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ON THE COVER

Iris Sung '27

Technological evolution is a constant guessing game. It happens organically, crossing between disciplines, and is so complex and dynamic that it never comes fully into frame. Rather, parts come into and out of focus, as the terrain of technological development continues to shift. And, the dynamic ambiguity is such that it only reaches full resolution when it is realized.

BEST MANUSCRIPT

Diana Nichvoloda '27 is a junior from Boonton, New Jersey, studying Economics and Philosophy with language citations in Ukrainian and Chinese. Her academic interests include political economy, immigration, labor economics, and development and post-conflict reconstruction. Outside of academics, Diana works at the Harvard Ukrainian Research Institute and also enjoys running, skiing, and learning languages.

FROM THE EDITORS

April 2026

Dear Harvard Community,

We are delighted to present the Spring 2026 issue of *The Harvard Undergraduate Research Journal* (THURJ), a student-run, biannual publication committed to showcasing and celebrating exceptional research from Harvard undergraduates of all disciplines and interests.

Founded in 2007, THURJ established itself as a hub for undergraduate research until the COVID-19 shutdown. Revived in Fall 2023 under Editor-in-Chief Ellie Shin '25, it released its first post-pandemic print edition. Almost three years later, THURJ is more active than ever and among Harvard's largest undergraduate organizations.

In a time of rapidly accelerating technological change, this semester's theme, *Tech-Driven Evolution*, reflects our belief in the dynamism of research. Alongside increasing globalization, advancements in fields like AI, gene editing, and computing have drastically changed our understanding of the world. Now, more than ever, research crosses borders, jumps disciplines, and charts new frontiers. This semester, to reflect our vision of cutting-edge, interdisciplinary research, we have revamped our peer design workflow, introducing clear, standardized guidelines for peer reviewer comments that mirror the expectations of formal academic journals. In addition, we have expanded our outreach to biotech corporations, startups, and other research-oriented organizations in order to build new partnerships and sponsorship opportunities to support our journal's continued growth.

We extend our gratitude to every member of THURJ for their dedication and commitment, and to our faculty reviewers, whose insights are essential to maintaining the quality of our publications. We also thank our faculty advisor, Dr. Andrew Berry, who embodies our belief in the importance of science communication and research engagement for the next generation of scientists and leaders. Finally, we are grateful to the Department of Science Education, Harvard Medical School, the School of Engineering and Applied Sciences, the Department of Arts and Humanities, and many others for their invaluable support.

In this edition, we feature a broad range of fields, from Ukrainian refugee settlement patterns and hybrid aerial-aquatic vehicles, to the health costs of caregiving and strong gravitational lensing, with three manuscripts of original research by Harvard undergraduates and six insightful commentaries on the cutting edge of research at Harvard and beyond. We hope that you enjoy reading and learning from these excellent pieces as much as we have.

Sincerely,

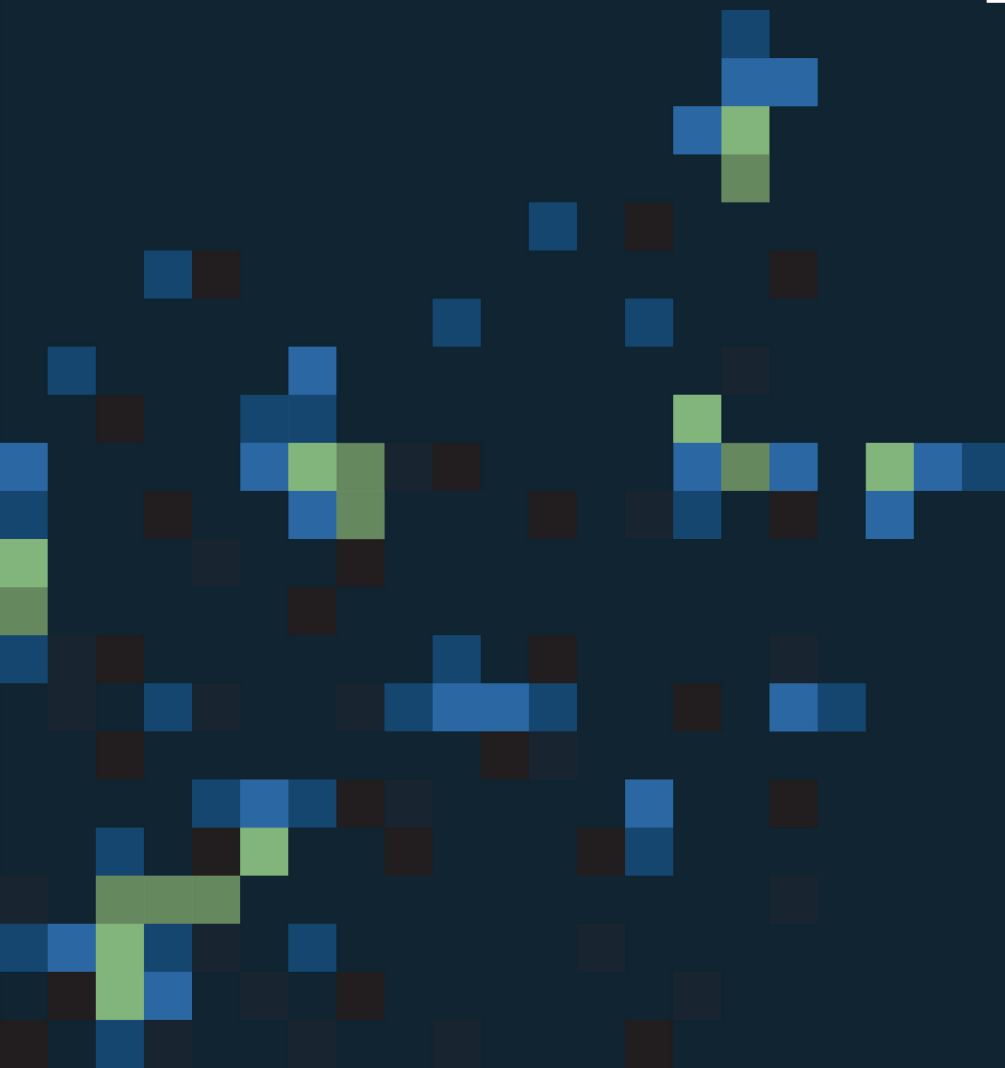


Maria Xu
Editors-in-Chief



Theo Tobel

Research



Distance, Diaspora, and Demographics: Examining Post-2022 Ukrainian Refugee Settlement

Diana Nichvoloda
Harvard College '27

This paper examines what drives Ukrainian refugees' destination choices in the aftermath of Russia's 2022 invasion by analyzing (1) which host country characteristics predict refugee inflows and (2) how refugee demographics relate to distance traveled and the size of host country Ukrainian diasporas. Using OECD, UNHCR, and UNDESA data, we find that geographic distance and preexisting Ukrainian migrant stock are the main determinants of where refugees settle, while macroeconomic and governance indicators play minimal roles. Using microdata from the August 2022 UNHCR Survey, we show that younger, highly educated respondents tend to travel farther, while larger households and those with intact housing remain closer to Ukraine. Refugees from Eastern Ukraine, as well as those expressing an intention to return permanently, tend to settle in countries with larger diasporas. These results highlight the central role of accessibility and preexisting networks, rather than economic opportunity, in shaping the settlement patterns of forced migrants.

Introduction

Russia's invasion of Ukraine during February 2022 triggered the largest refugee crisis in Europe since World War II. Within weeks, millions of Ukrainians—primarily women, children, and the elderly—fled their homes in search of safety, protection, and stability. As of 2025, about 6.8 million refugees remain abroad, with the majority living in European countries such as Poland, Germany, and the Czech Republic, while others made the longer journey to Canada and the United States (United Nations High Commissioner for Refugees, 2025). This unprecedented and sudden movement of people has reshaped many host countries' social and demographic landscapes and has forced them to reconsider their policies on immigration and refugees, integration, and humanitarian support.

In this paper, we attempt to understand how demographic factors, such as age, gender, education, family composition, and language skills, shape the destination choices of Ukrainian refugees. For example, families with young children may prioritize proximity and access to social services, whereas younger or more educated individuals might look for opportunities in countries with stronger labor markets or preexisting diaspora networks. This is important from a policy perspective, as the Russo-Ukrainian War shows no sign of ending, forcing host governments and international organizations to continue to plan housing, education, employment, and welfare services that align with the demographic realities of incoming populations. The composition of refugee flows has a strong influence on their integration trajectories, labor market impacts, and long-term settlement outcomes. Identifying these demographic drivers can help policymakers design more targeted and equitable responses to future refugee crises.

This paper answers two separate, but related questions. The first is, which host country characteristics, such as distance from Ukraine, gross domestic product (GDP) per capita, and

existing Ukrainian diaspora presence, are the most significant in determining the number of Ukrainian refugees that country received in the aftermath of the Russo-Ukrainian War? The second is, given that distance and existing diaspora presence are the most significant predictors of refugee inflows, how are refugee demographics, such as age, education, and household size, related to these factors? In other words, which kinds of refugees choose further versus closer countries, and which ones choose countries with a larger versus smaller diaspora presence?

Literature Review

A large body of research examines the determinants of international migration flows, particularly through the lens of two common models: gravity models and network theory. In gravity models of migration, flows are shaped by geographic distance, economic incentives, and migrant networks (Beine et al., 2016; Mayda, 2010). Distance increases the financial and informational costs of migration, while higher income levels and employment opportunities in destination countries attract migrants. The importance of migrant networks is also well established in the migration literature. The presence of earlier migrants from the same origin country reduces the financial and informational costs of migration by providing housing assistance, job referrals, and guidance on legal procedures. These networks also appear to reduce uncertainty about conditions in the destination and facilitate labor market integration upon arrival. Over time, this process generates “cumulative causation,” whereby each additional wave of migrants increases the likelihood of future migration to the same destination (Massey et al., 1993).

However, an important debate in the literature concerns whether the same mechanisms that apply to economic migrants also apply to forced migrants. While economic pull factors play a central role in voluntary migration decisions, research on asylum

seekers and refugees suggests that push factors and accessibility constraints often dominate forced migrants' decisions (Hatton, 2009; Neumayer, 2004). For example, refugees often prioritize geographic proximity and immediate safety over income maximization. Empirical studies of asylum flows to Europe find that distance and prior asylum applications are among the strongest predictors of refugee destinations, while GDP per capita and unemployment rates play weaker roles (Di Iasio and Wahba, 2023; Neumayer, 2004).

Within this broader debate, research on Ukrainian displacement following Russia's 2022 invasion has documented strong correlations between preexisting diaspora networks and refugee settlement patterns within Europe. Minora et al. (2022) and González-Leonardo et al. (2024) show that EU countries with larger pre-war Ukrainian diasporas received disproportionately large refugee inflows. Using both official statistics and digital connectivity measures such as Facebook's Social Connectedness Index, these studies argue that established migrant communities play a central role in shaping refugee settlement patterns.

At the same time, research on migrant self-selection suggests that migration is rarely random, even under conditions of forced displacement. Classical selection models (Borjas, 1987) predict that individuals differ in their ability and willingness to migrate depending on their human capital and migration costs. More recent work shows that refugees are also selectively distributed across destinations based on education, financial resources, and language skills (Aksoy and Poutvaara, 2021). In the Ukrainian context, van Tubergen et al. (2024) find that higher education, financial resources, and English proficiency are associated with relocating to more distant countries, while family structure and region of origin shape mobility patterns.

Despite these advances, two gaps remain in the literature. First, most existing studies of Ukrainian refugees focus exclusively on settlement patterns within Europe. Yet, the United States and Canada have emerged as major destinations for Ukrainian refugees through humanitarian parole and sponsorship programs. It is still unclear whether the determinants of refugee destination choice observed within Europe, particularly the dominance of distance and diaspora networks over economic factors, extend to transatlantic destinations. Second, while prior work documents the aggregate importance of diaspora size, less attention has been paid to how refugee demographics shape selection into geographically distant destinations versus diaspora-rich destinations.

This paper contributes to the broader literature on refugee destination choice by situating Ukrainian displacement within these theoretical debates. It examines whether the usual gravity-model mechanisms, distance and migrant networks, are also dominant when expanding the analysis beyond Europe, and which demographic characteristics predict selection into more distant or more network-dense destinations. In doing so, the paper speaks not only to the Ukrainian case, but to broader questions about how forced migrants balance accessibility, network support, and individual constraints when selecting destinations.

Data Sources and Sample Construction

This section describes the data used in this paper and provides relevant visualizations for the two main regressions.

Regression 1

In order to first answer the question how host country characteristics are correlated with the number of Ukrainians that migrate there, we use refugee stock data drawn from the Organisation for Economic Co-operation and Development (OECD) International Migration Database (2023 edition), specifically the table "Displaced persons from Ukraine in OECD countries," which shows the number of refugees from Ukraine in OECD countries as of June 2023, and draws on datasets collected by the UN Refugee Agency (UNHCR), Eurostat, The United Kingdom's Home Office, and the Immigration, Refugees and Citizenship Office of Canada. Due to the availability of data and geographic proximity to Ukraine, we choose to focus only on Ukrainian migrants to OECD countries. We drop New Zealand from the dataset since no Ukrainian migrants settled there, leaving us with 33 countries. A plot of the number of refugees in each country is shown in Figure 1A, as well as a map showing their geographic distribution (Fig. 1B).

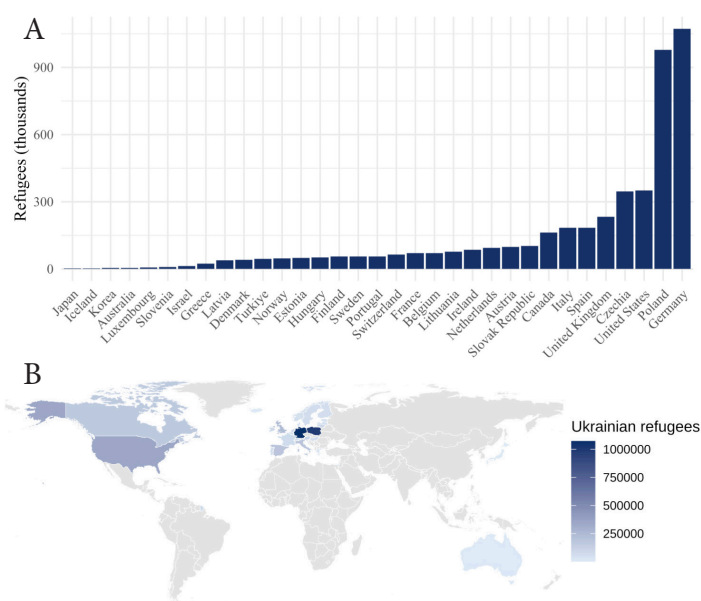


Figure 1. (A) Number of Ukrainian Refugees by Host Country. (B) Distribution of Ukrainian Refugees by Host Country (data as of June 2023).

The bar chart ranks OECD countries by the number of Ukrainian refugees hosted as of June 2023, showing a highly uneven distribution: Germany and Poland received the largest inflows, while most other countries hosted comparatively small numbers. The map depicts the geographic concentration of refugee settlement, with darker shading indicating higher refugee counts. Together, the figures demonstrate that Ukrainian refugees are disproportionately concentrated in a small set of primarily European and North American host countries.

We merge the data on the number of Ukrainian refugees by country with the GeoDist dataset from the Centre d'Etudes Prospectives et d'Informations Internationales (CEPII), which provides the bilateral geographic distance between pairs of countries' capitals in miles. For each OECD host country, we extract the distance between Kyiv (Ukraine's capital) and the capital city of the host country. Distance is measured in miles and log-

transformed in the regression specification to reflect diminishing marginal effects of distance on migration costs.

We also add datasets from the World Bank that show each host country's purchasing-power-parity adjusted GDP per capita, overall unemployment rate, and inflation rate. The unemployment rate we use is provided by the International Labor Organization (ILO), which uses modeled estimates where national data are missing, ensuring better cross-country comparability. Years 2020-2021 are excluded from the baseline average due to global pandemic-related economic volatility that was unrelated to Ukrainian displacement. Including them would risk conflating pandemic shocks with refugee-attractiveness fundamentals. The final macroeconomic and labor market variables are constructed as the average of 2018-2019 and 2022-2023 values, ensuring that they reflect both structural pre-war conditions and early-war host-country contexts while minimizing distortion due to the pandemic.

As a measure of preexisting Ukrainian diaspora presence, we use the United Nations Department of Economic and Social Affairs (UN DESA) International Migrant Stock Dataset (2020 Revision). This dataset provides the total number of international migrants by sex, as well as their places of origin and destination, for 233 countries and areas in the period from 1990 to 2024. We isolate the stock of Ukrainian-origin migrants in the 33 OECD countries of interest in the years 1990, 1995, 2000, 2005, and 2010, then use the average of the stocks as a proxy for Ukrainian diaspora presence. To avoid conflating pre-war diaspora networks with displacement caused by the 2014 annexation of Crimea and conflict in Donbas, we use 2010 as the cutoff point. Including 2015-2020 data would incorporate migration flows partially driven by conflict-related displacement, thereby biasing the diaspora measure toward mechanically predicting 2022 flows. A visualization of the Ukrainian diaspora presence is shown in Figure 2.

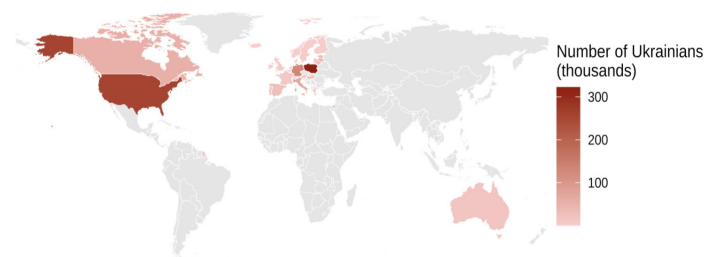


Figure 2. Average Number of Ukrainian Migrants by Destination Country, 1990–2010.

Compared to the contemporary refugee patterns shown in Figure 2, the preexisting Ukrainian diaspora is more heavily concentrated in North America and in a smaller set of European countries. Despite this, the historical distribution of the Ukrainian migrants still closely mirrors the present-day locations receiving the largest refugee inflows, suggesting strong continuity in migration networks over time.

Lastly, we add measures of host country institutional quality using the World Bank Worldwide Governance Indicators (WGI). These measures are produced by the World Bank and report on six broad dimensions of governance for over 200 countries over the period 1996-2023. The six WGI measures are Control of Corruption (CC), Government Effectiveness (GE), Political

Stability and Absence of Violence/Terrorism (PV), Rule of Law (RL), Regulatory Quality (RQ), and Voice and Accountability (VA). These indicators are based on over 30 underlying data sources, which include country-level surveys of households and firms and data collected by NGOs and public sector organizations, which are then rescaled and combined to create the aggregate indicators. Since the six indicators are highly correlated for each individual country, we merge them into one aggregate Democracy Indicator by averaging each country's percentile ranking for each individual indicator to avoid concerns about multicollinearity. We average the indicators across the years 2018-2023, since they are closest to the year of interest.

Regression 2

In order to address the second question, how refugee demographics are related to the distance and diaspora presence in their host countries, we use the UNHCR Survey of Intentions and Perspectives of Refugees from Ukraine. This survey is a multi-round data collection initiative designed to capture the evolving profiles, living conditions, and intentions of refugees displaced across a subset of European countries, including Belgium, Bulgaria, Czechia, Germany, France, Italy, Lithuania, Moldova, Poland, Romania, Slovakia, Spain, and Turkey. We were able to gain access to five of the six surveys: wave 2, conducted in September 2022, wave 3, conducted in February 2023, wave 4, conducted in June 2023, wave 5, conducted in Feb 2024, and wave 6, conducted in August 2024.

All rounds employ a core questionnaire covering household demographics, socioeconomic and protection conditions in host settings, access to housing, education, employment, and social services, and intentions regarding return to Ukraine. The data was collected using phone-based surveys, web-based surveys, and face-to-face interviews. We decided to use wave 2 of the survey for our regression, since it was the closest temporally to the outbreak of the Russo-Ukrainian War in February 2022, and best captures first-wave displacement patterns before substantial secondary migration and adaptation occurred.

In order to measure the geographic extent of displacement for each household, we construct a continuous travel distance variable linking the household's Ukrainian origin oblast to their current host country. Because the survey does not provide the exact coordinates of refugees' residences, we approximate displacement distance as follows: we assign each Ukrainian oblast the latitude and longitude of its administrative capital, and each host country the coordinates of its national capital. Then, we use the Haversine formula (via the R *geosphere* package) to compute the distance between origin and destination. The distance is measured in miles and log-transformed in regression models. While this standardized distance measure does not capture exact migration routes, it is a close proxy that can be used to compare relative displacement among different refugee groups.

We define key demographic characteristics from the UNHCR survey data. Due to the way in which the survey data was collected, Age, Education, Employment, Status of Dwelling, Gender, and Region are all categorical variables. We group survey participants into three categories by age (18-34, 35-59, and 60+) and group the survey's detailed education categories into two broad educational

attainment levels: Secondary Education and Higher Education. Similarly, we consolidate the survey's detailed "Status of Dwelling" categories into three categories: "Intact," "Partially damaged," and "Fully destroyed," and employment categories into Employed, Unemployed, Education/Training, and Missing/Other. We classify the region of origin in Ukraine into Central, East, South, North, and West, with "Kyiv city" observations assigned to the Central region.

We also create an indicator variable, "Return Permanently," which takes the value 1 if the refugee answered that they plan to return permanently to Ukraine for any of the 22 reasons listed on the survey. Similarly, we create indicator variables that take the value 1 if survey participants report speaking English and Russian, respectively. More information about variable definitions and coding can be found in the Appendix.

The only continuous variables we use are distance traveled and household size. Tables of summary statistics for continuous and categorical data are reported in Table 1.

A				B			
Variable	Category	Count	Percent	Variable	Category	Count	Percent
Age	18-34 yrs	120	26.20	Gender	Female	408	89.08
	35-59 yrs	288	62.88		Male	50	10.92
	60+ yrs	50	10.92	Region	Central	87	19.00
Education	Higher education	310	67.69		East	173	37.77
	Secondary education	146	31.88		North	41	8.95
	NA	2	0.44		South	131	28.60
Employment	Education/Training	22	4.80		West	26	5.68
	Employed	121	26.42	Return permanently	No	427	93.23
	Missing/Other	181	39.52		Yes	31	6.77
	Unemployed	134	29.26				

Table 1. Wave 2 Summary Statistics. (A) Continuous variables. (B) Categorical variables.

According to Table 1, respondents in Survey 2 traveled an average of 612 miles from their origin, though the large standard deviation (372 miles) indicates substantial heterogeneity. Household size averaged 2.9 members, with relatively small variation. The sample consists of 89% women, since men aged 18-60 are generally barred from leaving Ukraine under martial law, which is why we do not include gender in the regression. Most respondents are between 35 and 59 years old (63%), while younger adults represent 26% of the sample and older adults (60+) just 11%. Educational attainment in the sample is relatively high: 68% of respondents hold higher education degrees. Geographically, the sample has respondents originating from all major regions of Ukraine. The East constitutes the largest share (38%), followed by the South (29%) and Central regions (19%). The North and West account for smaller proportions of the sample, which is expected since the active war is taking place primarily in the East and South of the country. Only 6.8% of respondents report planning to return permanently to Ukraine.

Although UNHCR does not provide any statistics regarding the proportion of people who chose to respond to the survey, it is important to acknowledge that sampling bias may be present. Individuals who were more technologically connected or more engaged with local networks may have been more

likely to participate, so it is possible that respondents with higher educational attainment or stronger social resources are overrepresented in the sample. Similarly, those facing the greatest barriers - such as elderly individuals or households in financial distress - may be underrepresented because they were less able or willing to complete the survey.

Regressions and Results

In order to answer the two questions this paper poses, we run two Ordinary Least Squares (OLS) regressions, which we will describe separately.

Regression 1

The first regression determines which host country characteristics are most important in determining the number of Ukrainian refugees who move there. Because the distances to the USA, Canada, and Australia are so large, we use the log of the distance in the regression. For the same reason, we use the log of the number of migrants. The regression equation and descriptions of the terms are as follows:

$$\log(\text{Refugees})_i = \beta_0 + \beta_1 \log(\text{Distcap})_i + \beta_2 \text{Inflation}_i + \beta_3 \text{GDP}_i + \beta_4 \text{Unemployment}_i + \beta_5 \text{Migration Stock}_i + \beta_6 \text{Democracy Indicator}_i + \varepsilon_i$$

- $\log(\text{Refugees})_i$ is the log number of Ukrainian refugees in each country
- $\log(\text{Distcap})_i$ is the log of the distance between the host country's capital and Ukraine
- Inflation_i is the average inflation rate in each country, 2018-2019 and 2022-2023
- GDP_i is the average GDP converted by purchasing power parities in each country, 2018-2019 and 2022-2023
- Unemployment_i is the average overall unemployment rate in each country, 2018-2019 and 2022-2023
- Migration Stock_i is the average migration stock in each country, 1990-2010
- $\text{Democracy Indicator}_i$ is the average Democracy Indicator in each country, 2018-2023
- ε_i represents the error term.

The results of the regression are shown in Table 2.

The regression results indicate that log distance between countries' capitals and existing Ukrainian migrant stock are the two strongest predictors of current refugee inflows. The coefficient on log distance is statistically significant ($p < 0.01$), implying that a 10% increase in distance from Ukraine is associated with a 7.6% decrease in expected refugee arrivals, holding other factors constant. Therefore, distance appears to act as a barrier to refugees' relocation to host countries. The estimated coefficient on Ukrainian migrant stock is also significant ($p < 0.001$) and implies that an additional 1,000 members of the Ukrainian diaspora in a host country is associated with a 1.3% increase in refugee inflows. This pattern is suggestive of network effects: refugees tend to settle where prior Ukrainian communities already exist, which can offer assistance with housing and job search.

The macroeconomic and institutional variables included in the model do not exhibit statistically meaningful relationships

Term	Estimate	Std. Error	t-statistic	p-value
(Intercept)	11.070307	3.804608	2.9097	0.0073
Distance from Ukraine	-0.758925 **	0.257269	-2.9499	0.0066
Inflation	0.042064	0.044448	0.9464	0.3527
GDP	-0.000006	0.000018	-0.3372	0.7387
Unemployment	0.137687	0.090694	1.5181	0.1410
Migration Stock	0.000013 ***	0.000003	4.6295	0.0001
Democracy Indicator	0.048988	0.034840	1.4061	0.1715

, and * denote significance at the 5% and 1% levels, respectively.

Table 2. Determinants of Log Refugee Inflows.

with refugee inflows. The coefficients on inflation (0.042), GDP per capita (−0.000006), unemployment (0.138), and democratic quality (0.049) are all statistically insignificant, indicating that these features of host-country environments are not statistically associated with refugee destination patterns once distance and migrant networks are accounted for. This suggests that Ukrainian refugees are not systematically choosing countries based on economic opportunity or institutional quality, which is consistent with the fact that most refugees are forced to migrate and do not face the same conditions as typical economic migrants.

Regression 2

Given that the host country’s distance from Ukraine and preexisting Ukrainian diaspora are the most important characteristics determining the number of Ukrainian refugees that

settle there, the second regression determines the demographic characteristics that are predictive of migrants preferring to move longer/shorter distances, or to areas with larger/smaller existing diasporas. The first regression we run is as follows:

Regression 2a: Predicting Distance

$$\log(\text{Distance}) = \beta_0 + \beta_1 \text{Age}_i + \beta_2 \text{Education}_i + \beta_3 \text{Household Size}_i + \beta_4 \text{Employment}_i + \beta_5 \text{Region}_i + \beta_6 \text{Return Permanently}_i + \beta_7 \text{Dwelling Status}_i + \beta_8 \text{Speak Russian}_i + \beta_9 \text{Speak English}_i + \epsilon_i.$$

The results of the regression are shown in Table 3.

According to Table 3, the coefficient on Age (35-59 years) is negative and significant, meaning that respondents aged 35–59 tend to travel approximately 3% less distance than the reference category, adults aged 18–34. Similarly, individuals aged 60 and older travel 7.5% less distance. This suggests that young adult refugees are the most mobile, which may reflect greater family obligations, employment, or health constraints among middle-aged and older adults. As compared to respondents with only secondary education, those with higher education travel roughly 3.5% farther, which can be explained by the fact that higher education is associated with greater mobility and independence, potentially reflecting expanded professional networks, job opportunities, and access to resources. Also, each additional household member is associated with 0.8% less distance traveled, which may reflect the fact that larger households face higher logistical and financial barriers to moving long distances, though this effect is not statistically significant.

The results of the regression show that unemployed respondents travel 15.9% more distance than the reference category, who are employed in their destination country. Respondents currently in education or training travel 13.4% more distance. A possible

Predictor	Coefficient	Robust SE	p-value	Predictor	Coefficient	Robust SE	p-value
Age				Status of Dwelling			
35–59 yrs	-0.0297	0.0158	0.0598	Intact	-0.2736	0.0432	0.0000**
60+ yrs	-0.0749	0.0271	0.0058**	Partially damaged	-0.1643	0.0478	0.0006**
Education				Unknown	-0.1460	0.0448	0.0011**
Higher education	0.0354	0.0157	0.0239*	Return permanently	-0.0386	0.0209	0.0647
Household size	-0.0083	0.0050	0.0962	Speaks Russian	0.0961	0.0215	0.0000**
Employment				Speaks English	0.0188	0.0163	0.2481
Unemployed	0.1589	0.0182	0.0000**				
Education/Training	0.1336	0.0324	0.0000**				
Missing/Other	0.1661	0.0188	0.0000**				
Region							
East	0.2932	0.0196	0.0000**				
South	-0.0820	0.0237	0.0005**				
North	0.0086	0.0258	0.7389				
West	-0.5058	0.0258	0.0000**				

* denotes significance at the 5% level; ** denotes significance at the 1% level.

Table 3. Demographic Determinants of Distance Traveled.

Predictor	Coefficient	Robust SE	p-value	Predictor	Coefficient	Robust SE	p-value
Age				Status of Dwelling			
35–59 yrs	0.0353	0.0424	0.4045	Intact	0.6791	0.1165	0.0000**
60+ yrs	0.0729	0.0730	0.3182	Partially damaged	0.4395	0.1290	0.0007**
Education				Unknown	0.4532	0.1209	0.0002**
Higher education	0.1128	0.0422	0.0075**	Return Permanently	0.1200	0.0563	0.0332*
Household size	0.0360	0.0134	0.0071**	Speaks Russian	-0.1101	0.0574	0.0552*
Employment				Speaks English	0.0780	0.0438	0.0751*
Unemployed	-0.1496	0.0490	0.0023**				
Education/Training	-0.0774	0.0866	0.3712				
Missing/Other	-0.4926	0.0506	0.0000**				
Region							
East	0.0962	0.0529	0.0691*				
South	-0.2428	0.0640	0.0002**				
North	-0.0108	0.0697	0.8767				
West	-0.0502	0.0678	0.4591				

* denotes significance at the 5% level; ** denotes significance at the 1% level.

Table 4. Demographic Association with Host-Country Diaspora.

explanation is that respondents without stable jobs tend to travel farther in search of future job opportunities. However, reverse causality may also play a role, as those refugees whose living conditions are highly volatile may find it more difficult to secure stable employment.

Relative to the omitted Central region, migrants from the Eastern region of Ukraine tend to travel 29% more distance. Though part of this large effect comes from Eastern Ukraine simply being geographically farther from Europe than the other regions, Ukraine is not so large that this would explain the entire effect. Since Russia invaded Eastern Ukraine in 2014, long before the 2022 full-scale invasion, Eastern Ukrainians have experienced the devastation of war for longer than residents of the other regions, which may help explain why they would travel further distances if the opportunity to migrate presents itself. Conversely, those from the South travel 8.2% less distance, and those from the West travel 50.6% less distance. This effect can be explained given that these regions are minimally affected by the war, and are also geographically closer to Europe.

Relative to refugees whose dwellings in Ukraine that were completely destroyed, those with intact housing travel 27.3% less distance, those with partially damaged housing travel 16.4% less distance, and those with unknown dwelling status travel 14.6% less distance. This supports the idea that a remaining hope of saving their home causes people to stay closer to their place of origin, while those with nothing to return to are quicker to cut ties with their previous residence.

We add indicator variables only for Russian and English to the regression, since nearly all respondents reported speaking Ukrainian. Due to the widespread belief in the former Soviet Union that knowing Russian would open more doors than knowing Ukrainian, we were interested in whether refugee movement patterns in 2022 still reflect this belief. It seems that they do, as Russian speakers travel 9.6% more distance than those who do not speak Russian. However, this may also be due to many

of the destination countries being in the sphere of influence of the former Soviet Union, and so having a relatively large Russian-speaking population, making Russian knowledge an advantage for refugees.

After examining how demographic factors are correlated with the distance traveled by refugees, we look at how these factors are associated with the size of the diaspora in the host country in the second regression.

Regression 2b: Predicting Diaspora Association

$$\log(\text{Average Migrant Stock}) = \beta_0 + \beta_1 \text{Age}_i + \beta_2 \text{Education}_i + \beta_3 \text{Household Size}_i + \beta_4 \text{Employment}_i + \beta_5 \text{Region}_i + \beta_6 \text{Return Permanently}_i + \beta_7 \text{Dwelling Status}_i + \beta_8 \text{Speak Russian}_i + \beta_9 \text{Speak English}_i + \epsilon_i$$

The results of the regression are shown in Table 4.

According to Table 4, neither of the age categories produce significant effects, showing that there is essentially no difference in diaspora size preference among the three different age groups. On the other hand, the coefficients on higher education are significant, meaning that higher-educated respondents reside in countries with diaspora communities that are approximately 11.3% larger as compared to secondary-educated respondents, likely due to greater connections, resources, or preferring destinations with large skilled migration flows. Also, each additional household member corresponds to 3.6% larger diaspora destinations on average, showing that larger families tend to prefer destinations with larger Ukrainian diasporas, perhaps due to the greater community support they are able to receive.

Compared to the omitted category, which is migrants employed in their host country, unemployed migrants settle in countries with 15% smaller diaspora populations, while those who chose not to report their employment status settle in countries with 49.0% smaller diasporas. This may reflect employment status constraining people's residence choices,

but it is also possible that reverse causality is at work here - perhaps those who moved to countries with smaller Ukrainian diasporas were unable to find the connections they needed to help them find employment.

Compared to refugees coming from Central Ukraine, refugees coming from Eastern Ukraine travel to locations with countries with diasporas about 9.6% larger (though this effect was not statistically significant), while refugees from Southern Ukraine travel to locations with 24% smaller diasporas. There are no significant differences for Northern- or Western-origin refugees. This is likely due to the fact that ever since 2014, the conflict in Donetsk and Luhansk contributed to large-scale displacement from Eastern regions, creating substantial pre-war diaspora communities in many of the countries that received refugees during the 2022 war. A longer history of migration and existing strong networks abroad would explain why Eastern Ukrainians tend to travel to locations with larger diasporas. The reason for Southern migrants mostly moving to countries with smaller Ukrainian diasporas is harder to explain. Part of it is due to Russia's 2014 annexation of Crimea triggering a large initial wave of migration which had mostly dissipated by the time of the 2022 war, meaning that the refugees who stayed behind in 2014 and left in 2022 are likely to be systematically different from refugees in other regions, who are leaving their homes for the first time in 2022.

The coefficients on dwelling status indicate that respondents living in intact or partially damaged dwellings, as well as those reporting unknown housing conditions, are all significantly more likely to choose destination countries with larger Ukrainian diasporas. Specifically, relative to those with completely destroyed homes, individuals with intact homes settle in destinations where the Ukrainian diaspora is 68% larger, while individuals with partially damaged homes and those whose home status is unknown settle in destinations where the diaspora is 44 and 45% larger, respectively. Several mechanisms may explain this pattern. It is possible that people with intact or moderately damaged homes had greater financial resources or stability at the onset of displacement, enabling them to reach major diaspora hubs, which can be costlier but offer stronger institutional and community support. Second, those reporting "unknown" dwelling status likely experienced more chaotic or sudden displacement, but still ended up in established diaspora destinations because they offered clearer pathways for assistance, housing, and integration. In contrast, those coming from fully destroyed dwellings are less likely to end up in countries with large Ukrainian communities. This is explained by the fact that total destruction of housing and the immediate displacement it causes leaves families with little time or capacity to plan longer, more expensive journeys to well-known diaspora destinations. Instead, these individuals may evacuate to closer, randomly-chosen destinations. Households facing the most severe destruction may also face greater financial hardship, limiting their ability to afford travel to destinations with large diasporas abroad.

Expressing the intention to return to Ukraine permanently is associated with living in host countries whose Ukrainian communities are about 12% larger than those of people who

do not intend to return permanently. A possible explanation for this is that individuals who see their stay abroad as temporary may deliberately choose destinations where there is a strong, established Ukrainian community that offers cultural familiarity and easier access to Ukrainian-language services. It is also possible settling in locations with large Ukrainian diasporas and constantly being surrounded by their native culture may cause migrants to miss their home country more, leading them to express a greater intention to return to Ukraine permanently.

Russian-speaking Ukrainians settle in host countries whose Ukrainian diaspora size is roughly 11% smaller than that of non-Russian speakers, which is in line with the stigma that the current war has brought to speaking the "occupier's language." In contrast, English speakers settle in countries with Ukrainian diaspora populations that are 7.8% larger than those of non-English speakers. This is due to the fact that migrants who know English tend to be more highly educated and have greater access to social and employment networks.

While many of these findings align with earlier research on Ukrainian refugee settlement within Europe, this analysis adds to the literature by examining how individual demographic differences shape both how far refugees travel and the types of destinations they choose, particularly in terms of existing diaspora communities, within a single integrated framework.

Conclusion

This study examines the determinants of Ukrainian refugee movements following Russia's full-scale invasion, focusing on two separate but related dimensions. The first part of the paper determines the association between host-country characteristics and the number of Ukrainian refugees the countries received, finding that geographic distance and preexisting Ukrainian migrant communities are most important in determining refugee inflows from the current war. Refugees overwhelmingly relocate to countries that are geographically proximate and already home to substantial Ukrainian diasporas, while macroeconomic and institutional variables such as inflation, GDP per capita, unemployment, and democratic quality, are secondary to their decision. These findings highlight that for refugees, accessibility and the presence of established migrant networks matter more than economic incentives or institutional characteristics that typically drive voluntary migration.

The second part of the paper clarifies which demographic factors influence Ukrainian refugees to travel farther and which cause them to settle in host countries with larger existing diasporas. Younger age and higher education is associated with greater movement, suggesting that these types of refugees have greater access to resources and opportunity. Regional differences in movement strongly mirror the conditions of the war: Eastern-origin migrants, who have experienced armed conflict the longest, travel farther and tend to relocate to countries with larger diasporas, whereas Northern and Western-origin migrants settle in closer destinations with smaller Ukrainian communities. Employment status also plays a major role. Migrants who were able to find stable employment in their host countries relatively quickly travel less, while unemployed or irregularly employed respondents travel

farther distances but ultimately tend to settle in countries with smaller diasporas, reflecting the hardships migrants face when lacking stable employment or social services.

Together, these results show that Ukrainian refugee trajectories are shaped by a combination of structural constraints, existing migration networks, and individual demographic characteristics. Forced migrants do not face the same conditions as economic migrants; their observed settlement patterns are more closely aligned with geographic accessibility and availability of support, rather than economic opportunities. Understanding these complex dynamics is essential for designing policies that support these vulnerable populations of migrants in the face of relentless conflict.

Appendix

Education Categories

- The survey categories “Secondary”, “No education”, “Primary”, “Lower”, “Technical or Vocational”, “Specialization” are merged into a category called “Secondary Education”
- The survey categories “Bachelor”, “Master”, “Doctorate”, “Master or Doctorate” are grouped into a category called “Higher Education.”

Housing Status Categories

- The survey categories “Partially damaged/destroyed but uninhabitable” and “Partially damaged/destroyed, but habitable” are labeled as “Partially damaged”
- The survey category “Fully damaged/destroyed” is labeled as “Fully destroyed.”

Employment Categories

- The survey categories “Employed”, “Self-employed/ Own-business”, “Supporting family business”, “Formal employment (with a contract/paying social security)”, “In formal employment”, “Informal employment (without a contract/not paying social security)” are labeled as “Employed”
- The survey categories “Unemployed” and “Unemployed, looking for job” are labeled as “Unemployed.”
- The survey categories “Student”, “Full-time student”, “Professional training”, “Professional training/courses”, “Apprentice/Intern/Volunteer” are labeled as “Education/ Training.”
- All other observations are labeled as “Missing/Other.”

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A Tether Management System for Hybrid Aerial–Aquatic Vehicles

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Hybrid aerial-aquatic vehicles have the potential to transform marine ecosystem monitoring, offshore infrastructure inspection, environmental surveying, and search-and-rescue operations by seamlessly transitioning between air and water. However, a persistent challenge limiting submerged operation is maintaining reliable communication: radio-frequency (RF) signals are rapidly attenuated underwater, and acoustic communication suffers from limited bandwidth and high latency. As a result, a tether (a physical cable linking the vehicle to the surface) remains essential for real-time command and data transmission. This work presents the design and implementation of a novel dynamic tether management system that enables continuous remote control of an aerial-aquatic vehicle through a surface buoy. Mounted directly on the vehicle, the system actively regulates tether length using a custom tension-sensing feedback mechanism to keep the buoy at the water surface while preventing excess slack that could entangle the vehicle. The tether system is integrated into a custom-built quadcopter-based platform featuring waterproofed electronics and tiltable thruster arms for underwater thrust vectoring. The complete system was validated in three operational underwater modes: descent, ascent, and horizontal translation. This demonstrated stable communication and tether control throughout. By addressing a critical limitation in underwater remote control, this work advances the design of hybrid platforms capable of precise operation across aerial and aquatic environments.

Introduction

Unmanned underwater vehicles such as remotely operated vehicles (ROVs) are typically controlled from a surface station via a tether, which transmits operator commands, telemetry, and in some cases power (Christ & Wernli, 2011). Real-time operator control is required for a range of demanding applications, including deep-sea exploration, pipeline inspections, and military operations (Bogue, 2015; Izadi Moud et al., 2018; Fun Sang Cepeda et al., 2023). The tether is usually designed to be neutrally buoyant to minimize the force exerted on the vehicle (INVOCEAN Group, 2025). More recently, broader reviews of unmanned underwater vehicles have contextualized ROVs within the growing ecosystem of hybrid and autonomous platforms, emphasizing communication, energy efficiency, and multi-domain operation as emerging design frontiers (Xu et al., 2024). Surveys of inspection-class underwater vehicles further highlight the key design considerations of tethered vehicles, including propulsion, buoyancy, and telemetry subsystems (Capocci et al., 2017).

Transmitting operator commands via a physical tether is essential because radio-frequency (RF) signals are rapidly attenuated in water. For example, at 915 MHz, the effective penetration depth in seawater is only 1–2 cm (Smolyaninov et al., 2018), making wireless communication infeasible for submerged vehicles. As a result, tethered communication remains the most reliable method for maintaining a control link during underwater operation.

However, the need for a tether creates significant challenges. The tether restricts mobility due to limited length, and the reaction forces it transmits can introduce random perturbations to the vehicle. Although longer or thinner tethers can partially alleviate these limitations, the presence of any tether prevents the vehicle

from being deployed as conveniently as a purely aerial platform. Hybrid aerial-aquatic vehicles have sought to address the limitations of conventional ROVs by reducing deployment complexity; several designs demonstrate fully submersible vehicles that can fly from a launch point to a distant water entry site before reconfiguring for underwater operation (Zeng et al., 2022; Pedroso et al., 2022; Lyu et al., 2022; Lu et al., 2018). One notable platform, Medusa, uses a quadrotor as a mobile surface base to deploy a tethered underwater pod for sampling missions (Debruyn et al., 2020). The quadrotor lands on the water surface and lowers the pod by releasing a tether from a spool. However, Medusa's underwater pod was constrained by a small payload capacity and relied on water-jet propulsion, resulting in limited speed and efficiency.

Because aerial-aquatic vehicles are also subject to the limitations of underwater RF propagation, most existing platforms operate autonomously once submerged, performing pre-programmed tasks or navigating through pre-configured waypoints (Bovio et al., 2006). While considerable research has focused on cooperative localization and mapping strategies for underwater vehicles, comparatively less attention has been paid to enabling direct, real-time operator-in-the-loop control (O'Neill et al., 2022; Papalia et al., 2022). Although autonomy plays a critical role in underwater robotics, there are important scenarios such as search and rescue and underwater infrastructure inspection where hybrid systems combining autonomous behaviors with real-time operator control are essential for adapting to dynamic uncertainties.

To address this gap, this paper presents a dynamic tether management system that remains docked on the vehicle and enables real-time remote control during submerged operation. The system employs an antenna attached to a floating buoy that remains at the

water surface, conveying communication signals to and from the vehicle via the tether. As the vehicle travels underwater, the buoy tracks the vehicle's motion, remaining positioned above it due to controlled tension in the tether. A concept for a typical deployment is depicted in Figure 1. By integrating the tether management system entirely onboard the vehicle, this design eliminates the need for surface-based infrastructure or ground crew, significantly reducing deployment complexity compared to conventional ROV operations.

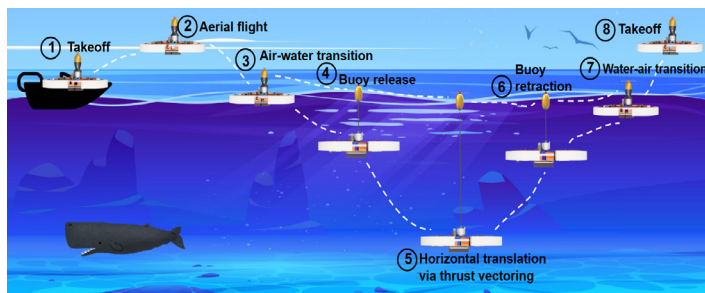


Figure 1. Full deployment and operation workflow: (1–3) aerial deployment and water entry, (4–6) submerged operation with dynamic tether and buoy management, and (7–8) resurfacing followed by aerial recovery.

Hybrid Aerial-Aquatic Vehicle Platform

The vehicle design (Figure 2) is based on a quadcopter frame with front and rear propellers mounted on tiltable arms capable of full 360-degree rotation. This tiltable-arm arrangement constitutes the vehicle's thrust vectoring capability: by rotating the front and rear motor arms independently, the vehicle can redirect its thrust vector in one dimension (pitch axis), enabling the same propellers to generate both lift in air and downforce underwater. This configuration is referred to herein as an "H-tilt" thruster layout because the two tilt axes and the vehicle body form an H-shaped kinematic structure when viewed from above. The same motors and propellers are used for both aerial and underwater propulsion. Underwater, the motors reach their maximum power output at only 40% throttle command due to the increased hydrodynamic load on the propellers and the current limitations of the electronic speed controllers. This results in a maximum underwater thrust of approximately 50% of the thrust generated in air, corresponding to approximately 9.8 N per propeller underwater, determined experimentally. As a result, motor commands for underwater control are scaled by a factor of 0.4 to ensure operation remains within the controller's safe and effective range.

The airframe is constructed from custom-machined carbon fiber plates and tubes, chosen for their high strength-to-weight ratio and rigidity, which are critical for minimizing vehicle mass while maintaining structural integrity during both aerial flight and underwater operation. To achieve positive buoyancy, closed-cell foam components are integrated into the frame, resulting in a net buoyant force of approximately 34.3 N against the vehicle's dry weight of 26.5 N. This means the vehicle requires 7.8 N of downward thrust to initiate submersion. Given that each of the four propellers generates up to 9.8 N of thrust underwater, the system achieves a combined downward thrust of approximately 39.1 N, yielding an effective underwater thrust-to-weight ratio of

approximately 5:1. This ratio provides sufficient control authority for submerged maneuvering, including the ability to overcome buoyancy and execute controlled descents, ascents, and horizontal translations.

All onboard electronics are protected through a conformal parylene coating applied via chemical vapor deposition, eliminating the need for bulky waterproof enclosures. The vehicle operates using a custom dual-mode flight control system deployed on a microcontroller (Teensy 4.1, PJRC, Sherwood, OR, USA), supporting both aerial flight stability and underwater maneuvering. In flight, the vehicle behaves like a conventional quadcopter. Underwater, the front and rear propeller arms tilt downward to generate downforce, and are biased forward or backward via differential tilt angles to achieve horizontal translation (referred to as differential vectoring in Figure 2). The system is capable of reaching speeds up to 1 m/s underwater, which is comparable to the cruise speeds of commercially available inspection-class ROVs in the same size category (Capocci et al., 2017).

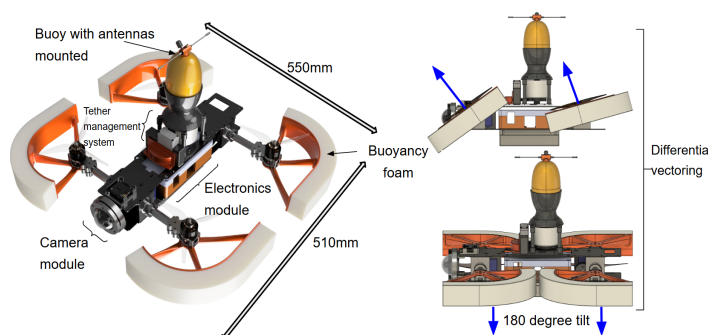


Figure 2. Full vehicle design highlighting key components and degrees of freedom. Differential vectoring refers to the independent tilting of the front and rear propeller arms to achieve combined downforce and horizontal thrust.

Tether Management System Design

The tether management system consists of three main components: a surface buoy with attached antenna, a tether connecting the buoy to the vehicle, and an onboard tether length management mechanism. As the vehicle operates at varying depths, the tether connecting it to the surface buoy must be carefully managed in length to ensure that the buoy remains at the surface for continuous radio communication. If too much tension is applied to the tether, the buoy risks being pulled underwater, compromising its ability to relay signals. On the other hand, releasing too much cable results in slack that raises the risk of entanglement with the environment or the vehicle's propellers, and causes sub-optimal buoy and antenna orientation at the surface. To address these challenges, the system dynamically adjusts the tether length in real time based on the tension state, which reflects the depth and horizontal motion of the vehicle. This ensures that the buoy remains afloat and stable on the surface while the vehicle retains freedom of motion underwater. The system also secures the buoy during aerial flight. By maintaining optimal tether tension, the system enhances the overall performance, safety, and operational flexibility of the vehicle during transitions between aerial and underwater modes.

Buoy Design

An ellipsoidal geometry was selected for the buoy because its continuously varying cross-sectional area produces a smoothly changing buoyancy force as the buoy is displaced vertically in the water. Unlike a cylindrical buoy, whose constant cross-section would produce an abrupt transition between fully floating and fully submerged states, the ellipsoidal shape creates a gradual, approximately linear relationship between submersion depth and upward buoyancy force over a useful operating range. This characteristic is important because it enables the tension-based control system to regulate buoy position with greater precision: small changes in tether tension correspond to proportional changes in buoy submersion, avoiding sudden jumps in force that would make the system difficult to control.

The buoy generates up to approximately 3 N of upward buoyancy force when fully submerged. This value was determined from the buoy’s displaced volume (approximately 306 cm³) and the density of water using Archimedes’ principle:

$$V_{\text{submerged}} \times g \approx 1000 \times 3.06 \times 10^{-4} \times 9.81 \approx 3.0 \text{ N}.$$

This buoyancy is sufficient to counteract the downward force exerted by the combined weight of a slightly negatively buoyant optical fiber tether when fully extended to a design depth of 100 meters, as illustrated in Figure 3.

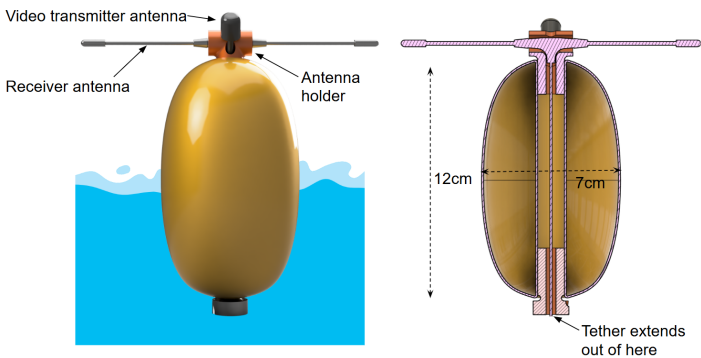


Figure 3. Buoy cross-section with attached antenna, showing key components and typical configuration when deployed.

Tension Sensing for Retraction

The tension in the tether provides sufficient information to determine how much of the buoy is submerged, since this tensional force balances with the upward buoyancy force generated by the buoy. A simple free-body diagram, as shown in Figure 4, demonstrates this force balance. With real-time feedback on the tether’s tension state, a closed-loop control system can continuously maintain a desired tension range corresponding to the expected buoyancy force when the buoy is partially submerged to the target level. This ensures that the tether remains slightly tensioned, thereby preventing slack that could result in entanglement with the vehicle’s propellers. Considering the case where the tether angle $\theta = 0$ (i.e., the vehicle is directly below the buoy), there exists an optimal buoyancy force, F_{optimal} , that the buoy experiences when it is partially submerged to the desired level.

The combined downward gravitational force of the buoy and fully extended tether is approximately 0.45 N. This value was calculated from the measured dry mass of the buoy (30 g) and the linear

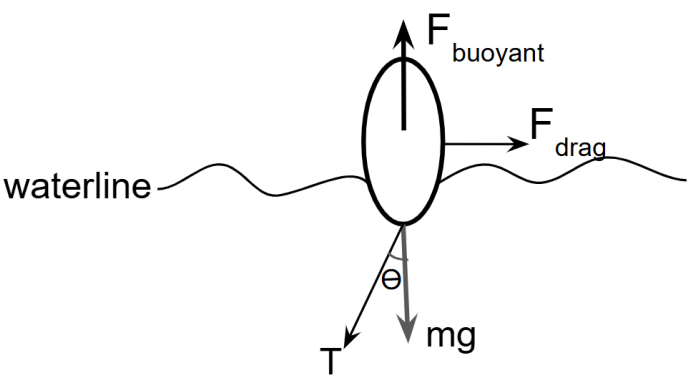


Figure 4. Free-body diagram of a partially submerged buoy showing the balance between buoyancy force (F_b), tether tension (T), gravitational force (mg), and the tether angle (θ).

density of the proposed optical fiber tether (approximately 1.2 g/m over 100 m), giving a total suspended mass of approximately 46 g and thus a gravitational force of $0.046 \text{ kg} \times 9.81 \text{ m/s}^2 \approx 0.45 \text{ N}$. This is much smaller than the maximum upward buoyancy force of 3.0 N when the buoy is fully submerged. Since this static gravitational offset remains constant across operating conditions and serves only to slightly shift the equilibrium position vertically, it can be neglected in a first-order analysis. With this simplification, the following relationships between tether tension and buoy position can be stated, as summarized in Table 1.

Condition	Buoy Position
$T \approx F_{\text{optimal}}$: partially submerged (ideal)	
$T \gg F_{\text{optimal}}$: fully submerged	
$T \ll F_{\text{optimal}}$: slack, unstable	

Table 1. Position of buoy with respect to tether tension.

F_{optimal} is determined by calculating the submerged volume of the buoy at the desired waterline position, as illustrated in Figure 5. The target waterline is set at approximately 60% submersion of the ellipsoid’s major axis. Using the volume formula for a partially submerged ellipsoid, $V_{\text{sub}} = (\pi ab/3)(3c - h) \times h^2/(c^2)$, where a , b , and c are the semi-axes and h is the submersion depth, the submerged volume at this target depth yields a buoyancy force of approximately 2.45 N (via $F_b = \rho_{\text{water}} \times V_{\text{sub}} \times g$). Accounting for the combined gravitational force of the buoy and tether (0.45 N), the net tether tension at the desired equilibrium is $F_{\text{optimal}} = 2.45 - 0.45 = 2.0 \text{ N}$. This is the tension setpoint used by the control system.

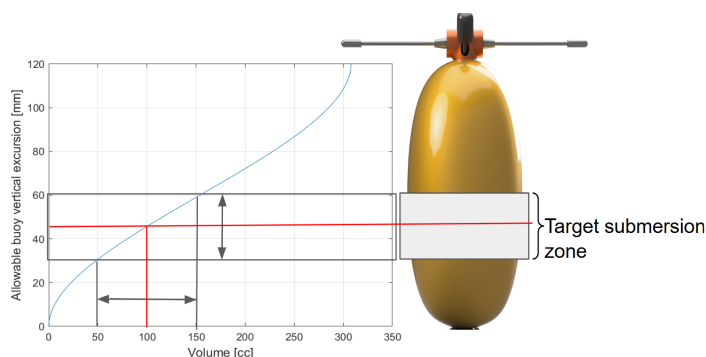


Figure 5. The desired submersion level of the buoy is used to calculate the submerged volume and thus the buoyancy force. The target waterline represented by the red horizontal line corresponds to approximately 60% submersion.

Tension Sensing Design

The system employs a single-point load cell (rated capacity: 5 N, resolution: ± 0.01 N) to measure the tension in the tether as it is wound or unwound about a spool. The tether is guided through a series of pulleys that redirect it while maintaining consistent tension. As the tether passes through the final pulley, the tension force is transmitted through a bracket that connects the pulley to the load cell. The final pulley is mounted on a bearing that allows it to rotate about the vertical axis, so that as the tether revolves around the spool during winding or unwinding, the force is always transmitted through the load cell's measurement axis, ensuring consistent readings regardless of the tether's angular position on the spool. Figure 6 shows the components of the spool and tension sensing system.

Control System Design

The control system architecture is shown in Figure 7. The system employs an adaptive proportional-derivative (PD) controller. The tether-buoy system exhibits behavior qualitatively similar to an overdamped system: when the buoy is fully submerged and the tether must be released to allow the buoy to breach the surface to the target zone, the buoy's upward thrust remains effectively constant and the tether tension changes gradually as cable is released or retracted. This results in a smooth, non-oscillatory approach to the tension setpoint without overshoot, which justifies treating the system as overdamped from a control perspective.

In this regime, a PD controller is sufficient. The proportional term drives the tension toward the setpoint, while the derivative term responds to rapid disturbances caused by vehicle motion or sudden changes in tension when the buoy breaches the surface and the submerged volume changes abruptly. An integral term was deliberately omitted: when the buoy is fully submerged, the tension tends to remain below the setpoint due to the constant buoyancy force, and a PD controller tolerates this small steady-state deviation. An integral term would accumulate this persistent error over time, causing the controller to respond more aggressively and potentially leading to overshoot or oscillations around the setpoint once the buoy nears the surface, undermining the otherwise smooth behavior of the system.

The adaptive nature of the controller involves modifying the proportional and derivative gains in real time based on the current length of deployed tether. These modifications compensate for the

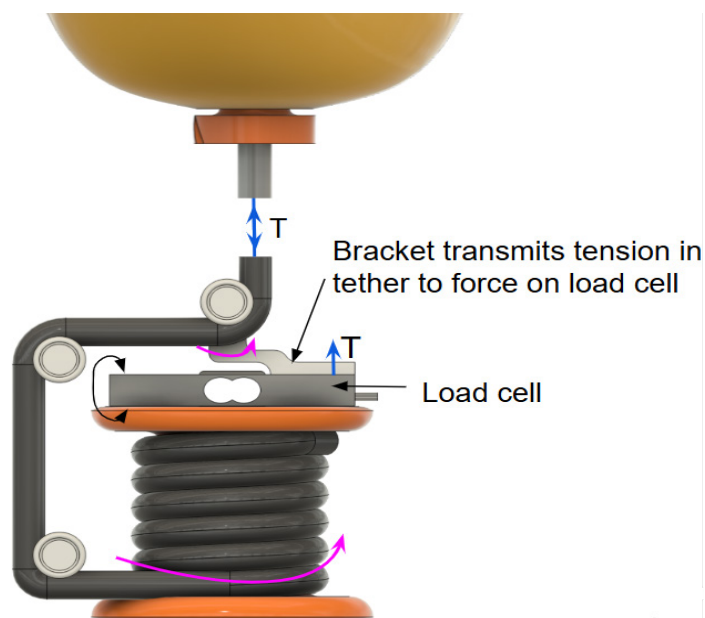


Figure 6. Spool design with load cell for measuring tension, showing the pulley routing, load cell bracket, and servo motor drive.

changes in the buoy's motion response characteristics as a function of tether length, as derived in the following section. The tension setpoint is $F_{\text{optimal}} = 2.0$ N, as determined in the tension sensing analysis above.

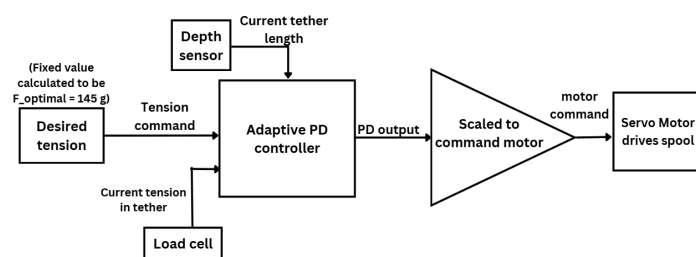


Figure 7. Control system block diagram showing the adaptive PD controller with tension feedback.

Motion Response

It is important to understand how tracking the desired tension (F_{optimal}) affects the buoy's behavior while the vehicle translates horizontally. The horizontal motion of the buoy can be modeled as a second-order linear system, as shown in Equation 1:

$$m_{\text{buoy}} \times \ddot{u} + c \times \dot{x} + (F_{\text{optimal}}/l) \times x = 0 \quad (1)$$

where m_{buoy} is the mass of the buoy, c is a velocity-dependent hydrodynamic drag coefficient, l is the current length of deployed tether, and x is the horizontal displacement of the buoy. This is a standard mass-spring-damper system with the effective spring constant $k = F_{\text{optimal}} / l$. The damping ratio ζ is given by Equation 2:

$$\zeta = \frac{c}{2\sqrt{F_{\text{optimal}} \times m_{\text{buoy}}/l}} \quad (2)$$

The system is expected to be overdamped ($\zeta > 1$) since the buoy should not overshoot or move ahead of the vehicle. As shown in Figure 8, the damping ratio increases with increasing tether length. In the current prototype, the maximum tether length tested was

10 m, constrained by the tank testing environment (described in the Experimental Methods section). At the design target of 100 m, the damping ratio is expected to be significantly higher, meaning the buoy will track the vehicle's horizontal motion more slowly at greater depths. This depth-dependent response is a fundamental characteristic of the system and must be accounted for by the adaptive controller, which adjusts its gains as a function of the deployed tether length to maintain adequate tracking performance across the full operating range.

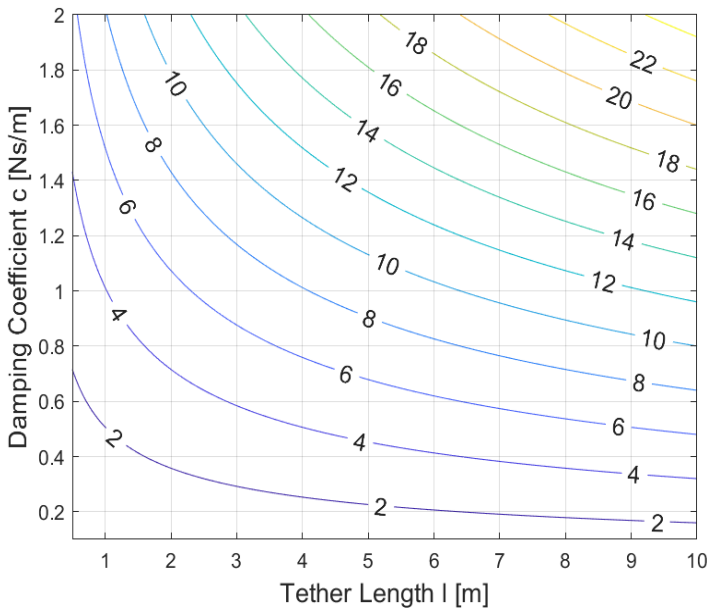


Figure 8. Characterization of damping ratio as a function of tether length and damping coefficient. The damping ratio increases with tether length, indicating reduced buoy responsiveness at greater depths.

Experimental Methods

For the purposes of this study, a lightweight string was used in place of a full optical fiber tether to validate the working principle of the tether management mechanism, focusing on system behavior and control without the added complexity of tether mass or stiffness. The proposed fiber optic tether design is described separately in the following section. The final assembled tether management system is shown in Figure 9.

The assembled system integrates the load cell for tension sensing, a servo motor to drive the spool for tether release and retraction, and the buoy to keep the antenna above the waterline. The system is mounted directly along the center of mass on the vehicle fuselage. The tether is connected to the flight controller on the vehicle, and the servo motor is powered from the vehicle's power system, as shown in Figure 2.

To validate the vehicle's transition from air to submerged operation, experiments were carried out in a test tank with dimensions 3 m × 3 m × 2 m. Given space constraints that precluded aerial flight within the test environment, the vehicle was manually placed on the water surface, where it then oriented its propellers downward to generate the necessary downforce for submersion. Since battery waterproofing is not addressed here, the system was powered via a tethered supply line.

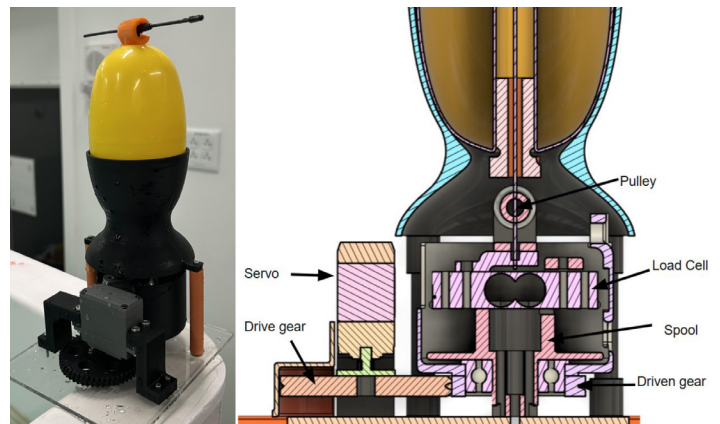


Figure 9. Test bench design of the tether management system highlighting key components including the spool, load cell, servo motor, and buoy.

The primary objective of the experiments was to evaluate the performance of the onboard tether management system during descent and horizontal translation. The vehicle's transition from aerial to underwater configuration is demonstrated in Figure 10.

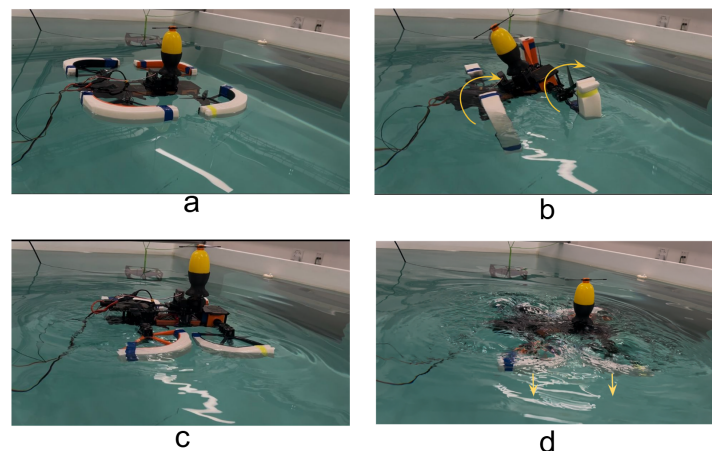


Figure 10. Sequence demonstrating the aerial to underwater transition. (a) Standard aerial flight configuration. (b) Propellers begin tilting downward. (c) Fully inverted position. (d) Vehicle initiates descent into the water.

Results and Discussion

The tether management system was evaluated during vehicle descent and horizontal translation in the test tank. During descent, as the vehicle submerged and increased its depth, the tether management system successfully released the buoy and regulated tether length to maintain the buoy at the water surface. Figure 11 shows a sequence from the descent test, demonstrating that the buoy remained partially submerged at the target waterline level throughout the vehicle's downward motion. The tension feedback loop responded to increasing depth by releasing tether at a rate that prevented both buoy submersion (which would indicate excessive tension) and slack accumulation (which would indicate insufficient tension).

During horizontal translation, the buoy tracked the vehicle's lateral motion as predicted by the motion response model. Figure 12 illustrates the forward and backward tracking behavior. The buoy followed the vehicle's horizontal position with a lag

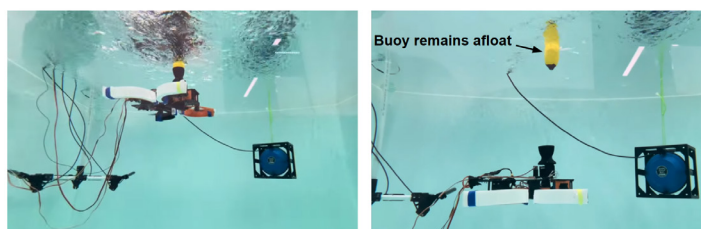


Figure 11. Demonstration of the buoy remaining partially submerged at the target waterline as the vehicle descends.

consistent with the overdamped response characteristics described by Equations 1 and 2. No oscillation or overshoot of the buoy was observed, confirming the appropriateness of the PD controller and the overdamped system model.

Throughout both descent and horizontal motion tests, the radio communication link between the operator and the vehicle was maintained without interruption, confirming that the buoy's surface position was preserved within the acceptable range. These results validate the core operating principle of the tension-based tether management approach: by controlling tether tension rather than directly measuring depth or buoy position, the system achieves robust performance without the need for additional environmental sensors that could be subject to drift or calibration errors in underwater conditions.

Several limitations of the current prototype should be noted. First, the experiments were conducted in a controlled tank environment with calm water; performance in open-water conditions with waves, currents, and turbulence remains to be evaluated. Second, the lightweight string used as a tether substitute does not capture the mass, stiffness, or drag characteristics of a full optical fiber tether, which may affect system dynamics at greater depths. Third, the maximum tested tether length was limited to approximately 2 m by the tank depth, well below the 10 m range modeled in the motion response analysis and the 100 m design target. Finally, battery waterproofing was not implemented, requiring the use of an external power supply tether that may have introduced additional drag and disturbance forces during testing.

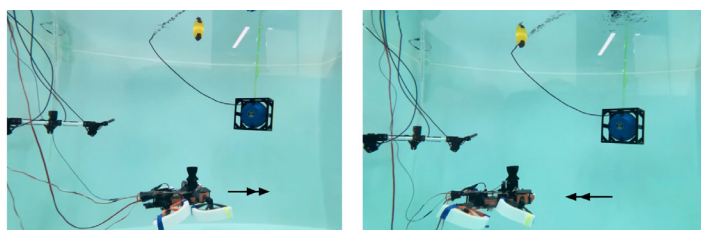


Figure 12. The forward and backward motion of the vehicle is tracked by the buoy, demonstrating the horizontal tracking capability of the tether management system.

Conclusion and Future Directions

This work presented the design, analysis, and experimental validation of a dynamic tether management system for hybrid aerial-aquatic vehicles. The system addresses a fundamental limitation in underwater remote control by providing continuous, reliable communication between an operator and a submerged vehicle through a surface buoy managed entirely by onboard

mechanisms. The key contributions of this work include: the development of a tension-based feedback approach that regulates tether length without requiring depth sensors or environmental measurements; the design of an ellipsoidal buoy that provides a smoothly varying buoyancy force suitable for closed-loop tension control; an analytical model of the buoy's horizontal motion response as a function of tether length, informing the design of an adaptive PD controller; and experimental validation of the complete system during descent and horizontal translation in a controlled environment.

The proposed system has direct applications in several domains where real-time operator control of submerged vehicles is essential. In offshore infrastructure inspection, the vehicle could enable operators to visually inspect underwater structures such as bridge pilings, pipelines, and offshore platform foundations while maintaining a real-time video link. For marine ecosystem monitoring, the system could allow researchers to conduct targeted biological sampling or observation of aquatic organisms with direct operator guidance. In search-and-rescue operations, the ability to deploy from air and transition to controlled underwater search patterns without pre-programming could significantly reduce response times and improve situational awareness in dynamic environments.

To support full-scale deployment, the current string-based tether used for prototype validation would be replaced by a single-mode optical fiber link. In this architecture, the buoy would house a radio antenna, a radio receiver module, and a single-board computer (Raspberry Pi 4 Model B) serving as the central processor. Operator commands received via the radio link would be processed onboard the buoy and transmitted down to the vehicle through an Ethernet-to-fiber-optic media converter. On the vehicle side, a corresponding media converter would translate the optical signal back to Ethernet, routing data to the flight controller and video transmitter. This fiber optic approach offers several advantages over the string substitute: it provides the bandwidth necessary for real-time HD video streaming alongside control commands and sensor telemetry, introduces negligible signal latency over the target 100 m operating depth, and its slight negative buoyancy is already accounted for in the buoy and tension control design presented in this work.

Several additional steps remain before the system is ready for field deployment. The fiber optic tether must be integrated and its communication performance validated at extended depths up to 100 m. The tether management system must then be tested in open-water environments where waves, currents, and wind introduce disturbances absent from the tank experiments. Onboard battery waterproofing must be implemented to eliminate the external power supply tether used in the current prototype. The adaptive controller gains must be tuned and validated across the full range of tether lengths from 0 to 100 m, as the motion response model predicts significantly different buoy dynamics at these extremes. Finally, autonomous path-planning algorithms that account for the tether's geometric constraints could be developed to complement the operator-in-the-loop control mode, enabling hybrid autonomous-manual operation for complex missions.

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A Tale of Two Cities: eIF4G1 and eIF4G2's Unexpected Mechanisms in Translation Initiation

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This study dissects the roles of two isoforms of eIF4G, eIF4G1 and eIF4G2, by combining in vitro luciferase assays on 48 putative transcripts with computational analysis. Unexpectedly, most putative eIF4G1-associated transcripts maintained or increased translation following eIF4G1 knockdown, suggesting that their translation can persist through alternative initiation routes when eIF4G1 levels are reduced. Similarly, a majority of putative eIF4G2-associated transcripts retained or increased translation following eIF4G2 knockdown, while a smaller subset exhibited reduced translation consistent with stronger eIF4G2 dependence. Notably, the addition of recombinant Nat1—the murine ortholog of human eIF4G2 (also known as DAP5/p97), a protein implicated in non-canonical translation initiation—partially altered translation output in a subset of eIF4G2-associated conditions, though no statistically significant global rescue relative to eIF4G2 knockdown was observed. Comprehensive motif discovery revealed a highly conserved GC-rich 16-nucleotide sequence whose composition is consistent with RNA G-quadruplex-forming sequences. Together, these results suggest that eIF4G isoforms act as context-dependent regulators of translational plasticity, with potential implications for stem cell biology and translational dysregulation in disease.

Introduction

Eukaryotic translation initiation is an intricate process. At least eleven eukaryotic initiation factors (eIFs), proteins that assist in assembling the ribosome on a messenger RNA (mRNA), work together to recruit the ribosome to mRNA and to position it at the start codon. First, they form a 43S pre-initiation complex recruited to the mRNA's 5' cap by the eIF4F complex. The eIF4F complex is made up of eIF4E (a cap-binding protein), eIF4G (a scaffolding protein that holds the complex together), and eIF4A (an RNA helicase). eIF4G1 is the predominant isoform of eIF4G and is known to be associated with internal ribosome entry site (IRES)-dependent translation, a cap-independent mechanism in which ribosomes are recruited directly to a structured RNA element within the mRNA, bypassing the need for a 5' cap.

As summarized in Figure 1, translation initiation can occur through cap-dependent mechanisms, relying on the eIF4F complex binding to the mRNA cap, or through cap-independent mechanisms, which utilize internal ribosome entry sites (IRES) or other structures to recruit ribosomes directly. Figure 1 highlights several key differences in the protein complexes involved in the initiation of translation, with Figure 1A showing canonical cap-dependent translation and Figure 1E showing IRES-mediated translation.

This study examines human embryonic stem cells as a defined model system and asks how candidate eIF4G1- and eIF4G2-associated transcripts behave when each factor is reduced. Additionally, this study examines whether adding recombinant Nat1, whose deletion impairs differentiation of mouse embryonic stem cells and whose protein complex lacks the eIF4E-binding capacity required for canonical cap-dependent translation, can modulate translational activity in eIF4G2 knockdowns (Sugiyama et al., 2017).

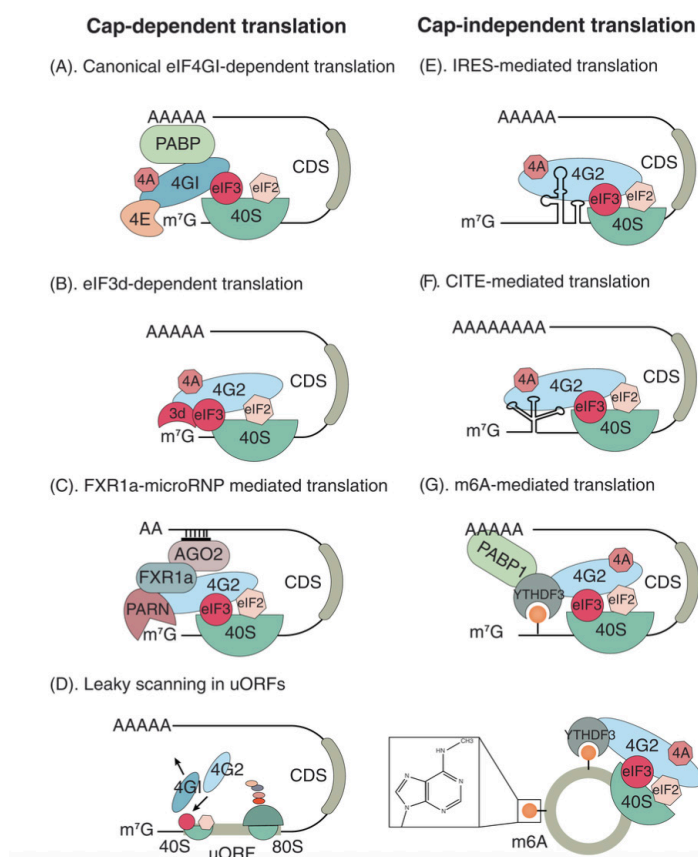


Figure 1. Known types of cap-dependent and cap-independent translation initiation (Liu et al., 2023).

Literature Review

Prior studies establish that eIF4G-family proteins are important organizers of translation initiation, but they also suggest that the two isoforms are not functionally identical. eIF4G1 is abundant and strongly associated with canonical cap-dependent initiation, whereas eIF4G2 has been implicated in specialized modes of initiation that become especially relevant for selected transcripts or under stress-related conditions.

Popular techniques to study the role of eIF4G have included *in vitro* translation (Smirnova, 2022) and ribosome profiling to examine how eIF4G proteins interact with ribosomes during translation (Mohammed, 2021) and polysome microarray analysis (Clarkson, 2010). Other techniques include proteomics and interactome analysis of eIF4G1 and eIF4G2 binding partners (Meril, 2023) and genetic manipulation of yeast and mammalian cell lines to clarify protein activities (Badura, 2012; Cunningham, 2023).

Current findings have led to multiple areas of ongoing debate. For example, the degree of functional overlap between eIF4G1 and eIF4G2 continues to be debated; some studies propose specific responsibilities (Cunningham, 2023), whereas others imply possible redundancy (Clarkson, 2010). The significance of eIF4G2 in cap-independent translation is also contentious (Liu, 2023; Smirnova, 2022). Other sources of debate include the function of eIF4G isoforms in oxidative stress responses (Cunningham, 2023; Badura, 2012), the roles of eIF4G1 and eIF4G2 in cancer (Jaiswal, 2018; Meril, 2023), and the regulation of particular mRNA subsets (Smirnova, 2022).

Compelling arguments arise from research that integrates many methodologies, including genetic manipulation, *in vitro* experiments, and proteomics. Smirnova's (2022) research offers strong evidence for eIF4G2's involvement in leaky scanning and reinitiation, corroborated by *in vitro* and cellular experiments. The evolving perspective of eIF4G2 as a versatile factor engaged in several translation processes is gaining prominence (Liu, 2023). This viewpoint harmonizes apparently conflicting results and proposes a more sophisticated comprehension of translation regulation.

While the literature review provides valuable insights, there are still significant gaps in the understanding of eIF4G1 and eIF4G2 functional redundancy in human cells. Transcript-specific effects of eIF4G1 and eIF4G2 knockdowns or knockouts have not been thoroughly investigated using RNA-seq in human cells. Accordingly, this study asked whether candidate eIF4G1-associated transcripts show reduced translation when eIF4G1 is knocked down, whether candidate eIF4G2-associated transcripts would show reduced translation following eIF4G2 knockdown, and whether Nat1 can partially restore translation in the eIF4G2-knockdown condition.

Hypothesis

Three hypotheses were tested:

- Candidate eIF4G1-associated transcripts would show reduced translation after eIF4G1 knockdown.
- Candidate eIF4G2-associated transcripts would show reduced translation following eIF4G2 knockdown.
- In the eIF4G2-knockdown condition, addition of Nat1 protein would partially restore translation of candidate eIF4G2-associated transcripts.

Methods

The study combined a wet-lab workflow and a computational analysis pipeline. The wet-lab component moved from transcript selection, to reporter-template preparation and lysate preparation (described in Supplementary Materials), to knockdown validation, and finally to luciferase-based *in vitro* translation measurements. The computational component was then used to analyze motifs, localization patterns, enrichment, and related sequence features among the candidate transcripts. Human embryonic stem cells from the H9 line (WAe009-A; RRID:CVCL_9773) were used throughout.

Gene Selection

Twenty-four putative eIF4G1-associated 5' UTRs and twenty-four putative eIF4G2-associated 5' UTRs were chosen from Sel-TCP-Seq data analysis, a technique that identifies mRNAs

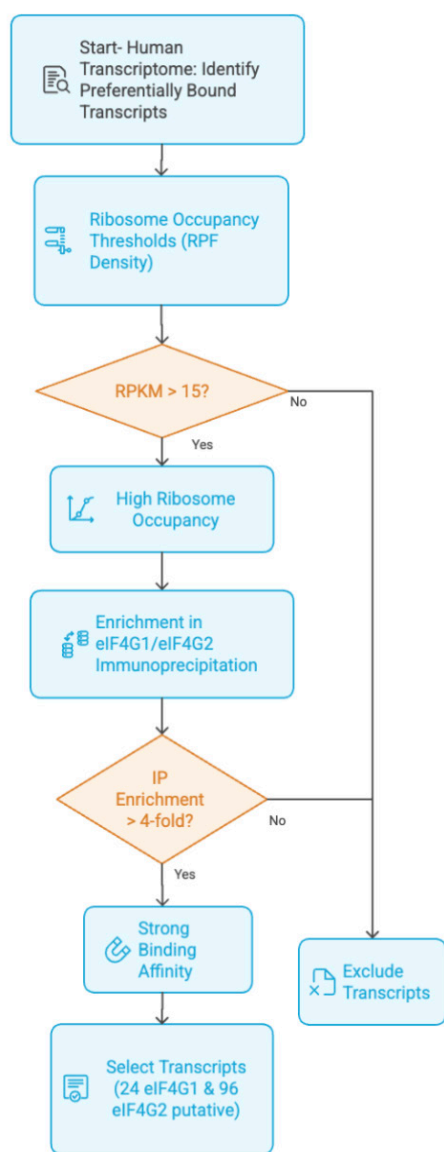


Figure 2. Schematic of the transcript-selection workflow for candidate eIF4G1- and eIF4G2-associated 5' UTRs.

associated with specific translation initiation factors. Ribosome density was calculated for each candidate transcript; only transcripts with RPKM (Reads per Kilobase per Million) ≥ 15 were retained, to exclude transcripts with low translational activity or background noise. Immunoprecipitation enrichment was then used as a second filter with a fold-enrichment threshold greater than 4x relative to input.

Using those criteria, 24 candidate eIF4G1-associated transcripts and 96 candidate eIF4G2-associated transcripts were initially identified, after which 24 transcripts from each group were advanced for downstream analysis. These transcript sets were used both for experimental reporter assays and for computational analyses aimed at identifying sequence motifs, structural features, and putative binding patterns that might help explain differences between canonical and non-canonical translation initiation.

Validate that knockdowns were successful: Western Blot Analysis

Protein levels of eIF4G1 and eIF4G2 in the mAID cell lines were analyzed using a Western blot - a standard technique in which proteins are separated by size, transferred to a membrane, and detected with antibodies - to confirm successful reduction of target protein levels in IAA-treated conditions relative to Dox controls. Protein detection was performed using rabbit primary antibodies against eIF4G1 and eIF4G2 followed by HRP-conjugated goat anti-rabbit secondary antibodies, with chemiluminescent detection on the Jess capillary-based Western blot platform. Knockdown was confirmed in the lysates as shown in Figure 3.

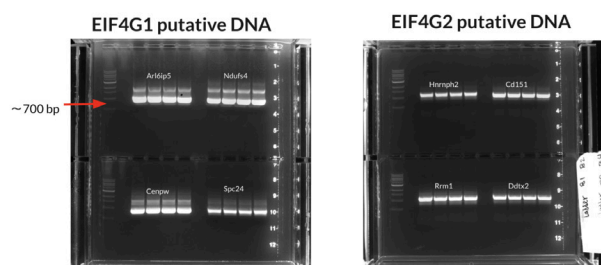


Figure 3. Western blot validation of eIF4G1 and eIF4G2 knockdown. Protein lysates from Dox (wild-type) and IAA-treated (knockdown) mAID cell lines were probed with antibodies against eIF4G1 and eIF4G2. Reduced band intensity in IAA-treated lanes relative to Dox controls confirms successful depletion of each target protein prior to use in luciferase assays (see Western Blot Analysis, Methods).

Experimental Variables

Independent variables were knockdown conditions (eIF4G1 mAID + 24-hour IAA treatment, eIF4G2 mAID + 24-hour IAA treatment, and eIF4G2 mAID + IAA + Nat1 rescue) and transcript groups (24 putative eIF4G1-dependent transcripts and 24 putative eIF4G2-dependent transcripts). The dependent variable was relative light units (RLUs), luminescence readout from the luciferase assay. Because luciferase signal is produced only after successful translation of the reporter, RLUs serve here as a proxy for translation-initiation output under each lysate condition. Baseline conditions were eIF4G1 mAID + Dox (wild type) and eIF4G2 mAID + Dox (wild type). Technical controls were identical lysate

preparation protocols across conditions and uniform luciferase assay parameters (reagent concentrations, incubation times).

Western-blot confirmation of eIF4G1/eIF4G2 depletion was used to verify that the lysates reflected the intended experimental conditions. Candidate transcripts were chosen from prior Sel-TCP-Seq analysis and then tested in matched reporter-assay conditions. Western blot confirmation of eIF4G1/eIF4G2 depletion is shown in Figure 3 and described in the Western Blot Analysis subsection. For statistical analysis, outliers were identified using a $1.5 \times \text{IQR}$ rule, and a sensitivity analysis using a $2.0 \times \text{IQR}$ cutoff was performed to evaluate whether the main conclusions were robust to that choice. Because many fold change distributions did not satisfy normality assumptions, non-parametric tests were used where appropriate, and Benjamini-Hochberg correction was applied to control the false-discovery rate across multiple comparisons.

Test hypotheses by measuring translation levels: Luciferase Assay

Translation activity was measured using a luciferase assay. In this assay, the candidate 5' UTR is fused to the coding sequence of luciferase, a light-producing enzyme. When the reporter mRNA is successfully translated, luciferase is produced and generates a measurable luminescence signal. The amount of light emitted therefore serves as a direct proxy for translation initiation activity under each lysate condition. Each reaction combined 100 μL Nano-Glo Buffer, 10 μL prepared IVT Buffer, 20 μL of diluted lysate, and the corresponding reporter mRNA. The assay was incubated for 1 hour at 37°C before luminescence was measured using a plate reader.

To summarize the experimental design: for each of the 48 candidate transcripts, one IVT reaction was run per lysate condition (five conditions total: eIF4G1 Dox, eIF4G1 IAA, eIF4G2 Dox, eIF4G2 IAA, eIF4G2 IAA + Nat1). Each plate was read three times (technical triplicates). Fold change was computed as the ratio of RLUs in the knockdown or rescue condition to RLUs in the corresponding wild-type (Dox) condition for each transcript. Average SEM values across triplicate plate readings are shown in Figure 4.

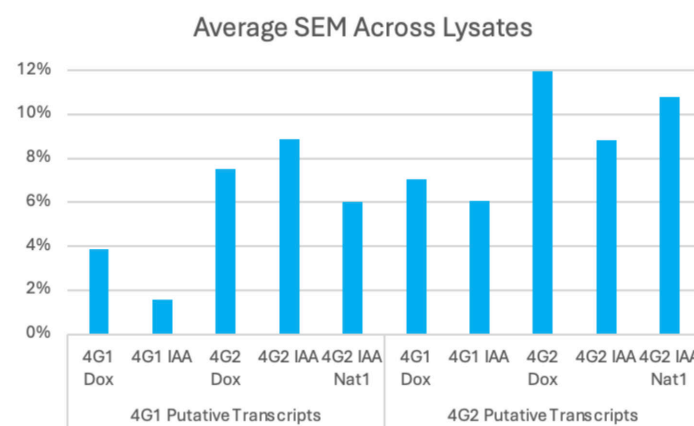


Figure 4. Technical replicate consistency across luciferase measurements. Average Standard Error of the Mean (SEM) across triplicate plate readings for each of the five lysate conditions, shown separately for eIF4G1-associated ($n=24$) and eIF4G2-associated ($n=24$) transcripts. SEM values below 12% indicate low within-experiment variability, supporting the reliability of the luminescence readout (see Luciferase Assay, Methods).

Hypothesis	Condition	% Upregulated	Mean Fold Change ± SEM (Pre-Outlier)	Mean Fold Change ± SEM (Post-Outlier)	Shapiro-Wilk P-value	Wilcoxon Statistic	Wilcoxon P-value
1: eIF4G1 Knockdown	IAA-4G1 / Dox-4G1	95.83%	6.50 ± 3.00	2.14 ± 0.16	0.000 (Normality NOT met)	0	0
2: eIF42 Knockdown	IAA-4G2 / Dox-4G2	58.33%	2.97 ± 0.89	1.87 ± 0.30	0.000 (Normality NOT met)	62.5	0.038
3A: Nat1 Restoration (vs. Dox-4G2)	Nat1 / Dox-4G2	66.67%	1.49 ± 0.17	1.38 ± 0.13	0.000 (Normality NOT met)	62	0.021
3B: Nat1 Restoration (vs. IAA-4G2)	Nat1 / IAA-4G2	37.50%	0.96 ± 0.13	0.96 ± 0.13	0.000 (Normality NOT met)	101	0.169

Table 1. Summary of translational changes and statistical analyses across the tested transcript groups. For each comparison, the table reports the number of transcripts analyzed before and after outlier removal, the mean fold change ± SEM, the percentage of transcripts with fold change greater than 1 (% upregulated), the Shapiro-Wilk normality result, and the Wilcoxon signed-rank p value with Benjamini-Hochberg-adjusted p value where applicable.

Computational Methods

All computational analyses were performed using a suite of tools that included custom Python code developed by the author or from the MEME Suite (version 5.5.7), along with complementary software packages. These tools were selected for their robust statistical frameworks and their ability to address various aspects of motif discovery, enrichment, localization, alignment, and annotation. The primary input sequences came from experimental data (48 transcripts), and corresponding control sequences were generated by shuffling the primary sequences while preserving k-mer frequencies, thereby maintaining intrinsic sequence characteristics. The integrated computation pipeline is described in the Supplementary Materials.

Selected Results

Translation initiation activity was quantitatively assessed by measuring the RLUs across 48 candidate transcripts under different lysate conditions (Figure 5). For the full fold-change summary across all transcripts and conditions, see Figure 5 and Table 1.

Hypothesis 1: Putative eIF4G1 transcripts would not be translated when eIF4G1 levels are significantly reduced.

Finding: The data do not support this hypothesis overall. Instead, most tested transcripts maintained or increased reporter output after eIF4G1 knockdown, as seen in Figure 6. Hypothesis 1 was therefore rejected.

A total of 24 transcripts were evaluated. Before outlier removal, the mean fold change was 6.50 ± 3.00 SEM, with 95.83% of transcripts exhibiting increased translation. After removing four outliers, twenty transcripts remained. These 20 transcripts had a mean fold change of 2.14 folds ± 0.16 SEM. The distribution of fold changes did not conform to normality (Shapiro-Wilk test, W = 0.571, P < 0.001), necessitating a Wilcoxon signed-rank test to test the hypothesis that the medians of the two samples differ.

The Wilcoxon signed-rank test indicated a statistically significant shift in translation after eIF4G1 knockdown (P < 0.001 see Table 1).

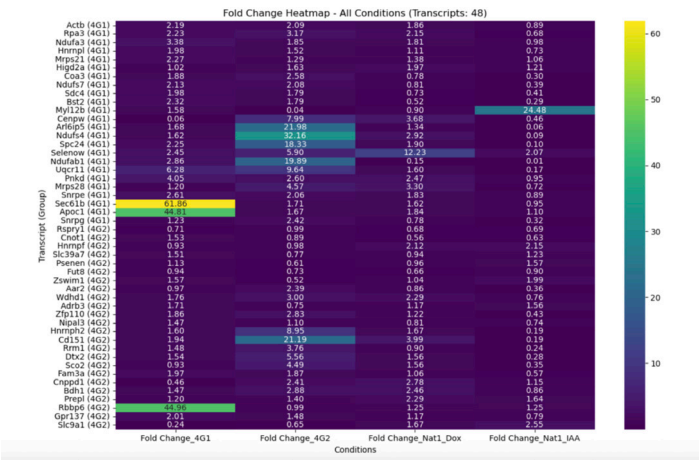


Figure 5. Summary of fold-change behavior across all 48 transcripts under four comparison conditions. (i) Fold change 4G1: eIF4G1 knockdown (IAA) vs. wild-type eIF4G1 (Dox); (ii) Fold change 4G2: eIF4G2 knockdown (IAA) vs. wild-type eIF4G2 (Dox); (iii-a) Fold change Nat1 Dox: Nat1-treated vs. wild-type eIF4G2 (Dox); (iii-b) Fold change Nat1 IAA: Nat1-treated vs. eIF4G2 knockdown (IAA). Values above 1 indicate increased translation in the first condition relative to the second.

In this dataset, the direction of that shift was predominantly upward rather than downward, indicating that the tested eIF4G1-associated transcripts did not behave as though they uniformly required eIF4G1 for reporter translation under these assay conditions. A secondary sensitivity analysis using a 2.0xIQR threshold reduced the number of excluded outliers from four transcripts to three. The qualitative direction of the result did not change, supporting the robustness of the main finding.

Hypothesis 2: Putative eIF4G2 transcripts would not be translated when eIF4G2 levels are significantly reduced.

Findings: Hypothesis 2 was partially supported. A similar approach was applied to evaluate eIF4G2 knockdown effects. The initial dataset comprised 24 transcripts, with a mean fold change of 2.97 ± 0.89 SEM. Translation levels increased in

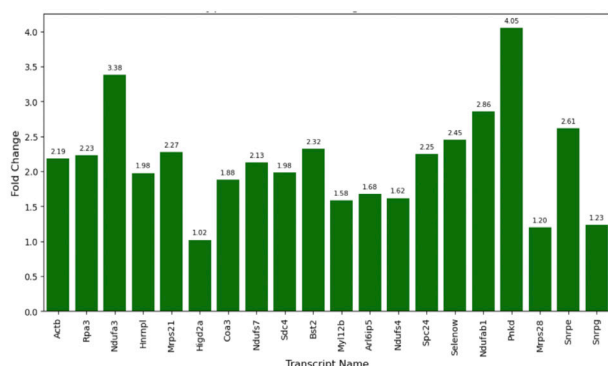


Figure 6. Fold changes in eIF4G1-associated transcripts upon eIF4G1 knockdown. Bar chart showing the ratio of RLUs in eIF4G1 knockdown (IAA) versus wild-type (Dox) conditions for each of the 20 remaining transcripts after outlier removal. Values above 1 indicate increased translation upon knockdown; values below 1 indicate decreased translation.

58.33% of transcripts and decreased in 41.67%. After removing two (2) outliers, a refined dataset of 22 transcripts remained with a mean fold change of 1.87 ± 0.30 SEM.

Similar to patterns seen with eIF4G1 putative transcripts, the distribution deviated from normality ($W = 0.781$, $p < 0.001$). The Wilcoxon signed-rank test confirmed a statistically significant alteration in translation ($p = 0.038$) and remained significant after Benjamini-Hochberg correction (adjusted $p = 0.038$) (see Table 1). It supports the observation that eIF4G2 knockdown significantly alters translation, though the effect is less pronounced compared to eIF4G1, as seen in Figure 7. The most upregulated transcripts included Cd151 (Fold Change (FC): 21.19), Hmnp2 (FC: 8.95), and Dtx2 (FC: 5.56), while Zswim1 (FC = 0.52) exhibited a marked decrease (see Supplemental Figure 4).

A secondary sensitivity analysis using a $2.0 \times \text{IQR}$ threshold did not change the number of excluded outliers for Hypothesis 2. The qualitative direction of the result was unchanged, supporting the robustness of the main finding, although alternate-threshold summary statistics are not shown here.

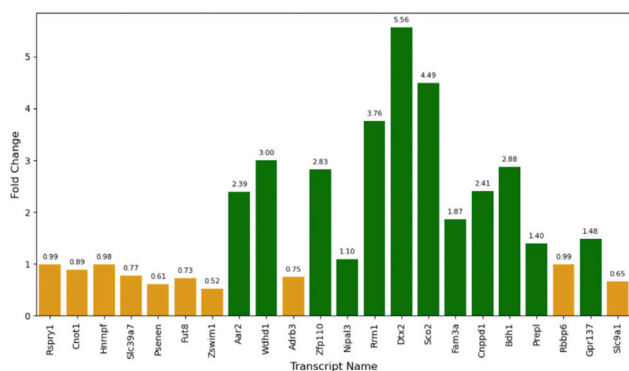


Figure 7. Fold changes in eIF4G2-associated transcripts upon eIF4G2 knockdown. Bar chart showing the ratio of RLUs in eIF4G2 knockdown (IAA) versus wild-type (Dox) conditions for each of the 22 remaining transcripts after outlier removal. Green bars indicate increased translation upon knockdown; orange bars indicate decreased translation.

Hypothesis 3: In eIF4G2 knockdown lysates, the addition of Nat1 protein will restore translational activity for putative eIF4G2 transcripts.

Findings: Our results partially support this hypothesis.

To assess whether Nat1 restores translation following eIF4G2 depletion, a comparative analysis of RLU values between Nat1 conditions and Dox (4G2) (Part A) and between Nat1 conditions and IAA (4G2) (Part B) was conducted.

In Part A, before outlier removal, the mean fold change was 1.49 ± 0.17 SEM, with 66.67% of transcripts showing increased translation. After removing one outlier, 23 transcripts remained, and the mean fold change was 1.38 ± 0.13 SEM. The data did not follow a normal distribution ($W = 0.623$, $p < 0.001$), and the Wilcoxon signed-rank test detected a statistically significant difference between the Nat1-treated condition and the Dox wild-type baseline ($p = 0.021$; adjusted $p = 0.042$ after Benjamini-Hochberg correction). This comparison shows that Nat1-treated lysates produce different translation output than untreated wild-type lysates, and indicates rescue relative to eIF4G2 knockdown - that comparison is addressed in Part B below. Notably, Cnppd1 (FC = 2.78) and Prepl (FC = 2.29) showed the largest upward shifts in this comparison (Figure 8).

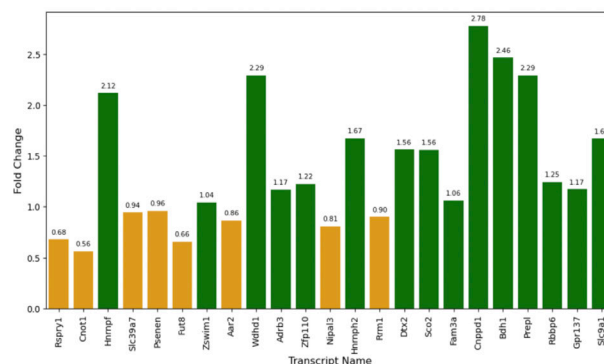


Figure 8. Fold changes comparing Nat1-treated to wild-type (Dox) eIF4G2 conditions (Part A). Bar chart showing the ratio of RLUs in the Nat1-treated condition versus the eIF4G2 Dox wild-type condition for each of the 23 remaining transcripts. Green bars indicate higher translation in the Nat1 condition; orange bars indicate lower. This comparison tests whether Nat1 shifts translation output relative to the untreated baseline, not relative to knockdown (see Part B, Figure 9).

In Part B, the mean fold change before and after outlier removal was 0.96 ± 0.13 SEM, with 37.50% of transcripts exhibiting increased translation and 62.50% showing decreased or unchanged translation. Following Benjamini-Hochberg correction ($FDR < 0.05$), the Wilcoxon signed-rank test remained non-significant (adjusted $p = 0.169$). The result indicates no statistically detectable difference in translation between Nat1-treated and eIF4G2-knockdown (IAA) conditions (adjusted $p = 0.169$; see Table 1, Figure 9). Accordingly, the data do not support a global rescue of eIF4G2-dependent translation by Nat1 under these conditions.

A secondary sensitivity analysis using a $2.0 \times \text{IQR}$ threshold did not change the number of excluded outliers for Hypothesis 3. The qualitative direction of the result was unchanged, supporting the robustness of the main finding, although alternate-threshold summary statistics are not shown here.

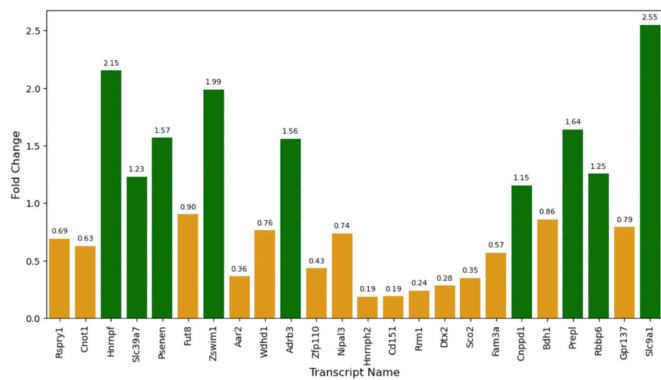


Figure 9. Fold changes comparing Nat1-treated to eIF4G2-knockdown (IAA) conditions (Part B). Bar chart showing the ratio of RLUs in the Nat1-treated condition versus the eIF4G2 IAA knockdown condition for each transcript. A ratio above 1 would indicate that Nat1 increased translation relative to knockdown. The Wilcoxon signed-rank test found no significant difference (adjusted $p = 0.169$), indicating no statistically detectable global rescue.

Comprehensive Computational Analysis Results

Out of the 48 transcripts tested, 40 showed increased translation when eIF4G1 or eIF4G2 was individually reduced. These are labeled Class 1. Seven transcripts selectively showed higher translation specifically under eIF4G1 knockdown conditions and displayed transcript-specific shifts in the Nat1-treated condition relative to eIF4G2 knockdown, but these shifts did not constitute a statistically significant global rescue (Part B adjusted $p = 0.169$); these are labeled Class 2. One additional transcript did not fit the defining pattern of either class and was treated as a Class 3 outlier, excluded from downstream computational analysis. Note that these classes are mutually exclusive - no transcript appears in more than one group. Because Class 2 contains only 7 transcripts, most computational results in that group did not reach statistical significance.

De Novo Motif Analysis

De novo motif analysis identified RNA structural features that enable transcripts to bypass canonical eIF4G1/2 dependency under stress. Using MEME, two key motifs were uncovered:

GC-Rich 16-nt Motif

The most statistically robust motif, a 16-nt sequence AGGAAGATGGAGGCCG ($E\text{-value} = 3.7 \times 10^{-6}$), was present in 100% of transcripts (40/40). The motif's presence in 40 sites suggests a high level of functional significance. Many DNA-binding proteins recognize motifs in the 6-20 nucleotide range. Therefore, the width of 16 is within the expected range for regulatory function. The genes closest to the Class 1 motif include Gpr137, Cd151, Sdc4, Mrps21, Apoc1, Uqcr11, Bst2, Ndufab1, Snrpe, and Snrpg. Instances of the motif have consistent p -values ranging from 2.72×10^{-4} to 1.70×10^{-3} , suggesting that these are likely bona fide binding sites (see Supplemental Figure 6).

Motif Enrichment Analysis Identifies YY1/YY2-Associated Motifs in Class 1 Transcripts

Motif enrichment analysis using AME (Analysis of Motif Enrichment) and SEA (Simple Enrichment Analysis) identified

significant enrichment of transcription factor binding motifs in Class 1 transcripts. Among the enriched motifs were several associated with YY1 and YY2, which are best interpreted as candidate signals rather than as direct mechanistic proof of translation-initiation control. Enriched motifs identified by AME and SEA are shown in Supplemental Figures 7 and 8, respectively. RBPMAP binding site analysis is also available in the Supplementary Materials.

In this dataset, enrichment of motifs annotated as YY1- or YY2-associated identifies candidate regulatory sequence features in Class 1 transcripts. The overlap between YY1/YY2-associated motif matches and transcripts with known stress-related functions (such as HIF1 α and c-MYC) may be biologically interesting in the context of prior work on stress-responsive translation (Semenza, 2012), and these connections suggest context for future investigation.

Sequence Conservation and IRES Motif Analysis

To validate motif discovery and assess cap-independent translation potential, 40 Class 1 transcripts were analyzed using BLASTN/IRESite and Clustal Omega. Key findings include candidate IRES-like sequence similarities, evolutionary conservation patterns, and insights into structural limitations.

Two candidate IRES-like sequence similarities, c-MYC and HIF1 α , were identified by BLASTN/IRESite. These matches provide directional guidance for studying IRES activity. The c-MYC mRNA contains an internal ribosome entry site (IRES) with a stem-loop III region that was identified by BLASTN analysis matching 12 plasmids with 100% identity (e.g., pSL200MLuc, $E = 0.01$). Clustal Omega alignment revealed conserved motifs in Zfp110 and Hmnp1 transcripts that resemble the c-MYC IRES region. Sequence similarities between the Class 1 transcripts and the c-MYC IRES region are suggestive of possible structural parallels and should be treated as candidate structural features for future investigation.

HIF1 α mRNA contains an IRES-like site exhibiting 88% sequence identity to the hypoxia-responsive plasmid pRhiff as identified by BLASTN/IRESite ($E = 0.5$). Clustal Omega alignment revealed a conserved 16 of 18 base pair motif in Slc9a1 and Psen1 transcripts. The absence of IRES-like matches in transcripts such as Actb and Snrpe is consistent with greater reliance on canonical initiation for those transcripts.

Deep evolutionary conservation of these motifs further underscores their functional importance. The c-MYC IRES motifs are conserved across diverse vertebrates, including humans, mice, cattle, sheep, chickens, and zebrafish, with structural elements like the 3' UTR Motif 17 preserved for over 350 million years. Similarly, HIF1 α hypoxia-responsive motifs are conserved across species ranging from humans to lungfish, with origins predating the divergence of bony and cartilaginous fish approximately 450 million years ago. PhyloP analysis shows high conservation scores of 3.5–4.0 across Class 1 motifs, highlighting their evolutionary and functional significance.

To account for the numerous statistical tests conducted throughout the pipeline, all p -values were adjusted using the Benjamini–Hochberg (BH) correction. This procedure controlled the false discovery rate and minimized the risk of Type I errors, ensuring that the reported significant findings are statistically robust.

Discussion

Our wet lab experiments, alongside our integrated computational analysis pipeline, support a model in which eIF4G isoforms act as context-dependent regulators rather than universally essential scaffolds. While not conclusive, the data are consistent with how RNA structural motifs contribute to maintaining translation when canonical factors are reduced.

The computational analyses help generate preliminary hypotheses for how that flexibility might arise. Motif enrichment and structural predictions suggest that some transcripts may contain features compatible with non-canonical initiation, including G-rich elements and IRES-like signatures. Some of the GC-rich sequence features may also warrant future testing for possible G-quadruplex formation. At the same time, such standalone analyses do not establish mechanisms, and are candidates for future validation.

These findings extend the existing literature on eIF4G isoform function in important ways. Prior work in yeast established that eIF4G paralogs can target distinct mRNA subsets and differentially regulate translation under stress (Cunningham et al., 2023; Clarkson et al., 2010). Studies in mammalian cells have further suggested that eIF4G2 participates in non-canonical initiation modes including leaky scanning and reinitiation (Smirnova et al., 2022; Shestakova et al., 2023). The present results are consistent with those frameworks and extend them to human embryonic stem cells using a transcript-level reporter approach, though direct mechanistic comparisons with prior studies require care given differences in assay systems and model organisms.

Nat1 altered translation output in a subset of eIF4G2-associated conditions. However, direct comparison between Nat1-treated and eIF4G2-knockdown conditions was not statistically significant. The current dataset therefore supports a transcript-dependent modulatory effect in human embryonic stem cells. This is consistent with the established biology of Nat1 in stem cells: Sugiyama et al. (2017) showed that Nat1 promotes translation of specific differentiation-inducing proteins in mouse embryonic stem cells rather than acting as a general translation factor, which may explain why its effects here are transcript-selective rather than global.

More broadly, the study supports that eIF4G1 and eIF4G2 appear to participate in overlapping but non-identical initiation landscapes, and transcript structure likely helps determine which route remains available when one factor is reduced. That conclusion is consistent with the broader literature on translational plasticity under stress.

The computational framework complements the wet-lab findings by generating hypotheses about which sequence features might contribute to translational flexibility. The observation that 58.33% of eIF4G2-associated transcripts retained or increased translation after eIF4G2 knockdown is consistent with the presence of alternative initiation features in their 5' UTRs, and provides direction for future studies on the specific mechanism. In this context, it is important to note that CLIP-seq and similar approaches would be needed to directly map eIF4G-RNA interactions.

Implications

If future experiments confirm that the GC-rich motif identified here (AGGAAGATGGAGGCCG) forms a functional G-quadruplex structure—for instance via SHAPE-MaP or direct biochemical assay—such structures could represent candidate vulnerabilities in cancers reliant on stress-adapted translation. G-quadruplex-forming sequences in 5' UTRs have been independently shown to regulate translation of oncogenes such as c-MYC, and G-quadruplex structures have been explored as therapeutic targets in colorectal cancer and renal cell carcinoma (Neha et al., 2020; Bugaut & Balasubramanian, 2012). CX-5461 (Pidnarulex), a G-quadruplex-stabilizing small molecule currently in Phase I clinical trials for BRCA1/2-deficient solid tumors and with demonstrated preclinical activity in colorectal cancer models (Xu & Hurley, 2022; Otto et al., 2022), is one example of how G-quadruplex biology is being translated toward the clinic. Sequence features identified in the present study lend themselves to further validation in disease contexts.

In cancer biology, that possibility is preliminary. While current data are not sufficient to establish therapeutic targeting strategies, they do nominate transcript features and candidate genes that could be evaluated in more focused disease-specific studies. Finally, the identification of candidate eIF4G2-binding transcripts involved in processes such as zinc transport (Slc39a7) and protein ubiquitination (Rspr1) nominates specific pathways for further study in the context of stress-adapted translation, and could be therapeutically relevant in cancer.

Limitations

Potential G-quadruplex formation and other related RNA structures were inferred only indirectly from GC-rich sequence features and therefore require experimental confirmation. Methods such as SHAPE-MaP, mutational analysis, or orthogonal biochemical assays would be needed to determine whether any such elements are used during initiation in these transcripts.

The fixed 24-hour IAA treatment window may also obscure earlier or transient responses to factor depletion. Time-course experiments would be required to distinguish immediate initiation effects from later compensatory changes.

The study does not include patient survival data or disease-specific analyses; claims about biomarker utility or TCGA-derived hazard ratios are not made here, as no such analysis was conducted. Disease-oriented connections are exploratory and need a separate, fully described analysis pipeline.

Conclusion

This study provides evidence that eIF4G isoforms do not function as universally essential scaffolds for all transcripts, and instead participate in overlapping and context-dependent modes of translation initiation. Three key findings emerge: 1) translational flexibility, 2) candidate disease relevance, and 3) candidate eIF4G2 specialization.

Nearly all eIF4G1-associated transcripts maintained or increased translation after eIF4G1 knockdown, and a majority of eIF4G2-associated transcripts did likewise after eIF4G2 knockdown. This is consistent with the operation of alternative initiation features within specific 5' UTRs, though the precise mechanisms - which

may include G-quadruplex-forming motifs, IRES-like elements, or other structural features - require experimental confirmation.

Several transcripts elevated upon knockdown - including Apoc1 and Cd151 - have documented roles in cancer progression (Liu et al., 2021), and the GC-rich sequence motif identified across Class 1 transcripts is compositionally consistent with G-quadruplex-forming elements that have been studied as therapeutic targets in colorectal and renal cell carcinomas (Neha et al., 2020; Bugaut & Balasubramanian, 2012). G-quadruplex-targeting agents such as CX-5461 have shown preclinical activity in colorectal cancer (Otto et al., 2022) and are under clinical investigation. These connections are hypothesis-generating and need future validation.

RBPMap analysis (see Supplementary Materials) identified high-density predicted binding sites for eIF4G2 in transcripts involved in ion transport (Slc39a7) and protein ubiquitination (Rspr1), raising the hypothesis that eIF4G2 may preferentially associate with stress-relevant transcripts. This interpretation is preliminary and requires biochemical validation.

Future work could test individual candidate motifs by targeted mutagenesis in reporter constructs or by CRISPR-based editing in cellular models. Such experiments would help determine whether the motifs highlighted here are necessary for the observed translation patterns. Additional biochemical and structural approaches, including RNA-structure probing and direct assays of ribosome recruitment, could further clarify how Nat1, eIF4G1, and eIF4G2 contribute to transcript-specific initiation choices. Integrating those experiments with richer transcriptomic datasets may ultimately help distinguish which features are broadly generalizable and which are specific to particular cell states, stress conditions, or transcript classes.

Code Availability

The code for this project is available at https://github.com/chiwibbeans/yamanaka_computational.

Supplementary Materials

Supplementary materials can be found online at thurj.com.

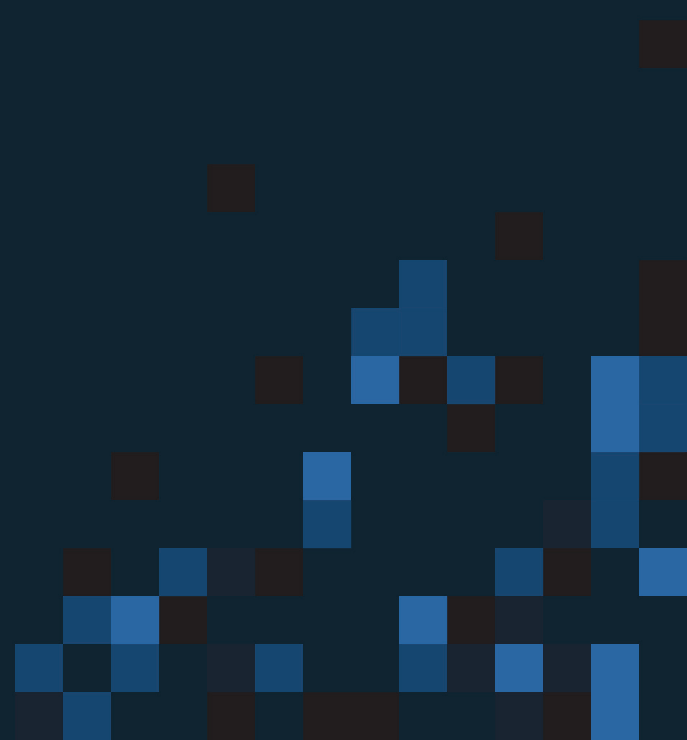
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Features



Needles in a Cosmic Haystack

Strong Gravitational Lensing as a Pioneer of 21st-Century Astronomy

By Ori Shi
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Image courtesy of ESA/Hubble.

Introduction

Strong gravitational lensing occurs when a massive object warps the fabric of spacetime, causing light from behind it to bend while it passes by (Treu, 2010). The resulting magnification makes strong gravitational lenses a long-coveted tool for studying everything from black holes to the birth of the universe. Though predicted by Einstein's Theory of Relativity as early as 1912, these "imperfect natural telescopes" have remained elusive, with astronomers discovering only a few dozen lenses by the turn of the 21st century (Treu, 2010). Yet the recent advent of astronomy's Big Data era, powered by telescopes like the Sloan Digital Sky Survey (2000) and the Vera Rubin Telescope (2025), has ushered in a profound change in the field (Barone et al., 2025). These survey-style telescopes have created a new epoch of data availability, and will soon be able to image millions of objects per night, covering ever-wider areas of the sky in myriad wavelengths.

However, the field of strong gravitational lensing now faces new challenges. The biggest hurdle is no longer detecting *enough* lenses (there are now over one thousand confirmed lenses), but rather efficiently identifying lenses within piles of data and building accurate simulations (Shajib et al., 2025). This article will explain the physical processes behind strong gravitational lensing, investigate the new issues faced by the field in its Big Data era, and introduce how researchers are turning to neural networks to break through these bottlenecks.

Strong Gravitational Lensing

Objects massive enough to warp spacetime (e.g., black holes, large galaxies, galaxy clusters; Treu, 2010) to the extent that causes strong gravitational lensing are called "deflectors." This curvature of spacetime refocuses and redirects light passing by it, and causes an observer on the other side to see magnified, multiplied, and distorted images of the light's source (Figs. 1 and 2). Thus, it is the precise alignment required between an observer, the deflector, and the source(s) that make strong gravitational lenses so rare.

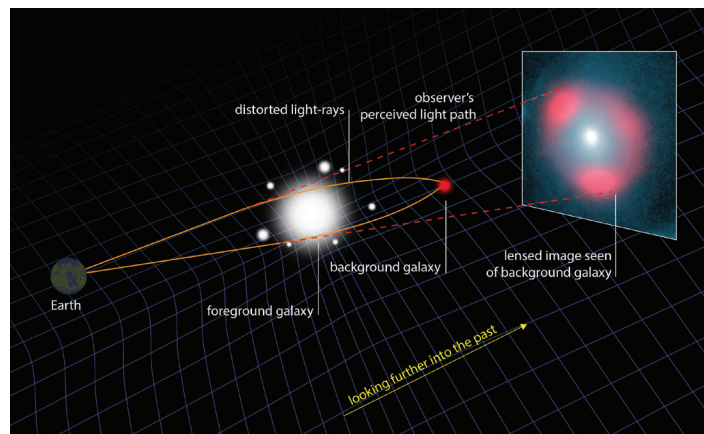


Figure 1. Light from a background galaxy bends as it travels through the warped spacetime around the foreground galaxy. (Image courtesy of Iris Sung; adapted from image courtesy of ESO/NRAO/NAOJ.)

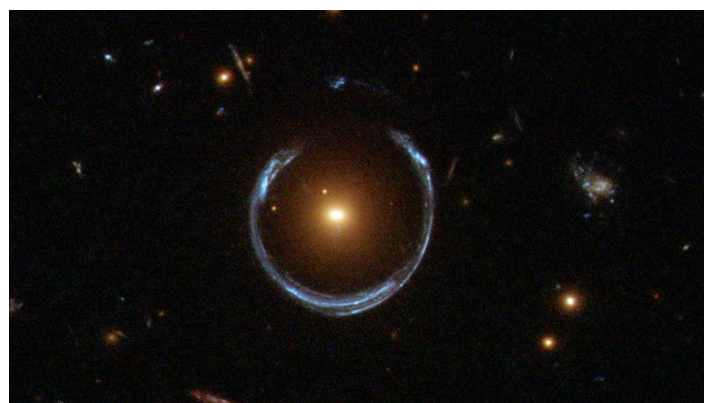


Figure 2. The most recognizable feature of a strong lens is its "Einstein Ring." These thin arcs come from the light of background galaxies being distorted by the orange deflector in the foreground. (Image courtesy of ESA/Hubble.)

Two properties make strong gravitational lenses a powerful tool to probe the universe's composition and evolution. First, recording how sharply light curves when passing by a deflector allows astronomers to measure the deflector's mass (Treu, 2010). This is crucial for astronomers to develop better understandings of otherwise "invisible" objects like black holes and dark matter. Second, the natural magnification of light from lensed sources allows astronomers to see faint and distant objects in greater detail than current telescopes can achieve (Zheng et al., 2012). Since light takes a finite amount of time to travel, seeing distant objects also means seeing further back in time. Thus, analyzing the source, deflector, and surroundings of strong gravitational

lenses can help astronomers glean information about a variety of objects and processes. For example, astronomers at the Harvard and Smithsonian Center for Astrophysics are using images of strong lenses with distant galaxy deflectors to model their mass distribution and weigh the massive black holes at their centers. By comparing these metrics of galaxies with different distances, which they are therefore viewing at different points in the past, astronomers can deduce how black holes evolve with respect to their host galaxies. (Bowden et al., 2025; Sahu et al., 2024).

Information and Computational Bottlenecks

Although studying any physical phenomenon in the 21st century requires collecting and analyzing many data points, astronomers who study gravitational lensing face uniquely high computational and information barriers to scientific progress.

Firstly, the unprecedented influx of data coming from powerful new telescope surveys has made the traditional way of discovering lenses too time- and resource-intensive. Since strong gravitational lenses are exceedingly rare, searching for them amidst the Big Data era is akin to trying to find a needle in an ever-growing haystack. Traditionally, astronomers identify lenses through a two-step observation and analysis process: They begin by manually looking through telescope images for lens-like objects. Then they differentiate real lenses from lookalikes by conducting targeted follow-up observations with a spectrograph, which spreads light out into a range of wavelengths and allows astronomers to tell whether the central source and surrounding arcs are truly separate objects (Fig. 3; Barone et al., 2025).

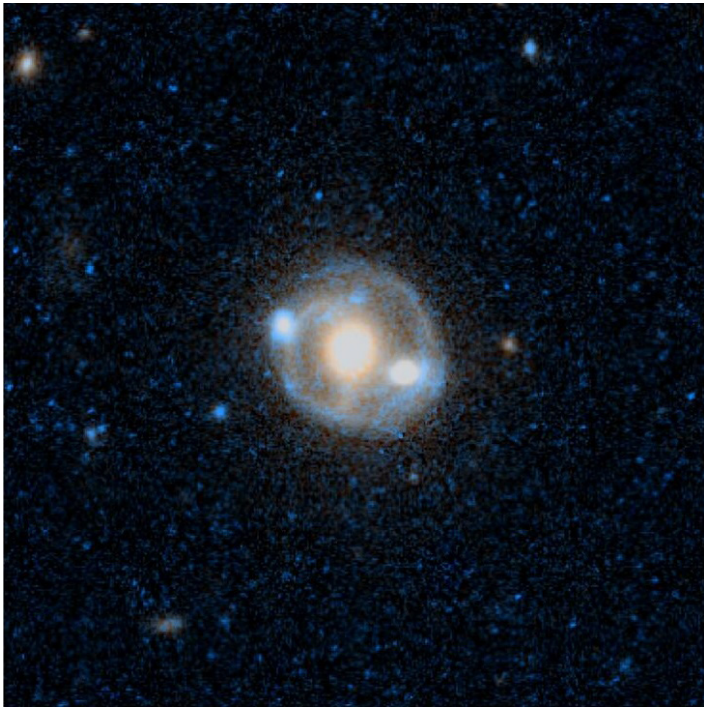


Figure 3. A ring galaxy with arms that look deceptively similar to the Einstein Ring produced through gravitational lensing. This object was confirmed to be an imposter after spectrographic imaging (Barone et al., 2025).

Critically, the arrival of survey-style telescopes means that it is no longer possible for researchers to identify lenses by parsing through

each image. If astronomers cannot meaningfully process most of the data, the huge leaps made by telescope instrumentalists will only translate into a tiny step forward in humanity's understanding of strong lenses. Researchers will not be able to find and take advantage of the hundreds of thousands of lenses hiding within the images of new surveys—and the lenses that they do identify and confirm with their limited follow-up time may not be the most scientifically valuable if they cannot see the broader picture in the cumulative set of lenses (Weiner et al., 2020).

Second, the complex environments that govern how gravitational lenses appear mean that immense computing power is required to work backwards from collected observations to the physical properties of the source and deflector. Many different source-deflector configurations can produce the same image for an observer on Earth. For example, two configurations with different deflector mass distributions and relative source positions can yield the same observed image. The absence of a one-to-one relationship that connects observations to a specific configuration of sources and deflectors means that astronomers must go through an iterative modeling process.

Traditionally, astronomers start by providing a model with an educated guess about the system's physical properties, such as the suspected mass, size, and matter distribution of the lens and source. The software then tweaks these parameters slightly, each time generating a new image of what a telescope would observe until it closely matches the actual observations. Therefore, generating a correct lens model requires first generating tens of thousands of incorrect models (Park et al., 2021). This inefficiency essentially wastes computational resources, something which astronomers can no longer afford as the amount of lenses grows faster than the amount of available computational power for any given lab (Park et al., 2021; Shajib et al., 2025). Since all applications of lenses must contain modeling at some step, efficient modeling poses the most critical bottleneck for better understanding of the universe.

Neural Networks Emerge as a Solution

Convolutional neural networks (CNNs) are a special type of neural network built for image classification and object recognition (IBM, n.d.). Their rapid and self-augmenting pattern recognition capability makes CNNs the perfect tool to push past strong gravitational lensing's most pressing computational bottlenecks. Excitingly, the promising results of groups currently developing CNNs suggest that neural networks will revolutionize the field of gravitational lensing.

One research group pushing the frontier of CNN-led lens identification is the ASTRO 3D Galaxy Evolution with Lenses (AGEL) Survey, headquartered at the Harvard-Smithsonian Center for Astrophysics. In 2022, AGEL trained a CNN to achieve a lens identification success rate of 88%, and published a survey of the 68 lenses which the neural network found (Tran et al., 2022). The role of neural networks as a turning point in lens identification is evident from the fact that, within four years, AGEL had confirmed the second-highest number of lenses of any survey, surpassed only by a group with 15 years of publications (SLACS, n.d.). A second round of data in 2025 saw a success rate of 96% (Barone et al., 2025). Critically, AGEL's progress will continue to accelerate: lenses

identified by current CNNs expand the datasets which train the next generation—making models more efficient and accurate.

On the modeling side, a team at the University of Chicago has created a fully-automated modeling system through training a CNN on a dataset of images and associated models. Given a new image of a strong gravitational lens, the CNN can propose a new model which a traditional modeling software only needs to iterate over a couple times before reaching a physical reconstruction that matches the image (Shajib et al., 2025). Whereas conventional modeling could take months under personal supervision, such CNNs will soon allow astronomers to create thousands of lens models on just one Graphics Processing Unit, with each iteration of an image generated in less than a second (Gentile et al., 2023; Park et al., 2021).

As more groups work on expanding the types of lenses that CNNs can model, astronomers will finally be able to tap into the full potential of lenses as cosmological probes. From studying how black holes evolve, to probing dark matter and quantifying the universe's accelerating expansion, neural networks are turning the 21st-century data deluge into a better understanding of the fundamental nature of the universe.

Looking Forward

Although strong gravitational lensing's unique computational barriers compelled the subfield's early adoption of neural networks, lensing is not the only subfield which neural networks will benefit. As lensing experts develop more neural networks, they will inspire, inform, and learn from other subfields of astronomy—especially ones that study rare phenomena or require intensive data analysis. For example, exoplanet astronomers are working on training networks to identify Earth-like planets amidst thousands of light curves (Wang, 2025). While the accelerating use of AI in science may be challenging for some to accept, the overarching benefit of neural network adoption in astronomy is clear: Ultimately, when astronomers are able to spend less time and resources on cranking computations, they'll be able to turn their attention to developing new questions to explore.

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Reshaping the Neural Architecture of Hunger

The Role of a GLP-1 Receptor Agonist

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Image courtesy of Getty Images, as featured in Young (2025).

Introduction

The World Health Organization reports that obesity rates have doubled in adults and quadrupled in adolescents over the last thirty years, and with obesity rates steadily rising immediate remedies to this global crisis have never been more urgent (Fasano, 2025). Yet since 2020, prescriptions for glucagon-like peptide-1 (GLP-1) receptor agonists, what many are calling the miracle drug for weight loss, have more than tripled, with approximately 11.8% of Americans reporting use of some form of GLP-1-based therapy (Bozick et al., 2025). These synthetic agents mimic the body's natural GLP-1 hormone, allowing them to bind to the same receptors and replicate its regulatory functions. Their easy access, self-moderated application, and efficient mass reduction makes losing weight feel effortless. Clinical trials have further demonstrated significant weight loss and cardiovascular benefits, and future directions show growing interest in applications for substance use disorders (Amorim et al., 2025).

However, as GLP-1 therapies continue to hit the market, conflicting information spreads alongside ongoing research, revealing just how much we have yet to uncover about GLP-1's actions and its long term effects. GLP-1 cells found in the brain, gut and nervous system all work together to reshape individuals' appetite, body weight, and regulatory processes. Utilizing an intricate signaling cascade, natural GLP-1 activates neural signals controlling motivation or suppression of hunger in the hypothalamus, and ultimately influences important neural pathways throughout the body. Examining not just GLP-1 receptor agonists' metabolic impact, but also its ability to modulate neural

circuits that govern appetite and motivation, reveals potential long-term neuromodulatory consequences of chronically altering the brain's regulatory systems.

The Evolutionary Architecture of Hunger

Hunger is an adaptive, layered system evolutionarily conserved to optimize survival in energy-scarce environments (Lea et al., 2023). However, the emergence of agricultural farming and industrialization provided a solution to what once threatened our survival. Now, with overwhelming availability of food and little cost expended to acquire food, we are confronted with an evolutionary mismatch between our evolved biology and current environment (Ayyad, 2026). Humans must manage a system that persistently drives food intake even when energy needs are met.

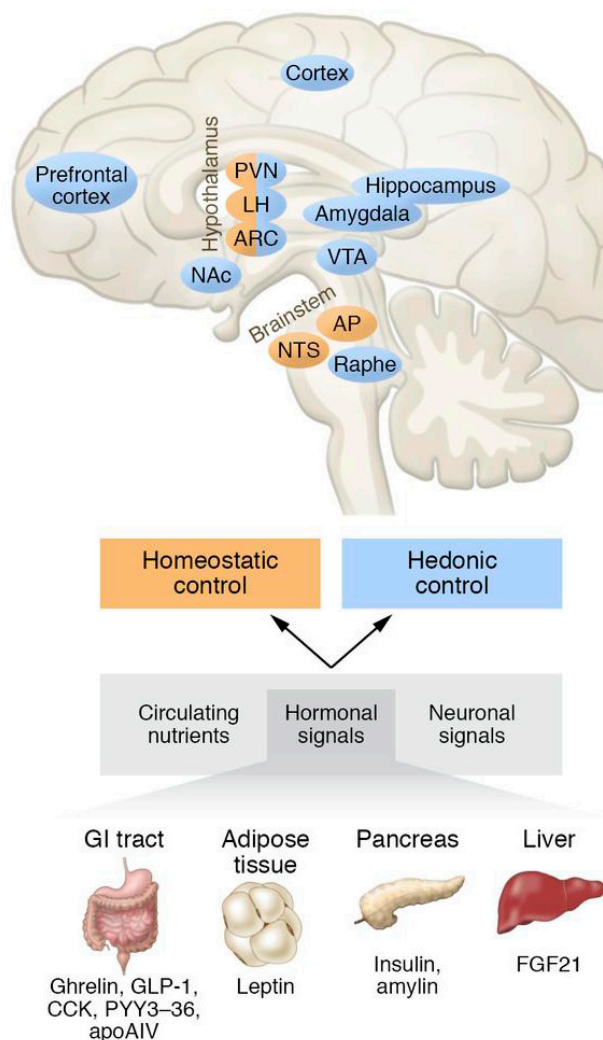


Figure 1. Key systems in appetite signaling. In orange is the homeostatic system, where physiological signals from vital organs send hunger level cues. In blue is the hedonic system that serves as a connection to reward centers responsible for food motivation (Stemmer et al., 2019).

Similar to other systems such as the visual and olfactory systems, hunger uses a form of parallel processing where multiple pathways can be activated simultaneously to create a unified response for addressing hunger signals. Our hedonic system influences

the psychological factors of appetite processing (Fig.1). It is responsible for regulating our motivations towards food signals, and the gratification of eating. Feelings of temptation or desire are governed by this system, both due to the abundance of highly saturated food, but also because of the presence of dopamine signaling, which amplifies the pleasure and incentive value of food (Kinasz et al., 2017).

This system is counterbalanced by our homeostatic system that activates based on physiological signals, relying on metabolic cues to trigger a response (Fig. 1). When someone experiences hunger, ghrelin hormone signals are activated from the gut and travel through the endocrine system to alert the body that it requires food (Fasano, 2025). Simultaneously, agouti-related peptide (AgRP) neurons, which strongly promote food consumption, respond to this energy deficit by expressing a persistent signal to seek out immediate sustenance (Chen et al., 2016).

Together, these primal systems drive food-seeking behavior and support the body's ability to restore nutritional balance. Yet, in the modern day, our psychological needs can override our physiological state due to constant food cues from endless food advertisements, or the oversaturation of fast food establishments. Together these low cost, high reward options prevent clear distinctions between hunger and satiety (Fasano, 2025). As a result, homeostatic signaling may remain chronically active or dysregulated, further contributing to excessive intake. Prolonged imbalance of hunger signals causes the body to become defensive of vital organs such as the heart and the brain. (Kim et al., 2025; Fasano, 2025).

Recognizing hunger as a tightly regulated system designed to resist energy deficits demonstrates its evolutionary complexity and reveals how clearly tied it is to our survival. Pharmacological suppression of GLP-1 receptor agonists intervene directly within this naturally selected arrangement, and present the potential to not simply correct a seemingly dysfunctional system, but rather intervene in regulatory systems meant to maintain internal balance. If these signals are chronically dampened, their long-term influence may extend beyond appetite reduction and into the broader scheme of human energy regulation.

Pharmacokinetics and GLP-1 Mechanism

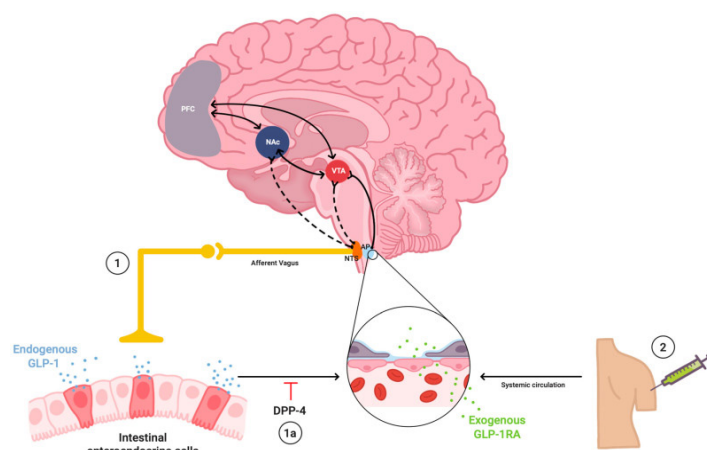


Figure 2. Endogenous GLP-1 is secreted in the body and is inhibited by DPP-4 (Amorim et al., 2025).

As part of this evolutionarily conserved architecture, satiety signals are designed to be brief and tightly regulated, preventing prolonged suppression of this critical system. Availability of endogenous GLP-1 is important for ensuring adequate regulation of blood sugar, and with a half-life of one to two minutes, approximately 10-20% of naturally produced GLP-1 is available for use (Peri et al., 2025). Hence, GLP-1 agonists' prolonged activation overcompensates for natural GLP-1's succinct signaling mechanism by elevating GLP-1 concentration.

Researchers have attempted to directly block GLP-1 inhibitor dipeptidyl peptidase-4 (DPP-4) as a manner to elevate GLP-1 concentration, but this has resulted in only a modest increase in GLP-1. This is caused by DPP-4 inhibition relying on meal-stimulated hormone release, but due to low baseline levels of natural GLP-1 in the body, inhibiting only results in minimal increase of GLP-1 concentration even when unsuppressed (Gilbert, 2020). For that reason, therapeutic GLP-1 receptor agonists today are structurally engineered to resist degradation and act independently of endogenous GLP-1 secretion (Fig. 2).

The development of these long lasting receptors is derived from the saliva of the Gila monster lizard, which contains a protein structurally analogous to GLP-1 (Deane et al., 2010). By synthetically replicating the venom, GLP-1 is modified from its intermittent signaling to produce prolonged receptor activation extending signaling from minutes to hours or even days. At the molecular level, this prolonged response prevents satiety signals from being turned off, causing meal-triggered GLP-1 responses to be stacked upon each other. At the physiological level, this sustained response dulls intracellular machinery that processes "I am eating" signals, and as a result fundamentally alters modulatory signaling of both blood sugar and hunger signaling (Gilbert, 2020).

Yet, with prolonged activation comes a shift in the appetite regulation system. Calcium signaling, essential for insulin secretion and metabolic balance, is disrupted by the active GLP-1 signal mimicked by the receptor agonist. This disruption consequently affects the signaling cascade in charge of indicating hunger or satiety (Kim et al., 2025). Under natural signaling, food is processed in short bursts as the meal gets digested, hence why we often feel full mid-meal, but hungry again within a few hours. However, with prolonged receptor engagement, signals from intracellular messengers are extended beyond their typical duration, and result in repeated activation of pathways that present a sense of fullness to the individual (Peri et al., 2025). It is precisely this shift from pulsed to sustained signaling that positions GLP-1 receptor agonists not just as metabolic regulators, but as key neurological moderators of appetite and reward processing.

Neuromodulation and Reward Pathways

Furthermore, the extended signaling of GLP-1 receptor agonists can influence more than just the intracellular processing of hunger, but neural pathways beyond appetite regulation alone. Through activation of established hunger pathways, coupled with prolonged signaling, GLP-1 receptor agonists can influence neuromodulation of reward circuits, and intervene directly in the brain's reward system to alter how motivation is processed. The mesocorticolimbic dopamine system is the brain's primary reward circuit network responsible for gratification, motivation, and in some cases, addiction. It comprises

the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC) (Amorim et al., 2025). Both receptors and GLP-1 producing neurons appear in these regions of the brain, which positions GLP-1 to be highly influential over motivational aspects of feeding (Mietlicki-Baase, 2014).

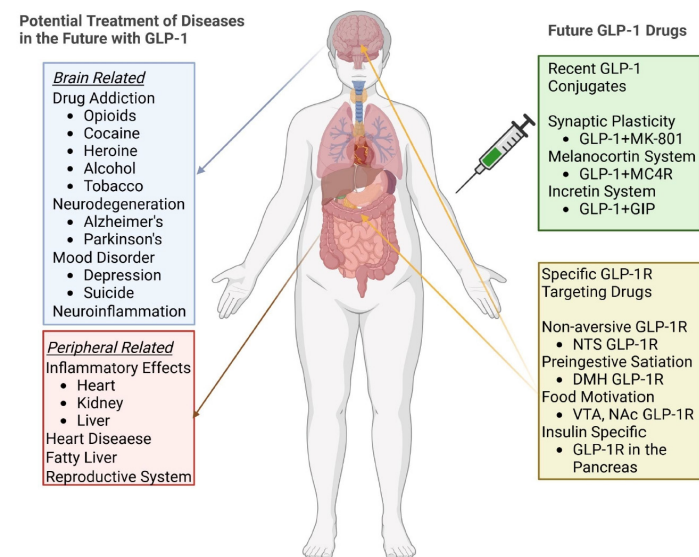


Figure 3. The potential applications of GLP-1 to medical treatments beyond diabetes and weight loss (Kim et al., 2025).

The hedonic system, our evolutionarily established system for reward signaling, functions as a component of the larger mesolimbic system that regulates reward. The hedonic pathways serve as the behavioral output of food motivation, while the mesocorticolimbic system expresses the biological mechanism underlying our behavioral drive to seek and consume it (Amorim et al., 2025; Fasano, 2025). To better understand the function of reward circuits and desire-seeking behavior induced by GLP-1, researchers tested rats' behavioral response to blocking GLP-1. In one experiment, rats learned to associate a location with a reward, yet after GLP-1 administration, they lost preference for that location, not because of forgotten association, but reduced motivation. Similarly, rats that had previously worked for rewards by pressing a lever showed no interest in doing so following GLP-1 suppression (Dickson et al., 2012). These studies offer insight into how motivational and hedonic values are transformed by GLP-1 blocking.

Previously, scientists believed dopamine signaling was the strongest explanation for reward modulation, associating increased levels of dopamine with higher levels of motivation (Alhadeff et al., 2012). However, emerging models suggest that manipulating the signaling of glutamate, the brain's primary excitatory neurotransmitter, may play a key role in motivation processing. With GLP-1 receptors positioned in the VTA, NAc, and PFC, their activation stimulates presynaptic glutamate neurons, increasing glutamate release. These elevated glutamate levels then signal target neurons, particularly medium spiny neurons in the NAc, which integrate incoming signals to determine behavioral responses (Mietlicki-Baase, 2014). This suggests that while dopamine signaling explains how motivation levels increase or decrease,

glutamate signaling demonstrates how motivation is evaluated and ultimately shapes goal-guided behavior.

This proposed model is particularly relevant in the context of addiction, as the same mesolimbic circuits that govern food-related reward also underlie substance-seeking behavior. Through glutamate mediated signaling, GLP-1 receptor agonists can expand the modulation of reward circuits, and extend signaling to the regions of the brain responsible for emotional processing and decision making. These regions intersect in hunger signaling through the gut-brain axis, which is a bidirectional system capable of regulating mood, motivation and reward seeking behavior via endocrine, neural, and immune pathways (Kinasz et al., 2017).

This broader neuromodulatory capacity has also opened avenues for exploring GLP-1's role in pain regulation. The dorsal horn acts as an initial relay center that determines how strongly pain signals are transmitted to the brain. Alterations in spinal excitatory synaptic transmission can therefore modify pain communication. Across species, pain levels are reduced after eating, and researchers have tried to explain this phenomenon with GLP-1 processing (Go et al., 2024). Studies in rats reveal that GLP-1 can attach to TRPV1 pain receptors, directly influencing the threshold at which the nervous system registers pain and discomfort. These synthetic agonists reduce excess excitation in the horn, thereby dampening the intensity of pain signals (Go et al., 2024).

Together, these findings point to a broader role for GLP-1 as a regulator of neural excitability across multiple systems involved in motivation, reward, and sensory experience. GLP-1's ability to simultaneously influence reward circuits, appetite pathways, and pain thresholds suggests that it is more than just a regulator for blood sugar, but also a multipurpose hormone with the potential of addressing more than just weight management, but chronic migraines, and addiction recovery (Go et al., 2024; Mietlicki-Baase, 2014).

Conclusion

GLP-1 signaling is tightly connected to the neural circuits that influence both metabolism and motivation, and the neuromodulatory effects of controlling this system requires further exploration. Its ability to effectively suppress hunger and assist with appetite regulation has increased its public standing as a strong weight loss therapeutic. GLP-1's presence within reward pathways, neurotransmitter signaling, and pain thresholds reflects how deeply integrated this hormone is within the body. GLP-1 receptor agonists alter this evolutionary stable system by dampening endogenous signaling with prolonged activation, and disrupting modulation of key reward centers.

As research continues to expand the therapeutic scope of GLP-1 receptor agonists, the methods of application used to administer the drug should adapt alongside it. Currently, GLP-1 receptor agonists extended activation provides the body with suppression of neural circuits, but ultimately returns back to its regular mechanism when treatment is halted. Therefore, people are obligated to take repeated dosages of GLP-1 receptor agonists at stronger concentrations without the system being corrected (Deane et al., 2010). Given the limited amount of present data on this rather novel drug, a growing list of common physiological side-effects is emerging under this current method.

Developing future approaches that avoid prolonged and ramped dosages, reduce indefinite suppression of the system, and recalibrate its relationship with metabolism and reward may be the first step towards reshaping our neural architecture of hunger.

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Invisible Patients

The Hidden Health Costs of Caregiving

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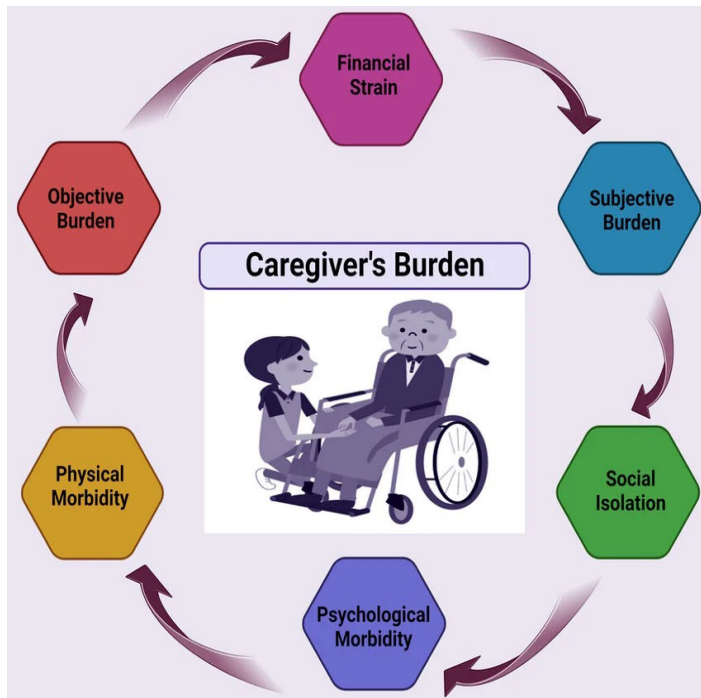


Figure courtesy of Sehar et al. (2023).

Introduction

The United States is rapidly aging—between the years 2004 and 2024, the aging population (65 and older) has increased by 5.6% (Lin & Horowitz, 2025). By 2034, this population will outgrow the population under 18 years of age (United States Census Bureau, 2018). The declining birth rate, size of the Baby Boomer generation, and heightened life expectancy have culminated in a massive need for caregivers, the majority of whom are family members. Roughly 24% of the U.S. population report fulfilling the role of a caregiver (The National Alliance for Caregiving & AARP, 2025), and caregivers often report the positive impact of caregiving on their interpersonal relationships, increased meaning in one's life, and a sense of giving back (American Psychological Association, 2011). Yet its repercussions—which include high stress, depression, and chronic inflammation (Christian, 2023)—remain invisible in the modern U.S. healthcare system.

Caregiving as a Chronic Biological Stressor

Caregiving produces biological responses comparable to other chronic stressors. Chronic stressors are defined as long-term activation of the stress response system, particularly the hypothalamic-pituitary-adrenal axis. This long-term activation

results in excessive exposure to cortisol (Mayo Clinic Staff, 2023), which increases the risk of heart disease, difficulties with memory and focus, depression, accelerated aging, and increased risk of health problems such as cognitive impairments and cardiovascular disease (Luecken & Lemery, 2004). In individuals experiencing high levels of psychosocial stress, proteins involved in managing inflammation may become dysfunctional, and this stress is associated with heart failure (Bidwell & Cothran, 2021). One population in which these physiological effects are especially pronounced is caregivers.

Although a clear definition is lacking, caregiver burden is widely understood to be a multifaceted strain perceived by the caregiver arising from prolonged exposure to chronic stressors, which can lead to widespread physiological dysregulation (Liu et al., 2020). Caregivers experience allostatic load, the cumulative burden of chronic stress and life events (Guidi et al., 2021). This burden is especially severe for those providing care for family members with mental illness, Parkinson's disease, dementia, and terminal cancer (Liu et al., 2020). Furthermore, men and women who provide care to a spouse with dementia experience more frequent infectious illness episodes, poorer immune responses, an increased risk of depression, and higher rates of hypertension (Christian, 2023). One of the many health risks that can be associated with caregiving is chronic inflammation and sustained overproduction of proinflammatory cytokines, which is linked to problems associated with aging such as cardiovascular disease, osteoporosis, arthritis, and type 2 diabetes (Christian, 2023). These effects have lasting impacts: Interleukin-6, a global marker of impending health deterioration, remains at similar levels in former and current caregivers, suggesting that the immunological impact continues years beyond the caregiving experience (Christian, 2023).

Psychological Stress and the Role of Stigma

The physical demands of caregiving are not the sole factors driving the health consequences. Psychological stress, often intensified by stigma—defined as societal labeling, stereotyping, and negative judgements—plays a critical role in shaping caregiver outcomes (Andersen et al., 2022). In caregivers, the particular manifestation is called caregiver affiliate stigma, in which caregivers internalize societal biases that eventually leads to negative self-perceptions and social withdrawal (Becerra Carrillo et al., 2024). Caregiver affiliate stigma encompasses three different types of stigma: public stigma, courtesy stigma, and family stigma. Public stigma involves the negative societal reaction toward individuals the caregiver is in charge of. Courtesy stigma extends the discrimination and negative perceptions of those with conditions needing caregivers transfers onto the caregivers themselves due to their association, affecting how they see themselves. Finally, family stigma involves the negative experiences of family members connected to the relatives with stigmatized conditions.

The combination of these stigmas results in increased caregiver burden and stress. For instance, it was found that caregiving for those with neurodegenerative disorders was associated with substantial psychological stress that exceeded physical strain (Becerra Carrillo et al., 2024). In addition to that, higher levels of affiliated stigma results in caregivers perceiving higher burden (Kaggwa et al., 2023). Essentially, the stigma tied to caregiving

and associated conditions intensifies stress, worsening mental and physical health, negative self-perception, and caregiver burden. For example, men who strongly identify with traditional male roles can feel judged for caregiving, tending to isolate themselves more, limiting emotional expression and support-seeking behaviors (Bhatt et al., 2022). In many cases, caregivers experience enacted stigma, such as staring and social exclusion, that pushes them to self-isolate as well (Sommers-Spijkerman et al., 2023). Altogether, these intersecting forms of stigma intensify caregiver burden by compounding psychological distress, ultimately exacerbating both mental and physiological health outcomes.

Structural Invisibility of Caregivers

Despite the substantial evidence of physiological and psychological risk, caregiving remains structurally invisible within healthcare and policy systems. Informal caregivers dedicate significant time and energy to work that is physically, socially, and emotionally demanding, yet their needs are rarely formally addressed in clinical care. They are often treated as secondary to patients, with limited institutional support or recognition of their health risks. In a national study, it was reported that only 16% percent of healthcare providers asked caregivers what resources they need for their own health and quality of life. This is in comparison to the 33% of caregivers that reported that they were asked what was needed to provide quality care to the care recipient (Barnhart, 2020). This invisibility persists despite evidence that the psychological burden associated with caregiving—particularly in the context of cancer—can exceed that of the patients themselves (Applebaum, 2015). This raises the question of why such a high-burden role remains consistently underrecognized.

One key explanation lies in cultural norms that frame caregiving as an expected moral obligation rather than a form of labor requiring support. In many communities, particularly among minority populations within the United States, caregiving is framed as a moral and spiritual responsibility, and an expression of intergenerational respect (Okigbo et al., 2025). The cultural emphasis on familism in Hispanic populations, for instance, drives caregivers to neglect their own health (Falzarano et al., 2021). This normalization contributes to the systematic overlooking of caregiver wellbeing. In conjunction with this, caregiving is often viewed as a natural, gendered duty, allowing others to overlook the wellbeing of caregivers. For example, in Japan, family caregiving is seen to be a common and expected part of relationships, particularly for women (Zarzycki et al., 2022).

Gender also plays a significant role in shaping concerns about caregiver health, with women accounting for roughly two-thirds of family caregivers (Barzallo et al., 2024). Despite a trend of more men taking on caregiving duties, female caregivers report a higher caregiver burden (Applebaum, 2015). Societal expectations often place women in the category of being selfless providers with roles centered on the home and family obligation. In contrast, there is a societal expectation that men be competitive, independent, and avoid weakness, shaping caregiving approaches that are more managerial (Barzallo et al., 2024). This expectation for men in caregiver roles leaves no room for emotion, further forcing male caregivers and the healthcare system to ignore their psychological

needs. These different expectations contribute to a system where caregiver health is deprioritized and result in unequal burdens and lack of support.

Conclusion

Chronic illness diffuses across relationships, and therefore care must consider both the person being cared for and the person's caregivers. Despite the essential work caregivers do, most health care delivery models focus primarily on patients, failing to engage, educate, or support informal care providers (McHugh et al., 2025). The lack of internal resources, including coping behaviors, and external resources—such as financial support, help from other family members and formal care—result in caregivers experiencing high levels of stress (Roth et al., 2015). If caregiving constitutes a health risk exposure, then public health systems bear the responsibility of implementing policies that mitigate its physiological and psychological consequences. Evidence shows that caregiver interventions are effective, with 23 out of 26 reviews reporting reduction in caregiver depression and 9 out of 16 reviews showing decreased caregiver burden (McHugh et al., 2025). However, the persistence of caregiver burden despite these findings suggests that existing interventions are not being implemented at the required scale or integrated into standard care.

This gap highlights a critical opportunity for health systems to move towards structural reform. Accordingly, efforts should focus on better preparing caregivers, reducing stress and guilt of failing through education, and improving dissemination of information to healthcare providers to increase awareness of caregiver health (Roth et al., 2015). External factors, such as finances, have been found to be an added stress to caregivers. Therefore, some have suggested economic support resources, such as travel reimbursement, primary caregiver compensation by insurers, and the development of more accommodating policies that support family leaves of absences, are also needed (Roth et al., 2015). Furthermore, caregivers' health should be incorporated into the care plan and documented in health records to reduce their invisibility. Such efforts address the economical and emotional needs of caregivers, targeting the root of the stress that makes caregiving a health risk. Making caregivers visible is not simply an ethical imperative, but a necessary step towards improving population health as the aging community continues to grow.

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Cellular Multitasking

Protein Moonlighting in Cancer

By Iphia Zhang
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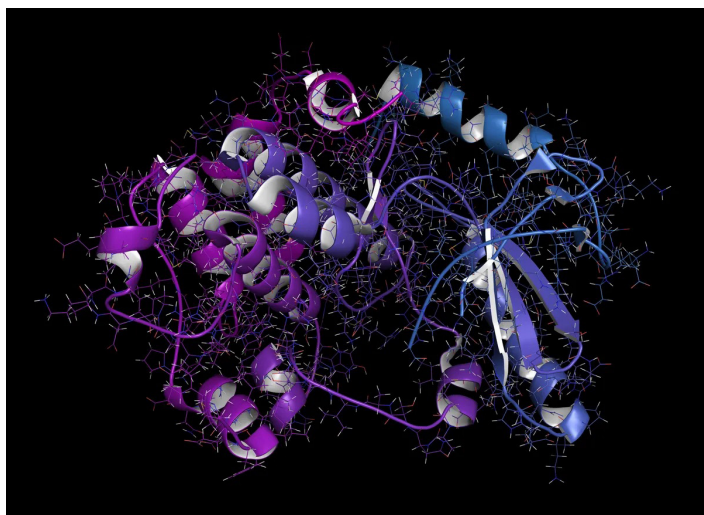


Figure courtesy of Alamy Stock.

Introduction

Cancer is a group of diseases characterized by uncontrolled cell division. Within cancer cells, the coordinated activities of molecules allow for adaptation to hostile environments and often confer resistance to treatment (Housman et al., 2014). Among these molecules are proteins, whose diverse roles play out all across the cell, from structural support and transport to signaling and metabolism (Morris et al., 2022). Traditionally, individual proteins have been viewed as having single, well-established functions, in line with George Beadle and Edward Tatum's well-known 'one gene-one enzyme' hypothesis (Beadle & Tatum, 1941). In the 1980s, protein multifunctionality was suggested when molecular biologists Joram Piatigorsky and Graeme Wistow noticed that some crystallins, structural proteins found in vertebrate eyes, also function as enzymes. Initially described as gene sharing, this phenomenon, where proteins can perform several unrelated functions, has become known as protein moonlighting (Huberts & van der Klei, 2010). Moonlighting proteins have recently emerged as potential targets in cancer therapy.

Many moonlighting proteins help maintain homeostasis by serving as receptors, signaling molecules, or gene expression regulators (Jeffery, 2017). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), for example, is a known enzyme in glycolysis, but can also influence gene expression by affecting the stability of DNA and gene products (Adamo et al., 2021). When cellular iron levels are low, GAPDH can also localize to the cell surface to act as a receptor for a protein that binds iron (Kumar et al., 2011).

However, moonlighting proteins can also contribute to disease – more than 78% of known moonlighting proteins are associated

with human pathologies. Changes in the cellular environment during disease development can activate the pathogenic moonlighting functions of moonlighting proteins (Huerta et al., 2023). For instance, GAPDH can also support hepatitis C infection of host cells by aiding in viral replication, and in many bacteria, glycolytic enzymes secreted to the cell surface support bacterial colonization of host cells (Raj et al., 2017; Rodríguez-Saavedra et al., 2021). Currently, cancer therapies commonly target proteins based on a single pathogenic function (Kędzierska & Bańkosz, 2024). However, targeting moonlighting proteins may enhance therapies, as inhibition of one protein can inhibit several pathways that together promote cancer survival. Exploiting the versatility of moonlighting proteins may allow medicine to better overcome the resilience of cancer cells.

Moonlighting Proteins in Cell Growth and the Cell Cycle

Moonlighting proteins are emerging as important players in the cell cycle, whose dysregulation gives rise to cancer. In the cell cycle, moonlighting proteins help repair DNA, trigger cell death, and interact with other cell cycle proteins to modulate progression through the cell cycle (Han et al., 2017; Manickavinayaham et al., 2020). The autosomal recessive hypercholesterolemia (ARH) protein, for example, has a primary function aiding the uptake of cholesterol from blood. However, ARH has also been shown to interact with the centrosome, an organelle that is vital for the partitioning of genetic material among dividing cells. During cell division, centrosomes build fibers that attach chromosomes, and ARH localizes to these attachment sites, helping to carry out proper division (Lehtonen et al., 2008).

Moonlighting proteins can also influence the cell cycle by acting in signaling pathways, thereby influencing a cascade of events. The Krebs cycle enzyme fumarate hydratase (FH) is one such protein. FH is primarily known to convert fumarate to malate in the Krebs cycle, but it also appears to be able to act as a tumor suppressor via inactivation of a growth receptor. In this way, FH helps maintain regulated growth of cells by preventing aberrant signaling (Wang et al., 2023). There appears to be a complex network of protein interactions that helps preserve the integrity of dividing cells, making it consequential when the proteins adopt rogue behavior.

Protein Moonlighting Supports Cancer Survival

Single moonlighting proteins may each sustain cancer cell proliferation through activity in multiple processes, thus therapeutically targeting them may significantly compromise cancer's resilience. Moonlighting proteins can help cancer cells rewire their metabolism, escape cell death, and invade nearby cells while evading the immune system (Adamo et al., 2021). A hallmark of cancer cells is their preference for energy generation via the oxygen-independent process of glycolysis, even in oxygen-rich environments (Liberti & Locasale, 2016). Many glycolytic enzymes are moonlighting proteins, including pyruvate kinase M2 (PKM2), which drives the final step of glycolysis (Gao et al., 2022). PKM2 supports cancer metabolism by allowing glycolysis to continually be used for energy production, but its moonlighting role also allows it to interact with proteins involved in pathways regulating cell death. PKM2 can both drive anti-cell death signaling and

inhibit cell-death pathways, thus its overexpression in cancer more directly bolsters cancer cell survival (Chen et al., 2026). PKM2 may be indicative of the therapeutic potential of other moonlighting proteins in cancer, where the inhibition of one protein can inhibit several processes necessary for proliferation, increasing cancer cell vulnerability.

Beyond resisting death at its site of origin, cancer can spread to healthy tissues, posing great therapeutic challenges and causing the majority of cancer-related deaths (Gerstberger et al., 2023). Metastasis requires the degradation of the molecular network surrounding cells, or the extracellular matrix (ECM). One moonlighting protein involved in this process is enolase, a glycolytic enzyme that can moonlight as a cell-surface receptor for a protein called plasminogen. Bound plasminogen can be converted into the plasmin protein, which can degrade the ECM. Thus, by promoting the production of ECM-degrading proteins, enolase aids cancer metastasis (Huang et al., 2022). Metastasis is also supported by the moonlighting function of the IDO1 protein, because cancer cells must also escape immune detection to metastasize. The IDO1 protein has a known enzymatic function in a signaling pathway, but it can also act as a signaling molecule in pathways suppressing immune cell activity. This activity hinders the ability of the immune system to detect cancer cells, allowing cancer cells to invade healthy tissues (Adamo et al., 2021).

Cancer cells are sustained by a complex network of interactions involving moonlighting proteins. This offers an opportunity for more effective targeting of cancer, as multiple processes needed for cancer cell survival may fall upon inhibition of just one protein's activity.

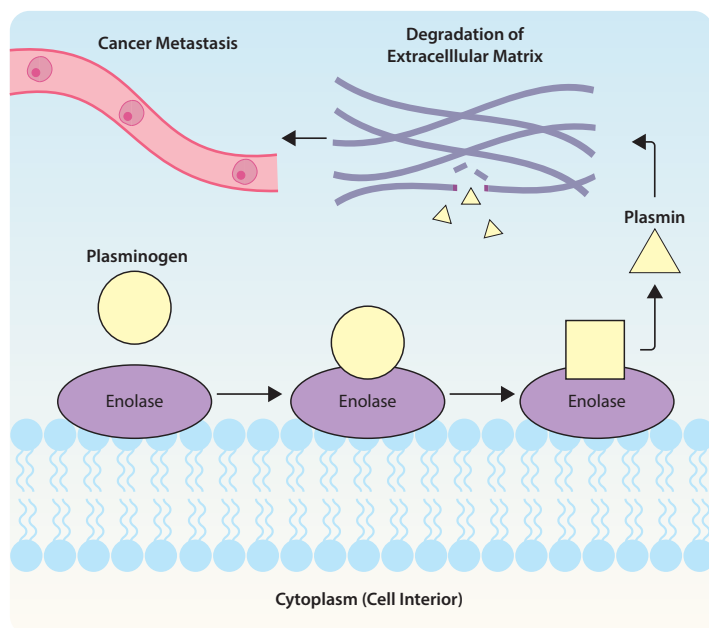


Figure 1. Enolase moonlighting supports cancer metastasis. (Figure courtesy of Krish Muniappan)

Targeting Moonlighting Proteins

Medicine has already made attempts to act on the understanding of protein moonlighting. Therapy against moonlighting proteins holds both promises and challenges. Inhibition of pathogenic

moonlighting proteins may be very effective at sensitizing cancer cells, as several abnormal activities can be targeted at once; however, this approach may lead to several side effects as the normal functions of the proteins may also be disrupted.

Challenges persist in targeting moonlighting proteins clinically, because some drugs may not produce an impactful response while others may produce undesired side effects. The drug epacadostat was developed against IDO1 and failed higher clinical trials when it was not sufficiently effective in cancer patients, possibly because the drug unintendedly led to further suppression of immune cells (Adamo et al., 2021). Additionally, as many existing therapies do, targeting a protein's moonlighting function may unavoidably affect its primary role, harming normal functions alongside pathological ones. Still, cancer medicine can benefit from targeting moonlighting proteins, as the activity of proteins enables the development of drug resistance that drives 90% of chemotherapy failures (Mansoori et al., 2017).

Laboratory investigations on targeting moonlighting proteins have revealed several new potential drugs and therapies. For example, the glycogen synthase kinase-3 (GSK-3) protein has a primary function in regulating the metabolism of sugars and several moonlighting roles in affecting signaling events associated with cell proliferation (Siddavaram Nagini et al., 2018). Tideglusib has been developed as a molecule to inhibit GSK-3, and has shown effectiveness in killing neuroblastoma cells that drive pediatric brain cancers (Mathuram et al., 2016). There have also been efforts to target enolase by making antibodies that bind and inhibit cell-surface enolase, leading to a reduction in metastases (Principe et al., 2015). Targeting moonlighting proteins alongside administration of other treatments may help medicine overcome the adaptability of cancer cells, making treatments more effective for more cancers and patients.

Conclusion

Cancer cells display remarkable resilience that complicates their biology and cancer medicine. The hostile molecular environments that cancer cells face, along with the increased energy demand and upregulated metabolism within the cells, make adaptation necessary for their survival. Moonlighting proteins are particularly useful to cancer cells in this regard, enabling cancer cells to perform more processes without having to produce new proteins. Protein moonlighting allows for greater optimization of energy use, supporting cell growth and division, as well as stronger resistance against cellular stress, enhancing cell survival. Moonlighting proteins therefore bolster the resilience of cancer cells, instilling in them significant therapeutic promise.

Cancer cells are dynamic and strategic, yet the processes that allow them these qualities make them vulnerable. Protein moonlighting is one such process, and probing its potentials further could uncover more strategic therapeutic targets, ultimately improving outcomes in cancer medicine.

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What Do You Mean?

Semantics Linguistics Research with Professor Kathryn Davidson

By Caroline Song
Harvard College '29



Figure courtesy of the Davidson Lab.

*Although language is all around us, we seldom stop to question why we speak the way we do. What are the implicatures and presuppositions of our conversations? How do we mentally represent information, and how do we convey this to other people? Are some languages more expressive than others? The study of semantics, the subfield of linguistics that deals with meaning, aims to address such topics through scientific methods. Kathryn Davidson directs the Meaning & Modality Lab and serves as a Professor of Linguistics at Harvard. Her work encompasses semantics, pragmatics, and development. She has written two books, *Semantics and Depiction* and *Formal Semantics and Pragmatics in Sign Languages*, and through her study of American Sign Language (ASL), she investigates how we view language, communication, and our interactions with the wider world.*

Caroline Song (CS): Could you tell me about your work and what you study?

Kathryn Davidson (KD): The subfield of linguistics that I work in is concerned with how language expresses meaning. That sounds so hard to pin down: “meaning,” what is that? We’re interested in trying to take insights from philosophy in terms of logic and theories of how language can convey meaning that have accumulated over millennia, insights from psychology about how our mind works, how we form concepts, and how we learn things, and linguistics in the ways that languages can vary.

We have the sensation that we are communicating facts about the world, and sometimes not even true facts about the world: things we want to happen, things we wish could happen, ways

things could have been but aren’t. We can use language to talk about things that aren’t even real! It’s incredibly expansive.

It can be something as simple as when I say, “Everyone understood the reading.” Clearly, I don’t mean every single person in the whole world. So, who is everyone? We do experiments in my lab where we give participants a piece of language and try to see what they understand to have followed from it in order to try and build theories of linguistic meaning. English is a natural starting point, because everybody in our lab speaks English and it’s very well studied. But, we also do a lot of work in American Sign Language, Nicaraguan Sign Language, and Japanese Sign Language. We have a lot of other spoken languages—we currently have projects on Mandarin, German, Bangla, Turkish, Hindi, and French.

With these languages, we can ask questions like: are languages conveying the same kinds of things for people? Are there places where they differ? Are there places where they can’t express the same kind of thing? You set up experiments collecting people’s inferences and, using quantitative analysis such as statistical modeling, try to build models of meaning.

CS: I think it’s neat how you can take something so nebulous and implicit, like meaning, and deal with it in a rigorous, scientific way.

KD: Exactly. There’s this nebulous notion of meaning people ponder as they gaze up. And as far as, what does it all mean? Sometimes we misunderstand each other. Are we coming in with different starting points, are we not making our message clear, what went wrong? How can we study it analytically?

A lot of people in the last year or two have been interested in the same kind of questions, but in artificial intelligence. It’s natural to use tools and models from natural language semantics on these AI models. Does ChatGPT know what I mean? Can AI also derive the same kind of inferences from linguistic sentences that humans do? We have a couple collaborations with computational linguists at Boston University and a collaboration with Johns Hopkins where we’re interested in modeling that.

CS: I know that you’ve done a lot of behavioral studies with groups of native speakers. I was wondering if you could tell me about some of that research.

KD: There’s a conference in June called Experiments in Linguistic Meaning. One of the projects that our group is presenting looks at how language and gesture trade off. If you’re trying to refer to an object, there are all kinds of ways I can direct your attention to make it clear what I’m referring to. In that project, we compare English speakers, Mandarin speakers, and American Sign Language signers. We’re interested in how they trade off verbal content—words that are clearly things you have to learn in your language, like big, yellow, and fuzzy—with gestures that you can also use to narrow down items—like showing how tall or wide an object is. We did a series of experiments where we were manipulating these various factors and also manipulating the objects that people had a choice to pick from on the screens.

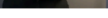
	unmodified	adjective	gesture
English	"Pass me the bowl"	"Pass me the small bowl"	"Pass me the [SMALL] _g ¹ bowl"
Mandarin	"Digei wo zhe ge wan" (Pass me this Cl. bowl)	"Digei wo zhe ² ge xiaode wan" (Pass me this Cl. small bowl)	"Digei wo zhe ge [XIAODE] _g wan" (Pass me this Cl. [SMALL] _g bowl)
ASL	 BOWL  2-GIVEo-1  BOWL  SMALL  2-GIVEo-1		

Table 1. Use of gesture, articles, and descriptors in ASL, English, and Mandarin for the item "bowl," where brackets indicate that a gesture has been used to substitute an adjective (Wang et al., 2026).

It seems like gestures are often superfluous. We usually want it to be backup information, redundant with what we're saying. That's true in spoken English. We were interested in sign languages where you have words, but then you have gestures with the same articulators. We found a really big difference between English and ASL. Then we realized that actually, maybe this wasn't because ASL is a sign language, but because it doesn't have the word "the" the same way that English does. So we thought we should look at a language that doesn't have the same kind of definite article. Mandarin is a great example. It turns out that ASL was behaving the way it was because of that feature. So, it shared this aspect with Mandarin; it was not about being a sign language.

CS: I saw that you did work on code switching in Mandarin definite noun phrases.

KD: Yes, that's led by Alice Wang, who is a grad student here. What I thought was beautiful about her study is she picked a bunch of things that are natural to code switch. Let's say she was in an English speaking context, but wanted to insert a Mandarin word for an opera. If you know you want to codeswitch the noun, how do you decide whether to put a determiner, definite article, demonstrative, or nothing? How do you build up that noun phrase? Do you make it fit the language of the noun that you're going into, or do you make it fit the context of the language you have been speaking up to that point? It turns out it's conditioned on what's called the matrix language, meaning the language that you're using before you code switch. If you're using English, you're going to use "the" and "that." You're even going to prefer Mandarin translation equivalents of those, more than you would prefer what, in the Mandarin context, would have been better. You could see the tradeoff, in the process of codeswitching.

There are so many interesting questions in code switching. It has potential to tell us about the way that language structure interfaces with the psycholinguistic process of getting it out of your mind. You pull from both languages that you know, think about the languages that the other person knows, and use them together to make the best sentence that you can.

CS: I'm someone who's bilingual in Mandarin and English. Looking at your studies, even if I have the implicit knowledge of the language, it's never something that I thought about. So I think that's really cool, that it's forcing me to learn new things about what I thought I already knew.

KD: It's such a good example. What do we know that we don't know we know? We know it implicitly, but we don't know it explicitly. So much linguistic knowledge is like that. Turns out that goes for knowledge about code switching, for example.

CS: I know that you're spent a lot of time examining ASL. Has there ever been a moment where you're studying ASL and you realize that it's broken a linguistic theory or done something that people who communicate primarily verbally wouldn't really think about?

KD: I think almost every linguist has had that experience, no matter what language they're studying. I think it's one of the things that most linguists share that is exciting when you're thinking about what's going on in a language. Quotation is something I like working on in this domain, because when we think about quotation, we often think of quotation marks written on a page. Learning how sign languages work inspired me to think differently about what quotation is, because actions and reported speech look very, very similar in sign languages. For example, if I say, "he was nailing this," and then I showed you how he was nailing it, I don't usually put the action in quotation marks. So it's interesting, because in sign languages, these two things look very similar.

CS: I know that your lab focuses on not just meaning, but also modality.

KD: By modality in this context, we mean, what is the way that the language is conveyed? Language can occur in lots of different modalities: It can be verbal, manual, visual, tactile, or written. For a long time, people just thought about written language. Yet there are many nuances to speech that don't get captured in text, like prosody. But if you extend that further for sign languages, there's much evidence that they have all the

Q1_Man

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李四有一个assignment，下周要交给老师。



Figure 1. English-to-Mandarin survey seen by experiment participants in “Code-switching in Mandarin and English Definite Noun Phrases” (Wang et al., 2026). Translation of question: “Lisi has an assignment, next week [they] have to give it to the teacher.” Participants are asked how “natural” or “unnatural” the two responses are, which are “that assignment is very difficult” and “assignment very difficult.”

complexity and characteristics of spoken languages, and they’re occurring in a different modality. My lab has a special focus on trying to think about how the mode of communication of a language constrains, expands, or influences the way that meanings are expressed.

CS: When you started out learning linguistics, did you always know that you were interested in semantics and discourse?

KD: When I was an undergraduate, I studied mathematics. But as I was doing that, I took these linguistics classes on the side, because that sounded fun, and I realized that the most mathematical of those were the semantics classes. In the semantics classes, they used complicated logic and game theory, but we applied it to language, and I thought that was the coolest thing I’d ever done. Linguistics, in general, is very much based on pattern recognition. I’ve never really wavered from the semantic side of things, but over time, I got more inspired to draw collaborations and insights from other aspects of linguistics, depending on the problem.

CS: Speaking of your process of doing linguistics, do you have any highlights or struggles that particularly stand out to you?

KD: I struggled to have any sense of what I would ever want to do, and I think I didn’t have a lot of pressure to have an answer to that. I think I was lucky, because I don’t think I would have ever come across linguistics. But in retrospect, that was great, because I had plenty of time to try new things, and through that you can really discover something you love even more than what you initially thought you would like. Usually those who end up here fell into it through some happy set of circumstances.

Sometimes people get very focused on one thing that they feel like they have to do, but some of my most interesting research projects came about because I was open to something a student wanted to try and isn’t what I suggested. I allowed myself to be open to it, and then they usually end up in a really interesting place. So being able to follow an unexpected path

is good, and maybe one of the most fun things about having a job as a researcher.

CS: With all the research that you’ve done over the years, why do you think that linguistics research is so important?

KD: I think there’s this clear fact that we uncover again and again: when you rigorously study languages, they’re all equal in a very deep sense. In surface ways, they might look different, but as soon as you do any rigorous analysis, they’re so clearly of equal complexity and equal productivity and equal value. Often in the world, languages are not treated as equal, whether it’s in an education context, legal context, or hiring context. The work we do as linguists reaffirms, again and again, the equality that’s often denied. In the context of sign language work—that’s a set of languages where still, many, many people do not see them as equal. Deaf kids are often encouraged to avoid learning sign language so that they can focus on speaking.

CS: Before I let you go, do you have a specific message you want to send out?

KD: It’s both a linguistics point, but it’s also a non-linguistics point, and I think it’s relevant for Harvard students in particular: Do not think about everything in life as an optimization. Because then you’re going to narrow yourself to some set of constraints against which you’re going to optimize, and you don’t know that those are the right constraints.

When it comes to languages, there are so many dimensions, there is so much value in the diversity there. It’s not that we just value the diversity for its own sake, but they each contribute unique things. And it doesn’t make sense to think about that as an optimization problem. Because usually, if you can manage to have something not perfectly optimal, things can happen in interesting ways.

This interview has been edited for length and clarity.

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Grades, Goals, and the Good Life

An Interview with Dr. Brendan Case

By Diana Nichvoloda
Harvard College '27



Image courtesy of Brendan Case.

Questions regarding the ethics and meaning of a “good life” have long occupied philosophers. These conversations continue today as universities strive to craft a student environment that at once is academically rigorous and allows for a “good life.” One scholar working at this intersection is Brendan W. Case, Th.D., the Associate Director of Research at Harvard University’s Human Flourishing Program. A theologian by training, Case investigates how moral philosophy, virtue ethics, and the role of religion in public life can inform contemporary debates about student life at Harvard via the Academic Flourishing Initiative.

Diana Nichvoloda (DN): Please tell me about yourself and the work of the Academic Flourishing Initiative. How do you define academic flourishing, and is that the same thing as academic success?

Brendan Case (BC): Broadly speaking, we at the Human Flourishing Program—housed in the Institute for Quantitative Social Sciences—study the nature, distribution, and determinants of flourishing—understood in a very expansive sense. Much of our work is organized around four institutional pathways to flourishing: marriage and family, education, workplaces, and religious communities.

Within our work on education, we’ve launched the Academic Flourishing Initiative, which centers on a concept we call “academic flourishing”: a state in which all aspects of an academic community are going well, deliberately mirroring our broader definition of human flourishing as a state in which all aspects of a person’s life are going well, including in the contexts in which they live. This is, by design, a very demanding definition. Strictly speaking, no individual or institution fully satisfies it, and so we often speak instead of the relative attainment of flourishing. Physical health offers a useful analogy: even though everyone eventually declines and dies, it still makes sense to say that some people are healthier than others. The same logic applies to flourishing more generally. When we apply this to academic institutions, we take a similarly expansive view. Success in core academic aims—teaching, learning, and research—is clearly central, but it is not the whole story. Universities exist to preserve, transmit, and generate knowledge, and that mission is essential to their identity. However, an institution that excels academically while its members are miserable, anxious, or disengaged would be deficient as a community. So, any reasonable account of academic flourishing must include the well-being of individuals. Beyond that, there are goods that belong to the community as a community—things like healthy institutional practices, effective governance, and the capacity to respond constructively to challenges. These are not reducible to individual outcomes.

Another crucial but often neglected dimension is the formative mission that many universities explicitly claim: shaping students into people of character who can contribute meaningfully to society. Mission statements from institutions like Stanford, Swarthmore, and Harvard all emphasize leadership, integrity, and contribution to the common good. If universities take these claims seriously, then their flourishing depends on whether they actually form students in these ways. Yet in practice, institutions rarely assess themselves on these dimensions. They focus heavily on academic outputs but pay far less attention to whether they are cultivating good citizens, supporting community well-being, or fostering healthy institutional cultures. A central goal of the Academic Flourishing Initiative is to bring these neglected aspects into view and encourage universities to take them seriously.

DN: That’s very interesting. What are universities most invested in right now, and how should they shift their focus?

BC: Universities tend to concentrate on a fairly narrow set of metrics, which are not unimportant but are often overemphasized. They pay close attention to the academic credentials of incoming students—like GPA and standardized test scores—and to student performance through grades. Faculty are evaluated primarily through research output, including publications and citations, especially in tenure and promotion decisions. Institutions also track

To what extent has university life helped you to...

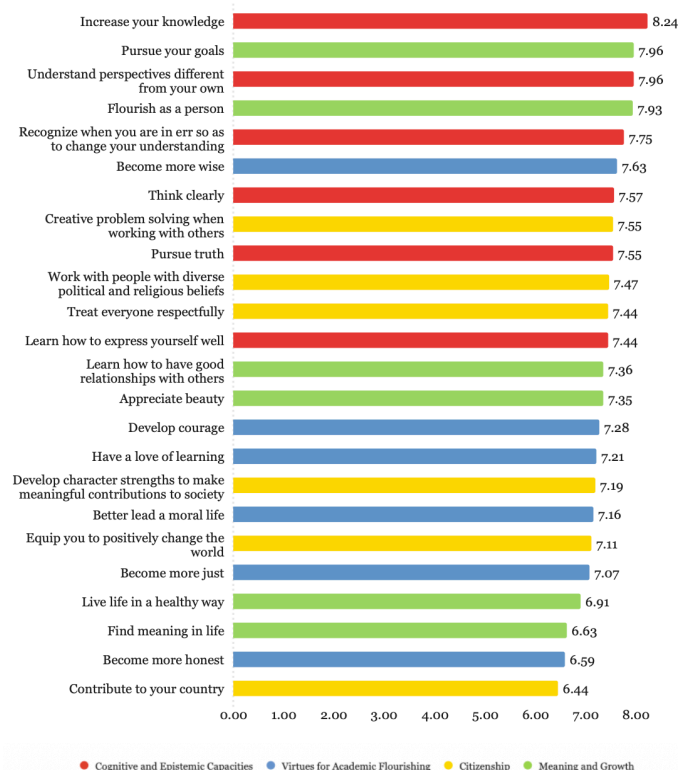


Figure 1. Across two sample universities, students reported that university life most enhanced their cognitive and epistemic capacities (e.g., increasing knowledge) and, to a lesser degree, citizenship (e.g., contributing to their country) and virtues for academic flourishing (e.g., becoming more honest). (Source: 2024-2025 Academic Flourishing Report)

alumni outcomes, particularly career success, partly because of its relevance for fundraising. In recent years, they have also focused heavily on student mental health, given the well-documented rise in anxiety, depression, and related conditions.

All of these areas matter, but there are problems with how they are measured and weighted. For example, citation counts and publication metrics are crude proxies for intellectual contribution and often create perverse incentives, encouraging quantity over quality. Similarly, while tracking mental health is important, the approach is typically deficit-focused: universities measure distress but rarely measure thriving. They do not systematically ask what leads students to feel engaged, fulfilled, and purposeful. As a result, they miss a large part of what matters. A better approach would not abandon these existing metrics but would broaden them, incorporating measures of positive development, community well-being, and institutional health. In other words, universities should complement their current focus on performance and problems with a more holistic understanding of what it means for a community to flourish.

DN: Is student mental health more of an individual responsibility than an institutional one? Some argue that students are voluntarily stretching themselves too thin—participating in too many classes and extracurriculars, and that this is the reason for their poor mental health. How do you see this debate?

BC: I think we should conceptualize a spectrum from individual responsibility at one end to structural influence at the other, and most cases of student mental health fall somewhere in between. At the individual level, there are always personal decisions, circumstances, and predispositions—including genetic factors—that shape outcomes. But when we observe large-scale changes, like the widespread rise in anxiety and depression among young people, it's unlikely that these are simply the result of individuals making poor choices. Human nature hasn't changed dramatically in the past fifteen years, so structural factors must be playing a significant role.

That said, universities are not solely responsible for these broader trends. What they do is shape the incentives that students respond to. At places like Harvard, there is what people often call a “hidden curriculum”—a set of informal expectations that push students toward intensive extracurricular involvement as a form of professional development. Many students believe that clubs, leadership roles, and networking opportunities are essential for future success, sometimes even more important than coursework. This can create a disconnect with faculty, who prioritize academic work. At the same time, grade inflation has made GPA less effective as a signal of distinction, which further encourages students to seek differentiation through other activities. These dynamics contribute to a high-pressure environment in which students feel compelled to do more and more. Many arrive already socialized from a very young age into a “resume-building” mindset, where every activity is evaluated in terms of its future payoff. While this produces highly driven individuals, it also creates a stressful and instrumental way of living. So, while individual choices matter, they are shaped by a broader system of incentives that universities help sustain.

DN: I agree; it seems that Harvard students are simply one component in the broader machine of social change. Still, what would the Academic Flourishing Initiative recommend that students do to lessen this pressure?

BC: One of our core ideas is that measurement itself can function as an intervention. The first step is simply recognizing the problem. To that end, we've developed the Academic Flourishing Survey, which measures a wide range of outcomes related to student development and institutional life. We've partnered with universities across the country, and we have also been able to include some of our questions in a Wall Street Journal survey of 500 colleges. These questions ask students to reflect on whether their university experience has helped them become wiser, more just, or better able to contribute to the world.

The results show substantial variation across institutions, even among peers. For instance, within the Ivy League, some schools perform much better than others on these dimensions; Harvard, interestingly, ranks lower than one might expect on measures like becoming wiser. These findings are open to interpretation, but they suggest that students do care about these broader aspects of their development. If universities made these goals more explicit and incorporated them into how they evaluate themselves, it could help shift institutional culture. For students, however, the challenge is that many of these pressures reflect a collective action problem. If

everyone else is optimizing for credentials—joining multiple clubs, building networks—it is difficult for any one individual to opt out without feeling disadvantaged. Similarly, in an environment of grade inflation and increasing reliance on AI tools, genuine engagement and superficial performance can appear indistinguishable. This creates strong incentives to prioritize appearances over substance. I sometimes describe this using Gresham's law: when bad money circulates alongside good money, it tends to drive the good money out. In a similar way, when low-effort strategies yield the same visible rewards as genuine effort, people are naturally drawn toward them.

This interview has been edited for length and clarity.

