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Article

Optimization of Natural Ventilation Strategies in Large-Space Buildings Based on Multi-Directional Wind Fields and Spatial Heterogeneity

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Abstract

Building energy conservation and emission reduction have become global priorities. Conventional sports facilities, owing to their substantial spatial dimensions, predominantly depend on mechanical HVAC systems, leading to elevated energy consumption and operational expenses. Consequently, the judicious application of natural ventilation is crucial for attaining a sustainable transformation of these structures. This study focuses on the National Fitness Center in Shenyang, a representative city located in a chilly climate. Utilizing the Ladybug Tools platform alongside computational fluid dynamics (CFD) numerical simulation techniques, multi-scenario simulations are performed for omnidirectional wind conditions and two varieties of window openings. An analysis is conducted on the indoor airflow distribution and wind speed characteristics across several functional regions of the large-space gymnasium under different wind directions. The study developed methodologies for identifying optimal ventilation durations and target wind velocities annually, quantified the influence of incident wind angles on ventilation efficacy, confirmed that appropriate building orientation can enhance ventilation efficiency by roughly 45%, and clarified the mechanisms and selection criteria for window types affecting indoor airflow patterns. The research findings offer a solid theoretical foundation and practical technical assistance for the ventilation design of national fitness centers to accommodate climatic conditions.

Keywords: natural ventilation; large space building; form optimization strategy; indoor airflow distribution; multi-directional wind analysis; spatial heterogeneity

1. Introduction

Indoor ventilation is an essential element in establishing healthy and comfortable building environments. It not only provides fresh air and eliminates carbon dioxide but also significantly contributes to the regulation of indoor thermal comfort [1]. Contemporary buildings frequently employ mechanical ventilation systems or conditioning apparatus, such as air conditioning, to uphold indoor environmental quality. Nonetheless, an overdependence on such systems may lead to significant energy loss [2]. Buildings constitute over 40% of worldwide energy usage, a percentage that is steadily increasing. Heating, ventilation, and air-conditioning (HVAC) systems are significantly energy-intensive, usually accounting for 40%–60% of a building's overall energy consumption [3]. In light of worldwide initiatives to attain "carbon peaking" and "carbon neutrality," optimizing natural ventilation design to diminish reliance on mechanical systems has emerged as a crucial strategy for improving building energy efficiency and reducing carbon emissions [4].

Natural ventilation constitutes a complicated multi-scale system that encompasses the city, neighborhood, and individual structures, wherein alterations in any component can substantially influence the ultimate indoor ventilation efficacy [5]. At the macroscopic level, initial studies

primarily concentrated on the adaptation of urban planning to climatic characteristics. Oke [6] established a theoretical framework for building layout that aligns with prevailing wind directions, offering quantifiable geometric control indices for the creation of contemporary “urban ventilation corridors.” Givoni [7] examined the influence of building scale and spacing on wind environments, observing that structures in the back rows of high-density clusters are susceptible to “wind shadows,” and he provided minimum spacing guidelines to facilitate successful cross-ventilation. Yuan and Ng [8] introduced the quantitative parameter “frontal area density” (FAD) to apply these principles in high-density urban environments, demonstrating that elevated FAD markedly decreases near-ground mean wind speed, thereby serving as a crucial metric for assessing wind conditions in modern cities.

At the micro-scales, subsequent research has shifted toward quantifying in finer detail the role of building-group layouts and individual building forms. Gomes et al. [9] and Yan et al. [10] simulated the wind pressure distribution on irregular building forms such as L-shaped, U-shaped and cruciform-shaped layouts. They found that concave areas are prone to generating significant local eddies and negative pressure zones, which directly affect the ventilation driving force of openings on building facades. Hang et al. [11] demonstrated, by comparing row-type and staggered-type building arrays, that staggered layouts can effectively disrupt the flow confinement within street canyons and significantly improve pollutant dispersion efficiency. With advances in computational power, research focus has moved toward refined airflow organization design at the individual building level. Blocken and Carmeliet [12] systematically analyzed the corner vortices and downwash effects induced by high-rise buildings, proposing that tapered facades can reduce pedestrian-level wind speeds by 30%–40%. Regarding specific facade constructions, Chu and Chiang [13] observed that when the inlet window area exceeds 20% of the floor area and the outlet window area is 1.2 times that of the inlet, the indoor average wind speed can increase by approximately 38%. Moreover, Perén [14] and Zhong [15] further refined the influence of window parameters, roof pitch, and the aspect ratio of windward walls on ventilation efficiency, confirming that well-designed details can significantly enhance the effectiveness of wind-driven natural ventilation.

Although existing research has accumulated substantial findings across different scales, limitations remain in addressing the complexities of real-world wind environments [16]. Natural wind exhibits significant temporal variations, with wind direction demonstrating high variability and uncertainty even within a single day [17]. However, previous simulation studies have predominantly treated a single “prevailing wind direction” as the core boundary condition. In reality, meteorological data analysis indicates that the occurrence frequency of a single prevailing wind direction typically does not exceed 50% of the total wind frequency. This implies that, during actual daily operation, a building is exposed to non-prevailing wind directions for more than half of the time. Ventilation strategies derived solely based on a single prevailing wind direction face a high risk of ineffectiveness when confronted with the variability of real wind conditions. Particularly for large-space buildings characterized by deep plans and high ceilings, their indoor airflow fields are more sensitive and complex in response to changes in external wind direction. How to maintain stable ventilation performance under dynamic conditions with frequent wind direction shifts is a critical challenge that urgently needs to be addressed.

Against this background, this study aims to move beyond the limitations of traditional research focused on a “single prevailing wind direction” and instead concentrate on the natural ventilation characteristics of large-space buildings under multi-directional wind conditions. Taking a typical large-space building as the baseline model, this research employs Computational Fluid Dynamics (CFD) numerical simulation methods. Through multi-scenario simulation analysis, it specifically investigates the influence patterns of different wind direction conditions on indoor airflow distribution. Consequently, it proposes optimized natural ventilation design strategies applicable to large-space buildings. The structure of this paper is organized as follows: Following the introduction, the second section systematically reviews the background and development trends of wind environment research in the architectural field. The third section elaborates in detail on the

foundational conditions and implementation procedures of this study, covering key information such as research tools, basic meteorological data, the baseline building model, and core design variables.

2. Materials and Methods

This section systematically expounds on the experimental design and technical framework of this study, primarily covering the selection basis of the research platform, the multi-dimensional feature analysis of typical meteorological data, the construction and simplification principles of the building model, the quantification standards of key design variables, and the implementation process of multi-condition numerical simulations. A scientifically standardized experimental scheme is the core prerequisite for ensuring the reliability of research conclusions. The specific process is as follows: (1) statistical characterization of the Typical Meteorological Year (TMY) data for the target region, with emphasis on extracting the temporal variation patterns of wind speed and direction, thereby highlighting the limitations of conventional studies that rely solely on a single prevailing wind direction for simulations; (2) conducting comprehensive indoor wind-field simulations based on the 16-directional wind-rose system, employing visualization techniques and statistical analysis to examine the distribution features of indoor airflow and the differences in ventilation efficiency under varied wind directions; (3) establishing comparative scenarios for two typical window opening types—top-hung and bottom-hung windows—and applying the controlled-variable method to quantitatively investigate the impact of different window configurations on indoor airflow organization patterns and the velocity distribution in key zones.

2.1. Research Tool

This study selects the open-source parametric platform Ladybug Tools (LBT) to establish the core research framework, balancing technical maturity and suitability for building performance simulation. Built upon the visual programming environment of Rhino and Grasshopper, LBT enables in-depth integration of design variables and performance evaluation indicators through its high modularity and parametric capabilities [18]. The research emphasizes two core modules: the Ladybug module is used for detailed parsing and preprocessing of temporal features in meteorological data (covering time-dependent parameters such as wind speed and direction), while the Butterfly module serves as a computational fluid dynamics (CFD) simulation engine, integrating the open-source solver OpenFOAM to achieve high-fidelity numerical simulation of wind fields both inside and around buildings [19]. Compared with conventional commercial software, LBT significantly improves the efficiency of multi-scenario sensitivity analysis under complex working conditions, offering a robust technical foundation for dynamic simulations under varying wind directions [20].

2.2. Basic Data

The reliability of meteorological data is essential for ensuring the accuracy of natural ventilation simulations. This study employs the Typical Meteorological Year (TMY) data for Shenyang as the fundamental boundary condition. The dataset is synthesized based on continuous observations from 1991 to 2020 provided by the China Meteorological Administration, following the *Standard for Building Meteorological Parameters* (JGJ/T 461–2019) and using the Sanders method. It comprises 8,760 hourly records, with wind speed recorded at a precision of 0.1 m/s and wind direction resolved to 1°. While preserving the completeness of long-term climatic statistical characteristics, the data effectively captures the dynamic features of wind speed fluctuations and directional shifts, thereby mitigating the randomness bias that can arise from a single observation year [21].

2.3. Building Models

This research establishes an experimental model utilizing a fitness center in Shenyang as a case study. The fitness center is a substantial public structure with dimensions of 100 m by 50 m and a

height of 10 m per story (Figure 1). The model was refined based on proven simplification approaches for simulating wind environments in buildings to enhance computing efficiency while maintaining accuracy [22]. We omitted minor structural components, such as slender columns that exert minimal influence on the total airflow within. We implemented spatial simplifications by omitting enclosed circulation cores and windowless zones that do not contribute to natural ventilation. Crucial distinctive characteristics were preserved, and the configuration of the primary partition walls, together with the dimensions and placements of the window and door openings, were meticulously replicated from field survey data. The optimized model retains the essential ventilation characteristics of an extensive, multi-zone configuration while adeptly regulating mesh dimensions. This enables the efficient execution of the subsequent series of multi-scenario numerical simulations.

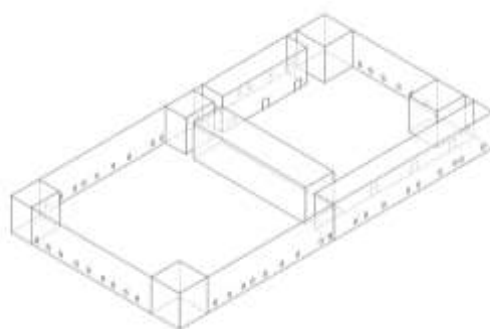


Figure 1. Modeling schematic diagram.

2.4. Design Variables

(1) Wind Direction: Wind direction is a key factor determining the airflow path and pressure distribution indoors. To comprehensively analyze the influence of the external environment on large-space buildings, this study does not adopt the conventional 8-directional division but employs a finer 16-directional system (with intervals of 22.5°) to conduct full-range CFD simulations, aiming to reveal the non-linear effect of wind direction variability on indoor ventilation performance [23].

(2) Window Form: Window form is designed to match the facade characteristics of the prototype building. This study selects the top-hung window as the baseline and introduces the bottom-hung window for comparison. By simulating and analyzing the differences in flow-guiding properties between the two forms, the research explores how the window-opening configuration affects the air-exchange efficiency inside the large space by altering the jet angle.

2.5. Experimental Setup

The simulation computational domain was constructed in strict accordance with the Best Practice Guidelines for building wind environment simulation [24,25]. The external domain extents were set as follows: upstream $5H$, downstream $10H$, lateral sides $2.5H$, and top $3H$, where H denotes the building height. The turbulence model used is the widely accepted standard $k-\epsilon$ model in the field of building wind environment research [26], which provides good robustness and computational efficiency in simulating complex vortex flows in large interior spaces [27]. Based on this setup, a virtual sensor array was deployed inside the building with 1 m spacing. Steady-state numerical simulations were performed for 16 wind-direction scenarios to obtain high-spatial-resolution wind-field distribution data.

3. Results and Discussion

3.1. The Complexity of Urban Wind Direction

The wind environment is vital for managing urban microclimates and energy exchange, affecting the aerodynamic properties of buildings and acting as a key indicator for evaluating living environment quality and thermal comfort in urban areas [28,29]. In contemporary architectural design, Computational Fluid Dynamics (CFD) numerical simulation has become a standard technique for optimizing building form and enhancing natural ventilation opportunities [30]. Nevertheless, contemporary simulation techniques often demonstrate predictive bias due to oversimplification. Simulations frequently overlook the complex local climatic context, neglecting the threshold constraints of meteorological parameters (such as outdoor temperature and relative humidity) on the effectiveness of natural ventilation, leading to inconsistencies between anticipated ventilation capacity and actual thermal needs [31]. In contrast, conventional studies rely predominantly on a single prevailing wind direction, failing to effectively capture the dynamic fluctuations and seasonal variations of wind fields in both spatial and temporal dimensions [32]. This study conducts a multi-parameter coupled analysis of the local meteorological context to accurately identify the ideal periods for natural ventilation, hence creating boundary conditions for subsequent high-fidelity numerical simulations [33].

Currently, the academic community has not reached a universal consensus on the critical range of outdoor temperatures suitable for natural ventilation [34]. Due to significant differences in climatic background, environmental endowments, and human thermal adaptability across regions, the corresponding appropriate temperature intervals exhibit pronounced spatial variability [35]. Synthesizing international and domestic research consensus on adaptive thermal comfort and building energy conservation, the 15–28 °C range is widely recognized as the optimal outdoor temperature interval for natural ventilation technology to yield benefits, effectively improve indoor air quality, and reduce mechanical cooling energy consumption [36,37]. Within this range, natural ventilation not only meets the needs for indoor humidity and pollutant removal but also helps maintain human thermal balance through convective heat exchange, making it a key basis for implementing passive energy-saving design in cold regions during transitional seasons and in hot-summer/cold-winter zones [38].

Based on a predefined temperature threshold, this study used the Ladybug Tools (LBT) simulation platform to quantitatively screen and analyze the multi-year hourly temperature observation dataset for Shenyang. The results (Figure 2) show that temperatures in Shenyang from April to October each year are highly compatible with the suitable range for natural ventilation, indicating significant bioclimatic regulation potential. By plotting the overall and monthly wind roses for this period (Figure 3), it can be seen that southerly (S) and south-southwesterly (SSW) winds dominate the statistical period. Although the proportion of north-northeasterly (NNE) winds increases from August to October, the overall wind-field characteristics remain stable. Quantitative analysis of the wind frequency data for April to October (Table 1) shows that, during the suitable ventilation period, the dominant wind directions are strongly concentrated in the S and SSW sectors, with occurrence frequencies of 19.2% and 17.3%, respectively, and corresponding average wind speeds of 2.67 m/s and 3.67 m/s. Frequencies for all other directions are below 10%, and the regional average wind speed over the study period is recorded as 2.83 m/s.

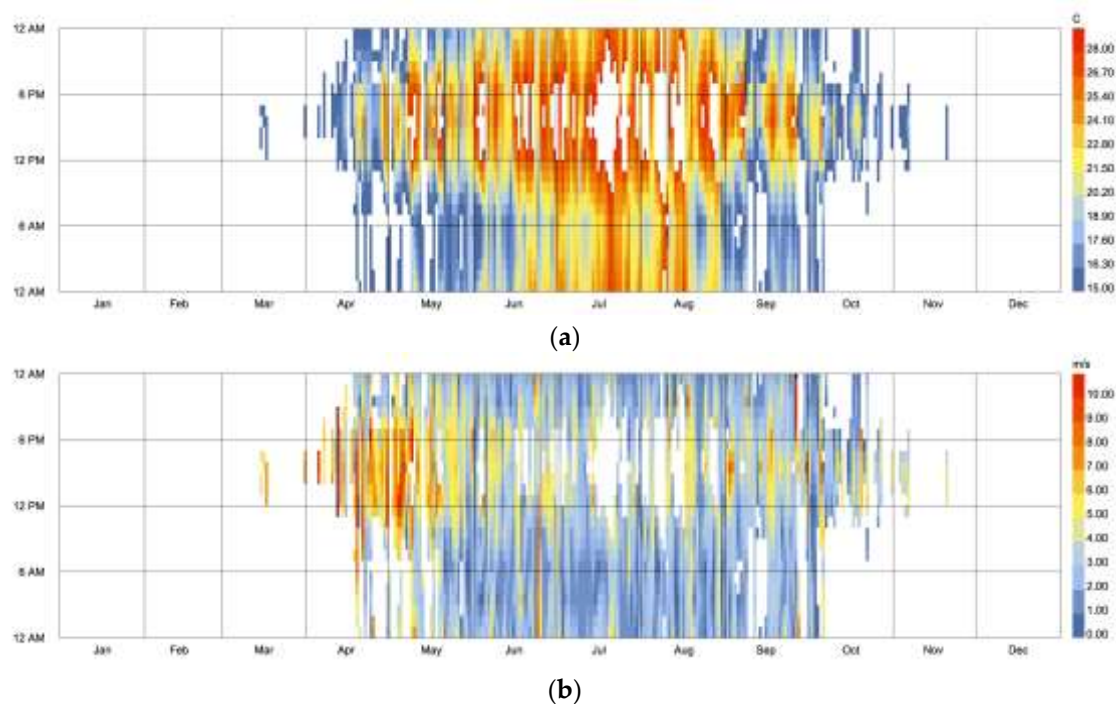


Figure 2. Outdoor wind speed and temperature during periods suitable for natural ventilation.

Based on the statistical results of wind-direction azimuths from April to October (Table 1), the prevailing wind field during the study period is primarily driven by three core directions: south (S), south-southwest (SSW), and north-northeast (NNE). Specifically, the flow-field characteristics in May to July and September are jointly dominated by S and SSW winds, with cumulative frequencies of 50.4%, 44.1%, 37.2%, and 37.5%, respectively. In August and October, the dominant wind direction shifts, with NNE becoming the primary contributor at frequencies of 15.2% and 14.9%, respectively. These quantitative features indicate that even in the months with the highest directional concentration, the coverage of a single prevailing wind direction does not approach the 50% threshold. This strongly confirms that in numerical simulations of wind environments, relying solely on a single wind direction as the boundary condition fails to accurately capture the dynamic characteristics of real wind fields, representing a significant methodological limitation.

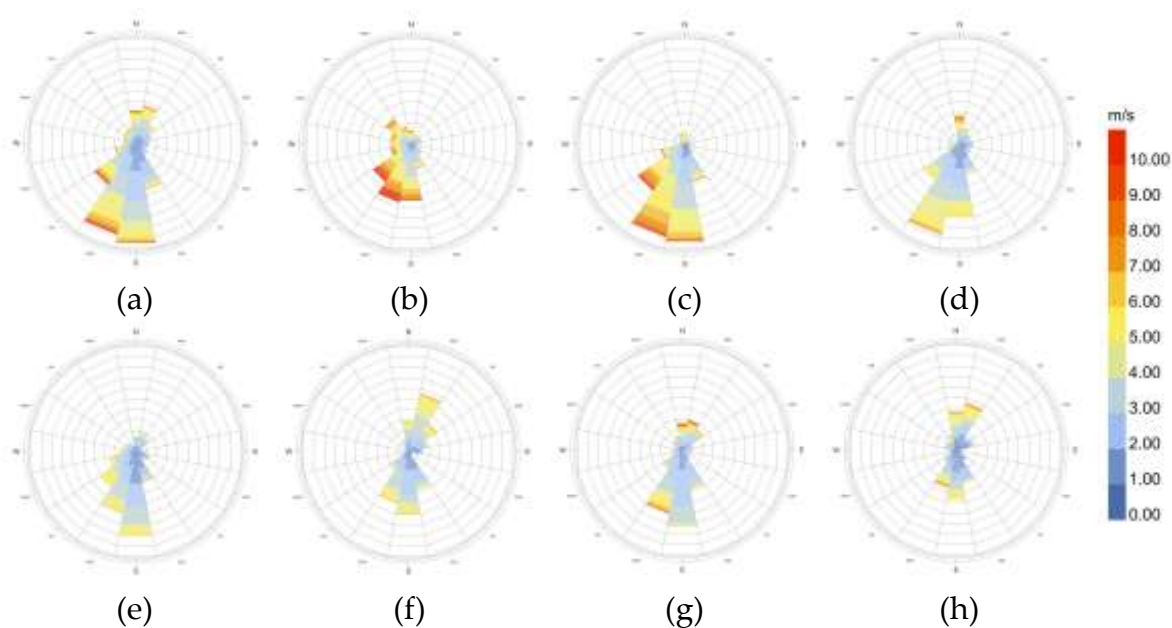


Figure 3. Wind Rose Chart at Different Time Periods.(a) April to October; (b) April; (c) May; (d) June ; (e) July; (f) August; (g) September; (h) October.

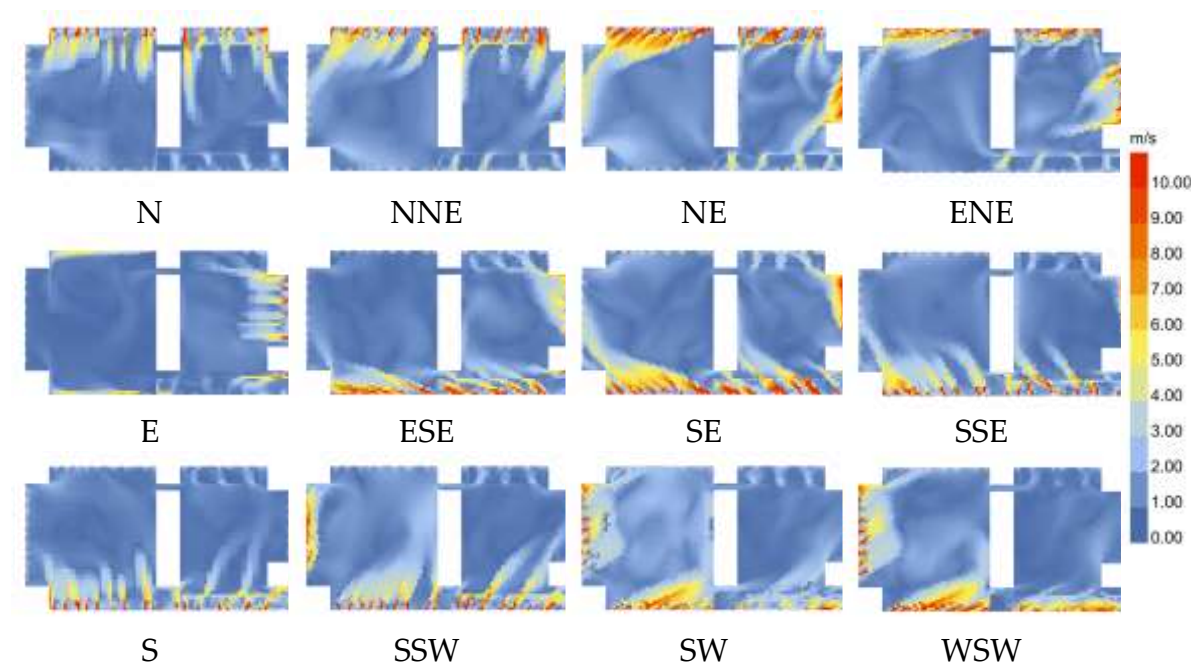
Table 1. Outdoor wind speed and temperature during periods suitable for natural ventilation.

The Degree of Angle	Direction	Ratio (%)	Speed (m/s)
-11.25 To 11.25	N	6.288941	3.366254
11.25 To 33.75	NNE	7.535047	2.981137
33.75 To 56.25	NE	4.614486	2.262869
56.25 To 78.75	ENE	3.290498	1.718935
78.75 To 101.25	E	2.706386	1.491367
101.25 To 123.75	ESE	2.414330	1.563710
123.75 To 146.25	SE	3.193146	1.503049
146.25 To 168.75	SSE	9.462617	2.013786
168.75 To 191.25	S	19.23676	2.672672
191.25 To 213.75	SSW	17.25078	3.675959
213.75 To 236.25	SW	9.287383	3.667296
236.25 To 258.75	WSW	4.108255	2.966351
258.75 To 281.25	W	2.492212	2.564063
281.25 To 303.75	WNW	2.375389	2.819672
303.75 To 326.25	NW	2.706386	3.174820
326.25 To 348.75	NNW	3.037383	3.026282

3.2. The Influence of Wind Direction

3.2.1. Indoor Average Wind Speed

Since the floor plan of the experimental model is not centrally symmetric, the indoor wind environment inevitably varies under different incident wind directions. Simulations were performed to analyze the indoor wind-velocity flow fields under 16 wind-direction scenarios (Figure 4). The results show that although good airflow is formed near the windows under all wind directions, the wind-speed distribution in the central indoor zone exhibits clear directional differences.



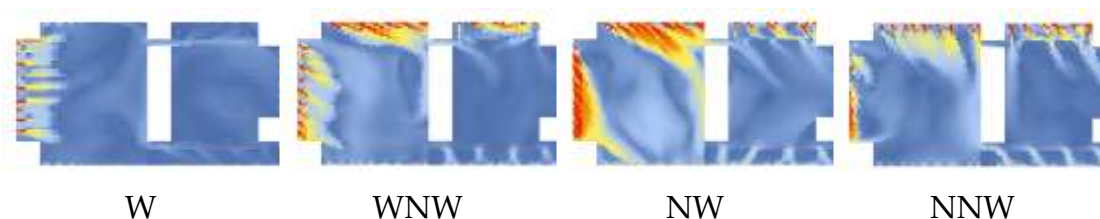


Figure 4. Contour plot of wind speed field in the indoor stand under different wind directions (top-hung).

Figure 5 reveals the correlation between wind direction and indoor average wind speed. Under 16 wind direction conditions, the average indoor wind speed is 0.155 m/s, with maximum and minimum values of 0.225 m/s and 0.089 m/s, respectively. There are significant differences in indoor ventilation performance under different wind directions. If a building selects an appropriate orientation based on the local wind direction, its ventilation performance can be improved by up to 45%. Conversely, improper orientation selection can lead to a ventilation performance loss of about 42%. Among the wind directions, northwest wind (NW), southwest wind (SW), northeast wind (NE), and southeast wind (SE) have the best ventilation efficiency, with average wind speeds of 0.225 m/s, 0.204 m/s, 0.198 m/s, and 0.181 m/s, respectively. At this time, the angle between the incoming wind direction and the building is 45°. The ventilation performance of west wind (W), east wind (E), south wind (S), and north wind (N) is relatively poor, with average wind speeds of 0.0899 m/s, 0.0896 m/s, 0.124 m/s, and 0.135 m/s, respectively. These wind directions are mostly perpendicular to the building facade, with the short sides of the building facing the wind for west wind (W) and east wind (E), resulting in the worst ventilation performance. It can be seen that the indoor ventilation performance of a building is strongly correlated with the building's windward face and windward angle. In design, the building's orientation should be as close to a 45° angle with the local prevailing wind direction as possible to achieve better natural ventilation performance.

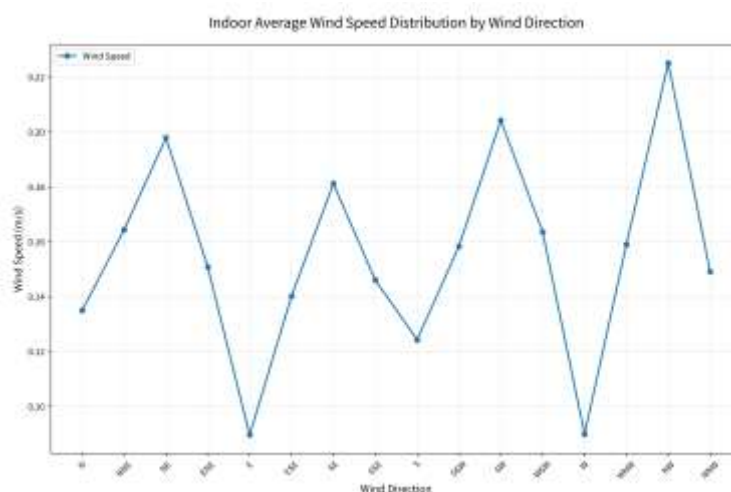


Figure 5. Indoor average wind speed distribution by wind direction.

3.2.2. Distribution of Wind Speed Ranges

According to Fanger's thermal comfort theory (PMV/PPD model), optimal air velocity is intrinsically linked to indoor temperature, humidity, and metabolic rates, with diverse functional requirements dictating specific velocity thresholds. ASHRAE Standard 55 (2017) recommends a comfort range between 0.1 m/s and 0.3 m/s. Furthermore, research by Zhu et al. (2018) and Liu et al. (2020) suggests that large-scale spatial volumes, such as gymnasiums, require slightly higher velocities—typically between 0.2 m/s and 0.4 m/s—to ensure effective air circulation without compromising the comfort of athletes and spectators.

south-southwest (SSW) and north-northwest (NNW), the average wind speed is 0.22 m/s; under other wind directions, it decreases to 0.14 m/s, representing a reduction of 36%. For the southern functional zone (SFZ) and northern functional zone (NFZ), when winds originate from the northern sector, the average wind speeds in the SFZ and NFZ are 0.12 m/s and 0.36 m/s, respectively. When winds shift to the southern sector, the corresponding average wind speeds become 0.36 m/s and 0.11 m/s. It can be observed that the windward zones exhibit higher average wind speeds and better ventilation performance, while the leeward zones, although relatively comfortable in terms of wind speed, contain extensive still-air areas.

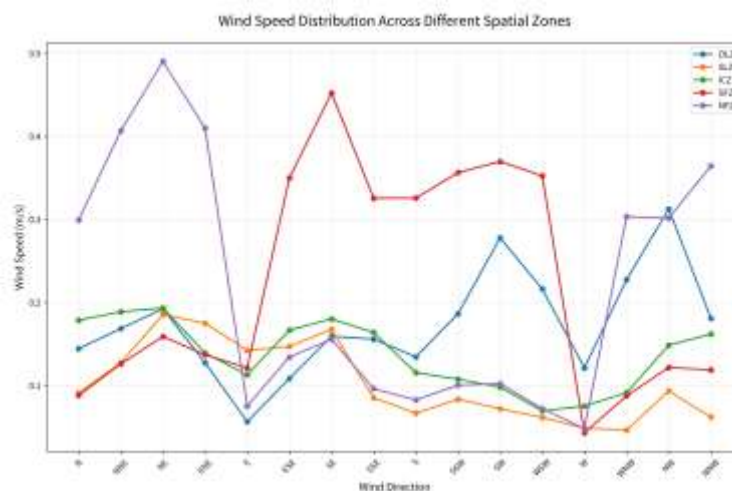


Figure 7. Wind frequency distribution across different spatial zones.

Spatial openness significantly influences indoor average wind speed. When the wind direction falls between north-northeast (NNE) and south-southeast (SSE), the indoor average wind speeds in the WLZ and ELZ are 0.14 m/s and 0.15 m/s, respectively, showing little difference. In contrast, when the wind direction lies between south-southwest (SSW) and north-northwest (NNW), the average wind speeds in these two zones become 0.22 m/s and 0.07 m/s, respectively, revealing a pronounced discrepancy. This difference arises because the ELZ is partially enclosed by the SFZ and NFZ on its north and south sides, leading to considerable wind-speed attenuation as airflow passes through, which substantially lowers its indoor average wind speed. Consequently, the ELZ, with its lower wind speed and more stable airflow, is better suited for sports sensitive to air movement, such as table tennis and badminton. Conversely, the WLZ, with its superior wind-speed conditions, is more appropriate for activities requiring stronger airflow, like basketball, volleyball, and tennis. In ventilation design, to enhance the ventilation efficiency of a large space, it is advisable to position the space on the prevailing-wind side and orient it at an angle of approximately 45° to the prevailing wind direction. If ventilation of two main functional zones must be balanced, the core large space (partially surrounded by auxiliary functional zones) should preferably be placed on the prevailing-wind side.

3.3. The Influence of Window Form

From the perspectives of safety and operational convenience, pivot windows are commonly adopted in public buildings, with top-hung and bottom-hung windows being the two most prevalent types. Top-hung windows are usually outward-opening, which minimizes visual and structural impact on the building facade, but their maximum opening angle is typically restricted. In contrast, bottom-hung windows are predominantly inward-opening, imposing no influence on the external facade while offering higher safety. In terms of indoor airflow organization, the core distinction between the two window types lies in their airflow-guiding characteristics: the air inlet of a top-hung

window is positioned slightly lower than that of a bottom-hung window, whereas the bottom-hung window exhibits a more pronounced directional guiding effect on the incoming airflow.

This study conducts a comparative analysis of the indoor airflow distribution characteristics under top-hung and bottom-hung window configurations. Figure 8 presents the indoor wind speed profiles for the bottom-hung window under different wind directions. The opening angles of both window types were set identically in the simulations, ensuring the same theoretical total air inflow. Simulation results show that the indoor average wind speeds under the two window modes are 0.1549 m/s and 0.1557 m/s, respectively, with a negligible difference of only 0.5%.

To further investigate the spatial distribution of the indoor wind field, cross-sections at the window plane and at the partition wall between windows were selected, and corresponding wind-field contour plots were generated (Figures 9). The contour plots indicate that airflow around the window openings is significantly stronger than in other indoor areas, with the primary influence of the airflow confined to a depth of 20–30 m from the window. Specifically, the top-hung window configuration promotes better air circulation near the window, but its effective airflow penetration depth is less than that of the bottom-hung window. The bottom-hung window enhances airflow closer to the floor level more effectively; however, this can result in high-speed zones near the floor, making it less suitable for sports such as table tennis that require specific wind conditions at ground level. From the airflow profiles on the non-window side, the bottom-hung window produces more uniform air infiltration, whereas the top-hung window tends to generate local vortices in the corresponding area. Considering the ventilation comfort requirements of sports activities, the two window types exhibit distinct suitability for different usage scenarios.

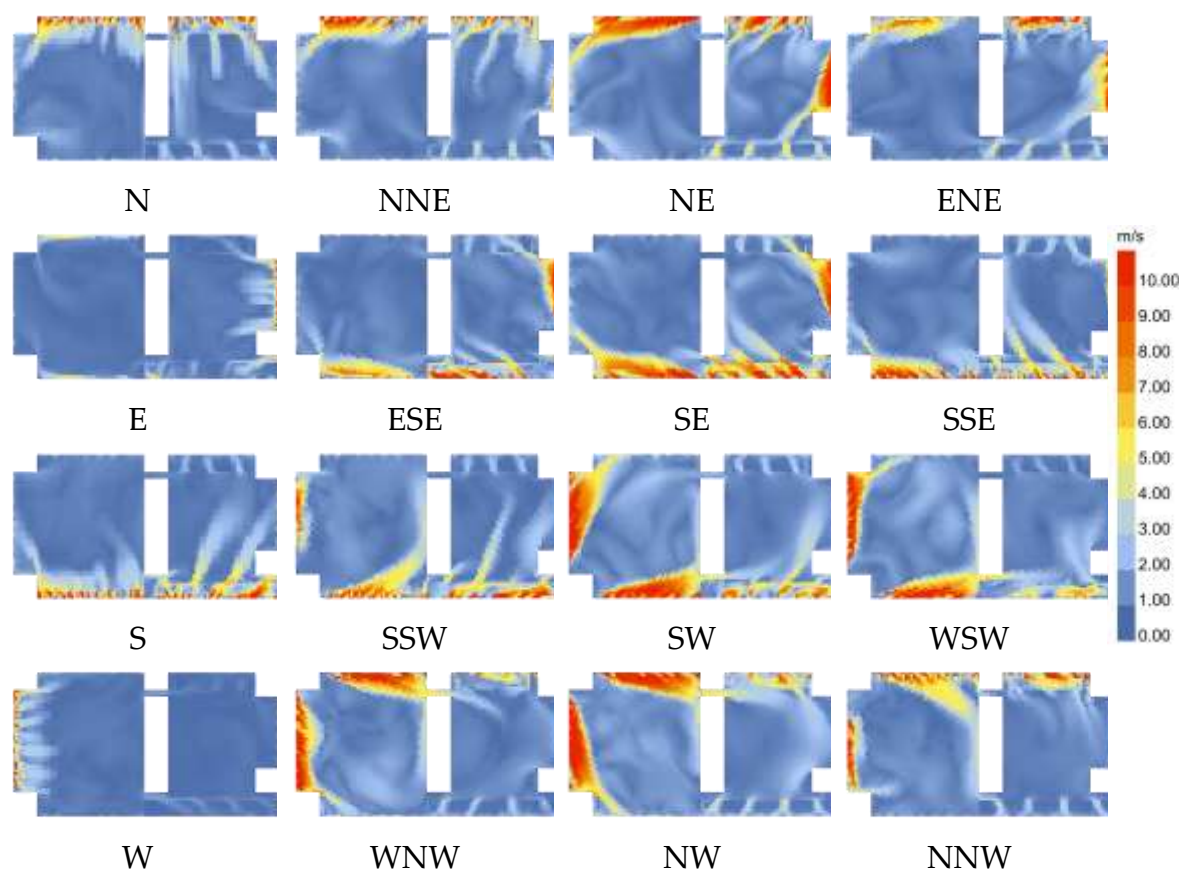
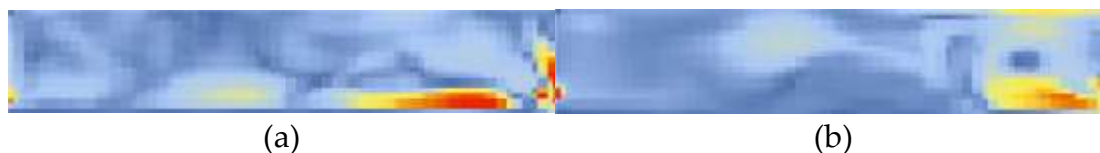


Figure 8. Contour plot of wind speed field in the indoor stand under different wind directions (bottom-hung).



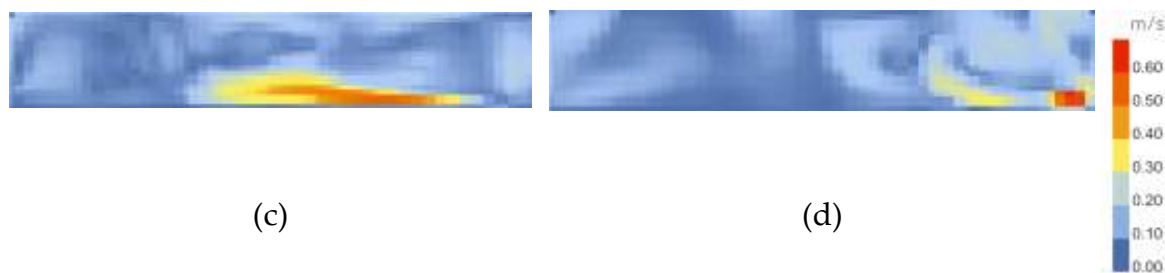


Figure 9. Wind speed contour plot on cross-section.(a)Cross-section cut at the top-hung window.(b)Cross-section cut at the bottom-hung window.(b)Cross-section not intersecting the top-hung window.(d)Cross-section not intersecting the bottom-hung window.

4. Conclusions

(1) Methodological Necessity of Multi-Directional Analysis

The methodological necessity of multi-directional analysis is underscored by the examination of TMY data filtered within the ideal temperature range of 15–28 °C, which indicates that even during months characterized by elevated wind concentration, the predominant wind constitutes less than 50% of the overall period. This affirms that dependence on a singular prevailing wind direction for building simulation results in substantial methodological bias, while a 16-directional framework accurately reflects the intricate nature of urban wind settings.

(2) Optimal Incidence Angle for Ventilation

The optimal incidence angle for ventilation: Indoor aerodynamic performance is significantly influenced by the wind's incident angle. Numerical calculations indicate that an oblique incidence (about 45° relative to the building's principal axes) maximizes both ventilation efficiency and flow homogeneity. Under these conditions, the average indoor wind speed attained a maximum of 0.225 m/s, markedly surpassing perpendicular (orthogonal) wind directions.

(3) Spatial Anisotropy and Functional Zoning

Indoor airflow has significant spatial variation. Windward functional zones experience elevated velocities (up to 0.36 m/s), but leeward zones are susceptible to standstill. The structural confinement of auxiliary rooms, such as the South and North Functional Zones, results in kinetic energy dissipation, decreasing the average velocity in enclosed large spaces (ELZ) by as much as 36% relative to open zones (WLZ).

(4) Design Guidelines for Expansive Structures

To improve environmental quality, high-demand ventilation zones (e.g., basketball courts) should be situated on the windward side and aligned at a 45° angle to the prevailing wind. Conversely, wind-sensitive functional zones (e.g., badminton or table tennis courts) ought to be deliberately situated in semi-enclosed or leeward locations where airflow is more stable and mitigated.

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Conflicts of Interest: The authors declare no conflicts of interest.

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