ORIGINAL CONTRIBUTION

Optimizing Emergency Stroke Transport Strategies Using Physiological Models

Daniel A. Paydarfar (ID), BS; David Paydarfar, MD; Peter J. Mucha (ID), PhD; Joshua Chang (ID), MD, PhD

BACKGROUND AND PURPOSE: The criteria for choosing between drip and ship and mothership transport strategies in emergency stroke care is widely debated. Although existing data-driven probability models can inform transport decision-making at an epidemiological level, we propose a novel mathematical, physiologically derived framework that provides insight into how patient characteristics underlying infarct core growth influence these decisions.

METHODS: We represent the physiology of time-dependent infarct core growth within an ischemic penumbra as an exponential function with consideration to rate-determining collateral blood flow. Monte Carlo methods generate distributions of infarct core volumes, which are translated to distributions of 90-day modified Rankin Scale scores. We apply the model to a stroke network that serves rural Bastrop County and urban Travis County by simulating transport strategies from thousands of potential patient pickup locations. In every pickup location, the simulation yields a distribution of outcomes corresponding to each transport strategy. A 2-sample Kolmogorov-Smirnov test and Student *t* test determine which transport strategy provides a significantly better probability of a good outcome for a given pickup location in each respective county (*P*<0.01).

RESULTS: In Travis County, drip and ship provides significantly better probabilities of a good outcome in 24.0% of the pickup locations, while 59.8% favor mothership. In Bastrop County, 11.3% of the pickup locations favor drip and ship, while only 7.1% favor mothership. The remaining pickup locations in each county are not statistically significant in either direction. We also reveal how differing rates of infarct core growth, the application of bypass policies, and the use of large vessel occlusion field tests impact these results.

CONCLUSIONS: Modeling stroke physiology enables the use of clinically relevant metrics for determining comparative significance between drip and ship and mothership in a given geography. This formalism can help understand and inform emergency medical service transport decision-making, as well as regional bypass policies.

Key Words: collateral circulation ■ geography ■ physiology ■ thrombectomy

Rapid neuronal loss from acute ischemic stroke occurs as the infarct core grows within its ischemic penumbra. The duration of ischemic stroke evolution is highly variable, ranging between 6 and 18 hours for large vessel occlusions (LVOs),[1] and the degree of collateral blood flow is a major determinant of the rate at which an infarct core achieves full ischemic volume.[2] LVOs are the most severe stroke type, with an incidence rate of 25% of ischemic stroke cases.[3] Endovascular thrombectomy (EVT) is the primary treatment method for LVOs and

can be administered at a comprehensive stroke center (CSC).[4] Non-LVOs, comprising of lacunar strokes related to small vessel disease as well as small emboli, comprise 75% of ischemic stroke cases,[3] and thrombolysis with intravenous tPA (tissue-type plasminogen activator) is the standard treatment for qualifying patients who present symptoms up to 4.5 hours prior at either a primary stroke center (PSC) or a CSC.[5,6] Stroke outcomes are time dependent, so it is pertinent for a suspected stroke patient to receive suitable treatment quickly.[7–9]

Nonstandard Abbreviations and Acronyms

CSC	comprehensive stroke center
DNS	drip and ship
EMS	emergency medical services
EVT	endovascular thrombectomy
LVO	large vessel occlusion
mRS	modified Rankin Scale
PSC	primary stroke center
tPA	tissue-type plasminogen activator

If a CSC is the closest stroke center to the patient pickup location in terms of transport time, then the patient is taken directly there as the best treatment options for any stroke type are available. When a PSC is closer to the patient pickup location than a CSC, emergency medical services (EMS) must decide between 2 strategies of emergency stroke transport. The first is drip and ship (DNS). This transport strategy takes the patient directly to the closer PSC where they are able to receive cerebrovascular imaging and tPA, then proceeds to the CSC if an LVO is identified. The second transport strategy is mothership, which bypasses the closer PSC for a more distant but EVT-capable CSC. While there are cases in which the optimal emergency transport strategy is clear (eg, a patient with unequivocal signs and symptoms of a non-LVO), EMS is often unable to ascertain a patient's stroke type with certainty given current field-testing capabilities. For these patients, the optimal transport strategy is ambiguous.[10]

We propose a novel framework that uses a physiological model of time-dependent infarct core growth and represents key, patient-specific parameters as population-based distributions. We then implement this framework in 2 case studies to provide insight into how physiology can influence and potentially inform emergency stroke transport decisions. These applications focus on the optimization of EMS transport decisions and regional bypass policies in the Travis and Bastrop Counties in Texas. A detailed description of Texas stroke center capabilities and resources can be found in the Texas Department of State Health Services report.[11]

METHODS

The materials that support the findings of this study are available from the corresponding author upon reasonable request.

Mathematical Model of Infarct Core Growth

If a stroke patient's ischemic region does not reperfuse, their infarct core will eventually attain the total ischemic penumbra volume. Mathematically, the physiology of a growing infarct core within the spatial constraint of its ischemic penumbra can be modeled as an exponential function.

Let $v(t)$ be the infarct core volume in mL at time t minutes after stroke onset, v_p be the constant, total volume of at-risk tissue encompassed by the ischemic penumbra, and τ be the collateral-dependent time constant in minutes. The dynamics of infarct core growth with respect to time are modeled as:

$$v(t) = v_p \times \left(1 - e^{-t/\tau}\right) \qquad (1)$$

where the time constant τ determines the rate at which the infarct core volume $v(t)$ achieves the ischemic penumbra volume v_p. In the case of a patient with an LVO, an infarct core with poor collateral blood flow tends to grow faster and to a larger ischemic penumbra volume, while stronger collateral blood flow tends to slow infarct core growth and decrease the maximum ischemic penumbra volume.[2] We constructed the time constant τ to be parameterized by a 12-point pial collateral score (0–11),[12] which is linearly dependent on large vessel ischemic penumbra volume.[12,13] Figure 1 provides a visualization of our exponential model of infarct core volume, which is consistent with existing experimentally and theoretically derived models.[12,13] The Mathematical Model of Infarct Core Growth and the Time Constant Parameterization sections in the Data Supplement provide further details of the model and its time constant.

We extended Equation 1 to relate infarct core volume to 90-day modified Rankin Scale (mRS), a measure of patient outcomes,[14] via the following linear function derived from Ernst et al's clinical study of outcome-volume association,[15]

$$mRS(t) = 0.0376 \times v(t) \qquad (2)$$

and imposed the constraint that 90-day mRS cannot exceed an upper limit of 6, which represents patient death on the scale. Thus, Equation 2 allowed us to compute a 90-day mRS outcome for any patient at time t after acute ischemic stroke onset. It is important to note that our framework uses a continuous scale of 90-day mRS outcomes because it provides a more mathematically sound basis for statistical testing and improves the accuracy of probability estimates.[16]
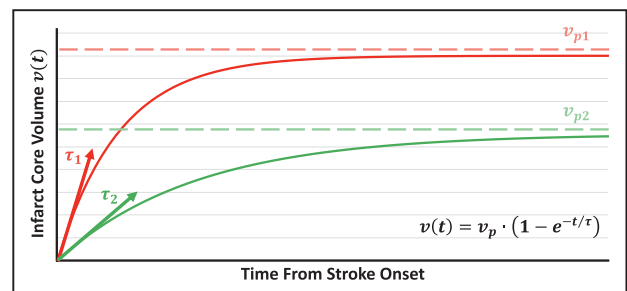

Figure 1. Visualization of Equation 1, the exponential function of infarct core volume.
Each example curve corresponds to a single patient's infarct core volume over time, eventually reaching their ischemic penumbra volume v_p if successful reperfusion is not achieved before full saturation. The time constant τ, parameterized by patient-specific collateral blood flow, determines the rate at which the infarct core achieves its maximum value v_p. Because τ_1 is steeper than τ_2 (ie, has a faster rate of growth), the red curve reaches v_{p1} sooner than the green curve reaches v_{p2}.

EMS Transport Times

The adjacent Travis and Bastrop Counties, Texas, are defined by the United States Census Bureau as urban and rural geographies, respectively. Their shared stroke network consists of 3 PSCs and 3 CSCs within Travis County, zero stroke centers within Bastrop County, and 7 PSCs outside of both counties (Figure 2). We assumed the following nontransport time intervals for this stroke network: stroke onset to departure from pickup location with EMS=60 minutes; door-to-needle (tPA)=30 minutes; needle-to-door-out=20 minutes; and door-to-puncture (EVT)=30 minutes. Time intervals specific to a stroke center type were kept constant across the network, but hospital-level variation can be integrated easily with the provision of relevant data.

To compute EMS transport times in Travis County, Texas, we created a coordinate grid with 10562 nodes spaced 500-meters apart, representing hypothetical patient pickup locations within the county. Of these nodes, 2872 (27.2%) have a CSC as the nearest stroke center, so the optimal decision is clear. The focus of our analysis was on the remaining 7690 (72.8%) locations for which the optimal transport strategy is uncertain. We overlaid an equivalently resolved coordinate grid onto Bastrop County with 14555 nodes, of which 11959 (82.0%) were of interest in this analysis. Node-specific EMS transport times to the nearest PSC, nearest CSC, and transfer from the PSC to its nearest CSC were calculated with ArcGIS SDK (Esri, v10.8), using average speed limits. Table I in the Data Supplement provides transport time data averaged across the nodes of interest in each respective county.

The total time for a DNS transport strategy is the sum of the time from stroke onset to departure from the pickup location, EMS transport time to the PSC, door-to-needle time, needle-to-door-out time, transport time to transfer from the PSC to its nearest CSC, and door-to-puncture time. A patient without LVO on the DNS strategy does not proceed past the PSC. The total time for a mothership transport strategy is the sum of the time from stroke onset to departure from the pickup location, EMS transport time to the CSC, and door-to-needle or door-to-puncture time depending on the stroke type.

Monte Carlo Patient Volume Generation

In lieu of a clinical data set, we used Monte Carlo methods to generate synthetic data to model infarct core growth for a population of patients with acute ischemic stroke. For every node of interest in the Travis and Bastrop Counties, we simulated 13000 patients each with a randomly generated ischemic penumbra volume v_p. Of the total patients in each location, there were 3900 patients with LVO (25% incidence
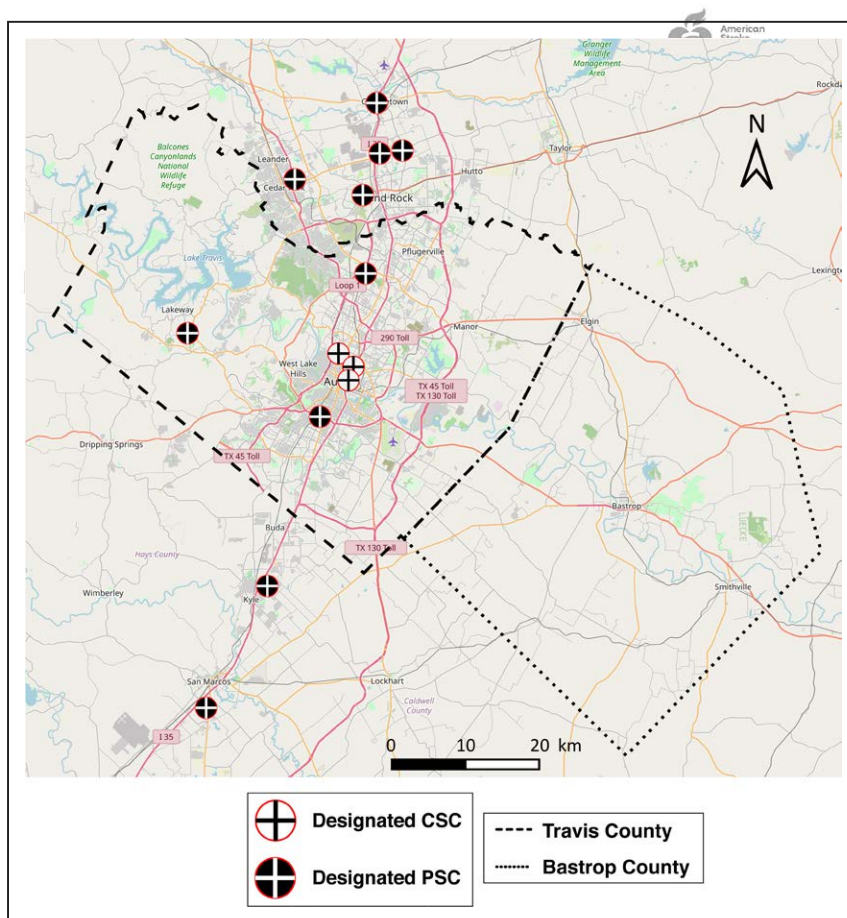

Figure 2. Map of Travis and Bastrop Counties.
A coordinate grid consisting of hypothetical patient pickup locations is generated within the boundaries of each respective county. Stroke centers outside of these boundaries are still considered for emergency medical services (EMS) transport in the simulations. CSC indicates comprehensive stroke center; and PSC, primary stroke center.

rate) with their v_p sampled from a skew-left β distribution, and 9100 patients without LVO (75% incidence rate) with their v_p sampled from a skew-right β distribution (see Figure I in the Data Supplement, eg, distributions). The total number of patients we simulated at each node of interest was chosen to maximize statistical power, thereby reducing type II error, and to avoid unreliable significance testing that may result from oversampling or undersampling volumes.

The respective skewness of the generated LVO and non-LVO v_p β distributions were derived from published 90-day mRS outcome distributions for patient with and without LVO subpopulations.[17] The mean, range, and SD of the LVO distribution resembles that of a sample of clinically measured LVO penumbra volumes.[18,19] Moreover, while non-LVO volumes include a similar range of volumes related to LVO cases that spontaneously recanalize, there is a preponderance of smaller stroke volumes of lacunar infarcts caused by small vessel disease,[20,21] further supporting the notion that non-LVO volumes tend to be skew-right.

Because we expanded Equation 1 to accommodate a distribution of ischemic penumbra volumes representative of a population of patients with acute ischemic stroke, the collateral-dependent time constant τ also became a distribution for the LVO subpopulation. However, we have not identified literature that addresses the time constant τ parameterization with respect to non-LVO collateral blood flow. Therefore, for the non-LVO subpopulation, we varied τ and present our results using 2 extreme time constant parameterizations for non-LVO infarct core growth. In one case, we assumed τ to be the largest time constant (slowest rate of infarct core growth) from the distribution of LVO time constants, and in the second case, we assumed τ to be the smallest (fastest rate of infarct core growth). The generation of synthetic patient data and the following simulations were performed in MATLAB (MathWorks, version r2017b). The Monte Carlo Patient Volume Generation section in the Data Supplement provides further details of the volume and time constant distributions.

Emergency Stroke Transport Simulations

Timely acute stroke interventions can lead to successful reperfusion of the ischemic region, preventing the infarct core from expanding to the full ischemic penumbra volume. For patients that successfully reperfuse, their infarct core volume at the time of treatment is defined as the final infarct core volume. Those that do not successfully reperfuse from any treatment have a final infarct core volume that is equal to their ischemic penumbra volume. In our simulations, we assumed that (1) administering tPA before EVT did not improve the probability of successful reperfusion with EVT for a patient with LVO (ie, the probabilities of successful reperfusion with tPA and EVT for a patient with LVO are independent)[22–24]; and (2) the probability of successful reperfusion for patients without LVO given tPA was time dependent.[25] Table II in the Data Supplement presents framework reperfusion parameters.[25–27]

For each node of interest in both counties, we simulated an emergency stroke transport scenario where the Monte Carlo generated stroke population (composed of 25% patients with LVO and 75% patients without LVO) followed the DNS strategy, and then re-ran the simulation with the mothership strategy. The resultant distributions of the population's final infarct core

volumes corresponding to each transport strategy were translated to distributions of 90-day mRS outcomes via Equation 2. We then constructed cumulative distribution functions of 90-day mRS respective to DNS and mothership in each node. Figure 3 visualizes the simulation framework, and the Emergency Stroke Transport Simulations section in the Data Supplement provides further details of its methodology.

Framework Assumptions

As with any model, we made a few assumptions to focus the scope of the study. First, all patients in the simulated population had a prehospital mRS of 0, as future studies are necessary to better understand stroke growth mechanisms in nonzero prehospital mRS subgroups. Second, all patients without and with LVO were eligible for tPA, and all patients with LVO were eligible for EVT. The inclusion of those who do not meet treatment eligibility criteria would likely create negligible and inconsequential differences in the cumulative distribution functions of 90-day mRS and, therefore, simulation results. Third, our population of patients with stroke did not include stroke mimic cases or intracerebral hemorrhage cases. An extensive review of the literature by a previously published simulation study concluded that mimic and hemorrhage cases can be considered to have a time invariant probability of a good outcome.[28] Clinical trials show that interventions of hemorrhagic stroke in the hyperacute window postonset do not improve outcomes relative to standard of care.[29–34] Because bypass times in the Travis and Bastrop Counties are <1 hour, including this subgroup would not affect simulation results.

From a clinical perspective, we assumed that for patients who respond to treatment, successful reperfusion occurred with negligible delay, and infarct core growth was halted. It is possible that treatment-to-reperfusion time intervals are not negligible, and if so, our framework results likely underestimate mothership favorability. Additionally, the probabilities of successful reperfusion given EVT or tPA for LVO patients were independent of time from onset of acute ischemic stroke. If these probabilities decrease with time in actuality, then our simulation results likely underestimate DNS favorability. While Menon et al[35] show that the probability of successful reperfusion for patients with LVO has a dependency on time from treatment with tPA, their model does not discuss the likely dependence of these results on patient-specific onset-to-treatment times. To integrate their model with our framework, data that relate the stroke onset-to-treatment and treatment-to-reperfusion windows is necessary.

Finally, we assumed that the transport decision made by EMS at the pickup location was carried through completely and there was no switch to another method of transportation at any point thereafter.

Case Study I: Optimal Transport Decisions Analysis

To determine which transport strategy provides significantly better probabilities of a good outcome (90-day mRS score 0–2) for each node of interest in a given county, we extracted the probability of a good outcome respective to DNS and mothership from their cumulative distribution functions outputted by the emergency stroke transport simulations. We repeated these
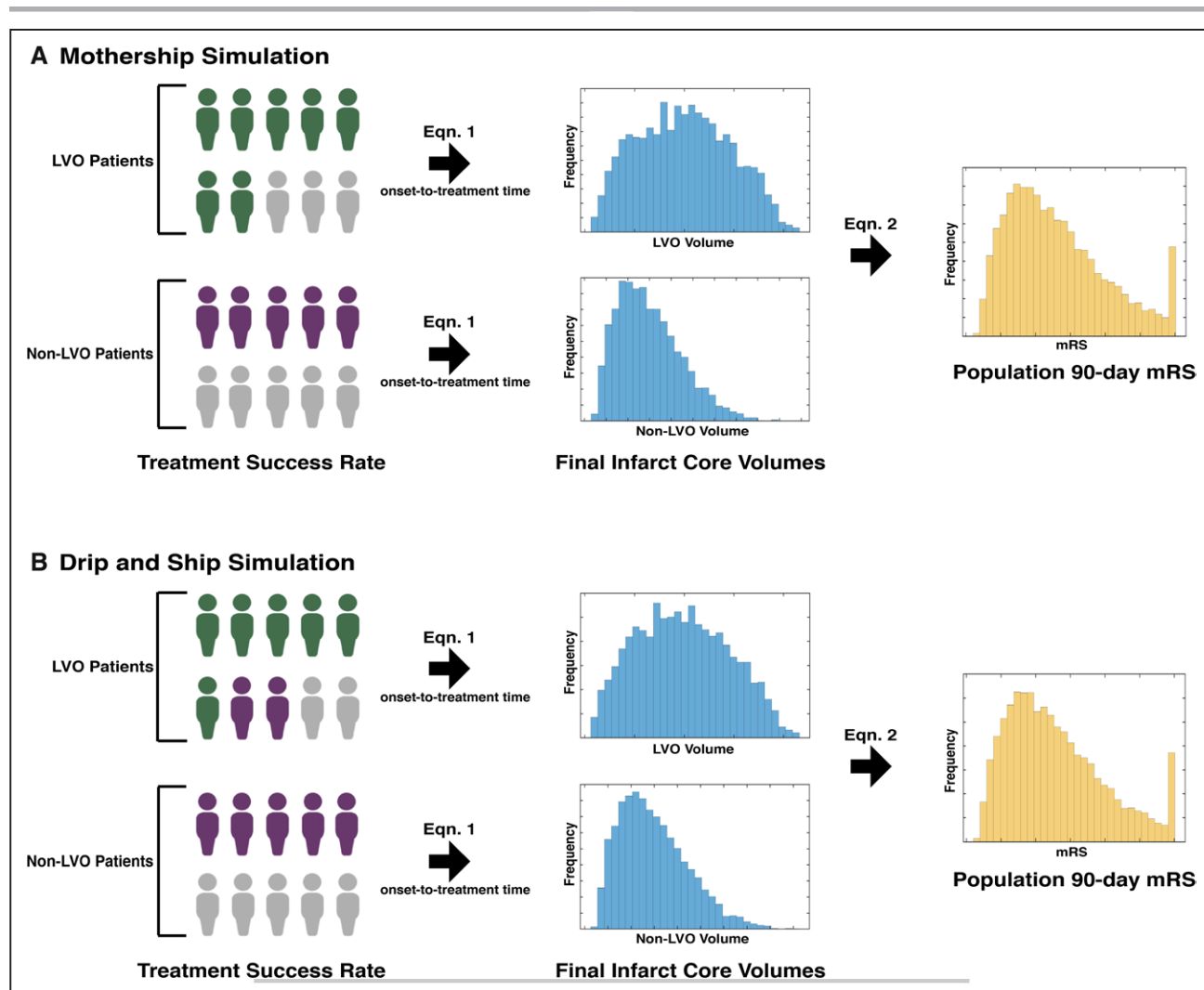
Figure 3. Mothership and drip and ship transport simulations run in each node of interest.
A, Mothership simulation, and (**B**) drip and ship simulation. Monte Carlo methods generate a population of patients with and without large vessel occlusions (LVOs). The time taken from stroke onset to successful reperfusion from treatment determines how much of a patient's penumbra volume their infarct core achieves (Equation 1). A patient with LVO has a probability of successful reperfusion from endovascular thrombectomy (EVT; green) at the comprehensive stroke center (CSC), or from tPA (tissue-type plasminogen activator; purple) at the primary stroke center (PSC). A patient without LVO has a probability of successful reperfusion from tPA (purple) at either stroke center. Those that do not successfully reperfuse from any treatment (gray) have a final infarct core volume that is equal to their ischemic penumbra. For nodes with exceptionally long transport times, the final infarct core volume could be approximately equal to the penumbra volume despite successful reperfusion from treatment. For a given transport strategy simulation, the distributions of final infarct core volumes of patients without and with LVO were aggregated and then translated to a distribution of 90-day mRS via Equation 2. For visualization purposes, the proportions of green, purple, and gray are not exactly to scale with the values presented in Table II in the Data Supplement. The illustrated patient populations on the left-hand side are not representative of the 25/75 stroke type distribution for the same reason.

simulations and extractions 20 times, yielding a distribution of 20 distinct probabilities of a good outcome given DNS and 20 distinct probabilities of a good outcome given mothership for every node of interest. A 2-sample, 1-sided Kolmogorov-Smirnov test compared the shape of these 2 distributions within each node and determined which transport strategy provides significantly better probabilities of a good outcome (a=0.01 level). In addition to the Kolmogorov-Smirnov test, we performed a 2-sample Student t test to determine statistical significance between the means of the DNS and mothership distributions of a probability of a good outcome in each node (a=0.01 level). These 2 statistical tests provided a useful combination that can detect, respectively, significant differences between the variances and means of the distributions in question. Furthermore, we used the Cohen's d statistic for effect size to quantify the magnitude of statistical significance in the nodes that favor DNS or mothership. Cohen's d is a metric of practical significance that measures the standardized difference in means (extent of overlap or separation between distributions), in units of standard deviations, between the DNS and mothership distributions of 90-day mRS good outcomes. QGIS mapping software (QGIS Development Team, v3.12) was used for visualizing statistical results. The Cohen's d Effect Size section in the Data Supplement provides further detail on the statistical methods, and a sensitivity analysis of select model parameters is included in the Data Supplement.

Case Study II: Optimal Bypass Policy Analysis

Bypass time is defined as the added transport time taken to reach the more distant CSC from the pickup location compared with going directly to the closer PSC. There are bypass policy recommendations provided by the American Heart Association and by regional health care networks establishing that if the bypass time from a given pickup location exceeds the policy recommended threshold, then a patient suspected to have an LVO should be transported directly to the PSC.[36]

The Tiger/Line Shapefiles published online annually by the United States Census Bureau provide population data for the 580 geographic census block groups in Travis County (2010 census total county population ≈1.03 million).[37] We uniformly distributed each block-group's population among the nodes in its geographic boundaries. For example, if a census block group with a population of 1000 enclosed 100 nodes, then each node in that block group would be assigned a population of 10. Using this census data and the node-specific probabilities of a good outcome outputted by the simulation, we assessed the number of people with a good outcome per 1000 stroke cases in Travis County under a range of bypass policies, without LVO field testing. These results were compared with an ideal threshold of stroke care, defined as the number of people with a good outcome per 1000 stroke cases if EMS used an LVO field test with 100% sensitivity and specificity and always transported the patient to the center that provides the highest probability of a good outcome for their stroke type. The bypass policy that yields the smallest deviation in the number of people with a good outcome per 1000 stroke cases from the ideal threshold is considered the optimal county-wide bypass policy without LVO field testing.

We also extended this methodology to incorporate common LVO field tests,[38] such as the Los Angeles motor scale (Los Angeles motor scale ≥4; sensitivity=0.66, specificity=0.86), Cincinnati prehospital stroke severity scale (≥2; sensitivity=0.56, specificity=0.86), and the prehospital acute stroke severity scale (≥2; sensitivity=0.71, specificity=0.84). For each field test, we used a range of bypass policies for suspected LVO patients only, while always sending those with a negative test to the PSC. Assessing the number of people with a good outcome per 1000 stroke cases in Travis County, we used the same ideal threshold as before to determine the optimal county-wide bypass policy. We repeated these analyses for Bastrop County (39 block groups, 2010 census total county population ≈74.17 thousand).

RESULTS

Optimal Transport Decisions

Of the 7690 nodes of interest in Travis County, we find that DNS provides significantly better probabilities of a good outcome in 13.3% and mothership provides significantly better probabilities of a good outcome in 74.2%, assuming a fast rate of non-LVO infarct core growth (Kolmogorov-Smirnov test, Student t test: P<0.01; Figure 4A). The remaining 12.5% are not statistically significant in either direction.

Assuming a slow rate of non-LVO infarct core growth, DNS provides significantly better probabilities of a good outcome in 24.0% of the nodes of interest and mothership provides significantly better probabilities of a good outcome in 59.8% (Kolmogorov-Smirnov test, Student t test: P<0.01; Figure 4B). The remaining 16.2% are not statistically significant in either direction.

Figure 5 presents heatmaps of Travis County colored by Cohen's d effect size statistic, showing dissipation of the effective significance of the mothership transport strategy over DNS when considering pickup locations that are increasingly distant from CSCs.

The northwest corner of Travis County is one of the most isolated locations from road and highway access in Travis County because the Colorado River encompasses it (the river is most easily discernible in Figure 2). We see that the regions of insignificance in this corner under the assumption of a fast rate of non-LVO infarct core growth (Figure 4A or Figure 5A) convert to DNS significant when assuming a slow rate instead (Figure 4B or Figure 5B).

Optimal Bypass Policies

In Travis County, bypass policies from 10 through 21 minutes without LVO field testing yield the optimal number of people with a good outcome per 1000 strokes, assuming a fast rate of non-LVO infarct core growth (Figure 6A). Furthermore, Figure 6A shows that implementing any LVO field test in conjunction with bypass policies only for suspected LVO patients decreases the number of people with a good outcome per 1000 strokes.

Under the assumption of a slow rate of non-LVO infarct core growth, administering Los Angeles motor scale or prehospital acute stroke severity scale and always sending suspected LVO patients directly to the CSC is optimal (Figure 6B). However, using the Cincinnati prehospital stroke severity scale LVO field test with bypass policies only for suspected LVO patients yields fewer people with a good outcome per 1000 strokes than implementing bypass policies without LVO field testing.

The Bastrop County statistical significance analysis yields a great deal of variation in transport strategy favorability depending on the rate of non-LVO infarct core growth, and its optimal bypass policies are similar to Travis County. The Data Supplement presents the results of the Bastrop County simulation.

DISCUSSION

Herein, we propose a framework with a physiology-based, mathematical model of infarct core growth. Monte Carlo methods allowed us to generate synthetic patient data, and emergency stroke transport simulations outputted distributions of 90-day mRS outcomes corresponding to DNS and mothership in every node. Although the probability of a good outcome was deemed the most clinically relevant metric, this framework has the capability to also make statistical comparisons between the transport strategies with respect to all outcomes 0 to 6 on the 90-day mRS scale. An analysis
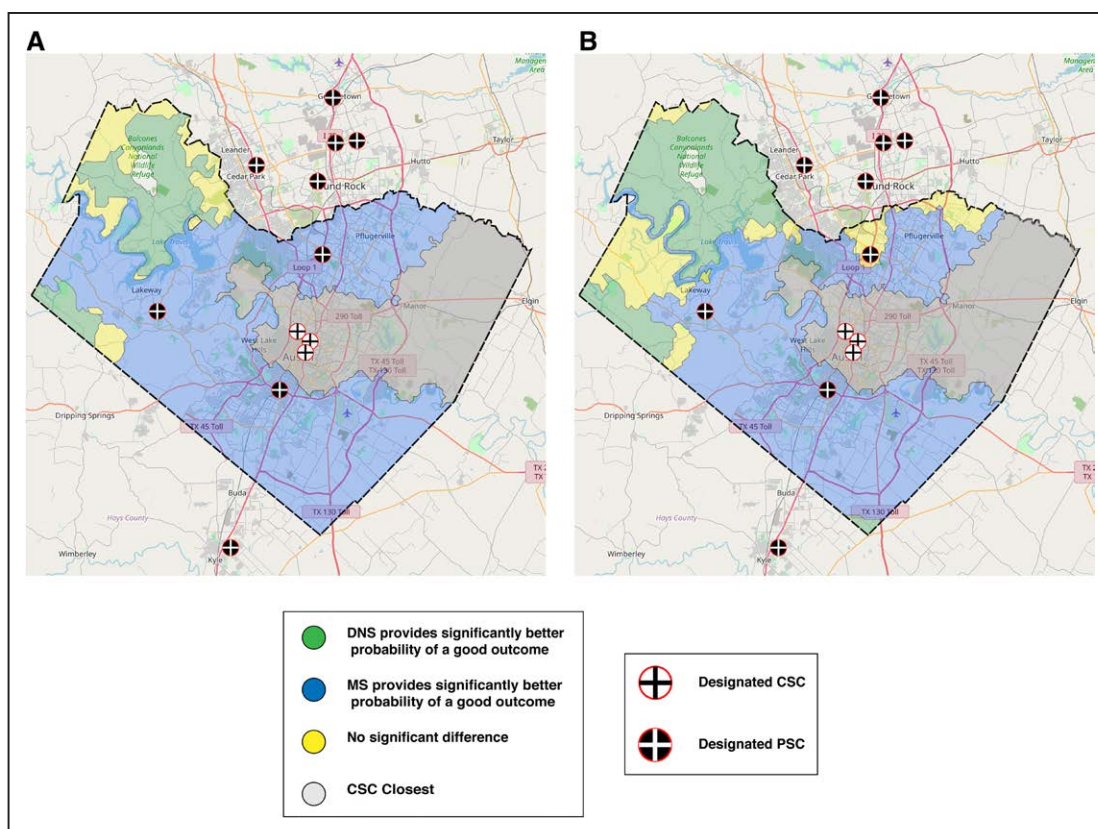
Figure 4. A map of the optimal emergency transport strategy depending on patient pickup location.
Drip and ship (DNS) provides a significantly better probability of a good outcome (90-d mRS [modified Rankin Scale] score 0–2) in fewer nodes assuming a fast rate of non-large vessel occlusion (LVO) infarct core growth (**A**) compared with when slow rate is assumed (**B**). Mothership (MS) provides significantly better probabilities of a good outcome in fewer nodes if the non-LVO infarct core growth rate is slow (**B**) compared with when a fast rate is assumed (**A**). Access to transportation routes can account for the difference between DNS and MS favorability, as seen in the northwest region of Travis County. Note that the colorless area in the northwest region is occupied by the Balcones Canyonlands National Wildlife Refuge and does not contain any nodes.

of the comprehensive outcome scale would be particularly useful in studying burdens of cost or other health care value metrics, such as cost-effectiveness models that seek to optimally place new stroke centers or upgrade existing centers by equilibrating health care costs and patient outcomes.

This work builds on previous, foundational studies of emergency stroke transportation.[39–42] Some of these studies compare the 2 emergency stroke transport strategies using conditional probability models derived from large clinical datasets and are able to compute probabilities of a good outcome on the 90-day mRS scale, dependent on the time from stroke onset-to-treatment, the type of stroke and corresponding treatment, and the particular transport strategy.[28,39–42] This data-driven approach of emergency stroke transportation modeling offers validity and accuracy only within the bounds of the dataset (ie, the patients and geographic times the model is derived from) and cannot identify underlying patient-specific, physiological mechanisms that account for trends in the data. The proposed framework serves as a foundation to resolve these issues by providing a ground-up model that accounts for inherent, population-level variability, or stochasticity, of

physiology-based independent variables. As a result, the framework can be applied to any geography, and cause-effect relationships motivating the results of the study are easily identifiable. Furthermore, it can determine statistically significant differences in outcomes between emergency stroke transportation strategies contingent on the stochasticity of these clinically relevant independent variables, whereas the data-driven models are deterministic in their current form and do not compute statistical significance.

In our first case study, optimizing transport decisions, we show that in both counties a fast rate of non-LVO infarct core growth decreases the number of nodes that favor DNS and increases the number of nodes that favor mothership compared with when a slow rate is assumed. From a physiological perspective, if a non-LVO patient's infarct core growth rate is fast and their pickup location is sufficiently remote from any stroke center, then their infarct core will quickly achieve a significant proportion of the ischemic penumbra volume before time of treatment, regardless of transport strategy. By extension, the non-LVO subpopulation's distribution of final infarct core
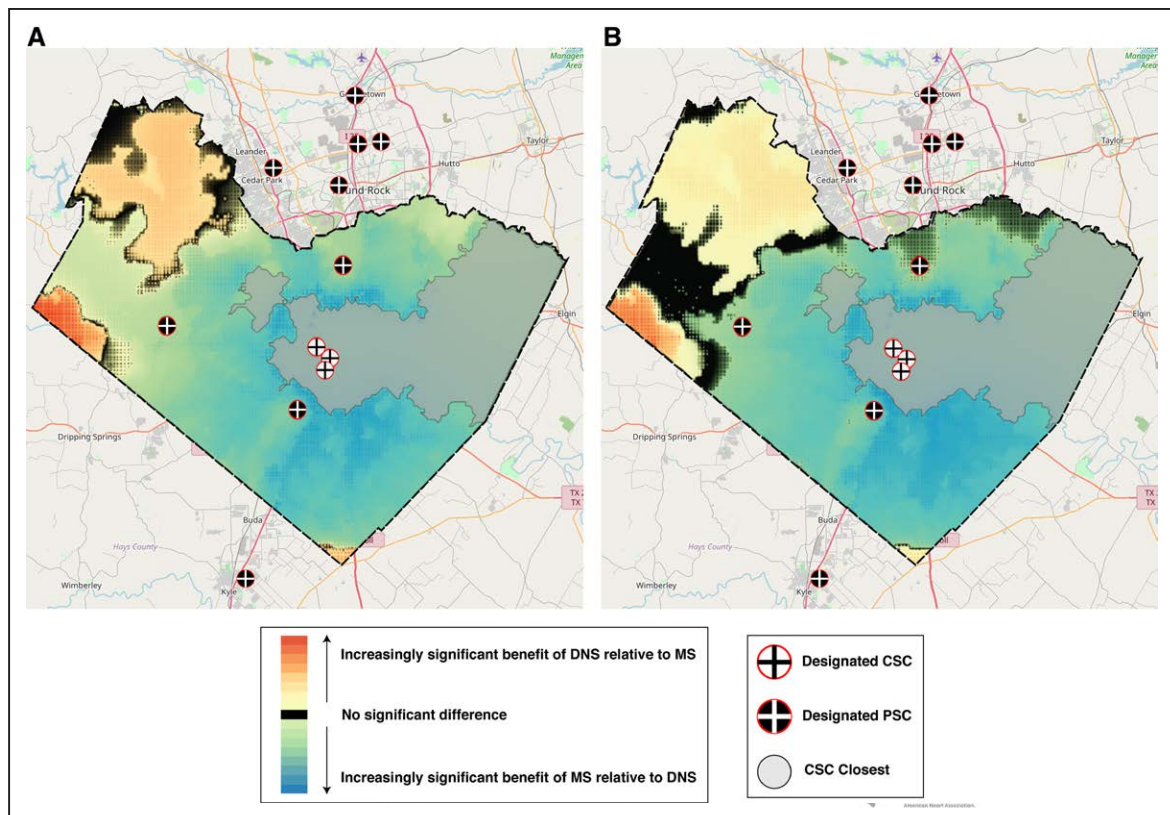
Figure 5. A heatmap showing Cohen's d effect size.
Assuming a fast rate of non-large vessel occlusion (LVO) infarct core growth (**A**), drip and ship (DNS) yields more relative benefit in the northwest region bounded by the Colorado River compared with when a slow rate of non-LVO infarct core growth is assumed (**B**). With either choice of non-LVO infarct core growth rate, the magnitude of mothership (MS) statistical significance decreases as the transport time to the comprehensive stroke centers (CSCs) in the city-center increases (relative to the transport time to the nearest primary stroke center [PSC]).

volumes will differ marginally between strategies, so DNS will not provide significantly better good outcomes as often for a mixed stroke population transported from these locations. This case study also reveals that geographies with long onset-to-treatment times (eg, Bastrop County) are likely to have a greater proportion of nodes that do not significantly favor any strategy relative to geographies closer to stroke centers (eg, Travis County), irrespective of infarct core growth rates. As onset-to-treatment time increases, the likelihood that any stroke patient's infarct core will achieve a significant proportion of the penumbra volume before treatment also increases. When transport times are exceptionally long, final infarct core volumes are approximately equal, translating to a lack of statistical favorability towards either transport strategy.

The physiological rationale for cases in which there is no statistical significance between DNS and mothership may lend some insight into the recent, preliminary results of the RACECAT study (Direct Transfer to Endovascular Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory).[43] In particular, they report that there was no benefit in outcomes due to the choice of emergency stroke transport in Catalonia, Spain. Catalonia's mean transport times to the nearest PSC and nearest CSC exceed the rural Bastrop County's

by ≈42 minutes and 110 minutes, respectively. Although more information is needed, we postulate that Catalonia's exceptionally long transport times led to considerable growth of patient infarct core volumes with either transport strategy. Consequently, there were negligible differences between the distributions of final infarct core volumes, and therefore outcomes, corresponding to patients randomly assigned to DNS or mothership.

In addition, our analysis of optimal bypass policies in the second case study revealed counterintuitive results. We found that under the assumption of a fast rate of non-LVO infarct core growth in either county, implementing any LVO field test in conjunction with bypass policies only for suspected LVO patients performs worse than implementing bypass policies without LVO field testing. This result follows from our first case study, showing that under the same rate assumption, mothership provides significantly better probabilities of a good outcome than DNS in a majority of Travis County (Figure 4). These mothership-favored regions cover the densely populated areas of Travis County (eg, Austin proper and its suburbs), so a county-wide bypass policy completely washes out the DNS preference of the few, less-populated regions. By implementing LVO field tests, we introduce rates of misclassification inherent to these tests. Evidently, a majority of the county significantly
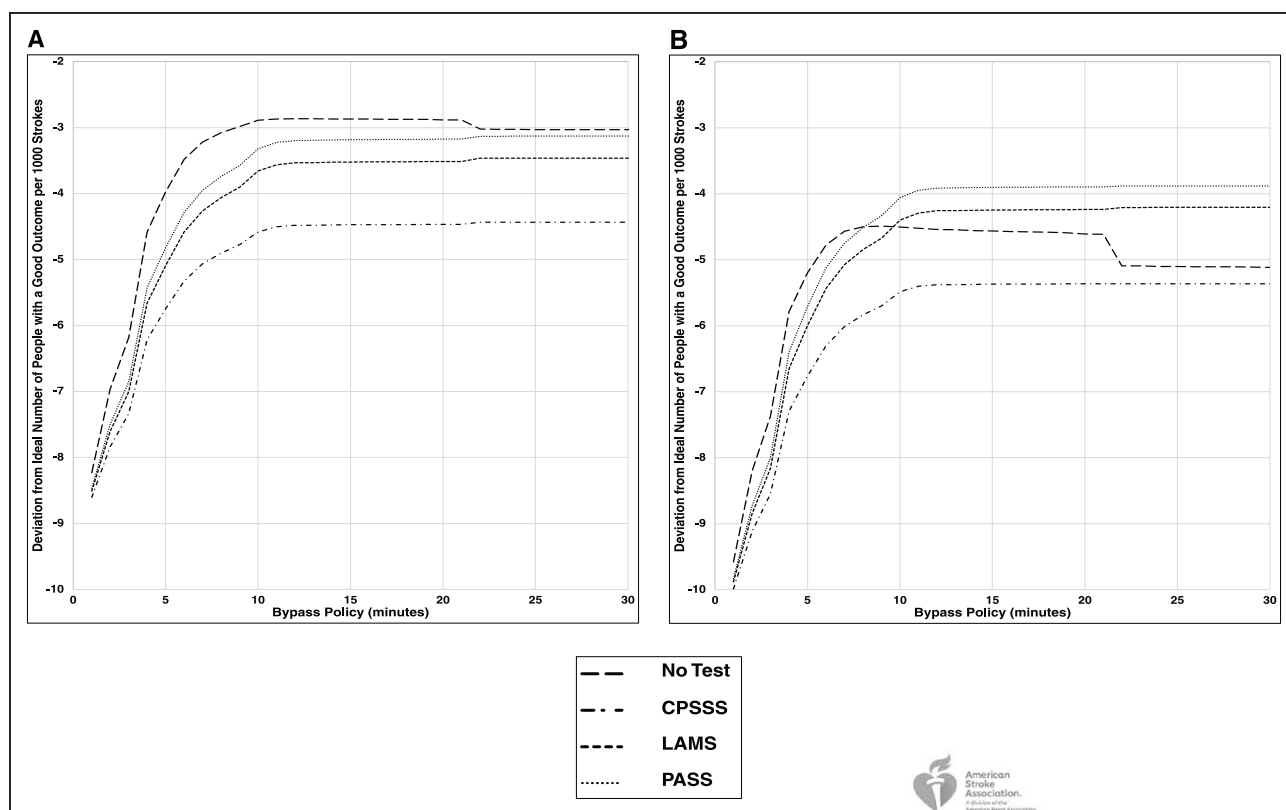
Figure 6. Efficacy of bypass policies depending on large-vessel occlusion (LVO) field test.
Assuming a fast rate of non-LVO infarct core growth, bypass policies 10 through 21 minutes are optimal without LVO field testing (**A**). Under the assumption of a slow rate of non-LVO infarct core growth, using the Los Angeles motor scale (LAMS) or prehospital acute stroke severity scale (PASS) field tests and always sending suspected LVO patients directly to the comprehensive stroke center (CSC) is optimal (**B**).

favors mothership, so misclassifying LVO patients as non-LVO and transporting them to the PSC causes substantial harm (false negatives). The implementation of a bypass policy without LVO field testing eliminates this harm by transporting all patients directly to the CSC. Importantly, the outcomes of patients without LVO transported from remote pickup locations do not differ significantly between DNS or mothership under this rate assumption. Field testing, therefore, negligibly benefits the non-LVO subpopulation and does not offset the harm done to the misclassified LVO patients taken to the PSC.

Conversely, assuming a slow rate of non-LVO infarct core growth, we found that implementing LVO field tests in conjunction with bypass policies only for suspected LVO patients performed better than implementing bypass policies without LVO field testing (with the exception of Cincinnati prehospital stroke severity scale in Travis County). Under this rate assumption, the non-LVO's in remote pickup locations benefit significantly more from transport to the PSC. As a result, implementing bypass policies without LVO field testing harms the entire non-LVO subpopulation (false-positives and true negatives alike), whereas field testing mitigates this harm by accurately classifying a proportion of the patients without LVO for optimal transport to the PSC (true negatives). The drastic differences in optimal emergency stroke transport policy stemming from

the rate of non-LVO infarct core growth underscores the critical importance of gaining empirical data of the physiological kinetics of this stroke type's growth rate.

It is important to note the potential resource constraints associated with emergency stroke transport decision-making. This analysis did not consider the common resource burdens or triage difficulties that often plague stroke centers. For instance, under the assumption of a slow rate of non-LVO infarct core growth, our simulation suggests always sending suspected LVO patients (Los Angeles motor scale or prehospital acute stroke severity scale) directly to the nearest endovascular capable center, yet a consequence of this directive may be a large buildup of patients in triage. This inefficiency would directly translate to worsened patient outcomes. Furthermore, Bastrop County is relatively close to a metropolitan center and extensive stroke network, so it would be important to analyze other rural geographies that do not have the same level of access to emergency stroke care resources.

CONCLUSIONS AND OPPORTUNITIES FOR MODEL IMPROVEMENT

We hope to bring a new perspective to the discussion of emergency stroke transport by elucidating the relevance of physiology in decision-making. As noted previously,

data-driven models map time from stroke onset to reperfusion directly to a probability of a good outcome. Our model generalizes this relationship by explicitly considering the underlying patient-specific, physiological variables that are fundamental determinants of stroke outcomes. By doing so, we are able to expand these clinically relevant factors to account for variation in a patient population, thereby gaining insight into the physiology that substantially influences optimal decisions.

Future work will modify the Equation 1 time constant to accommodate age, hypertension, or other patient comorbidities that may also affect infarct core growth rates. Early knowledge of a patient's stroke type and degree of collateral blood flow with CT-capable ambulances would allow for personalized emergency transport decisions with our framework. In addition, the time from stroke onset to reperfusion can be expanded into a statistical distribution to account for the inherent stochasticity of prehospital, transport and hospital time intervals found in a given geography and stroke center network (eg, traffic, triage delays, etc). These model capabilities pose valuable opportunities to tailor our estimates with region-specific data that encapsulates as much realistically occurring variability as possible.

As our mathematical understanding of stroke physiology improves, our framework can provide more reliable estimates to inform transport decisions and policies. Our case studies highlight the importance for clinical studies that empirically measure infarct core growth rates in humans. The non-LVO infarct core growth rate is not currently defined by clinical data but evidently has a large influence on optimal decisions and policies. In the same regard, the parameterization of the LVO time constant uses data from nonhuman experiments, which may affect the accuracy of our estimates. Moreover, while it remains to be seen if the 90-day mRS-volume relationship (Equation 2) varies by population, Ernst et al report uncertainty in this association which directly translates to uncertainty in our modeling results (see Sensitivity Analysis in the Data Supplement). The precision of our estimates would improve with data that reports a 90-day mRS-volume relationship to a greater degree of confidence. Additionally, all probabilities of successful reperfusion are taken from clinical trials that define successful reperfusion as a Thrombolysis in Cerebral Infarction score ≥2b, but scores ≥2a will be considered in future work given clinical studies that provide such data, as partial reperfusion can affect final infarct volume.

ARTICLE INFORMATION

Affiliations

Carolina Center for Interdisciplinary Applied Mathematics, Department of Mathematics (D.A.P., P.J.M.), University of North Carolina, Chapel Hill. Departments of Neurology (D.P., J.C.) and Population Health (J.C.), Dell Medical School, Mulva Clinic for the Neurosciences and Oden Institute for Computational Engineering and Sciences, The University of Texas at Austin.

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Disclosures

None.

Supplemental Materials

Expanded Materials, Methods, and Results
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