibe Beyza YÜCEL[1]

1 Medical Laboratory Techniques, Health Services of Vocational School, Giresun University, Giresun, 28200 Türkiye, beyza.yucel@giresun.edu.tr (ORCID: 0000-0002-2632-8325)

1. INTRODUCTION

Triazole compounds are a class of compounds given to five-membered single-ring heterocyclic compounds containing two carbon (C) atoms and three nitrogen (N) atoms (Liu et al., 2017). These compounds with the molecule formula $C_2H_3N_3$ are known as 'triazocyclopentadiene' and were first introduced to the scientific community by Bladin in the 1800s with the name triazole (Temple, 1981). This cyclic structure was named by Andreocci 'pyrodiazole' in 1889 with a molecular weight of 69.07 g/mol (Potts, 1960). There are 3 isomer structures of triazole compounds that the first of which is vicinal (v)-1,2,3-triazole, the form in which three of the nitrogen atoms in the structure are one after the other, and the second one is symmetrical (s)-1,2,4-triazole, where two of the nitrogen atoms are one after the other and the other nitrogen is in conjugated state, and the third one is the 1,3,4-triazole form where two nitrogen atoms that do not contain hydrogen come one after the other (Shawni & Parhangi, 1980) (Figure 1).



v-1,2,3-triazole structure form *s-1,2,4-triazole structure form* *1,3,4-triazole structure form*

Figure 1. *Triazole structures form*

The triazole compound also has different isomeric structures such as pyrazoline and imidazole compounds, which are similar heterocyclic structures due to the heteroatom N in structure. The tautomer structures of v-1,2,3 triazole and s-1,2,4 triazole isomer structures are given in Figure 2 and all isomer structures have aromatic character.

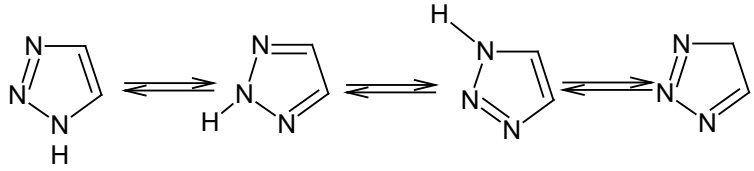
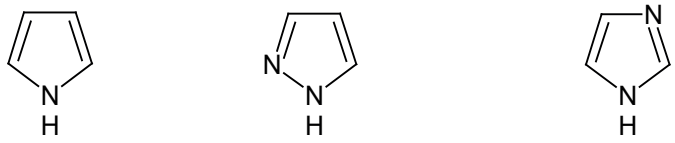


Figure 2. *Triazole isomer structures*

In both the v- and s-isomer structures of the triazole, the electronic configuration of the nitrogen atom to which the hydrogen is attached is similar to the nitrogen atom in the pyrrole system, and the electronic configuration of the other two nitrogen atoms in the triazole ring is similar to the configuration of the nitrogens in the diazole compounds.



pyrrole *pyrazole (diazole compound)* *imidazole*

Figure 3. *Heterocyclic five-membered rings with different numbers of N atoms*

Although the tautomer is in the 3rd place in the s-1,2,4-triazole isomer structure, the isomer ratio is not very high. The most stable tautomer structures among them are structures 1 and 2, shown in Figure 4. (Dewar & Morita, 1969)

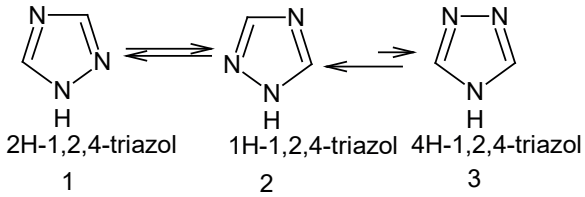


Figure 4. *Tautomers of the s-1,2,4 triazole isomer*

The nomenclature of s-1,2,4-triazole compounds is 1,2,4-1H when the H bonded N atom is numbered 1 if no substituent group is attached; If there is a substituent group on the H bonded N atom, it is written as 1,2,4-4H, that is, the number on which nitrogen atom is attached to the subtitue is indicated. The isomer structure in which the triazole compound is predominantly found in aqueous solution is the 2H-1,2,3-triazole tautomer structure (Adrien & Taylor, 1989).

2. PHYSICAL AND CHEMICAL PROPERTIES

The 2 isomers v-1,2,3 triazole and s-1,2,4-triazole structures that are predominantly found in triazole compounds show physical and chemical differences. It is very stable compared to other organic heterocyclic compounds in which there are 3 consecutive N atoms in the 1,2,3-triazole compound. The 1,2,4-triazole compound undergoes pyrolysis at 500 °C, and the formation of the aziridine molecule occurs with the release of N_2 gas.

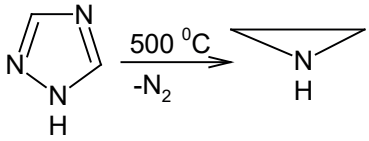


Figure 5. *Aziridine ring formation*

Since the melting point of 1,2,3-triazole compound is at 23-25 °C, it is liquid at room temperature. This compound in colorless liquid form boils at

203 °C under a pressure of 752 mm Hg. Although its density is 1.192 g/mL and higher than water, there isn't big difference (Polat, 2015).

The 1,2,4-triazole is solid form at room temperature. It is a white powder and odorless. Melting points is at 119-121 °C. Its boiling point is much higher than the 1,2,3-triazole compound and is 260 °C. It is seen that the boiling points of both isomer compounds are higher than that of water. Its density is 1.39 g/mL and is higher than the other isomer. Triazole compounds have gained aromatic character with the contribution of π bond electrons in the ring together with the electron pair in the N atoms in their structure (Tamimy, 2001).

Triazole compounds show basic properties due to the N-H in the structure. However, this basicity cannot to be in strong degrees. If substituents are found on the ring, there will also be changes in the basicity value. For example, if an electron-withdrawing group such as $-NO_2$ is attached to the ring C atoms, the acidity value will increase because it attracts the delocalized electrons in the ring. In this cases the basicity value will also decrease while the acidity will increase. Otherwise, when an electron donating group such as $-CH_3$ is attached to the ring, this time more electrons will be released to the ring, so the acidity will decrease and the basicity character will increase (Fidan, 2007).

Triazole compounds have dipole moment because of H-binding capacity of N atoms in the ring. For this reason, triazole compounds are generally soluble in water or mostly in polar solvents such as ethanol and methanol, depending on the substituent groups attached to N atoms and π bonds. Triazole compounds are a biologically important group of compounds due to their ability to form bonds similar to peptide bonds in amino acid compounds, both creating a richness in terms of molecular diversity due to the fact that they are added to the ring by making bonds from π bonds C atoms. In recent years, there has been an increase in the number of studies on the synthesis of triazole compounds and derivatives, and some biological activity studies, due to the molecular diversity with the addition from different locations and the fact that the functionally formed compounds have an effect on a wide area such as anticancer, anti-inflammatory, antifungal, psoriasis and muscle relaxant drug actives (Akkaya, 2013).

3. SPECTROSCOPIC PROPERTIES

^{1}H-NMR spectrum of 1,2,3-triazole compounds without any substituents, the proton signal at the C atom is seen as a broad peak at δ 8.13 ppm-8.04 ppm. However, the proton signal in 1,2,4-triazole compounds is generally seen in the higher area at δ 7.85 ppm. The H atoms attached to the N atom, on the other hand, give a very sharp signal at 13.9 ppm. This peak enlarges at 37 °C depending on the ambient temperature and a broad peak is observed.

1,2,4-triazole compounds absorb strongly at 205 nm specifically in the UV spectrum. In the case of an electron-rich subtituent such as a phenyl group in the 1 position, this value shifts to 239 nm. When the phenyl group is subtituent at 3 position, a peak is observed at 241 nm and 224.5 nm. When there are more substituents, a change in the UV absorption value is observed.

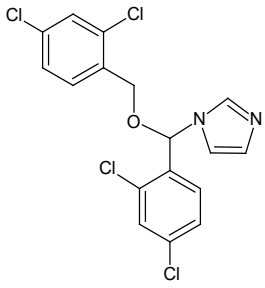
The presence of a voltage peak between 3294 cm^{-1} (N-H stretching vibrations, 1464 cm^{-1} (N=N) and a C=N voltage peak between 1500-1350 cm^{-1} in the IR spectrum of triazole compounds plays a decisive role in the identification of these compounds.

In the mass spectra, on the other hand, there is a molecular peak that occurs in di- and triphenyl derivatives of triazole compounds and in 1,2,4-triazole compounds with separation over molecular ions (Tamimy, 2001).

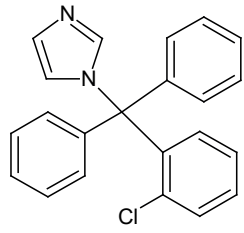
4. BIOLOGICAL ACTIVITY

Triazole derivative compounds have started to attract attention, especially by scientists in the field of pharmaceutical chemistry, due to their properties such as being stable even in a strongly oxidizing environment, and easily binding to biomolecules with the increase in the solubility of triazole compounds as a result of the bonding of various substituents with different bonds due to their chemical structure.

Since triazole compounds generally show antifungal activity, their first use was in the medical field. Until the discovery in 1967 that azole compounds have antifungal activities, only a few drugs were used for this purpose, such as amphotericin B and flucytosine. After the use of compounds such as miconazole and clotrimazole as the first diazole compounds, azole compounds as antimycotic agents started to be used only after 1974. One of the most important reasons why azole compounds attract attention especially in the field of antimycotics, it has attracted attention due to its low toxicity rate, increased activity and very few side effects (Ayhan, 1988). However, intravenous use of fluconazole and oral use of itraconazole containing 1,2,4-triazole ring started in the 1990s.

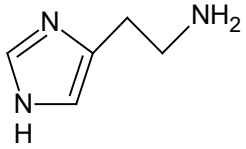


Mikonazol

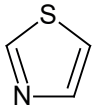


Klotrimazol

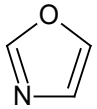
Triazole compounds are isosteres in compounds such as oxazole, pyrazole and imidazole in the synthesis of new drug active substances containing different substituents. In addition, it is seen that heterocyclic compounds such as pyrimidine, imidazole, triazole and thiazole are present in the structures of drugs used for the treatment or under clinical development of cancer, which has become the biggest problem of recent years (Zhao et al., 2012). When a compound is formed with the triazole ring instead of the imidazole ring in the histamine structure, it has been found that the new compound synthesized acts like histamine molecule (Ainsworth & Jones, 1976).



Histamine



Thiazole



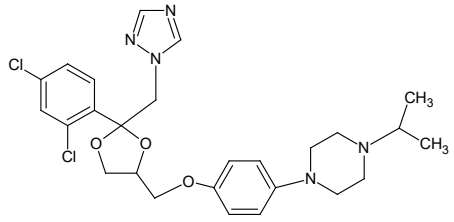
Oxazole

Many compounds containing 1,2,3 and 1,2,4-triazole rings appear to have sedative, antimicrobial, antimalarial, antibacterial, antifungal effects as well as antiviral, anti-inflammatory, antituberculosis and antitumor, anticonvulsant, diuretic, anti-HIV and Alzheimer's effects (Gallardo et al., 2007; Kini, Robins & Avery, 1989; Avula et al., 2018; Youssif et al., 2016). Although the biological activities of triazole compounds are in a very wide area for example; Ribavirin (antiviral), Rizatriptan (antimigraine), Alprazolam (psychotropic) and Letrozole (rheumatism inhibitor and anticancer). Vorozol, letrozole and anastrozole are used in the treatment of breast cancer. Triazolam is a drug used as a sedative and relaxant. Fuluconazole is used in antifungal, intraconazole, ravuconazole, voriconazole antimicrobial therapy.

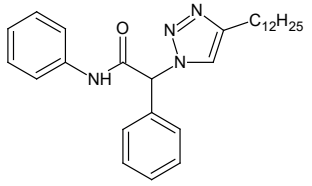
Tuberculosis, known as one of the oldest diseases in human history caused by *Mycobacterium tuberculosis* bacteria, is an infectious disease that causes death if left untreated. Vaccines were started to be used for the treatment of this disease in the 1920s, but later in the 1970s, vaccines were developed and started to be applied to newborns and children. For this purpose, the synthesis of antituberculosis drugs was started in 1943 by synthesizing para amino salicylic acid and later streptomycin compounds (Türkmen, 2020). The drugs used by synthesizing and developing new heterocyclic compounds have renewed themselves, and in this sense, the anti-tuberculosis activities of new 1,2,4- and 1,2,3-triazole compounds have been investigated and effective compounds have been identified (Papakonstantinou, Pouli, Marakos & Chytyroglou, 2002;Gao et al., 2019).

Terconazole is a triazole derivative drug used locally in the treatment of vulvovaginal candidiasis. In order to give itraconazole, which has antifungal activity, to the body in different ways, it has become necessary to develop

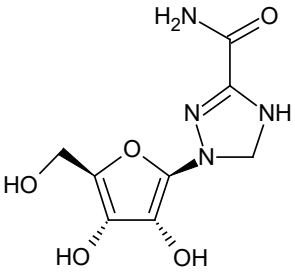
its current form. In the following periods, voriconazole and posaconazole compounds with similar molecular structures were synthesized and started to be used clinically. The general mechanism of these compounds with antifungal activity is the inhibition of demethylation of 14-α-methylsteroids accumulated in the cell membrane of the fungi during cell membrane degradation.



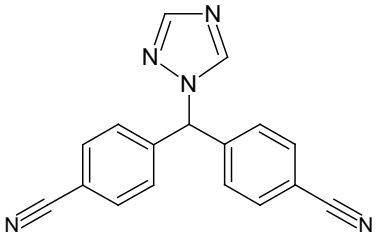
Antifungal (Terconazole)



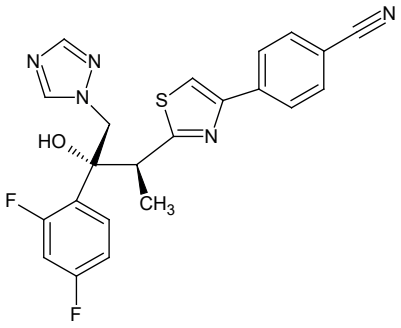
Hypocholesterol Activity



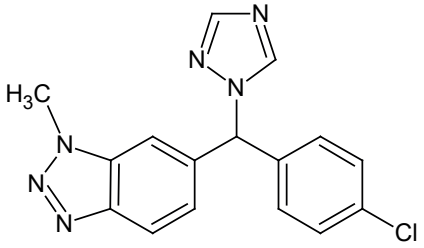
Antiviral (Ribavirin)



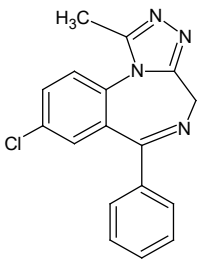
Antirheumatic-anticancer (Letrozole)



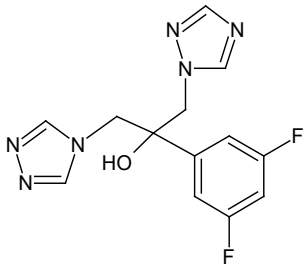
Antimicrobial (Ravuconazole)



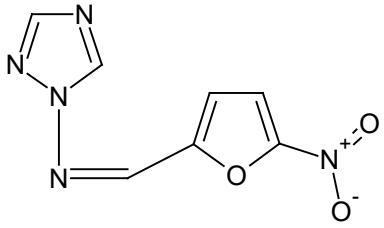
Anticancer (Vorozol)



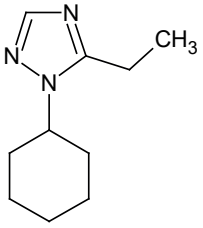
Anxiolytic (Alprazolam)



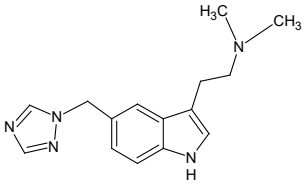
Antifungal (Fluconazole)



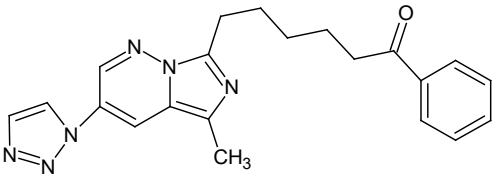
Antibacterial (Furazonal)



Antidepressant (Hexanol)



Antimigraine (Rizatriptan)

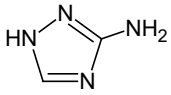


Anti-HIV activity

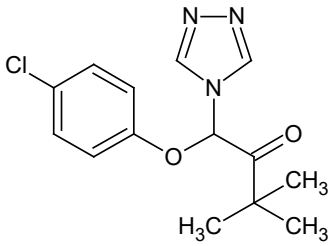
Figure 6. Drug active ingredient some triazole compounds

5. USAGE AREAS

Most of the heterocyclic compounds are natural compounds, and the organism in which they are found also undertakes different tasks. Triazole compounds are also important compounds for plants and are necessary for their development and growth, as well as strengthening the defense mechanisms of plants against damage by themselves and their environment. In this respect, it is also known that some 1,2,4-triazole derivative compounds show herbicide activity (Kalhor & Dadras, 2013). Especially 3- and 4-amino subtitue compounds of 1,2,4-triazole compounds are used as herbicides. The use of this compound, whose trade name is Amitrol, is known for this purpose.



Amitrole



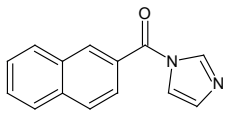
Beytone

Triazole compounds are also used as inhibitor molecules against corrosion. In particular, the inhibitory effects of triazole derivative compounds, substituted such as oxygen, sulfur, and nitro groups, are quite high. In addition, triazole compounds are also used in the industrial sector and are also used for optical whitening of polyester and cellulose fabrics. In this sense, it also has uses in the field of textiles. Apart from these, these compounds also take on the task of protecting plants against external factors. It is a triazole derivative that protects the plant against strong weather conditions such as frost. In addition, it is also used synthetically as insecticide, herbicide pesticides, artificial acceptors, dye properties, agrochemicals, additives.

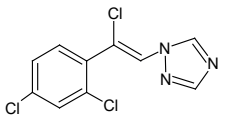
Triazole compounds are a biologically important compound group due to their properties such as forming more complex and important compounds by forming bonds such as hydrogen and peptide bonds with other groups, dissolving in the organism and showing activity. The most important feature of triazole compounds is that they can form multi-molecular compounds due to the presence of many N atoms and double bonded C atoms in their structure. Thanks to this feature, triazole compounds have an important place in the medical field in terms of creating new drugs containing more molecules as an alternative to the drugs used. In addition, the triazole ring is a compound that will play an active role in binding different compounds to its own structure by acting as a bridge in the production of new drugs with more than one effect area. In other words, the biological activity of the triazole ring can be changed with the substitution reaction. In this way, it is a molecule that can be used as a basic molecule to develop new various active molecules that are biologically very functional, for example, that can show both antirheumatic-anticancer activity. There are studies in the literature in which thion, amine, and alkyl substituted compounds of the active triazole compound show antiulcer and blood pressure lowering activities (El-Sayed, Abdelaziz, Wardakhan & Mohareb, 2016; Victoria, Lina, Narzullo & Idibeg, 2014; Perekhoda, Kadamov, Saidov & Georgiyants, 2015).

Synthesis and availability of new compounds effective on fungal organisms is an area of interest. It is important to develop new compounds and use them as alternative medicine because microorganisms gain resistance

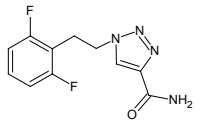
against the active ingredient of the drug over time and in diseases that weaken the immune system such as AIDS and cancer, which require long-term and high dosages of drug treatment, fungal organisms easily spread and cause disease.



Nafimidone (imidazole)



Loreclazole (1,2,4-triazole)



Rufinamide (1,2,3-triazole)

Drugs containing derivatized compounds such as ureite, oxime ether, oxime ester and azole compounds are generally used as the main ingredient of drugs used in the antiepileptic (AED) treatment of neurological system diseases such as migraine and pain originating from the nervous system. Nafimidon, which contains imidazole and naphthalene groups, is one of the most preferred compounds among active pharmaceutical ingredients. Afterwards, it was found that the compound formed by replacing the imidazole ring with a triazole ring showed highly effective anticonvulsant activity. Loreclazole and Rufinamide are important compounds among the third generation antiepileptic drugs used for this purpose.

The best known activity of triazole compounds, which is one of the azole group compounds, is expanding their field of action by showing anticonvulsant activity as well as antifungal activities. This group of antifungal drugs also show an extra antibacterial effect, and they are compounds that generally have effective results in oral intake, are slower to metabolize, have a wider effect area, are sensitive to fungal enzymes, and are superior to antifungal drugs used for this purpose. Some triazole compounds have antibacterial effects as well as antifungal effects. In other words, to summarize, it is seen in the studies in the literature that this class of compounds can have more than one activity.

6. SYNTHESIS REACTIONS OF TRIAZOLE COMPOUNDS

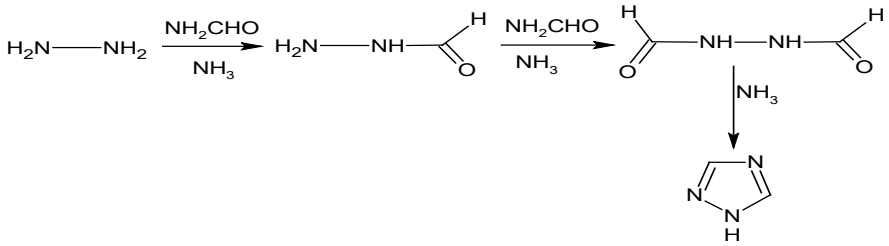
6.1. Synthesis of 1,2,4-Triazole Compounds

6.1.1. Synthesis of 1,2,4-triazole compounds from substituted hydrazine compounds

In this synthesis process, the method of obtaining 1,2,4-triazole compounds by first reacting hydrazine or substituted hydrazine compounds with electrophilic groups such as formamide compounds is the most widely used first method.

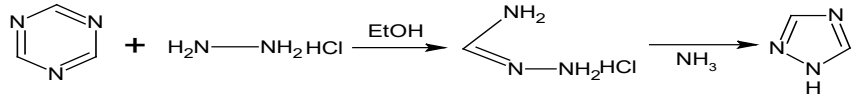
It was synthesized for the first time in 1885 by heating Bladin dicyanophenylhydrazine and acid anhydrides in a basic medium in KOH/

NaOH medium (Bladin, 1885). Afterwards, 1,2,4-triazole compound was synthesized by Pellizzari as a result of the reaction that continued with the separation of ammonia molecules from the reaction medium as a result of the reaction of formyl hydrazine and formamide.



Due to the necessity of very high temperatures such as 250-280°C for the realization of these reactions and the low reaction efficiency, other synthesis methods have started to be tried. In the following years, formamide was reacted with hydrazine sulfate instead of formyl hydrazine and 1,2,4-triazole reaction was carried out with a higher yield of 53%.

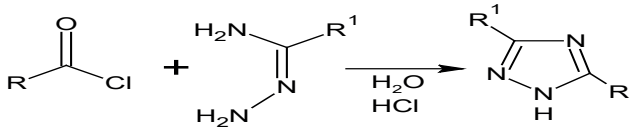
Grundman and Ratz tried another way in 1956 and synthesized 1,2,4-triazole with 95% yield by reacting s-triosine and hydrazine hydrochloride, and they performed the synthesis with a very high yield compared to previous years and trials (Grundamann & Ratz, 1956).



Ainsworth and Jones, in 1976, increased the yield of the triazole compound to 70-80% as a result of reacting the NH_3 molecule formed in the reaction medium with N,N-diformylhydrazine under high pressure (Ainsworth & Jones, 1976).

6.1.2. Synthesis of 1,2,4-triazole compounds from amidhydrazones

Di-substituted 2,4 disubstituted 1,2,4-triazole compounds are formed as a result of the reaction of amidhydrazone compounds with carboxylic acid chloride or carboxylic acid anhydrides (İkizler, 1996).

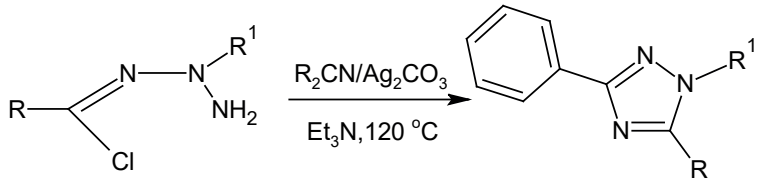


6.1.3. Synthesis of 1,2,4-triazole compounds from nitrilimine compounds

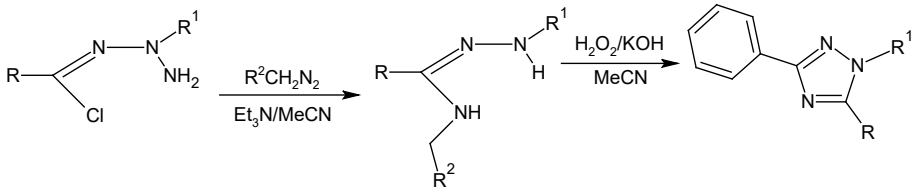
Synthesis of triazole compounds with 1,3 addition of triazine compounds

of nitrilimine and derivative compounds is another widely used method. The best example of these reactions; It is the reaction of nitrile imine compound with tetrazole compound. (X = NH).

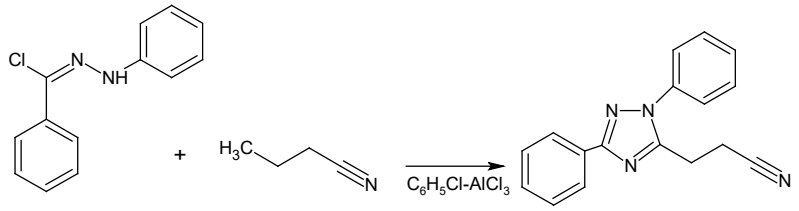
In another reaction in this way, di-substituted 1,2,4-triazole compounds are synthesized by heating in the presence of Ag_2CO_3 in the presence of triethylamine at 120 °C.



In another way, the synthesis process is carried out with substituted nitrilimine in the presence of methyl cyanide in the presence of triethyl amine.



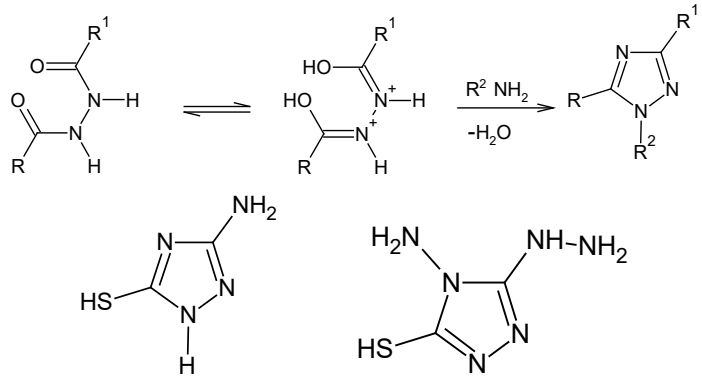
In addition, 1,2,4-triazole compounds can be synthesized by using imine derivatives instead of imine. 1,3-diphenyl-5-n-propyl-1H-1,2,4-triazole is obtained from the reaction of N-phenyl benzhydrazidoyl chloride and n-butyronitrile compounds in dry o-dichlorobenzene and aluminum chloride medium.



6.1.4. Synthesis of 1,2,4-triazole compounds from diacylhydrazine compounds

1,2,4-triazine derivative compounds are formed as a result of the reaction of acylhydrazine compounds formed by the bonding of 2 identical or 2 different substituents of these molecules, which can also be symmetrical, with primary amine compounds or NH_3. With this reaction, mercapto triazole

compounds that can show different biological activities can be synthesized.



3-amino 5-mercapto-1,2,4-triazole *3-hydrazino-4-amino-5-mercapto 1,2,4-triazole*

6.1.5. Synthesis of 1,2,4-triazole compounds from different heterocyclic structures

In this method, triazole synthesis usually takes place with the addition of nitrogen to a five-membered ring to convert a heterocyclic compound into a triazole compound. Oxadiazoles or thiadiazoles give triazole derivatives with aliphatic, aromatic or heterocyclic primary amines. The mechanism of this reaction is thought to be the first nucleophilic opening of the heterocyclic ring over the heteroatom, which is different from the nitrogen atom in the ring, and then the closure of the ring and the conversion to the triazole compound with the separation of the different heteroatom from the ring in the last step. A few examples of this are given below (Figure 7).

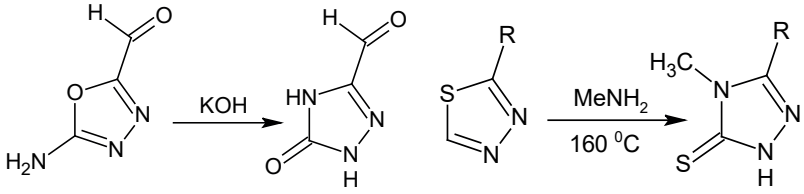


Figure 7. Synthesis of triazole compounds from different heterocyclic structures

The synthesis of amino substituted 3,5 diaryl 1,2,4-triazole compounds takes place together with 25% hydrochloric acid of tetrazine compounds. In the presence of reducing agents, zinc and acetic acid or sodium alkoxide, 3,5-diaryl 1,2,4-triazole compounds are formed.

6.2. Synthesis of 1,2,3-Triazole Compounds

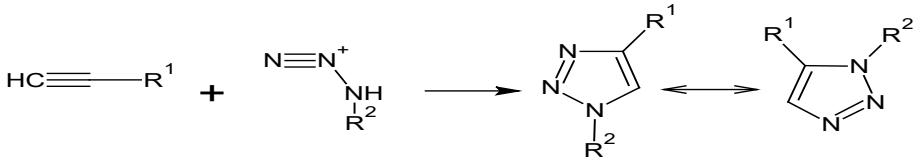
The synthesis of such triazole compounds for the first time was realized by Arthur as a result of the reaction between azide compounds and ester derivative compounds, and they saw that regional isomeric triazole compounds were

formed at the end of this reaction (Michael, 1893). Although the synthesis of the triazole compound was carried out in the 1800s, the type of reaction and the mechanism of this reaction were noticed and clarified by Huisgen in the 1950s, and the term 1-3 dipolar addition reaction emerged (Huisgen, Szeimies & Möbius, 1967). In the realization and development of Diels-alder and various cycloaddition reactions, the Huisgen method, which was called the Click reaction by Sharpless in the following years, has an important place especially in the field of polymer chemistry.

Reactions called click reactions:

- Huisgen 1,3 dipolar ring addition reaction
- Huisgen metal-catalyzed ring addition reaction
- Diels-Alder reaction
- Nucleophilic ring opening
- Addition reactions
- It can be listed as thiol-ene reaction.

Huisgen reactions are reaction types that are specific to the reagents, and they are reactions in which 1,2,3-triazole compounds are synthesized as a result of the cyclization of azide and alkyne compounds at relatively high temperatures. In this reaction, the substituted R^1 group attached to the alkyne molecule is the electron-withdrawing group, and the substituted R^2 group attached to the azide molecule is the electron-donating group. Since the terminal N atom in the azide molecule is nucleophilic, it will easily react with electrophilic groups and molecules such as the alkyne molecule. Compared to the conditions of 1,2,3-triazole compounds synthesized by previous methods, this method is accepted as the basic synthesis method in the synthesis of triazole compounds due to its positive aspects such as the difficulty of by-product formation in this reaction, which takes place under milder conditions, and the higher reaction efficiency compared to previous syntheses.



Alkyne *alkyl azide* *1,4-isomer* *1,5-isomer*

Figure 8. General synthesis reaction of 1,2,3-triazole compounds

Although this addition and cyclization reaction in organic synthesis was an important synthesis method of that period, the need to develop some points in the synthesis method arose due to reasons such as the low efficiency of these reactions in general, the fact that they took place at high temperatures, the long reaction time due to the absence of catalysis, and the formation of the products formed as a mixture of 1,4- and 1,5- isomers in the reaction medium (Khan et al., 2017).

In 1984, catalysis started to be used to use in these reaction types, and compounds containing Cu and Cu as catalysts were preferred and progress was made in terms of reaction time and efficiency. For these types of cyclization reactions made using a catalyst, Sharpless et al. called the click reaction (Kolb & Sharpless, 2003).

For this reason, there are two methods for the synthesis of 1,2,3-triazole compounds: reactions using metal catalysts and reactions without metal catalysts. As it is known, catalysts are substances that decrease the activation energy of the reactions and enable the reaction to take place faster than it should, as well as increase the reaction efficiency since there is no formation of by-products and leave the environment at the end of the reaction without any change in its chemical structure. Catalysts come in many varieties, either homogeneous, heterogeneous or organic. Many acids and bases are used as homogeneous catalysts in organic synthesis reactions. Transition metals are generally used as heterogeneous catalysts, and the majority of transition metals are usually elements such as palladium, platinum, and radium with large atomic numbers. In addition, the molecules that serve as catalyst molecules in biological reactions are enzymes as it is known. In this context, the catalyst molecules can sometimes be a metal, sometimes an organic molecule such as an enzyme, and sometimes an acid or base.

6.2.1. 1,2,3-Triazole Synthesis Without Using Metal Catalyst

In this reaction, which takes place over the 3+2 cycloaddition reaction, 1,2,3-triazole compounds with different substituents are synthesized without using any metal catalyst as a heterogeneous catalyst. Alkene with a double bond in its structure as the starting material for the general synthesis in these reactions by Huisgen as the starting material for the general synthesis, a molecule such as alkene , enamine, aldehyde, ketone and enamion, which has a double bond in its structure, or alkyne molecules with 3 bonds and azide reagents with different substituents such as Ar-N_3, Ph-N_3, Ts-N_3, NaN_3, RN_3 in a highly polar solvent environment such as DMSO, DMF, diethyl amine $(CH_3)_2NH$), diclorometha ne (CH_2Cl_2). In this method, when the alkyne used is a terminal alkyne compound, the triazole compound formed at the end of the reaction is synthesized as a mixture of 1,4- and 1,5- regioisomers.

Although these synthesis reactions can be synthesized between 3 hours and 48 hours at 70-80 °C, which can be considered as milder conditions when we look at the literature, there is a mixture of isomers in the reaction medium. This situation reveals both the decrease in yield due to the formation of the triazole compound to be synthesized as an isomer, and the need for an extra purification process in separating the isomer mixture of the synthesized compound (Figure 8).

6.2.2. 1,2,3-Triazole Synthesis Using Metal Catalyst

In the following years, new reagents and new methods have been started to be tried in order to eliminate the problems encountered in the synthesis of 1,2,3-triazole compounds without the use of catalysts.

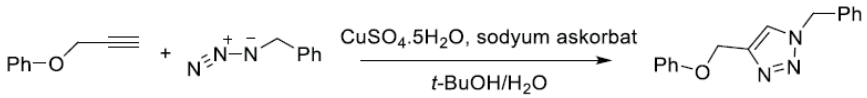


Figure 9. $CuSO_4$-catalyzed synthesis of 1,2,3-triazole compounds

Rostovtsev et al. tried a new method to control the selective synthesis of 1,4- and 1,5-substituted regioselective isomers in the cycloaddition reaction. They investigated the use of copper salts as a catalyst in this reaction and found that only 1,4-substituted-1,2,3-triazole of these isomer structures of Cu(I) catalyst was formed in the environment (Rostovtsev, Green, Fokin & Sharpless, 2002). The general mechanism for this reaction is shown in Figure BB below. shown as in. In addition, the fact that the reaction rate is faster between 107-108 compared to the metal-free reaction made by Huisgen has also increased the interest in using catalysis and pioneered the testing of new catalysts (Berg & Straub, 2013).

Generally; Cu_2O, Cu halides (CuI, CuCl, CuBr), Cu_2SO_4 as Cu salts were used in synthesis reactions. There are studies in which 1,2,3-triazole synthesis is carried out using transition metals such as Ag, Au, Ru, other than Cu metal and its salts (Liu et al., 2012; McNulty & Keskar, 2012; Rej, Chanda, Chiu & Huang, 2014; Şahin, 2021).

There are some reasons for choosing Cu and Cu salts as catalysts in click reactions in general. There are advantages, to list a few of them such as allowing to work in a wide range of pH 4-12, allowing the reaction in open air without the need for a closed isolated system, allowing the formation of regioselective products, that is, the desired isomer structure to be synthesized selectively, reducing the reaction conditions to milder conditions instead of more aggressive conditions, and making the reaction time, which extends up to 48 hours in the Huisgen reaction, in much shorter times (Çetin, 2004).

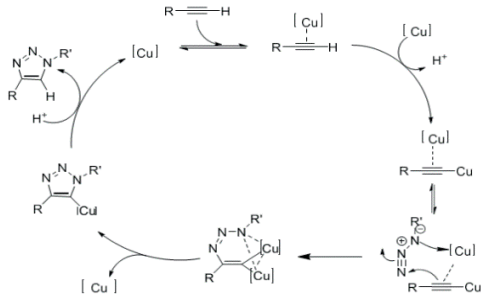


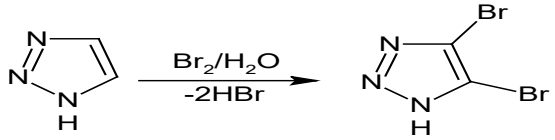
Figure 10. Cu-catalyzed regioselective synthesis mechanism of 1,2,3-triazole

7. REACTIONS OF TRIAZOLE COMPOUNDS

7.1. Electrophilic Substitution:

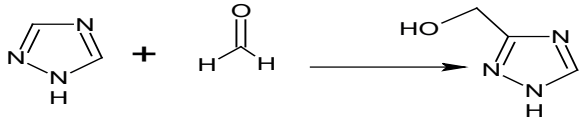
Triazole compounds can perform electrophilic substitution reactions due to the fact that π bond electrons in triazole compounds are very easy to be bonded by electron-withdrawing atoms or groups due to their structure. Triazole compounds -chlorine, -bromine and -iodine substituted triazole compounds that react with halogens under very mild conditions can be synthesized.

4,5-dibromo 1,2,3-triazole compounds were synthesized by adding Br_2 to 1,2,3-triazole compounds by this method.



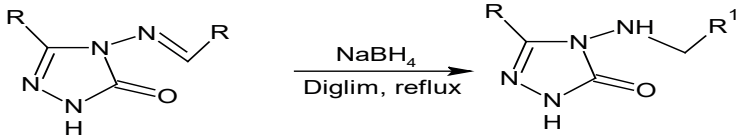
The same is true for 1,2,4-triazoles, and the N-X (X: -Cl, -Br, -I) bond in the newly formed halo-substituted 1,2,4-triazole compound can be broken quite easily, and the substitution reaction can take place.

Nitration, sulfolation, and Friedel-Crafts alkylation and acylation reactions do not occur from electrophilic substitution reactions that take place in an acidic environment, although reactions with halides are possible. When it reacts only with formaldehyde at 130 °C, 3-hydroxymethyl 1,2,4-triazole compounds are formed.



7.2. Reduction Reaction

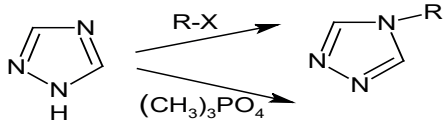
Triazole compounds in cyclic structure with aromatic character are quite stable against oxidation reactions. But it is just as sensitive to reduction. In order for these compounds to enter into a reaction, including hydrolysis reactions, the environment must be adjusted to be acidic or basic. If an oxidizing reagent such as $KMnO_4$, CrO_3, H_2O_2 is added to the medium, oxidation of only the side chain substitution groups of triazole compounds will occur. These reagents do not cause any change in the main ring. For example, the reaction of Schiff-based 1,2,4-triazole compounds synthesized by Akkaya in his study with $NaBH_4$ ended with the opening of the double bond in the side chain (Akkaya, 2013).



In the reduction reactions that occur with H_2 addition reaction in the presence of metals such as Pt, Ni, Zn, if strong reducing reagents such as $LiAlH_4$, $NaBH_4$ are present in the environment, there is a possibility of further reaction. In addition to these reactions, metal-coordinated triazole compounds are synthesized due to the tendency of the H atom on the N atom to be replaced by metals (Çetin, 2004). Triazole compounds and their derivatives are biologically important compounds because they can bind to various enzyme and receptor molecules in vivo, along with various bonds such as ion-dipole bonds, coordination bonds, and π-π bonds.

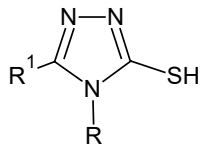
7.3. Alkylation Reaction

1,2,4-triazole reacts with alkyl halides and alkyl phosphates at 25-100 °C to synthesize alkyl-1,2,4-triazole compounds. There are two positions that can be alkylated in the 1,2,4-triazole compound, the 1st N atom and the 4th N atom. Although 1- and 4-alkyl triazole compounds are formed at the end of the reaction, the main product is 1-alkyl 1,2,4-alkyl triazole compound, since the N atom in the 1-position is more nucleophilic than the N atom in the 4-position.

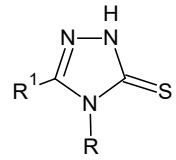


8. CONCLUSION

In the literature, there are many studies in which triazole compounds derivatized with many different groups such as $–NH_2$, -SH, =S, =O, -R group were synthesized and their different biological activities were studied. For example, the number of studies on the antifungal activities of thione and thiol derivatized 1,2,4-triazole compounds is quite high.

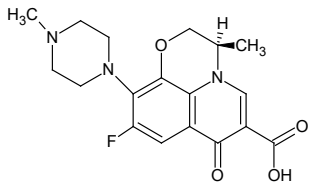


thiol

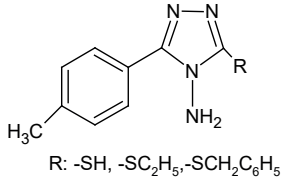


thion

The French patented 3-mercapto-1,2,4-triazole compound synthesized by Pesson from thiosemicarbazides was found to be fungicidal, herbicide and bactericidal compounds (Pesson, 1962).



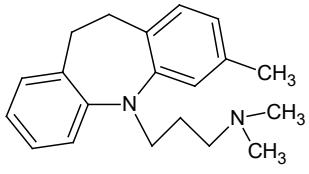
Oflaxacin



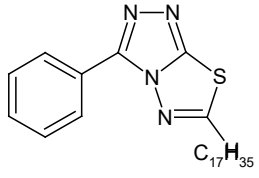
1-substituted aminomercaptotriazole

Jubie et al. synthesized 1-substituted aminomercaptotriazole compound based on ofloxacin, a well-known antibacterial drug, and investigated the antibacterial and antifungal activity of this compound. They found that the compounds had more effective activity than ofloxacin against Gram-positive bacteria *Staphylococcus aureus, Staphylococcus epidermidis* and *Bacillus subtilis* strains (Jubie et al., 2012a).

In another study, Jubie et al. synthesized 3-phenyl-6-heptadecyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole as an antidepressant agent like clomipramine and examined the effect of this compound on its antidepressant activity in vivo. They found that it showed close activity with the standard clomipramine used (Jubie et al.,2012b).

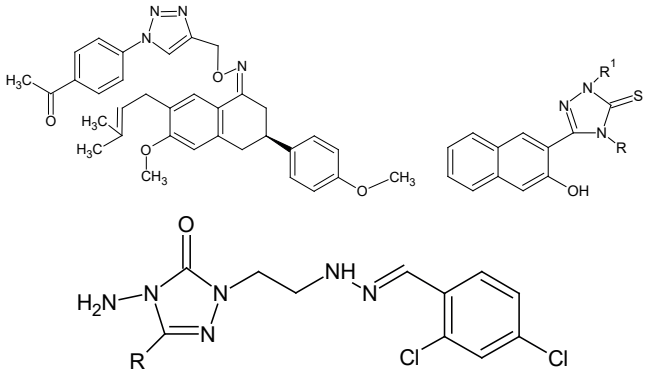


Clomipramine

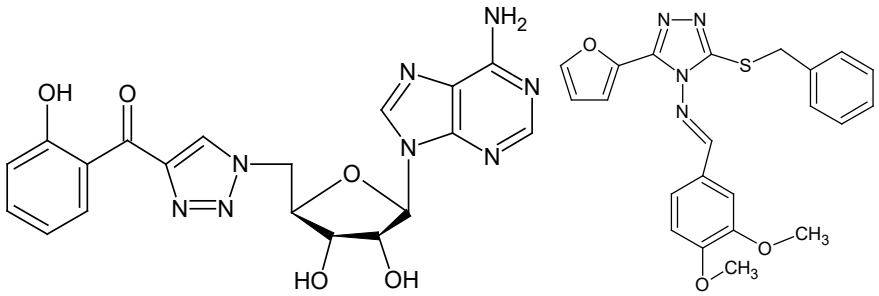


3-phenyl-6-heptadecyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole

In another study, they synthesized thion compounds with 1,2,3-triazole and 1,2,4 triazole structure and 1,2,4-triazol-3-one ringed arylidenhydrazide compounds. They investigated the anticancer effects of these compounds (Bozorov, Zhao & Aisa, 2019; Duran, Doğan & Rollas, 2002; Demirbaş, 2004). Arylidenhydrazide compound is an effective compound against breast cancer and has been found to show activity. The chemical structures of a few of these compounds are shown below, respectively.



As a result of the antituberculosis activity determination of the 1,2,3-triazole compound shown below, synthesized by Reddyrajula et al., this compound was found to be a good *Mycobacterium tuberculosis* inhibitor.



Wu et al. have detected anti-HIV-1 activity against HIV-1 infected MT-4 cells as a result of their biological activity study by synthesizing the 5-alkylthio compound of 4-amino-3-(2-furyl)-5-mercapto-1,2,4-triazoles.

REFERENCES

Adrien, A. & Taylor P. J. (1989). The tautomerism of 1,2,3-triazole in aqueous solution. *Journal of the Chemical Society,* 2(11), 1903-1905. https://doi.org/10.1039/P29890001903.

Ainsworth, C. & Jones, R.C. (1976). Isomeric and nuclear-substituted β-aminoethyl-1,2,4-triazoles. *Journal of the American Chemical Society*, 77: 621-624. https://doi.org/10.1021/ja01608a028.

Akkaya, E. (2013). Synthesıs Of Some 1,2,4-Triazol-3-One Derivatives and Identifying Their Structure, M. Sc. Thesis, Graduate School of Natural and Applied Sciences, Recep Tayyip Erdoğan University, Rize, Türkiye.

Avula, S. K., Khan, A., Rehman, N. U., Anwar, M. U., Al-Abri, Z., Wadood, A., Riaz, M., Csuk, R., & Al-Harrasi, A. (2018). Synthesis of 1H-1,2,3-triazole derivatives as new α-glucosidase inhibitors and their molecular docking studies. *Bioorganic Chemistry*, 81, 98-106. https://doi.org/10.1016/j.bioorg.2018.08.008.

Ayhan, G. (1988). Studies on Synthesis of Some New Antifungal Compounds, Master Thesis. Institute of Health Sciences, Ankara University, Ankara, Türkiye.

Berg, R. & Straub, B. F. (2013). Advancements in the mechanistic understanding of the copper-catalyzed azide-alkyne cycloaddition. *Beilstein Journal of Organic Chemistry*, 9, 2715-2750. https://doi: 10.3762/bjoc.9.308.

Bladin, J.A., (1885). Ueber von Dicyanphenylhydrazin abgeleitete Verbindungen. *Berichte der deutschen chemischen Gesellschaft*, 18, 1544-1551. https://doi.org/10.1002/cber.188501801335.

Bozorov, K., Zhao, J. & Aisa, H.A. (2019). 1,2,3-Triazole-containing hybrids as leads in medicinal chemistry: A recent overview. *Bioorganic & Medicinal Chemistry*, 15;27(16):3511-3531. https://doi.org/10.1016/j.bmc.2019.07.005.

Çetin, A. (2004), Synthesis and Characterization of Some Compounds Containing 1,3,4-Oxadiazole, 1,3,4-Thiadiazole and 1,2,4-Triazole Rings, Ph.D. Thesis, Institute of Science and Technology, Fırat University, Elazig, Turkey.

Dewar, M. J. S. & Morita, T. (1969). Ground states of conjugated molecules. XII. Improved calculations for compounds containing nitrogen or oxygen. *Journal of the American Chemical Society*,91,796-802. https://doi.org/10.1021/JA01051A023.

Demirbaş, A. (2004). A convenient synthesis of 3,6-disubstituted-1,4-dihydro-[1,2,4,5] tetrazines and preparation of new acetic acid derivatives containing 5-oxo-4 phenylamino-4,5-dihydro-[1,2,4]triazole. *Turkish Journal of Chemistry*, 28:311-323.

Duran, A., Doğan, H.N., Rollas, S. (2002). Synthesis and preliminary anticancer activity of new 1,4-dihydro-3-(3-hydroxy-2-naphthyl)-4-substituted-5H-1,2,4-triazoline-5- thione. *Il Farmaco* 57(7),559-564. https://doi.org/10.1016/s0014-827x(02)01248-x.

El-Sayed, N.N., Abdelaziz, M.A., Wardakhan, W.W., Mohareb, R.M. (2016). The

knoevenagel reaction of cyanoacetylhydrazine with pregnenolone: synthesis of thiophene, thieno [2, 3-d] pyrimidine, 1, 2, 4-triazole, pyran and pyridine derivatives with anti-inflammatory and anti-ulcer activities. *Steroids,* 107, 98-111. https://doi.org/10.1016/j.steroids.2015.12.023.

Fidan, S. (2007). Quantum Chemical Studies on 1,2,4-Triazole and Its Derivatives, M. Sc. Thesis, Graduate School of Natural and Applied Sciences. Osmangazi University, Eskişehir, Türkiye.

Gallardo, H., Conte, G., Bryk, F., Lourenço, M.C., Costa, M.S., Ferreıra, V.F. (2007). Synthesis and evaluation of 1-alkyl-4-phenyl-[1,2,3]-triazole derivatives as antimycobacterial agent. *Journal of the Brazilian Chemical Society*, 18(6), 1285-1291. https://doi.org/10.1590/S0103-50532007000600027.

Gao, F., Chen, Z., Ma, L., Fan, Y., Chen, L., & Lu, G. (2019). Synthesis and biological evaluation of moxifloxacin-acetyl-1, 2, 3-1H-triazole-methylene-isatin hybrids as potential anti-tubercular agents against both drug-susceptible and drug-resistant Mycobacterium tuberculosis strains. *European Journal of Medicinal Chemistry*, 180, 648-655. https://doi.org/10.1016/j.ejmech.2019.07.057.

Grundmann, C. & Ratz, R. (1956). Triazines. XVI. A New Synthesis for 1,2,4-Triazoles. *Journal of Organic Chemistry*, 21(9),1037-1038. https://doi.org/10.1021/jo01115a610.

Huisgen, R., Szeimies, G., & Möbius, L. (1967). 1.3-Dipolare Cycloadditionen, XXXII. Kinetik der Additionen organischer Azide an CC-Mehrfachbindungen. *Chemische Berichte*, 100(8), 2494-2507. https://doi.org/10.1002/cber.19671000806.

İkizler, A. (1996). Heterocyclic Compounds, K.T.Ü. Faculty of Science Publications No:38, Trabzon, 236-241.

Jubie, S., Prabitha, P., Kumar, R. R., Kalirajan, R., Gayathri, R., Sankar, S. et al. (2012a). Design, synthesis, and docking studies of novel ofloxacin analogues as antimicrobial agents. *Medicinal Chemistry Research*, 21 (7), 1403-1410. https://doi.org/10.1007/s00044-011-9655-8.

Jubie, S., Ramesh, P. N., Dhanabal, P., Kalirajan, R., Muruganantham, N. ve Antony, A. S. (2012b). Synthesis, antidepressant and antimicrobial activities of some novel stearic acid analogues. *European Journal of Medicinal Chemistry*, 54, 931-935. https://doi.org/10.1016/j.ejmech.2012.06.025.

Kalhor, M. & Dadras, A. (2013). Synthesis, characterization, and herbicidal activities of new 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, and 1,2,4-triazoles derivatives bearing (R)-5-chloro-3-fluoro-2-phenoxypyridine. *Heterocyclic Compounds*, 50(2), 220-224. https://doi.org/10.1002/chin.201339149.

Khan, M. F., Verma, G., Akhtar, W., Marella, A., Alam, M., Akhter, M., Husain, A., Hasan, S. M., Shaquiquzzaman, M. & Haider, S. (2017). Synthetic trends followed for the development of 1,2,3-Triazole Derivatives. *International Journal of Drug Development and Research*, 9(2), 22–25.

Kini, G.D., Robins, R.K., Avery, T.L. (1989). Synthesis and antitumor activity of ribavirin imidates. A new facile synthesis of ribavirin amidine (1-beta-Dribofuranosyl- 1,2,4-triazole-3-carboxamidine hydrochloride. *Journal of Medicinal Chemistry*, (32), 1447-9. https://doi.org/10.1021/jm00127a008.

Kolb, H. C. & Sharpless, K. B. (2003). The growing impact of click chemistry on drug discovery. *Drug discov today*, 8(24), 1128-1137. https://doi.org/10.1016/s1359-6446(03)02933-7

Liu, Y., Nie, G., Zhou, Z., Jia, L. & Chen, Y. (2017). Copper-catalyzed oxidative.

cross-dehydrogenative coupling/oxidative cycloaddition: Synthesis of 4-acyl-1, 2, 3-triazoles *The Journal of Organic Chemistry*, 82(17), 9198-9203. https://doi.org/10.1021/acs.joc.7b01429.

Liu, P. N., Li, J., Su, F. H., Ju, K. D., Zhang, L., Shi, C., Sung, H. H. Y., Williams, I. D., Fokin, V. V., Lin, Z., & Jia, G. (2012). Selective formation of 1,4-disubstituted triazoles from ruthenium- catalyzed cycloaddition of terminal alkynes and organic azides: scope and reaction mechanism. *Organometallics*, 31(13), 4904-4915. https://doi.org/10.1021/om300513w.

McNulty, J., & Keskar, K. (2012). Discovery of a robust and efficient homogeneous silver(I) catalyst for the cycloaddition of azides onto terminal alkynes. *European Journal of Organic Chemistry*, 28, 5462–5470. https://doi.org/10.1002/ejoc.201200930.

Michael, A. (1893). Ueber die einwirkung von diazobenzolimid anf acet ylendicarbonsauremethylester. *Journal Für Praktische Chemie*, 48(1), 94–95. https://doi.org/10.1002/PRAC.18930480114.

Papakonstantinou, G.S., Pouli, N., Marakos, P. and Chytyroglou, L. A. (2002). Synthesis antimicrobial and antifungal activity of some new 3-substituted derivatives of 4-(2, 4-dichlorophenyl)- 5-adamantyl-1H-1,2,4-triazole. *Farmaco,* 57, 973-977. https://doi.org/10.1016/s0014-827x(02)01227-2.

Perekhoda, L., Kadamov, I., Saidov, N., Georgiyants, V. (2015). Synthesis of novel substituted 4-phenyl-5-phenoxymethyl-3-mercapto-1,2,4-triazole (4 H) derivatives as potential anti-ulcer agents. Scripta Scientifica Pharmaceutica, 2(2), 46-52. https://doi.org/10.14748/ssp.v2i2.1300.

Pesson, M. (1962). 3-Mercapto-1,2,4-triazoles. *Chemical Abstracts*, 57, 9860f. Fr. Pat, 1273881.

Polat, S. (2015). Structural characterization and biological functions of 4-Ethyl-5-(2-

hydroxyphenyl)-2H-1,2,4-triazole-3(4H)-thione, M. Sc. Thesis, Graduate School of Natural and Applied Sciences. Fırat University, Kahramanmaraş, Türkiye.

Potts, K.T. (1960), The chemistry of 1,2,4-triazoles. *Chemical Reviews*, 60, 87-127.

Rej, S., Chanda, K., Chiu, C.Y., & Huang, M. H. (2014). Control of regioselectivity over gold nanocrystals of different surfaces for the synthesis of 1,4-disubstituted triazole through the click reaction. *Chemistry - A European Journal*, 20(48), 15991–15997. https://doi.org/10.1002/chem.201403958.

Rostovtsev, V.V., Green, L.G., Fokin, V.V., Sharpless, K.B. (2002). A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective "Ligation" of azides and terminal alkynes. *Angewandte Chemie International Edition,* 41,2596–2599. https://doi.org/10.1002/1521-3773(20020715)41:14<2596::AIDANIE2596>3.0.CO;2-4

Shawali, A.S. & Parhayi, C. (1980). Hydrazidoyl Halides in the Synthesis of Heterocycles. *Journal of Heterocyclic Chemistry,* 17,833-854. http://dx.doi.org/10.1002/jhet.5570170501.

Şahin, İ. (2021). Synhtesıs, Characterization and Investigatıion of Various Biological Properties Of 1,2,3-Triazole Based New Conjugates. Ph.D Thesis, Institute for Graduate Studies in Science and Technology, Kahramanmaraş, Türkiye.

Tamimy, V. (2001). Synthesis of Schiff Bases Derived from 3-Amino-1,2,4-Triazole and Investigation of Transition Metal Complexes. M. Sc. Thesis, Graduate School of Natural and Applied Sciences, İstanbul University, İstanbul, Türkiye.

Temple, C. (1981). The Chemistry of Heterocyclic Compounds; v.37 Triazoles 1,2, 4, John Wiley and Sons Inc., New York.

Türkmen, Y. (2020). Synthesis Of 4-(1,2,3-Triazoyl)Arylmethanone Compounds which may have Anti-Tuberculosis Effect. M. Sc. Thesis, Graduate School of Natural and Applied Sciences, Gazi University, Ankara, Türkiye.

Victoriya, G., Lina, P., Narzullo, S., Idibeg, K. (2014). Synthesis, docking studies, and biological evaluation of anti-ulcer activity of 4-allyl-5-(4-R1)-phenylthiomethyl1,2,4-triazole-3-yl mercaptoacetic acid derivatives. *European Chemical Bulletin*, 3(5):466-471. https://doi.org/10.17628/ECB.2014.3.466.

Youssif, B. G. M., Mohamed, Y. A. M., Salim, M. T. A., Inagaki, F., Mukai, C., & Abdu-Allah, H. H. M. (2016). Synthesis of some benzimidazole derivatives endowed with 1,2,3-triazole as potential inhibitors of hepatitis C virüs. *Acta Pharmaceutica*, 66, 219-231. https://doi.org/10.1515/acph-2016-0014

Zhao, P. L., Duan, A. N., Zou, M., Yang, H. K., You, W. W. & Wu, S. G. (2012). Synthesis and cytotoxicity of 3,4-disubstituted-5-(3,4,5-trimethoxyphenyl)-4H- 1,2,4-triazoles and novel 5,6-dihydro-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole derivatives bearing 3,4,5-trimethoxyphenyl moiety. *Bioorganic & Medicinal Chemistry Letters* 22 (13), 4471-4474. https://doi.org/10.1016/j.bmcl.2012.03.023.