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Prof. Dr. Edip BAYRAM
Prof. Dr. Günay ÖZTÜRK

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CHAPTER 1

NUMERICAL APPROXIMATION OF THE MODIFIED EQUAL WIDTH (MEW) EQUATION UTILIZING A IMPLICIT FINITE DIFFERENCE SCHEME WITHIN THE LIE-TROTTER SPLITTING FRAMEWORK

*Melike KARTA*¹

¹ Doç. Dr. Department of Mathematics, Faculty of Science and Arts, Ağrı İbrahim Çeçen University, Ağrı, Turkey ORCID: <https://orcid.org/0000-0003-3412-4370>

Introduction

This study focuses on the derivation of a computational approach for the (MEW) equation

$$u_t - u_{xxt} + \epsilon U^2 u_x = 0$$

contingent on the conditions specified below

$$U(x, 0) = g(x)$$

and

$$U(a, 0) = U(b, 0) = 0,$$

$$U_x(a, 0) = U_x(b, 0) = 0,$$

$$U_{xx}(a, 0) = U_{xx}(b, 0) = 0$$

for which the solitary wave result can be expressed as follows:

$$U(x, t) = c \operatorname{sech}[k(x - x_0 - vt)].$$

Here, $v = \frac{c^2}{2}$ and $k = \frac{1}{\mu}$ where t and x designate the temporal and locational variables, respectively. The parameters ϵ and μ are assumed to be constants that are greater than or equal to zero. Moreover, $f(x)$ represents a smooth function, while U denotes elevation of the free aquatic surface. The (GEW) equation can be expressed in the following form. It is subject to the corresponding physical conditions as $x \rightarrow \pm\infty$, where t denotes the time variable and x represents the spatial coordinate. Here, the parameters involved in the equation are assumed to be positive. For $p = 1$, equation (1) reduces to the (EW) equation originally investigated by Morrison et al. [2]. Furthermore, for the appropriate choice of the parameters, it yields the (MEW) equation. Under a restricted set of initial and boundary conditions, the equation has attracted significant discussion in the literature, and a variety of analytical and Computational approaches have been employed to investigate its exact or approximate solutions. Among the analytical studies, Wang et al. [6] investigated wave-propagating findings of the MEW equation within the framework of dynamical system theory. Wazwaz [3] obtained analytical solutions by employing the sine–cosine ansatz together with the tanh method. An alternative analytical treatment was presented by Jin [4], who applied the homotopy-based perturbation approach. Hamdi et al. [1] acquired closed-form solutions for the (GEW) equation as well as the EW-Burgers equation. Lu [5] employed the variational iteration approach to construct exact approximations, whereas Taghizadeh [7] investigated the equation using the improved simple equation technique. In another analytical study, Taha and Noorani [8] employed the G'/G-expansion technique. Rui et al. [9], on the other hand, examined the equation from the perspective of integral bifurcation analysis. Numerical investigations of the EW-type equations have also been carried out using a wide range of discretization techniques. Cheng and Liew [10] developed the modified element-free Galerkin (IEFG) approach formulation for obtaining numerical approximations. Esen [11] and Karakoç and Geyikli [12] investigated Galerkin-type formulations based on lumped Galerkin approaches, employing B-splines basis functions, respectively. Earlier, Gardner and Gardner [13] applied the classical Galerkin method to the EW equation. Finite difference approaches were considered by Esen and Kutluay [14] as well

as Raslan et al. [15], while Essa [16] investigated a multigrid-based computational procedure. Several finite element and spline-based formulations have subsequently been proposed. Geyikli and Karakoç [17] and Karakoç and Geyikli [18] studied approximate findings using the subdomain finite element approach in conjunction with B-splines, respectively. For the MEW equation, Geyikli and Karakoç [19] employed a Petrov–Galerkin formulation, whereas Roshan [20] applied the same type of approach to the GEW equation. Evans and Raslan [21] developed a collocation procedure based on quadratic B-splines for the GEW equation. A meshless collocation technique incorporating radial basis functions was investigated by Dereli [22]. Başihan et al. [23] combined a finite difference formulation with the differential quadrature method to construct a numerical scheme. Further developments have focused on improving the accuracy and computational efficiency of spline-based methods. Karakoç et al. [24] considered several linearization strategies within a B-spline collocation finite element framework. Çelikkaya [25] investigated the equation by combining a Strang splitting scheme with a cubic B-spline collocation approach. Zaki [26] employed a Petrov–Galerkin formulation using quintic B-splines, while Saka [27] developed collocation algorithms based on quintic B-spline functions. More recent contributions include the study of Başihan et al. [28], which introduced a different computational perspective for the equation, and the work of Yağmurlu and Karakaş [29], who proposed a method based on trigonometric cubic B-splines.

Finite Difference Methods

Among the finite difference methods, the implicit, and Crank–Nicolson schemes are among the most widely used approaches. In this study, the implicit finite difference method is employed, which is obtained by taking the average of the explicit and implicit finite difference formulations.

$$F(x, t, u, u_x, u_t, u_{xx}, u_{xt}, \dots) = 0$$

Consider a partial differential equation under the prescribed subject to the prescribed constraints. The computational domain of the model problem, $(x, t) \in [a, b] \times [0, T]$, is divided into a uniform grid. The spatial area $[a, b]$ is generally separated into M equal subintervals of length $h = x_{i+1} - x_i$ ($x_i = ih, i = 0(1)M$). Thus, the spatial grid is defined by $a = x_0 < x_1 < x_2 < \dots < x_{M-1} < x_M = b$. Similarly, the time range $[0, T]$ is divided into N equal subintervals with time step size $k = t_{n+1} - t_n$ ($t_n = nk, n = 0(1)N$). Hence, the temporal grid is given by $0 = t_0 < t_1 < \dots < t_{N-1} < t_N = T$. The intersections of the spatial and temporal grids form the discrete grid points (x_i, t_n) ($i = 0(1)M, n = 0(1)N$). In this way, the continuous computational domain is transformed into a discrete domain. The values of the numerical solution at the grid points are then determined by incorporating the prescribed initial and boundary conditions into the numerical scheme.

Lie-Trotter Splitting

Splitting methods are generally based on decomposing a complex equation into a set of sub-equations, each representing different physical characteristics, so that the resulting problems can be solved more easily than the original equation. These methods offer several advantages in numerical computations, particularly in terms of computational efficiency, accuracy, and stability. They are generally explicit and relatively straightforward to implement. The Lie–Trotter and Strang splitting methods are among the commonly used approaches in this class.

In this study, the Lie Trotter technique is employed in the time direction to decompose the MEW equation into two subproblems, namely a linear problem and a nonlinear problem. Let A and B denote the two operators associated with these subproblems. First, the A -operator is solved over a time interval of $\Delta t = k$ using the initial condition of the original problem. The solution obtained from this step is then taken as the initial condition for the B -operator. Next, the B -operator is solved over a time interval of $\Delta t = k$ using the newly obtained initial condition. The resulting solution is subsequently used as the initial condition for the A -operator. Finally, the A -operator is solved once again over a time interval of $\Delta t = k$ with the updated initial condition. The solution obtained after these three consecutive steps yields a numerical representation of the solution to the original equation.

Application of the Method

The (MEW) equation, will be decomposed into two sub-equations using the Lie–Trotter splitting technique, one of which is linear in time and the other nonlinear in time

$$u_t - \mu u_{xxt} = 0,$$

$$u_t - u_{xxt} + \epsilon u^2 u_x = 0.$$

Implicit finite difference method in both time and space, obtained through Taylor-series expansion will be applied to each sub-equation, resulting in two distinct matrix schemes as follows:

$$\left(-\frac{\mu}{h^2}\right)u_{i-1}^{n+1} + \left(\frac{1}{k} + \frac{2\mu}{h^2}\right)u_i^{n+1} + \left(-\frac{\mu}{h^2}\right)u_{i+1}^{n+1} = \left(-\frac{\mu}{h^2}\right)u_{i-1}^n + \left(\frac{1}{k} + \frac{2\mu}{h^2}\right)u_i^n + \left(-\frac{\mu}{h^2}\right)u_{i+1}^n,$$

$$\begin{aligned} &\left(-\frac{\mu}{k} - \frac{\epsilon}{2h}(u_i^n)^2\right)u_{i-1}^{n+1} + \left(\frac{1}{k} + \frac{2\mu}{k}\right)u_i^{n+1} + \left(-\frac{\mu}{k} - \frac{\epsilon}{2h}(u_i^n)^2\right)u_{i+1}^{n+1} \\ &= \left(-\frac{\mu}{h^2}\right)u_{i-1}^n + \left(\frac{1}{k} + \frac{2\mu}{k}\right)u_i^n + \left(-\frac{\mu}{h^2}\right)u_{i+1}^n \end{aligned}$$

Subsequently, these two schemes will be combined using the splitting technique and solved computationally in MATLAB to obtain the corresponding numerical solutions.

Numerical Examples and Results

For the (MEW) equation, three fundamental invariants associated with mass, momentum, and energy are preserved [11]. The performance of the numerical scheme is evaluated by calculating the error norms.

$$\begin{aligned} I_1 &= h \sum_{j=0}^N U_j, & I_2 &= h \sum_{j=0}^N [U_j^2 + \mu(U_j')^2], & I_3 &= h \sum_{j=0}^N U_j^4 \\ L_2 &= \|U^{tam} - U^{num}\|_2 \cong \sqrt{h \sum_{i=0}^N |U_i^{tam} - U_i^{num}|^2} \\ L_\infty &= \|U^{tam} - U^{num}\|_\infty \cong \underbrace{Max}_i |U_i^{tam} - U_i^{num}| \end{aligned}$$

The approximate solutions of the equation will be obtained by solving the two resulting matrix formulations in MATLAB through the operator splitting technique. The error norms will be evaluated and compared with the corresponding results reported in prior studies, with the evaluated presented in tabular form. Furthermore, By contrasting the numerical and exact solutions, the suggested method's validity will be assessed, and the results will be illustrated graphically in two-dimensional form and tables.

Example 1: A Single Solitary Wave Traveling

To assess the capability of the advised approach in comparison with previously reported works, a single solitary wave dynamics is investigated through a series of numerical experiments presented in the corresponding tables and figures. The computational settings, including the wave amplitudes, temporal step sizes, and spatial domains, are varied across the considered cases. Nevertheless, the spatial intervals $[0,80]$ and $[0,70]$, together with the parameter choices $\mu = 1$ and $x_0 = 30$, are predominantly adopted throughout the simulations. For consistency and to enable a meaningful comparison, the parameter configurations employed in the reference studies are also retained in the corresponding test cases. The computational findings indicate that the numerical solutions generated through the combination of the splitting technique and the finite difference discretization are in reliable accordance with the corresponding findings available in the literature, particularly those reported in [24]. In addition, the numerical invariants exhibit a high degree of conservation over the entire computational interval. These results suggest that the proposed numerical scheme successfully reproduces the essential characteristics of the solitary-wave dynamics while maintaining consistency with previously established numerical results.

Table 1. Invariant quantities and error norms are examined for a single solitary-wave solution with, $\Delta t = 0.05$, $\mu = 1$ for $c = 1.0$ over the computational domain $[0, 80]$.

method	t	I_1	I_2	I_3	$L_2 \times 10^3$	$L_\infty \times 10^3$
LTS.imp.dif.	0	3.1415927	2.6666667	1.3333333	0.00000	0.00000
	5	3.1415926	2.6666666	1.3333333	2.48528	1.16834
	10	3.1415926	2.6666666	1.3333333	2.55167	1.15789
	15	3.1415926	2.6666665	1.3333332	2.76145	1.15679
	20	3.1415925	2.6666665	1.3333332	2.74740	1.16456
SS.Coll. [25]	20	3.1415922	2.6666685	1.3333329	2.49435	1.78185
HM(Pres.) [28]	20	3.1416760	2.6667600	1.3334280	1.50692	0.92893

Table 2. Invariant quantities and error norms are examined for a single solitary-wave solution with $\Delta t = 0.01$, $\mu = 1$, for $c = 1.0$ over $[0, 80]$.

method	t	I_1	I_2	I_3	$L_2 \times 10^3$	$L_\infty \times 10^3$
LTS.imp.dif.	0	3.1415927	2.6666667	1.3333333	0.00000	0.00000
	5	3.1415927	2.6666667	1.3333333	2.22329	1.15452
	10	3.1415927	2.6666667	1.3333333	2.23245	1.16420
	15	3.1415927	2.6666667	1.3333333	2.24103	1.16431
	20	3.1415927	2.6666667	1.3333333	2.24313	1.05429
FD. [14]	20	3.1415790	2.6666350	1.3333310	0.14945	0.09870
SD. [17]	20	3.1415838	2.6666592	1.3333251	3.61948	2.25768
SD. [18]	20	3.1415860	2.6666612	1.3333279	3.61297	2.25401
DL.Coll. [24]	20	3.1415842	2.6666609	1.3333253	3.98833	2.84859
HM(Pres.) [28]	20	3.1416120	2.6667230	1.3333890	0.02601	0.01908

Table 3. Numerical assessment of the invariant quantities and error norms for a single solitary wave with $\mu = 1$, $\Delta t = 0.05$ for $c = 0.75$ over $[0, 80]$.

method	t	I_1	I_2	I_3	$L_2 \times 10^3$	$L_\infty \times 10^3$
LTS.imp.dif.	0	2.356194	1.5000000	0.4218750	0.00000	0.00000
	5	2.356194	1.5000000	0.4218750	2.24678	1.50232
	10	2.356194	1.5000000	0.4218750	2.25689	1.53450
	15	2.356194	1.5000000	0.4218750	2.26687	1.52251
	20	2.356194	1.5000000	0.4218750	2.26740	1.50340
SS.Coll. [25]	20	2.356194	1.5000012	0.4218750	2.03819	1.46910
HM(Pres.) [28]	20	2.356221	1.5000350	0.4218947	0.14153	0.08585

Table 4. Numerical assessment of the invariant quantities and error norms for a single solitary wave with $\Delta t = 0.01, \mu = 1$ for $c = 0.75$ over $[0, 80]$.

method	t	I_1	I_2	I_3	$L_2 \times 10^3$	$L_\infty \times 10^3$
LTS.imp.dif.	0	2.356194	1.4807980	0.4218750	0.00000	0.00000
	5	2.356194	1.4807980	0.4218750	2.24341	1.59051
	10	2.356194	1.4807980	0.4218750	2.23201	1.57901
	15	2.356194	1.4807980	0.4218750	2.22345	1.57843
	20	2.356194	1.4807980	0.4218750	2.22890	1.60238
FD. [14]	20	2.3561860	1.499979	0.421874	0.05193	0.03667
SD. [17]	20	2.356189	1.499997	0.4218732	1.48146	0.93623
SD. [18]	20	2.356189	1.4999969	0.421873	1.48020	0.93594
DL.Coll. [24]	20	2.356189	1.4999982	0.421873	2.24293	1.62010
HM(Pres.) [28]	20	2.356156	1.4999630	0.4218543	0.01595	0.01218

Table 5. Numerical evaluation of the invariant quantities and error norms associated with a single solitary-wave solution under the prescribed parameter settings, $\Delta t = 0.05, \mu = 1$ for $c = 0.5$ over $[0, 80]$.

method	t	I_1	I_2	I_3	$L_2 \times 10^3$	$L_\infty \times 10^3$
LTS.Coll.	0	1.5707963	0.6666667	0.0833333	0.00000	0.00000
	5	1.5707963	0.6666667	0.0833333	0.00241	0.00203
	10	1.5707963	0.6666667	0.0833333	0.00475	0.00387
	15	1.5707963	0.6666667	0.0833333	0.00702	0.00516
	20	1.5707963	0.6666667	0.0833333	0.00920	0.00640
SS.Coll. [25]	20	1.5707963	0.6666673	0.0833333	1.05855	0.86024

Table 6. Numerical evaluation of the invariant quantities and error norms associated with a single solitary-wave solution under the prescribed parameter settings, $\Delta t = 0.01, \mu = 1$ for $c = 0.5$ over $[0, 80]$.

method	t	I_1	I_2	I_3	$L_2 \times 10^3$	$L_\infty \times 10^3$
LTS.imp.dif.	0	1.570796	0.6666667	0.0833333	0.00000	0.00000
	5	1.570796	0.6666667	0.0833333	0.05670	0.05886
	10	1.570796	0.6666667	0.0833333	0.05567	0.04858
	15	1.570796	0.6666667	0.0833333	0.05563	0.04865
	20	1.570796	0.6666667	0.0833333	0.05483	0.04897
FD. [14]	20	1.570792	0.6666588	0.0833333	0.01864	0.01509
SD. [17]	20	1.570793	0.6666655	0.0833330	0.42152	0.27116
SD. [18]	20	1.570793	0.6666653	0.0833330	0.42111	0.27119
DL.Coll. [24]	20	1.570793	0.6666660	0.0833330	1.06979	0.86864
HM(Pres.) [28]	20	1.5708080	0.6666710	0.0833345	0.00662	0.00450

Table 7. Numerical evaluation of the invariant quantities and error norms associated with a single solitary-wave solution under the prescribed parameter settings, $\Delta t = 0.05, \mu = 1$ for $c = 0.5$ over $[0, 70]$.

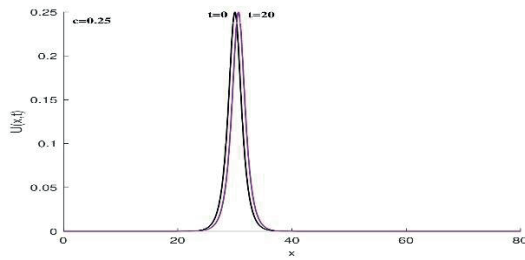
method	t	I_1	I_2	I_3	$L_2 \times 10^3$	$L_\infty \times 10^3$
LTS.imp.dif.	0	1.570796	0.6666667	0.0833333	0.00000	0.00000
	5	1.570796	0.6666667	0.0833333	1.01032	1.01245
	10	1.570796	0.6666667	0.0833333	1.01854	1.01356
	15	1.570796	0.6666667	0.0833333	1.00976	1.01684
	20	1.570796	0.6666667	0.0833333	1.00498	1.00610
	20	1.570735	0.6666084	0.0833187	0.09475	0.03564
MQ. [22]	20	1.570766	0.6666460	0.0833281	0.03186	0.02476
G. [22]	20	1.571058	0.6669421	0.0834022	0.25540	0.19890
IMQ. [22]	20	1.570560	0.6664956	0.0832905	0.17124	0.13536
Q. [22]	20	1.57078	0.66666	0.08333	0.01172	0.00852
PG. [26]	20	1.570796	0.6666667	0.0833333	0.00920	0.00640
QBCM1. [27]	20	1.570796	0.6666667	0.0833333	0.00920	0.00640
QBCM2. [27]	20	1.570796	0.6666667	0.0833333	0.00860	0.00568
QBCM3. [27]	20	1.570796	0.6666667	0.0833333		

Table 8. Numerical evaluation of the invariant quantities and error norms associated with a single solitary-wave solution under the prescribed parameter settings. $\Delta t = 0.2, \mu = 1$ for $c = 0.25$ over $[0, 80]$.

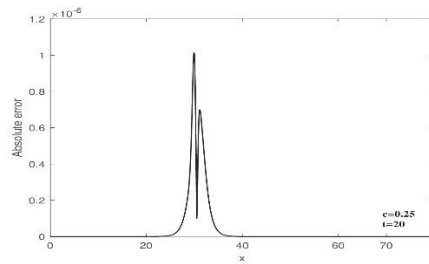
method	t	I_1	I_2	I_3	$L_2 \times 10^4$	$L_\infty \times 10^4$
LTS.imp.dif.	0	0.7853982	0.6666667	0.0052083	0.000000	0.000000
	5	0.7853982	0.6666667	0.0052083	3.202034	2.314835
	10	0.7853982	0.6666667	0.0052083	3.202034	2.305890
	15	0.7853982	0.6666667	0.0052083	3.014090	2.304745
	20	0.7853982	0.6666667	0.0052083	3.012734	2.304782
	20	0.7853977	0.1664736	0.0052083	2.701647	2.576377
FD. [14]	20	0.7853977	0.1664736	0.0052083	2.701647	2.576377
Coll. [21]	20	0.7852864	0.1665818	0.0052061	2.021476	1.569539
T-Coll. [29]	20	0.7850300	0.1666259	0.0052058	1.471099	0.897036

Table 9. Numerical evaluation of the invariant quantities and error norms associated with a single solitary-wave solution under the prescribed parameter settings, $\Delta t = 0.1, \mu = 1, \Delta t = 0.1$ for $c = 0.25$ over $[0, 80]$.

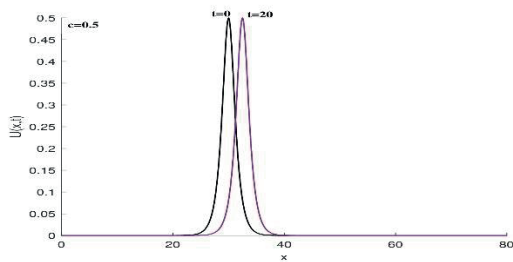
method	t	I_1	I_2	I_3	$L_2 \times 10^6$	$L_\infty \times 10^6$
LTS.imp.dif.	0.0	0.7853982	0.1666666	0.0052083	0.00000	0.00000
	0.2	0.7853982	0.1666666	0.0052083	4.56781	6.56789
	0.4	0.7853982	0.1666666	0.0052083	4.56890	6.58900
	0.6	0.7853982	0.1666666	0.0052083	4.56888	6.58890
	0.8	0.7853982	0.1666666	0.0052083	4.56789	6.59087
	1.0	0.7853982	0.1666666	0.0052083	4.56989	6.59134
FD. [15]1.	1.0	0.785341	0.166453	0.0052071	29.6099	23.5070
FD. [15]2.	1.0	0.787173	0.167079	0.0052460	727.192	411.7200
FD. [15]3.	1.0	0.785398	0.166473	0.0052083	17.7110	10.8337
HM(Pres.) [28]	1.0	0.7853981	0.1666666	0.0052083	0.2706	0.2164



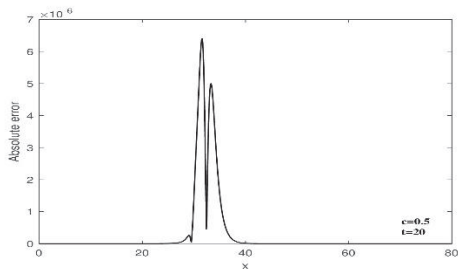
(a)



(b)



(c)



(d)

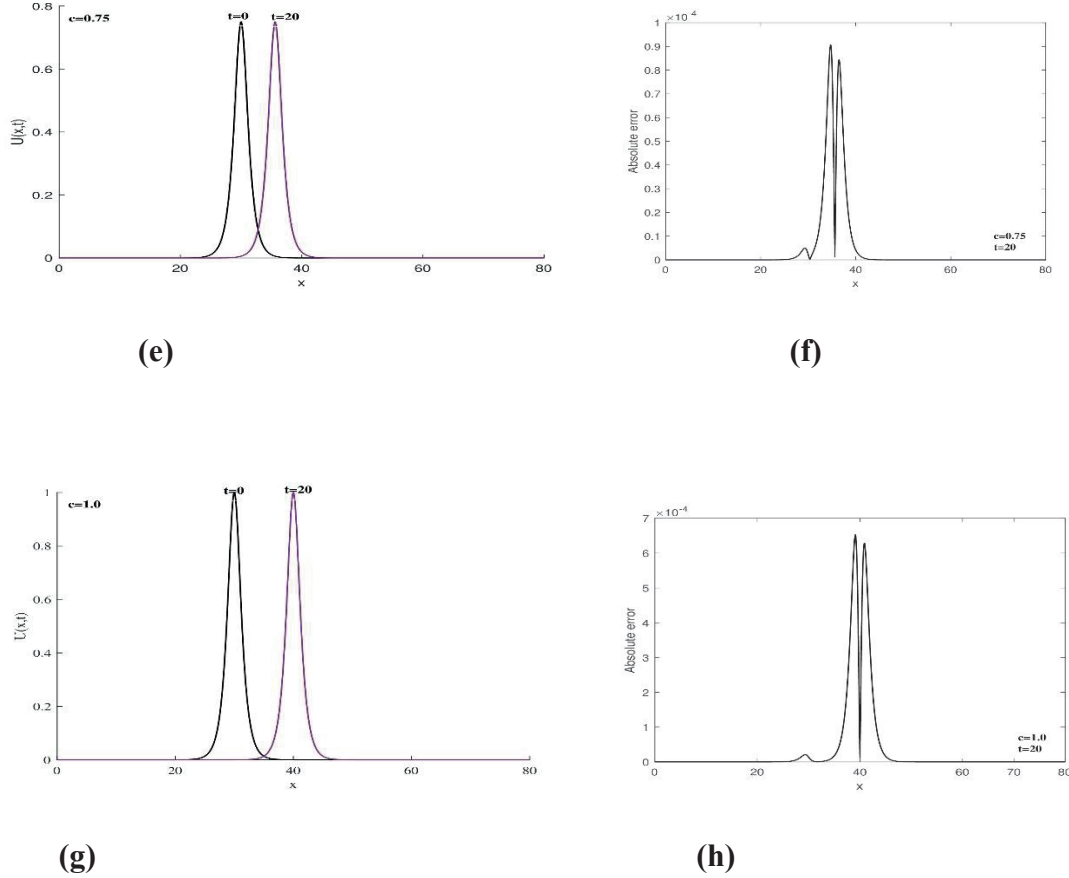


Figure 1. Movement of a single solitary wave at $t=20$ for different amplitude values c .

Conclusion

In this study, a computational framework founded on the Lie–Trotter splitting technique and a finite difference discretization is established for the (MEW) equation. The study begins with an examination of the existing literature concerning numerical treatments of the considered equation, followed by a detailed investigation of the propagation of a single solitary wave. The numerical solutions obtained from the advised scheme are subsequently compared with previously published results, and the evolution of the wave profile is illustrated through graphical representations. The numerical experiments and tabulated results indicate that the suggested approach provides reliable approximations and reproduces the characteristic behavior of the solitary-wave solution with satisfactory accuracy. The consistency observed between the computed solutions and the available reference findings further supports the numerical applicability of the method. Therefore, the proposed splitting-based finite difference framework may serve as a practical numerical approach for studying nonlinear partial differential equations that emerge in a variety of applied mathematics areas and provide mathematical representations of physical systems.

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CHAPTER 2

NUMERICAL INVESTIGATION OF TOPOLOGICAL TRANSITIONS IN THE ALLEN–CAHN EQUATION BY AN ADI METHOD

Berat KARAAGAC¹, Mustafa Habil GURSOY²

¹ Prof. Dr. Tarsus Üniversitesi, Mühendislik Fakültesi, Mühendislik Temel Bilimleri eratkaraagac@tarsus.edu.tr

² Prof. Dr. İnönü Üniversitesi, Fen-Edebiyat Fakültesi, Matematik Bölümü habil.gursoy@inonu.edu.tr

1 Introduction

In phase-field methods, the sharp interface separating two phases is not tracked directly. Instead, the thin transition layer between the phases is represented by a continuous scalar field. The Allen–Cahn equation is one of the fundamental models of this approach and was originally developed to describe the motion of antiphase boundaries in binary alloys (Allen & Cahn, 1979). The regions in which the phase-field variable takes values approximately equal to $+1$ and -1 represent the two distinct phases, while the zero level set represents the location of the diffuse interface separating them. In this study, the two-dimensional Allen–Cahn equation is considered in the normalization

$$u_t = \varepsilon^2 \Delta u + u - u^3, \quad \Delta u = u_{xx} + u_{yy}, \quad (1)$$

where $\varepsilon > 0$ is the parameter controlling the interface thickness. In this normalization, the time scale must be made explicit in order to establish the connection with mean-curvature motion. Introducing the rescaled time variable $s = \varepsilon^2 t$ and

$$v(x, y, s) = u\left(x, y, \frac{s}{\varepsilon^2}\right),$$

equation (1) transforms into

$$v_s = \Delta v + \frac{1}{\varepsilon^2} (v - v^3). \quad (2)$$

For suitably prepared initial data, and as long as the limiting interface remains smooth, the interface evolves by mean curvature in the limit $\varepsilon \rightarrow 0$ with respect to the rescaled time s (Chen, 1992). Consequently, in the original variable t , the leading-order behavior of the normal velocity under the thin-interface approximation is expressed as

$$V_n \approx -\varepsilon^2 \kappa.$$

Here $\mathbf{n}_\Gamma$ is the unit normal, defined in (9), oriented from the negative phase toward the positive phase; V_n denotes the normal velocity in this direction, and $\kappa = \nabla \cdot \mathbf{n}_\Gamma$ denotes the signed curvature. Consequently, when the initial geometry is kept independent of ε , the natural time scale for macroscopic interface motion is $t = O(\varepsilon^{-2})$. This scaling provides a theoretical basis for examining the dependence of hole-closure times on the parameter ε . The times reported in the numerical experiments correspond to the original variable t .

A color map of a phase-field solution can visualize the merging of regions or the disappearance of holes. However, to track such changes quantitatively and reproducibly, it is useful to additionally compute the topological properties of the phase regions. In this study, the positive phase region of the solution is defined as

$$\Omega_+(t) = \{(x, y) \in \Omega: u(x, y, t) > 0\}, \quad (3)$$

where, for the planar regions considered, the zeroth Betti number β_0 gives the number of connected components and the first Betti number β_1 gives the number of holes. The Euler characteristic is then computed from the relation

$$\chi(t) = \beta_0(t) - \beta_1(t) \quad (4)$$

(Edelsbrunner & Harer, 2010; Klette & Rosenfeld, 2004). In the numerical implementation, the topology of the continuous phase region is not computed directly. Instead, a binary mask is formed by thresholding the numerical solution at the grid points at zero, and the connected components and holes of this mask are counted. The topological measures computed in this way characterize the discrete representation of the positive phase. Changes observed in these measures between successive recording times are treated as numerically detected topological events. However, the resulting event times should not be interpreted as the exact transition times of the continuous problem. These estimates depend on the accuracy of the numerical solution, the grid resolution, the discrete neighborhood rule employed, and the interval between recording times.

In the numerical solution of the Allen–Cahn equation, spatial derivatives are discretized using central finite differences, and a factorized alternating-direction implicit (ADI) approach is used for time advancement. ADI methods decompose the solution of multidimensional parabolic problems into successive operations performed along the coordinate directions (Peaceman & Rachford, 1955; LeVeque, 2007). Owing to the second-derivative discretization and factorization used in this study, at each time step, tridiagonal one-dimensional systems are solved along the two coordinate directions instead of a single large two-dimensional linear system. The diffusion term is treated implicitly, whereas the nonlinear reaction term is evaluated explicitly using the solution at the previous time level. The purpose of this study is to present an explicit and reproducible computational framework that couples the numerical solution of Allen–Cahn dynamics with discrete topological measures in order to track the topological evolution of the positive phase. To this end:

1. a finite-difference and factorized ADI discretization is derived for the two-dimensional problem;
2. the numerical error and convergence behavior are examined using the method of manufactured solutions;
3. topological changes in the discrete representation of the positive phase are tracked automatically through β_0 , β_1 , and χ ;
4. the closure processes of holes with different radii are examined, and the

consistency of the computed closure times with the ε^{-2} scaling is evaluated.

2 Mathematical Model

2.1 The Allen–Cahn Initial–Boundary Value Problem

On the rectangular domain $\Omega = (a, b) \times (c, d) \subset \mathbb{R}^2$, the following dimensionless Allen–Cahn equation is considered:

$$\frac{\partial u}{\partial t} = \varepsilon^2 \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) + u - u^3, \quad (x, y) \in \Omega, \quad t > 0. \quad (5)$$

Here $u \approx +1$ and $u \approx -1$ represent the two stable phases, and $\varepsilon > 0$ controls the characteristic thickness of the diffuse interface. The initial condition is given by

$$u(x, y, 0) = u_0(x, y), \quad (x, y) \in \Omega, \quad (6)$$

and a homogeneous Neumann boundary condition is used in the topological experiments:

$$\nabla u \cdot \mathbf{n}_\Omega = 0, \quad (x, y) \in \partial\Omega, \quad t > 0, \quad (7)$$

where $\mathbf{n}_\Omega$ is the outward unit normal of the computational domain Ω . This condition sets the normal component of the diffusive flux on the boundary to zero. Nevertheless, owing to the reaction term, the Allen–Cahn equation does not in general conserve the quantity $\int_\Omega u \, dx \, dy$.

The interface separating the phases is defined as the zero level set of the solution,

$$\Gamma(t) = \{(x, y) \in \Omega : u(x, y, t) = 0\}. \quad (8)$$

At the smooth points of the interface where $\nabla u \neq 0$, the unit normal is chosen so as to point from the negative phase toward the positive phase,

$$\mathbf{n}_\Gamma = \frac{\nabla u}{|\nabla u|}. \quad (9)$$

This direction points, at the boundary of a hole formed by the negative phase, from the hole outward into the positive phase. The interface normal $\mathbf{n}_\Gamma$ should not be confused with the outward normal $\mathbf{n}_\Omega$ of the computational domain. The signed curvature and the normal velocity with respect to the original time t are defined, respectively, as

$$\kappa = \nabla \cdot \mathbf{n}_\Gamma, \quad V_n = \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n}_\Gamma, \quad (10)$$

where $\mathbf{X} = \mathbf{X}(\alpha, t)$ is a parametrization of the moving interface and α is the curve parameter. In the curvature computation, the normal field is likewise defined in a neighborhood of the interface by $\nabla u / |\nabla u|$. Taking into account the time scaling $s = \varepsilon^2 t$ discussed in the Introduction, for suitably prepared initial data and as long as the limiting interface remains smooth, the thin-interface approximation with respect to the original time t takes the form (Chen, 1992):

$$V_n \approx -\varepsilon^2 \kappa \quad (11)$$

This relation is not an exact equality for finite ε , but rather the leading-order asymptotic behavior of the interface motion. To illustrate the relationship between the choice of normal direction and the shrinkage of a hole, consider a circular negative-phase region with fixed center and radius $r(t)$. Denoting the outward radial unit vector from the center by $\mathbf{e}_r$, at the boundary of the hole one has

$$\mathbf{n}_\Gamma = \mathbf{e}_r, \quad \kappa = \frac{1}{r(t)}, \quad V_n = \frac{dr}{dt}.$$

Hence, in the regime $r(t) \gg \varepsilon$, in which the influence of other interfaces and of the outer boundary can be neglected,

$$\frac{dr}{dt} \approx -\frac{\varepsilon^2}{r(t)} < 0 \quad (12)$$

is obtained. Thus, under the chosen sign conventions for the normal and the curvature, the hole radius is seen to decrease with time. For fixed ε , as the hole radius $r(t)$ shrinks and becomes comparable to the interface thickness, the condition $\varepsilon/r(t) \ll 1$ required by the thin-interface approximation ceases to hold; consequently, in the late stage close to closure, the radius determined from the phase-field solution is expected to deviate from the asymptotic curve predicted by (12).

2.2 Energy Structure

Under the homogeneous Neumann boundary condition, equation (5) is the $L^2(\Omega)$ gradient flow of the energy functional

$$E_\varepsilon[u] = \int_\Omega \left[\frac{\varepsilon^2}{2} |\nabla u|^2 + \frac{1}{4} (1 - u^2)^2 \right] dx dy. \quad (13)$$

The first term of the energy penalizes spatial variation in the phase field, whereas the double-well potential term attains its minimum at the phase values $u = \pm 1$. Taking the homogeneous Neumann boundary condition into account, the variational derivative of the energy is obtained as

$$\frac{\delta E_\varepsilon}{\delta u} = -\varepsilon^2 \Delta u + u^3 - u, \quad (14)$$

so that the Allen–Cahn equation can be written as

$$u_t = -\frac{\delta E_\varepsilon}{\delta u}. \quad (15)$$

For a sufficiently smooth solution, differentiating the energy with respect to time and applying integration by parts in the spatial variables yields

$$\begin{aligned}
 \frac{d}{dt} E_\varepsilon[u(t)] &= \int_{\Omega} [\varepsilon^2 \nabla u \cdot \nabla u_t + (u^3 - u)u_t] \, dx \, dy \\
 &= \int_{\Omega} (-\varepsilon^2 \Delta u + u^3 - u)u_t \, dx \, dy \\
 &\quad + \varepsilon^2 \int_{\partial\Omega} u_t (\nabla u \cdot \mathbf{n}_\Omega) \, dS,
 \end{aligned}$$

where dS is the arc-length element on the boundary. The boundary integral vanishes owing to the homogeneous Neumann condition (7). Using equation (5) then gives

$$\frac{d}{dt} E_\varepsilon[u(t)] = - \int_{\Omega} |u_t|^2 \, dx \, dy = -\|u_t\|_{L^2(\Omega)}^2 \leq 0. \quad (16)$$

This identity shows that the energy does not increase over time along the continuous solution. However, energy decay alone does not guarantee that the number of connected components or holes of the positive phase changes monotonically. For this reason, the energy and the topological measures are regarded as complementary indicators that track different properties of the solution. The energy law (16) for the continuous problem is not automatically inherited by the time discretization employed here. In particular, in the present scheme, in which the nonlinear reaction term is evaluated explicitly, treating the diffusion term implicitly alone does not guarantee unconditional energy stability. For this reason, the discrete energy computed from the numerical solution is separately monitored at the chosen recording times. The energy decay observed in these records is a numerical observation for the parameters examined and should not be interpreted as a proof that the scheme is energy stable for every $\Delta t > 0$.

3 Finite-Difference and Factorized ADI Discretization

3.1 Spatial and Temporal Grid

On the domain $\Omega = (a, b) \times (c, d)$, let the grid spacings be defined as

$$h_x = \frac{b-a}{N_x}, \quad h_y = \frac{d-c}{N_y}.$$

Let the uniformly spaced grid points be

$$x_i = a + ih_x, \quad i = 0, \dots, N_x, \quad y_j = c + jh_y, \quad j = 0, \dots, N_y,$$

and let the time levels be $t_n = n\Delta t$. The numerical approximation of $u(x_i, y_j, t_n)$ is denoted by $U_{i,j}^n$. The second derivatives are discretized by central differences at the interior grid points along the corresponding coordinate direction:

$$\delta_{xx} U_{i,j} = \frac{U_{i+1,j} - 2U_{i,j} + U_{i-1,j}}{h_x^2}, \quad (17)$$

$$\delta_{yy} U_{i,j} = \frac{U_{i,j+1} - 2U_{i,j} + U_{i,j-1}}{h_y^2}. \quad (18)$$

For sufficiently smooth solutions, the truncation errors of these approximations at the interior points are of order $O(h_x^2)$ and $O(h_y^2)$, respectively. The treatment at the boundary points is defined separately below.

3.2 Semi-Implicit Time Discretization

Let the nonlinear reaction term be defined as $g(u) = u - u^3$. Treating the diffusion term implicitly at the new time level and the reaction term explicitly at the previous time level yields the scheme

$$\frac{U^{n+1} - U^n}{\Delta t} = \varepsilon^2(\delta_{xx} + \delta_{yy})U^{n+1} + g(U^n), \quad (19)$$

where U^n represents the vector of all grid values and $g(U^n)$ is computed componentwise. This discretization is a first-order-in-time IMEX Euler scheme. Rearranging terms gives

$$[I - \Delta t \varepsilon^2(\delta_{xx} + \delta_{yy})]U^{n+1} = U^n + \Delta t g(U^n), \quad (20)$$

where I is the identity operator. If equation (20) is solved directly, a two-dimensional sparse linear system must be solved at every time step.

3.3 Approximate Factorization

The two-dimensional operator is approximated by the product of two operators, each acting along one coordinate direction:

$$I - \Delta t \varepsilon^2(\delta_{xx} + \delta_{yy}) \approx (I - \Delta t \varepsilon^2 \delta_{xx})(I - \Delta t \varepsilon^2 \delta_{yy}). \quad (21)$$

Expanding the product gives

$$\begin{aligned} (I - \Delta t \varepsilon^2 \delta_{xx})(I - \Delta t \varepsilon^2 \delta_{yy}) \\ = I - \Delta t \varepsilon^2(\delta_{xx} + \delta_{yy}) + \Delta t^2 \varepsilon^4 \delta_{xx} \delta_{yy}, \end{aligned} \quad (22)$$

which shows that replacing the unfactorized operator by this product introduces an additional mixed-difference term. Using this approximation, the full time step is defined as

$$(I - \Delta t \varepsilon^2 \delta_{xx})(I - \Delta t \varepsilon^2 \delta_{yy})U^{n+1} = U^n + \Delta t g(U^n). \quad (23)$$

Rewriting this scheme in the form of a time derivative gives

$$\begin{aligned} \frac{U^{n+1} - U^n}{\Delta t} &= \varepsilon^2(\delta_{xx} + \delta_{yy})U^{n+1} + g(U^n) \\ &\quad - \Delta t \varepsilon^4 \delta_{xx} \delta_{yy} U^{n+1}. \end{aligned} \quad (24)$$

For a smooth solution with fixed ε and bounded derivatives on the grid, the term added by the factorization is of order $O(\Delta t^2)$ in the factored equation. However, once the equation is divided by Δt , this contribution is of order $O(\Delta t)$. The factorization therefore preserves the first-order-in-time consistency of the IMEX Euler scheme.

At interior points, the local truncation error in the time-derivative form is of order

$$O(\Delta t + h_x^2 + h_y^2).$$

This consistency assessment alone does not constitute a proof of global convergence; the global error behavior must also take into account stability and the accuracy of the boundary treatment.

3.4 ADI Sweeps

Equation (23) is implemented through two successive one-dimensional solves:

$$(I - \Delta t \varepsilon^2 \delta_{xx})U^* = U^n + \Delta t [U^n - (U^n)^3], \quad (25)$$

$$(I - \Delta t \varepsilon^2 \delta_{yy})U^{n+1} = U^*. \quad (26)$$

Substituting the expression obtained from the second equation,

$$U^* = (I - \Delta t \varepsilon^2 \delta_{yy})U^{n+1},$$

into the first equation reproduces the factorized scheme exactly. Here, U^* is not an approximation of the physical solution at time $t_{n+1/2}$; it is an intermediate variable used in solving the factorized linear system. Both sweeps use the coefficient Δt , and $\Delta t/2$ is not employed. Equation (25) produces tridiagonal linear systems in the x -direction for fixed j , and equation (26) produces tridiagonal linear systems in the y -direction for fixed i . In this way, the time step is completed without assembling the full two-dimensional matrix.

3.5 Time-Step Size and Stability

Considering only the diffusion subproblem, for a mode corresponding to eigenvalues $-\lambda_x$ and $-\lambda_y$ of the discrete x - and y -operators, the amplification factor is

$$G = \frac{1}{(1 + \Delta t \varepsilon^2 \lambda_x)(1 + \Delta t \varepsilon^2 \lambda_y)}, \quad \lambda_x, \lambda_y \geq 0.$$

Hence $0 < G \leq 1$, and the parabolic time-step restriction characteristic of explicit diffusion schemes is not required for this subproblem. Nevertheless, this result does not imply unconditional stability of the full scheme, which includes the explicit reaction term. Large time steps may lead to loss of accuracy, to solution values falling outside the expected range, or to an increase in the discrete energy. The time step should therefore be chosen so as to resolve the reaction dynamics and the interface motion with sufficient accuracy. In the numerical experiments, the discrete energy is monitored at the chosen recording times. The energy decay observed in these records is a numerical observation for the parameters examined and does not constitute proof of unconditional energy stability.

3.6 Discretization of the Neumann Boundary

The homogeneous Neumann boundary condition is incorporated into the difference operators through the use of ghost points. For an arbitrary grid function V , at the left boundary one imposes

$$\frac{V_{1,j}-V_{-1,j}}{2h_x} = 0 \implies V_{-1,j} = V_{1,j}.$$

Substituting this relation into the second-derivative formula gives

$$\delta_{xx}V_{0,j} = \frac{2(V_{1,j}-V_{0,j})}{h_x^2}. \quad (27)$$

Analogously, at the other edges the relations

$$V_{N_x+1,j} = V_{N_x-1,j}, \quad V_{i,-1} = V_{i,1}, \quad V_{i,N_y+1} = V_{i,N_y-1}$$

are used. These operations are embedded in the boundary rows of the δ_{xx} and δ_{yy} operators and are applied to the unknowns in the corresponding ADI sweeps.

Smoothness and compatibility conditions are important when assessing the accuracy at the boundary. For instance, under $u_x(a, y, t) = 0$, the Taylor expansion

$$\frac{2[u(a+h_x, y, t)-u(a, y, t)]}{h_x^2} = u_{xx}(a, y, t) + \frac{h_x}{3}u_{xxx}(a, y, t) + O(h_x^2)$$

holds. Hence the condition $u_x = 0$ alone is not sufficient to show that the second-derivative approximation at the boundary is second order.

For the present unforced Allen–Cahn problem, if the solution and the boundary data are sufficiently smooth and compatible, then along the left boundary $u_{xt} = u_{xyy} = 0$. Differentiating the equation with respect to x gives

$$0 = u_{xt} = \varepsilon^2(u_{xxx} + u_{xyy}) + (1 - 3u^2)u_x = \varepsilon^2u_{xxx},$$

so that, under these conditions, $u_{xxx} = 0$, and the boundary approximation likewise attains order $O(h_x^2)$. Analogous arguments apply at the other edges.

4 Discrete Topological Measurement

At each recorded time level t_n , a binary mask is formed by thresholding the numerical solution at zero:

$$B_{i,j}^n = \begin{cases} 1, & U_{i,j}^n > 0, \\ 0, & U_{i,j}^n \leq 0. \end{cases} \quad (28)$$

Here $B_{i,j}^n = 1$ denotes the foreground representing the positive phase, and $B_{i,j}^n = 0$ denotes the background. The background includes negative values together with grid values that are exactly zero. Thresholding is performed solely for the purpose of topological measurement; the solution U^n used in time advancement is not replaced by binary values. Connectivity in digital images depends on the neighborhood relation adopted. In this study, 4-connectivity is used for the foreground and the complementary 8-connectivity is used for the background (Klette & Rosenfeld, 2004; Bykov et al., 1998). Under 4-connectivity only horizontal and vertical neighbors are considered, whereas under 8-connectivity diagonal neighbors are also included in the connectivity relation. Consequently, two foreground pixels that touch only at a corner are

not counted as directly connected, whereas two background pixels in the same configuration are considered connected. For the purpose of identifying holes, the region outside the image window is treated as background solely for topological counting purposes. This convention does not alter the Neumann boundary condition of the Allen–Cahn problem. The image frame consists of the pixels with indices $i = 0$, $i = N_x$, $j = 0$, or $j = N_y$. The topological measures are computed through the following steps: [label=.,leftmargin=2em]

1. The 4-connected components of the foreground pixels with $B^n = 1$ are labeled. The number of components is recorded as β_0^n .
2. The 8-connected components of the background pixels with $B^n = 0$ are labeled.
3. Background components containing at least one pixel of the image frame are regarded as connected to the exterior background and are excluded from the hole count.
4. The number of background components not touching the frame is recorded as β_1^n .
5. The Euler characteristic is computed under the adopted digital-topology convention as $\chi^n = \beta_0^n - \beta_1^n$.

Here, β_0^n , β_1^n , and χ^n characterize the topological properties of the binary mask under the chosen (4,8) neighborhood pair. These values are not assumed to coincide, at every grid resolution, with the topological invariants of the continuous positive-phase region $\Omega_+(t_n)$. Moreover, since different combinations of the numbers of connected components and holes can yield the same Euler characteristic, β_0^n and β_1^n are tracked separately. The topological counts and the approximate event times determined from them depend on the numerical solution error, the threshold value, the grid resolution, and the interval between recording times. In particular, for structures that shrink to only a few pixels in width, the results may become sensitive to these choices. If more than one topological change occurs within the same recording interval, the individual events may also become difficult to resolve separately. Finally, a decrease in the number of holes alone does not by itself prove a geometric closure event. The merging of two holes, or the opening of a hole to the exterior background, can likewise reduce this count. For this reason, the geometric interpretation of the events should be made in conjunction with the topological counts together with the phase-field and interface images.

5 Numerical Experiments

5.1 Convergence Test via the Method of Manufactured Solutions

To measure the order of convergence, a forced problem was used on the domain $\Omega = (0,1)^2$:

$$u_t = \varepsilon^2 \Delta u + u - u^3 + f(x, y, t), \quad (29)$$

with the exact solution chosen as

$$u_{\text{exact}}(x, y, t) = e^{-t} \sin(\pi x) \sin(\pi y). \quad (30)$$

The corresponding source term is

$$f = -2u_{\text{exact}} + 2\varepsilon^2 \pi^2 u_{\text{exact}} + u_{\text{exact}}^3. \quad (31)$$

A homogeneous Dirichlet boundary condition was applied. The parameters were set to $\varepsilon = 0.1$, $T = 0.05$, $h_x = h_y = h$, and $\Delta t = 0.5h^2$. The discrete error norms were computed as

$$\|e\|_{2,h} = (h^2 \sum_{i,j} |e_{i,j}|^2)^{1/2}, \quad \|e\|_{\infty} = \max_{i,j} |e_{i,j}|. \quad (32)$$

Table 1: Manufactured-solution test. The observed order is computed as $p = \log_2(E_h/E_{h/2})$.

N	Steps	Δt	$\ e\ _{2,h}$	p_2	$\ e\ _{\infty}$	p_{∞}
20	40	1.2500×10^{-3}	3.5356×10^{-7}	—	6.8632×10^{-7}	—
40	160	3.1250×10^{-4}	9.1336×10^{-8}	1.953	1.7721×10^{-7}	1.953
80	640	7.8125×10^{-5}	2.3018×10^{-8}	1.988	4.4653×10^{-8}	1.989
160	2560	1.9531×10^{-5}	5.7663×10^{-9}	1.997	1.1186×10^{-8}	1.997

Table 1 shows that the observed order approaches two in both the discrete L^2 norm and the maximum norm. This result does not imply that the method is second order in time. The scheme is first order in time and second order in space; since $\Delta t = O(h^2)$ was chosen in the experiment, the temporal and spatial errors appear jointly at the $O(h^2)$ scale.

5.2 Closure of Three Holes

The topological experiment was carried out on the domain $\Omega = (-1,1)^2$ under homogeneous Neumann boundary conditions. The computation used $N_x = N_y = 200$, $h_x = h_y = 0.01$, $\Delta t = 0.002$, $\varepsilon = 0.08$, and final time $T = 5$. The centers and initial radii of the three holes were chosen as

$$(-0.48, 0.25), r_1 = 0.11; \quad (0.03, -0.30), r_2 = 0.16; \quad (0.43, 0.28), r_3 = 0.22.$$

The signed distance to the union of these three mutually disjoint disks was defined as

$$d(x, y) = \min_{k=1,2,3} (\sqrt{(x - x_k)^2 + (y - y_k)^2} - r_k), \quad (33)$$

and the diffuse-interface initial field was constructed as

$$u_0(x, y) = \tanh\left(\frac{d(x, y)}{\sqrt{2} \varepsilon}\right). \quad (34)$$

Thus $u_0 < 0$ inside the holes and $u_0 > 0$ in the exterior positive phase. Because of the minimum operation, the function d may fail to be differentiable at points where the nearest hole changes; hence this definition does not imply that the initial field is smooth throughout the domain.

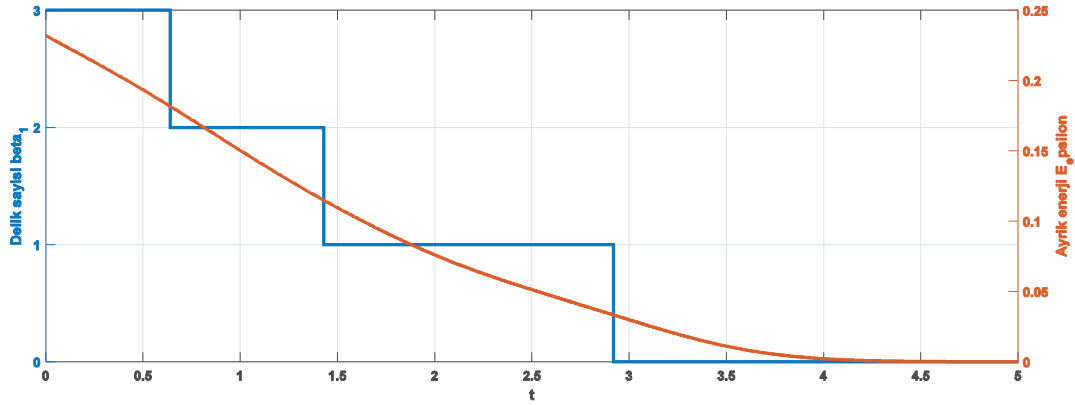


Figure 1: Appearance of the phase field at selected times. The black curves denote the $u = 0$ interface.

Since the positive phase initially consists of a single connected component and three holes,

$$(\beta_0, \beta_1, \chi) = (1, 3, -2)$$

is obtained. Topological measurements were recorded every five time steps, that is, at intervals of $\Delta t_{\text{rec}} = 0.01$. Decreases in the number of holes were first detected at the recordings $t = 0.64, 1.43$, and 2.92 . The transition times bounded by successive recordings are expressed as

$$\begin{aligned} t_{3 \rightarrow 2} &\in (0.63, 0.64], \\ t_{2 \rightarrow 1} &\in (1.42, 1.43], \\ t_{1 \rightarrow 0} &\in (2.91, 2.92], \end{aligned} \quad (35)$$

where the subscripts denote the corresponding transition in the value of β_1 . These intervals reflect only the recording resolution of the discrete solution and do not constitute error bounds on the true event times of the continuous problem. The spatial grid, the time step, and the threshold value used in constructing the binary image may also affect the measured event times. Moreover, tracking only the total number of holes does not by itself determine at what time the hole of a particular initial radius disappears. At the final recording time $T = 5$,

$$(\beta_0, \beta_1, \chi) = (1, 0, 1)$$

is obtained.

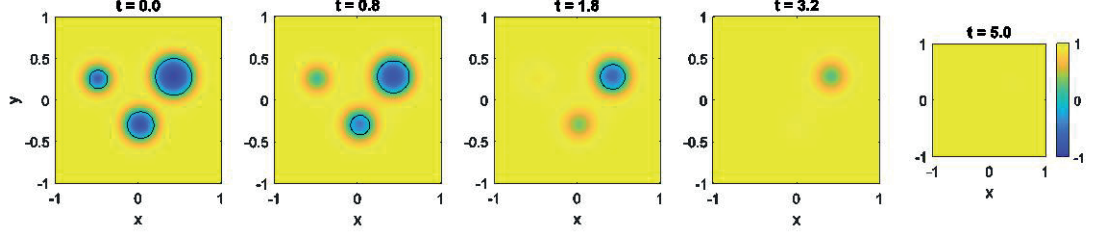


Figure 2: Time evolution of the number of holes together with the recorded discrete energy. No positive difference exceeding a tolerance of 10^{-10} was detected between successive energy records.

Figure 2 shows, together, the stepwise change in the number of holes and the decreasing trend of the recorded discrete energy values. The discrete energy decreased from $E_\varepsilon^h(0) = 0.232269$ to $E_\varepsilon^h(5) = 3.4330 \times 10^{-5}$. Successive energy records were compared using a tolerance of 10^{-10} , and no increase exceeding this tolerance was found. This check is limited solely to the recorded values; it does not prove that the energy decreases at every intermediate time step between recordings, nor does it prove general and unconditional energy stability of the scheme employing the explicit reaction term.

5.3 Effect of the Parameter ε on Event Times

Simulations were performed for $\varepsilon = 0.06, 0.08$, and 0.10 using the same initial geometry. In all computations, $N_x = N_y = 200$, $h_x = h_y = 0.01$, and $\Delta t = 0.002$ were held fixed. In contrast, the final times of the computations were chosen as $T = 9, T = 5$, and $T = 3.5$ for $\varepsilon = 0.06, 0.08$, and 0.10 , respectively. These durations allowed the final hole transition to be recorded in all three computations. Topological measurements were recorded at intervals of $\Delta t_{\text{rec}} = 0.01$. The values t_1, t_2 , and t_3 in Table 2 denote the times at which the reduced hole count was first recorded following the $3 \rightarrow 2, 2 \rightarrow 1$, and $1 \rightarrow 0$ transitions, respectively.

Table 2: Interface parameter and topological event times.

ε	t_1	$\varepsilon^2 t_1$	t_2	$\varepsilon^2 t_2$	t_3	$\varepsilon^2 t_3$
0.06	1.19	0.00428	2.72	0.00979	5.61	0.02020
0.08	0.64	0.00410	1.43	0.00915	2.92	0.01869
0.10	0.41	0.00410	0.89	0.00890	1.77	0.01770

In the normalization used in equation(5), the thin-interface approximation suggests a characteristic time scale proportional to ε^{-2} . The scaled recorded event times $\varepsilon^2 t_k$ are broadly comparable, but they are not constant. The present experiments do not isolate the contributions of finite interface thickness, spatial and temporal discretization, and the recording interval to this variation. A more conclusive assessment requires spatial and temporal refinement studies for each fixed ε , together with sufficiently frequent recording of the topological measures. Keeping h/ε fixed across different values of ε provides comparable interface resolution, but does not replace these convergence tests.

6 Discussion

The results demonstrate that the discrete topological properties of the positive phase can be measured by thresholding the Allen–Cahn phase field, without constructing an additional interface-tracking equation. Changes in the numbers of connected components and holes provide integer-valued indicators that complement visual inspection. Topological transitions are detected through changes in these indicators, and the event times are bounded between successive recording times. For this reason, the reported recording times should not be interpreted as the exact event times of the continuous problem. From a computational standpoint, the factorized ADI approach allows the two-dimensional linear system at each time step to be replaced by the solution of one-dimensional tridiagonal systems. Jointly examining the energy and topology histories, in turn, makes it possible to assess the energy evolution of the solution together with the connectivity structure of the phase regions within the same computational framework. Nevertheless, energy decay does not imply monotonic changes in topological invariants, nor does it by itself establish the accuracy of the numerical solution.

For the three values of ε examined in Table 2, all transitions are recorded earlier as the parameter increases. However, the scaled values $\varepsilon^2 t_k$ are not exactly constant. The relative spread of the scaled times computed from the tabulated event times, $(\max - \min)/\min$, is approximately 4.6%, 10.0%, and 14.1% for $k = 1, 2, 3$, respectively. The ε^{-2} time scale

predicted by the thin-interface approximation should therefore be regarded here as an asymptotic benchmark. The present study, which considers only three values of ε , is insufficient to establish a general power law or exact quantitative agreement between the recorded event times and the theoretical closure-time predictions. The relative contributions of the finite interface thickness, the spatial and temporal discretization, and the recording interval to the observed differences were not measured separately in this study.

7 Conclusion

A factorized ADI method based on central differences was applied to the two-dimensional Allen–Cahn equation, and the topological changes in the binary representation of the positive phase were tracked quantitatively through the Betti numbers and the Euler characteristic. The first-order-in-time scheme exhibited approximately second-order combined convergence in the manufactured-solution test with homogeneous Dirichlet boundary conditions under the choice $\Delta t = 0.5h^2$. For the three-hole initial geometry, the transitions $\beta_1: 3 \rightarrow 2 \rightarrow 1 \rightarrow 0$ were detected automatically, and the transition times were bounded by the recording intervals. The Euler characteristic, initially -2 , became 1 in the final state. In the parameter study, the topological transitions were recorded earlier as the examined values of ε increased. Establishing this finding as a general scaling law would require a broader parameter study together with independent convergence checks on the event times. Future work may consider anisotropic diffusion, spatially varying ε , external forcing terms, or Allen–Cahn models posed on surfaces. For these extensions, the energy structure of the model, the boundary conditions, and the stability of the discrete scheme should be reassessed. The topological analysis may likewise be extended, using a level-set filtration rather than a single threshold, to persistent homology diagrams.

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CHAPTER 3

A LIE-TROTTER SPLITTING-BASED ALGORITHM FOR THE NUMERICAL TREATMENT OF THE REGULARIZED LONG WAVE-BURGERS (RLW- BURGERS) EQUATION USING AN IMPLICIT FOURTH ORDER DIFFERENCE DISCRETIZATION

Melike KARTA¹, Kadriye NAZLIAYDIN²

¹ Doç. Dr. Department of Mathematics, Faculty of Science and Arts, Ağrı İbrahim Çeçen University, Ağrı, Turkey ORCID: <https://orcid.org/0000-0003-3412-4370>

² YLO, Faculty of Science and Arts, Ağrı İbrahim Çeçen University, Ağrı, Turkey kadriyenzazliaydin@gmail.com

Introduction

Nonlinear partial differential equations (PDEs) provide a mathematical framework for describing a wide range of physical phenomena encountered in nature. However, the analysis of their initial and boundary value problems, as well as the derivation of exact analytical solutions, is often a challenging task. For this reason, considerable attention is devoted to the development of reliable approximate methods for obtaining solutions to such equations. One notable example is the Regularized Long Wave–Burgers (RLW–Burgers) equation, which can be expressed in the form

$$U_t - U_{xxt} - \alpha u_{xx} + \beta u_x + \gamma uu_x = 0 \quad (1)$$

This nonlinear equation combines dispersive, dissipative, and nonlinear effects and has been employed as a mathematical model for various physical processes. The above equation is considered together with the following initial and boundary value problem:

$$\begin{aligned} U(x, 0) &= g(x), a \leq x \leq b, \\ U(a, t) &= U(b, t) = 0, t > 0. \end{aligned} \quad (2)$$

The governing equation, u_t represents the temporal variation of the wave, whereas u_{xxt} accounts for the dispersive effect. The term u_{xx} describes the dissipative behavior of the wave, while u_x characterizes its propagation. The nonlinear term uu_x represents the convective transport of the wave. Here, $g(x)$ denotes the function used in the numerical computations. Also, α , β , and γ represent constants satisfying $\alpha, \beta, \gamma \geq 0$. The symbols x and t are used for the spatial coordinate and time, respectively, and the subscripts correspond to partial derivatives with respect to these variables. Obtaining exact analytical solutions for this wave equation is often a challenging task and, in many cases, may not be feasible. Consequently, a variety of numerical techniques have been developed and employed to obtain approximate solutions, resulting in a substantial body of literature on the numerical treatment of this equation. Omrani and Ayadi (2008) proposed a numerical scheme based on a Crank–Nicolson-type finite difference formulation and investigated its convergence and error behavior. Arora et al. (2014) introduced a fully discretized scheme for obtaining approximate solutions by combining a Crank–Nicolson-type finite difference approach with a fourth-order B-spline collocation technique for the spatial discretization. Zarebnia and Parvaz (2020) developed a numerical scheme for the solution of the equation by employing a finite difference approach for the temporal discretization and a collocation method based on B-spline basis functions for the spatial discretization. The resulting scheme was reported to have an accuracy of $O(h^2) + O(k^2)$. Kutluay et al. (2023) proposed a Crank–Nicolson-type numerical scheme for solving the equation, in which the nonlinear term was treated using the Richtmyer linearization technique. Similarly, Hamarat (2023) employed a Rubin–Graves-type linearization procedure to handle the nonlinear term and developed a Crank–Nicolson-type scheme. Karta (2023), on the other hand, investigated the numerical solution of the BBM–Burgers equation by combining a collocation method with the Strang time-splitting technique. Building upon the numerical studies available in the literature, this project aims to investigate the numerical solution of the

BBM–Burgers equation by combining an implicit finite-difference scheme with the Lie–Trotter splitting technique. Within this framework, the original equation will be decomposed into two simpler subproblems, which will then be treated separately. To the best of our knowledge, the proposed combination of these numerical techniques has not previously been considered for the BBM–Burgers equation, which provides a distinctive aspect of the present study. Furthermore, the proposed approach will be tested on a benchmark problem and its numerical performance will be compared with the results reported in previous studies. The aim is to assess the accuracy and efficiency of the proposed methodology and to determine whether it can provide improved numerical results.

Finite Difference Methods

For the numerical discretization of partial differential equations, several finite difference formulations are available, with explicit, implicit, and Crank–Nicolson approaches being among the widely used alternatives. Implicit discretization methods are often preferred when enhanced numerical stability is required, since they can remain stable over a wider range of computational parameters. A consequence of this formulation, however, is that a system of algebraic equations must be solved at every new time level (Thomas, 1995). Finite difference methods have found widespread use in numerical PDE studies because of their relatively simple formulation and their suitability for problems defined on structured computational grids. Moreover, with an appropriate choice of discretization, these methods can provide highly accurate numerical approximations. When nonlinear terms are present, suitable linearization techniques or iterative procedures can be incorporated into the finite difference framework to obtain stable and dependable numerical solutions.

Consider a general partial differential equation of the form

$$F(x, t, u, u_x, u_t, u_{xx}, u_{xt}, \dots) = 0$$

subject to appropriate initial and boundary conditions. Let the computational domain be defined by $(x, t) \in [a, b] \times [0, T]$. To obtain a discrete representation of the problem, the spatial and temporal intervals are divided into a finite number of subintervals. The spatial interval $[a, b]$ is partitioned into M uniform segments according to

$$a = x_0 < x_1 < x_2 < \dots < x_{M-1} < x_M = b$$

where the spatial mesh size is denoted by $h = x_{i+1} - x_i$ ($x_i = ih, i = 0(1)M$). Similarly, the time interval $[0, T]$ is divided into N equal time levels satisfying

$$0 = t_0 < t_1 < \dots < t_{N-1} < t_N = T$$

with the time-step size given by $k = t_{n+1} - t_n$ ($t_n = nk, n = 0(1)N$). The intersections of the spatial and temporal meshes define the discrete points (x_i, t_n) ($i = 0(1)M, n = 0(1)N$), which constitute the computational grid. Consequently, the continuous problem is transformed into a discrete problem defined at these grid points. The prescribed initial and boundary conditions are then incorporated into the corresponding grid values, providing the necessary data for the numerical computation of the solution at the remaining nodes.

Lie-Trotter Splitting

The operator splitting approach is based on reformulating a complex mathematical model into a collection of simpler subproblems, each of which is associated with a particular component or physical mechanism of the original equation. Since these subproblems are generally easier to handle individually, the overall computational procedure can be simplified considerably. Splitting-based approaches can also offer practical benefits in terms of computational cost, numerical accuracy, and stability, depending on the formulation and implementation adopted. Their relatively straightforward structure makes them attractive for the numerical treatment of nonlinear evolution equations. Among the commonly used splitting strategies are the Lie–Trotter and Strang splitting methods, which differ mainly in the way the subproblems are sequenced during the time integration process. Consider a mathematical evolution equation expressed in terms of two operators, A and B. The operator splitting framework separates the original problem into two subproblems, allowing the individual components to be handled independently before their effects are combined to approximate the solution of the complete equation. In a first-order splitting scheme, the operators are applied successively within each time step. Thus, the numerical evolution is obtained by advancing the solution according to one operator and subsequently using the resulting state as the initial data for the second operator (Marchuk, 1990).

In the present study, the Lie–Trotter splitting method is employed to divide the temporal evolution of the RLW-Burgers equation into its linear and nonlinear contributions. Let A and B denote the operators associated with these two parts. At a given time level, the initial approximation is first advanced according to the A-operator over a time step of size k . The resulting numerical solution is then taken as the input for the B-subproblem, which is evolved over the same time interval. The state obtained from this second stage constitutes the approximation at the new time level. By repeating this sequential procedure at each time step, the effects of the two operators are incorporated successively, providing a numerical approximation to the solution of the original RLW-Burgers equation.

Application of the Method

Within the scope of this study, the BBM–Burgers equation will be decomposed into two sub-equations through an operator splitting approach, separating the linear and nonlinear components of the governing equation. The resulting subproblems are given by

$$A = u_t - u_{xxt} - \alpha u_{xx} + \beta u_x = 0$$

and

$$B = u_t - u_{xxt} + \gamma u u_x = 0$$

For each subproblem, implicit finite-difference schemes will be constructed by approximating the temporal and spatial derivatives through finite-difference formulas derived from Taylor series expansions. This procedure will lead to two distinct matrix-based numerical formulations. Subsequently, the resulting schemes will be coupled through the splitting procedure and implemented in MATLAB to compute the corresponding numerical solutions.

The numerical results obtained from the proposed methodology will then be compared with selected results available in the literature. The outcomes of these comparisons will be presented in the form of tables and graphical representations, allowing the accuracy and performance of the proposed approach to be examined. The completion of these computational analyses and comparisons will constitute the final stage of the project.

$$\begin{aligned} \left(-\frac{\mu}{h^2}\right)u_{i-1}^{n+1} + \left(\frac{1}{k} + \frac{2\mu}{h^2}\right)u_i^{n+1} + \left(-\frac{\mu}{h^2}\right)u_{i+1}^{n+1} &= \left(-\frac{\mu}{h^2}\right)u_{i-1}^n + \left(\frac{1}{k} + \frac{2\mu}{h^2}\right)u_i^n + \left(-\frac{\mu}{h^2}\right)u_{i+1}^n, \\ \left(-\frac{\mu}{k} - \frac{\epsilon}{2h}(u_i^n)^2\right)u_{i-1}^{n+1} + \left(\frac{1}{k} + \frac{2\mu}{k}\right)u_i^{n+1} + \left(-\frac{\mu}{k} - \frac{\epsilon}{2h}(u_i^n)^2\right)u_{i+1}^{n+1} \\ &= \left(-\frac{\mu}{h^2}\right)u_{i-1}^n + \left(\frac{1}{k} + \frac{2\mu}{k}\right)u_i^n + \left(-\frac{\mu}{h^2}\right)u_{i+1}^n \end{aligned}$$

Subsequently, these two schemes will be combined using the splitting technique and solved computationally in MATLAB to obtain the corresponding numerical solutions.

Numerical Examples and Results

In this section, the numerical solution of the model test problem is computed. The reliability of the computed results is examined by means of suitable error measures, which are used to quantify the deviation of the numerical solution from the reference solution:

$$\begin{aligned} L_2 &= \|U^{tam} - U^{num}\|_2 \cong \sqrt{h \sum_{i=0}^M |U_i^{tam} - U_i^{num}|^2} \\ L_\infty &= \|U^{tam} - U^{num}\|_\infty \cong \underbrace{\max_i |U_i^{tam} - U_i^{num}|}_i \end{aligned}$$

Several quantitative error measures will be calculated to examine the quality of the numerical results. These values will be presented in tables and compared with the corresponding findings available in the literature. In addition, the numerical approximations will be compared with the exact solutions to further investigate the reliability of the proposed approach. The comparison results will be visualized through two-dimensional plots and summarized in tabular form.

Benchmark Problem 1:

This problem, the BBM–Burgers equation is considered with the parameter values $\alpha = \beta = \gamma = 1$ over the spatial domain $[a,b]=[-10,10]$, with $F(x,t)=0$. The resulting homogeneous problem is given by

$$u_t - u_{xxt} - u_{xxt} + u_x + uu_x = 0, \quad x \in [-10,10], \quad t > 0$$

The problem is supplemented with the following initial condition:

$$u(x, 0) = \exp(-x^2), \quad x \in [-10,10]$$

and homogeneous boundary conditions:

$$u(-10, t) = 0$$

$$u(10, t) = 0, \quad t \geq 0$$

Numerical computations for this test problem are carried out using the L  e-Trotter-splitting technique.

Tablo 1. Utilizing $k = 0.01$ and $N = 300$, numerical values of u obtained at selected spatial grid points are examined for several T -values. The resulting data are then set alongside the values presented in references [7] and [5] to assess the agreement between the numerical results.

	X	$T = 1$	$T = 2$	$T = 4$	$T = 10$
Mevcut	-6	-0.0137505338	-0.0172781589	-0.0097049546	-0.0005375274
	-4	0.5729517417	0.2872814481	0.0557669464	-0.0020600140
	-2	0.2743957593	0.3586630357	0.2401799150	0.0084856129
	0	0.777001084	0.1753560378	0.2614626660	0.0469203633
	2	0.01988163157	0.0658215863	0.1787430273	0.1031992226
	4	0.0047096255	0.021510996	0.0938553695	0.1501090117
	6	0.0010652708	0.0063863428	0.0417122301	0.1642528015
[7]	-6	-0.0137505008	-0.0172781384	-0.0097049407	-0.0005375241
	-4	0.5729522151	0.2872812764	0.0557664765	-0.0020600354
	-2	0.2743955907	0.3586639854	0.2401808968	0.0084854921
	0	0.0776994781	0.1753353171	0.2614630677	0.0469203573
	2	0.0198162024	0.0658211715	0.1787429081	0.1031994926
	4	0.0047096453	0.0214510172	0.0938549477	0.1501093908
	6	0.0010652925	0.0063863592	0.0417120485	0.1642529939
[5]	-5	-0.0010923500	-0.0010473800	0.0005281950	-0.0000298137
	0	0.5727480000	0.2869880000	0.0555430000	-0.0021879900
	5	0.0396689000	0.1099050000	0.2152390000	0.0736685000

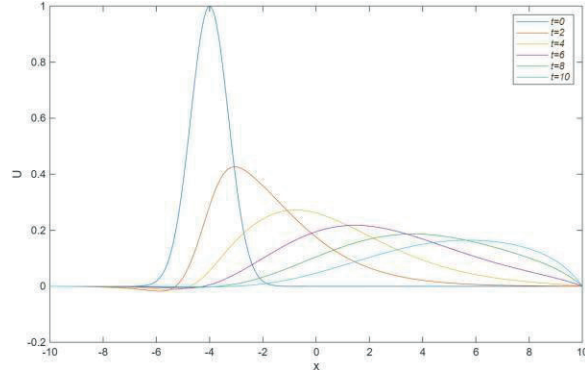


Figure1: Two-dimensional plots of u at different time levels T , obtained for $N = 300$ and $k = 0.01$.

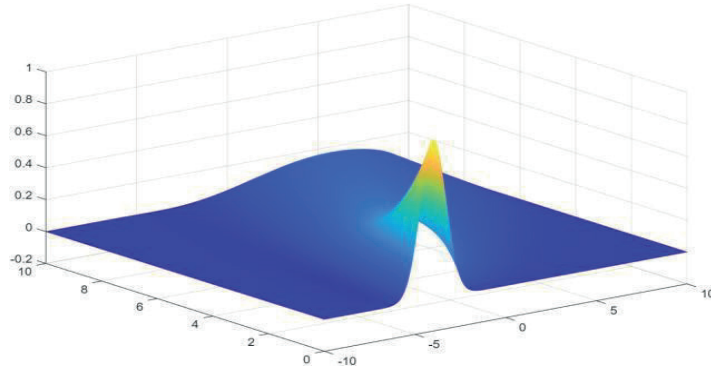


Figure2: Two-dimensional plots of u at different time levels T , obtained for $N = 300$ and $k = 0.01$.

Tablo 2:. Numerical values of u corresponding to selected spatial locations and various T -levels are listed for $k=0.01$ and $N=100$, together with the reference values reported in [7] and [11].

	T	$X = -8$	$X = -6$	$X = -4$	$X = -2$	$X = 0$	$X = 2$	$X = 4$	$X = 6$	$X = 8$
Mevcut	1	$-5.25E-5$	-0.00040	-0.0298	-0.01377	0.57448	0.27346	0.07753	0.01979	0.00457
	2	$-4.86E-5$	-0.00038	-0.00288	-0.1753	0.28934	0.35778	0.17484	0.06557	0.02057
	3	$-3.44E-5$	-0.00028	-0.00215	-0.01424	0.13388	0.32159	0.24258	0.12476	0.04990
	4	$-2.19E-5$	-0.00019	-0.00146	-0.01012	0.05669	0.24056	0.26097	0.17759	0.08812
	5	$-2.31E-5$	-0.00012	-0.00095	-0.00677	0.02072	0.16136	0.23853	0.20859	0.12635
	6	$-7.59E-6$	$-7.73E-5$	-0.00060	-0.00438	0.00511	0.10055	0.19506	0.21310	0.15535
	7	$-4.25E-6$	$-4.70E-5$	-0.00037	-0.00277	-0.00092	0.05914	0.14742	0.19610	0.16943
	8	$-2.32E-6$	$-2.81E-5$	-0.00023	-0.00173	-0.00272	0.03295	0.10512	0.16671	0.16792
	9	$-1.24E-5$	$-1.66E-5$	-0.00014	-0.00107	-0.00279	0.01728	0.07160	0.139339	0.15414
	10	$-6.49E-7$	$-9.66E-6$	$-8.54E-5$	-0.00066	-0.00230	0.00836	0.04691	0.10177	0.13304
[7]	1	$-5.25E-5$	-0.00040	-0.00299	-0.01377	0.57448	0.27346	0.07753	0.01979	0.00457
	2	$-4.86E-5$	-0.00039	-0.00288	-0.01754	0.28935	0.35779	0.17485	0.06558	0.02058
	3	$-3.45E-5$	-0.00029	-0.00216	-0.01424	0.13389	0.32160	0.24259	0.12477	0.04991
	4	$-1.32E-5$	-0.00019	-0.00147	-0.01012	0.05670	0.24057	0.26097	0.17760	0.08813
	5	$-1.32E-5$	-0.00012	-0.00096	-0.00677	0.02073	0.16136	0.23854	0.20860	0.12635
	6	$-7.59E-6$	$-7.74E-5$	-0.00061	-0.00438	0.00511	0.10056	0.19506	0.21311	0.15526
	7	$-4.25E-6$	$-4.71E-5$	-0.00038	-0.00278	-0.00093	0.05915	0.14743	0.19610	0.16943
	8	$-2.32E-6$	$-2.82E-5$	-0.00023	-0.00174	-0.00272	0.03296	0.10512	0.16672	0.16793
	9	$-1.24E-6$	$-1.66E-5$	-0.00014	-0.00108	-0.00280	0.01729	0.07161	0.13340	0.15415
	10	$-6.50E-7$	$-9.67E-6$	$-8.55E-5$	-0.00066	-0.00230	0.00837	0.04691	0.10177	0.13304
[11]	1	$-5.21E-5$	-0.00040	-0.00297	-0.01379	0.57275	-0.27451	0.07772	0.01980	0.00456
	2	$-4.83E-5$	-0.00038	-0.00285	-0.01734	0.28699	0.35876	0.17540	0.06572	0.02059
	3	$-3.43E-5$	-0.00028	-0.00112	-0.01397	0.19200	0.32177	0.24327	0.12512	0.05001
	4	$-2.19E-5$	-0.00019	-0.00144	-0.00986	0.05554	0.24007	0.26141	0.17809	0.08835
	5	$-1.32E-5$	-0.00012	-0.00094	-0.00655	0.02017	0.16059	0.23856	0.20904	0.12668
	6	$-7.72E-6$	$-7.70E-5$	-0.00059	-0.00422	0.00493	0.09983	0.19474	0.21300	0.15568
	7	$-4.39E-6$	$-4.71E-5$	-0.00037	-0.00267	-0.00091	0.05860	0.14693	0.19606	0.16963
	8	$-2.44E-6$	$-2.84E-5$	-0.00023	-0.00166	-0.00262	0.03262	0.10461	0.16646	0.16793
	9	$-1.34E-6$	$-1.69E-5$	-0.00014	-0.00103	-0.00267	0.61712	0.07177	0.17301	0.15395
	10	$-7.22E-7$	$-9.97E-6$	$-8.47E-5$	-0.00063	-0.00219	0.00832	0.04658	0.10135	0.13269

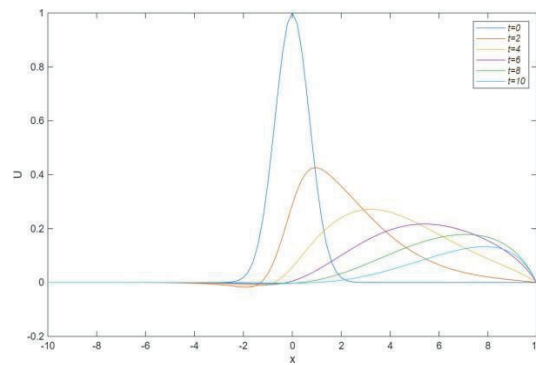


Figure 3. Two-dimensional profiles of u at different time levels for $k = 0.01$ and $N = 100$

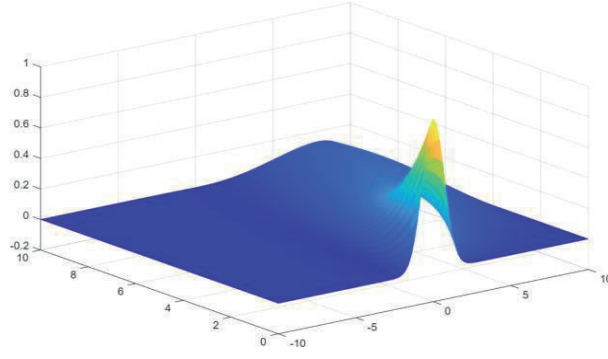


Figure 4. Three-dimensional profiles of u at different time levels for $k = 0.01$ and $N = 10$.

It can be concluded that the results obtained by the proposed algorithm are quite satisfactory when compared with some existing results. Moreover, while the other approaches are based on Galerkin and collocation methods, the present method achieves highly competitive results. This demonstrates the effectiveness and attractiveness of the proposed approach. Furthermore, the graphs of the approximate solutions are in very good agreement with the exact solutions.

Conclusion

In this work, a numerical scheme based on the Lie–Trotter splitting strategy combined with a finite difference discretization has been developed for the numerical treatment of the RLW–Burgers equation. The proposed formulation separates the governing equation into suitable subproblems, allowing the linear and nonlinear contributions to be handled within a splitting framework. Numerical simulations are carried out to examine a benchmark test problem and to evaluate the performance of the proposed method. The numerical solutions are compared with reference results reported in the literature, and the evolution of the wave profile is presented through graphical and tabulated results. The obtained results demonstrate that the proposed method successfully captures the essential characteristics of the wave propagation and produces stable and accurate numerical approximations. The close agreement between the computed solutions and the available reference data confirms the reliability and consistency of the numerical formulation. Overall, the results indicate that the Lie–Trotter splitting combined with a finite difference discretization provides an effective computational strategy for the RLW–Burgers equation. The proposed framework can also be considered a useful numerical tool for the investigation of nonlinear partial differential equations arising in applied mathematics and for the mathematical modeling of various physical phenomena.

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CHAPTER 4

FLAVONOID–DNA INTERACTIONS: MOLECULAR MECHANISMS, STRUCTURE–ACTIVITY RELATIONSHIPS AND BIOLOGICAL EFFECTS

*Nuray YILDIRIM*¹

¹ Asst. Prof. Dr., Çanakkale Onsekiz Mart University, Vocational School of Health Services, nurayyildirim@comu.edu.tr, <https://orcid.org/0000-0002-4807-5357>

1. Introduction

A substantial part of the biological activity of flavonoids comes from their direct or indirect interaction with DNA. For many years their health effects were put down almost entirely to free-radical scavenging, but antioxidant activity alone cannot explain how they induce apoptosis or act as chemopreventive agents (Arif et al., 2017). Flavonoid–DNA interaction has therefore become a field in its own right.

Flavonoids are plant-derived polyphenolic secondary metabolites, consumed widely through fruit, vegetables, tea, cocoa, wine and legumes (Hu et al., 2025), and also sold without prescription as high-dose supplements (Vanhees et al., 2011). Exposure is widespread, which gives the question of DNA binding real toxicological weight.

Because nucleic acids carry hereditary information, any change in the structure or function of DNA affects how a cell works and divides (Raskar et al., 2026). Flavonoids reach DNA by four routes: direct non-covalent binding to the duplex; oxidative damage through redox cycling of transition metals; indirect strand breaks caused by acting on topoisomerases; and epigenetic change through inhibition of DNA methyltransferases.

The effects run in both directions. Depending on concentration, redox conditions, metal ions and the conformation of the target, a flavonoid may protect DNA or damage it. Jomová et al. (2019) showed that the switch between antioxidant and pro-oxidant behaviour in phenolic compounds depends largely on the number and position of hydroxyl groups and on the capacity to chelate redox-active metals.

2. Chemical Structure of Flavonoids

A flavonoid's DNA binding, and its interaction with the enzymes that act on DNA, depend mainly on the groups attached to its three-ring C6–C3–C6 skeleton. Two benzene rings (A and B) are joined by an oxygen-containing pyran ring (C). Three features matter most: the C2=C3 double bond and the C4 keto group in ring C, and the number of hydroxyl groups on ring B (Bandelet et al., 2008; Tawani et al., 2017).

The subclasses follow from differences in this skeleton. Flavonols (quercetin, myricetin, kaempferol, fisetin, morin, galangin) carry a C3-OH together with the C2=C3 double bond. Flavones (apigenin, luteolin, chrysin, baicalein) keep the double bond but lack the C3-OH. Flavanones (naringenin, hesperetin) have a saturated C ring, and taxifolin, a dihydroflavonol, sits close to them. In isoflavones (genistein, daidzein, orobol, prunetin) the B ring is attached at C3 instead of C2. Flavan-3-ols or catechins (EGCG, EGC, ECG, epicatechin) have no C4 keto group.

These differences predict behaviour. The C-ring double bond keeps quercetin planar, which supports intercalation; naringenin lacks it, is less planar, and binds in a groove instead (Tu et al., 2015). Catechins, having no C4 keto group, cannot act as classical topoisomerase II poisons and fall back on a redox-dependent mechanism (Bandelet et al., 2008).

Most dietary flavonoids occur as glycosides, and the position of the sugar decides its effect. Mass spectrometry of ten aglycones and ten glycosides showed that a sugar chain on ring A or B strengthens binding to duplex DNA, whereas glycosylation of quercetin on ring C has a smaller effect; the same work established that the 4'-OH group is indispensable for aglycones (Wang et al., 2008). Among *Puerariae Radix* flavonoids the affinity order was quercetin > formononetin > daidzein > puerarin > 4'-methoxy puerarin > puerarin 6''-O-xyloside, and quercetin, the strongest binder, was the only one that inhibited DNA amplification (Chen et al., 2020).

3. DNA as a Target

Most studies use calf thymus DNA (ct-DNA) because it is available and its B form is well characterised; fish sperm and chicken blood DNA are also common. All are mixed-sequence samples, so they say little about sequence preference.

B-form DNA offers four regions. The narrow, deep minor groove suits small, flexible, hydrogen-bonding molecules, especially in A–T rich stretches. The wider major groove is accessible but serves mainly as a protein recognition surface. Planar aromatic systems fit between stacked base pairs, which is intercalation. Cationic or metal-chelated species bind the negatively charged sugar–phosphate backbone electrostatically (Sirajuddin et al., 2013; Ochima et al., 2026).

Sequence preference has had little attention. With the octamer d(CCAATTGG)₂, baicalein, chrysin and flavone bound near A–T rich regions, while intercalation between base pairs appeared only with d(CGATCG)₂ (Kumar & Nair, 2021). A molecular dynamics study of flavopiridol and quercetin across five eight-nucleotide sequences found that ligand binding increased the flexibility of the whole duplex only for GGGGCCCC, while the other sequences became more rigid; of that added rigidity, about 50–70% came from the sugar–phosphate backbone (Mitrasinovic, 2015).

Guanine-rich sequences can also fold into four-stranded G-quadruplexes, and a triple-helical form exists as well.

Finally, DNA is not naked inside a cell. Chromatin-bound copper, histone packaging and the replication machinery are absent from purified ct-DNA. As Arif et al. (2015) showed in

human lymphocytes, flavonoid-induced breakage depends on mobilising chromatin-bound copper, which is why binding data alone do not predict what happens in cells.

4. Non-covalent Binding Modes

Four modes are described: intercalation, groove binding, electrostatic interaction and mixtures of these. They differ in strength, in how far they distort DNA, and in what follows in the cell. No single measurement settles the question, so the standard practice is a panel of methods that check one another. UV–Vis titration gives the binding constant; fluorescence quenching reports complex formation; competitive displacement of ethidium bromide tests for intercalation and of Hoechst 33258 for the minor groove; viscometry detects the lengthening of the helix that only intercalation causes; melting temperature measures how far binding stabilises the duplex; circular dichroism shows conformational change; cyclic voltammetry registers the shift in peak potential; and docking predicts the site.

In intercalation a flat ring system slides between adjacent base pairs, held by π – π stacking. The signs appear together: the UV–Vis band weakens and shifts to longer wavelengths, fluorescence drops when the compound displaces ethidium bromide, the melting temperature rises, viscosity increases, and the peak potential moves to more positive values. Jabeen et al. (2019) saw all of these for morin and several metal complexes, with binding constants near 10^4 M^{-1} . Hesperetin and naringenin raised the melting temperature of DNA by up to 5°C , showing that binding stabilises the duplex (Hegde et al., 2012), and fisetin and quercetin are usually placed in this class (Jana et al., 2012).

A groove binder sits in the minor groove, usually in A–T rich stretches, held by hydrogen bonds and van der Waals contacts. Base stacking is left intact, so viscosity and melting temperature barely change. 3-Hydroxyflavone is the textbook case (Jana et al., 2012); galangin behaves the same way (Naik et al., 2022), as do taxifolin, daidzein and S-equol against fish sperm DNA, with constants near 10^4 M^{-1} (Kılıçaslan, 2025). Myricetin is the surprise: six hydroxyl groups in all, three of them on the B ring, yet still a groove binder at roughly 10^3 M^{-1} (Das et al., 2026).

Thermodynamics sharpens the picture. Myricetin binding runs on hydrophobic forces of a non-classical kind, with favourable enthalpy but unfavourable entropy (Das et al., 2026), which is striking because hydrophobic interactions usually come with positive enthalpy. Kolaflavanone binds the minor groove with both terms in its favour, $\Delta H = -18.16 \text{ kJ/mol}$ and $\Delta S = 38.60 \text{ J/mol/K}$ at 25°C , a constant near $10^5 \text{ L}\cdot\text{mol}^{-1}$ and a docking affinity of -7.4 kcal/mol

for the A–T region; a salt-dependence analysis put the polyelectrolytic contribution below 11% of the free energy (Ochima et al., 2026).

Electrostatic binding is the weakest, around 10^2 M^{-1} . The ligand never enters the helix, so the melting temperature is unchanged and intercalating dyes keep their fluorescence. Jabeen et al. (2019) assigned this mode to Fe-morin, Cu-quercetin, Fe-quercetin and primuletin. What decides the mode is the metal and the chelation site rather than the flavonoid alone: morin intercalates as the free ligand and as its copper complex but binds electrostatically as its iron complex, while primuletin does the reverse.

Pure modes are rare. For baicalein, chrysin and flavone, absorption data suggested intercalation while displacement assays supported only partial insertion and circular dichroism hinted at a tilted arrangement (Kumar & Nair, 2021). Mixed modes were also proposed for new derivatives (Janjua et al., 2011), and morin switches mode with concentration. Much of the disagreement in the literature follows from differences in DNA source, ionic strength, solvent and ligand-to-DNA ratio. Solvent is a recurring problem: flavonoids dissolve poorly in water, so they are diluted from DMSO stocks, sometimes at ratios as high as 9:1 (Janjua et al., 2011), and Jabeen et al. (2019) worked in 20% methanol at 310 K.

5. Structure–Activity Relationships

Small structural changes shift the binding mode predictably. The clearest link is between B-ring hydroxylation and mode: 3-hydroxyflavone, with no extra B-ring hydroxyl, binds in the groove, while fisetin and quercetin intercalate (Jana et al., 2012). The relationship is not linear, though. Myricetin carries three B-ring hydroxyls, more than fisetin or quercetin, yet still prefers the groove (Das et al., 2026), and across five flavonoids the ct-DNA affinity ran quercetin > myricetin > luteolin > kaempferol > apigenin (Das et al., 2017), so position matters as much as number.

Flavonoids chelate transition metals at three sites: 3-OH/4-keto, 5-OH/4-keto, and the ortho-dihydroxy group on ring B. Cu^{2+} binds effectively only when ring C carries both 3-OH and 4-CO and the C2–C3 bond is unsaturated (Jomová et al., 2019). Luteolin, lacking 3-OH, chelates through 5-OH and 4-CO (Jomová et al., 2022), and galangin through the cinnamoyl unit (Jomová et al., 2024).

Arif et al. (2015) ranked five flavonols for cellular DNA breakage as myricetin > fisetin > quercetin > kaempferol > galangin and concluded that an anticancer flavonoid should carry ortho-dihydroxy groups on ring B and hydroxyls at positions 3 and 5. This order does not match binding affinity, which suggests that redox capacity matters as much as binding strength.

Calorimetry supports that: binding constants stayed near 10^2 M^{-1} for all five, with both ΔH and ΔS negative, and docking gave six hydrogen bonds for myricetin against one for galangin, with energies from -6.13 to -5.01 kcal/mol .

6. Metal Ions and Flavonoid–Metal Complexes

Transition metals change the character of the interaction, shifting both the binding mode and the redox behaviour. Coordination usually raises affinity: quercitrin, myricitrin and rutin bind intercalatively on their own, while their Cu(II) complexes bind more tightly because the metal adds an electrostatic contribution (Atabey-Özdemir et al., 2017). Among newer complexes, a dicyanamide-bearing Zn(II)–quercetin complex interacted with DNA more effectively than its azide-bearing Cu(II) counterpart, binding purely in the groove, and showed strong anticancer activity with little damage to normal cells (Mudi et al., 2023).

Nuclease activity separates complexes from free ligands most sharply. Free flavonoids protected DNA against cleavage in the presence of peroxide, whereas their Cu(II) and Zn(II) complexes cut the backbone in several places, copper the more aggressive; myricitrin was twice as cytotoxic to peripheral blood mononuclear cells with metal ions as without (Atabey-Özdemir et al., 2017).

Where the metal binds decides the outcome. Luteolin holds Cu(II) through 5-OH and 4-CO, and that arrangement suppressed hydroxyl and superoxide radical formation in a Cu-Fenton system by about 80% (Jomová et al., 2022). Myricetin, morin and taxifolin go the other way, forming stable Cu(II) complexes that damage DNA through the Fenton reaction (Jomová et al., 2019). Since tissue, cell and serum copper are raised in malignancy, cancer cells should be more exposed to copper-driven oxidative breakage, which explains preferential cytotoxicity better than the antioxidant model does (Arif et al., 2017).

7. Pro-oxidant Activity and Oxidative DNA Damage

Flavonoids are known as antioxidants, yet they have been shown since the early 1990s to damage DNA oxidatively under the right conditions. The mechanism starts with reduction of Cu(II) to Cu(I); the reduced copper then reacts with hydrogen peroxide to make reactive oxygen species. Yoshino et al. (1999) showed that myricetin, baicalein and quercetin cleaved plasmid and calf thymus DNA in the presence of copper, that catalase protected against the breaks, and that the process yielded 8-hydroxy-2'-deoxyguanosine. Ahmad et al. (1992) found that cleavage efficiency tracked the decay of the charge-transfer complex with copper, the capacity to generate active oxygen, and the stoichiometry of Cu(II) binding, which makes the effect predictable rather than incidental.

Comet assays carried the mechanism into cells. Arif et al. (2015) traced flavonol-induced breakage in human lymphocytes to mobilisation of chromatin-bound copper, and the same group (2017) found breakage greater in the presence of copper, with myricetin inhibiting MDA-MB-231 proliferation dose-dependently. Their most direct evidence for selectivity is that normal breast epithelial cells resisted myricetin but became sensitive after four weeks in medium containing 25 μM Cu(II). Das et al. (2017) tied binding and damage together: quercetin and myricetin together damaged K562 cells more than either alone, copper increased the damage, and quercetin bound DNA more tightly at the low pH of the tumour microenvironment.

Among phenolic compounds more broadly, cleaving activity with Cu(II) was highest for 1,4-hydroquinones, lower for catechols and lowest for single-phenol compounds; the breaks resisted hydroxyl radical scavengers but were prevented by singlet oxygen scavengers, pointing to another reactive species (Li & Trush, 1994). In *Rhus javanica* flavonoids, neocuproine experiments established Cu(I) as an obligatory intermediate (Lin et al., 2007).

Concentration decides the direction. High concentrations of baicalein protected cells from ROS-induced damage, while low concentrations failed to block the pro-oxidant action of copper and ascorbate (Jomová et al., 2023). This reversal is the clearest reason flavonoid supplements cannot be judged on a "more is better" logic.

8. Topoisomerase-Mediated Effects

The strongest biological effects come not from binding but from inhibiting DNA topoisomerases, enzymes required for replication, transcription and division (Sitarek et al., 2024). The critical distinction is between catalytic inhibitors, which suppress activity without producing breaks, and poisons, which stabilise the enzyme–DNA cleavable complex and leave persistent double-strand breaks. Constantinou et al. (1995) found that myricetin, quercetin, fisetin and morin inhibit both topo I and topo II, while phloretin, kaempferol and 4',6,7-trihydroxyisoflavone inhibit only topo II; prunetin, quercetin, kaempferol and apigenin stabilised the topo II complex, but none stabilised the topo I complex. In Chinese hamster V79 cells, luteolin, quercetin, genistein, apigenin and acacetin were strongly clastogenic, and the effect required intercalation except for genistein, whereas myricetin, daidzein, baicalein, fisetin and galangin behaved as catalytic inhibitors (Snyder & Gillies, 2002).

Austin et al. (1992) established the structural requirements across some 30 compounds: an unsaturated bond between positions 2 and 3 of the pyrone ring plus hydroxyls at 5, 7, 3' and 4' favour cleavage, while substitution at 3, 6 and 5' is tolerated, and the absence of 3', 4' and 5' substituents can be offset by a hydroxyl at position 6, as in baicalein. Bandele et al. (2008)

refined this into four groups, and the division follows the C4 keto rule set out earlier: EGCG and EGC as redox-dependent poisons, kaempferol and quercetin as traditional poisons, myricetin as both, and ECG and EC as inactive. Their two rules are that C4'-OH is critical for traditional poisoning, with extra hydroxyls at C3' and C5' pushing a compound towards redox-dependent behaviour, and that the planar aromatic C ring with a C4-keto group forming a pseudo ring with C5-OH is required for traditional poisoning.

Activity on purified enzyme does not always survive in cells. Using a cell-based assay in K562 cells, quercetin and apigenin produced moderate topo II complexes and no topo I complexes, fisetin produced neither and acted as a catalytic inhibitor of both, and myricetin produced high levels with both; fibroblasts lacking topo II β resisted myricetin-induced growth inhibition, marking that isoform as a target (López-Lázaro et al., 2010). Isoflavones differ again: genistein and orobol induce topo II-dependent cleavage without intercalating, and high salt largely abolishes the cleavage, confirming a cleavable-complex mechanism (Yamashita et al., 1990).

9. Genotoxicity, MLL Translocations and Infant Leukemia

The most contested public health question is whether poisoning behaviour can produce chromosomal translocations, a concern that arises from the chemical resemblance between flavonoids and etoposide. Strick et al. (2000) reported site-specific cleavage in the breakpoint cluster region of the MLL gene in primary haematopoietic progenitor cells from healthy newborns and adults, at a site overlapping that of etoposide and doxorubicin, and proposed that maternal intake could induce MLL breaks in utero. MLL translocations occur in about 80% of infant leukemias, and the finding drew immediate attention (Ross, 2000).

Using the neutral comet assay, Barjesteh van Waalwijk van Doorn-Khosrovani et al. (2007) found dose-dependent double-strand breaks in primary human CD34⁺ cells exposed to quercetin, genistein and kaempferol, with mis-repair producing translocations overlapping those seen in infant leukemia, mostly by microhomology-mediated end joining; 8–10% of quercetin-exposed cells showed MLL monosomy or trisomy. They noted that differences in metabolism between mother and fetus can leave the fetal side more exposed. Azarova et al. (2010) clarified the mechanism: genistein induced both Top2 α and Top2 β cleavage complexes, caused proteasomal degradation of Top2 β , and the γ -H2AX signal depended on both the isozyme and proteasome activity. In vivo, Atm-mutant mice showed more Mll rearrangements after exposure than wild-type animals, and prenatal exposure through genistein- or quercetin-

enriched feed raised rearrangement frequency with a slight rise in malignancy (Vanhees et al., 2011).

The picture is not uniform. Myricetin-induced breaks were largely abolished by the topoisomerase II catalytic inhibitor dexrazoxane, genistein- and quercetin-induced breaks only partly, while luteolin- and kaempferol-induced breaks increased with dexrazoxane, indicating a largely Top2-independent route; combinations did not behave additively (Goodenow et al., 2020). A reporter system quantifying MLL–AF9 translocations ranked genistein and quercetin as strongly associated and kaempferol, fisetin, flavone and myricetin as weakly but consistently so, with translocation frequency falling by more than one log at later stages of myelopoiesis, which ties risk to a developmental window (Baria et al., 2019).

This literature argues for caution with supplements during pregnancy, as distinct from ordinary dietary amounts. Causality in humans is not established: the evidence comes from *in vitro* systems, cell models and genetically sensitised animals, and the preliminary epidemiological studies summarised by Ross (2000) suggest an association without resolving exposure measurement. Prospective human data measuring fetal exposure directly remain the clearest gap.

10. Non-canonical DNA Structures

G-quadruplexes are concentrated in oncogene promoters and telomeric repeats, and ligands that stabilise them can suppress the associated gene. Screening nine flavonoids against the c-myc promoter sequence Pu24T, Tawani et al. (2017) found quercetin the strongest binder and solved the first solution structure of such a complex by NMR, showing quercetin stacked on the 5' and 3' G-tetrads through π – π interactions. Quercetin's affinity for this quadruplex is roughly 300-fold higher than for duplex ct-DNA and about 10-fold higher than for the c-kit quadruplex; binding raised the melting temperature of Pu24T from 70.0 °C to 80.0 °C, and in HeLa cells quercetin induced apoptosis with an IC_{50} of 4.0 μ M and downregulated c-myc. The coordinates are deposited as 2N6C. For kaempferol, FRET showed stabilisation by reducing affinity for the complementary strand (Paul et al., 2019), and plant metabolites including quercetin and kaempferol suppressed c-MYC expression through a G4-mediated route in cells (Zenkova et al., 2022).

Fisetin binds at the G-tetrad face, mostly along the diagonal loop (Sengupta et al., 2013), and EGCG interacts with the c-MYC quadruplex by external stacking or groove engagement rather than intercalation (Tang, 2025). Synthetic derivatives are promising: a nitro-flavone bound c-MYC preferentially among five quadruplexes with a constant near 10^5 M^{-1} and

produced DNA damage, G1/S arrest and apoptosis in melanoma cells (Mitra et al., 2021), while Licoflavone B and Ginkgetin suppressed c-Myc transcription in myeloma cells below 8 μM (Liu et al., 2022).

Triplex targeting is newer. Quercetin-derived 5-substituted tetramethoxyflavonoids bound triplex DNA strongly without affecting duplex structures, with affinities comparable to neomycin, and the amino-containing side chain at position 5 proved critical (Rangel et al., 2022). Selectivity over duplex DNA is what decides therapeutic value; aloe compounds, for instance, bound c-KIT and c-MYC more tightly than duplex DNA (Das & Dutta, 2021), and selectivity for polymorphic quadruplex structures is now treated as the central design parameter (Bag et al., 2023).

11. DNA Methyltransferase Inhibition

Flavonoids also act on the enzymes that modify DNA chemically. Hypermethylation of CpG islands silences tumour suppressor genes, and DNA methyltransferases maintain it. Fang et al. (2003) showed that EGCG inhibits DNMT competitively with a K_i of 6.89 μM and an IC_{50} near 20 μM , and that 5–50 μM over 12–144 hours reversed hypermethylation of p16INK4a, RAR β , MGMT and hMLH1 in oesophageal cancer cells. Modelling placed EGCG in the catalytic pocket of DNMT1 through hydrogen bonds with Pro1223, Glu1265, Cys1225, Ser1229 and Arg1309; the gallate interaction with Glu1265 and Pro1223 explains why EGC and EC, which lack a galloyl group, are weak inhibitors.

The mechanism is not uniform. Catechin, epicatechin, EGCG and the flavonoids quercetin, fisetin and myricetin all inhibited methylation, with IC_{50} values of 1.0–8.4 μM for most and 0.21–0.47 μM for EGCG. Catechol-containing polyphenols act largely indirectly, by raising S-adenosyl-L-homocysteine during their own O-methylation, whereas the potency of EGCG rests on direct inhibition and is independent of its own methylation (Lee et al., 2005).

The evidence base is predominantly preclinical. Because most polyphenols have low bioavailability, the effect of a single compound at ordinary dietary levels is probably negligible (Fang et al., 2007), and recent systematic reviews repeat the point: most studies report inhibition, but protocol variability and preclinical weighting limit translation (Campisi et al., 2025).

12. Protective Effects and the Dual Nature

The same molecules protect DNA under other conditions. Quercetin above 10 μM and myricetin at 100 μM reduced hydrogen peroxide-induced strand breaks and oxidised pyrimidines in human lymphocytes, and neither was genotoxic alone, while α -tocopherol and

β -carotene gave no protection (Duthie et al., 1997). In HepG2 cells, quercetin acted both by direct chemical interaction and by strengthening antioxidant defences, and quercetin and ursolic acid also raised the rate of DNA repair; rutin had no effect at any level, which shows that glycosylation can cost protective efficacy (Ramos et al., 2008). Quercetin also protected human lymphocytes against BPDE–DNA adduct formation dose-dependently, although a four-week juice intervention that raised plasma quercetin from 5.0 to 10.6 nM reduced ex vivo oxidative damage by 41% without reaching significance (Wilms et al., 2005). Catechin and epicatechin protected against N-nitrosamine damage where quercetin did not (Delgado et al., 2009).

Szeto and Benzie (2002) isolated the role of the membrane: antioxidants that protected in whole cells caused damage in lysed cells, suggesting that the membrane limits access of these double-edged compounds. The variables that decide direction are therefore concentration, free transition metal, compartmentalisation and the redox state of the cell. Arif et al. (2017) made the duality visible in one series: the ranking of five flavonols for protection against tert-butyl hydroperoxide damage is identical to their ranking for copper-dependent DNA breakage, so the strongest antioxidant is also the strongest pro-oxidant.

Repair is modulated too, and the direction depends on cell type. Naringenin lowered the 8-OHdG/dG ratio in prostate cancer cells and raised hOGG1 and DNA polymerase β expression (Gao et al., 2006), and an apple flavonoid fraction facilitated repair in normal bronchial epithelial cells through DNA-PKcs phosphorylation (Vazhappilly & Rupasinghe, 2017). In cancer cells the opposite happens: quercetin and thymoquinone raised damage markers while lowering RAD51, Ku70 and XRCC1 (Karimian et al., 2022), and apigenin and hesperidin increased double-strand breaks and suppressed repair genes, enhancing doxorubicin cytotoxicity (Korga-Plewko et al., 2020).

13. Bioavailability and Physiological Relevance

Nearly all of the above comes from in vitro work using aglycones at micromolar concentrations, and whether those concentrations occur in humans is the field's most serious question. After oral dosing in rats, the parent form of quercetin was undetectable in blood; only glucuronide and sulfate conjugates circulated, and the same was true after rutin (Yang et al., 2005). Kinetic modelling predicted aglycone bioavailability of 0.004% at a dietary dose of 0.4 mg/kg and 0.1% at a supplementary 12 mg/kg, with 95–99% of the dose converted to monoglucuronides within 1.5–2.5 hours (Boonpawa et al., 2014). Flavanones behave the same way (Najmanová et al., 2020). The 10.6 nM plasma level reached in the intervention of Wilms et al. (2005) is three to four orders of magnitude below the 10–100 μ M used in binding studies.

Three considerations keep this from being fatal. Circulating conjugates are not inert, and enterohepatic recirculation and tissue-bound metabolites contribute to the observed effects (Oliveira et al., 2026); gut microbial transformations also alter absorption (Hu et al., 2025). Local concentrations in the intestinal epithelium, liver and fetal compartment can exceed plasma. And the source matters: ordinary dietary intake and high-dose supplementation are different exposures (Fang et al., 2007). The mechanisms are real and chemically defined; whether they operate at a nutritional scale must be asked separately for each compound, dose and tissue. That flavonoid metabolites have scarcely been tested for DNA interaction is the most conspicuous gap in the literature.

14. Applications and Research Gaps

The most direct application is the design of DNA-targeted anticancer agents. Jabeen et al. (2019) linked intercalation to cytostatic activity, groove binding to an absence of apoptosis, and electrostatic binding to no significant antiproliferative effect, with Cu-quercetin cytotoxic to MCF-7 at an LC_{50} of 52 μ M; the correlation should be treated as provisional, since the paper's text and tables disagree on activity against HeLa cells. Structure-based optimisation is the second route, improving enzyme selectivity, uptake and efficacy (Parua et al., 2026).

Selectivity is the main obstacle, because duplex DNA is present in every cell. Targeting oncogene promoter quadruplexes or exploiting the raised copper of cancer cells are more promising, as is the tighter binding of quercetin at tumour pH (Das et al., 2017). Combination with conventional drugs shows synergy and may reduce resistance and toxicity (Parua et al., 2026), as the doxorubicin work illustrates (Korga-Plewko et al., 2020), although acting through repair suppression raises the question of mutagenic risk in normal tissue.

Four gaps stand out. Circulating species are conjugates, yet binding studies almost all use aglycones. Differences in solvent, ionic strength, DNA source and ligand ratio make binding constants hard to compare, so standard protocols would help. Association and dissociation kinetics are barely studied; the single-molecule work of Paul et al. (2019), which gave a relaxation time of 10–50 μ s and an association rate near the diffusion limit, is a rare exception. And no prospective cohort measures maternal flavonoid exposure against MLL rearrangements directly. High-resolution structures are scarce as well: the quercetin–c-myc complex (Tawani et al., 2017) is one of few at atomic detail.

15. Conclusion

Flavonoid–DNA interaction cannot be reduced to one mechanism. Binding mode is structurally predictable from B-ring hydroxylation, the C2=C3 double bond, the C4 keto group

and glycosylation, though not linearly, as myricetin shows. The strongest biological effects come from enzyme-mediated routes rather than from binding itself: topoisomerase II poisoning, copper-mediated oxidative breakage and methyltransferase inhibition. The dual nature is structural rather than an artefact, since the same chemistry that scavenges radicals also reduces copper, which makes dose and context decisive and argues for care with high-dose supplements in pregnancy. The weakest point of the field is physiological validity, because most mechanisms have been shown at concentrations and in chemical forms that do not circulate. Progress will likely come from standardised studies using real metabolites, more high-resolution structures, and from targeting oncogene promoter quadruplexes or tumour-specific conditions rather than duplex DNA, an approach whose feasibility the triplex-selective quercetin derivatives already demonstrate.

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CHAPTER 5

THE INFLUENCE OF STERIC AND ELECTRONIC EFFECTS ON THE NUCLEOPHILIC ADDITION REACTIONS OF AMINES

*Nurcan BERBER*¹

¹ Eczane Hizmetleri Bölümü, Sağlık Hizmetleri MYO Çanakkale Onsekiz Mart Üniversitesi, <https://orcid.org/0000-0002-1595-585X>

1. Introduction

Amines are among the most important nucleophiles in organic chemistry. More than 80% of small-molecule drugs contain at least one nitrogen atom, and the C–N bond is one of the most frequently constructed bonds in pharmaceutical synthesis (Long, Li, & Zhang, 2025; Vitaku, Smith, & Njardarson, 2014). Amines serve as starting materials, intermediates, catalysts, and ligands; their additions to carbonyl compounds give imines, enamines, hemiaminals, and the products of reductive amination, all of which are central to synthesis.

The reactivity of an amine depends mainly on two factors. The electronic environment controls how electron-rich the nitrogen lone pair is, and therefore how easily it can donate electrons to an electrophile. The steric environment controls how easily that lone pair can physically reach the electrophilic atom. These two factors are not independent, and they often pull in opposite directions: a substituent that increases electron density at nitrogen (good for electronic donation) frequently also adds bulk (bad for steric access).

In a typical nucleophilic addition to a carbonyl, the amine approaches the C=O carbon along the so called Bürgi Dunitz trajectory, at an angle of about 107° to the C=O axis. The nitrogen lone pair donates into the π^* orbital of C=O, and a tetrahedral intermediate forms. Depending on the conditions, this intermediate then loses water to give an imine (with primary amines), or an iminium ion that may tautomerize to an enamine (with secondary amines bearing an α -CH on the carbonyl) (Eisenstein, 2024). The reaction is described in detail in Figure 1.

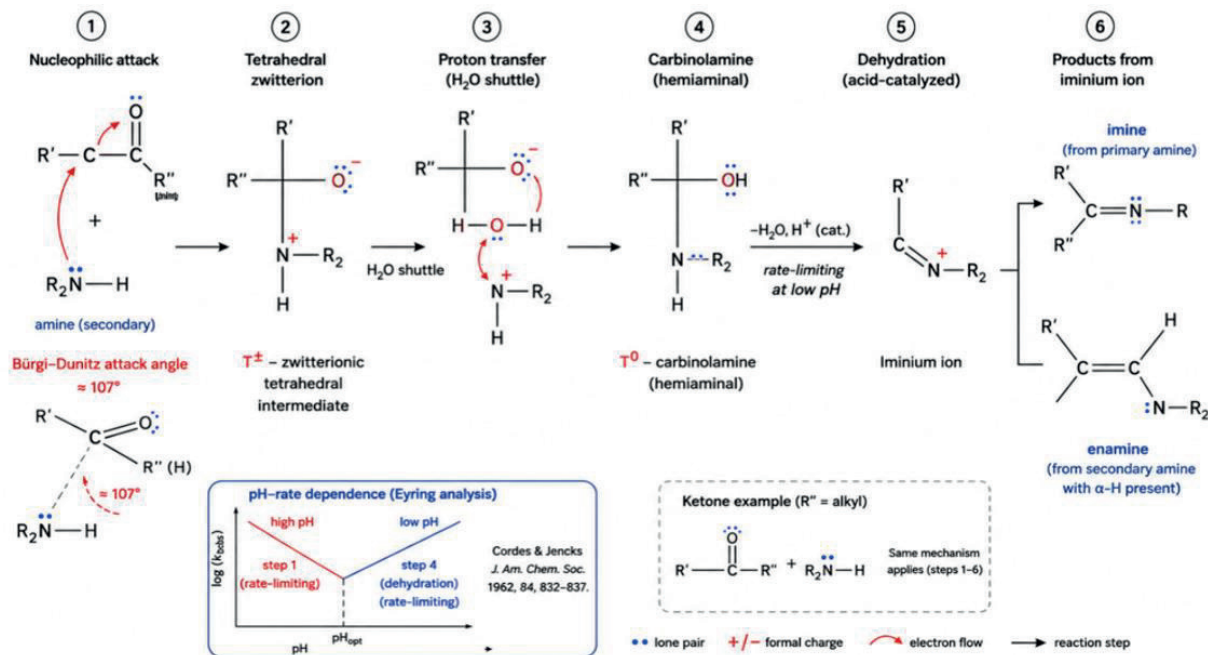


Figure 1. Mechanism of amine addition to a carbonyl compound

Two theoretical frameworks help organize amine reactivity. The HSAB (Hard and Soft Acids and Bases) principle of Pearson classifies nucleophiles and electrophiles by their hardness; amines are borderline-to-soft donors and pair well with the moderately soft carbonyl carbon (Kaya, 2025). Frontier Molecular Orbital (FMO) theory describes the same interaction in orbital terms: the rate of addition

increases when the HOMO of the amine is close in energy to the LUMO of the carbonyl, and when the orbital coefficients are large at the reacting atoms (Svatunek, 2026). Both frameworks predict the same qualitative trends: electron-rich, sterically accessible amines react fastest.

2. The Nucleophilic Character of Amines

2.1 Primary, secondary, and tertiary amines

Primary amines (RNH_2) have two N–H bonds and a relatively exposed lone pair. They form imines with aldehydes and ketones. Secondary amines (R_2NH) have one N–H and react with carbonyl compounds to give iminium ions, which can tautomerize to enamines if the carbonyl has an α -hydrogen. Tertiary amines (R_3N) have no N–H and cannot form stable C–N adducts with carbonyls; they act mainly as Brønsted/Lewis bases. They are still important as nucleophilic catalysts (for example DMAP in acylation chemistry), but their mechanism is different.

A common observation is that the order of basicity (pK_aH in water) does not match the order of nucleophilicity. In water the pK_aH values of primary and secondary alkylamines are almost identical (around 10.6), yet their rates of reaction with carbonyl compounds can differ by orders of magnitude. This decoupling is the central practical lesson of this chapter: pK_a is a rough guide, but it is not a substitute for a true nucleophilicity measurement.

2.2 Aliphatic vs aromatic amines

Aromatic amines (anilines) are much less basic than aliphatic ones because the lone pair is partially delocalized into the aromatic ring (pK_aH of aniline ≈ 4.6 vs ≈ 10.6 for alkylamines) (Montgomery, 2019). They are also less nucleophilic, but the difference is smaller than the basicity gap suggests: in acetonitrile, $\text{N}(\text{aniline}) \approx 12.6$ while $\text{N}(\text{piperidine}) \approx 17.4$, i.e. about five orders of magnitude in rate (Brotzel, Chu, & Mayr, 2007; Kanzian, Nigst, Maier, Pichl, & Mayr, 2009). Anilines are still useful in Schiff base formation, especially with aldehydes, because their imines are stabilized by conjugation with the aromatic ring.

2.3 Basicity vs nucleophilicity

Basicity measures how strongly an amine binds a proton (a thermodynamic equilibrium with a very small, hard electrophile of no steric demand). Nucleophilicity measures how fast an amine attacks a carbon electrophile (a kinetic quantity with often considerable steric demand). The most useful contemporary scale of nucleophilicity is the Mayr Patz scale, which uses benzhydrylium cations as reference electrophiles and the equation $\log k(20^\circ\text{C}) = s_\text{n}(\text{N} + \text{E})$, where N is a nucleophile-specific parameter and E is an electrophile-specific parameter (Mayr & Patz, 1994; Mayr et al., 2001; Mayr & Ofial, 2016). More than 1200 nucleophiles have been characterized this way, providing a quantitative reactivity database for synthesis design.

A useful example: DBU and Hünig's base (DIPEA) both have aqueous $\text{pK}_\text{aH} > 10$, but neither is a good carbon-nucleophile because the bulk around N blocks access to electrophilic carbons. They behave as strong Brønsted bases that ignore C-electrophiles, exactly the selectivity needed for many synthetic operations (Darnell, Lippus, Toom, & Leito, 2026; Smith, 2025).

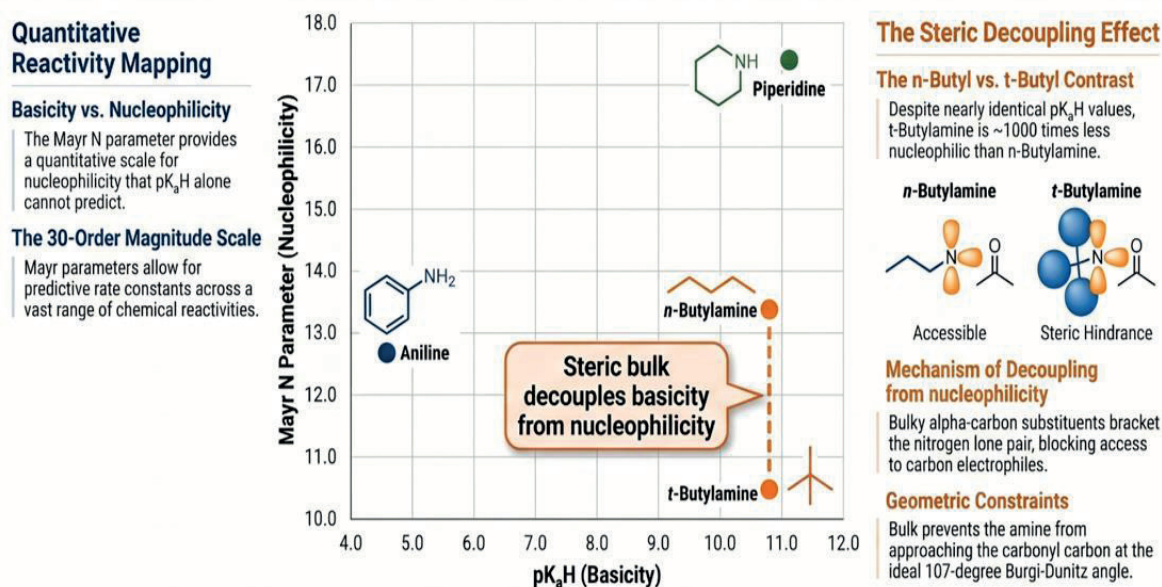


Figure 2. Relationship Between Amine Basicity and Nucleophilicity

3. Steric Effects

3.1 The concept of steric hindrance

Steric hindrance is the energy cost of bringing two atoms or groups into close contact. It arises mainly from closed-shell (Pauli) repulsion between filled orbitals and from the distortion of bond angles and torsions that accompanies the approach. The classical quantitative descriptor is Taft's E_s parameter (Kohn, Becke, & Parr, 1996); modern alternatives include the Sterimol parameters and the buried-volume $\%V_{bur}$ descriptor (Cavallo, Correa, Costabile, & Jacobsen, 2005).

3.2 The effect of bulky substituents on rate

The clearest illustration is the n-butyl / isopropyl / tert-butylamine series. All three have nearly identical pK_aH (~10.7), but their Mayr N parameters in water are 13.4, 12.0, and 10.5 respectively. This corresponds to a rate decrease of approximately 1000 from the n-propyl to the t-butyl amine for the same electrophile (Brotzel et al., 2007). The effect is purely steric: the three methyl groups on the α -carbon of t-butylamine bracket the lone pair and prevent the carbonyl carbon from approaching at the favorable Bürgi–Dunitz angle (in Figure 3).

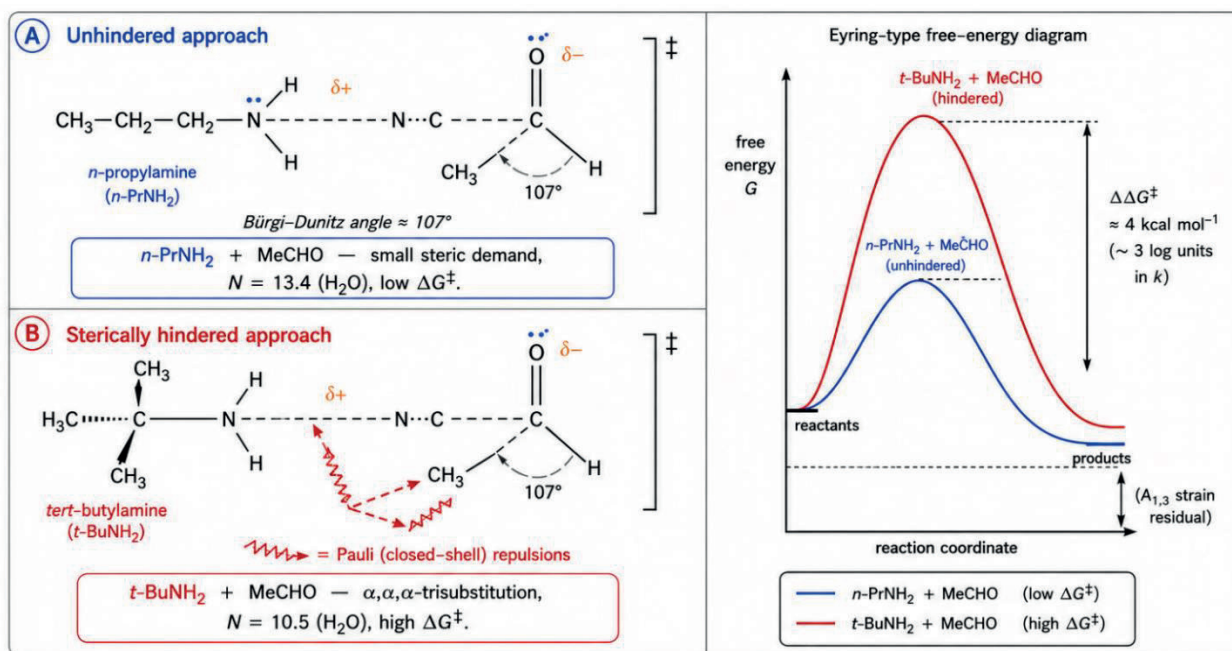


Figure 3. Schematic illustration of the steric effect on the transition state for amine addition to a carbonyl carbon (Brotzel et al., 2007).

Similarly, diisopropylamine is about 100 times less nucleophilic than diethylamine, even though they have nearly the same basicity (Kanzian et al., 2009). The endpoint of this trend is the family of hindered bases such as 2,2,6,6-tetramethylpiperidine (TMP) and Hünig's base, which are essentially non-nucleophilic toward carbon electrophiles.

3.3 Cyclic vs acyclic amines

Cyclic secondary amines such as piperidine and pyrrolidine react significantly faster than their acyclic analogs. Piperidine has an *N* value of 17.4 in acetonitrile, compared to 15.1 for diethylamine (Kanzian et al., 2009). There are two reasons. First, the ring fixes the geometry around nitrogen, so less rotational freedom is lost on going from the free amine to the tetrahedral or trigonal adduct. Second, the ring positions the lone pair in an exposed equatorial orbital, with no substituents bracketing it. These same features make pyrrolidine and proline the catalysts of choice for enamine organocatalysis (Cavallo et al., 2005; Pihko, Majander, & Erkkilä, 2009).

4. Electronic Effects

4.1 Inductive effects

Inductive effects act through the σ-framework. Electron-donating groups (alkyl, +I) raise the energy of the nitrogen lone pair, making the amine a stronger base and a (potentially) better nucleophile. Electron-withdrawing groups (CF₃, CN, COR, -I) lower it. For example, 3,3,3-trifluoropropylamine is several orders of magnitude less nucleophilic than *n*-propylamine because of α-fluorination. The inductive contribution is captured by Taft's σ* and Charton's σ_I scales (Alagarsamy, Narendhar, Sulthana, Sabarees, & Solomon, 2025; Garwood, Chen, & Nagib, 2024).

4.2 Resonance effects

Resonance effects operate when the nitrogen lone pair can delocalize into an adjacent π -system. In aniline, the lone pair donates into the benzene ring, which lowers basicity (by ~ 5 pKa units relative to cyclohexylamine) and lowers nucleophilicity. Amides are an extreme case: the lone pair is so strongly delocalized into the C=O that amides are essentially non-nucleophilic at nitrogen under most conditions.

For substituted anilines, the electronic effect of a para substituent follows the Hammett equation. Mayr-style nucleophilicities of para-X-anilines plot linearly against σ_p with negative slopes ($\rho \approx -5$ to -6), confirming that electron-donating groups (OMe, NMe₂) increase N, while electron-withdrawing groups (NO₂, CN) decrease it (Amira, Salma, Wahiba, & Taoufik, 2021; El Abed, Slama, Mahdhaoui, & Boubaker, 2025). Para-methoxy aniline is roughly five orders of magnitude more nucleophilic than para-nitroaniline.

4.3 Hyperconjugation and α,β -unsaturated amines

Hyperconjugation ($\sigma \rightarrow n^*$ or $n \rightarrow \sigma^*$) is usually a small contribution, but it becomes important in α,β -unsaturated amines: enamines have a fully delocalized $n_N \rightarrow \pi^* C=C$ system, which makes the β -carbon highly nucleophilic. This is the basis of the enormous field of enamine organocatalysis pioneered by List, MacMillan, and Jørgensen (Cavallo et al., 2005; Kubyshkin & Rubini, 2024; MacMillan, 2008).

4.4 The pKa–nucleophilicity relationship

Within one family of amines, log k usually correlates linearly with pKaH (a Brønsted plot) with a slope (β_{nuc}) between 0.3 and 0.8. The size of β_{nuc} indicates where the transition state lies on the reaction coordinate: small β_{nuc} means an early TS (a reactive electrophile), larger β_{nuc} a later TS. Across different amine families the correlation breaks down, because the steric and resonance environments differ. This is why a single scalar like Mayr's N, which integrates over both effects, is more useful for cross-family comparisons than pKaH alone (Brotzel et al., 2007; Mayr & Ofial, 2016).

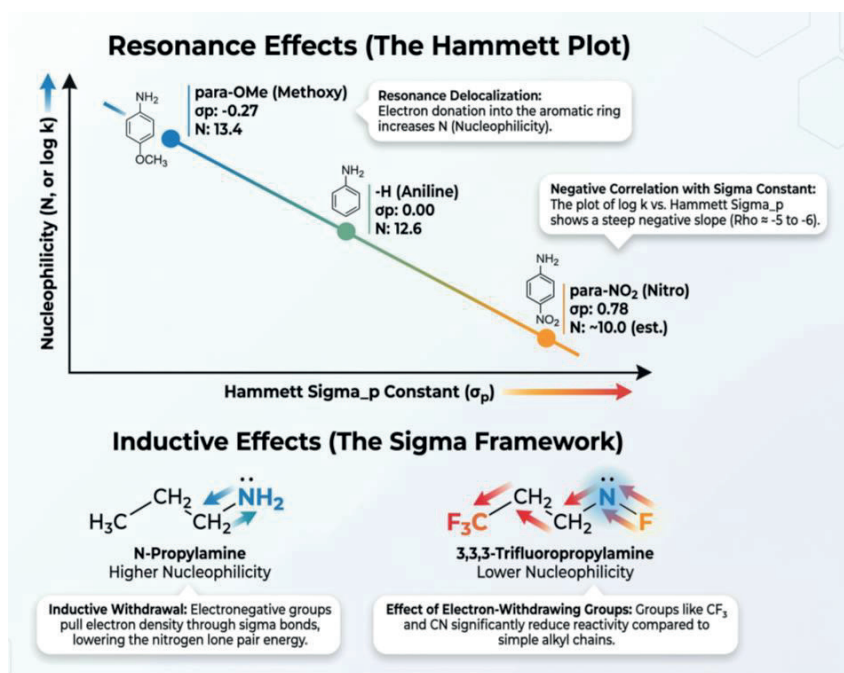


Figure 4. Electronic determinants of amine nucleophilicity

5. Solvent and Medium Effects

Solvent affects amine nucleophilic addition in three main ways. First, polar protic solvents (water, alcohols) stabilize the developing negative charge on the carbonyl oxygen in the zwitterionic tetrahedral intermediate ($T^\pm$) by hydrogen bonding, which accelerates the addition step. Second, the same solvents also solvate the ammonium form of the amine, lowering the concentration of the free, reactive amine; the two effects partially cancel. Third, water can act as a proton shuttle, helping the conversion of the zwitterionic $T^\pm$ to the neutral carbinolamine T^0 (Farooq & Ngaini, 2020).

In aprotic dipolar solvents (DMSO, DMF, acetonitrile), there is no hydrogen-bonding stabilization of $T^\pm$, but the free amine concentration is much higher because the ammonium form is poorly solvated. The net effect is that most amines have similar reactivities in water and in acetonitrile, but the N parameter shifts by about ± 1 log unit between solvent classes (Brotzel et al., 2007; Kanzian et al., 2009). The pH and temperature dependence of the reaction are described by classical Brønsted–Eyring relations and are not discussed further here.

6. Nucleophilic Addition to Carbonyl Compounds

6.1 Aldehydes and ketones

Aldehydes are much more reactive than ketones, for two reasons. Sterically, the aldehyde carbonyl carbon bears only one substituent and a hydrogen, so it is easily approached. Electronically, the second alkyl group of a ketone destabilizes the developing partial positive charge less effectively through hyperconjugation than two hydrogens would. The equilibrium constant for carbinolamine formation is therefore larger for aldehydes than for ketones, and the rate of addition is roughly 100–1000 times faster (Darnell et al., 2026; Eisenstein, 2024).

6.2 Schiff base (imine) formation

When a primary amine adds to a carbonyl, the carbinolamine intermediate loses water to give an imine (Schiff base, $R-N=CR'R''$). The mechanism is shown in Figure 1. The pH–rate profile of imine formation is bell-shaped, with a maximum near the pK_aH of the amine. At low pH, the protonated amine is unreactive; at high pH, the carbinolamine dehydration step is slow. Acid catalysis at moderate pH accelerates the dehydration step by protonating the OH group of the carbinolamine, making water a better leaving group (Eisenstein, 2024; Murugesan et al., 2020).

6.3 Enamines and iminium ions

Secondary amines react with carbonyls to give iminium ions, $R_2N^+=CR'R''$, because there is no N–H to lose. If the carbonyl has an α -hydrogen, the iminium tautomerizes to the corresponding enamine, $R_2N-CR'=CHR''$. Enamines are powerful nucleophiles (the nitrogen lone pair donates strongly into the $C=C$ π system, raising its HOMO), and they are the central intermediate of enamine organocatalysis (Cavallo et al., 2005; Jiao et al., 2022; Kubyshevskii & Rubini, 2024). Proline, MacMillan's imidazolidinones, and the Jørgensen–Hayashi diarylprolinol silyl ethers are the most widely used catalysts in this family. Their chiral information is transferred to the substrate exclusively through steric shielding of one face of the enamine/iminium (in Figure 5).

6.4 Reductive amination

Reductive amination is the most widely used C–N bond-forming reaction in pharmaceutical synthesis. The amine and the carbonyl form an iminium ion, which is then reduced in situ by a hydride source (typically sodium triacetoxyborohydride $\text{NaBH}(\text{OAc})_3$ or sodium cyanoborohydride NaBH_3CN , or H_2 with a transition-metal catalyst) (Afanasyev, Kuchuk, Usanov, & Chusov, 2019; Murugesan et al., 2020). The hydride reduces the iminium faster than the parent carbonyl, providing useful chemoselectivity. The method tolerates a wide range of functional groups and is used at multi-tonne scale in the synthesis of many active pharmaceutical ingredients.

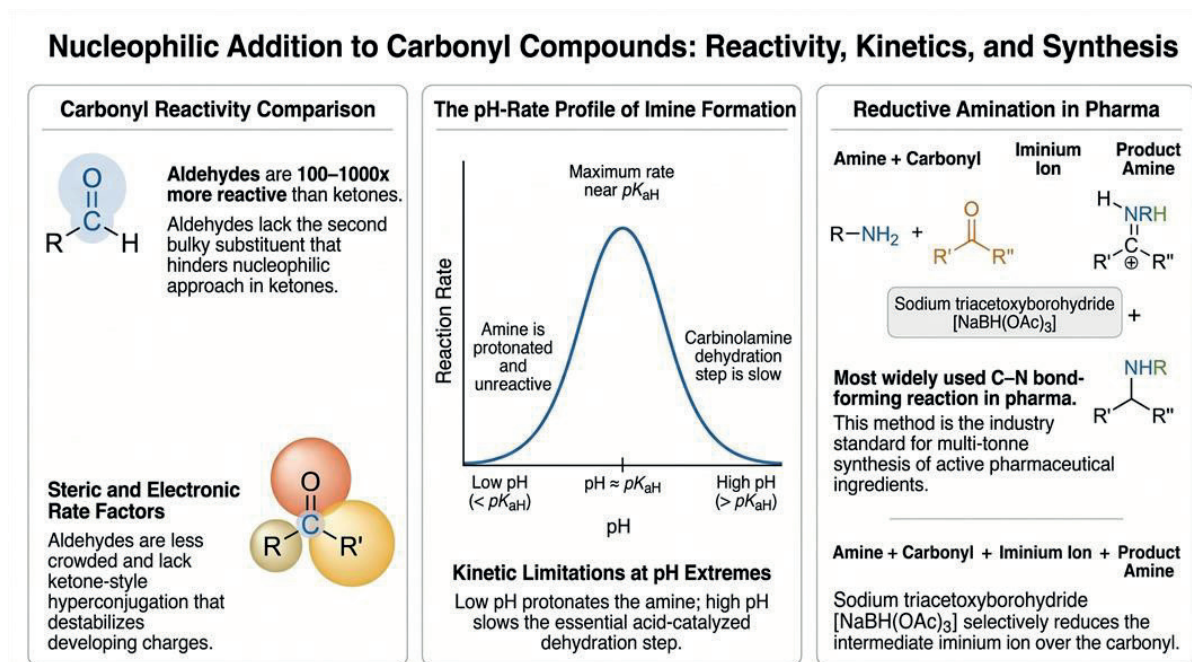


Figure 5. Nucleophilic Addition to carbonyl compounds

Table 1. Steric and electronic effects on amine nucleophilicity (Amira et al., 2021; Brotzel et al., 2007; El Abed et al., 2025; Kanzian et al., 2009; Mayr & Patz, 1994; Mayr et al., 2001).

Factor	Origin	Effect on Nucleophilicity (N)	Example
α -Branching at N	Steric shielding of the lone pair	Strong decrease ($\sim 1\text{--}3$ log k)	n-PrNH_2 ($N \approx 13.3$) > i-PrNH_2 (12.0) > t-BuNH_2 (10.5), water
+I (alkyl) groups	Raise HOMO at N	Modest increase	$\text{Me}_2\text{NH} > \text{MeNH}_2 > \text{NH}_3$ (gas phase)
–I groups (CF_3 , CN)	Lower HOMO at N	Decrease	$\text{CF}_3\text{CH}_2\text{NH}_2 \ll \text{EtNH}_2$
Aryl conjugation	Lone pair delocalized into π^*	Strong decrease ($\sim 10^4$ vs alkyl)	PhNH_2 (12.6, MeCN) vs piperidine (17.4)
para-EDG on aniline	Resonance donation	Increase	$4\text{-MeO-aniline} > \text{aniline} > 4\text{-NO}_2\text{-aniline}$
Cyclic ring (5–6)	Lone pair exposed; less entropy loss	Increase	Piperidine > $\text{Et}_2\text{NH} > \text{i-Pr}_2\text{NH}$
Hindered bases	Bulk on N blocks C-attack	High pK_aH , low N	DIPEA, DBU, TMP

7. Biological and Pharmaceutical Relevance

In biological systems, the same steric and electronic principles apply, but the amine is embedded in an enzyme active site that imposes additional geometric constraints. Two well-studied examples are PLP (pyridoxal-5'-phosphate) dependent transaminases and imine reductases (IREDs). Transaminases form a Schiff base between an active-site lysine and the PLP cofactor and exchange amino groups between amino acids and α -keto acids; the size and shape of the substrate-binding pocket determine which substrates can approach the cofactor (Savile et al., 2010). IREDs and reductive aminases (RedAms) reduce imines and perform formal reductive amination with high enantioselectivity; they have become platform biocatalysts for chiral amine synthesis (Aleku, 2024; Mangas-Sanchez et al., 2017).

The industrial synthesis of sitagliptin (Januvia®) by an evolved (R)-selective ω -transaminase is the iconic example of biocatalytic chiral amine production. The second-generation Codexis process converts a prochiral ketone directly into the chiral primary amine with >99.95% enantiomeric excess at multi-tonne scale (Savile et al., 2010). Similar biocatalytic platforms are now used in the synthesis of many CNS drugs, antivirals, and anti-cancer agents.

In medicinal chemistry, amine basicity and steric bulk are key handles for tuning drug properties. Replacing a methyl group with CF₃ next to an amine lowers basicity, improves metabolic stability, and changes membrane permeability. Constraining a flexible amine into a pyrrolidine or piperidine ring can dramatically increase target affinity by reducing conformational entropy. These design choices are at the heart of lead optimization in drug discovery (Hili & Yudin, 2006; Trowbridge, Walton, & Gaunt, 2020).

Table 2. Comparative pKaH and nucleophilicity of selected amines (Amira et al., 2021; Brotzel et al., 2007; El Abed et al., 2025; Kanzian et al., 2009; Mayr & Patz, 1994; Mayr et al., 2001; Orlandi, Escudero-Casao, & Licini, 2021).

Amine	Class	pKaH (H ₂ O)	N (Mayr)	Reactivity vs PhCHO
NH ₃	primary	9.25	9.6 (H ₂ O)	low
n-BuNH ₂	1° alkyl	10.6	13.4 (H ₂ O)	high
t-BuNH ₂	1° alkyl, hindered	10.7	10.5 (H ₂ O)	low (steric)
Benzylamine	1° benzyl	9.3	13.5 (MeCN)	high
Aniline	1° aryl	4.6	12.6 (MeCN)	moderate
4-MeO-aniline	1° aryl, +M	5.3	13.4 (MeCN)	moderately high
4-NO ₂ -aniline	1° aryl, -M	1.0	~10 (est.)	very low
Et ₂ NH	2° acyclic	11.0	15.1 (MeCN)	high
Piperidine	2° cyclic	11.2	17.4 (MeCN)	very high
Morpholine	2° cyclic, β -O	8.4	15.6 (MeCN)	high
i-Pr ₂ NH	2° hindered	11.0	13.4 (MeCN)	moderate
Et ₃ N	3° acyclic	10.7	—	no C–N adduct with C=O
L-Proline	2° cyclic, bifunct.	10.6	~18 (DMSO)	iminium/enamine catalyst

8. Computational and Modern Approaches

Density Functional Theory (DFT) is now the standard tool for studying amine addition mechanisms. Functionals such as M06-2X and ω B97X-D, combined with PCM or SMD solvent models, reproduce experimental rate constants within an order of magnitude. Including one or two explicit water molecules in the QM region is essential for modeling imine formation in aqueous solution, because water acts as a proton shuttle in the rate-limiting step (Ding, Cui, & Li, 2015; Farooq & Ngaini, 2020).

Hammett-type correlations remain a powerful tool for analyzing substituent effects in aromatic amines. The Yukawa–Tsuno extension introduces a resonance-demand parameter r^+ that helps distinguish between resonance- and induction-dominated transition states. Conceptual DFT provides further descriptors: the global nucleophilicity index ω^{-1} and the local Fukui function $f^-(r)$ at nitrogen identify the most nucleophilic atom and predict the order of reactivity within a family (Domingo, Ríos-Gutiérrez, & Pérez, 2016; Orlandi et al., 2021).

Machine learning has recently entered the field. Multivariate regression on Mayr's database of 341 nucleophiles by Orlandi and coworkers identified proton affinity, solvation free energy, and a steric metric as the three dominant predictors of N (Orlandi et al., 2021). Graph neural networks and transformer models trained on reaction databases now achieve respectable performance on yield and selectivity prediction for amine-forming reactions (Coley et al., 2019; Schwaller, Vaucher, Laino, & Reymond, 2021). These tools complement, rather than replace, the classical conceptual frameworks discussed above.

9. Industrial Applications

Amine synthesis is one of the largest single activities in fine-chemical manufacture. The principal industrial routes are: (i) reductive amination of carbonyls with hydride or H_2 ; (ii) Buchwald–Hartwig and Ullmann amination for aryl C–N bonds; (iii) biocatalytic transamination and imine reduction for chiral amines; and (iv) asymmetric hydrogenation of N-acyl imines and enamides (Afanasyev et al., 2019; Aleku, 2024; Cabré, Verdaguer, & Riera, 2021; Mangas-Sanchez et al., 2017; Murugesan et al., 2020; Savile et al., 2010).

Green-chemistry considerations are reshaping the field. Hydrogen-borrowing amination uses alcohols instead of alkyl halides as alkylating agents and produces water as the only byproduct (Cabré et al., 2021; Irrgang & Kempe, 2019). Heterogeneous base-metal catalysts (Ni, Co, Mn) developed primarily by the Beller group have largely replaced precious-metal catalysts for many reductive amination processes (Murugesan et al., 2020). Continuous-flow chemistry has reduced solvent consumption and improved heat transfer in industrial-scale runs. Biocatalytic methods operate in water and achieve enantioselectivities that are difficult to match by purely chemical means (Aleku, 2024; Mangas-Sanchez et al., 2017; Savile et al., 2010).

10. Conclusions

Steric and electronic effects together determine the nucleophilic behavior of amines. Electronic effects (induction, resonance, hyperconjugation) control how readily the nitrogen lone pair donates electrons; steric effects control how easily that lone pair can reach an electrophilic carbon. The two factors are coupled: most structural changes modify both at once. Modern reactivity scales such as Mayr's N parameter integrate the two contributions into a single quantitative descriptor and provide predictive rate constants over more than 30 orders of magnitude.

Three directions are likely to shape the next decade. First, machine-learning models trained on large reaction datasets are starting to replace explicit DFT for routine reactivity prediction, allowing real-time synthesis planning. Second, biocatalysis (transaminases, imine reductases, amine dehydrogenases) is rapidly closing the substrate-scope gap with chemocatalysis and is becoming the method of choice for

chiral amines at industrial scale. Third, photoredox and electrochemical methods are opening single-electron-transfer mechanisms for C–N bond formation that are inaccessible to polar chemistry. In every case, the classical principles of steric and electronic control remain the conceptual framework what changes is the precision with which we can manipulate them.

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