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An Extensible Compartment-Based Ordinary Differential Equation Model to Provide Spatial Heterogeneity of Vertical Bioreactors to Whole Cell Metabolic Models

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Abstract

Large-scale aerobic bioreactors exhibit spatial gradients in dissolved oxygen and substrate from incomplete mixing and transport limitations, leading to heterogeneous microenvironments that influence cellular metabolism and complicate scale-up. Classical well-mixed models cannot capture these gradients, limiting their predictive power for industrial processes and their integration with whole-cell metabolic models. In this study, we present a simple and extensible multi-vertical compartment model for an aerobic bioreactor, formulated as a system of coupled ordinary differential equations derived from finite-volume discretization of the one-dimensional advection–dispersion–reaction framework. The reactor volume is divided into vertically stacked compartments, each assumed well mixed locally while connected through axial advection and axial dispersion. Biomass growth is described using dual-substrate Monod kinetics with substrate and oxygen limitation, and stoichiometric consistency is maintained through yield-based uptake relations. Substrate feed is introduced at the top compartment, while oxygen transfer is modelled via a volumetric mass transfer term, enabling counter-current gradients to emerge. The model is implemented in Python and solved using a stiff ODE integrator, allowing flexible configuration of compartment number, operating parameters, and feed strategies. Simulation results demonstrate the emergence of spatial gradients and their impact on biomass distribution under different operating conditions. This framework provides a computationally efficient bridge between reactor-scale heterogeneity and whole-cell metabolic modelling.

Keywords: Compartmental modelling, Aerobic bioreactor, Axial advection, Axial dispersion, Dual-substrate Monod kinetics, Spatial heterogeneity, Finite-volume discretization, Whole-cell metabolic modelling

Introduction

In large-scale aerobic bioreactors; environmental gradients, such as dissolved oxygen (DO) and substrate, arise due to incomplete mixing is incomplete and transport limitations; resulting in microenvironments that can alter metabolic activity, reduce biomass yield, and affect product formation, leading to scale-up challenges not observed in well-mixed laboratory bioreactors [1–3]. Classical reactor models assume perfect mixing (ideal continuous-stirred tank reactors, CSTRs [4]), which precludes spatial gradients and cannot account for the heterogeneities that occur in industrial settings. By extension, this meant that mathematical models of whole cell metabolism, such as genome-scale models (GSMs) and whole cell kinetic models (WCKMs) [5–13], are not expected to be accurate in predicting metabolite productions and usages in industrial bioreactor settings as they do not take such spatial heterogeneity into account [14].

To capture spatial structure with reduced computational cost compared to full computational fluid dynamics (CFD) simulations which are highly computational intensive [15, 16], compartmental models have been developed. In these models, the reactor volume is discretized into multiple well-mixed "zones" or compartments connected by finite exchange flows. Each compartment has its own local concentrations of reacting species, and exchanges between compartments represent bulk circulation and dispersion in the reactor [17, 18].

Mathematically, compartment models can be interpreted as finite-volume discretization of the convection–dispersion–reaction partial differential equations that govern transport and reaction in the reactor. By assuming homogeneous concentrations within each compartment and conserving mass across adjacent zones, a system of coupled ordinary differential equations (ODEs) emerges. These ODEs capture advection, dispersion (or mixing), biochemical reaction kinetics, and external feed or gas transfer terms. The compartmental ODE approach has been shown to reproduce spatially resolved behaviour predicted by CFD while reducing computational cost by several orders of magnitude, thereby enabling dynamic simulation of industrial fed-batch processes in their entirety [18].

Dynamic compartmental models have been successfully applied to industrial-scale aerobic fermentations. For example, Bisgaard et al. [19] developed a data-based compartment model for a 600 cubic metre *Escherichia coli* fed-batch fermentation in a bubble column reactor, using flow-informed exchange rates to simulate substrate and oxygen gradients and evaluate the impact of feed strategies on mixing performance and overall process outcomes. Similarly, chemical engineering research has detailed strategies for constructing dynamic compartment models that allow volume changes during fed-batch operations and maintain agreement with CFD predictions for glucose and dissolved oxygen distributions in stirred tanks [18].

This suggests that it may be possible for compartment-based bioreactor models to provide spatial information to whole cell metabolic models; thereby, improving their predictive accuracy. Hence, this study presents a simple and extensible compartment-based ordinary differential equation (ODE) model of a vertical bioreactor which can be used to provide spatial information to whole cell metabolic models. This compartment-based model assumes that oxygen enters the bioreactor from the bottom while substrate (the feedstock) enters from the top, which provides a base model for extension to other flows in opposite directions. In addition, the model can simulate any number of vertical compartments.

Single Compartment Bioreactor Model

Consider a single well-mixed, homogenous compartment representing an aerobic bioreactor in which biomass, substrate, and dissolved oxygen are spatially uniform due to sufficient mixing; and dynamically coupled through growth, substrate consumption, and oxygen transfer. This is consistent with classic bioreactor modelling and is suitable as the building block for compartmental or scale-down analyses.

In classical Monod kinetics [20, 21], the specific growth rate of a microorganism is depending on the limiting substrate S, $\mu(S) = \mu_{max}[S / (K_S + S)]$. However, when there more multiple limiting substrates; such as, limiting substrate S and dissolved oxygen O; the specific growth rate $\mu(S,O)$ of a microorganism can be modelled using dual-substrate Monod kinetics [22] where μ_{max} is the maximum specific growth rate under non-limiting conditions; K_S and K_O are the Monod half-saturation constants for substrate and oxygen, respectively; by capturing growth limitation by the least available essential [23]: $\mu(S,O) = \mu_{max}\{[S / (K_S + S)][O / (K_O + O)]\}$.

From a stoichiometric perspective, substrate and oxygen are consumed in proportion to biomass growth. Under the assumption of growth-associated uptake, the specific substrate consumption rate r_S and the specific oxygen uptake rate r_O can be related to the growth rate via yield coefficients; $r_S = -(\mu(S,O)\, X / Y_{X/S})$ and $r_O = -(\mu\ (S,O)\, X / Y_{X/O})$; where $Y_{X/S}$ is the biomass yield on substrate (g biomass per g substrate) and $Y_{X/O}$ is the biomass yield on oxygen (g biomass per g oxygen). These relations enforce elemental mass balance and are standard in aerobic process models [24, 25]. Positive values of r_S and r_O represent consumption of substrate and oxygen, respectively. Hence, the net biomass synthesis rate r_X then captures growth proportional to existing biomass, consistent with exponential growth kinetics when resources are abundant [20], $r_X = \mu\ (S,O)\ X$.

The temporal dynamics of biomass (X), substrate (S), and dissolved oxygen (O) in the well-mixed compartment are governed by ordinary differential equations (ODEs) that couple biological reaction rates with feed or dilution terms. Biomass increases with growth and can decrease by dilution when there is an inlet feed flow F into a volume V (e.g., continuous operation). In fed-batch mode, $F = 0$ for the biomass equation but for generality the dilution term is included [3,7]: $dX/dt = \mu(S,O)X - (F / V)X$.

Substrate is consumed to support biomass growth and may also be introduced via feed at concentration S_{in}. The second term represents external substrate addition and dilution of existing substrate in the reactor volume [3,7]: $dS/dt = -(\mu(S,O)X / Y_{X/S}) + [(F / V)(S_{in} - S)]$. Dissolved oxygen is then modelled as $dO/dt = [k_L a(O^* - O)] - (\mu(S,O)\ X / Y_{X/O})$, with $k_L a$ is the volumetric oxygen mass transfer coefficient, and O^* is the dissolved oxygen saturation concentration under prevailing temperature and gas composition. The first term represents oxygen transfer from the gas to the liquid phase, and the second term is the oxygen uptake by biomass [26, 27].

Multi-Vertical Compartment Bioreactor Model

To account for spatial heterogeneity along the vertical axis of a stirred bioreactor, the single well-mixed compartment model was extended to a multi-compartment representation [17, 28]. The reactor volume V was discretized into N vertically stacked compartments of equal volume $V_i = V / N$. Within each compartment $_i$, biomass (X_i), substrate (S_i), and dissolved oxygen (O_i) are assumed spatially homogeneous while mass exchange occurs between adjacent compartments via axial advection and axial dispersion [29, 30]. Axial advection (or axial convection) refers to the transport of a substance (like substrate, oxygen, or biomass) along the length of the reactor due to actual fluid flow while axial dispersion refers to the mixing or spreading of a substance along the reactor axis due to molecular diffusion and turbulent fluctuations rather than actual flow. This approach represents a finite-volume approximation of the 1-D advection–dispersion equation and is commonly used as a reduced-order alternative to full CFD modelling [1, 18].

Within each compartment, biological kinetics follow the same dual-substrate Monod formulation [22] described for the single-compartment case, $\mu_i = \mu_{max}\{[S_i / (K_S + S_i)][O_i / (K_O + O_i)]\}$; with the local reaction rates as $r_{X,i} = \mu_i X_i$, $r_{S,i} = -(\mu_i X_i / Y_{X/S})$, and $r_{S,O} = -(\mu_i X_i / Y_{X/O})$. These expressions are standard for aerobic growth under dual limitation [26], and ensure stoichiometric consistency between biomass formation and substrate/oxygen uptake.

Macroscopic circulation induced by impeller pumping produces convective transport along the vertical direction. Axial advection is represented as exchange between adjacent compartments using an inter-compartment volumetric flow rate Q. For species C (representing X, S, or O), the net advective flux into compartment i [1] as: $(dC_i/dt)_{adv} = [(Q / V_i)(C_{i-1} - C_i)] - [(Q / V_i)(C_i - C_{i+1})]$. Turbulent mixing and macro-eddies introduce diffusive-like spreading along the reactor height. This is modelled using an axial dispersion coefficient D_{ax}. The discrete second-order central difference approximation gives $(dC_i/dt)_{disp} = (D_{ax} / \Delta z^2)(C_{i+1} - 2C_i + C_{i-1})$ where Δ_z is the height of each compartment.

As a result, the mass balances for each compartment $i = 1, \ldots, N$, the dynamic balances become

$dX_i/dt = \mu_i X_i + (dX_i/dt)_{adv} + (dX_i/dt)_{disp}$, $dS_i/dt = -(\mu_i X_i / Y_{X/S}) + (dS_i/dt)_{adv} + (dS_i/dt)_{disp}$; where substrate feed introduced at the top compartment is implemented as an inlet boundary condition $dS_1/dt = \ldots + [(F / V_1)(S_{in} - S_1)]$, and $dO_i/dt = [k_L a(O^* - O_i)] - (\mu_i X_i / Y_{X/O}) + (dO_i/dt)_{adv} + (dO_i/dt)_{disp}$. For the bottom compartment, oxygen gas sparging is represented through the same $k_L a$ term.

Implementation and Usage

The multi-vertical compartment model described above was implemented in pure Python to allow efficient and flexible simulation of bioreactor dynamics without resorting to computationally intensive CFD simulations. The model is encapsulated within a VerticalBioreactor class, which organizes the reactor into *N* vertical compartments, each tracking biomass X_i, substrate S_i, and dissolved oxygen O_i. This means that the compartment 1 is the bottom-most compartment of the bioreactor and compartment *N* is the top. The ODE system for all compartments is solved simultaneously using the scipy.integrate.solve_ivp() function, with the stiff solver BDF [31, 32].

The Python implementation adopts a flat state vector structure, where all compartment states are concatenated as $[X_1, S_1, O_1, X_2, S_2, O_2, \ldots, X_N, S_N, O_N]$. This arrangement allows straightforward mapping of computed time derivatives back to the solver. Each compartment's rate of change is computed as the sum of local biological kinetics, axial advection, axial dispersion, and any applicable feed or gas transfer terms, following the governing equations presented previously.

Model parameters are defined in a Python dictionary and can be easily modified (see Table 1 for entire list of parameters). By default, the code provides physically reasonable values for typical aerobic fermentations; however, all parameters, including the number of compartments *N*, can be overridden from the command line, enabling rapid exploration of reactor configurations and operating conditions. For example, the model can be executed for seven compartments and a longer simulation time with the command "python compferm.py *N=7* simulation_time= 30".

Initial conditions for all compartments are specified as vectors of biomass, substrate, and oxygen concentrations, which are concatenated into the solver state vector. Temporal integration is performed over the desired simulation interval, and the solver returns time-resolved concentration profiles for all compartments. These profiles can be directly extracted into structured arrays for biomass, substrate, and oxygen, enabling further analysis, plotting, or export. Simulation results can be saved directly to CSV files, facilitating post-processing, visualization, or integration with downstream metabolic models. For instance, the Python implementation generates a table with columns for time and compartment-specific concentrations of X_i, S_i, and O_i, allowing convenient inspection of spatial and temporal gradients across the reactor.

Parameter	Default Value	Unit	Description
N	5	No unit	Number of compartments
simulation_time	20	Hour	Number of hours to simulate
number_of_steps	500	No unit	Number of time steps
filename	result.csv	No unit	Name of result file
mu_max	0.5	Per hour	Maximum specific growth rate (*E. coli*: 0.6–1.2/h; Yeast: 0.3–0.5/h; Mammalian cells: 0.02–0.05/h)
K_S	0.2	Gram per hour	Monod half-saturation constant for substrate; Low K_S means high affinity for substrate. High K_S means organism requires higher substrate concentration to grow efficiently.
K_O	0.001	Gram per hour	Half-saturation constant for dissolved oxygen; Oxygen saturation (O_star) is usually around 0.007–0.009 g/L at 30°C in water.
Yxs	0.5	Gram per gram	Gram of biomass yield per gram of substrate
Yxo	1.0	Gram per gram	Gram of biomass yield per gram of oxygen
Q_up	2.0	Litre per hour	Upward liquid circulation rate
Q_down	2.0	Litre per hour	Downward liquid circulation rate
D_ax	0.5	Litre per hour	Axial dispersion coefficient representing turbulent diffusion / back-mixing between adjacent compartments. Higher D_ax means smoother gradients. Lower D_ax means sharper gradients.
V	1.0	Litre	Volume per compartment, which is proxy to one unit of height.
F_S	0.2	Litre per hour	Substrate feed flow rate entering the top compartment. If this is zero, batch reactor. If positive, fed-batch or continuous mode.
S_in	20.0	Grams per litre	Substrate concentration in feed stream
O_star	0.008	Grams per litre	Oxygen saturation concentration

Table 1: Parameters for Model. "Litre" is used as proxy for a unit of height; hence, 0.5 litre per hour for axial dispersion (D_ax) represents dispersion of half a compartment height.

Finally, the model design is extensible: additional compartments, alternative feed strategies, variable oxygenation profiles, or more complex reaction kinetics can be incorporated with minimal modification to the core ODE solver. This implementation provides a practical framework for linking compartmental bioreactor simulations with genome-scale or whole-cell metabolic models, thereby enabling predictive analyses of industrial-scale fermentation processes while maintaining computational efficiency.

With this, a trial simulation using default parameter values can be performed using "python compferm.py". The result is shown in Figure 1 suggesting that the biomass of all 5 compartment is relatively constant despite substantially reduced dissolved oxygen in the top 2 compartments (compartments 4 and 5). Doubling the height (from 1 to 2 litres) and substrate demand (from 0.5 to 1 gram of substrate per gram of biomass) changes the command from "python compferm.py" to "python compferm.py *V*=2 *Yxs*=1.0" (Figure 2) demonstrates more biomass variation between different compartments at about 11 to 12 hours as dissolved oxygen gets depleted. This suggests that the code is executable.

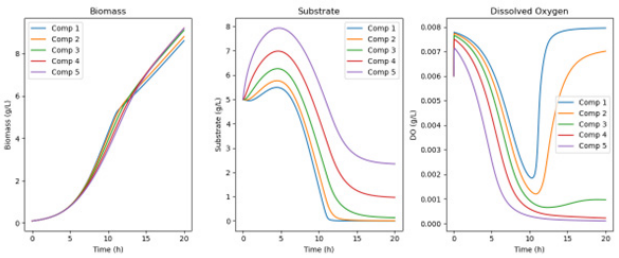

Figure 1: Simulation Results using Default Values.

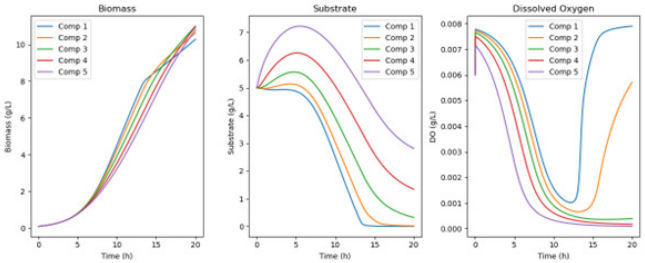

Figure 2: Doubling the Height and Substrate Demand from Default Values.

Conclusion

A computationally efficient multi-compartment ODE model was developed to capture vertical substrate and oxygen gradients in aerobic bioreactors. The framework enables dynamic simulation of spatial heterogeneity and offers a practical foundation for integrating reactor-scale transport effects with whole-cell metabolic models.

Supplementary Materials

The Python simulation file, compferm.py, can be download at https://bit.ly/compferm.

Conflict of Interest

The author is a director of AdvanceSyn Private Limited, which is involved providing consultancy service in fermentation and metabolic modelling.

References

1. Lara AR, Galindo E, Ramírez OT, Palomares LA (2006) Living with heterogeneities in bioreactors: understanding the effects of environmental gradients on cells. *Molecular Biotechnology* 34(3):355–381.
2. Soini J, Pajulampi U, Sandqvist J, Matzen A, Neubauer P (2006) Two-compartment bioreactor as a scale-down model to study the effect of glucose overflow and anaerobiosis on large-scale recombinant protein production processes. *Microbial Cell Factories* 5(Suppl 1):P26.
3. Arulrajah P, Lievonen AE, Subaşı D, Pagal S, Weuster-Botz D, Heins A-L (2025) Scale-down bioreactors-comparative analysis of configurations. *Bioprocess and Biosystems Engineering* 48(10):1619–1635.
4. Gujer W (2008) *Systems Analysis for Water Technology* (Springer Berlin Heidelberg, Berlin, Heidelberg).
5. Kwan ZJ, Teo W, Lum AK, Ng SM, Ling MH (2024) Ab Initio Whole Cell Kinetic Model of Stutzerimonas balearica DSM 6083 (pbmKZJ23). *Acta Scientific Microbiology* 7(2):28–31.
6. Arivazhagan M, Senthilkumar A, Yeo KY, Saisudhanbabu T, Le MA, Wong TB, Lukianto VR, Ling MH (2025) Ab Initio Whole Cell Kinetic Model of Bifidobacterium bifidum BGN4 (bbfMA24). *Acta Scientific Nutritional Health* 9(1):42–45.
7. Senthilkumar A, Madhunisha A, Yeo KY, Saisudhanbabu T, Le MA, Wong TB, Lukianto VR, Ling MH (2025) Ab Initio Whole Cell Kinetic Model of Lactobacillus acidophilus NCFM (lacAS24). *Journal of Clinical Immunology & Microbiology* 6(1):1–5.
8. Saisudhanbabu T, Yeo KY, Arivazhagan M, Senthilkumar A, Le MA, Wong TB, Lukianto VR, Ling MH (2025) Ab Initio Whole Cell Kinetic Model of Limosilactobacillus fermentum EFEL6800 (lfeTS24). *EC Clinical and Medical Case Reports* 8(4):01–04.
9. Yeo KY, Arivazhagan M, Senthilkumar A, Saisudhanbabu T, Le MA, Wong B, Lukianto VR, Ling MH (2025) Ab Initio Whole Cell Kinetic Model of Yarrowia lipolytica CLIB122 (yliYKY24). *Medicon Medical Sciences* 8(4):01–06.
10. Wong TB, Le MA, Arivazhagan M, Senthilkumar A, Yeo KY, Saisudhanbabu T, Lukianto VR, Ling MH (2025) Ab Initio Whole Cell Kinetic Models of Escherichia coli BL21 (ebeTBSW25) and MG1655 (ecoMAL25). *Scholastic Medical Sciences* 3(2):01–04.
11. Maiyappan S, Sim SS, Ramesh G, Low L, Matarage ML, Ling MH (2025) Four Ab Initio Whole Cell Kinetic Models of Bacillus subtilis 168 (bsuLL25) 6051-HGW (bshSM25), N33 (bsuN33SS25), FUA2231 (bsuGR25). *Journal of Clinical Immunology & Microbiology* 6(2):1–6.
12. Ambel WB, Tan LP, Toh D, Thirunavukarasu D, Natarajan K, Ling MH (2025) UniKin2 – A Universal, Pan-Reactome Kinetic Model. *International Journal of Research in Medical and Clinical Science* 3(2):77–80.
13. RajKumar AA, Ning Kang CK, Verma S, Nanthakumarvani D, Abul-Hasan S, Perumal LH, Ling MH (2026) Ab initio Whole Cell Kinetic Model of Desulfovibrio desulfuricans L4 (ddsAAR26). *Journal of Clinical Immunology & Microbiology* 7(1):1–5.

14. Wang G, Haringa C, Tang W, Noorman H, Chu J, Zhuang Y, Zhang S (2020). Coupled metabolic-hydrodynamic modeling enabling rational scale-up of industrial bioprocesses. *Biotechnology and Bioengineering* 117(3):844–867.

15. Kumar M (2023). Performance Analysis of Computational Fluid Dynamics Workloads on HPC in the Cloud. *2023 14th International Conference on Computing Communication and Networking Technologies (ICCCNT)* (IEEE, Delhi, India), pp 1–5.

16. Zhao W, Wang W, Zhang G, Wan D, Stern F, Abdel-Maksoud M (2025). Computational Fluid Dynamics Technologies and Applications for Offshore Floating Structures: Progress and Perspectives. *Engineering*:S2095809925007271.

17. Nørregaard A, Bach C, Krühne U, Borgbjerg U, Gernaey KV (2019). Hypothesis-driven compartment model for stirred bioreactors utilizing computational fluid dynamics and multiple pH sensors. *Chemical Engineering Journal* 356:161–169.

18. Nadal-Rey G, McClure DD, Kavanagh JM, Cassells B, Cornelissen S, Fletcher DF, Gernaey KV (2021). Development of dynamic compartment models for industrial aerobic fed-batch fermentation processes. *Chemical Engineering Journal* 420:130402.

19. Bisgaard J, Zahn JA, Tajsoleiman T, Rasmussen T, Huusom JK, Gernaey KV (2022) Data-based dynamic compartment model: Modeling of E. coli fed-batch fermentation in a 600 m3 bubble column. *Journal of Industrial Microbiology & Biotechnology* 49(5):kuac021.

20. Monod J (1949). The growth of bacterial cultures. *Annual Review of Microbiology* 3(1):371–394.

21. Chang ED, Ling MH (2019) Explaining Monod in terms of Escherichia coli metabolism. *Acta Scientific Microbiology* 2(9):66–71.

22. Losa JP, Santos FM, Alvim-Ferraz MCM, Martins FG, Pires JCM (2020). Dynamic Modeling of Microalgal Growth. *Encyclopedia of Marine Biotechnology*, ed Kim S (Wiley), 1st Ed., pp 547–567.

23. Stewart HA, Al-Omari A, Bott C, De Clippeleir H, Su C, Takacs I, Wett B, Massoudieh A, Murthy S (2017). Dual substrate limitation modeling and implications for mainstream deammonification. *Water Research* 116:95–105.

24. Enfors S-O, Jahic M, Rozkov A, Xu B, Hecker M, Jürgen B, Krüger E, Schweder T, Hamer G, O'Beirne D, Noisommit-Rizzi N, Reuss M, Boone L, Hewitt C, McFarlane C, Nienow A, Kovacs T, Trägårdh C, Fuchs L, Revstedt J, Friberg PC, Hjertager B, Blomsten G, Skogman H, Hjort S, Hoeks F, Lin H-Y, Neubauer P, Van Der Lans R, Luyben K, Vrabel P, Manelius Å (2001). Physiological responses to mixing in large scale bioreactors. *Journal of Biotechnology* 85(2):175–185.

25. Garcia-Ochoa F, Gomez E, Santos VE, Merchuk JC (2010). Oxygen uptake rate in microbial processes: An overview. *Biochemical Engineering Journal* 49(3):289–307.

26. Garcia-Ochoa F, Gomez E (2009) Bioreactor scale-up and oxygen transfer rate in microbial processes: an overview. *Biotechnology Advances* 27(2):153–176.

27. Schaepe S, Kuprijanov A, Sieblist C, Jenzsch M, Simutis R, Lübbert A (2013). kLa of stirred tank bioreactors revisited. *Journal of Biotechnology* 168(4):576–583.

28. Delafosse A, Collignon M-L, Calvo S, Delvigne F, Crine M, Thonart P, Toye D (2014). CFD-based compartment model for description of mixing in bioreactors. *Chemical Engineering Science* 106:76–85.

29. Vrábel P, Van Der Lans RGJM, Luyben KChAM, Boon L, Nienow AW (2000). Mixing in large-scale vessels stirred with multiple radial or radial and axial up-pumping impellers: modelling and measurements. *Chemical Engineering Science* 55(23):5881–5896.

30. Losoi P, Konttinen J, Santala V (2024). Modeling large-scale bioreactors with diffusion equations. Part I: Predicting axial dispersion coefficient and mixing times. *Biotechnology and Bioengineering* 121(3):1060–1075.

31. Curtiss CF, Hirschfelder JO (1952). Integration of Stiff Equations. *Proceedings of the National Academy of Sciences of the United States of America* 38(3):235–243.

32. Gear CW (1967). The numerical integration of ordinary differential equations. *Mathematics of Computation* 21(98):146–156.