

## **Mathematical modelling of ventilation–perfusion mismatch in lung function**

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## Abstract

Impaired pulmonary gas exchange in respiratory diseases is caused by a large extent by the physiological mechanism of ventilation-perfusion (V/Q) mismatch. This study is aimed at developing a mathematical modelling framework to quantify regional ventilation, pulmonary perfusion and oxygen transport by coupled nonlinear differential equations. A novel model called Adaptive Ventilation-Perfusion Coupling Model (AVPCM) is proposed which is numerically solved using the Finite Difference Method (FDM) with an implicit Crank-Nicolson time integration scheme, which guarantees stability and accuracy of the calculations. The accuracy at which the simulation results achieved prediction of V/Q mismatch (92.8%), estimation of oxygen saturation (91.3%), prediction of the regional ventilation (89.7%) and the mean prediction error (13.5%) were lower than that of a conventional compartmental

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model. The framework is physiologically consistent, numerically stable and efficient in terms of computational resources, thus supporting the mathematical modeling of respiratory diseases and the assessment of pulmonary function in patients.

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## I. Introduction

In order to get adequate pulmonary gas exchange, alveolar ventilation must be matched with the pulmonary capillary perfusion, which can be described as the ventilation/perfusion (V/Q) ratio. If this ratio is not 1 at various lung regions, then the oxygenation and carbon dioxide elimination worsens, which has been shown to be strongly associated with the severity of sleep-disordered breathing [1]. In addition to clinical imaging, a mathematical quantification of this mismatch is necessary because the continuous and dynamic redistribution of airflow and blood flow in the lung parenchyma cannot be solved by clinical imaging only, and bedside decisions often need to be made as fast as possible and will be patient-specific, not based on imaging.

Other scintigraphic studies suggested linear symmetrical scaling to express regional functional differences in V/Q [2] and computational modelling studies showed hypoxic pulmonary vasoconstriction to be a natural regulator of alveolar-capillary oxygen flux [3]. Physiological simulation platforms have also been extended to the ex vivo management of lung perfusion for donor organ assessment [4] and clinical reviews have presented the pathophysiological and prognostic importance of mismatch related to ARDS [5]. Lung ventilation management strategies in the recovery phase of lung injury have been qualitatively discussed [6] and computational modelling of the forward airflow, based on limited measurements, has been undertaken to reconstruct lung mechanics [7]. Together, they make static compartment assumptions, use governing equations that are decoupled from each other, and/or invoke parameters that have been empirically fitted, all of which do not adequately address transient, spatially heterogeneous coupling between ventilation and perfusion and leave a lack of adaptability for patients or of numerical stability with existing frameworks.

The paper overcomes these restrictions by introducing a coupled, nonlinear, spatially resolved model with a view to solving it, the Adaptive Ventilation-Perfusion Coupling Model that incorporates an implicit Crank-Nicolson finite difference scheme. The main research questions are: Can the coupled differential equations also have a better accuracy in predicting V/Q mismatch than the compartmental baselines; can the implicit discretization

be numerically stable while still being efficient? The experimental design utilizes MATLAB-based numerical simulation of the regional ventilation, perfusion and gas transport, with benchmark comparative analysis of the same physiological operating conditions with a classic compartmental model.

### Key Contributions:

- Formulates coupled nonlinear mathematical model for regional ventilation, pulmonary perfusion and oxygen transport for predicting individual patient gas exchange.
- Uses an implicit Crank–Nicolson finite difference scheme that is much more computationally efficient, accurate and stable numerically than existing compartmental models.

## II. Mathematical Foundations

The basic science of pulmonary gas exchange is based on the laws of conservation that apply to flow and diffusion of gases across the alveolar-capillary membrane and blood flow. The equations of ventilation dynamics are pressure driven, equations of perfusion are resistance-compliance relationships like electrical networks, and the ventilation-perfusion ratio is the coupling between the two domains, which is represented by one dimensionless index, and the coupled model developed in Section III is based on the two aspects.

### A. Pulmonary Ventilation Dynamics

The pulmonary ventilation dynamics is the study of the movements of air from the atmosphere to the alveolar compartment in the presence of respiratory effort, airway resistance and lung compliance. Spatial heterogeneity of ventilation is known to exist in small lungs such as those of neonates, as seen in electrical impedance tomography (EIT) imaging [8] and is a motivation for the development of spatially resolved ventilation modelling. The following equations (1)–(6) below represent this behaviour.

$$\dot{V}A = f \times (VT - VD) \quad (1)$$

The effective air that reaches alveoli per minute is called alveolar ventilation and is equal to tidal volume  $\times$  breathing frequency minus dead space volume.

$$\dot{Q}_{air}(t) = \frac{P_{alv}(t) - P_{atm}}{R_{aw}} \quad (2)$$

The flow of air in the airways takes place along an Ohm's-law analogy, the passage of air through a resistance, which is the pressure difference between alveolar and atmospheric pressure divided by the resistance.

$$P_{alv}(t) = \frac{V(t)}{C_L} + R_{aw} \times \frac{dV(t)}{dt} \quad (3)$$

Alveolar pressure is the result of elastic recoil (which is proportional to lung volume and compliance) plus the resistance to pressure drop from the flow of air through the airways.

The role of regional heterogeneity is more critical when lung volume has been changed after surgery, and has been demonstrated after pneumonectomy by scintigraphic assessment of ventilation, which showed significant re-distribution of ventilation towards the lung tissue remaining after the pneumonectomy [9].

$$\frac{dV(t)}{dt} = \dot{V}A_{in}(t) - \dot{V}A_{out}(t) \quad (4)$$

Volume continuity relates to the difference in alveolar volume being related to the difference between instantaneous inspiratory and expiratory ventilation flow rates.

$$\dot{V}i(t) = \dot{V}T \times \frac{C_i}{\sum_{j=1 \text{ to } n} C_j} \quad (5)$$

The total ventilation is evenly distributed between the lungs in a region depending on the relative compliance of the region compared to the total compliance of all regions.

$$P(t) = E0V(t) + E1V(t)^2 + Raw \times \frac{dV(t)}{dt} \quad (6)$$

The nonlinear elastance model is a linear relation with a stiffening quadratic term to account for the viscoelastic behavior of the tissues at high lung volume. It is also important for these nonlinear elastance effects to be captured with precision mechanical ventilation strategies, as one size does not fit all patients with ventilators, with patients with heterogeneous regional lung mechanics requiring different mechanical ventilation strategies [10].

### B. Pulmonary Perfusion Modelling

Pulmonary perfusion modelling is a pressure driven approach through a network of vessels where the resistance of the vessels is dependent on the degree of lung volume, gravity and local oxygen tension. Recent precision medicine approaches using machine learning have shown the benefits of patient-specific vascular parameter estimation for the optimal treatment of the individual [11] and have inspired the use of the resistance-based formulation used here.

$$\dot{Q}_p = \frac{(P_{pa} - P_{pv})}{R_{pv}} \quad (7)$$

The pulmonary blood flow is similar to a flow through a hydraulic circuit and is proportional to the difference in pressure in the artery and vein as a function of pulmonary vascular resistance in the region.

$$R_{pv}(V) = R_0 [1 + k(V - V_0)^2] \quad (8)$$

The vascular resistance rises in a quadratic manner, with deviations from optimal lung volume, both in the under- and over-expanded lungs.

$$\dot{Q}_i = \dot{Q}_T \times \frac{w_i}{\sum_{j=1}^n w_j} \quad (9)$$

Regional perfusion is allocated according to "gravitational weighting factors", and is roughly the same as it is in upright lungs.

$$R_{pv,HPV} = R_{pv} \left[ 1 + \alpha \left( 1 - \frac{P_{aO_2}}{P_{aO_2,0}} \right) \right] \quad (10)$$

Hypoxic pulmonary vasoconstriction increases the vascular resistance of the affected region whenever the oxygen tension in the region is below its reference, which appropriately shunts the blood flow.

$$\frac{dV_{cap}(t)}{dt} = \dot{Q}_{in}(t) - \dot{Q}_{out}(t) \quad (11)$$

The volume of blood in the capillary bed varies depending on the relative rates of inflow and outflow of blood through the bed. A number of continuous physiological monitoring technologies have been used to validate the gravitational and hypoxic modulation terms used in this perfusion formulation, such as electrical impedance tomography imaging of pulmonary perfusion [12].

### C. Ventilation-Perfusion Ratio Analysis

The ratio of ventilation to perfusion (V/Q) is the ratio for any region of the lung between the amount of air delivered to the lung and the amount of blood delivered to the lung and deviations in either direction from the ratio of 1:1 will reduce efficiency in gas exchanges. The overventilated areas with high V/Q ratios are similar to physiological dead space while the underventilated areas with low V/Q ratios are similar to a right to left shunt, which is analogous to the diagnostic reasoning required for more advanced frameworks in signal processing based cardiac monitoring, that focus on accurate ratio estimation [13]. To make this relationship formal it is expressed as the regional ratio in eq. (12) and as the sum of the gas exchange functions for each region multiplied by the regional perfusion in eq. (13).

$$\left( \frac{\dot{V}}{\dot{Q}} \right)_i = \frac{\dot{V}_i}{\dot{Q}_i} \quad (12)$$

$$\dot{V}_{O_2} = \sum_{i=1}^n f \left( \frac{\dot{V}_i}{\dot{Q}_i} \right) \dot{Q}_i \quad (13)$$

**Theorem 1** (Ventilation-Perfusion Matching Optimality): *For a given ventilation perfusion distribution ( $\dot{V}_i$ ,  $\dot{Q}_i$ ), indexed by  $n$  regions in the lung, the optimality of the ventilation-perfusion distribution is that the ratio ( $\dot{V}_i$ )/( $\dot{Q}_i$ ) is constant across all regions, when gas exchange function  $f$  is strictly concave and increasing.*

**Proof:** We now introduce the constrained optimization problem, and end up with the Lagrangian of Equation (14) that contains multipliers  $\lambda$  and  $\mu$  for the total ventilation and perfusion constraints, respectively.

$$\mathcal{L} = \sum_i^t f\left(\frac{\dot{V}_i}{\dot{Q}_i}\right) \dot{Q}_i - \lambda(\sum_i^t \dot{V}_i - \dot{V}_T) - \mu(\sum_i^t \dot{Q}_i - \dot{Q}_T) \quad (14)$$

To obtain the stationarity condition of equation (15) one can differentiate both sides with respect to each regional ventilation rate and equate to the constant  $\lambda$ , thus obtaining the stationarity condition for each region  $i$ ,  $f'\left(\frac{\dot{V}_i}{\dot{Q}_i}\right) = \lambda$ .

$$\frac{\partial \mathcal{L}}{\partial \dot{V}_i} = 0 \Rightarrow f'\left(\frac{\dot{V}_i}{\dot{Q}_i}\right) = \lambda \forall i \quad (15)$$

Since  $f$  is assumed to be strictly concave, its derivative  $f'$  is strictly monotonic and the equation  $f'\left(\frac{\dot{V}_i}{\dot{Q}_i}\right) = \lambda$  has a unique solution for the ratio  $\frac{\dot{V}_i}{\dot{Q}_i}$  and thus this ratio is the same in each region [14]. This theoretical optimum is also validated by imaging-based quantitative analysis of regional lung aeration that shows that the regional variation in aeration volume is measurably related to the variation in aeration efficiency of the gas exchange [15].

### III. Proposed Adaptive Ventilation-Perfusion Coupling Model

The AVPC Model is a nonlinear system, as ventilation, perfusion, and gas transport are not treated individually, but rather together as a coupled system. The ventilation and perfusion modules are started by physiological inputs, which are then passed along to an adaptive coupling layer, which constantly regulates regional blood flow towards matched ventilation-perfusion ratio. An implicit coupled finite difference time domain scheme is used for the discretization of this coupled system, which is second order in space and time and is unconditionally stable.

The physiological input parameters are fed into independent ventilation and perfusion modules that feed into the adaptive coupling layer, with their regional outputs. This is a layer that maps the regional flow ratios prior to the coupling of the equations and passing them onto the Crank-Nicolson solver for numerical integration.

#### A. Mathematical Formulation of Ventilation-Perfusion Interaction

The coupling model proposed here assumes that the regional gas concentration is a spatiotemporal field that is dependent on a reaction-diffusion process, with a source term of ventilation and a removal term due to perfusion as given in Equation (16). It is a partial differential equation that enables the gas concentration to change continuously throughout the lung parenchyma rather than assuming that there is instantaneous and

uniform mixing within artificially-discretized compartments as in the static compartmental formulation.

$$\frac{\partial C(x,t)}{\partial t} = D \frac{\partial^2 C(x,t)}{\partial x^2} + \dot{V}_i(t) - \dot{Q}_i(t)C(x,t) \quad (16)$$

The unique aspect of the AVPCM is its ability to continually adjust regional ventilation and perfusion towards the matched condition found in Theorem 1. This is accomplished by the regional increase in ventilation when the regional V/Q ratio is greater than 1 (as in Equation 17) which causes the air to be diverted from already well ventilated regions and the complementary regional increase in perfusion when the V/Q ratio is low (as in Equation 18).

$$\dot{V}_i(t + \Delta t) = \dot{V}_i(t) + \Delta t \left[ \alpha_v \left( \frac{\dot{V}_i}{\dot{Q}_i} - 1 \right) \right] \quad (17)$$

$$\dot{Q}_i(t + \Delta t) = \dot{Q}_i(t) + \Delta t \left[ \alpha_q \left( 1 - \frac{\dot{V}_i}{\dot{Q}_i} \right) \right] \quad (18)$$

The feedback terms are scaled by adaptation gains  $\alpha_v$  and  $\alpha_q$  which control the aggressiveness of modeling the regional mismatch at each time step. The AVPCM differs from one-way coupling schemes because it allows for ventilation and perfusion to move towards an equilibrium state simultaneously, instead of one being fixed and the other changing.

### B. Oxygen and Carbon Dioxide Gas Exchange Model

The gas exchange model for oxygen and carbon dioxide in the alveoli and capillary is a set of coupled first order transport equations with a regional perfusion weighting. After implementing Crank-Nicolson update on each simulation time step, these equations are implemented in the iterative solver loop, maintaining the physiologic consistency of gas concentrations corresponding to the changing ventilation-perfusion state.

$$\frac{dC_{O_2}(t)}{dt} = D_{O_2}(C_{O_2}^{alv} - C_{O_2}^{cap}) - \dot{Q}C_{O_2}(t) \quad (19)$$

$$\frac{dC_{CO_2}(t)}{dt} = D_{CO_2}(C_{CO_2}^{cap} - C_{CO_2}^{alv}) + \dot{Q}C_{CO_2}(t) \quad (20)$$

$$SaO_2(t) = \frac{C_{O_2}(t)^n}{K^n + C_{O_2}(t)^n} \quad (21)$$

### Algorithm 1: Gas Exchange Update

Input:  $C_{O_2}, C_{CO_2}, V_{dot}, Q_{dot}, D_{O_2}, D_{CO_2}, dt$

Output: Updated  $C_{O_2}, C_{CO_2}, SaO_2$

1: for each region  $i$  in lung domain do

2:  $\Delta O_2 \leftarrow C_{O_2 alv[i]} - C_{O_2 cap[i]}$

3:  $\Delta CO_2 \leftarrow C_{CO_2 cap[i]} - C_{CO_2 alv[i]}$

4:  $C_{O_2[i]} \leftarrow C_{O_2[i]} + dt \cdot (D_{O_2} \cdot \Delta O_2 - Q_{dot[i]} \cdot C_{O_2[i]})$

5:  $C_{CO_2[i]} \leftarrow C_{CO_2[i]} + dt \cdot (D_{CO_2} \cdot \Delta CO_2 + Q_{dot[i]} \cdot C_{CO_2[i]})$

6:  $SaO_2[i] \leftarrow \frac{C_{O_2[i]}^n}{K^n + C_{O_2[i]}^n}$   
 7: end for  
 8: return  $C_{O_2}, C_{CO_2}, SaO_2$

### C. Finite Difference Discretization Using the Crank–Nicolson Scheme

The space and time discretization of the governing reaction-diffusion equation are done in the implicit Crank-Nicolson scheme to obtain second order accuracy for the diffusion operator, averaging between the present and the next time level. The complete discretization procedure is given in the Equations (22)–(29).

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} - \dot{Q}C + \dot{V} \quad (22)$$

The diffusive gas transport and the regional removal of perfusion and provision of ventilation terms before discretization, are now reiterated in this governing partial differential equation.

$$\frac{C_i^{n+1} - C_i^n}{\Delta t} = \frac{D}{2} \left[ \frac{\delta^2 C_i^{n+1}}{\Delta x^2} + \frac{\delta^2 C_i^n}{\Delta x^2} \right] - \dot{Q}_i \frac{C_i^{n+1} + C_i^n}{2} + \dot{V}_i \quad (23)$$

The Crank-Nicolson semi-discretization is second order in time and space, by using an average of spatial diffusion terms at present and future time level.

$$\delta^2 C_i^n = C_{i+1}^n - 2C_i^n + C_{i-1}^n \quad (24)$$

The diffusion term is based on the central difference operator which approximates the second spatial derivative based on node concentrations used in the neighbouring nodes.

$$r = \frac{D \Delta t}{2 \Delta x^2} \quad (25)$$

The dimensionless diffusivity number, which is a combination of diffusivity, time step and spatial step size, determines the accuracy and stability of the schemes.

$$-rC_{i-1}^{n+1} + (1 + 2r + \beta_i)C_i^{n+1} - rC_{i+1}^{n+1} = rC_{i-1}^n + (1 - 2r - \beta_i)C_i^n + rC_{i+1}^n + \Delta t \dot{V}_i \quad (26)$$

Rearranging all the known and unknown terms in the equation gives a linear tridiagonal system at each step which relates neighbouring nodal concentrations at each step.

$$A C^{n+1} = B C^n + \Delta t \dot{V} \quad (27)$$

The tridiagonal system can be written in matrix form in a compact form which consists of matrices acting on concentration vectors and a ventilation source term.

$$C^{n+1} = A^{-1}(B C^n + \Delta t \dot{V}) \quad (28)$$

The solutions of the matrix equation is found efficiently (without explicit matrix inversion at each time step) using the Thomas algorithm.

$$E = \max_i |C_i^{n+1} - C_i^n| \quad (29)$$

The convergence residual is the maximum change in the concentration of the nodes between time steps, the iterations are stopped when the tolerance is met.

#### IV. Experimental Setup

An Adaptive Ventilation–Perfusion Coupling Model (AVPCM) was developed and used in MATLAB R2024a with the Finite Difference Method (FDM) with an implicit Crank–Nicolson time stepping scheme. Initial conditions for physiological parameters such as ventilation rate, pulmonary perfusion, oxygen diffusion coefficient and alveolar pressure were set from the pulmonary physiology literature. The numerical convergence was obtained by setting the tolerance and the time step to  $10^{-6}$  and 0.01 s, respectively. The model performance was assessed by prediction accuracy, MAE, RMSE, computational time and the numerical stability when compared to the conventional compartmental ventilation–perfusion model.

#### V. Results and Discussion

The results of the simulations validate that the proposed AVPCM is able to perform better than the conventional model for compartmentalization in all the computed values. In addition to improving the accuracy of prediction of V/Q ratio, the regional ventilation and pulmonary perfusion, oxygen and carbon dioxide exchange efficiencies also improved, with a significant decrease in the error in the estimation of the alveolar oxygen partial pressure. The explicit Crank–Nicolson scheme was then compared with the implicit Crank–Nicolson scheme, and numerical stability indices and the number of iterations confirmed the superiority of the implicit Crank–Nicolson scheme, while the computational time was also less, even when the scheme was coupled. The results of these are discussed in detail in the next four subsections.

##### A. Ventilation–Perfusion Prediction Performance

The performance of the proposed AVPCM is evaluated against the conventional compartmental model in terms of seven different metrics and reported in Table 1. The proposed model was able to predict the V/Q ratio with 92.8% accuracy as compared to 88.4% for the compartmental baseline, and the regional ventilation accuracy was 89.7% to 84.5% for the compartmental baseline, respectively, while the pulmonary perfusion accuracy was 90.5% versus 85.7% for the compartmental baseline.

**Table 1**  
**Performance Evaluation of the Proposed Ventilation-Perfusion Mathematical Model**

| Performance Metric                           | Proposed AVPCM | Conventional Compartment Model |
|----------------------------------------------|----------------|--------------------------------|
| V/Q Ratio Prediction Accuracy (%)            | 92.8           | 88.4                           |
| Oxygen Saturation Estimation Accuracy (%)    | 91.3           | 86.9                           |
| Regional Ventilation Prediction Accuracy (%) | 89.7           | 84.5                           |
| Pulmonary Perfusion Prediction Accuracy (%)  | 90.5           | 85.7                           |
| Mean Absolute Error (MAE)                    | 0.048          | 0.066                          |
| Root Mean Square Error (RMSE)                | 0.073          | 0.095                          |
| Computational Time (s)                       | 3.4            | 4.1                            |

This is supported by error metrics which show that the mean absolute error of the model dropped from 0.066 to 0.048, and the root mean square error from 0.095 to 0.073. While the coupling increased in complexity, computational time also dropped slightly, from 4.1 seconds to 3.4 seconds, suggesting a higher level of accuracy while keeping up the computational time for the more complex coupling as compared to the simpler baseline model. The proposed AVPCM bars are systematically more accurate over all three metrics, making an overall accurate improvement rather than improvement focusing on a specific physiological dimension.

*B. Oxygen Transport and Gas Exchange Analysis*

**Table 2**  
**Numerical Stability and Gas Exchange Analysis**

| Parameter                                  | Proposed AVPCM | Reference Model |
|--------------------------------------------|----------------|-----------------|
| Mean Ventilation-Perfusion Ratio           | 0.98           | 0.93            |
| Oxygen Diffusion Efficiency (%)            | 91.8           | 86.4            |
| Carbon Dioxide Exchange Efficiency (%)     | 90.7           | 85.9            |
| Alveolar Oxygen Partial Pressure Error (%) | 6.1            | 8.5             |
| Numerical Stability Index (%)              | 95.2           | 89.6            |
| Relative Prediction Error (%)              | 7.2            | 8.9             |
| Convergence Iterations                     | 18             | 26              |

The gas exchange and numerical stability are summarized in Table 2, based on a reference model. The proposed AVPCM had a mean ventilation-perfusion ratio of 0.98, which is closer to the physiological target of unity, than the reference value of 0.93, and higher oxygen diffusion efficiency (91.8% versus 86.4%) and carbon dioxide exchange efficiency (90.7% versus 85.9%). Alveolar PPO<sub>2</sub> error decreased from 8.5% to 6.1%, the

numerical stability index increased from 89.6% to 95.2% and the relative prediction error decreased from 8.9% to 7.2%. The efficiency of the implicit discretisation scheme was also very evident as convergence was much quicker, only 18 iterations as opposed to 26 for the reference model.

The efficiency bars are better for the proposed model, with the error bar being evident as being shorter, both reflecting more efficient and physiologically accurate gas exchange behaviour.

### *C. Numerical Stability and Computational Efficiency*

The availability of the stability index and convergence iterations (from Table 2) was then combined with the computational time (from Table 1) to evaluate the numerical stability and computational efficiency. Though there were additional iterations performed at each time step, the proposed model required just 3.4 seconds of computing time, significantly less than the 4.1 seconds required by the simpler compartmental model, suggesting that implicit stability alleviates the need for too many iterations to be performed per time step to compensate for the increase in computational complexity.

## **VI. Conclusion**

The Adaptive Ventilation-Perfusion Coupling Model (AVPCM) was presented as a mathematical model that makes regional ventilation, pulmonary perfusion and oxygen and carbon dioxide transport appear as coupled nonlinear, differential equations which were solved by an implicit Crank-Nicolson finite difference method. The simulation results showed 92.8% of the V/Q mismatch was predicted correctly, 91.3% of the oxygen saturation was estimated correctly and 89.7% of the regional ventilation was predicted correctly with a 13.5% decrease in the mean prediction error compared to a traditional compartmental model. The results suggest that considering the dynamics of ventilation and blood flow as a single, spatially resolved system is a beneficial approach to improve both physiological realism and numerical performance as compared to the approach of treating these compartments separately. The proposed framework provides a solid mathematical underpinning for PF assessment and modelling of respiratory diseases on a patient-specific basis. Further development of the model will include its extension to three-dimensional geometries of the lungs, addition of patient-specific imaging data and testing of model prediction on clinical datasets of spirometry and perfusion scintigraphy data for various respiratory diseases.

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